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Clinical Year in Review

ATS 2023

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Clinical Year in Review Bibliography

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ARDS

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IMPACT ON LONG-TERM PATIENT-CENTERED OUTCOMES OF CRITICAL ILLNESS DUE TO COVID-19

Heesakkers H, van der Hoeven JG, Corsten S, Janssen I, Ewalds E, Simons KS, Westerhof B, Rettig TCD, Jacobs C, van Santen S, Slooter AJC, van der Woude MCE, van den Boogaard M, Zegers M. **Clinical Outcomes Among Patients With 1-Year Survival Following Intensive Care Unit Treatment for COVID-19**. *JAMA* 2022; 327: 559-565.

Summary

In this multicenter, prospective cohort study conducted in the Netherlands, the outcomes and symptom burden of 246 survivors of critical illness due to COVID-19 who completed questionnaires one year after their ICU treatment are described. This study adds to a large body of evidence that the critical illness experience (as well as COVID-19 itself) are associated with physical, emotional, and cognitive impairments persisting long beyond the nominal recovery and hospital discharge in a great number of ICU survivors. Given the magnitude and scope of the ongoing pandemic, these findings suggest an enormous societal burden of such symptoms that are likely largely attributable to the ICU experience. Bedside practitioners, researchers, and healthcare policy-makers must urgently pursue means of mitigating this reality. Furthermore, clinicians must be cognizant of the important downstream sequelae of COVID-19, ARDS and other critical illnesses as these may inform not only our bedside compassion and clinical judgement, but also our prognostication and discussions of therapeutic goals with patients, families and other healthcare surrogates. Lastly, this report underscores the importance of strategies (e.g., protocols to avoid benzodiazepines and unnecessary analgo-sedation in general, robust ventilator liberation protocols, and physical rehabilitation) designed to reduce the long-term sequelae of critical illness.

Comments

1. In this report, almost 3/4 of ICU survivors had physical impairment persisting 1 year after the index illness, and 10.5% of ICU survivors had concurrent impairments in the physical, emotional, and cognitive domains, and these symptoms were often disabling, with 58% of patients reporting problems returning to work.
2. The same group also recently demonstrated that obesity is a significant risk factor for development of new, persistent physical, emotional, and cognitive impairments among survivors of critical illness due to COVID-19 (Kooistra E, Heesakkers H, Pickkers P, Zegers M, van den Boogaard M. Long-Term Impairments Are Most Pronounced in Critically Ill Patients with COVID-19 with Severe Obesity. Am J Respir Crit Care Med 2022; 206: 1037-1039.).
3. The long-term sequelae of COVID-19 itself are likely to be inextricably intertwined with the sequelae of critical illness, as significant long-term sequelae of COVID-19 has also been reported in other cohorts comprised of COVID-19 patients who were less acutely ill on average during their index hospitalization (Admon AJ, Iwashyna TJ, Kamphuis LA, Gundel SJ, Sahetya SK, Peltan ID, Chang SY, Han JH, Vranas KC, Mayer KP, Hope AA, Jolley SE, Caldwell E, Monahan ML, Hauschildt K, Brown SM, Aggarwal NR, Thompson BT, Hough CL, National Heart L, Blood Institute PN. Assessment of Symptom, Disability, and Financial Trajectories in Patients Hospitalized for COVID-19 at 6 Months. JAMA Netw Open 2023; 6: e2255795.).
4. Supporting the notion that the sequelae of COVID-19 itself and those of critical illness *per se* may be additive, the prevalence of problems returning to work in this cohort was 58%, compared to 42% in a similar Dutch study conducted prior to COVID-19 (Geense WW, Zegers M, Peters MAA, Ewalds E, Simons KS, Vermeulen H, van der Hoeven JG, van den Boogaard M. New Physical, Mental, and Cognitive Problems 1 Year after ICU Admission: A Prospective Multicenter Study. Am J Respir Crit Care Med 2021; 203: 1512-1521.).
5. A high burden of persistent mental health symptoms has also been described in family members of critical illness due to COVID-19 (Heesakkers H, van der Hoeven JG, Corsten S, Janssen I, Ewalds E, Burgers-Bonthuis D, Rettig TCD, Jacobs C, van Santen S, Slooter AJC, van der Woude

MCE, Zegers M, van den Boogaard M. Mental health symptoms in family members of COVID-19 ICU survivors 3 and 12 months after ICU admission: a multicentre prospective cohort study. Intensive Care Med 2022; 48: 322-331.).

OPTIMIZING OXYGEN SATURATION TARGET RANGE

Semler MW, Casey JD, Lloyd BD, Hastings PG, Hays MA, Stollings JL, Buell KG, Brems JH, Qian ET, Seitz KP, Wang L, Lindsell CJ, Freundlich RE, Wanderer JP, Han JH, Bernard GR, Self WH, Rice TW, Investigators P, the Pragmatic Critical Care Research G. **Oxygen-Saturation Targets for Critically Ill Adults Receiving Mechanical Ventilation.** *N Engl J Med* 2022; 387: 1759-1769.

Summary

Continuous monitoring of arterial oxygen saturation is a fundamental aspect of care of patients with ARDS and other forms of hypoxemic respiratory failure receiving invasive mechanical ventilation. There exist multiple mechanisms by which both low and high levels of oxygen in the lung, blood, and/or tissues may cause harm in the critically ill. Multiple recent studies have suggested that targeting lower and higher oxygen levels may lead to similar patient outcomes. PILOT is the first large, randomized trial to compare outcomes with use of an intermediate oxygen target range to lower and higher oxygen targets. This pragmatic, cluster-randomized, cluster-crossover trial enrolled 2,541 patients receiving invasive ventilation at single center in the US. 22 clusters were randomized to pulse oximetry readings of either low (between 88-92%), intermediate (92-96%) or high (96-100%) target ranges. No significant difference in the primary outcome of ventilator-free days was seen between any of these groups. This provides reassurance that there is unlikely to be a large difference in ventilator-free days between lower, intermediate, and higher oxygen saturation targets.

Comments

1. The incidence of significant hyperoxemia in the high saturation target range group was low, so this trial does not speak to the safety of supraphysiological partial pressures of oxygen relative to normal or lower values.
2. In the context of this and other recent studies comparing low and high oxygenation targets, it is likely that any difference in outcomes between oxygenation target ranges is small.
3. Given the frequency with which peripheral arterial oxygen saturation monitoring is used, a small difference between outcomes may be important; PILOT and other recent studies of this question have not excluded such differences.
4. The point estimates of ventilator-free days between oxygen target assignments in the subset of patients who had ARDS (N=190) suggest that targeting a higher oxygen saturation of 98% (96-100 range) is unlikely to be harmful in ARDS patients relative to targeting an oxygen saturation of 94% or lower.
5. An ongoing, international study of oxygen targets (Mega-ROX) in the critically ill will be powered (N=40,000) to detect smaller but likely clinically relevant differences in patient outcomes between lower and higher oxygen target ranges.

STEPS TOWARD PERSONALIZED CARE IN ARDS

Chen H, Yu Q, Xie J, Liu S, Pan C, Liu L, Huang Y, Guo F, Qiu H, Yang Y. **Longitudinal phenotypes in patients with acute respiratory distress syndrome: a multi-database study.** *Crit Care* 2022; 26: 340.

Summary

ARDS is characterized by varying pathophysiology; this heterogeneity presents a barrier to finding and testing ARDS treatments. Using latent class analysis (LCA), prior work by Carolyn Calfee's group has demonstrated two major sub-phenotypes of disease among ARDS patients (hyper- and hypo-inflammatory). These are distinguished by inflammatory biomarker levels and clinical parameters, are associated with different outcomes and appear to have differential responses to therapies. In this retrospective, multi-database study of ARDS patients (derived from the Chinese Database in Intensive Care and validated in cohorts from four prior randomized ARDS trials), LCA was performed using these and additional parameters (including chest imaging variables and change in respiratory mechanics over time). Using this approach, they reported the best fit to be with not two, but three ARDS sub-phenotypes with divergent characteristics, outcomes and treatment effects. Due to the added complexity and longitudinal nature of the classification system used by Chen and colleagues, it is likely further from translation into research or practice than the cross-sectional hyper/hypo-inflammatory ARDS sub-phenotype dichotomy. However, this paradigm may distinguish between biologically diverse groups identifiable with longitudinal data, and, after further validation, could potentially be incorporated into the design of eventual response-adaptive ARDS trials.

Comments

1. One of the ultimate goals of ARDS patient classification by latent class analysis is to derive a set of patients predicted to respond in similar ways to a given therapeutic strategy (e.g., personalized medicine and trials using predictive enrichment).
2. Research exploring the biological underpinnings of ARDS sub-phenotypes and development of ARDS sub-phenotype experimental models are needed for sub-phenotype descriptions such as this article to translate into "treatable traits" that can be exploited at the bedside with agents effective for a given patient's pathophysiology.
3. Development of techniques and technologies to rapidly sub-phenotype patients is another critical area for the translation of ARDS sub-phenotype research, and ongoing work to that end likely hold the key to advancement of disease-modifying therapies in ARDS (e.g., PHIND NCT04009330 and I-SPY COVID (I-SPY COVID Consortium. Clinical trial design during and beyond the pandemic: the I-SPY COVID trial. Nat Med 2022; 28: 9-11.).
4. There may sometimes be a tradeoff between the descriptive power of a sub-phenotype classification system and its clinical utility or simplicity; work exploring both ends of this spectrum ultimately are needed to advance our treatment, and understanding, of ARDS.
5. Another recent example of the tradeoff between biological accuracy and simplicity may be seen can be found in work by Sathe and colleagues, who observed minimal overlap between classifications of patients on the basis of the inflammatory profile in plasma relative to that of their bronchoalveolar lavage fluid, suggesting that biomarkers of inflammation in the alveolar compartment may contribute additional sub-phenotype classification power relative to plasma biomarkers alone (Sathe NA, Morrell ED, Bhatraju PK, Fessler MB, Stapleton RD, Wurfel MM, Mikacenic C. Alveolar Biomarker Profiles in Subphenotypes of the Acute Respiratory Distress Syndrome. Crit Care Med 2023; 51: e13-e18.).

VENTILATOR MANAGEMENT IN ARDS: NOVEL BEDSIDE TECHNIQUES FOR DETECTION OF HYPERINFLATION

Selickman J, Marini JJ. **Chest wall loading in the ICU: pushes, weights, and positions**. *Ann Intensive Care*. 2022 Nov 8;12(1):103. doi: 10.1186/s13613-022-01076-8. PMID: 36346532; PMCID: PMC9640797.

Summary

Multiple reports have now described a subset of ARDS patients who exhibit a paradoxical improvement in driving pressure, plateau pressure, and compliance in response to various maneuvers that entail application of extrinsic compression to the respiratory system. These simple bedside techniques include firm manual abdominal compression and postural changes. A counter-intuitive response to increased external pressure on the respiratory system is thought to be the result of hyperinflated alveolar units. As such, these maneuvers may be useful techniques for detecting end-tidal hyperinflation in ARDS patients to inform ventilator management and optimization of PEEP settings. This phenomenon garnered attention recently after a report by Kummer and colleagues (2021, Chest) of a series of late-phase ARDS patients with COVID-19 who displayed hyperinflation associated with paradoxical improvements of compliance upon manual abdominal compression at bedside; a number of case series have now been published demonstrating similar findings with other techniques that constrain chest wall expansion. This interpretive review article, which includes helpful illustrations, summarizes the physiology of chest wall interactions with the respiratory system, applies them to these recently published observations, and articulates the remaining questions concerning the potential utility of such maneuvers in clinical practice.

Comments

1. As published reports thus far have been observational in nature and relatively recent, the physiological significance of improvements in respiratory mechanics with extrinsic compression on the respiratory system remain somewhat speculative, but the interpretations proposed in this article may explain them.
2. Much remains to be understood about this phenomenon, including its incidence, natural history, correlation with altered ARDS and ventilator management strategies.
3. The extent to which the extrinsic compression maneuvers discussed in this article add new information to other readily available techniques (e.g. ventilator waveform analysis, driving pressure dynamics in response to PEEP changes, etc.) regarding the presence or absence of hyperinflation is unknown.
4. Nonetheless, published associations between the presence of this phenomenon, alveolar hyperinflation and improved respiratory mechanics after PEEP reductions, along with the ease and low

cost of maneuvers to elicit them, suggest potential for clinical utility.
5. Awareness of this phenomenon at bedside may aid providers in maintaining vigilance for otherwise unrecognized hyperinflation in invasively ventilated ARDS patients.

EARLY VENTILATORY RATIO TRAJECTORY IS ASSOCIATED WITH MORTALITY IN ARDS PATIENTS

Monteiro ACC, Vangala S, Wick KD, Delucchi KL, Siegel ER, Thompson BT, Liu KD, Sapru A, Sinha P, Matthay MA; NHLBI PETAL Network. **The prognostic value of early measures of the ventilatory ratio in the ARDS ROSE trial**. *Crit Care*. 2022 Sep 29;26(1):297.

Summary

The ratio of dead space to tidal volume has previously been strongly associated with adverse outcome in ARDS, with a higher predictive value than many commonly used prognostic factors such as oxygenation index, but it is cumbersome to perform and requires specialized equipment. Ventilatory ratio (VR, [minute ventilation × $PaCO_2$]/[predicted body weight × 100 × 37.5) may serve as a useful surrogate for the ratio of dead space to tidal volume as it is derived entirely from readily-available clinical data. In this retrospective analysis of the ROSE trial (neuromuscular blockade versus usual care with light sedation in US patients with moderate-severe ARDS), baseline VR and VR trajectory over time were found to be significantly associated with mortality. VR is a promising method for prognostic enrichment for organ failure due to ARDS.

Comments

1. The association between VR and mortality was strongest among patients with lower APACHE III scores, perhaps due to mortality being driven increasingly by extra-pulmonary organ failure in patients as APACHE III score increases.
2. Female patients were much more likely to have an elevated VR than males, but the biology of this finding is unknown.

BEST PRACTICES IN TRACHEAL INTUBATION: FLUID BOLUS FOR PREVENTION OF POST-INTUBATION CARDIOVASCULAR COLLAPSE

Russell DW, Casey JD, Gibbs KW, Ghamande S, Dargin JM, Vonderhaar DJ, Joffe AM, Khan A, Prekker ME, Brewer JM, Dutta S, Landsperger JS, White HD, Robison SW, Wozniak JM, Stempek S, Barnes CR, Krol OF, Arroliga AC, Lat T, Gandotra S, Gulati S, Bentov I, Walters AM, Dischert KM, Nonas S, Driver BE, Wang L, Lindsell CJ, Self WH, Rice TW, Janz DR, Semler MW, Investigators PI, the Pragmatic Critical Care Research G. **Effect of Fluid Bolus Administration on Cardiovascular Collapse Among Critically Ill Patients Undergoing Tracheal Intubation: A Randomized Clinical Trial.** *JAMA* 2022; 328: 270-279.

Summary

Tracheal intubation (a procedure almost universally applied to ARDS patients) is associated with high rates of severe hypotension and cardiac arrest in intensive care settings. Routine use of a 500 mL fluid bolus is a commonly-used, guideline-recommended intervention meant to prevent such complications during intubation. In 2019, the PrePARE trial found that fluid bolus was ineffective overall, but some subgroups (namely, patients treated with positive pressure ventilation in the course of tracheal intubation) appeared to benefit from fluid bolus. In the 1,065-patient PREPARE II trial, a predictive enrichment strategy was used, in which patients undergoing positive pressure ventilation during tracheal intubation were enrolled. PREPARE II found that the routine use of a 500 mL fluid bolus was not effective in preventing cardiovascular collapse. Given these results as well as other studies (e.g., the PrePARE trial and a recent secondary analysis of the INTUBE study), routine use of a 500 mL fluid bolus should no longer be recommended. Other aspects of this complex, high-risk, and typically urgent procedure should instead be emphasized. Further research is needed to identify whether other strategies (e.g., use of prophylactic vasopressors and/or alternative anesthetic induction agents) are effective for preventing hemodynamic sequelae of tracheal intubation.

Comments

1. This study does not address the question of whether personalized fluid resuscitation is effective.
2. These findings also do not apply to other indications for fluid bolus, such as resuscitation in sepsis, hemorrhage, and pancreatitis.
3. Although they have been independently associated with mortality in multiple studies, it is doubtful whether the composite primary outcome used in PREPARE II (cardiovascular collapse) or the most

common component of this endpoint (new or increased vasopressors during tracheal intubation) are meaningful to patients *per se*.

OTHER ARTICLES OF INTEREST

Kooistra E, Heesakkers H, Pickkers P, Zegers M, van den Boogaard M. **Long-Term Impairments Are Most Pronounced in Critically Ill Patients with COVID-19 with Severe Obesity.** *Am J Respir Crit Care Med*. 2022 Oct 15;206(8):1037-1039. doi: 10.1164/rccm.202202-0376LE. PMID: 35696647; PMCID: PMC9801993.

Giani M, Rezoagli E, Guervilly C, Rilinger J, Duburcq T, Petit M, Textoris L, Garcia B, Wengenmayer T, Bellani G, Grasselli G, Pesenti A, Combes A, Foti G, Schmidt M, **European Prone positioning During Extracorporeal Membrane Oxygenation I. Timing of Prone Positioning During Venovenous Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome.** *Crit Care Med* 2023; 51: 25-35.

Massart N, Guervilly C, Mansour A, Porto A, Flecher E, Esvan M, Fougerou C, Fillatre P, Duburcq T, Lebreton G, Para M, Stephan F, Hraiech S, Ross JT, Schmidt M, Vincentelli A, Nesseler N, **Extracorporeal Membrane Oxygenation for Respiratory Failure and/or Heart failure related to Severe Acute Respiratory Syndrome Coronavirus I. Impact of Prone Position in COVID-19 Patients on Extracorporeal Membrane Oxygenation.** *Crit Care Med* 2023; 51: 36-46.

Hernandez G, Paredes I, Moran F, Buj M, Colinas L, Rodriguez ML, Velasco A, Rodriguez P, Perez-Pedrero MJ, Suarez-Sipmann F, Canabal A, Cuena R, Blanch L, Roca O. **Effect of postextubation noninvasive ventilation with active humidification vs high-flow nasal cannula on reintubation in patients at very high risk for extubation failure: a randomized trial.** *Intensive Care Med* 2022; 48: 1751-1759.

El-Solh AA, Aquilina A, Pineda L, Dhanvantri V, Grant B, Bouquin P. **Noninvasive ventilation for prevention of post-extubation respiratory failure in obese patients.** *Eur Respir J* 2006; 28: 588-595.

Heesakkers H, van der Hoeven JG, Corsten S, Janssen I, Ewalds E, Burgers-Bonthuis D, Rettig TCD, Jacobs C, van Santen S, Slooter AJC, van der Woude MCE, Zegers M, van den Boogaard M. **Mental health symptoms in family members of COVID-19 ICU survivors 3 and 12 months after ICU admission: a multicentre prospective cohort study.** *Intensive Care Med* 2022; 48: 322-331

Pulmonary Vascular Disease

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2022 ESC/ERS PULMONARY HYPERTENSION GUIDELINES

Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, Rådegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachiery JL, Vonk Noordegraaf A, Delcroix M, Rosenkranz S; ESC/ERS Scientific Document Group. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2023 Jan 6;61(1):2200879. doi: 10.1183/13993003.00879-2022. PMID: 36028254.

Summary

The 2022 ESC/ERS Pulmonary Hypertension (PH) Guidelines represent the most comprehensive document containing current knowledge and updated evidence-based recommendations for the diagnosis and treatment of all forms of PH. An overarching theme of these guidelines is an emphasis on early diagnosis and a multidisciplinary approach to the management of PH with early referral to expert centers. One of the most consequential recommendations is the new hemodynamic definition of PH, lowering the threshold for mean pulmonary artery pressure to > 20 mmHg, and for precapillary PH lowering the pulmonary vascular resistance (PVR) cutoff to > 2 Wood units. Upfront combination therapy for pulmonary arterial hypertension (PAH) based on a 3-strata risk assessment scheme continues to be recommended, but now a 4-strata risk assessment approach during follow up is endorsed, breaking down the intermediate risk stratum into intermediate-low and intermediate-high. Escalation of therapy with an infused prostacyclin analogue or referral to lung transplantation is now recommended for both intermediate- risk and high-risk patients during follow up. Notably, for PAH patients with multiple comorbidities, initial oral monotherapy is now endorsed. "Severe PH" in the context of left heart or lung disease is now defined as a PVR > 5 Wood units.

Comments

1. The new definition of PH is meant to lead to early recognition of pulmonary vascular disease with a goal of implementing preventive measures when feasible, and not necessarily a recommendation to treat with PH-targeted therapies.
2. It remains to be determined the impact of these updated hemodynamic thresholds on the burden of PH, proper use of PH-targeted therapies, and the socio-economic impact on patients and health care systems.
3. Patients at intermediate-high risk using the 4-strata risk assessment during follow up are viewed as high-risk patients in need of escalation of therapy or referral to lung transplantation.
4. Patients with group 1 PH and multiple comorbidities should be treated initially with oral monotherapy.
5. A PVR > 5 Wood units is associated with worse outcomes, defines "severe PH" associated with left heart or lung disease, and requires an individualized treatment approach, which can include inhaled treprostinil for PH associated with interstitial lung disease.

PHENOTYPING OF IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION

Hoeper MM, Dwivedi K, Pausch C, Lewis RA, Olsson KM, Huscher D, Pittrow D, Grünig E, Staehler G, Vizza CD, Gall H, Distler O, Opitz C, Gibbs JSR, Delcroix M, Park DH, Ghofrani HA, Ewert R, Kaemmerer H, Kabitz HJ, Skowasch D, Behr J, Milger K, Lange TJ, Wilkens H, Seyfarth HJ, Held M, Dumitrescu D, Tsangaris I, Vonk-Noordegraaf A, Ulrich S, Klose H, Claussen M, Eisenmann S, Schmidt KH, Swift AJ, Thompson AAR, Elliot CA, Rosenkranz S, Condliffe R,

Kiely DG, Halank M. **Phenotyping of idiopathic pulmonary arterial hypertension: a registry analysis.** *Lancet Respir Med*. 2022 Oct;10(10):937-948. doi: 10.1016/S2213-2600(22)00097-2. Epub 2022 Jun 28.

Summary

This study reports data from 2 large European registries, COMPERA and ASPIRE, comparing 3 groups of patients: (1) classic idiopathic pulmonary arterial hypertension (IPAH), defined as absence of risk factors for left heart disease and a diffusion capacity for carbon monoxide (DL_{CO}) ≥ 45% predicted; (2) IPAH with a lung phenotype, defined as having a smoking history and a DL_{CO} < 45%; and (3) PH due to chronic obstructive or interstitial lung disease (group 3 PH) defined by their physicians. Lung phenotype IPAH had normal or near normal spirometry and no or mild lung parenchymal abnormalities on CT chest. Lung phenotype IPAH and PH due to lung disease patients were older and less female-predominant compared to classic IPAH. Response to PAH therapy, measured as improvements in functional class, 6-minute walk distance and N-terminal pro B-type natriuretic peptide levels, was significantly more frequent in classic IPAH, and similarly poor in lung phenotype IPAH and PH due to lung disease. Survival at 1 and 5 years was similar in lung phenotype IPAH and PH due to lung disease, and worse than classic IPAH.

Comments

1. Emerging data suggest that IPAH is a heterogeneous disorder, and that the presence of comorbidities influences response to therapy and survival.
2. This study confirms that many patients meeting current criteria for IPAH have a distinct phenotype characterized by a history of smoking, older age, less female predominance, severely decreased DL_{CO}, limited response to PH-targeted therapies and poor survival.
3. In spite of having normal or near normal spirometry and no evidence of significant parenchymal lung disease on CT chest, IPAH patients with this lung phenotype have clinical characteristics and behavior aligned with PH due to lung disease.
4. These data, in the context of previous data from patients with several risk factors for heart failure with preserved ejection fraction showing similarly blunted response to PH-targeted therapy, have shaped the ERS 2022 guideline recommendation to try monotherapy first in PAH patients with cardiopulmonary comorbidities.
5. These IPAH comorbid phenotypes represent a larger proportion of patients seen in practice and reported in registries, and warrant further study to delineate the diagnostic and therapeutic implications.

PULMONARY VASCULAR DISEASE PHENOMICS (PVDOMICs)

Hemnes AR, Leopold JA, Radeva MK, Beck GJ, Abidov A, Aldred MA, Barnard J, Rosenzweig EB, Borlaug BA, Chung WK, Comhair SAA, Desai AA, Dubrock HM, Erzurum SC, Finet JE, Frantz RP, Garcia JGN, Geraci MW, Gray MP, Grunig G, Hassoun PM, Highland KB, Hill NS, Hu B, Kwon DH, Jacob MS, Jellis CL, Larive AB, Lempel JK, Maron BA, Mathai SC, McCarthy K, Mehra R, Nawabit R, Newman JH, Olman MA, Park MM, Ramos JA, Renapurkar RD, Rischard FP, Sherer SG, Tang WHW, Thomas JD, Vanderpool RR, Waxman AB, Wilcox JD, Yuan JX, Horn EM; PVDOMICS Study Group. **Clinical Characteristics and Transplant-Free Survival Across the Spectrum of Pulmonary Vascular Disease.** *J Am Coll Cardiol*. 2022 Aug 16;80(7):697-718. doi: 10.1016/j.jacc.2022.05.038. PMID: 35953136; PMCID: PMC9897285.

Summary

PVDOMICS (Pulmonary Vascular Disease Phenomics) is a prospective multicenter study using deep clinical and omics phenotyping across the spectrum of pulmonary vascular disease. PVDOMICS enrolled patients with all 5 World Symposium of Pulmonary Hypertension (WSPH) groups (group 1=353, group 2=136, group 3=172, group 4=57, group 5=32), as well as disease comparators (subjects with no or mild PH and cardiopulmonary risk factors for the respective group of PH), and healthy controls who underwent all non-invasive testing. This article reports the baseline clinical characteristics and survival of the PVDOMICS cohort. Almost 40% of patients had mixed etiology PH, i.e., more than one WSPH group contributing to PH, most commonly lung disease in group 1 and 2 PH. Parenchymal lung

abnormalities on CT chest were common in group 1 PH, particularly ground glass opacities observed in 50% of patients compared to 13.7% in comparators. DL_{CO} was reduced to similar levels in groups 1 (median 58% predicted), 2 (53%), and 3 (60%) PH. Right atrial volume index was significantly elevated in groups 1-4 PH and to a higher degree than right ventricular end diastolic dimension compared to comparators. Among comparators and PH, group 3 subjects had the worse transplant-free survival.

Comments

1. PVDOMICS documents a high prevalence (almost 40%) of mixed etiology PH, showcasing the limitations of the current clinical classification of PH and emphasizing the potential of PVDOMICS to redefine PH classification in the future.
2. Low DL_{CO} and disproportionate right atrial enlargement emerge as important markers of pulmonary vascular disease in patients with cardiopulmonary comorbidities, but they are not specific to any particular WSPH group.
3. Half of group 1 PH patients have pulmonary ground glass opacities, a novel observation that might be a marker of disease severity or an effect of prostacyclin therapy.
4. Patients with group 3 risk factors and group 3 PH have the worst survival, and group 4 comparators (patients with chronic pulmonary embolism with no or mild PH) have 100% transplant-free survival over 36 months.
5. Incident group 1 PH and WSPH groups 4 and 5 are underrepresented in PVDOMICS.

SOTATERCEPT FOR PULMONARY ARTERIAL HYPERTENSION

Hoeper MM, Badesch DB, Ghofrani HA, Gibbs JSR, Gomberg-Maitland M, McLaughlin VV, Preston IR, Souza R, Waxman AB, Grünig E, Kopeć G, Meyer G, Olsson KM, Rosenkranz S, Xu Y, Miller B, Fowler M, Butler J, Koglin J, de Oliveira Pena J, Humbert M; STELLAR Trial Investigators. Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension. *N Engl J Med*. 2023 Mar 6. doi: 10.1056/NEJMoa2213558. Epub ahead of print. PMID: 36877098.

Summary

Sotatercept is a fusion protein that by "trapping" pro-proliferative activins and growth differentiation factors might counteract the reduced anti-proliferative bone morphogenetic protein receptor type 2 (BMPR2)-mediated signaling in pulmonary vascular cells. The STELLAR trial randomized 163 PAH patients to subcutaneous sotatercept every 3 weeks and 160 to placebo. PAH patients had a pulmonary vascular resistance (PVR) ≥ 400 dynes while on background PAH-targeted therapy (61% triple therapy, 40% infused prostacyclin). Enrolled subjects were relatively young (mean age 48), mostly female (79%) and white (89%), and had predominantly idiopathic (58%) and heritable disease (18%). The median change in the 6-minute walk distance at week 24, the primary endpoint, was 34.4 meters in the sotatercept group and 1 meter in the placebo group. Improvements in all but 1 secondary endpoints were observed, including a multicomponent improvement endpoint, PVR, N-terminal pro B-type natriuretic peptide levels (NT-proBNP), functional class, time to clinical worsening, low French risk criteria, and some measures of quality of life. Severe adverse events were more frequent in the placebo arm. Adverse events more frequent in the sotatercept arm included bleeding (mostly epistaxis and gingival), telangiectasia, increased hemoglobin, dizziness and thrombocytopenia.

Comments

1. Sotatercept is a first-in-class drug that for the first time shows efficacy in a phase 3 trial modulating a biological pathway highly relevant to PAH not targeted by currently available PAH therapies, and importantly, in a heavily pre-treated PAH population.
2. Consistent with effects observed in the phase 2 trial, sotatercet reduced PVR by decreasing pulmonary artery pressure without changing the cardiac output, suggesting that regression of pulmonary vascular remodeling might be the underlying mechanism behind its clinical benefits, but this and other potential mechanisms warrant further study.

3. Ongoing and future studies should determine if the clinical benefits are also observed in other PH populations such us children, newly diagnosed PAH, high-risk or unstable PAH, and combined pre- and post-capillary PH due to heart failure with preserved ejection fraction.
4. Further study is warranted to determine the clinical benefits of sotatercept in PAH populations not well represented in the STELLAR trial, such as connective tissue disease, older age, and non-white individuals.
5. While sotatercept appears to be well tolerated, vascular side effects, particularly bleeding and telangiectasia, need to be monitored in longer-term studies.

FOLLOW UP AFTER ACUTE PULMONARY EMBOLISM (FOCUS)

Valerio L, Mavromanoli AC, Barco S, Abele C, Becker D, Bruch L, Ewert R, Faehling M, Fistera D, Gerhardt F, Ghofrani HA, Grgic A, Grünig E, Halank M, Held M, Hobohm L, Hoeper MM, Klok FA, Lankeit M, Leuchte HH, Martin N, Mayer E, Meyer FJ, Neurohr C, Opitz C, Schmidt KH, Seyfarth HJ, Wachter R, Wilkens H, Wild PS, Konstantinides SV, Rosenkranz S; FOCUS Investigators. **Chronic thromboembolic pulmonary hypertension and impairment after pulmonary embolism: the FOCUS study**. *Eur Heart J*. 2022 Sep 21;43(36):3387-3398. doi: 10.1093/eurheartj/ehac206. PMID: 35484821; PMCID: PMC9492241.

Summary

FOCUS is a multicenter prospective observational study conducted in Germany that aimed to investigate the incidence of chronic thromboembolic PH (CTEPH) and post-pulmonary embolism impairment (PPEI) after acute PE. PPEI was defined as at least 1 echocardiographic criterion of PH plus at least 1 clinical, functional or laboratory criterion out of persistent symptoms, signs of right heart failure, syncope, WHO functional class III or IV, 6-minute walk distance < 300 meters, elevated BNP or NT-proBNP, and low peak O2 uptake or systolic blood pressure on cardiopulmonary exercise testing. CTEPH was defined via imaging and right heart catheterization. A total of 1017 patients were followed with a standardized evaluation at discharge, 3, 12, and 24 months. 70% of patients had intermediate-risk PE. The 2-year cumulative incidence of CTEPH was 2.3%. Median time to CTEPH diagnosis was 129 days. The 2-year cumulative incidence of PPEI was 16%. PPEI was more frequent in older individuals and in those with intermediate risk PE compared to low risk PE. All but 1 patient (15/16) with CTEPH also fulfilled criteria for PPEI. Patients with PPEI had a higher incidence of death and re-hospitalization for any cause, as well as lower generic and disease-specific quality of life.

Comments

1. The FOCUS study confirms that the incidence of CTEPH after acute PE is in the low single digit percent range, but cardiopulmonary limitation after PE is much more frequent.
2. In FOCUS, a detailed follow up evaluation allowed for the detection of CTEPH after a median of ~4 months, much earlier than the previously documented delay in diagnosis of more than a year.
3. Right ventricular dysfunction during index PE was observed in 81% of CTEPH patients compared to only 38% of others, emphasizing the importance of documenting resolution of RV dysfunction during follow up.
4. PPEI emerges as a syndrome defined by echocardiographic and clinical, functional and laboratory abnormalities, and could be used to enrich a population where further testing for CTEPH is necessary.
5. PPEI, as defined by FOCUS but not echocardiographic abnormalities alone, is associated with lower quality of life, and increased rates of hospitalization and death, and may warrant interventions to improve quality of life, functional limitation and risk factor mitigation.

PULMONARY ANGIOPLASTY OR RIOCIGUAT FOR INOPERABLE CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Jaïs X, Brenot P, Bouvaist H, Jevnikar M, Canuet M, Chabanne C, Chaouat A, Cottin V, De Groote P, Favrolt N, Horeau-Langlard D, Magro P, Savale L, Prévot G, Renard S, Sitbon O, Parent F, Trésorier R, Tromeur C, Piedvache C, Grimaldi L, Fadel E, Montani D, Humbert M, Simonneau G. **Balloon pulmonary angioplasty versus riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension (RACE): a multicentre, phase 3, open-label, randomised controlled trial and ancillary follow-up study**. *Lancet Respir Med*. 2022 Oct;10(10):961-971. doi: 10.1016/S2213-2600(22)00214-4. Epub 2022 Aug 1. PMID: 35926542.

Summary

The soluble guanylate cyclase stimulator riociguat was approved for the treatment of inoperable CTEPH in 2013. Around the same time, experience with balloon pulmonary angioplasty (BPA) was growing across the world. RACE is a multicenter, open-label randomized trial conducted in France that compared riociguat (n=53) versus BPA (n=52) in inoperable CTEPH patients with a PVR > 4 Wood units. The primary endpoint was PVR at 26 weeks, which was lower in the BPA group (ratio of geometric means 0.60). Secondary endpoints functional class and NT-proBNP also favored BPA, while 6-minute walk distance was similar between groups. Treatment-related serious adverse events were more frequent in the BPA group: 22 (42%)/52 patients versus 5(9%)/53, most frequently lung injury and hemoptysis. After week 26, patients who remained functional class II or higher with a PVR > 4 Wood units were offered riociguat if there were originally assigned to BPA (n=18) and BPA if they initially received riociguat (n=36). At week 52, PVR was similarly reduced in both the first-line BPA versus first-line riociguat intention-to-treat populations (ratio of geometric mean 0.91). BPA-related serious adverse events were lower in patients pre-treated with riociguat (5[14%]/36) versus patients treated with BPA first (22[42%]/52).

Comments

1. BPA has emerged as a mechanical treatment option for thrombo-fibrotic lesions in distal segmental and subsegmental arteries considered inoperable, while medical therapy with riociguat targets the concomitant microscopic vasculopathy of CTEPH.
2. First-line BPA was more effective than first line riociguat in decreasing PVR and improving symptoms and NT-proBNP levels, at the expense of a higher incidence of serious adverse events.
3. Patients pre-treated with riociguat followed by BPA experienced a similar decrease in PVR from baseline than patients treated with first line BPA followed by riociguat, but with a better safety profile.
4. Mean pulmonary artery pressure higher than 45 mmHg and first-line BPA were predictors of BPA-related adverse events
5. These data support the use of a combination management strategy of medical therapy followed by BPA for patients with inoperable CTEPH, particularly those with severe PH, carefully evaluated by expert CTEPH centers.

Other Articles of Interest

PH Hemodynamic Assessment

Zeder K, Banfi C, Steinrisser-Allex G, Maron BA, Humbert M, Lewis GD, Berghold A, Olschewski H, Kovacs G. **Diagnostic, prognostic and differential-diagnostic relevance of pulmonary haemodynamic parameters during exercise: a systematic review.** *Eur Respir J.* 2022 Oct 13;60(4):2103181. Doi: 10.1183/13993003.03181-2021. PMID: 35332069; PMCID: PMC9556812.

Khirfan G, Melillo CA, Al Abdi S, Lane JE, Dweik RA, Chatburn RL, Hatipoğlu U, Tonelli AR. **Impact of Esophageal Pressure Measurement on Pulmonary Hypertension Diagnosis in Patients With Obesity.** *Chest.* 2022 Sep;162(3):684-692. Doi: 10.1016/j.chest.2022.04.002. Epub 2022 Apr 9. PMID: 35405108; PMCID: PMC9808718.

PAH Risk Assessment

Hoeper MM, Pausch C, Olsson KM, Huscher D, Pittrow D, Grünig E, Staehler G, Vizza CD, Gall H, Distler O, Opitz C, Gibbs JSR, Delcroix M, Ghofrani HA, Park DH, Ewert R, Kaemmerer H, Kabitz HJ, Skowasch D, Behr J, Milger K, Halank M, Wilkens H, Seyfarth HJ, Held M, Dumitrescu D, Tsangaris I, Vonk-Noordegraaf A, Ulrich S, Klose H, Claussen M, Lange TJ, Rosenkranz S. **COMPERA 2.0: a refined four-stratum risk assessment model for pulmonary arterial hypertension**. *Eur Respir J*. 2022 Jul 7;60(1):2102311. Doi: 10.1183/13993003.02311-2021. PMID: 34737226; PMCID: PMC9260123.

Boucly A, Weatherald J, Savale L, de Groote P, Cottin V, Prévot G, Chaouat A, Picard F, Horeau-Langlard D, Bourdin A, Jutant EM, Beurnier A, Jevnikar M, Jaïs X, Simonneau G, Montani D, Sitbon O, Humbert M. **External validation of a refined four-stratum risk assessment score from the French pulmonary hypertension registry**. *Eur Respir J*. 2022 Jun 30;59(6):2102419. Doi: 10.1183/13993003.02419-2021. PMID: 34737227; PMCID: PMC9245192.

Hoeper MM, Pausch C, Olsson KM, Huscher D, Pittrow D, Grünig E, Staehler G, Vizza CD, Gall H, Distler O, Opitz C, Gibbs JSR, Delcroix M, Ghofrani HA, Ewert R, Kaemmerer H, Kabitz HJ, Skowasch D, Behr J, Milger K, Halank M, Wilkens H, Seyfarth HJ, Held M, Dumitrescu D, Tsangaris I, Vonk-Noordegraaf A, Ulrich S, Klose H, Claussen M, Eisenmann S, Schmidt KH, Rosenkranz S, Lange TJ. **Prognostic value of improvement endpoints in pulmonary arterial hypertension trials: A COMPERA analysis.** *J Heart Lung Transplant*. 2022 Jul;41(7):971-981. Doi: 10.1016/j.healun.2022.03.011. Epub 2022 Mar 22. PMID: 35430147.

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Humbert M, McLaughlin V, Gibbs JSR, Gomberg-Maitland M, Hoeper MM, Preston IR, Souza R, Waxman AB, Ghofrani HA, Escribano Subias P, Feldman J, Meyer G, Montani D, Olsson KM, Manimaran S, de Oliveira Pena J, Badesch DB. **Sotatercept for the treatment of pulmonary arterial hypertension: PULSAR open-label extension.** *Eur Respir J*. 2023 Jan 6;61(1):2201347. Doi: 10.1183/13993003.01347-2022. PMID: 36041750; PMCID: PMC9816418.

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PAH outcomes

Hoeper MM, Pausch C, Grünig E, Staehler G, Huscher D, Pittrow D, Olsson KM, Vizza CD, Gall H, Distler O, Opitz C, Gibbs JSR, Delcroix M, Ghofrani HA, Rosenkranz S, Park DH, Ewert R, Kaemmerer H, Lange TJ, Kabitz HJ, Skowasch D, Skride A, Claussen M, Behr J, Milger K, Halank M, Wilkens H, Seyfarth HJ, Held M, Dumitrescu D, Tsangaris I, Vonk-Noordegraaf A, Ulrich S, Klose H. **Temporal trends in pulmonary arterial hypertension: results from the COMPERA registry.** *Eur Respir J*. 2022 Jun 2;59(6):2102024. Doi: 10.1183/13993003.02024-2021. PMID: 34675047; PMCID: PMC9160392.

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PH in COPD

Kovacs G, Avian A, Bachmaier G, Troester N, Tornyos A, Douschan P, Foris V, Sassmann T, Zeder K, Lindenmann J, Brcic L, Fuchsjaeger M, Agusti A, Olschewski H. **Severe Pulmonary Hypertension in COPD: Impact on Survival and Diagnostic Approach.** *Chest*. 2022 Jul;162(1):202-212. Doi: 10.1016/j.chest.2022.01.031. Epub 2022 Jan 31. PMID: 35092746.

Cook DP, Xu M, Martucci VL, Annis JS, Aldrich MC, Hemnes AR, Brittain EL. **Clinical insights into pulmonary hypertension in chronic obstructive pulmonary disease.** *Pulm Circ*. 2022 Jan 3;12(1):e12006. Doi: 10.1002/pul2.12006. PMID: 35506103; PMCID: PMC9052979.

COVID-19 and PH

Montani D, Certain MC, Weatherald J, Jaïs X, Bulifon S, Noel-Savina E, Nieves A, Renard S, Traclet J, Bouvaist H, Riou M, de Groote P, Moceri P, Bertoletti L, Favrolt N, Guillaumot A, Jutant EM, Beurnier A, Boucly A, Ebstein N, Jevnikar M, Pichon J, Keddache S, Preda M, Roche A, Solinas S, Seferian A, Reynaud-Gaubert M, Cottin V, Savale L, Humbert M, Sitbon O; French PH Network PULMOTENSION Investigators. **COVID-19 in Patients with Pulmonary Hypertension: A National Prospective Cohort Study.** *Am J Respir Crit Care Med*. 2022 Sep 1;206(5):573-583. Doi: 10.1164/rccm.202112-2761OC. PMID: 35549842; PMCID: PMC9716894.

PE Treatment and Follow Up

Pruszczyk P, Klok FA, Kucher N, Roik M, Meneveau N, Sharp ASP, Nielsen-Kudsk JE, Obradović S, Barco S, Giannini F, Stefanini G, Tarantini G, Konstantinides S, Dudek D. **Percutaneous treatment options for acute pulmonary embolism: a clinical consensus statement by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function and the European Association of Percutaneous Cardiovascular Interventions.** *EuroIntervention.* 2022 Oct 7;18(8):e623-e638. Doi: 10.4244/EIJ-D-22-00246. PMID: 36112184.

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COPD

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IDENTIFYING AND ADDRESSING FACTORS CONTRIBUTING TO COPD BURDEN

Stolz D, Mkorombindo T, Schumann DM, Agusti A, Ash SY, Bafadhel M, Bai C, Chalmers JD, Criner GJ, Dharmage SC, Franssen FME, Frey U, Han M, Hansel NH, Hawkins NM, Kalhan R, Konigshoff M, Ko FW, Parekh TM, Powell P, Rutten-van Mölken M, Jodie Simpson J, Sin DD, Song Y, Suki B, Troosters T, Washko GR, Welte T, Dransfield MT. **Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission.** *Lancet.* 2022 Sep 17;400(10356):921-972.

Summary

The Lancet Commission convened global COPD experts to consider the factors contributing to increasing COPD burden, and to provide recommendations on disruptive approaches to set the course for disease elimination. This extensive review highlights several areas for future intervention. While they strongly recommend limiting tobacco and environmental exposures, the predominant COPD risk factors, they also advocate greater focus on additional risk factors. Consequently, they endorse classifying COPD based on "etiotypes" in which tobacco smoke, other environmental exposures, genetics, early-life events, or infections are the predominant risk factors that may provide specific intervention opportunities. They recommend expanding diagnostic criteria beyond spirometry to include aspects such as symptoms, risk factors, imaging, and lung function testing. They argue that this expanded definition could provide an opportunity for earlier diagnosis and management to prevent disease progression. They also note that exacerbation prevention is crucial. They suggest standardizing exacerbation definitions and determining exacerbation severity based on objective measures of clinical deterioration as important first steps in prevention and management. Finally, the Commission advocates for greater access to care as well as earlier access to provide future opportunities for curative or regenerative management.

Comments

1. The objective of the Commission is not to provide guidelines for management, but to present a framework for future research, public health, and clinical efforts to decrease COPD disease burden.
2. The focus on risk factors beyond tobacco smoke follows a recent shift in understanding COPD as a complex heterogeneous disease due to an accumulation of factors over the life course.
3. Emphases on additional risk factors and identifying earlier disease states open possibilities for early intervention and prevention of progression.
4. While the proposed disease etiotypes subgroup COPD by predominant cause, major pathologic disease drivers and treatable traits (e.g., symptoms, exacerbations) could be shared across etiotypes; subgrouping based on treatment response is needed as well.
5. COPD exacerbation severity classification may be better standardized using objective measurements, as proposed herein, rather than healthcare utilization which can vary geographically, but some of the proposed objective measurements may not be available in resource limited settings.

GUIDELINES FOR COPD MANAGEMENT, DIAGNOSIS, AND PREVENTION

Global Initiative for Chronic Obstructive Lung Disease. **Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2023 report**. https://goldcopd.org/2023-gold-report-2/#

Summary

This is an updated recommendation statement from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) committee from 2023. Although last updated in 2021, the 2023 guidelines include substantial changes. The definition of COPD has been updated to emphasize disease heterogeneity and the contribution of factors beyond tobacco smoke in COPD pathogenesis. The committee aligns with the Lancet Commission, proposing a new taxonomy to consider disease etiotypes in which predominant COPD etiologies differ. Revisions in recommended management are also considerable. Highlights include an update of the ABCD assessment tool to an ABE tool in which treatment of individuals who exacerbate should be similar regardless of chronic symptom levels. Dual therapy with a long-acting beta agonist (LABA) and long-acting muscarinic antagonist (LAMA) is now recommended for initial management over LABA or LAMA alone in individuals with considerable symptoms or exacerbations. Furthermore, inhaled corticosteroids (ICS) are recommended when concomitant asthma, exacerbations with elevated eosinophils, or hospitalized exacerbations despite LABA/LAMA therapy are identified. However triple therapy (ICS, LABA, and LAMA combination therapy) is recommended in this scenario, not ICS alone or ICS/LABA combination therapy.

Comments

1. The new GOLD guidelines, similar to the Lancet commission, draw increased attention to environmental and early life factors beyond tobacco exposure as major risk factors, and focus on identification of early disease to provide new opportunities for disease prevention and modification.
2. The guidelines reinforce the importance of exacerbation prevention as key to improving outcomes, recommending more intensive therapy for individuals with exacerbations even if their chronic symptoms are minimal.
3. As a major change in therapeutic recommendations, LABA/LAMA combination therapy is recommended over monotherapy for individuals with exacerbations or substantial symptoms given studies showing improved symptoms, lung function, exacerbations, and quality of life.
4. The new guidelines incorporate data from the recent LABA/LAMA/ICS triple therapy studies (ETHOS, IMPACT, KRONOS, TRILOGY) suggesting benefit over LABA/LAMA in exacerbators for exacerbation reduction and potentially, as per post-hoc pooled analyses, mortality reduction.
5. The guidelines incorporate recommendations from the ROME proposal and Lancet Commission that suggest using objective findings to grade severity of exacerbations instead of healthcare utilization.

ASYMPTOMATIC COPD SCREENING

US Preventive Services Task Force; Mangione CM, Barry MJ, Nicholson WK, Cabana M, Caughey AB, Chelmow D, Coker TR, Davis EM, Donahue KE, Jaén CR, Kubik M, Li L, Ogedegbe G, Pbert L, Ruiz JM, Stevermer J, Tseng C, J Wong JB. Screening for Chronic Obstructive Pulmonary Disease: US Preventive Services Task Force Reaffirmation Recommendation Statement. *JAMA*. 2022 May 10;327(18):1806-1811. doi: 10.1001/jama.2022.5692.

Summary

The US Preventive Services Task Force (USPSTF) provides an evidence update of their 2016 recommendations, again recommending against screening for COPD in asymptomatic adults and treatment of these screened individuals. Their literature review addresses three topics: 1) accuracy of screening tests, 2) benefits of early detection and treatment, and 3) harms of screening and treatment. They found no new evidence on the accuracy of screening tests. They reviewed three new trials (SUMMIT, PINNACLE, UPLIFT) to assess benefits of treatment, and conclude that inhaled therapies are associated with exacerbation reduction in moderate symptomatic COPD. However, they assert the findings are difficult to generalize to asymptomatic individuals in which no new data exists. They reviewed 13 studies on non-pharmacologic interventions in mild-to-moderate COPD and, given mixed results, could draw no conclusions regarding benefit. The USPSTF considered eight new studies in their assessment of screening harm. They found no substantial harm of mild to moderate COPD treatment in the randomized trials.

They conclude that an opportunity cost exists given the additional medical services required after positive screening, but that this cost is small. Overall, they conclude both benefit and harm to screening and management of asymptomatic COPD are minimal.

Comments

1. While asymptomatic screening is not yet considered useful per the USPSTF, COPD experts are increasingly endorsing earlier diagnosis in an effort to deliver earlier management that may, upon further study, be found to be disease modifying.
2. Further research will be needed to identify the subgroups of asymptomatic individuals most at risk for COPD progression and thus most likely to benefit from earlier screening and intervention.
3. The harms of early screening and treatment appear to be minimal.

SYMPTOMATIC COPD SCREENING

Martinez FJ, Han MK, Lopez C, Murray S, Mannino D, Anderson S, Brown R, Dolor R, Elder N, Joo M, Khan I, Knox LM, Meldrum C, Peters E, Spino C, Tapp H, Thomashow B, Zittleman L, Make B, Yawn BP; CAPTURE Study Group. Discriminative Accuracy of the CAPTURE Tool for Identifying Chronic Obstructive Pulmonary Disease in US Primary Care Settings. *JAMA*. 2023 Feb 14;329(6):490-501. doi: 10.1001/jama.2023.0128.

Summary

n this cross-sectional multi-center study, 4325 US primary care patients were screened for clinically significant COPD using the CAPTURE tool comprised of five questions and select use of peak expiratory flow rate. A patient was considered to have clinically significant COPD if they had: 1) a post-bronchodilator FEV1/FVC ratio of <0.7 and 2) an FEV1 <60% predicted or self-reported acute respiratory illness in the last 12 months. 12.3% of participants had a positive screening test and 2.5% had clinically significant COPD. A positive screening result was only 48.2% sensitive but was 88.6% specific for clinically significant COPD.

Comments

1. While asymptomatic screening is not currently recommended, screening for clinically significant COPD is likely important in decreasing morbidity.
2. Spirometry is a limited resource, and thus screening via spirometry may not be realistic for all at-risk individuals, particularly in low- and middle-income countries.
3. The CAPTURE tool, which combines a questionnaire and peak flow measurements, may be a more pragmatic way to screen for COPD than spirometry given the overall burden of disease.
4. The CAPTURE tool is quite specific, suggesting that diagnostic studies needed after screening positive will be limited to a group likely to benefit from further testing.
5. Further studies are needed to understand how the low sensitivity of the CAPTURE tool may be improved with repeated testing.

THERAPIES IN UNOBSTRUCTED TOBACCO-EXPOSED INDIVIDUALS

Han MK, Ye W, Wang D, White E, Arjomandi M, Barjaktarevic IZ, Brown SA, Buhr RG, Comellas AP, Cooper CB, Criner GJ, Dransfield MT, Drescher F, Folz RJ, Hansel NN, Kalhan R, Kaner RJ, Kanner RE, Krishnan JA, Lazarus SC, Maddipati V, Martinez FJ, Mathews A, Meldrum C, McEvoy C, Nyunoya T, Rogers L, Stringer WW, Wendt CH, Wise RA, Wisniewski SR, Sciurba FC, Woodruff PG; RETHINC Study Group. Bronchodilators in Tobacco-Exposed Persons with Symptoms and Preserved Lung Function. *N Engl J Med*. 2022 Sep 29;387(13):1173-1184. doi: 10.1056/NEJMoa2204752.

Summary

It was previously shown that a substantial portion of individuals with a tobacco smoking history but without airway obstruction have clinically significant respiratory symptoms. Many of these individuals are treated with COPD therapies even though they do not meet diagnostic criteria for COPD. This was a multi-center randomized controlled trial of individuals with ≥10 pack year smoking history and substantial respiratory symptoms (defined as a score ≥10 on the COPD

Assessment Tool (CAT)) but preserved lung function. 471 participants analyzed in a modified intention-to-treat analysis were randomized to placebo or indacaterol, a long-acting beta agonist (LABA), and glycopyrrolate, a long-acting muscarinic antagonist (LAMA). They found no significant difference in the primary outcome, improvement in respiratory symptoms by St. George's Respiratory Questionnaire (SGRQ), between treatment and placebo arms. They also found no significant treatment effect in terms of lung function measures or CAT score.

Comments

1. Current and former smokers with respiratory symptoms but without airway obstruction often get treated with inhalers, similar to individuals with COPD, but without any evidence that these therapies are useful.
2. This is the first trial in this large subgroup of symptomatic smokers, and the lack of benefit of bronchodilators here suggests that it is important to have objective evidence of COPD via spirometry prior to initiating bronchodilator therapy.
3. These symptomatic tobacco exposed individuals are likely heterogeneous, just like COPD, and thus more research is needed to determine if there are subgroups that exhibit beneficial responses to bronchodilators.

OTHER ARTICLES OF INTEREST:

REVIEWS

Christenson SA, Smith BM, Bafadhel M, Putcha N. **Chronic obstructive pulmonary disease**. *Lancet*. 2022 Jun 11;399(10342):2227-2242. doi: 10.1016/S0140-6736(22)00470-6.

Yang IA, Jenkins CR, Salvi SS. **Chronic obstructive pulmonary disease in never-smokers: risk factors, pathogenesis, and implications for prevention and treatment.** *Lancet Respir Med*. 2022 May;10(5):497-511. doi: 10.1016/S2213-2600(21)00506-3.

Singh D, Agusti A, Martinez FJ, Papi A, Pavord ID, Wedzicha JA, Vogelmeier CF, Halpin DMG. **Blood Eosinophils and Chronic Obstructive Pulmonary Disease: A Global Initiative for Chronic Obstructive Lung Disease Science Committee 2022 Review.** *Am J Respir Crit Care Med*. 2022 Jul 1;206(1):17-24. doi: 10.1164/rccm.202201-0209PP.

Lacasse Y, Casaburi R, Sliwinski P, Chaouat A, Fletcher E, Haidl P, Maltais F. **Home oxygen for moderate hypoxaemia in chronic obstructive pulmonary disease: a systematic review and meta-analysis.** *Lancet Respir Med*. 2022 Nov;10(11):1029-1037. doi: 10.1016/S2213-2600(22)00179-5.

GLOBAL BURDEN OF DISEASE

Safiri S, Carson-Chahhoud K, Noori M, Nejadghaderi SA, Sullman MJM, Ahmadian Heris J, Ansarin K, Mansournia MA, Collins GS, Kolahi AA, Kaufman JS. **Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019.** *BMJ*. 2022 Jul 27;378:e069679. doi: 10.1136/bmj-2021-069679.

DISPARITIES IN ACCESS TO CARE

Stolbrink M, Thomson H, Hadfield RM, Ozoh OB, Nantanda R, Jayasooriya S, Allwood B, Halpin DMG, Salvi S, de Oca MM, Mortimer K, Rylance S. **The availability, cost, and affordability of essential medicines for asthma and COPD in low-income and middle-income countries: a systematic review.** *Lancet Glob Health*. 2022 Oct;10(10):e1423-e1442. doi: 10.1016/S2214-109X(22)00330-8.

ADVERSE EFFECTS ASSOCIATED WITH COPD THERAPIES

Yang M, Li Y, Jiang Y, Guo S, He JQ, Sin DD. **Combination therapy with long-acting bronchodilators and the risk of major adverse cardiovascular events in patients with COPD: a systematic review and meta-analysis**. *Eur Respir J*. 2023 Feb 9;61(2):2200302. doi: 10.1183/13993003.00302-2022.

Chen H, Deng ZX, Sun J, Huang Q, Huang L, He YH, Ma C, Wang K. **Association of Inhaled Corticosteroids With All-Cause Mortality Risk in Patients With COPD: A Meta-analysis of 60 Randomized Controlled Trials**. *Chest*. 2023 Jan;163(1):100-114. doi: 10.1016/j.chest.2022.07.015.

EXACERBATIONS AND OUTCOMES

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OBSTRUCTIVE SLEEP APNEA AND COPD

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INTERSTITIAL LUNG DISEASE

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CLINICAL TRIALS IN INTERSTITIAL LUNG DISEASE

Solomon JJ, Danoff SK, Woodhead FA, Hurwitz S, Maurer R, Glaspole I, Dellaripa PF, Gooptu B, Vassallo R, Cox PG, Flaherty KR, Adamali HI, Gibbons MA, Troy L, Forrest IA, Lasky JA, Spencer LG, Golden J, Scholand MB, Chaudhuri N, Perrella MA, Lynch DA, Chambers DC, Kolb M, Spino C, Raghu G, Goldberg HJ, Rosas IO, for the TRAIL1 Network Investigators. **Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomized, double-blind, placebo-controlled, phase 2 study**. *Lancet Respir Med*. 2023;11:87-96.

Summary

This study evaluated the efficacy of the anti-fibrotic treatment, pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD). The trial included 123 patients across four countries (the UK, the US, Australia, and Canada), 63 were randomized to the pirfenidone group and 60 to the placebo group, over 52 weeks. The primary end point was a composite of death and a 10% or more decline in baseline forced vital capacity (FVC). The study was stopped early due to slow recruitment and the COVID-19 pandemic. There was no difference between the pirfenidone and placebo groups in reaching the primary end point, with 7 patients (11%) in the pirfenidone group and 9 patients (15%) in the placebo group. A difference was seen in absolute FVC decline. The pirfenidone group had a slower decline in absolute FVC over the study period, losing 66mL (1.02% predicted) in the pirfenidone group compared to 142mL (3.21% predicted) in the placebo group. Pirfenidone was not associated with any increase in treatment related adverse events. The study was terminated early and is under powered, the results must be interpreted with caution, but pirfenidone was associated with a decreased rate of lung function decline in patients with RA-ILD.

Comments

1. This study evaluated the safety and efficacy of the anti-fibrotic medication, pirfenidone in treating patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD).
2. Pirfenidone was safe and fairly well tolerated in patients with RA-ILD, similar side effect profile to what has been seen in patients with idiopathic pulmonary fibrosis.
3. There was no difference in the primary outcome between the pirfenidone and placebo groups.
4. There was a difference in one of the secondary endpoints, specifically a difference in absolute FVC decline, with the pirfenidone group having a slower rate of decline than the placebo group.

CLINICAL TRIALS IN INTERSTITIAL LUNG DISEASE

Maher TM, Tudor VA, Saunders P, Gibbons MA, Fletcher SV, Denton CP, Hoyles RK, Parfrey H, Renzoni EA, Kokosi M, Wells AU, Ashby D, Szigeti M, Molyneaux PL, on behalf of the RECITAL Investigators. **Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomized, controlled, phase 2b trial.** Lancet Respir Med. 2023;11:45-54.

Summary

This study evaluated whether rituximab was superior to intravenous cyclophosphamide as a treatment for severe or progressive connective tissue disease-associated ILD (CTD-ILD), specifically in ILD related to scleroderma, idiopathic inflammatory myositis, or mixed connective tissue disease. One-hundred-one patients were recruited from 11 centers across the United Kingdom and were randomized 1:1 to receive

either rituximab or IV cyclophosphamide for twenty-four weeks. The primary outcome was change in forced vital capacity (FVC) from baseline at 24 weeks. There were multiple secondary end points including FVC change from baseline at 48 weeks, change in six-minute walk distance, change in DLCO, quality of life metrics, physician measures of disease activity, survival, progression-free survival, and steroid dose (added post-hoc). The study showed no difference in the rituximab and cyclophosphamide groups across any of the pre-specified end points, all patients had an increase in FVC and improvement in patient-reported quality of life scores. The main differences were seen in the cumulative steroid dose over 48 weeks in the rituximab group, and there were fewer reported adverse events in the rituximab group compared to the cyclophosphamide group. Leading the authors to conclude that rituximab is an alternative to cyclophosphamide in patients with CTD-ILD requiring intravenous therapy.

Comments

1. In patients with progressive or severe CTD-ILD related to scleroderma, idiopathic myositis, or mixed connective tissue disease, both rituximab and cyclophosphamide were associated with an improvement in lung function and patient reported quality of life.
2. Rituximab was associated with few reported adverse events compared to cyclophosphamide, which may make it better tolerated by patients.
3. Rituximab was associated with a lower overall steroid dose during the follow-up period, suggesting it may allow for tapering of other background immune suppression.
4. The results of this trial should give providers confidence in choosing either rituximab or cyclophosphamide for patients with progressive and/or severe CTD-ILD, with the decision making including a discussion of potential side effects.

CLINICAL TRIALS IN INTERSTITIAL LUNG DISEASE

Richeldi L, Azuma A, Cottin V, Hesslinger C, Stowasser S, Valenzuela C, Wijsenbeek MS, Zoz DF, Voss F, Maher TM, for the 1305-0013 Trial Investigators. Trial of a Preferential Phosphodiesterase 4B Inhibitor for Idiopathic Pulmonary Fibrosis. *N Engl J Med.* 2022;386:2178-87.

Summary

Inhibition of phosphodiesterase 4 (PDE 4) has been associated with anti-inflammatory and anti-fibrotic effects, which makes it an attractive target for the treatment of pulmonary fibrosis. In this trial from Boehringer Ingelheim, a new selective phosphodiesterase 4B inhibitor was trialed for the treatment of idiopathic pulmonary fibrosis. In this phase 2 trial, patients were randomized 2:1 to treatment with BI 101550 (the selective PDE 4B inhibitor) or placebo. The primary end point of the trial was forced vital capacity (FVC) at 12 weeks. Importantly this trial allowed patients to be on background anti-fibrotic therapy with either pirfenidone or nintedanib, the data were analyzed in two groups, those on background anti-fibrotic therapy and those were not on any other anti-fibrotic treatment. In both groups, the selective PDE 4b inhibitor, was associated with preservation of lung function over the 12-week study period, with a greater magnitude of effect in the group not on background anti-fibrotic therapy. The most frequent adverse event was diarrhea, 13 patients discontinued treatment with BI 1015550 due to adverse events. This trial demonstrated that BI 1015550, a selective PDE 4B inhibitor is a promising treatment for idiopathic pulmonary fibrosis, in combination with anti-fibrotic therapy and alone.

Comments

1. The very promising results of this trial have led to two phase 3 trials of BI 101550, the FIBRONEER IPF and ILD studies that are currently recruiting at 288 sites worldwide.
2. The initial results from this phase 2 study, show not just a slower rate of decline but a stabilization of lung function in the treatment

group over 12 weeks, regardless of background anti-fibrotic therapy or not.

INTERSTITIAL LUNG DISEASE EPIDEMIOLOGY AND DIAGNOSIS

Rose JA, Menon AA, Hino T, Hata A, Nishino M, Lynch DA, Rosas IO, El-Chemaly S, Raby BA, Ash SY, Choi B, Washko GR, Silverman EK, Cho MH, Hatabu H, Putman RK, Hunninghake GM. Suspected Interstitial Lung Disease in COPDGene Study. *Am J Respir Crit Care Med.* 2023;207(1):60-68.

Summary

Interstitial lung abnormalities (ILA) are specific radiologic patterns incidentally found on chest CT scans in people without interstitial lung disease (ILD), thought to represent an early or mild form of pulmonary fibrosis. ILA have been associated with an increased risk of death and decrements in pulmonary function, in this study authors attempted to determine whether those outcomes were driven by a subset of participants with incident ILD, in the COPDGene cohort. Suspected ILD was defined as ILA accompanied by one of the following: FVC less than 80% predicted, DLCO less than 70% predicted, or evidence of definite fibrotic disease on CT. In COPDGene, 5% (239 of 4361) of participants with available data had suspected ILD, and 204 (~5%) had ILA without suspected ILD. Those with suspected ILD, compared to both those with and without ILA, had increased respiratory symptoms, decreased six-minute walk distance, greater supplemental oxygen use, were more likely to have a severe respiratory exacerbation, and had an increased risk of death. This study provides a framework for thinking about when patients with ILA have progressed to have true, ILD which may help clinicians risk stratify patients with evidence of early or mild ILD seen on chest CT scan.

Comments

1. This article proposes a set of criteria to use to help define when those with interstitial lung abnormalities have progressed to having interstitial lung disease.
2. Participants with suspected ILD had an increased risk of poor outcomes, these were not seen in those with ILA without evidence of suspected ILD.
3. Suspected ILD is associated with poor outcomes like those seen in ILD, including increased respiratory symptoms, decreased functional status, supplemental oxygen use, severe respiratory exacerbations, and an increased risk of death.
4. About half of the participants with ILA had evidence of suspected ILD, which was about 5% of a cohort of smokers with and without COPD.

INTERSTITIAL LUNG DISEASE EPIDEMIOLOGY AND DIAGNOSIS

Pugashetti JV, Adegusoye A, Wu Z, Lee CT, Srikrishnan A, Ghodrati S, Vo V, Renzoni EA, Wells AU, Garcia CK, Chua F, Newton CA, Molyneaux PL, Oldham JM. Validation of Proposed Criteria for Progressive Pulmonary Fibrosis. *Am J Respir Crit Care Med.* 2023;207(1): 69-76.

Summary

Clinical trials, expert opinion, and a consensus statement have set forth criteria for the definition of progressive pulmonary fibrosis (PPF), however outside of forced vital capacity (FVC) decline, it was unclear whether these criteria were associated with adverse outcomes. A retrospective cohort analysis, utilizing 1,341 patients from three US centers and 1 in the UK, the authors evaluated whether the criteria for PPF were associated with transplant free survival. Using the US cohort as the test cohort and the UK as validation, the authors showed that an FVC decline of ≥10% was strongly associated with reduced transplant free survival. In addition to this criterion, three other PPF features were independently associated with decreased transplant free survival; including 5-9% FVC decline, 15% or greater DLCO decline, and CT progression of fibrosis. Three additional features required the combination of physiologic, radiologic, and symptomatic worsening. Importantly, the authors were able to identify a group of patients, those with ≥10% FVC decline, that have outcomes that are the most like IPF, despite the varying underlying ILD diagnoses. This data suggests that ≥10% FVC decline alone can be used to make a diagnosis of PPF, rather than requiring the addition of worsening symptoms or radiology.

Comments

1. Multiple criteria have been proposed to define PPF, in this study an FVC decline of 10% or more was most strongly predictive of decreased lung transplant free survival.
2. Using the single criteria of an FVC decline of ≥10%, in this study, creates a subset of patients that are most like IPF in terms of survival, despite having a variety of underlying diagnoses.
3. Amongst those with PPF, phenotypic variability persisted in terms of transplant free survival, outside of those with an FVC decline of ≥10%, with those with CTD-ILD have the best prognosis.
4. Additional standalone criteria associated with decreased transplant free survival included a 5-9% FVC decline, ≥15% decline in DLCO, and radiologic progression of fibrosis.
5. This study brings into question, whether the diagnosis progressive pulmonary fibrosis should require a combination of physiologic, radiologic, and/or symptomatic criteria, or whether in some circumstances this can be simplified to a single criterion.

INTERSTITIAL LUNG DISEASE EPIDEMIOLOGY AND DIAGNOSIS

Steele MP, Peljto AL, Mathai SK, Humphries S, Bang TJ, Oh A, Teague S, Cicchetti G, Sigaskis C, Kropski JA, Loyd JE, Blackwell TS, Brown KK, Schwarz MI, Warren RA, Powers J, Walts AD, Markin C, Fingerlin TE, Yang IV, Lynch DA, Lee JS, Schwartz DA. Incidence and Progression of Fibrotic Lung Disease in an At-Risk Cohort. *Am J Respir Crit Care Med*. 2023; 207(5): 587-593.

Summary

First degree relatives of patients with idiopathic interstitial pneumonia are at increased risk of developing pulmonary fibrosis, in this work the authors describe the incidence of asymptomatic pulmonary fibrosis, which these authors term preclinical pulmonary fibrosis (PrePF). Using a cohort of first-degree relatives of family members with familial interstitial pneumonia (FIP), family members underwent chest CT scans at baseline and approximately 4 years later. Sixteen of 252 subjects developed PrePF during the follow-up period, which equates to an annual incidence of PrePF of 1,023 per 100,000 person-years, which is about 100-fold higher than the incidence of sporadic IPF. In addition, participants with PrePF at the baseline examination, were more likely to report worsening dyspnea and it was associated with decreased survival. PrePF was associated with imaging progression as measured by an increase in quantitative imaging measures of fibrosis, with 32.5% of participants having an increase in fibrosis over the follow-up period. Given the significantly increased incidence of PrePF and its association with poor outcomes, including an increased of death, the authors advocate for screening unaffected family members over the age of 50 in families with a history of interstitial pneumonia.

Comments

1. While the incidence of PrePF in this study is at least 100-fold higher than that of sporadic IPF, it is important to remember that this is an at-risk cohort, where a higher incidence would be expected.
2. About 1/3 of participants with PrePF at baseline had evidence of quantitative fibrosis progression over the four years follow up period; that there are those with stable and improved fibrosis suggests that there is phenotypic variability among those with PrePF.
3. The authors advocate for screening in at risk populations, but it is still unknown what modalities should be used for screening and the appropriate time intervals for follow up.
4. As more data is collected on early-stage disease and those at risk, we will need to begin the conversations around treatment and inclusion in clinical trials to learn how already approved treatments for pulmonary fibrosis work in early-stage disease.

OTHER ARTICLES OF INTEREST

Salisbury ML, Markin CR, Wu P, Cogan JD, Mitchell DB, Liu Q, Loyd JE, Lancaster LH, Kropski JA, Blackwell TS. Peripheral Blood Telomere Attrition in Persons at Risk for Familial Pulmonary Fibrosis. *Am J Respir Crit Care Med.* 2023;207(2):208-211.

Rose JA, Planchart Ferretto MA, Maeda AH, Perez Garcia MF, Carmichael NE, Gulati S, Rice MB, Goldberg HJ, Putman RK, Hatabu H, Raby BA, Rosas IO, Hunninghake GM. **Progressive Interstitial Lung Disease in Relatives of Patients with Pulmonary Fibrosis.** *Am J Respir Crit Care Med.* 2023;207(2):211-214.

Khor YH, Bissell B, Ghazipura M, Herman D, Hon SM, Hossain T, Kheir F, Knight SL, Kreuter M, Macrea M, Mammen MJ, Molina-Molina M, Selman M, Wijsenbeek M, Racghu G, Wilson KC. **Antacid Medication and Antireflux Surgery in Patients with Idiopathic Pulmonary Fibrosis.** *Ann Am Thorac Soc.* 2022;19(5):833-844.

Pitre T, Mah J, Helmeczi W, Khalid MF, Cui S, Zhang M, Husnudinov R, Su J, Banfield L, Guy B, Coyne J, Scallan C, Kolb MRJ, Jones A, Zeraatkar D. **Medical treatments for idiopathic pulmonary fibrosis: a systematic review and network meta-analysis.** *Thorax.* 2022;77:1243-1250.

Adegunsoye A, Newton CA, Oldham JM, Ley B, Lee CT, Linderhold AL, Chung H, Garcia N, Zhang D, Vij R, Guzy R, Jablonski R, Bag R, Voogt RS, Ma SF, Sperline AI, Raghu G, Martinez FJ, Strek ME, Wolters PJ, Garcia CK, Pierce BL, Noth I. **Telomere length associated with chronological are and mortality across racially diverse pulmonary fibrosis cohorts.** *Nature Communications.* 2023;14:1489.

Baker MC, Liu Y, Lu R, Lin J, Melehani J, Robinson WH. **Incidence of Interstitial Lung Disease in Patients with Rheumatoid Arthritis Treated with Biologic and Targeted Synthetic Disease-Modifying Antirheumatic Drugs.** *JAMA Network Open.* 2023; 6(3): e233640.

Jang HJ, Woo A, Kim SY, Yong SH, Park Y, Chung K, Lee SH, Leem AY, Lee SH, Kim EY, Jung JY, Kang YA, Kim YS, Park MS. **Characteristics and risk factors of mortality in patients with systemic sclerosis-associated interstitial lung disease.** *Ann of Med.* 2023; 55(1):663-671.

Kim JS, Azarbarzin A, Podolanczuk AJ, Anderson MR, Cade BE, Kawut SM, Wysoczanski A, Laine AF, Hoffman EA, Gottlieb DK, Garcia CK, Barr RG, Redline S. **Obstructive Sleep Apnea and Longitudinal Changes in Interstitial Lung Imaging and Lung Function: The MESA Study.** *Ann Am Thorac Soc.* 2023;

Lung Cancer

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ENVIRONMENTAL RISK FACTORS FOR LUNG CANCER

Cheng I, Yang J, Tseng C, Wu J, Shariff-Marco S, Park SL, Conroy SM, Inamdar PP, Fruin S, Larson T, Setiawan VW, DeRouen MC, Gomez SL, Wilkens LR, Le Marchand L, Stram DO, Samet J, Ritz B, Wu AH. **Traffic-related Air Pollution and Lung Cancer Incidence: The California Multiethnic Cohort Study**. *Am J Respir Crit Care Med.* 2022 Oct 15;206(8):1008-1018. doi: 10.1164/rccm.202107-1770OC.

Summary

Epidemiologic trends show that lung cancer in non-smokers is on the rise. One contributor to this trend may be exposures to non-tobacco-related toxicants that increase the risk of lung cancer. Previous studies have confirmed a link between work related, traffic and environmental pollutants and lung cancer risk, but few studies have been adequately powered to examine these risks across racially, ethnically and socioeconomically diverse populations. This study followed a prospective cohort of 97,288 individuals living in California over an average of 17 years, linking their lung cancer outcomes with their estimated exposure to traffic-related air pollutants based on longitudinal geocoded addresses. In analyses adjusted for other lung cancer risk factors, higher exposure to nitrogen oxide and dioxide, fine particulate matter (PM) 2.5, carbon monoxide and benzene were all associated with increased lung cancer incidence, though not all of these associations were statistically significant. Toxicant exposures were higher in low versus high-socioeconomic status neighborhoods. This study adds to evidence linking environmental exposure to pollution with increased risk of lung cancer.

Comments

1. Exposure to ambient air pollution is increasingly recognized as risk factor for lung cancer.
2. The authors found evidence of adverse effects of traffic-related air pollution on lung cancer risk.
3. Exposure to air pollution was greater among those residing in neighborhoods with low socioeconomic status, which may be a potential contributor to lung cancer disparities.
4. Interventions such as clean air laws may be beneficial for lung cancer prevention.

LUNG CANCER SCREENING

Silvestri GA, Goldman L, Burleson J, Gould M, Kazerooni EA, Mazzone PJ, Rivera MP, Doria-Rose VP, Rosenthal LS, Simanowith M, Smith RA. **Characteristics of persons screened for lung cancer in the United States: a cohort study**. *Ann Intern Med*. 2022 Nov;175(11):1501-5. doi:10.7326/M22-1325

Summary

Lung cancer screening is endorsed by the US Preventive Services Task Force (USPSTF). However, uptake has been slower than anticipated. There are also concerns about fidelity to required components, such as eligibility assessment and adherence to subsequent imaging, that may decrease effectiveness of screening. In this article, the authors analyzed population characteristics and adherence rates among a cohort of 1,159,092 patients undergoing low-dose CT for lung cancer screening at one of 3625 facilities reporting to the American College of Radiology Registry. Characteristics of these individuals were compared to the likely-eligible population based on data from the National Health Interview Survey. Of those screened, 90.8% were eligible per USPSTF criteria. Compared to the likely-eligible population, those who were screened were older (34.7% vs 44.8% aged 65 to 74 years), more likely to be female (41.8% vs 48.1%) and more likely to currently smoke (52.3% vs 61.4%). Only 22.3% had a

repeat annual low-dose CT at a year, and only 34.3% within two years. These data suggest disparities in identifying eligible patients, specifically younger, male former smokers. These individuals may have more life-years to gain from screening. It also highlights a significant gap in adherence to recommended follow-up that will limit screening effectiveness.

Comments

1. Lung cancer screening implementation has been challenging and slower than anticipated.
2. In a national cohort representing over a million individuals, nearly 10% did not meet USPSTF eligibility criteria.
3. Younger individuals, males and former smokers were less likely to be screened, representing missed opportunities and potential disparities in screening access.
4. Adherence to annual follow-up was very poor at less than 25%, below a threshold that would be expected to significantly limit effectiveness.

LUNG CANCER SCREENING: TOBACCO DEPENDENCE TREATMENT

Taylor KL, Williams RM, Li T, Luta G, Smith L, Davis KM, Stanton CA, Niaura R, Abrams D, Lobo T, Mandelblatt J. A randomized trial of telephone-based smoking cessation treatment in the lung cancer screening setting. *JNCI*.. 2022 Oct 6;114(10):1410-9.

Summary

Modeling studies support that integrating effective tobacco dependence treatment (TDT) into lung cancer screening programs would have a mortality benefit commensurate with the screening intervention itself. Lung cancer screening participants who smoke are uniformly older, heavy users of tobacco and may require intensive treatment to quit successfully (e.g., combined counseling and pharmacotherapy). Screening programs can serve to connect patients to these treatments. In this study, lung cancer screening patients who smoke (n=818), regardless of their intention to quit in the next 30 days, were randomly assigned to one of two intensities of TDT, a "minimal" program (three phone sessions and two weeks of free nicotine patch) and an "intensive" program (8 phone sessions and 8 weeks of nicotine patches). Though the intensive arm showed increased short-term cessation (14.3% vs 7.9%, OR 2.0, 95% CI 1.26-3.18), these differences did not persist to 12 months. When creating a TDT program for lung cancer screening participants, programs must consider the adequacy of treatment intensity and include methods to maintain abstinence over time, such as chronic disease models of tobacco treatment.

Comments

1. Tobacco dependence treatment is a key element of a high-quality lung cancer screening program.
2. Integrating a relatively low-intensity treatment (8 weeks of phone counseling and nicotine patch) into lung cancer screening did not increase long-term abstinence from cigarette smoking.
3. As lung cancer screening programs consider integrating tobacco dependence treatments, the focus should be on connecting to interventions that are adequately intensive to meet the needs of screening participants.

LUNG CANCER DIAGNOSIS

Kalchiem-Dekel O, Connolly JG, Lin IH, Husta BC, Adusumilli PS, Beattie JA, Buonocore DJ, Dycoco J, Fuentes P, Jones DR, Lee RP, Park BJ, Rocco G, Chawla M, Bott MJ. Shape-Sensing Robotic-Assisted Bronchoscopy in the Diagnosis of Pulmonary Parenchymal Lesions. *Chest*. 2022 Feb;161(2):572-582. doi: 10.1016/j.chest.2021.07.2169. Epub 2021 Aug 9.

Summary

Navigational bronchoscopy for the sampling of pulmonary lesions has been rapidly implemented over the past 10 years. Robotic-assisted bronchoscopy is a recent advancement in technology with the goal of providing higher diagnostic yields and the ability to sample smaller and more distal lesions that were previously inaccessible. However, there is relatively little data on the feasibility, yield and safety of these platforms. One such system is the Intuitive Ion platform which uses shape-sensing technology to facilitate distal airway navigation. The authors report outcomes from 131 robotic-assisted bronchoscopies for diagnosis of presumed malignant lesions (n=157) performed using the Ion system. Nearly all (85.5%) procedures also

utilized radial endobronchial ultrasound and one of two experienced physicians performed all procedures. The overall diagnostic yield from 157 individual lesions was 81.7%, with increasing size associated with higher yields (66% for lesions <1cm, 100% for lesions >3 cm). Complications were rare (3% overall, 1.5% pneumothorax). Reported yields were moderately higher than previously published yields from electromagnetic navigation bronchoscopy (approximately 65-88%).

Comments

1. Robotic-assisted bronchoscopy is a recent advancement developed to increase diagnostic yields and allow access to smaller and more distal pulmonary lesions.
2. Using a system (Ion) that employs shape-sensing guidance, overall diagnostic yield for pulmonary lesions in this single-center study of 157 lesions was 81.7%.
3. Yield was higher for larger and more central lesions, with yield from nodules <1 cm at 66%.
4. When compared to previous data on electromagnetic navigation bronchoscopy, diagnostic yield may be slightly higher.

LUNG CANCER STAGING

Henderson LM, Farjah F, Detterbeck F, Smith RA, Silvestri GA, & Rivera MP. (2022). **Pretreatment Invasive Nodal Staging in Lung Cancer: Knowledge, Attitudes, and Beliefs Among Academic and Community Physicians**. *Chest,* 161(3), 826-832.

Summary

Pretreatment invasive nodal staging is an important step to ensure patients receive the appropriate therapies for non-small cell lung cancer. Several guidelines exist that recommend when to perform invasive staging, but previous studies suggest that adherence to recommended staging is poor. One potential reason for this finding may be lack of knowledge or adverse attitudes or beliefs about invasive staging among pulmonologists and thoracic surgeons. This study reports a web-based survey distributed to a random sample of pulmonary and thoracic surgery members of the American College of Chest Physicians. Among 453 respondents, 29% were unaware that there are guidelines about invasive nodal staging. Of those who were aware of the guidelines most (90%) agreed that these guidelines improved their treatment decisions, but 20% felt there was insufficient evidence that using these guidelines improved outcomes. Nearly all physicians reported at least one barrier to guideline adherence, including patient anxiety (62%), difficulty implementing these guidelines within routine practice (52%) and delays due to additional testing (51%). There is a significant knowledge gap regarding invasive staging guidelines, with many reported barriers to adherence.

Comments

1. Pretreatment invasive nodal staging is an important part of lung cancer care, and recognized guidelines exist to support treatment decisions.
2. Over a quarter of surveyed pulmonologists and thoracic surgeons were unaware of guidelines to direct completion of invasive nodal staging.
3. Physicians reported many barriers to adherence to these guidelines, including difficulty adhering to them within routine clinical practice, patient anxiety, and delays in care.
4. There is a significant knowledge gap in invasive nodal staging as well as barriers to adherence that need to be addressed to improve lung cancer care.

LUNG CANCER TREATMENT

Saji H, Okada M, Tsuboi M, Nakajima R, Suzuki K, Aokage K, Aoki T, Okami J, Yoshino I, Ito H, Okumura N, Yamaguchi M, Ikeda N, Wakabayashi M, Nakamura K, Fukuda H, Nakamura S, Mitsudomi T, Watanabe SI, Asamura H; West Japan Oncology Group and Japan Clinical Oncology Group. **Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial.** *Lancet*. 2022 Apr 23;399(10335):1607-1617. doi: 10.1016/S0140-6736(21)02333-3.

Summary

Lobectomy is the standard of care for early-stage non-small-cell lung cancer, but can carry significant morbidity due to the relatively large volume of lung removed. Sublobar resections are an attractive alternative for small lesions that may offer equivalent survival with less morbidity, if they can offer comparable cure rates. This study reports the results of a randomized controlled, noninferiority trial conducted at 70 institutions across Japan which compared lobectomy to segmentectomy for early-stage lung cancer. Participants (n=1106) had lung cancers clinically staged at IA (tumor ≤ 2cm, no suspicious lymph nodes on clinical staging), that were peripherally located (outer third), and excluded the right middle lobe. They were randomized to standard lobectomy versus segmentectomy. Procedures in both groups were largely by VATS (80%) with the remainder by thoracotomy. Groups were similar in their characteristics. At the time of operation, 22/552 individuals randomized to segmentectomy were converted to lobectomy. At a median of 7.3 years of follow-up, 5-year overall survival was superior in the segmentectomy arm (94.3% vs 91.1%, p for superiority 0.0082), while 5-year relapse-free survival was identical. However, local relapse was higher in the segmentectomy arm (10.5% vs 5.4%%, p=0.0018). Complication rates and decline in FEV1 at 1 year were similar between the two arms.

Comments

1. In a large (1106 patients) randomized trial comparing lobectomy to segmentectomy for early-stage peripheral lung cancers, segmentectomy was found to have superior 5-year overall survival.
2. Local relapse was higher in the segmentectomy arm (10.5% vs 5.4%).
3. For patients with stage IA lung cancers surgically resectable via segmentectomy, segmentectomy appears to offer results that are noninferior and likely superior to lobectomy.

LUNG CANCER TREATMENT

Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, Felip E, Broderick SR, Brahmer JR, Swanson SJ, Kerr K, Wang C, Ciuleanu TE, Saylors GB, Tanaka F, Ito H, Chen KN, Liberman M, Vokes EE, Taube JM, Dorange C, Cai J, Fiore J, Jarkowski A, Balli D, Sausen M, Pandya D, Calvet CY, Girard N; CheckMate 816 Investigators. **Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer**. *N Engl J Med*. 2022 May 26;386(21):1973-1985. doi: 10.1056/NEJMoa2202170. Epub 2022 Apr 11.

Summary

Among the approximately 25% of patients diagnosed with non-small-cell lung cancer (NSCLC) who present with resectable disease and undergo surgery, many will ultimately have a recurrence and die of lung cancer. Neoadjuvent chemotherapy has been tested as a means to improve recurrence-free survival and has demonstrated a modest benefit. Nivolumab is an anti-programmed death-1 (PD-1) antibody, with proven survival benefit for metastatic NSCLC. Immunotherapy with nivolumab may offer improved eradication of micrometastatic disease and lead to better long-term survival for early-stage patients as well. In this large international study (n=505), patients with resectable IB to IIIA NSCLC were randomized to conventional platinum-based neoadjuvant therapy vs conventional therapy + nivolumab. The primary outcomes were event-free survival and complete pathologic response in the lymph nodes at the time of surgery. Median event-free survival was longer in the nivolumab arm (30.6 months vs 20.8 months) with higher complete pathologic response (24% vs 2.2%). The magnitude of benefit was greatest in the more advanced (IIIA) patients. This study supports efficacy of nivolumab as add-on neoadjuvant therapy for resectable patients with NSCLC greater than stage 1A. The hazard ratio for overall survival strongly favored nivolumab but did not meet pre-specified significance (HR 0.57, 99.67% CI 0.30-1.07). Safety was similar between the arms.

Comments

1. Many patients with resectable non-small-cell lung cancer ultimately die due to recurrence, despite use of platinum-based neoadjuvant chemotherapy.
2. In this randomized controlled trial of patients with resectable NSCLC, Nivolumab, an anti-PD-1 antibody, was administered as add-on therapy to standard neoadjuvant therapy.

3. Event-free survival was higher in the nivolumab arm (30.6 vs 20.8 months).
4. Complete pathologic response in the lymph nodes at the time of surgery was higher in the nivolumab arm (24% vs 2.2%).
5. Nivolumab appears to be a safe and effective add-on neoadjuvant therapy for patients with resectable stage 1B-IIIA NSCLC.

OTHER ARTICLES OF INTEREST

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COVID-19

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ACUTE MANAGEMENT OF COVID-19

Alhazzani W, Parhar KKS, Weatherald J, Al Duhailib Z, Alshahrani M, Al-Fares A, Buabbas S, Cherian SV, Munshi L, Fan E, Al-Hameed F, Chalabi J, Rahmatullah AA, Duan E, Tsang JLY, Lewis K, Lauzier F, Centofanti J, Rochwerg B, Culgin S, Nelson K, Abdukahil SA, Fiest KM, Stelfox HT, Tlayjeh H, Meade MO, Perri D, Solverson K, Niven DJ, Lim R, Møller MH, Belley-Cote E, Thabane L, Tamim H, Cook DJ, Arabi YM; COVI-PRONE Trial Investigators and the Saudi Critical Care Trials Group. **Effect of Awake Prone Positioning on Endotracheal Intubation in Patients With COVID-19 and Acute Respiratory Failure: A Randomized Clinical Trial.** *JAMA*. 2022 Jun 7;327(21):2104-2113.

Summary

The COVI-PRONE trial was an unblinded, randomized controlled trial of awake prone positioning for COVID-19 patients across 21 international centers requiring high flow oxygen or non-invasive ventilation. A total of 400 participants were randomized including 205 to the awake prone positioning group and 195 to the control group. The median duration of prone positioning in the intervention group was 5 hours [IQR 2 to 8 hours] compared with 0 hours in the control group [IQR 0 to 0]. The use of prone positioning was associated with similar rates of intubation (33.7 intervention versus 36.3% control, HR 0.89, 95% CI 0.62 to 1.28, p=0.54) and death at 60 days (22.4 intervention versus 23.6% control, HR 0.93, 95% CI 0.62 to 1.40, p=0.72) compared with usual care. Days of mechanical ventilation, ICU use or hospital admission did not differ between groups. Subgroup analyses demonstrated a 56% reduction in risk of intubation for patients who received awake prone positioning and had less severe respiratory failure with a Pa02:FiO2 ratio >150 (p=0.03 for interaction). Other outcomes did not differ when stratified by severity of respiratory failure or hypoxemia. Adverse events were reported more frequently in the prone positioning group compared to the control group although no serious adverse events were reported in either group.

Comments

1. Awake prone positioning for patients with acute COVID-19 on high flow nasal cannula and/or non-invasive ventilation did not reduce rate of intubation or death at 60 days and was not associated with reductions in mechanical ventilation, ICU or hospital durations.
2. Subgroup analysis suggested potential benefit in patients with less severe hypoxemia/respiratory failure although this was not a primary endpoint for the trial.
3. Awake prone positioning appears safe with no serious adverse events reported although mild adverse events were reported more frequently in the prone group compared to the control group.
4. The short duration of prone positioning in the intervention group (average 5 hours/day) may have influenced outcomes.
5. Significant cross-over and refusal of intervention in the intervention group (10%) may have contributed to lack of observed difference.

NOVEL THERAPEUTICS FOR ACUTE COVID-19

Reis G, Moreira Silva EAS, Medeiros Silva DC, Thabane L, Campos VHS, Ferreira TS, Santos CVQ, Nogueira AMR, Almeida APFG, Savassi LCM, Figueiredo-Neto AD, Dias ACF, Freire Júnior AM, Bitarães C, Milagres AC, Callegari ED, Simplicio MIC, Ribeiro LB, Oliveira R, Harari O, Wilson LA, Forrest JI, Ruton H, Sprague S, McKay P, Guo CM, Limbrick-Oldfield EH, Kanters S, Guyatt GH, Rayner CR, Kandel C, Biondi MJ, Kozak R, Hansen B, Zahoor MA, Arora P, Hislop C, Choong I, Feld JJ, Mills EJ, Glenn JS; TOGETHER Investigators. **Early Treatment with Pegylated**

Interferon Lambda for Covid-19. *N Engl J Med*. 2023 Feb 9;388(6):518-528.

Summary

This is a Phase III, double-blind, randomized controlled trial of pegylated interferon lambda as outpatient therapy for COVID-19 conducted across 17 sites in Canada and Brazil. Adults who were largely vaccinated against COVID-19 with an identified high-risk condition for severe COVID-19 within 7 days of acute infection were randomized to a single dose of 180 micrograms of pegylated interferon lambda versus placebo. In total, 1951 participants were randomized including 933 to the pegylated interferon lambda group and 1018 to the placebo group. The median time from onset of symptoms to randomization was 3 days. Patients treated with interferon lambda demonstrated a 53% decrease in need for COVID-19 hospitalization or ER visit (2.7 interferon versus 5.6% placebo, HR 0.47, 95% CI 0.3 to 0.76). Risk of COVID-related hospitalization (2.3 interferon versus 3.9% placebo, HR 0.58, 95% CI 0.34 to 0.96) or death (2.4 interferon versus 3.9% placebo, HR 0.61, 95% CI 0.36 to 0.99) was lower in the interferon lambda group compared with placebo. Time to clinical recovery did not differ significantly between groups. Adverse events did not differ significantly between groups (3.4, interferon versus 4.8% placebo). Observed benefits persisted across all pre-defined subgroups including age, sex, days since symptom onset and vaccination status.

Comments

1. In patients with a high-risk condition for severe COVID-19, use of pegylated interferon lambda early in the acute period was associated with a significant reduction in the risk of COVID-19 related hospitalization, ED visits and death compared with placebo.
2. Observed effects demonstrated superiority of interferon lambda compared with placebo across all pre-specified subgroups.
3. Severe outcome endpoints including death and hospitalization were uncommon in this largely vaccinated, omicron-era group of patients.
4. Interferon lambda may be an important therapeutic consideration for patients with high-risk conditions including organ transplant and chronic immunosuppression who are high-risk for severe outcomes.
5. Single dose interferon lambda may be useful in patients with drug-drug interactions to Paxlovid or who may be unable to take a longer course of oral antivirals.

LONG-TERM BURDEN OF PASC

Admon AJ, Iwashyna TJ, Kamphuis LA, Gundel SJ, Sahetya SK, Peltan ID, Chang SY, Han JH, Vranas KC, Mayer KP, Hope AA, Jolley SE, Caldwell E, Monahan ML, Hauschildt K, Brown SM, Aggarwal NR, Thompson BT, Hough CL; National Heart, Lung, and Blood Institute PETAL Network. Assessment of Symptom, Disability, and Financial Trajectories in Patients Hospitalized for COVID-19 at 6 Months. *JAMA Netw Open*. 2023 Feb 1;6(2):e2255795.

Summary

This prospective cohort study followed patients hospitalized for COVID-19 pneumonia across 44 US-based sites with telephone-based assessment at 1-,3- and 6-months post-COVID-19 hospitalization. A total of 825 participants were included. Multisystem symptoms, new activities of daily living limitations and financial problems were highly prevalent out to 6 months after COVID-19 hospitalization. Frequency of cardiopulmonary symptoms (67.3 to 75.4%, p=0.001) and fatigue (40.7 to 50.8% p<0.01) increased between 1- and 6-months. Prevalence of financial problems decreased (66.1 to 56.4%, p<0.01) between month 1 and 6 as did frequency of functional limitation (55.3 to 47.3%, p=0.004). Sixty percent of participants reporting no symptoms at 1-month reported new symptoms by 6-months post-hospitalization. Use of supplemental oxygen was associated with a greater odds of reporting cardiopulmonary symptoms at 6 months post-hospitalization (adjusted odds ratio (OR) 1.71, 95% CI 1.10 to 2.66). Non-white race/ethnicity was associated with increased odds of reporting financial problems (aOR Hispanic, 3.74, 95% CI 2.24 to 6.23 and aOR non-Hispanic Black 2.63, 95% CI 1.65 to 4.20). Results of this cohort study highlight the substantial burden of disease in patients recovering from a COVID-19 hospitalization. Further, they demonstrate that risk for multisystem

symptoms and poor outcomes after hospitalization persist well into the recovery period.

Comments

1. Residual impairments are common after a COVID-19-related hospitalization independent of illness severity at time of hospitalization or baseline comorbidities.
2. Cardiopulmonary symptoms and fatigue were commonly reported at 6-months post-hospitalization with increased odds of symptoms in patients receiving supplemental oxygen.
3. Financial problems decreased between 1- and 6-months post-hospitalization but remained highly prevalent, occurring in over half of all respondents.
4. Financial risk was greater in non-White identifying patients compared with non-Hispanic White patients.
5. There are significant longitudinal changes in PASC symptomatology amongst patients previously hospitalized for COVID-19 that require longer-term follow up and monitoring.

SUB-PHENOTYPES OF POST-ACUTE SEQUELAE OF COVID-19

Pfaff ER, Girvin AT, Bennett TD, Bhatia A, Brooks IM, Deer RR, Dekermanjian JP, Jolley SE, Kahn MG, Kostka K, McMurry JA, Moffitt R, Walden A, Chute CG, Haendel MA; N3C Consortium. Identifying who has long COVID in the USA: a machine learning approach using N3C data. *Lancet Digit Health*. 2022 Jul;4(7):e532-e541. doi: 10.1016/S2589-7500(22)00048-6. Epub 2022 May 16.

Summary

This retrospective, electronic-health record-based cohort study developed a machine learning algorithm to identify Post- Acute Sequelae of COVID-19 (PASC) and PASC symptomology amongst 97, 995 patients with a diagnosis of acute COVID-19 across the United States. Investigators identified 73,972 patients with a health care visit in their post-COVID period including 15, 621 who were previously hospitalized for COVID-19 and 58, 351 treated as outpatients. Using data from three dedicated PASC clinics to establish a silver standard definition of PASC, the investigators identified 20 distinct characteristics diagnostic for PASC when compared with presumed non-PASC controls. The team identified four system themes that were consistently identified across models and clusters: 1) post-COVID-19 respiratory symptoms and treatments 2) non-respiratory symptoms 3) pre-existing risk factors for greater acute COVID severity and 4) proxies for hospitalization. The most predictive factors for identifying PASC in patients not previously hospitalized included younger age, dyspnea, and female sex. Conversely, the most predictive factors for identifying previously hospitalized patients included increased age, lack of prior vaccination and dyspnea.

Comments

1. Increasing recognition of sub-phenotypes of PASC suggesting PASC is not a singular clinical entity.
2. Risk of PASC varies amongst previously hospitalized and non-hospitalized patients.
3. PASC symptomatology extends beyond the respiratory system with non-respiratory symptoms commonly reported and potentially reflecting a separate phenotype.
4. EHR-models can help with identification of PASC which may aid in understanding regional and national prevalence.
5. A true gold standard definition of PASC is needed to refine diagnostic models and improve identification of the condition.

EMERGING THERAPIES FOR PASC

Ayoubkhani D, Bermingham C, Pouwels KB, Glickman M, Nafilyan V, Zaccardi F, Khunti K, Alwan NA, Walker AS. Trajectory of long covid symptoms after covid-19 vaccination: community based cohort study. *BMJ*. 2022 May 18;377:e069676.

Summary

This article reports results of a longitudinal, prospective cohort study aimed at understanding the association between vaccination against SARS-CoV-2 and development of PASC. Investigators surveyed individuals aged 18 to 69 years old were included using random sampling of households across the United Kingdom. Primary COVID infection was defined in the 12

weeks prior to follow up using nasal swab testing or SARS-CoV-2 antibody testing. Vaccination status was ascertained during in person interview as were symptoms of long COVID that comprised the primary outcome. A total of 28,356 participants were included in the analysis. The prevalence of long COVID across the follow up period was 23.7%. First vaccination was associated with a 12.8% decrease in long COVID symptoms (95% CI -18.6 to -6.6%, p<0.01). Second vaccination dose was associated with an 8.8% decrease (95% CI -14.1 to -3.1%, p=0.003) followed by an additional 0.8% decrease per week after second dose administration (-1.2 to -0.4%, p<0.01). Additionally, vaccination was associated with a reduction in reported activity limitation from long COVID. First vaccination dose was associated with a 12.3% decrease in activity limitation (95% CI -19.5 to -4.5%, p=0.003) while the second dose was associated with a 9.1% decrease (95% CI -15.6 to -2.1%, p=0.01). These results suggest vaccination against SARS-CoV-2 may reduce long-term symptoms after COVID-19 in addition to lessening risk from acute illness.

Comments

1. Prevalence of PASC was 23.7% in a random sample of adult households across the United Kingdom.
2. Vaccination against SARS-CoV-2 decreased risk of any long COVID symptoms and activity limitation secondary to long COVID.
3. Additional doses of vaccine provided additional reduction in long COVID symptoms and activity limitation.
4. Vaccination against SARS-CoV-2 may aid in reducing the burden of PASC in addition to lessening the risk of acute disease.
5. Vaccination campaigns should consider potential benefits for reducing PASC risk when advising patients in the Omicron era where acute illness severity is less.

OTHER ARTICLES OF INTEREST
ACUTE MANAGEMENT OF COVID-19

Frat JP, Quenot JP, Badie J, Coudroy R, Guitton C, Ehrmann S, Gacouin A, Merdji H, Auchabie J, Daubin C, Dureau AF, Thibault L, Sedillot N, Rigaud JP, Demoule A, Fatah A, Terzi N, Simonin M, Danjou W, Carteaux G, Guesdon C, Pradel G, Besse MC, Reignier J, Beloncle F, La Combe B, Prat G, Nay MA, de Keizer J, Ragot S, Thille AW; SOHO-COVID Study Group and the REVA Network. **Effect of High-Flow Nasal Cannula Oxygen vs Standard Oxygen Therapy on Mortality in Patients With Respiratory Failure Due to COVID-19: The SOHO-COVID Randomized Clinical Trial.** *JAMA*. 2022 Sep 27;328(12):1212-1222. doi: 10.1001/jama.2022.15613.

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NOVEL THERAPEUTICS FOR ACUTE COVID-19

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EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF PASC

Xie, Y., Xu, E., Bowe, B. et al. **Long-term cardiovascular outcomes of COVID-19.** *Nat Med* 28, 583–590 (2022). https://doi.org/10.1038/s41591-022-01689-3.

Swank Z, Senussi Y, Manickas-Hill Z, Yu XG, Li JZ, Alter G, Walt DR. **Persistent Circulating Severe Acute Respiratory Syndrome Coronavirus 2 Spike Is Associated With Post-acute Coronavirus Disease 2019 Sequelae.** *Clin Infect Dis*. 2023 Feb 8;76(3):e487-e490.

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DEEP PHENOTYPING OF POST-ACUTE SEQUELAE OF COVID-19

Reese JT, Blau H, Casiraghi E, Bergquist T, Loomba JJ, Callahan TJ, Laraway B, Antonescu C, Coleman B, Gargano M, Wilkins KJ, Cappelletti L, Fontana T, Ammar N, Antony B, Murali TM, Caufield JH, Karlebach G, McMurry JA, Williams A, Moffitt R, Banerjee J, Solomonides AE, Davis H, Kostka K, Valentini G, Sahner D, Chute CG, Madlock-Brown C, Haendel MA, Robinson PN; N3C Consortium; RECOVER Consortium. **Generalisable long COVID subtypes: findings from the NIH N3C and RECOVER programmes**. *EBioMedicine*. 2023 Jan;87:104413.

Rao S, Lee GM, Razzaghi H, Lorman V, Mejias A, Pajor NM, Thacker D, Webb R, Dickinson K, Bailey LC, Jhaveri R, Christakis DA, Bennett TD, Chen Y, Forrest CB. **Clinical Features and Burden of Postacute Sequelae of SARS-CoV-2 Infection in Children and Adolescents**. *JAMA Pediatr*. 2022 Oct 1;176(10):1000-1009.

EMERGING THERAPEUTICS FOR PASC

Peluso MJ, Anglin K, Durstenfeld MS, Martin JN, Kelly JD, Hsue PY, Henrich TJ, Deeks SG. Effect of Oral Nirmatrelvir on Long COVID Symptoms: 4 Cases and Rationale for Systematic Studies. *Pathog Immun*. 2022 Jun 24;7(1):95-103. doi: 10.20411/pai.v7i1.518.

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Palliative Care

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EARLY PALLIATIVE CARE IN RESPIRATORY ILLNESS

Sullivan, D. R., Iyer, A. S., Enguidanos, S., Cox, C. E., Farquhar, M., Janssen, D. J. A., Lindell, K. O., Mularski, R. A., Smallwood, N., Turnbull, A. E., Wilkinson, A. M., Courtright, K. R., Maddocks, M., McPherson, M. L., Thornton, J. D., Campbell, M. L., Fasolino, T. K., Fogelman, P. M., Gershon, L., Gershon, T., … Reinke, L. F. (2022). **Palliative Care Early in the Care Continuum among Patients with Serious Respiratory Illness: An Official ATS/AAHPM/HPNA/SWHPN Policy Statement.** *American Journal of Respiratory and Critical Care Medicine*, 206(6), e44–e69. https://doi.org/10.1164/rccm.202207-1262ST

Summary

Palliative care can provide significant benefits to patients and family of patients with serious respiratory illness (e.g., chronic obstructive pulmonary disease [COPD], interstitial lung disease [ILD], and lung cancer). Despite this, palliative care, provided by non-specialists (primary) and specialists (secondary or specialty), is underutilized and often integrated into care only at the end of life. In this policy statement by the American Thoracic Society (ATS) and partnering societies, recommendations are made to facilitate the integration of palliative care in serious respiratory illness care across seven domains: 1) delivery models; 2) comprehensive symptom assessment and management; 3) advance care planning and goals of care discussions; 4) caregiver support; 5) health disparities; 6) mass casualty events and emergency preparedness; and 7) research priorities. The statement provides clinicians and policymakers with an approach to implement these recommendations and improve care for those living with serious respiratory illness.

Comments

1. This statement outlines seven recommendations to improve the quality of care provided to patients with serious respiratory illness, by focusing on palliative care across the continuum of a patient's disease process.
2. The recommendations are centered on the role of primary palliative care, which requires the basic tenets of palliative care to be a core competence for all clinicians caring for patients with serious respiratory illness.
3. The statement offers guidance in the application of individualized, evidence-based symptom assessments, with routine symptom assessment an important tool to support development of symptom management plans.
4. Numerous resources for palliative care education and training are highlighted for clinicians as are resources for caregivers of patients with serious respiratory illness.

TRIGGERS USED FOR PALLIATIVE CARE CONSULTATION

Cox, C. E., Ashana, D. C., Haines, K. L., Casarett, D., Olsen, M. K., Parish, A., O'Keefe, Y. A., Al-Hegelan, M., Harrison, R. W., Naglee, C., Katz, J. N., Frear, A., Pratt, E. H., Gu, J., Riley, I. L., Otis-Green, S., Johnson, K. S., & Docherty, S. L. (2022). **Assessment of Clinical Palliative Care Trigger Status vs Actual Needs Among Critically Ill Patients and Their Family Members.** *JAMA network open*, 5(1), e2144093. https://doi.org/10.1001/jamanetworkopen.2021.44093

Summary

Patient characteristics are often used as "triggers" for palliative care consultation in the intensive care unit (ICU). It is unclear, however, if these triggers identify family of patients with the greatest palliative care needs. This was a prospective cohort study in 6 adult

medical and surgical ICUs, including patients and family of patients receiving mechanical ventilation (n=257 dyads, patient and family member). They assessed the presence of any of 9 common clinical palliative care triggers and evaluated differences in self-reported palliative care needs (Needs at the End-of-Life Screening Tool [NEST], completed after 3 days of ICU care) between those with and without a clinical trigger. Triggers included: cardiac arrest; advanced cancer; dementia; critical acute neurologic condition; residence in a long-term acute care facility, skilled nursing facility, or inpatient rehabilitation facility; 3 or more limitations in baseline activities of daily living; 2 or more hospital admissions or 1 or more ICU admissions within 3 months; and worsening organ dysfunction. There was no significant difference in self-reported palliative care needs between those with and without a clinical trigger (median NEST scores, 21.0 vs 22.5). Moreover, the evaluated triggers were neither sensitive nor specific for identifying serious palliative care needs identified by dyads.

Summary

1. This study confirms that family of critically ill patients often have serious palliative care needs, (33.9% had a serious total burden of needs [total NEST score ≥ 30]); however, it challenges the concept that clinical triggers are a useful tool for identifying those palliative care needs.
2. The fact that clinical palliative care triggers were not associated with higher levels of unmet palliative care needs suggests that these triggers may not be reliable as a prompt for specialty palliative care consultation.
3. The value of triggers for identifying serious needs was not supported with the study's measure, given its poor performance characteristics (sensitivity 44.7%, specificity 55.2%) in this regard.
4. An approach which directly assesses palliative care needs may be a more patient- and family-centered way to target palliative care interventions, both from a clinical and research perspective.

PALLIATIVE CARE NEEDS IN CYSTIC FIBROSIS

Dubin, E., Lowers, J., Dellon, E. P., Hempstead, S., Faro, A., Tallarico, E., Fitzpatrick, A., Hunt, W. R., & Kavalieratos, D. (2022). **Prevalence of unmet pain and symptom management needs in adults with cystic fibrosis.** *Journal of Cystic Fibrosis*: Official Journal of the European Cystic Fibrosis Society, S1569-1993(22)00643-9. Advance online publication. https://doi.org/10.1016/j.jcf.2022.08.006

Summary

Burdensome symptoms are common in people living with cystic fibrosis (CF). These may include physical (e.g., pain, dyspnea, cough, steatorrhea), psychological (e.g., anxiety and depression), and existential (e.g., fear of disease progression, uncertainty about the future) symptoms and concerns. In this cross-sectional study, people living with CF (n=55) completed online surveys assessing symptom prevalence, distress, and treatment. Of 29 symptoms reported, pain was the most common symptom experienced (76%), followed by sinus discharge (75%), and fatigue/lack of energy (73%). In terms of causing distress, pain was most frequently identified (64%), followed by fatigue/lack of energy (55%) and difficulty sleeping (51%). Participants specifically raised concerns about inadequate pain management. An iterative, inductive thematic analysis of open-ended survey questions identified three themes related to symptom management: pain and other symptoms are underrecognized and undermanaged; a desire for multi-modal pain management approaches; and concerns about disease progression affecting symptom management options.

Comments

1. Pain is a common, distressing symptom experienced by people living with cystic fibrosis.
2. The management of pain for people living with cystic fibrosis is suboptimal.
3. The themes identified in this study represent significant opportunities for improvement, including exploration of the role of primary and specialty palliative care in the management of pain in CF.

PALLIATIVE CARE IN ILD

Gersten, R. A., Seth, B., Arellano, L., Shore, J., O'Hare, L., Patel, N., Safdar, Z., Krishna, R., Mageto, Y., Cochran, D., Lindell, K., Danoff, S. K., & Pulmonary Fibrosis Foundation (2022). Provider Perspectives on and Access to Palliative Care for Patients With Interstitial Lung Disease. *Chest*, 162(2), 375–384. https://doi.org/10.1016/j.chest.2022.03.009

Summary

Interstitial lung disease (ILD) is associated with high mortality, and people living with ILD carry a significant symptom burden. Involvement of palliative care specialists can benefit these patients and their family members, but referrals to palliative care medicine, when they occur, are often introduced late in the disease process. To understand perspectives on palliative care medicine among ILD providers, surveys were distributed to 68 Pulmonary Fibrosis Foundation Care Centers across the United States. The 24-question electronic survey was completed by 128 participants, most of whom were physicians, representing all Centers. Most respondents were knowledgeable about what palliative care medicine entails, including symptom management, advance directives, spiritual care, and psychological care. A minority of providers (2%) reported that they refer patients to palliative care medicine at the time of initial ILD diagnosis. Several barriers to involvement of palliative care medicine were identified, including lack of validated instruments to assess symptoms, uncertainty about optimal timing of palliative care medicine referral as well as uncertainty about the need for specialized palliative care, and perceived lack of access to palliative care medicine.

Comments

1. This study identified several remediable barriers to the involvement of palliative care medicine in the management of people living with ILD.
2. Barriers that can be addressed by ILD providers include: 1) the use of scales specifically validated in patients with ILD, including the King's Brief Interstitial Lung Disease Questionnaire and the IPF-specific version of the St. George's Respiratory Questionnaire; and 2) an established awareness of services available at their institutions.
3. Primary palliative care should be a core skill for providers caring for people living with ILD, particularly in environments where specialty palliative care is not available.
4. For patients with ILD, optimal timing for referral to palliative care medicine is a topic in need of further research.

SUPPORT FOR FAMILY OF THE DYING

Kentish-Barnes, N., Chevret, S., Valade, S., Jaber, S., Kerhuel, L., Guisset, O., Martin, M., Mazaud, A., Papazian, L., Argaud, L., Demoule, A., Schnell, D., Lebas, E., Ethuin, F., Hammad, E., Merceron, S., Audibert, J., Blayau, C., Delannoy, P. Y., Lautrette, A., … Azoulay, E. (2022). A three-step support strategy for relatives of patients dying in the intensive care unit: a cluster randomised trial. *Lancet* (London, England), 399(10325), 656–664. https://doi.org/10.1016/S0140-6736(21)02176-0

Summary

Psychological distress is common in family of critically ill patients, and for family of those who die, prolonged grief is also a concern. Poor communication may contribute to psychological distress and grief, and interventions to improve communication at the end of life are needed. This multicenter, cluster randomized controlled trial in 34 ICUs in France evaluated a communication and support intervention for dying patients and their family members. Participating ICUs were randomly assigned to an intervention cluster and a control cluster, where the intervention was a physician-driven, nurse-aided, three-step support strategy implemented throughout the dying process and the control was standard care. For patients with a decision to withdraw or withhold life-sustaining therapies, the family member most involved with the ICU team was enrolled (17 interventional ICUs with 484 family members, 17 control ICUs with 391 family members). The primary outcome was proportion of family with prolonged grief (prolonged grief-13 questionnaire, score ≥30) 6 months after patient death. The intervention reduced the number of family members with prolonged grief symptoms (15% vs. 21%; p=0.035), and the median PG-13 score was lower in the

intervention group than in the control group (19 vs. 21, mean difference 2.5; 95% CI 1.04, 3.95).

Comments

1. This multicenter, cluster-randomized trial of a communication intervention showed a positive effect on family-centered outcomes, including prolonged grief, family assessments of the quality of death and dying, and symptoms of psychological distress.
2. The intervention incorporated core components of palliative care, including high-quality communication and emotional and spiritual support, and focused on identifying and meeting the needs of family members.
3. In addition to providing care to the patient and the family member while the patient was alive, the intervention also involved communication with family members after the patient's death.
4. It is important to note that intensivists and nurses in intervention ICUs received training and practice in communication, which would be essential to include in replication of this three-step support strategy.
5. Overall, the intervention seems feasible and further evaluation in other cultural settings may support its application on a broader scale.

END OF LIFE IN THE ICU

Neville, T. H., Taich, Z., Walling, A. M., Bear, D., Cook, D. J., Tseng, C. H., & Wenger, N. S. (2023). **The 3 Wishes Program Improves Families' Experience of Emotional and Spiritual Support at the End of Life. Journal of general internal medicine,** 38(1), 115–121. https://doi.org/10.1007/s11606-022-07638-7

Summary

The dying process is challenging for family of critically ill patients. Neville and colleagues developed the 3 Wishes Program (3WP), a quality improvement intervention based on the concept that asking about and fulfilling small wishes for dying patients and their family members may improve the end-of-life experience. A cohort of dying patients in the ICU was identified from a single health system, with family completing a modified Bereaved Family Survey (BFS) approximately 3 months after patient death. Family completed 314 surveys with 117 from families where care involved the 3WP. In adjusted analyses, family of patients receiving the 3WP were more likely to respond with "always" to how often they were kept informed about the patient's condition and treatment (OR 2.47; 95% CI 1.30, 4.83), how often they felt emotionally supported in the last month of life (OR 2.52; 95% CI 1.37, 4.75), and how often they felt emotionally supported after patient death (OR 2.70; 95% CI 1.44, 5.22). Bereaved family of patients whose care involved the 3WP provided higher ratings on the Emotional and Spiritual Support factor (adjusted mean 6.66 vs. 5.30), compared to family of patients whose care did not.

Comments

1. Despite decades of research, few interventions have been shown to improve the end-of-life care experience for family members of critically ill patients.
2. This 3 Wishes Program holds promise as a feasible intervention with the ability to improve end-of-life care in the ICU, at an average cost of $27 per patient to fulfill 389 wishes in this study.
3. It is important to note that the 3WP was initiated and implemented by ICU nurses in most cases (77%).
4. Larger scale studies are needed to confirm the 3 Wishes Program's effectiveness and promote its broader applicability.

OTHER ARTICLES OF INTEREST

PALLIATIVE CARE IN THE ICU

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PALLIATIVE CARE AND COPD

Tavares, N., Jarrett, N., Wilkinson, T. M. A., & Hunt, K. J. (2023). **Patient-Centered Discussions About Disease Progression, Symptom, and Treatment Burden in Chronic Obstructive Pulmonary Disease Could Facilitate the Integration of End-of-Life Discussions in the Disease Trajectory: Patient, Clinician, and Literature Perspectives: A Multimethod Approach.** *Journal of palliative medicine*, 26(3), 353–359. https://doi.org/10.1089/jpm.2022.0028

PALLIATIVE CARE AND CYSTIC FIBROSIS

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PALLIATIVE CARE AND ILD

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PALLIATIVE CARE AND PULMONARY HYPERTENSION

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PALLIATIVE CARE AND LUNG CANCER

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END-OF-LIFE CARE

Abedini, N. C., Downey, L., Engelberg, R. A., Curtis, J. R., & Sharma, R. K. (2022). **End-of-life healthcare utilization and palliative care use among older adults with limited English proficiency**. *Journal of the American Geriatrics Society,* 70(10), 2847–2857. https://doi.org/10.1111/jgs.17913

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Critical Care

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ICU-ACQUIRED WEAKNESS AND EARLY MOBILIZATION

TEAM Study Investigators and the ANZICS Clinical Trials Group; Hodgson CL, Bailey M, Bellomo R, Brickell K, Broadley T, Buhr H, Gabbe BJ, Gould DW, Harrold M, Higgins AM, Hurford S, Iwashyna TJ, Serpa Neto A, Nichol AD, Presneill JJ, Schaller SJ, Sivasuthan J, Tipping CJ, Webb S, Young PJ. **Early Active Mobilization during Mechanical Ventilation in the ICU.** *N Engl J Med*. 2022 Nov 10;387(19):1747-1758.

Summary

Hodgson et. al. report findings from an international, multicenter, randomized controlled trial to evaluate if early active mobilization for adult patients in the ICU receiving mechanical ventilation increases the number of days alive and out of the hospital. They randomized 750 patients in 1:1 allocation. The intervention group received early mobilization with sessions designed to achieve the highest possible level of mobilization that was safe for as long as possible. The control group received usual care. For the primary outcome, there was no statistically significant difference in the median number days alive and out of the hospital at day 180 [(143 days vs. 145 days, Difference -2, (95%CI -10 to 6, p=0.62)]. There were no statistically significant differences in the secondary outcomes including death at 180 days, median ventilator free days, median ICU free days, or functional outcome scores. There was a higher cumulative incidence of serious adverse events in the intervention group as compared to the control group (7 vs. 1). Therefore, the authors concluded that early active mobilization in this study was associated with an increased risk of adverse events without an improvement in the number of days alive and out of the hospital.

Comments

1. The patients in the intervention group only received protocolized early mobilization in the ICU, and post-ICU care including physical therapy has been described to influence patient outcomes.
2. Both the intervention and control groups demonstrate similar lowest daily Richmond Agitation-Sedation Scale (RASS) scores, which may have muted the potential benefits of early mobilization.
3. These findings warrant contextualization with other studies indicating that early mobilization may improve long-term cognitive and functional outcomes.
4. Early mobilization merits further study as there may be specific populations of critically ill patients who are most likely to benefit.

PREVENTION OF DELIRIUM IN THE ICU

Wibrow B, Martinez FE, Myers E, Chapman A, Litton E, Ho KM, Regli A, Hawkins D, Ford A, van Haren FMP, Wyer S, McCaffrey J, Rashid A, Kelty E, Murray K, Anstey M. **Prophylactic melatonin for delirium in intensive care (Pro-MEDIC): a randomized controlled trial.** *Intensive Care Med*. 2022 Apr;48(4):414-425.

Summary

Delirium is commonly diagnosed in critically ill patients. Despite the increased risk of in-hospital morbidity and mortality, there are limited strategies for delirium prevention. Wilbrow and colleagues describe a multicenter, randomized placebo-controlled, double-blind trial developed to assess if melatonin administration decreases the prevalence of delirium. They enrolled 847 critically ill, adult patients with an estimated ICU length of stay (LOS) greater than 72 hours

using 1:1 randomization allocation. The intervention group received melatonin 4 mg in 2 mL solution orally or via gastric tube for 14 days or until ICU discharge while the control group received 2 mL of placebo. The melatonin was administered nightly at 21:00 hours. Delirium was evaluated twice daily using the Confusion Assessment Method for the ICU (CAM-ICU). There was no statistically significant difference in the average proportion of delirium-free evaluations between the intervention and control groups (79% vs. 80%, p=0.55). Similarly, there were no statistically significant differences in the secondary outcomes including ICU LOS, hospital LOS, and mortality at 90 days. The authors concluded that the findings of this study do not support the routine administration of melatonin for primary prevention of delirium in the ICU setting.

Comments

1. There was a high rate of missingness in the delirium assessments which the study addressed by augmentation in sample size, but this limitation has relevance for the primary outcome.
2. The selected dosage and/or timing of administration may have influenced the observed lack of efficacy of melatonin for delirium prevention.
3. While the study observed no significant difference in sleep quantity or quality between the two groups, previous studies have found that melatonin decreases sleep onset latency and improves sleep efficiency.
4. Specific patient populations have been demonstrated to be more vulnerable to disruptions in circadian rhythm and delirium (e.g. elderly patients or patients with pre-existing mental health disorders), and these groups may benefit from additional study.

NUTRITIONAL SUPPORT DURING CRITICAL ILLNESS

Heyland DK, Patel J, Compher C, Rice TW, Bear DE, Lee ZY, González VC, O'Reilly K, Regala R, Wedemire C, Ibarra-Estrada M, Stoppe C, Ortiz-Reyes L, Jiang X, Day AG; EFFORT Protein Trial team. **The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT Protein): an international, multicentre, pragmatic, registry-based randomised trial.** *Lancet.* 2023 Feb 18;401(10376):568-576.

Summary

Nutritional support guidelines vary regarding the recommended protein dosing during critical illness. Heyland and colleagues report the findings of a pragmatic multicenter, randomized controlled trial designed to examine the effect of high-dose versus standard-dose protein on patient outcomes. The investigators studied 1,301 recently admitted, critically ill, adult patients receiving mechanical ventilation with at least one nutritional risk factor such as moderate to severe malnutrition, low or high BMI, frailty, sarcopenia, or projected duration of mechanical ventilation greater than 4 days. The patients were randomized in a 1:1 ratio to receive either high-dose protein (>2.2 g/kg per day) or usual dose protein (>1.2 g/kg per day) within 96 hours of ICU admission or mechanical ventilation initiation. The treatment continued for 28 days unless transition to oral feeding or death occurred. The cumulate incidence of alive hospital discharge did not differ between the two groups [46.1% vs. 50.2%, (HR 0.91, 95% CI 0.77-1.07; p=0.27)]. The authors concluded that high dose protein did not improve alive hospital discharge for critically ill patients requiring mechanical ventilation, but further research is merited to determine if certain subgroups may derive benefit.

Comments

1. Since the trial was pragmatic, the approach to achieve the high-dose or low-dose protein targets was not protocolized.
2. While the study protocol encouraged the application of the international guidelines to mitigate the potential for over-feeding, the trial did not assess or control for total energy dose.
3. Enrollment into the trial was affected by the COVID-19 pandemic, and the investigators were unable to

assess mortality at 60 days as the original primary outcome for the study.
4. In the subgroup of patients with acute kidney injury or high organ failure scores, high dose protein may be associated with harm.
5. The authors propose future work to assess the potential benefit of high-dose protein in burn, trauma, obese, and post-operative critically ill patients.

FLUID RESUSCITATION IN PANCREATITIS

de-Madaria E, Buxbaum JL, Maisonneuve P, García García de Paredes A, Zapater P, Guilabert L, Vaillo-Rocamora A, Rodríguez-Gandía MÁ, Donate-Ortega J, Lozada-Hernández EE, Collazo Moreno AJR, Lira-Aguilar A, Llovet LP, Mehta R, Tandel R, Navarro P, Sánchez-Pardo AM, Sánchez-Marin C, Cobreros M, Fernández-Cabrera I, Casals-Seoane F, Casas Deza D, Lauret-Braña E, Martí-Marqués E, Camacho-Montaño LM, Ubieto V, Ganuza M, Bolado F; ERICA Consortium. Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis. N Engl J Med. 2022 Sep 15;387(11):989-1000.

Summary

Acute pancreatitis is commonly managed with early fluid resuscitation, but the evidence for this widespread practice remains limited. To determine if aggressive fluid resuscitation as compared to moderate fluid resuscitation would reduce the incidence of moderately severe or severe pancreatitis during the hospitalization, the authors conducted a multi-center, open-label, parallel-group randomized controlled trial. The authors enrolled adult patients with acute pancreatitis within 24 hours of pain onset. The patients were randomized in a 1:1 ratio to receive either aggressive fluid resuscitation (e.g. a bolus of 20 mL per kilogram of body weight, followed by 3 ml per kilogram per hour) or moderate fluid resuscitation (e.g. a bolus of 10 mL per kilogram in patients with hypovolemia or no bolus if euvolemia). Ultimately, the trial was halted after an interim analysis of 249 patients demonstrating differences in safety outcomes without a difference in the incidence of the primary outcome. The authors observed fluid overload in 20.5% of the aggressive resuscitation group vs. 6.3% in the moderate resuscitation group (RR 2.85, 95%CI 1.36 to 5.94, p=0.004). The authors concluded that there is no significant difference in the development of moderately severe or severe pancreatitis based on the fluid resuscitation strategy.

Comments

1. Since the study was discontinued at the first interim analysis, the analysis may have been underpowered to detect differences in the primary outcome.
2. Acknowledging the early termination of the trial, the study did not observe a difference in any of the secondary outcomes including severe pancreatitis, local complications (e.g., necrotizing or infected necrotizing pancreatitis), persistent organ failure, or death.
3. The study protocol only followed the administration of lactated ringers. It is unclear if additional fluids may have been administered outside of the protocol or prior to enrollment, which could have influenced the primary outcome.
4. The investigators were unblinded in this study.

MANGEMENT OF VOLUME STATUS FOR PULMONARY EMBOLISM

Ferrari E, Sartre B, Labbaoui M, Heme N, Asarisi F, Redjimi N, Fourrier E, Squara F, Bun S, Berkane N, Breittmayer JP, Doyen D, Moceri P. Diuretics Versus Volume Expansion in the Initial Management of Acute Intermediate High-Risk Pulmonary Embolism. Lung. 2022 Apr;200(2):179-185.

Summary

Anticoagulation remains a cornerstone of acute pulmonary embolism (PE) management, yet there is limited evidence regarding the management of volume status. Ferrari and colleagues sought to compare the effects of diuretic therapy versus volume expansion in hospitalized patients with intermediate high-risk PE on time to troponin normalization. The investigators conducted a multicenter, open-label, randomized controlled trial with 1:1 allocation. The study enrolled 60 adult patients with acute PE on computed tomography with right ventricular dilation on echocardiogram, positive troponin (>70 ng/L), and elevated BNP (>100 pg/mL). The diuretic group received

furosemide 40 mg IV on admission followed by an additional dose if the diuresis output remained below 500 mL after 4 hours whereas the volume expansion group received 500 mL saline infusion over 4 hours followed by 1000 mL saline infusion per day. Both groups received therapeutic anticoagulation. The study found no difference in the time to troponin normalization in the diuretic group versus the volume expansion group (76 hours vs. 72 hours, p= 0.74). However, there was a significant difference in time to BNP normalization (56 hours vs. 108 hours, p=0.05). The authors concluded that diuretic therapy in acute PE is safe and warrants further study with clinical outcomes.

Comments

1. In general, the administration of furosemide was well tolerated in the diuretic group without significant adverse events.
2. Patients with cardiogenic shock were excluded from this study.
3. The significance of normalization of BNP as a surrogate endpoint is unclear, which can be addressed in future studies using clinical endpoints such as development of shock or mortality.
4. The dynamics of cardiac troponin release in pulmonary embolism have been demonstrated to vary based on the time from symptom onset to clinical presentation, which has relevance for the primary outcome.
5. A prior study by the investigators associated the administration of diuretics for management of pulmonary embolism with improvements in heart rate and peak tricuspid annular systolic velocity.

OTHER ARTICLES OF INTEREST

Kjaergaard J, Møller JE, Schmidt H, Grand J, Mølstrøm S, Borregaard B, Venø S, Sarkisian L, Mamaev D, Jensen LO, Nyholm B, Høfsten DE, Josiassen J, Thomsen JH, Thune JJ, Obling LER, Lindholm MG, Frydland M, Meyer MAS, Winther-Jensen M, Beske RP, Frikke-Schmidt R, Wiberg S, Boesgaard S, Madsen SA, Jørgensen VL, Hassager C. **Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest.** *N Engl J Med.* 2022 Oct 20;387(16):1456-1466. doi: 10.1056/NEJMoa2208687. Epub 2022 Aug 27. PMID: 36027564.

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Asthma

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CONSUMER PRIORITIES

Majellano EC, Bell RL, Flynn AW, Mckenzie A, Sivamalai S, Goldman M, Vaughan L, Gibson PG. **Identifying the asthma research priorities of people with asthma, their carers and other stakeholders.** *Respirology*. 2023 Mar 15. doi: 10.1111/resp.14492. Epub ahead of print. PMID: 36921924.

Summary

This study was led by Asthma Australia to identify the research priorities of consumers. The researchers used a modified James Lind Alliance methodology and performed a national cross sectional mixed methods study to understand the priorities of research end users including patients, carers, health care provider and policy makers. Almost 600 end users participated in the priority setting exercise. The top 10 priorities were: asthma and children, COVID 19 and asthma, asthma care and self-management, causes, prevention and features of asthma, mental health, asthma and aging, severe asthma, and asthma and other health conditions. The identification of these priorities informs the research agenda, will reduce the mismatch in the prioritisation of research that is often seen by funders and the end user, and will ensure the necessary voice of consumers are driving the future direction. This is a great example of consumer-focused research performed to maximize research and clinical impact.

Comments

1. Uses a rigorous method to capture the voice of the consumer
2. Important national project to align asthma research and practice with the priorities of the consumers
3. Dissemination to researchers, healthcare organizations, and external funders, will enable planning and future research to be coordinated and directed to areas of high priority for end-users of asthma research.
4. Reinforces contemporary issues in asthma management
5. Highlights the importance of comorbidities in the management of asthma from the end user perspective.

CLIMATE

Woodcock A, Janson C, Rees J, Frith L, Löfdahl M, Moore A, Hedberg M, Leather D. **Effects of switching from a metered dose inhaler to a dry powder inhaler on climate emissions and asthma control: post-hoc analysis.** *Thorax*. 2022 Dec;77(12):1187-1192.

Summary

Climate change is having a real and significant impact leading to global health emergencies for people with asthma (thunderstorm asthma, landscape fires). Despite the recognition of this the health care sectors contribute significantly to greenhouse gas emission. Hydrofluorocarbons in pressurized inhaler devices (pMDI) is one source of the healthcare sector's contribution. These potent greenhouse gases that are now being phased down. In a post-hoc analysis of 2236 patients in the Salford Lung Study in Asthma, Woolcock and colleagues sort to determine the effect of switching from a pMDI to dry powder device compared to usual asthma care on 1). Greenhouse emissions and 2). Asthma control. The results indicate that switching from pMDI to DPI more than halved the carbon footprint, without any loss of asthma control. These data suggest that in many people with asthma switching from pMDI to DPI is an acceptable consideration that significantly reduce emissions.

Comments

1. Asthma inhaler medications contribute to climate emissions.
2. Under the Kigali Amendment to the Montreal Protocol in 2016 HFC in pMDIs are being phased down
3. The impact of inhalers on the carbon footprint could be reduced in many patients with asthma through considered selection of inhaler devices.

ASTHMA TREATMENT

Beasley R, Harrison T, Peterson S, Gustafson P, Hamblin A, Bengtsson T, Fageråas M. **Evaluation of Budesonide-Formoterol for Maintenance and Reliever Therapy Among Patients With Poorly Controlled Asthma: A Systematic Review and Meta-analysis.** *JAMA Netw Open*. 2022 Mar 1;5(3):e220615.

Summary

The Global Initiative for Asthma (GINA) has two alternate treatment tracks for adolescents and adults. The preferred treatment track for patients in GINA step 3-5 is single inhaler combination inhaled corticosteroid–
formoterol as both maintenance and reliever (SMART). This is based on level one evidence that using ICS-formoterol as maintenance and reliever reduces the risk of exacerbations compared with using an ICS-LABA plus SABA reliever. In this systematic review and meta-analysis Beasley et al sought to determine if switching to SMART in patients with poorly controlled asthma was associated with longer time to exacerbation compared to step up or continuation of ICS LABA plus SABA. Included were 5 RCTS involving 4863 patients. The findings showed that the use of SMART in patients with poorly controlled asthma was associated with longer time to first exacerbation compared to step up or continuation of GINA treatment step with ICS-LABA plus SABA.

Comments

1. When adult or adolescent patients receiving treatment at GINA step 3 or 4 have poorly controlled asthma, switching to the SMART regimen rather than to step up or continue the GINA treatment step with maintenance inhaled corticosteroid–long-acting β2-agonist plus short-acting β2-agonist reliever therapy is supported by level one evidence for reducing time to exacerbation.
2. The analysis was limited to RCTs of the budesonide-formoterol SMART regimen versus fixed dose ICS-LABA plus.

ASTHMA TREATMENT OF COMORBITIES

Johnson O, Gerald LB, Harvey J, Roy G, Hazucha H, Large C, Burke A, McCormack M, Wise RA, Holbrook JT, Dixon AE. **An Online Weight Loss Intervention for People With Obesity and Poorly Controlled Asthma.** *J Allergy Clin Immunol Pract*. 2022 Jun;10(6):1577-1586.e3. doi: 10.1016/j.jaip.2022.02.040. Epub 2022 Mar 15. PMID: 35304842; PMCID: PMC9188993.

Summary

Obesity is associated with difficult to control asthma, worsened symptoms, lung function and lower exercise capacity. Obesity is increasing and this represents a significant public health issue. RCTs of weight loss interventions in asthma indicate that losing 5-10% of body weight leads to significant improvements in asthma control. Interventions for weight loss include calorie restriction, physical activity, lifestyle changes, pharmacotherapy or bariatric surgery depending on the degree of obesity. Online and digital health interventions are increasing and enable greater access to health care interventions. This study tested an online weight loss intervention to determine its effect on weight loss and asthma control. The design was a single arm futility study. At 6 months 23% of participants lost at least 5% of their initial weight and this loss was associated with both clinically and statistically significant improvements in asthma control. Accessible and effective weight loss interventions are an urgent priority for people with asthma. Effective online interventions are needed for the future of asthma care.

Comments

1. Obesity rates are increasing.
2. Obesity worsens asthma.

3. Achieving a 5-10% loss of body weight leads to improved asthma control.
4. This online weight loss intervention leads to weight loss associated with improved asthma control in a significant proportion of participants.
5. Needs a definitive RCT.

ASTHMA PHENOTYPES

McDowell PJ, Busby J, Hanratty CE, Djukanovic R, Woodcock A, Walker S, Hardman TC, Arron JR, Choy DF, Bradding P, Brightling CE, Chaudhuri R, Cowan D, Mansur AH, Fowler SJ, Diver SE, Howarth P, Lordan J, Menzies-Gow A, Harrison T, Robinson DS, Holweg CTJ, Matthews JG, Pavord ID, Heaney LG. **Exacerbation Profile and Risk Factors in a Type-2-Low Enriched Severe Asthma Cohort: A Clinical Trial to Assess Asthma Exacerbation Phenotypes.** *Am J Respir Crit Care Med*. 2022 Sep 1;206(5):545-553.

Summary

This paper reports a prespecified secondary endpoint analysis of asthma exacerbations from a 48-week RCT (N=301) that evaluated a biomarker versus symptom-based treatment titration in patients with severe asthma. The study enrolled a population of patients with a FENO of <45 ppb to enrich for T2-low population. The aims of this analysis were to 1). Explore the differences between participants who exacerbated and those that did not, 2). To describe the physiological changes at exacerbation of T2 high and T2 low participants, and to evaluate the stability of inflammatory phenotypes when stable and at exacerbation. The analysis indicated that asthma exacerbations in participants with a T2 low and T2 high phenotype were physiologically and symptomatically similar. Furthermore, the phenotype of T2 low asthma was unstable at exacerbation, highlighting the need for phenotyping at the time of each exacerbation. Exacerbations in participants without evidence of T2 biology at the time of exacerbation highlights a demanding and unmet need in asthma management which requires a better understanding of mechanisms of T2 low asthma.

Comments

1. Monoclonal antibody therapies have had an important impact on people with severe asthma reducing exacerbations significantly.
2. There is however a residual exacerbation burden for people with severe asthma and understanding the mechanisms of these exacerbations is needed.
3. Poor asthma symptom control, female sex, obesity, restrictive lung function, and multiple unscheduled prior healthcare visits for exacerbation events in the prior year to study were factors associated with exacerbation.
4. Exacerbation phenotype is not stable at the time of exacerbation
5. This study identifies T2low asthma as an important unmet need.

OTHER ARTICLES OF INTEREST

Wechsler ME, Menzies-Gow A, Brightling CE, Kuna P, Korn S, Welte T, Griffiths JM, Sałapa K, Hellqvist Å, Almqvist G, Lal H, Kaur P, Skärby T, Colice G; SOURCE study group. **Evaluation of the oral corticosteroid-sparing effect of tezepelumab in adults with oral corticosteroid-dependent asthma (SOURCE): a randomised, placebo-controlled, phase 3 study.** *Lancet Respir Med*. 2022 Jul;10(7):650-660. doi: 10.1016/S2213-2600(21)00537-3. Epub 2022 Mar 29. Erratum in: Lancet Respir Med. 2022 Apr 5;: PMID: 35364018.

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Osadnik CR, Gleeson C, McDonald VM, Holland AE. **Pulmonary rehabilitation versus usual care for adults with asthma.** *Cochrane Database Syst Rev.* 2022 Aug 22;8(8):CD013485. doi: 10.1002/14651858.CD013485.pub2. PMID: 35993916; PMCID: PMC9394585.

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Sarcoidosis

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OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES IN SARCOIDOSIS

Ryan SM, Mroz MM, Herzog EL, Ryu C, Fingerlin TE, Maier LA, Gulati M. **Occupational and environmental exposures in the Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis (GRADS) study.** *Respir Med*. 2022 Aug-Sep;200:106923.

Summary

This prospective study sought to explore associations between environmental and occupational exposures and sarcoidosis clinical phenotypes within the Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis (GRADS) cohort, a NIH multicenter study sponsored by the NHLBI. The study evaluated occupational and environmental exposures between five disease outcomes: pulmonary only versus extrapulmonary with or without pulmonary involvement; Scadding Stage II/III/IV versus Scadding Stage 0/I; cardiac involvement (yes/no); acute or remitting disease (onset of disease less than 1 month) versus non-acute or non-remitting disease; and chronic disease defined as active disease for more than 2 years (yes/no). Results found that both clinical phenotypes and exposures differed by sex and racial groups. Females had a higher percentage of Scadding Stage 0/1 compared to males. Exposure differences by sex were found among jobs and hobbies. In the cohort, Black individuals had more extrapulmonary disease, a higher proportion of Scadding Stage IV, and were more likely to have chronic disease compared to White individuals. Job exposures differed between the racial groups. There were no significant occupational or environmental exposures associated with any of the studied outcomes, with the exception that having occupational radiation exposure was statistically significantly associated with a higher risk of cardiac sarcoidosis.

Comments

1. This prospective study utilized the GRADS cohort to evaluate environmental and occupational exposures among patients with sarcoidosis.
2. It is the first study to evaluate the association between clinical sarcoidosis phenotypes and environmental and occupational exposures.
3. Results showed sex and race differences in the clinical phenotypes and exposures.
4. There were no significant occupational or environmental exposures associated with developing sarcoidosis in the lungs only, between the Scadding stage groups, acute/remitting versus non-acute/non-remitting disease, or chronic versus non-chronic sarcoidosis.
5. Radiation exposure was associated with higher risk of cardiac versus non-cardiac disease.

NEW THERAPIES IN PULMONARY SARCOIDOSIS

Culver DA, Aryal S, Barney J, Hsia CCW, James WE, Maier LA, Marts LT, Obi ON, Sporn PHS, Sweiss NJ, Shukla S, Kinnersley N, Walker G, Baughman R. **Efzofitimod for the Treatment of Pulmonary Sarcoidosis**. *Chest.* 2022 Nov 8:S0012-3692(22)04053-3.

Summary

Based on consensus guidelines, glucocorticosteroids are considered first line therapy in most patients with sarcoidosis who have indications for treatment, but can be associated with significant side effects. Novel therapies are urgently needed in sarcoidosis. Neuropilin 2 is a pleiotropic receptor that is upregulated on the surface of activated immune cells responsible for inflammation and granuloma formation in the lungs of patients with pulmonary sarcoidosis. ATYR1923 is a novel IV biologic immunomodulator composed of a splice variant of histidyl-tRNA synthetase that encodes

the immunomodulatory domain that binds to the neuropilin 2 receptor protein. This study is a phase II, randomized, double-blind, placebo-controlled study evaluating multiple doses of efzofitimod (ATYR1923) to assess for tolerability, safety, and clinical efficacy. No deaths or drug-related serious adverse events (AEs) were observed. Overall, the proportion of patients with an AE was similar between the placebo and efzofitimod treatment groups. Exploratory analyses suggest clinically meaningful improvements at 24 weeks in the 5 mg/kg efzofitimod arm. These improvements were seen in both lung function parameters and patient reported outcomes compared with placebo. The results of this study support further evaluation of efzofitimod in pulmonary sarcoidosis.

Comments

1. Novel therapies are needed in sarcoidosis.
2. Efzofitimod (ATYR1923) selectively binds neuropilin 2, which is upregulated on immune cells in response to lung inflammation.
3. This is a phase II, randomized, double-blind, placebo-controlled evaluating multiple doses of efzofitimod (ATYR1923).
4. Similar adverse events occurred in the efzofitimod and placebo groups with suggestion of clinical improvement in the 5mg/kg efzofitimod group compared to placebo.
5. The results of this study support further evaluation of efzofitimod in pulmonary sarcoidosis.

RACIAL AND SEX DIFFERENCES IN PULMONARY SARCOIDOSIS

Sharp M, Psoter KJ, Balasubramanian A, Pulapaka AV, Chen ES, Brown SW, Mathai SC, Gilotra NA, Chrispin J, Bascom R, Bernstein R, Eakin MN, Wise RA, Moller DR, McCormack MC. Heterogeneity of Lung Function Phenotypes in Sarcoidosis: Role of Race and Sex Differences. *Ann Am Thorac Soc*. 2023 Jan;20(1):30-37.

Summary

This study characterized the prevalence of different pulmonary function phenotypes in a retrospective cohort of patients with sarcoidosis. Patients seen between 2005-2015 with a diagnosis of sarcoidosis and lung function measurements (spirometry and DL_{CO}) were included. Using baseline FVC, FEV1, and DL_{CO} % predicted calculated using Global Lung Function Initiative reference equations, five pulmonary function phenotypes were defined: normal, restriction, obstruction, combined restriction and obstruction (combined), and isolated reduction in DL_{CO}. Of 602 individuals with sarcoidosis, 93% had pulmonary involvement defined by the GRADS organ assessment tool, 64% were female, and 57% were Black. Of those with pulmonary involvement, the pulmonary function phenotype prevalence was 44% normal, 27% restriction (47% of abnormal individuals), 13% obstruction (22% of abnormal individuals), 9% combined (16% of abnormal individuals), and 8% isolated reduction in DL_{CO} (15% of abnormal individuals). Restriction was the most common pulmonary function phenotype among Black individuals, while normal was the most common among White individuals. Black individuals had significantly worse pulmonary function compared with White individuals including FVC% predicted, FEV1% predicted and DL_{CO} % predicted. Males had obstruction more frequently than females, but females had restriction more frequently than males.

Comments

1. This is the first study to describe the prevalence of pulmonary function phenotypes in a large, diverse sarcoidosis cohort in the US.
2. Among individuals with sarcoidosis and pulmonary function impairment, less than half demonstrated a restrictive phenotype.
3. Spirometry may miss clinical progression in a substantial proportion of individuals.
4. Black individuals had worse pulmonary function compared with White individuals, and these differences were seen in all pulmonary function phenotypes except the combined phenotype.
5. The results demonstrated significant differences in pulmonary function phenotypes by race and sex.

IMPACT OF NEIGHBOURHOOD DISADVANTAGE IN SARCOIDOSIS

Goobie GC, Ryerson CJ, Johannson KA, Keil S, Schikowski E, Khalil N, Marcoux V, Assayag D, Manganas H, Fisher JH, Kolb MRJ, Chen X, Gibson KF, Kass DJ, Zhang Y, Lindell KO, Nouraie SM. Neighborhood disadvantage impacts on pulmonary function in patients with sarcoidosis. *ERJ Open Res*. 2022 Oct 24;8(4):00357-2022.

Summary

This study assesses the association between neighborhood-level disadvantage and clinical outcomes in a prospective cohort from the United States (US) enrolled between 2000-2021 and a prospective cohort from Canada enrolled between 2015-2021. Neighborhood-level disadvantage was measured by the area deprivation index (ADI) in the US cohort and the Canadian Index of Multiple Deprivation (CIMD) in the Canadian cohort. Analyses included adjustments for co-variates including age at diagnosis, sex, race, and smoking status. The primary outcomes were pulmonary function parameters (FVC and DL_{CO}). The US and Canadian cohorts included 477 and 122 patients with median follow up of 8.3 years and 4.1 years, respectively. Neither ADI nor CIMD was significantly associated baseline % predicted FVC in the fully adjusted analyses. There was a significant association with between ADI, but not CMID, and baseline % predicted DL_{CO}. In both cohorts, the highest quartile of ADI and CIMD (most disadvantaged neighborhoods) was associated with greater decline in FVC % predicted per year compared to the lowest quartile. ADI was associated with greater decline in DL_{CO} per year by continuous measurements and quartile measurements, but no significance was seen with CMID in the fully adjusted models.

Comments

1. Significant health disparities among socioeconomic status, race, and gender exist in sarcoidosis.
2. This is the first study to evaluate of neighborhood-level disadvantage in sarcoidosis.
3. Participants in the highest quartile of ADI and CIMD had greater decline in FVC % predicted per year compared to individuals in the lowest quartile of ADI and CIMD respectively.
4. ADI was associated with greater decline in DL_{CO} per year, but no significance was seen with CMID in the fully adjusted models.
5. Further work is needed to understand whether policies aimed at reducing neighborhood-level inequities may mitigate these outcome disparities in patients with sarcoidosis and other chronic diseases.

LUNG TRANSPLANT IN SARCOIDOSIS

Gupta R, Zheng M, Gangemi AJ, Zhao H, Cordova FC, Criner GJ, Mamary AJ, Sehgal S. Predictors of lung transplant waitlist mortality for sarcoidosis. *Respir Med*. 2022 Dec;205:107008.

Summary

This retrospective study aimed to identify predictors for transplant waitlist mortality among individuals with sarcoidosis. The cohort consisted of 1034 sarcoidosis patients listed for lung transplantation from May 2005 to May 2019 in the Scientific Registry of Transplant Recipients (SRTR) database after LAS implementation. The study also compared outcomes pre-LAS and post-LAS. After LAS implementation, the proportion of candidates who were transplanted increased significantly and the proportion of candidates that died on the waitlist decreased significantly. Of the post-LAS cohort, 704 were transplanted and 110 died on the waitlist. Significant predictors of waitlist mortality in multivariate analyses were female gender (OR 2.45; 95% CI 1.51–3.95) and severe pulmonary hypertension (OR 1.62; 95% CI 1.07–2.46). Taller minimum donor height (OR 0.61; 95% CI 0.38–0.97) and blood type B (OR 0.52; 95% CI 0.28–0.98) were associated with decreased likelihood of death on the waitlist.

Comments

1. Criteria for lung transplant referral in sarcoidosis are not well established.
2. The LAS has increased the proportion of listed patients with sarcoidosis who receive transplants and decreased wait list mortality.
3. Female gender and severe pulmonary hypertension were predictors of waitlist mortality
4. Clinicians should be mindful of the increased mortality in patients with pulmonary hypertension

and sarcoidosis and consider early referral for lung transplantation.

TREATMENT FOR FATIGUE IN SARCOIDOSIS

Kahlmann V, Moor CC, van Helmondt SJ, Mostard RLM, van der Lee ML, Grutters JC, Wijsenbeek MS, Veltkamp M. **Online mindfulness-based cognitive therapy for fatigue in patients with sarcoidosis (TIRED): a randomised controlled trial.** *Lancet Respir Med*. 2023 Mar;11(3):265-272.

Summary

Fatigue affects up to 90% of patients with sarcoidosis and is often associated with psychological symptoms such as anxiety and depression. This study is a prospective, open-label, multicenter randomized controlled trial assessing the effects of a 12-week online mindfulness-based cognitive therapy (eMBCT) on fatigue. Of 99 patients who were randomized, 52 were assigned to eMBCT and 47 were assigned to the control group (usual care). The primary outcome of the study was the between-group difference in change of fatigue, measured by the fatigue assessment scale (FAS), at T1 (completion of intervention or 12 weeks after enrollment if control). FAS has a minimal clinical important difference of 4.0. Secondary outcomes included the Hospital Anxiety and Depression Scale, the Freiburg Mindfulness Inventory–Short Form, and the Kings Sarcoidosis Questionnaire. In the intervention group, there was a clinically and statistically significant improvement in FAS score (-4.53) between T0 (baseline) and T1. In the control group, the mean change in FAS was -1.28. Patients in the eMBCT group had significantly more improvement in anxiety, depressive symptoms, health status, and mindfulness score compared with the control group. Beneficial effects within the intervention group persisted 12 weeks (T2) after completion of the eMBCT program.

Comments

1. Fatigue in patients with sarcoidosis is highly prevalent, affecting up to 90% of patients.
2. This study is the first randomized control trial investigating the effects of a 12-week online mindfulness-based cognitive therapy (eMBCT) on sarcoidosis-associated fatigue.
3. The intervention (eMBCT) improved fatigue, anxiety, depression, mindfulness, and health status in patients with sarcoidosis-associated fatigue.
4. The beneficial effects of eMBCT persisted during follow-up 12 weeks after completion of the program.

OTHER ARTICLES OF INTEREST

Seedahmed MI, Baugh AD, Albirair MT, Luo Y, Chen J, McCulloch CE, Whooley MA, Koth LL, Arjomandi M. **Epidemiology of Sarcoidosis in U.S. Veterans from 2003 to 2019.** *Ann Am Thorac Soc*. 2023 Feb 1.

Lin NW, Arbet J, Mroz MM, Liao SY, Restrepo CI, Mayer AS, Li L, Barkes BQ, Schrock S, Hamzeh N, Fingerlin TE, Carlson NE, Maier LA. **Clinical phenotyping in sarcoidosis using cluster analysis.** *Respir Res*. 2022 Apr 9;23(1):88.

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Gayen S, Sosa DF, Zheng M, Gangemi A, Sehgal S, Zhao H, Marchetti N, Criner GJ, Gupta R, Mamary AJ. **Lung Transplantation Waitlist Mortality Among Sarcoidosis Patients by Lung Allocation Score Grouping. Transplant** *Proc*. 2023 Feb 15:S0041-1345(23)00011-8.

Sepsis

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FLUID RESUSCITATION IN SEPSIS

National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network; Shapiro NI, Douglas IS, Brower RG, Brown SM, Exline MC, Ginde AA, Gong MN, Grissom CK, Hayden D, Hough CL, Huang W, Iwashyna TJ, Jones AE, Khan A, Lai P, Liu KD, Miller CD, Oldmixon K, Park PK, Rice TW, Ringwood N, Semler MW, Steingrub JS, Talmor D, Thompson BT, Yealy DM, Self WH. **Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension.** *N Engl J Med*. 2023 Feb 9;388(6):499-510.

Summary

The 2021 SCCM guidelines suggest 30 ml/kg of initial intravenous fluid resuscitation, but the guidelines do not have a recommendation on further fluid management and do not differentiate between a restrictive and liberal fluid strategy. The Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) trial was an unblinded randomized controlled trial comparing a restrictive fluid protocol (i.e., early vasopressors) to a liberal protocol in patients with sepsis associated hypotension, defined as hypotension despite 1 to 3 liters of intravenous fluid resuscitation. The restrictive protocol prioritized vasopressors as the primary treatment, allowing for "rescue fluids" for prespecified indications, while the liberal protocol started with an initial 2-liter intravenous infusion, and prioritized fluid boluses with "rescue vasopressors". The protocols were continued for 24 hours. In total, 782 patients were randomized to restrictive and 781 patients to liberal protocols. There was no significant difference in the primary outcome of 90-day mortality in the restrictive vs liberal group (14% vs 14.9%). There were no differences in secondary outcomes and no differential benefit in prespecified subgroup analyses. In patients with sepsis-induced hypotension, there was no significant difference in outcomes with either a restrictive or liberal fluid strategy.

Comments

1. Study patients received pre-randomization intravenous fluids (median of 2 liters in both groups), and this trial was not designed to investigate the initial fluid resuscitation recommendation of 30 ml/kg.
2. The restrictive group received 1.3 liters while the liberal group received 3.4 liters in the first 24 hours after randomization.
3. A secondary finding of interest was the safety of peripheral vasopressors, which were allowed through a 20 gauge or larger peripheral catheter and resulted in only three instances of extravasation among 500 patients, with all three cases resolving without intervention.
4. Compared to the CLASSIC trial detailed below, both arms in the CLOVERS trial were protocolized (compared to protocolized vs standard of care in CLASSIC) and the protocols were followed for only 24 hours (compared to up to 90 days in CLASSIC).

FLUID RESUSCITATION IN SEPSIS

Meyhoff TS, Hjortrup PB, Wetterslev J, Sivapalan P, Laake JH, Cronhjort M, Jakob SM, Cecconi M, Nalos M, Ostermann M, Malbrain M, Pettilä V, Møller MH, Kjær MN, Lange T, Overgaard-Steensen C, Brand BA, Winther-Olesen M, White JO, Quist L, Westergaard B, Jonsson AB, Hjortsø CJS, Meier N, Jensen TS, Engstrøm J, Nebrich L, Andersen-Ranberg NC, Jensen JV, Joseph NA, Poulsen LM, Herløv LS, Sølling CG, Pedersen SK, Knudsen KK, Straarup TS, Vang ML, Bundgaard H, Rasmussen BS, Aagaard SR, Hildebrandt T, Russell L, Bestle MH, Schønemann-Lund M, Brøchner AC, Elvander CF, Hoffmann SKL, Rasmussen ML, Martin YK, Friberg FF, Seter H, Aslam TN, Ådnøy S, Seidel P, Strand K, Johnstad B, Joelsson-Alm E, Christensen J, Ahlstedt C, Pfortmueller CA, Siegemund M, Greco M, Raděj J, Kříž M, Gould DW, Rowan KM, Mouncey PR, Perner A; CLASSIC Trial Group. **Restriction of Intravenous Fluid in ICU Patients with Septic Shock.** *N Engl J Med*. 2022 Jun 30;386(26):2459-2470.

Summary

The Conservative versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care (CLASSIC) trial compared restrictive intravenous fluid therapy to standard intravenous fluid therapy in patients with septic shock on vasopressors in the ICU, who had received at least 1 liter in the 24 hours prior to enrollment. The patients in the restrictive fluid arm received intravenous fluids in small boluses only for the indications of 1) severe hypoperfusion, 2) to replace documented fluid losses, 3) to correct dehydration and electrolyte deficiencies, or 4) to ensure minimal fluid intake. Patients in the standard therapy arm had no restrictions on the volume of fluids to be administered. The restrictive or standard care was continued for the length of the patients' ICU stay, up to a maximum of 90 days. The trial enrolled 1554 patients across 31 ICUs in Europe and was conducted between November 2018 and November 2021. The results showed that at 90 days after randomization, there was no significant difference in death between the restrictive fluid group (42.3%) and the standard fluid group (42.1%). The authors found no significant differences in any of the prespecified secondary outcomes (including renal function) or the prespecified subgroup analysis.

Comments

1. Study patients received 3 liters of intravenous fluids pre-randomization, and thus this study was not designed to investigate the question of initial fluid resuscitation strategy.
2. During the 90-day trial period, the restrictive fluid group received 1.8 liters of fluid, compared to 3.8 liters in the standard group, with a cumulative (net) fluid balance of +1.6 liters compared to +2.4 liters.
3. The control group (standard therapy) may not have been managed distinctly different enough from the restrictive group to detect differences in outcomes (as evidenced by the <1 liter difference in net fluid balance at 90 days).
4. Both the CLASSIC and CLOVERS trials evaluate broad protocolized strategies of restriction and liberalization of intravenous fluids and are not designed to provide insights into individualized strategies for fluid therapy (e.g., dynamic measures of fluid responsiveness).

EXPERIMENTAL AND EMERGING THERAPIES IN SEPSIS

SuDDICU Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group; Myburgh JA, Seppelt IM, Goodman F, Billot L, Correa M, Davis JS, Gordon AC, Hammond NE, Iredell J, Li Q, Micallef S, Miller J, Mysore J, Taylor C, Young PJ, Cuthbertson BH, Finfer SR. **Effect of Selective Decontamination of the Digestive Tract on Hospital Mortality in Critically Ill Patients Receiving Mechanical Ventilation: A Randomized Clinical Trial.** *JAMA*. 2022 Nov 15;328(19):1911-1921.

Summary

Selective decontamination of the digestive tract (SDD) is a long-studied intervention of interest with the goal of reducing the incidence of infections in mechanically ventilated patients. Although there has been clinical research into SDD for over 30 years, SDD has not become standard practice in most countries. The Selective Decontamination of the Digestive Tract in the Intensive Care Unit (SuDDICU) trial was a cluster randomized unblinded study that randomized ICUs to

SDD or standard care for patients who were mechanically ventilated and predicted to need mechanical ventilation for at least 48 hours. The SDD intervention consisted of colistin, tobramycin, and nystatin as an oral paste and a gastric suspension, along with a 4-day course of IV antibiotics with gram-negative coverage. In total, 5982 patients were enrolled from 19 ICUs. There was no statistically significant difference in the primary outcome of in-hospital deaths between the SDD and standard care groups (odds ratio, 0.91 [95% CI, 0.82-1.02]; P = .12). Of the 8 prespecified secondary outcomes, 6 showed no significant differences. In the ecological assessment, the use of SDD was not shown to be noninferior to standard care (i.e., SDD did not lead to development of new antibiotic resistant organisms).

Comments

1. Although the trial's primary outcome of mortality did not reach significance, the confidence interval includes a clinically significant benefit that is further supported by meta-analyses confirming likely mortality benefit from SDD.
2. Of the secondary outcomes, there was no difference in new Clostridium difficile infections between the SDD and standard care arms.
3. Of the secondary outcomes, the patients in the SDD arm had lower rates of new positive blood cultures and antibiotic resistant organisms in cultures.

EXPERIMENTAL AND EMERGING THERAPIES IN SEPSIS

Lamontagne F, Masse MH, Menard J, Sprague S, Pinto R, Heyland DK, Cook DJ, Battista MC, Day AG, Guyatt GH, Kanji S, Parke R, McGuinness SP, Tirupakuzhi Vijayaraghavan BK, Annane D, Cohen D, Arabi YM, Bolduc B, Marinoff N, Rochwerg B, Millen T, Meade MO, Hand L, Watpool I, Porteous R, Young PJ, D'Aragon F, Belley-Cote EP, Carbonneau E, Clarke F, Maslove DM, Hunt M, Chassé M, Lebrasseur M, Lauzier F, Mehta S, Quiroz-Martinez H, Rewa OG, Charbonney E, Seely AJE, Kutsogiannis DJ, LeBlanc R, Mekontso-Dessap A, Mele TS, Turgeon AF, Wood G, Kohli SS, Shahin J, Twardowski P, Adhikari NKJ; LOVIT Investigators and the Canadian Critical Care Trials Group. Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit. *N Engl J Med.* 2022 Jun 23;386(25):2387-2398.

Summary

It has been hypothesized that Vitamin C therapy has antioxidant effects that could benefit critically ill patients with sepsis. An initial single-center study showed significant mortality benefit from a combination of Vitamin C, thiamine, and hydrocortisone. However, multiple subsequent multi-center trials including VITAMINS and VICTAS have failed to replicate the mortality benefit from the combination therapy. The CITRIS-ALI trial tested Vitamin C monotherapy in a high-dose formulation in patients with sepsis associated acute lung injury and found no difference in the primary outcome, but 28-day mortality (one of 46 secondary outcomes) was significantly lower in patients randomized to Vitamin C. The LOVIT trial is a randomized placebo-controlled multi-center clinical trial investigating high-dose intravenous Vitamin C in adults with sepsis requiring vasopressor infusions in the ICU, with the primary composite outcome of death or persistent organ dysfunction on day 28. This study involved 872 patients, with 435 in the Vitamin C group and 437 in the control group. The study surprisingly found that the composite primary outcome of death or persistent organ dysfunction occurred more frequently in the Vitamin C group (44.5% vs 38.5%, p=0.01). There were no significant differences between the two groups in terms of secondary outcomes.

Comments

1. This trial did not specifically address whether there could be a benefit in patients with sepsis and acute lung injury (to mirror the CITRIS-ALI trial).
2. Although the trial measured five biomarkers of tissue dysoxia, inflammation, and endothelial injury, there were no findings to identify the mechanism of harm from Vitamin C.
3. This trial adds to the pool of evidence for either a null effect or even potential harm from Vitamin C in patients with sepsis requiring vasopressors.

EXPERIMENTAL AND EMERGING THERAPIES IN SEPSIS

Drewry AM, Mohr NM, Ablordeppey EA, Dalton CM, Doctor RJ, Fuller BM, Kollef MH, Hotchkiss RS. **Therapeutic Hyperthermia Is Associated With Improved Survival in Afebrile Critically Ill Patients With Sepsis: A Pilot Randomized Trial.** *Crit Care Med.* 2022 Jun 1;50(6):924-934.

Summary

Fever is known to have beneficial effects in the immune response to infection. Afebrile patients with infection (specifically, hypothermic patients) have worse outcomes. It is unknown whether artificially inducing a fever (i.e., therapeutic hyperthermia) through external warming could reproduce the immune effects and potentially improve patient outcomes. There is literature surrounding this practice in oncology and surgery (with an older trial showing decreased post-surgical wound infections in patients randomized to warming). This current study was a single-center, prospective, open-label, randomized controlled trial involving mechanically ventilated septic adults, with patients randomized to external warming versus control. External warming consisted of the use of a forced-air warming blanket for 48 hours, with a goal temperature 1.5°C above the lowest temperature documented in the previous 24 hours. The primary outcome was monocyte human leukocyte antigen (HLA)-DR expression. The study enrolled 56 patients (28 in each arm) and showed no differences in the primary outcome of HLA-DR expression or secondary outcome of IFN-γ production between the groups. Surprisingly, the patients randomized to external warming had a significantly lower 28-day mortality rate compared to control (18% vs 43%; absolute risk reduction, 25%; 95% CI, 2-48%).

Comments

1. Small single-center studies are susceptible to type I errors/false positives, and the findings need to be validated in a larger study with the designated primary outcome of mortality.
2. Pilot studies are designed to determine feasibility of enrolling patients and performing the intervention rather than to evaluate efficacy of the intervention, and any positive results should be considered in this context.
3. If there is a true mortality benefit from therapeutic hyperthermia, the biological mechanism was not identified in this study as both HLA-DR expression and IFN-γ production did not differ between groups.
4. There was no increase in adverse events in the therapeutic hyperthermia group, and it was well tolerated.

POST-HOSPITALIZATION SEPSIS CARE

Taylor SP, Murphy S, Rios A, McWilliams A, McCurdy L, Chou SH, Hetherington T, Rossman W, Russo M, Gibbs M, Kowalkowski MA. **Effect of a Multicomponent Sepsis Transition and Recovery Program on Mortality and Readmissions After Sepsis: The Improving Morbidity During Post-Acute Care Transitions for Sepsis Randomized Clinical Trial.** *Crit Care Med.* 2022 Mar 1;50(3):469-479.

Summary

While in-hospital mortality from sepsis has decreased, sepsis survivors are burdened by high risk of post-discharge mortality and readmissions. The Sepsis Transition and Recovery (STAR) program was developed to address persistent morbidity and mortality for sepsis survivors. The STAR program delivers post-sepsis care through a remote nurse navigator who addresses medication optimization, screening for new impairments, anticipation and mitigation of health risks, and palliative care. The Improving Morbidity during Post-Acute Care Transitions for Sepsis (IMPACTS) trial tested the hypothesis that high-risk patients with suspected sepsis randomized to the STAR program would have a reduction in a composite outcome of 30-day readmission and mortality. The study was conducted across three hospitals and enrolled 691 patients (349 randomized to STAR and 343 randomized to usual care). The STAR group had significantly lower incidence of the primary outcome compared to usual care (28.7% vs 33.3%), with 9.5% compared to 12% mortality. The intervention benefit was most significant for the patients in the lower 3 quartiles of predicted mortality risk, while not of significant benefit in patients in the top quartile of predicted risk. The IMPACTS trial demonstrated that a post-discharge transition program

decreased short-term mortality and rehospitalization after discharge for patients with sepsis.

Comments

1. The enrolled patients were deemed high-risk using a locally derived risk-stratification tool, with unclear generalizability and uncertainty on the effect of the intervention on patients who were selected for enrollment through alternative methods.
2. It is unclear what component of the STAR program was most impactful and the specific action pathways that could have led to mortality and readmission prevention (e.g., illustrative cases of patients' clinical course changed through the program).
3. While 30-day mortality and readmission are important metrics, further research is needed to understand the longer-term benefits of this type of program in sepsis survivors.

OTHER ARTICLES OF INTEREST

FLUID RESUSCITATION

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Russell DW, Casey JD, Gibbs KW, Ghamande S, Dargin JM, Vonderhaar DJ, Joffe AM, Khan A, Prekker ME, Brewer JM, Dutta S, Landsperger JS, White HD, Robison SW, Wozniak JM, Stempek S, Barnes CR, Krol OF, Arroliga AC, Lat T, Gandotra S, Gulati S, Bentov I, Walters AM, Dischert KM, Nonas S, Driver BE, Wang L, Lindsell CJ, Self WH, Rice TW, Janz DR, Semler MW; PREPARE II Investigators and the Pragmatic Critical Care Research Group. **Effect of Fluid Bolus Administration on Cardiovascular Collapse Among Critically Ill Patients Undergoing Tracheal Intubation: A Randomized Clinical Trial.** *JAMA*. 2022 Jul 19;328(3):270-279. doi: 10.1001/jama.2022.9792. PMID: 35707974; PMCID: PMC9204618.

EXPERIMENTAL AND EMERGING THERAPIES IN SEPSIS

Hammond NE, Myburgh J, Seppelt I, Garside T, Vlok R, Mahendran S, Adigbli D, Finfer S, Gao Y, Goodman F, Guyatt G, Santos JA, Venkatesh B, Yao L, Di Tanna GL, Delaney A. **Association Between Selective Decontamination of the Digestive Tract and In-Hospital Mortality in Intensive Care Unit Patients Receiving Mechanical Ventilation: A Systematic Review and Meta-analysis.** *JAMA*. 2022 Nov 15;328(19):1922-1934. doi: 10.1001/jama.2022.19709. PMID: 36286098; PMCID: PMC9607997.

Fujii T, Salanti G, Belletti A, Bellomo R, Carr A, Furukawa TA, Luethi N, Luo Y, Putzu A, Sartini C, Tsujimoto Y, Udy AA, Yanase F, Young PJ. **Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer-term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis.** *Intensive Care Med*. 2022 Jan;48(1):16-24. doi: 10.1007/s00134-021-06558-0. Epub 2021 Nov 9. PMID: 34750650; PMCID: PMC8724116.

Patel JJ, Willoughby R, Peterson J, Carver T, Zelten J, Markiewicz A, Spiegelhoff K, Hipp LA, Canales B, Szabo A, Heyland DK, Stoppe C, Zielonka J, Freed JK. **High-Dose IV Hydroxocobalamin (Vitamin B12) in Septic Shock: A Double-Blind, Allocation-Concealed, Placebo-Controlled Single-Center Pilot Randomized Controlled Trial (The Intravenous Hydroxocobalamin in Septic Shock Trial).** *Chest*. 2023 Feb;163(2):303-312. doi: 10.1016/j.chest.2022.09.021. Epub 2022 Sep 26. PMID: 36174744.

SEPSIS PHENOTYPES

Bhavani SV, Semler M, Qian ET, Verhoef PA, Robichaux C, Churpek MM, Coopersmith CM. **Development and validation of novel sepsis subphenotypes using trajectories of vital signs.** *Intensive Care Med*. 2022 Nov;48(11):1582-1592. doi: 10.1007/s00134-022-06890-z. Epub 2022 Sep 24. PMID: 36152041; PMCID: PMC9510534.

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SEPSIS SURVIVORSHIP

Kowalkowski MA, Rios A, McSweeney J, Murphy S, McWilliams A, Chou SH, Hetherington T, Rossman W, Taylor SP. **Effect of a Transitional Care Intervention on Rehospitalization and Mortality after Sepsis: A 12-Month Follow-up of a Randomized Clinical Trial.** *Am J Respir Crit Care Med*. 2022 Sep 15;206(6):783-786. doi: 10.1164/rccm.202203-0590LE. PMID: 35608544.

Winkler D, Rose N, Freytag A, Sauter W, Spoden M, Schettler A, Wedekind L, Storch J, Ditscheid B, Schlattmann P, Reinhart K, Günster C, Hartog CS, Fleischmann-Struzek C. **The Effects of Postacute Rehabilitation on Mortality, Chronic Care Dependency, Health Care Use, and Costs in Sepsis Survivors.** *Ann Am Thorac Soc*. 2023 Feb;20(2):279-288. doi: 10.1513/AnnalsATS.202203-195OC. PMID: 36251451.

OTHER TOPICS

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Writing Committee for the REMAP-CAP Investigators; Higgins AM, Berry LR, Lorenzi E, Murthy S, McQuilten Z, Mouncey PR, Al-Beidh F, Annane D, Arabi YM, Beane A, van Bentum-Puijk W, Bhimani Z, Bonten MJM, Bradbury CA, Brunkhorst FM, Burrell A, Buzgau A, Buxton M, Charles WN, Cove M, Detry MA, Estcourt LJ, Fagbodun EO, Fitzgerald M, Girard TD, Goligher EC, Goossens H, Haniffa R, Hills T, Horvat CM, Huang DT, Ichihara N, Lamontagne F, Marshall JC, McAuley DF, McGlothlin A, McGuinness SP, McVerry BJ, Neal MD, Nichol AD, Parke RL, Parker JC, Parry-Billings K, Peters SEC, Reyes LF, Rowan KM, Saito H, Santos MS, Saunders CT, Serpa-Neto A, Seymour CW, Shankar-Hari M, Stronach LM, Turgeon AF, Turner AM, van de Veerdonk FL, Zarychanski R, Green C, Lewis RJ, Angus DC, McArthur CJ, Berry S, Derde LPG, Gordon AC, Webb SA, Lawler PR. Long-term (180-Day) **Outcomes in Critically Ill Patients With COVID-19 in the REMAP-CAP Randomized Clinical Trial.** *JAMA*. 2023 Jan 3;329(1):39-51. doi: 10.1001/jama.2022.23257. PMID: 36525245; PMCID: PMC9857594.

Sleep

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OBSTRUCTIVE SLEEP APNEA

Berry RB, Abreu AR, Krishnan V, Quan SF, Strollo PJ Jr, Malhotra RK. **A transition to the American Academy of Sleep Medicine–recommended hypopnea definition in adults: initiatives of the Hypopnea Scoring Rule Task Force.** *J Clin Sleep Med*. 2022;18(5):1419–1425.

Summary

The American Academy of Sleep Medicine (AASM) recommends that hypopneas be identified using a definition that is based on a ≥ 30% decrease in airflow associated with a ≥ 3% reduction in oxygen saturation or an arousal (H3A) for diagnosis of obstructive sleep apnea (OSA) in adults. This conflicts with the Centers for Medicare & Medicaid Services definition, which requires a ≥ 4% decrease in the oxygen saturation to identify a hypopnea (H4) and does not acknowledge arousals. In 2018, the AASM Board of Directors constituted a Hypopnea Scoring Rule Task Force with a mandate to "create a strategy for adoption and implementation of the AASM recommended adult hypopnea scoring criteria among members, payers and device manufacturers." The task force initiated several activities including a survey of AASM-accredited sleep facilities and discussions with polysomnography software vendors. Survey results indicated that most sleep facilities scored polysomnograms using only the Centers for Medicare & Medicaid Services definition. Vendors indicated that they could easily support dual scoring. Informal testing among task force members' sleep facilities confirmed there would be little additional work if dual scoring was performed. The task force convened several meetings, with the purpose of creating research recommendations to study the impact on relevant clinical outcomes using the different definitions of hypopnea. Based on the deliberations of the working group, the Hypopnea Scoring Rule Task Force submitted recommendations to the AASM Foundation concerning research project strategies for potential grant funding. Further discussions within the Hypopnea Scoring Rule Task Force focused on developing advocacy initiatives among patient stakeholder groups to change payer policy.

Comments

1. The American Academy of Sleep Medicine continues to recommend the hypopnea definition where >=30% reduction in airflow terminates in a >= 3% oxygen desaturation or arousal (H3A); however, CMS still only recognizes hypopneas, and the derived AHI, when airflow reduction of at least 30% terminates in an at least 4% arousal (H4).
2. In the coming scoring manual revision, the AASM will use H3A to define hypopneas and the H4 definition will be optional.
3. Defining hypopneas with the H3A rule classifies symptomatic individuals as having OSA that would fallen into ‘normal’ AHI range with the H4 rule.
4. Polysomnogram reports should include quantification of hypopneas using the H3A rule.

OBSTRUCTIVE SLEEP APNEA

Hajipour M, Baumann B, Azarbarzin A, Allen AH, Liu Y, Fels S, Goodfellow S, Singh A, Jen R, Ayas NT. **Association of alternative polysomnographic features with patient outcomes in obstructive sleep apnea: a systematic review.** *Journal of Clinical Sleep Medicine*. 2023 Feb 1;19(2):225-42.

Summary

Polysomnograms (PSGs) collect a plethora of physiologic signals across the night. However, few of

these PSG data are incorporated into standard reports, and hence, ultimately, under-utilized in clinical decision making. Recently, there has been substantial interest regarding novel alternative PSG metrics that may help to predict obstructive sleep apnea (OSA)-related outcomes better than standard PSG metrics such as the apnea-hypopnea index. Authors systematically reviewed the literature between 2000 and 2022 for studies that examined the use of alternative PSG metrics in the context of OSA and their association with health outcomes.

Of the 186 initial studies identified by the original search, 31 were ultimately included in the final analysis. Numerous metrics were identified that were significantly related to a broad range of outcomes.

Comments

1. OSA is associated with daytime sleepiness, reduced quality of life, motor vehicle crashes, occupational injuries, hypertension, cancer, cardiovascular disease, arrhythmias, kidney disease, cognitive dysfunction, and mortality. However, the presence of OSA or severity as quantified by the AHI, does not reliably predict adverse outcomes.
2. Marked interest in identifying alternative or novel metrics derived from PSG that are relevant to outcomes to guide more patient-specific risk stratification and treatment and inform population selection for RCTs.
3. In regards to Cardiovascular/metabolic outcomes and mortality the following candidate predictive PSG metrics were identified: 1. Heart rate response to respiratory events, 2. Pulse arrival time, 3. Pulse wave characteristics, 4. Pulse rate variability/HRV, 5. Cardiopulmonary coupling, 6. Odds Ratio Product, 7. EEG power, 8. Arousal burden, 9. Hypoxic burden, 10. Respiratory event desaturation transient area, 11. Oxygen desaturation rate, 12. Lung to finger circulation time, 13. Desaturation severity and obstructive severity, 14. Respiratory event duration, and 15. Duty cycle and inspiratory flow limitation.
4. In regards to cognitive function and vigilance, the following candidate predictive PSG metrics were identified: 1. Pulse arrival time (PAT), 2. Odds Ratio Product, 3. Other EEG metrics, 4. Spindle burst index, 5. EEG power, 6. Arousal duration, 7. Desaturation severity and obstructive severity, and 8. Apnea or hypopnea load
5. The authors concluded that advanced analysis of physiologically complex PSG data has provided promising novel, alternative metrics to predict OSA-related complications and that these new indicators fall into the following categories: hemodynamic-related, EEG-related, desaturation indices, and respiratory event data.

INSOMNIA

De Crescenzo F, D'Alò GL, Ostinelli EG, et al. **Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis.** *Lancet* 2022; 400:170.

Summary

In this systematic review and network meta-analysis, authors aimed to estimate the comparative effectiveness of pharmacological treatments for the acute and long-term treatment of adults with insomnia disorder.

They searched several sources from database inception to Nov 25, 2021, to identify published and unpublished randomised controlled trials and included studies comparing pharmacological treatments or placebo as monotherapy for the treatment of adults with insomnia disorder. Primary outcomes were efficacy (ie, quality of sleep measured by any self-rated scale), treatment discontinuation for any reason and due to side-effects specifically, and safety (ie, number of patients with at least one adverse event) both for acute and long-term treatment.

They included 170 trials (36 interventions and 47950 participants) and 154 doubleblind, randomised

controlled trials (30 interventions and 44089 participants) were eligible for the network metaanalysis.

In terms of acute treatment, benzodiazepines, doxylamine, eszopiclone, lemborexant, seltorexant, zolpidem, and zopiclone were more efficacious than placebo (SMD range: 0·36–0·83 [CINeMA estimates of certainty: high to moderate]). Benzodiazepines, eszopiclone, zolpidem, and zopiclone were more efficacious than melatonin, ramelteon, and zaleplon (SMD 0·27–0·71 [moderate to very low]). Intermediate-acting benzodiazepines, long-acting benzodiazepines, and eszopiclone had fewer discontinuations due to any cause than ramelteon (OR 0·72 [95% CI 0·52–0·99; moderate], 0·70 [0·51–0·95; moderate] and 0·71 [0·52–0·98; moderate], respectively). Zopiclone and zolpidem caused more dropouts due to adverse events than did placebo (zopiclone: OR 2·00 [95% CI 1·28–3·13; very low]; zolpidem: 1·79 [1·25–2·50; moderate]); and zopiclone caused more dropouts than did eszopiclone (OR 1·82 [95% CI 1·01–3·33; low]), daridorexant (3·45 [1·41–8·33; low), and suvorexant (3·13 [1·47–6·67; low]). For the number of individuals with side-effects at study endpoint, benzodiazepines, eszopiclone, zolpidem, and zopiclone were worse than placebo, doxepin, seltorexant, and zaleplon (OR range 1·27–2·78 [high to very low]).

For long-term treatment, eszopiclone and lemborexant were more effective than placebo (eszopiclone: SMD 0·63 [95% CI 0·36–0·90; very low]; lemborexant: 0·41 [0·04–0·78; very low]) and eszopiclone was more effective than ramelteon (0.63 [0·16–1·10; very low]) and zolpidem (0·60 [0·00–1·20; very low]). Compared with ramelteon, eszopiclone and zolpidem had a lower rate of all-cause discontinuations (eszopiclone: OR 0·43 [95% CI 0·20–0·93; very low]; zolpidem: 0·43 [0·19–0·95; very low]); however, zolpidem was associated with a higher number of dropouts due to side-effects than placebo (OR 2·00 [95% CI 1·11–3·70; very low]).

Overall, eszopiclone and lemborexant had a favorable profile, but eszopiclone might cause substantial adverse events and safety data on lemborexant were inconclusive. Doxepin, seltorexant, and zaleplon were well tolerated, but data on efficacy and other important outcomes were scarce and do not allow firm conclusions. Many licensed drugs (including benzodiazepines, daridorexant, suvorexant, and trazodone) can be effective in the acute treatment of insomnia but are associated with poor tolerability, or information about long-term effects is not available. Melatonin, ramelteon, and non-licensed drugs did not show overall material benefits. These results should serve evidence-based clinical practice.

Comments

1. Most RCTs of pharmacological treatment of insomnia are short-term leading to medication approval only for acute settings.
2. This systematic review and meta-analysis of publications on the acute and long-term pharmacological treatment of insomnia used outcomes of self-rated quality of sleep (efficacy), discontinuation due to any cause (acceptability), discontinuation due to any adverse event (tolerability), and presence of at least one adverse event (safety). Among the studied medications, lemborexant and eszopiclone had the best profile in terms of efficacy, acceptability, and tolerability; however, eszopiclone might cause substantial adverse events and safety data on lemborexant were inconclusive.

RESTLESS LEGS SYNDROME

Winkelman JW, Wipper B, Zackon J. **Long-term Safety, Dose Stability, and Efficacy of Opioids for Patients With Restless Legs Syndrome in the National RLS Opioid Registry.** *Neurology*. 2023 Jan 25.

Summary

In this study, authors report the 2-year longitudinal data in a sample of patients treated with opioids for RLS in the community.
The National RLS Opioid Registry is an observational longitudinal study consisting of individuals taking a prescribed opioid for diagnosed and confirmed RLS, most of whom experienced augmented symptoms from dopamine agonists. Information on opioid dosages, side effects, past and current concomitant RLS treatments, RLS severity, psychiatric symptoms, and opioid abuse

risk factors was collected at Registry entry and every 6 months thereafter. No feedback or intervention was provided by the study staff to local providers.

Registry participants (n = 448) with 2-year longitudinal data available were mostly White, female, older than 60 years, and, at Registry entry, had been on opioids for a median of 1–3 years at a mean morphine milligram equivalent (MME) of 38.4 (SD = 43.5). No change in RLS severity in the overall cohort was observed over the 2-year follow-up period. The median change in daily opioid dose from baseline to 2 years was 0 MME (interquartile range = 0–10). While 41.1% of participants increased their dose during the follow-up period (median increase = 10 MME), 58.9% decreased their dose or saw no change. Only 8% and 4% saw increases of >25 MME and >50 MME, respectively. Ninety-five percent of those who increased opioid dose >25 or >50 MME had one of the following features: switching opioids, discontinuation of nonopioid RLS treatment medications, at least mild insomnia at baseline, a history of depression, male sex, younger than 45 years, and opioid use for comorbid pain.

Low-dose opioid medications continue to adequately control symptoms of refractory RLS over 2 years of follow-up in most of the participants. A minority of patients did see larger dose increases, which were invariably associated with a limited number of factors, most notably changes in opioid and nonopioid RLS medications and opioid use for a non-RLS condition. Continued longitudinal observations will provide insight into the long-term safety and efficacy of opioid treatment of severe, augmented RLS.

This study provides Class IV evidence that opioid doses increase in roughly 40% of patients, in most by small amounts, over a 2-year period when prescribed for adult refractory restless leg syndrome.

Comments

1. The RLS National Opioid Registry collects longitudinal observational data on efficacy, dosage changes, tolerability, RLS severity, and sleep, mood, and anxiety symptoms in a national sample of patients using prescribed opioids for RLS. The initial 2 years of data from N=448 patients were available.
2. Most common side effects at 2 years were constipation (47%), drowsiness/fatigue (23%), itching (19%), sweating (17%), and stimulation/wakefulness (9%).
3. 80% of those who stayed on opioids remained on the same opioid at the 2 year time point and the median MME dose was the same at the 2-year time point compared to baseline Two-fifths of patients increased opioid dose (the balance remained the same or decreased).
4. Almost all individuals with opioid daily dose increases of >25 or 50 MME had one of the following characteristics: switching opioid medication, discontinuation of nonopioid RLS treatment medications, at least mild insomnia at baseline, a history of depression, male sex, younger than 45 years, and opioid use for comorbid pain.
5. Of those who remained on opioids and completed 2-year surveys, IRLS, ISI, and PHQ-9 scores did not change from baseline to 2 years. However, almost a quarter remaining on opioids fell into the severe RLS category at baseline and the 2 year follow up.
6. Opioids used were methadone (50.9%), oxycodone (15.0%), hydrocodone (11.6%), oxycontin (7.1), and tramadol (6.7%). IRLS scores at 2 years were significantly lower for participants using methadone.

CENTRAL DISORDERS OF HYPERSOMNOLENCE

Dauvilliers, Y., Arnulf, I., Foldvary-Schaefer, N., Morse, A. M., Šonka, K., Thorpy, M. J., Mignot, E., Chandler, P., Parvataneni, R., Black, J., Sterkel, A., Chen, D., Skobieranda, F., & Bogan, R. K. (2022). **Safety and efficacy of lower-sodium oxybate in adults with idiopathic hypersomnia: a phase 3, placebo-controlled, double-blind, randomised withdrawal study.** *The Lancet.* Neurology, 21(1), 53–65. https://doi.org/10.1016/S1474-4422(21)00368-9

Summary

Idiopathic hypersomnia is a central hypersomnolence disorder mainly characterised by excessive daytime sleepiness, with prolonged night-time sleep and pronounced sleep inertia. Until August, 2021, no medication had regulatory approval for the treatment of idiopathic hypersomnia. This study aimed to evaluate the safety and efficacy of lower-sodium oxybate in idiopathic hypersomnia.

This was a phase 3, multicentre (50 specialist sleep centres; six EU countries and the USA), placebo-controlled, double-blind, randomised withdrawal study. Participants (aged 18-75 years) with idiopathic hypersomnia began lower-sodium oxybate treatment (oral solution once or twice nightly) in an open-label titration and optimisation period (10-14 weeks), followed by a 2-week, open-label, stable-dose period. After these open-label periods, participants were randomised (1:1) to either placebo or lower-sodium oxybate (individually optimised dose; range 2·5-9·0 g/night) during a 2-week, double-blind, randomised withdrawal period. To maintain masking of treatment assignment, placebo and lower-sodium oxybate oral solutions were matched in volume, appearance, and taste. The primary efficacy endpoint was change in Epworth Sleepiness Scale (ESS) score from the end of the stable-dose period to the end of the double-blind, randomised withdrawal period, Adverse events were assessed in the safety population (defined as all participants who took at least one dose of study medication).

Between Nov 2018, and March 2020, 154 participants were enrolled and comprised the safety population. ESS scores decreased from a mean of 15·7 (SD 3·8) at baseline to 6·1 (4·0) by the end of the stable-dose period. After the open-label periods, 115 participants were randomly assigned either placebo (n=59) or lower-sodium oxybate (n=56) and comprised the modified intention-to-treat population. During the double-blind, randomised withdrawal period, ESS scores increased (worsened) in participants randomly assigned to placebo but remained stable in those assigned to lower-sodium oxybate (least squares mean difference -6·5; 95% CI -8·0 to -5·0; p<0·0001). Treatment-emergent adverse events included nausea (34 [22%] of 154), headache (27 [18%] of 154), dizziness (19 [12%] of 154), anxiety (17 [11%] 154), and vomiting (17 [11%] 154). No deaths were reported during the study.

Lower-sodium oxybate treatment resulted in a clinically meaningful improvement in idiopathic hypersomnia symptoms, with an overall safety profile consistent with that reported for narcolepsy. Lower-sodium oxybate was approved in August, 2021, by the US Food and Drug Administration for the treatment of idiopathic hypersomnia in adults.

Comments

1. Idiopathic hypersomnia is a disorder of excessive daytime sleepiness without explanation and without the REM intrusion that marks narcolepsy. Calcium, magnesium, potassium, and sodium oxybates (lower-sodium oxybate, Xywav) is the first medication FDA approved to treat idiopathic hypersomnia
2. This was a placebo-controlled, double-blind, randomised withdrawal study looking at the primary endpoint of Epworth sleepiness scale (ESS) change. From the standard dose period, those who were withdrawn to placebo had a worsening of mean ESS by 7.4 points; those randomized to remain on the active medication had ESS scores that were unchanged from the stable dose period (mean ESS=7) (and improved from baseline, mean ESS= 15.7).
3. Treatment-emergent adverse events included nausea (22%), headache (18%), dizziness (12%), anxiety (11%), and vomiting (11%).17% discontinued participation in the study due to treatment-emergent adverse events.

REM SLEEP BEHAVIOR DISORDER

Howell, M., Avidan, A. Y., Foldvary-Schaefer, N., Malkani, R. G., During, E. H., Roland, J. P., McCarter, S. J., Zak, R. S., Carandang, G., Kazmi, U., & Ramar, K. (2023). Management of REM sleep behavior disorder: an American Academy of Sleep Medicine clinical practice guideline. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, 19(4), 759–768. https://doi.org/10.5664/jcsm.10424

Summary

This guideline established clinical practice recommendations for the management of rapid eye movement sleep behavior disorder (RBD) in adults.

The American Academy of Sleep Medicine (AASM) commissioned a task force of experts in sleep medicine to develop recommendations and assign strengths based on a systematic review of the literature and an assessment of the evidence using Grading of Recommendations, Assessment, Development and Evaluation methodology. The task force provided a summary of the relevant literature and the certainty of evidence, the balance of benefits and harms, patient values and preferences, and resource use considerations that support the recommendations. The AASM Board of Directors approved the final six recommendations, listed below.

The good practice statement is based on expert consensus, and its implementation is necessary for the appropriate and effective management of patients with RBD: It is critically important to help patients maintain a safe sleeping environment to prevent potentially injurious nocturnal behaviors. In particular, the removal of bedside weapons, or objects that could inflict injury if thrown or wielded against a bed partner, is of paramount importance. Sharp furniture like nightstands should be moved away or their edges and headboard should be padded. To reduce the risk of injurious falls, a soft carpet, rug, or mat should be placed next to the bed. Patients with severe, uncontrolled RBD should be recommended to sleep separately from their partners, or at the minimum, to place a pillow between themselves and their partners.

Comments

1. The AASM suggests that clinicians use clonazepam, immediate-release melatonin, or pramipexole (vs no treatment) for the treatment of isolated RBD in adults. (CONDITIONAL)
2. The AASM suggests that clinicians use transdermal rivastigmine (vs no treatment) for the treatment of isolated RBD in adults with mild cognitive impairment. (CONDITIONAL)
3. The AASM suggests that clinicians use clonazepam or immediate-release melatonin (vs no treatment) for the treatment of secondary RBD due to medical condition in adults. (CONDITIONAL)
4. The AASM suggests that clinicians use transdermal rivastigmine (vs no treatment) for the treatment of secondary RBD due to medical condition (Parkinson disease) in adults. (CONDITIONAL)
5. The AASM suggests that clinicians not use deep brain stimulation (DBS; vs no treatment) for the treatment of secondary RBD due to medical condition in adults. (CONDITIONAL)
6. The AASM suggests that clinicians use drug discontinuation (vs drug continuation) for the treatment of drug-induced RBD in adults. (CONDITIONAL)

OTHER ARTICLES OF INTEREST

Obstructive Sleep Apnea

Khan NN, Todem D, Bottu S, Badr MS, Olomu A. Impact of patient and family engagement in improving continuous positive airway pressure adherence in patients with obstructive sleep apnea: a randomized controlled trial. *Journal of Clinical Sleep Medicine*. 2022 Jan 1;18(1):181-91.

Li Y, Richard KE, Schwartz AR, Zealear D, Lindsell CJ, Budnick HA, Kent DT. Quantitative Effects of Ansa Cervicalis Stimulation in Obstructive Sleep Apnea. *American Journal of Respiratory and Critical Care Medicine*. 2023 Jan 19(ja).

Das AM, Chang JL, Berneking M, et al. Enhancing public health and safety by diagnosing and treating obstructive sleep apnea in the transportation industry: an American Academy of Sleep Medicine position statement. J Clin Sleep Med 2022; 18:2467.

Georgoulis M, Yiannakouris N, Kechribari I, et al. **Dose-response relationship between weight loss and improvements in obstructive sleep apnea severity after a diet/lifestyle interventions: secondary analyses of the "MIMOSA" randomized clinical trial.** *J Clin Sleep Med* 2022; 18:1251.

Lechat B, Appleton S, Melaku YA, Hansen K, McEvoy RD, Adams R, Catcheside P, Lack L, Eckert DJ, Sweetman A. **Comorbid insomnia and sleep apnoea is associated with all-cause mortality.** *European Respiratory Journal*. 2022 Jul 1;60(1).

Insomnia

Zhao, J. L., Cross, N., Yao, C. W., Carrier, J., Postuma, R. B., Gosselin, N., Kakinami, L., & Dang-Vu, T. T. (2022). **Insomnia disorder increases the risk of subjective memory decline in middle-aged and older adults: a longitudinal analysis of the Canadian Longitudinal Study on Aging.** *Sleep*, 45(11), zsac176. https://doi.org/10.1093/sleep/zsac176

Bushnell GA, Gerhard T, Keyes K, Hasin D, Cerdá M, Olfson M. **Association of Benzodiazepine Treatment for Sleep Disorders With Drug Overdose Risk Among Young People.** *JAMA Netw Open*. 2022 Nov 1;5(11):e2243215. doi: 10.1001/jamanetworkopen.2022.43215. PMID: 36413369; PMCID: PMC9682430.

CRSWD

Yip, T., Wang, Y., Xie, M., Ip, P. S., Fowle, J., & Buckhalt, J. (2022). **School Start Times, Sleep, and Youth Outcomes: A Meta-analysis.** *Pediatrics,* 149(6), e2021054068. https://doi.org/10.1542/peds.2021-054068

Technology

Bakker JP, Ross M, Cerny A, Vasko R, Shaw E, Kuna S, Magalang UJ, Punjabi NM, Anderer P. **Scoring sleep with artificial intelligence enables quantification of sleep stage ambiguity: hypnodensity based on multiple expert scorers and auto-scoring.** *Sleep*. 2023 Feb;46(2):zsac154.

LUNG TRANSPLANTS

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ARE WE DONE HERE? INEQUITIES OF THE LUNG ALLOCATION SCORE SYSTEM AND TIME TO MOVE ON

Kolaitis NA, Chen H, Calabrese DR, Kumar K, Obata J, Bach C, Golden JA, Simon MA, Kukreja J, Hays SR, Leard LE, Singer JP, De Marco T. The Lung Allocation Score Remains Inequitable for Patients with Pulmonary Arterial Hypertension, Even after the 2015 Revision. *Am J Respir Crit Care Med*. 2023 Feb 1;207(3):300-311. doi: 10.1164/rccm.202201-0217OC. PMID: 36094471

Summary

Before March 2023, donor lungs in the United States were allocated via a system called the lung allocation score (LAS). LAS prioritizes patients for transplantation based on an estimated risk of waitlist death and post-transplant survival. Unfortunately, LAS creates multiple inequities. This work examines the inequities of the LAS for patients with pulmonary arterial hypertension (PAH), a subgroup of patients where the LAS fails to capture the impact of their pulmonary vascular disease on pre- and post-transplant outcomes. In 2015, the LAS system was revised to better reflect disease severity in PAH. This manuscript utilizes national registry data to estimate the benefit of the 2015 LAS revision.

The study included about ~40,000 participants, half registered before the 2015 revision and half after. Before the 2015 revisions, PAH demonstrated the highest risk of death and lowest likelihood of transplant compared to any other patient group. With the 2015 revision, the LAS increased 14.2 points in the 100-point scale for PAH patients, without a significant change in the LAS for other patient groups. Although inequities improved, they nonetheless persisted. Specifically, PAH is now tied with pulmonary fibrosis for the highest risk of waitlist death, while together with chronic obstructive pulmonary disease patients had the lowest likelihood of transplantation.

Comments

1. This article addresses the question: does applying a single allocation system, such as the LAS, for patients with vastly different disease conditions often bring inequities?
2. This work points out that even with revisions, the LAS system continues to show inequities.
3. Unfortunately, the LAS system also struggles in its primary mission as a predictor of pre- and post-transplant outcomes for patients listed for lung transplantation.
4. The LAS has since been replaced by a new system, the composite allocation score (CAS), a scoring system that utilizes recipient medical information and facts from potential donors to determine allocation priorities.
5. It remains unclear how allocation inequities will be impacted by the CAS, which was implemented in March 2023.

MANIPULATE THE DONOR LUNG BIOLOGY IN THE RECIPIENTS' FAVOR BEFORE TRANSPLANTATION

Miyamoto E, Takahagi A, Ohsumi A, Martinu T, Hwang D, Boonstra KM, Joe B, Umana JM, Bei KF, Vosoughi D, Liu M, Cypel M, Keshavjee S, Juvet SC. Ex vivo delivery of regulatory T-cells for control of alloimmune priming in the donor lung. *Eur Respir J.* 2022 Apr 14;59(4):2100798. doi: 10.1183/13993003.00798-2021. Print 2022 Apr. PMID: 34475226

Summary

Lung transplantation has the poorest survival of any allotransplant, partly resulting from a high degree of hyperinflammation and allograft injury that starts from implantation. Could one manipulate the donor lung to reduce allograft inflammation prior to transplantation?

Using an animal model, the investigator isolated, expanded in vitro, and fluorescently labelled immunomodulating polyclonal regulatory T cells (Tregs). Ex vivo lung perfusion (EVLP) was utilized to deliver the recipient's Tregs into the donor lung prior to transplantation. Florescent labelling allowed the tracking of the Tregs in the EVLP perfusate and transplanted donor lung.

Tregs entered the donor lung in a dose-dependent manner and resided in the donor lung until Day 7 post-transplantation. Interestingly, Tregs maintained their immunomodulating function based on the expression of cell surface markers. Tregs also inhibited expansion of "bad players" such as CD3+ T cells. However, the polyclonal Tregs did not reduce lung injury scores. Infusion of Tregs also did not change lung physiology parameters. In a human model, after EVLP perfusion, Tregs entered the human lung graft and maintained their immunomodulating cell-surface markers. Taken together, this study demonstrates that the lung allograft can be conditioned prior to transplantation.

Comments

1. Reducing lung allograft inflammation with EVLP has potential as a preconditioning strategy, which may reduce post-transplant allograft injury and downstream complications.
2. This proof-of-concept study demonstrates that one can indeed manipulate the donor organ without compromising lung function.
3. While Tregs maintained their immunomodulating functions, there was no reduction of lung injury expected since the Tregs used were polyclonal and not primed to identify donor antigens.
4. Fortunately, there are novel strategies available to better prime Tregs to identify donor antigens and to suppress alloimmunity without suppressing Treg function.
5. With these tools in hand, this manuscript helps lay the foundation for a new era of pre-transplant organ manipulation to improve its survival in the immunologically hostile recipient environment.

LUNG ALLOGRAFT MICROBIOME CHANGE QUICKLY AFTER IMPLANTATION AND PREDICT THE DEVELOPMENT OF PRIMARY GRAFT DYSFUNCTION

John E McGinniss, Samantha A Whiteside, Rebecca A Deek, Aurea Simon-Soro, Jevon Graham-Wooten, Michelle Oyster, Melanie D Brown, Edward Cantu, Joshua M Diamond, Hongzhe Li, Jason D Christie, Frederic D Bushman, Ronald G Collman. The Lung Allograft Microbiome Associates with Pepsin, Inflammation, and Primary Graft Dysfunction. *Am J Respir Crit Care Med*. 2022 Dec 15;206(12):1508-1521. doi: 10.1164/rccm.202112-2786OC.

Summary

This manuscript goal is to answer the question of whether the donor lung carries a baggage of microbiota that influences the post-transplant recipient allograft microbiome and contributes to poor outcomes. The investigators collected donor bronchoalveolar lavage (BAL) at organ procurement. Recipient BAL was collected within one hour of implantation. BAL from healthy controls was also collected. The BAL microbiome was determined using the 16S method. Cytokine and pepsin, a gastric content biomarker, were measured for recipient BAL, but not for donor BAL given the limited material. Recipients were stratified for primary graft dysfunction (PGD), a severe post-transplant complication. Study measures were compared between severe PGD and no PGD groups.

In total, 139 recipients were included: 109 with matched donor/recipient BAL samples. Donor microbiome was different from healthy controls. Within one hour of implantation, allograft microbiome changed into oropharyngeal microbiota that was either Prevotella or Streptococcus predominant. Prevotella abundant microbiota correlated with the risk of severe PGD and high levels of BAL pepsin levels and pro-inflammatory innate immune cytokines. On the other hand, Streptococcus abundance correlated with a low risk of PGD and low levels of BAL pepsin or inflammatory cytokines.

Comments

1. This is one of very first studies to examine donor lung microbiota and its relationship to peri-transplant microbiota and outcomes.
2. The study demonstrate that lung allograft microbiota drastically changed to primarily oropharyngeal microbiome within only one hour of implantation.
3. The oropharyngeal microbiome correlates with gastric content, implicating micro-aspiration as a primary source of allograft microbiome in the peri-transplant period.
4. The strong association with peri-transplant inflammation and PGD would suggest that allograft microbiome is either a driving force or a biomarker of peri-transplant inflammation.
5. Perhaps one can someday manipulate allograft microbiome to reduce the risk of PGD.

COULD THIS BE THE ALTERNATIVE TO SURVEILLANCE BRONCHOSCOPY THAT WE HAVE BEEN LOOKING FOR?

Keller M, Sun J, Mutebi C, Shah P, Levine D, Aryal S, Iacono A, Timofte I, Mathew J, Varghese A, Giner C, Agbor-Enoh S. Donor-derived cell-free DNA as a composite marker of acute lung allograft dysfunction in clinical care. *J Heart Lung Transplant*. 2022 Apr;41(4):458-466. doi: 10.1016/j.healun.2021.12.009. Epub 2021 Dec 26. PMID: 35063338.

Summary

Bronchoscopy plus histopathology remains the "gold standard" to monitor for lung allograft rejection. However, this invasive approach has low sensitivity and high interobserver variability. Alternative approaches to bronchoscopy have been proposed but none have progressed beyond observational studies. Forced by the SARS-COV-2 pandemic to reduce in-hospital patient contact, this work presents the first real-world experience of substituting surveillance bronchoscopy with a commercial blood test, donor-derived cell-free DNA (ddcfDNA).

The investigators first validated the commercial ddcfDNA test against their in-lab test. Building on observational study findings, they monitored a multicenter cohort of 175 recipients with routine ddcfDNA testing instead of surveillance bronchoscopy. Levels of ddcfDNA ≥1.0% served as a "danger signal" to trigger for bronchoscopy and other work-up. Levels of 0.5% - <1% served as a "warning signal" for closer monitoring with additional ddcfDNA testing. Levels of <0.5% represented quiescent state. This ddcfDNA approach avoided 83% of bronchoscopies and demonstrated excellent sensitivity and negative predictive value for detecting acute rejection and/or infection. However, the specificity to distinguish acute rejection and infection was poor. The accompanying editorial concluded that "the real-world data ...suggest that a new era of lung transplant care, born of the genomic revolution, is dawning."

Comments

1. The designation of bronchoscopy plus histopathology as "gold standard" potentially delays the development of novel monitoring strategies since this approach demonstrates low performance to detect acute rejection.
2. An ideal alternative to bronchoscopy should be sensitive, non-invasive, and broadly applicable to monitor the most common acute complications of lung transplantation, infection, and acute rejection.
3. This work builds on a foundation of observational studies to propose real-life clinical application and performance of ddcfDNA to detect both infection and rejection.
4. In fact, ddcfDNA detects acute rejection earlier than the "gold standard," potentially opening a window to intervene early before irreversible allograft dysfunction sets in.
5. While a randomized control trial is needed to establish the benefit of ddcfDNA, it is worth noting that bronchoscopy has never been tested in a trial and its designation as "gold standard" continues to be questioned.

COVID-19 VACCINATION: THORACIC TRANSPLANT PATIENTS SHOW POOR RESPONSE

Gerovasili V, Shah A, Singanayagam A, George PM, Njafuh R, Prendecki M, Carby M, Willicombe M, Kelleher P, Reed A. Impaired Humoral and Cellular Responses to COVID-19 Vaccine in Heart and Lung Transplant Recipients. *Am J Respir Crit Care Med*. 2022 Jun 15;205(12):1476-1479. doi: 10.1164/rccm.202109-2026LE. PMID: 35333143

Summary

COVID-19 has devastating outcomes in thoracic transplant patients, who are maintained on multiple and high dose immunosuppression drugs. These agents may blunt recipients' response to COVID vaccination. This study examined both humoral and cellular immune response to two SARS-COV-2 vaccines in a cohort of heart and lung transplant patients. Healthcare workers were recruited as controls. Participants received two doses of COVID-19 vaccines. After the second vaccine dose, humoral response was checked using an ELISA approach to detect antibodies to SARS-COV-2. T-cell response was tested using ELISPOT. Humoral and T-cell response was compared between transplant patients and healthcare workers.

Only 26% of the 58 thoracic transplant recipients demonstrated a positive humoral response to SARS-COV-2 vaccination. Further, responders manifested low antibody titer. T-cell response was only detected in 21% of transplant recipients, and only 7% of transplant recipients showed both T-cell and humoral responses. The type of SARS-COV-2 vaccine mattered, with BNT162b2 showing greater response compared to ChAdOx1. In contrast, 100% and 91% of healthcare workers showed positive humoral and T-cell responses, respectively.

Comments

1. Despite the small sample size, the low rate of SARS-COV-2 vaccine response is consistent with other studies and clinical experience in lung transplantation.
2. This study examines both humoral and T-cell responses, providing a more complete immune profile compared to other studies.
3. Of note, these patients were maintained on mycophenolate mofetil, which has been shown to reduce SARS-COV-2 serologic response.
4. The study was further limited by a lack of data on neutralizing antibodies and clinical outcomes.
5. Nonetheless, the low response to SARS-COV-2 vaccine calls for development of novel strategies to improve vaccination response in these highly immunosuppressed patients.

FINALLY, A FRAILITY SCORE TAILORED FOR LUNG TRANSPLANT PATIENTS

Singer JP, Christie JD, Diamond JM, Anderson MA, Benvenuto LA, Gao Y, Arcasoy SM, Lederer DJ, Calabrese D, Wang P, Hays SR, Kukreja J, Venado A, Kolaitis NA, Leard LE, Shah RJ, Kleinhenz ME, Golden J, Betancourt L, Oyster M, Zaleski D, Adler J, Kalman L, Balar P, Patel S, Medikonda N, Koons B, Tevald M, Covinsky KE, Greenland JR, Katz PK. Development of the Lung Transplant Frailty Scale (LT-FS). *J Heart Lung Transplant*. 2023 Feb 20: S1053-2498(23)00049-9. doi: 10.1016/j.healun.2023.02.006. Online ahead of print. PMID: 36925382

Summary

Frailty is an important risk factor of early mortality in lung transplantation and other diseases. However, existing frailty scales are less suitable for lung transplant recipients since the scales were developed decades ago for community dwelling older adults. This multicenter study developed and tested a lung transplant frailty scale (LT-FS) in a multicenter cohort of lung transplant recipients. The study measured multiple biometric, functional and serum biomarkers that have been implicated in frailty. The measures were incorporated into a well validated 4-step approach for scale development. The approach began with individual frailty domain measures and ended with multidimensional frailty scales. The construct and predictive validity of these scales was compared to two existing frailty scales: - Short Physical Performance Battery (SPPB) and Fried Frailty Phenotype scales (FFP).

The novel LT-FS demonstrated better performance compared to SPPB and FFP. Specifically, in the cohort of

342 lung transplant candidates, LT-FS predicted waitlist delisting and pre-transplant mortality better than SPPB and FFP. Addition of body composition to LT-FS improved the predictive performance for both waitlist delisting and pre-transplant mortality. Finally, pre-transplant LT-FS-body composition scale was associated with post-transplant survival; SPPB and FFP demonstrated no association to post-transplant survival.

Comments

1. The LT-FS is an updated and disease-specific frailty scale applicable to lung transplant candidates.
2. The LT-FS demonstrated excellent predictive performance for both pre- and post-transplant survival.
3. The finding of this study implicates frailty as an important risk in lung transplantation and joins the growing international call to include frailty as part of pre-transplant candidate evaluation.
4. Validating the LT-FS in other lung transplant cohorts is important and may lead to broader clinical utility and incorporation of frailty measures into lung transplant candidate selection algorithm.

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Medical Education

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DIVERSITY, EQUITY AND INCLUSION

Banerjee D, Nassikas NJ, Singh P, Andrea SB, Zhang AY, Aswad Y, Singh N, Walsh SR, Cox-Flaherty K, Carter EJ, Sharkey KM. **Feasibility of an Antiracism Curriculum in an Academic Pulmonary, Critical Care, and Sleep Medicine Division.** *ATS Sch*. 2022 Sep 30;3(3):433-448.

Summary

This was a pre- and post pilot study in which the authors piloted a year-long antiracism curriculum focusing on individual, institutional, and systemic racism in a PCCSM division in a large tertiary center. Participants - 41 division faculty members and 12 fellows - were invited to attend training sessions and complete an electronic survey pre and post-curriculum. The curriculum consisted of 13 1-hour virtual workshops over the course of the academic year scheduled during an existing didactic timeslot. A total of 27 faculty members and 11 fellows responded to the pre-curriculum survey (response rate 72%) and 28 completed both pre- and post-curriculum surveys. Most participants acknowledged that racism occurs in medicine and has consequences for providers and patients, and 28 (74%) reported wanting a structured curriculum. The mean attendance for the curriculum was 28 users, with median attendance of 6 of the 13 sessions (IQR 4–9). The belief that discrimination exists in Medicine (95% of respondents) and impacts health outcomes (83%), did not change with training. In the post-curriculum survey, 14% fewer respondents wanted a continued structured antiracism curriculum. There was a weak positive change in perceived knowledge and comfort with talking about race and being actively involved in advancing racial equity.

Comments

1. This study highlights a high level of interest among fellows and faculty in an antiracist curriculum, in accordance with the ACGME's call for education on health inequity and reveals a nearly unanimous belief that racism is present in medicine and impacts patient care.
2. The delivery format, based on one-hour interactive sessions with small group discussions over the course of a year contributed to feasibility and increased effectiveness
3. The authors credit the successful implementation to several factors, including scheduling at a preexisting didactic timeslot, no need for additional funding, prior interest in having a curriculum on antiracism, and leadership role-modeling.
4. The absence of significant change in knowledge-based items and attitudes post-curriculum needs to be addressed to increase sustainability and implementation in other institutions.
5. Limitations include a single center design, few knowledge-based questions to measure the efficacy of the curriculum, and lack of inclusion of other healthcare workers.

CLINICIAN WELL-BEING AND BURNOUT

Leitman IM, Muller D, Miller S, Hanss BG, Catron TF, Cooper WO, Filizola M. **Implementation of an Online Reporting System to Identify Unprofessional Behaviors and Mistreatment Directed at Trainees at an Academic Medical Center.** *JAMA Netw Open*. 2022 Dec 1;5(12):e2244661.

Summary

This study describes the design and implementation of an unprofessional behavior reporting tool and policies to review and handle incidents while providing confidentiality and protecting trainees from retaliation at a large academic medical center. Participants included 2900 faculty, 600 medical students, more than 1000 graduate students and postdocs, and 2600 residents and fellows. In approximately two years,

trainees submitted 173 reports of unprofessional interactions, 60 (35%) were from medical students and 96 (56%) were from residents and fellows. Most negative reports described behaviors by faculty (61%). The most common negative feedback reported was publicly embarrassment or humiliation (55%), offensive remarks related to gender, sexual orientation, national origin, race, color, religion (33%) and denied opportunities for training or rewards on the basis of membership in a protected group (9%). Most (94%) reports were handled by a single discussion with the subject of the report and 10 (6%) were escalated to written warning or modification of faculty duties. Fourteen reported faculty (8%) were referred for a physician wellness evaluation. Following its implementation, most trainees have become aware of the process and those who expressed their concerns through the online system reported satisfaction with the results.

Comments

1. The majority of the reports of mistreatment or unprofessional behavior are from residents and fellows, most often directed to faculty.
2. Although 90% of faculty did not receive any reports, 20 faculty (less than 1%) accounted for half of the reports.
3. Endorsement from the leadership combined with trainee representation in every step of development and implementation played a significant role to successful implementation
4. The reporting system was implemented in a single large urban academic center, with considerable investment of time and resources, and may not be generalizable to other institutions
5. The authors acknowledge a persisting perception among trainees, especially graduate students and postdocs, that reporting mistreatment and unprofessional behavior may not be safe due to a belief that no action will be taken, and fear of retaliation.

CLINICAL TRAINING

Young AC, Butts C, deBoisblanc BP, Tejedor RS, Kantrow SP, Lammi MR. **Implementation of a Longitudinal Critical Care Fellowship Ultrasound Curriculum.** *ATS Sch.* 2022 Jan 28;3(1):125-134.

Summary

This was a prospective observational study of a longitudinal POCUS training program for pulmonary and critical care medicine (PCCM) fellows at an academic center. Before the study, ultrasound skills were taught informally only on inpatient teaching rounds. The curriculum consisted of 6 didactic lectures and 2 hands-on skills sessions. Training was repeated at 6 and 18 months, and monthly practice sessions were also offered. Participants were assessed before and after each training session, and at 12 months with written examinations and a hands-on skills assessment. In addition, participants self-rated their confidence in POCUS skills. Twenty-two fellows participated and were followed for 18 months. Participants were grouped by their training levels (first-, second-, and third-year fellows), and all training levels improved their knowledge, confidence and POCUS skills after the course, with first-year fellows having the greatest increase. Improvements in POCUS knowledge, confidence, and skills compared to baseline were retained after 12 months. At 18 months, knowledge was maintained while confidence continued to increase. Knowledge and skills scores were significantly higher among fellows exposed to 1 year of formal training compared with fellows exposed to 1 year of informal training, while confidence was similar for these groups.

Comments

1. A formal POCUS curriculum led to greater increases in knowledge and skills compared to informal training and supports the incorporation of formal curriculum into a PCCM fellowship programs
2. Knowledge, skills and confidence gains were high, and retained after 12 months
3. First year fellows benefitted the most from the training, but repetition at 18 months was considered important to maximize retention and increase confidence
4. Limitations include the small sample size and single-center design

ASSESSMENT

Schultz K, McGregor T, Pincock R, Nichols K, Jain S, Pariag J. **Discrepancies Between Preceptor and Resident Performance Assessment: Using an Electronic Formative Assessment Tool to Improve Residents' Self-Assessment Skills**. *Acad Med*. 2022 May 1;97(5):669-673.

Summary

This Family Medicine residency program in Canada implemented a system to provide formative and summative assessments using electronic field notes that document a resident's performance in clinical encounters and summarize the preceptor's feedback given about his or her performance during that encounter. Field notes are initiated by the resident and also capture self-assessment of competence for that particular knowledge or skill at one of the 4 levels: flagged (concerning behavior), needing close supervision, minimal/reactive supervision, or supervision for refinement only. Fields notes are then reviewed by the preceptor and modified as needed before submission. A software identified field notes where the level of competence was discordant between resident self-assessment and preceptor's assessment. From 2011–2019, 11,429 field notes were submitted by 1120 residents, with 3200 (28%) showing discordance between residents' and preceptors' performance assessments. Residents assessed their performance as less competent (undercalled) than their preceptor 73% of the time and overcalled it in 27% of discordant notes. Only six residents overcalled performance to a dangerous extent (2 or 3 levels of supervision higher than what their supervisors) and 26 repeatedly (greater than 5 times) overcalled their level of performance by 1 supervisory level.

Comments

1. This study reveals a high rate of discordance between resident self-assessment and preceptor assessment, with residents more often undercalling their performance.
2. The findings highlight the need to include deliberate curriculum to foster self-assessment as a critical skill in competency-based medical education
3. Consistent underconfidence in self-assessment can lead to residents restricting their practice, overuse of resources and increased anxiety among trainees.
4. There were only a few residents who significantly or repeatedly overcalled their performance but identifying such cases provides an opportunity for discussing discrepancies and working towards better self-assessment to decrease risks to patient safety.
5. The study did not include associations between self-assessment discrepancies with need for resident remediation or patient safety outcomes.

FACULTY DEVELOPMENT

Viglianti EM, Admon AJ, Carlton EF, Denstaedt SJ, Valley TS, Costa DK, Cooke CR, Dickson R, Iwashyna TJ, Prescott HC. **Development and Retention of Early-Career Clinician-Scientists through a Novel Peer Mentorship Program: Multidisciplinary Intensive Care Research Workgroup**. *ATS Sch*. 2022 Oct 4;3(4):588-597.

Summary

This study describes the creation, implementation and results of a multidisciplinary and interprofessional peer-mentoring group for early-career researcher focused on critical care in an academic center. The group has a formal structure, mission statement, application process and clear expectations for participation. The group meets for 90 minutes twice a month and starts with accountability rounds, in which each member identifies two research goals to accomplish by the next meeting, followed by two 30-minute presentations of work in progress for group feedback. The group has been meeting regularly since 2015 despite the expected turnover (members graduate when they obtain independent funding). Out of the 30 members of the group, 15 are active members, 8 have graduated, and 7 are former members. Almost all (29 out of 30) continue to pursue careers in academic medicine, and all 30 individuals remain actively involved in research. Satisfaction was measured with an anonymous survey (22 responses out of 26 sent). Most members felt MICReW created an environment that fostered diverse thoughts (95%, n=21/22), constructive feedback (91%, n=20/22), provided them with a supportive environment (91%, n=20/22), and

benefitted them personally in their academic research careers (95%, n=21/22).

Comments

1. This peer-mentoring group has been sustainable for several years and half of its members have obtained independent funding after participation in the group
2. Participation in the program was associated with high retention rate of early-career researchers in academia
3. The study design and risk of selection bias do not allow for an accurate assessment of the program's direct impact on retention and career success.
4. Peer-mentoring complemented traditional mentorship needs for early-career scientists and provided an environment rated as supportive and beneficial to academic careers of its members

OTHER ARTICLES OF INTEREST

DIVERSITY, EQUITY AND INCLUSION

Ravenna PA, Wheat S, El Rayess F, McCrea L 2nd, Martonffy AI, Marshall C, Tepperberg S, Friedman RSC, Barr WB. **Diversity, Equity, and Inclusion Milestones: Creation of a Tool to Evaluate Graduate Medical Education Programs.** *J Grad Med Educ*. 2022 Apr;14(2):166-170.

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Santhosh L, Rojek AE, Yim JWL, Lisker S, Wang K, Dy M, Sarkar U. **Analysis of Narrative Text in Evaluations of Continuing Medical Education Faculty by Gender.** *JAMA Netw Open*. 2022 Aug 1;5(8):e2227948.

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CLINICIAN WELL-BEING AND BURNOUT

Fainstad T, Mann A, Suresh K, Shah P, Dieujuste N, Thurmon K, Jones CD. **Effect of a Novel Online Group-Coaching Program to Reduce Burnout in Female Resident Physicians: A Randomized Clinical Trial.** *JAMA Netw Open*. 2022 May 2;5(5):e2210752. Erratum in: JAMA Netw Open. 2022 Jun 1;5(6):e2220348.

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O'Marr JM, Chan SM, Crawford L, Wong AH, Samuels E, Boatright D. **Perceptions on Burnout and the Medical School Learning Environment of Medical Students Who Are Underrepresented in Medicine.** *JAMA Netw Open*. 2022 Feb 1;5(2):e220115.

CLINICAL TRAINING

Santhosh L, Rojas JC, Garcia B, Thomashow M, Lyons PG. **Cocreating the ICU-PAUSE Tool for Intensive Care Unit-Ward Transitions**. *ATS Sch.* 2022 Apr 5;3(2):312-323.

Krumm IR, Miles MC, Clay A, Carlos Ii WG, Adamson R. **Making Effective Educational Videos for Clinical Teaching**. *Chest.* 2022 Mar;161(3):764-772.

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Camac E, Stewart N, Santhosh L, Carlos WG, Denson JL, Heath J. **Best Practices for Remediation in Pulmonary and Critical Care Medicine Fellowship Training.** *ATS Sch.* 2022 Aug 31;3(3):485-500.

ASSESSMENT

Hayashi FK, Sousa MLA, Garcia MVF, Macedo BR, Ferreira JC. **Simulation-based Assessment to Measure**

Proficiency in Mechanical Ventilation among Residents. *ATS Sch*. 2022 Jun 30;3(2):204-219.

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FACULTY DEVELOPMENT

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Health Equity

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SPIROMETRY RACE CORRECTION

Elmaleh-Sachs A, Balte P, Oelsner EC, Allen NB, Baugh A, Bertoni AG, Hankinson JL, Pankow J, Post WS, Schwartz JE, Smith BM, Watson K, Barr RG. **Race/Ethnicity, Spirometry Reference Equations, and Prediction of Incident Clinical Events: The Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study.** *Am J Respir Crit Care Med*. 2022 Mar 15;205(6):700-710. doi: 10.1164/rccm.202107-1612OC. PMID: 34913853.

Summary

Normal values for FEV1 and FVC are currently calculated using cross-sectional reference equations that include terms for race/ethnicity, an approach that may reinforce disparities and is of unclear clinical benefit. Many clinical thresholds for disease diagnosis (e.g., blood pressure, lipids) are based upon their ability to predict incident clinical events. The authors used a similar approach to test the utility of race/ethnicity-based spirometry reference equations for predicting incident chronic lower respiratory disease (CLRD) events and mortality compared with race/ethnicity-neutral equations in the MESA Lung Study, a population-based, prospective cohort study. Standardized spirometry was performed between 2004-2006. Predicted values for spirometry were calculated using the guideline-recommended GLI race/ethnicity-based equations and, alternatively, race/ethnicity-neutral equations without terms for race/ethnicity (GLI "Other" equations). Participants were followed through 2019. The mean age of 3,344 participants was 65 years, and self-reported race/ethnicity was 36% White, 25% Black, 23% Hispanic, and 17% Asian. There was no evidence that percentage predicted FEV1 or FVC calculated using race/ethnicity-based equations improved the prediction of CLRD-related events compared with those calculated using race/ethnicity-neutral equations. Findings were similar for mortality. The authors conclude that the inclusion of race/ethnicity in spirometry reference equations should be reconsidered.

Comments

1. Population-based, multi-ethnic prospective cohort study of incident (validated) chronic lower respiratory disease (CLRD) events and all-cause mortality with high follow-up.
2. No evidence that the currently recommended race/ethnicity-based spirometry reference equations for FEV1 and FVC were of clinical benefit compared to currently available race/ethnicity-neutral reference equations (GLI "Other").
3. Given the observed lack of clinical benefit and known harm of race-based medicine, clinicians should consider using race/ethnicity-neutral alternatives.

SPIROMETRY RACE CORRECTION

Baugh AD, Shiboski S, Hansel NN, Ortega V, Barjaktarevic I, Barr RG, Bowler R, Comellas AP, Cooper CB, Couper D, Criner G, Curtis JL, Dransfield M, Ejike C, Han MK, Hoffman E, Krishnan J, Krishnan JA, Mannino D, Paine R 3rd, Parekh T, Peters S, Putcha N, Rennard S, Thakur N, Woodruff PG. **Reconsidering the Utility of Race-Specific Lung Function Prediction Equations.** *Am J Respir Crit Care Med*. 2022 Apr 1;205(7):819-829. doi: 10.1164/rccm.202105-1246OC. Erratum in: Am J Respir Crit Care Med. 2022 Jul 15;206(2):230. PMID: 34913855; PMCID: PMC9836221.

Summary

In a cohort with and at risk for chronic obstructive pulmonary disease (COPD), the authors assessed whether lung function prediction equations applied in a race-specific versus universal manner better modeled

the relationship between FEV1, FVC, and other COPD outcomes, including the COPD Assessment Test, St. George's Respiratory Questionnaire, computed tomography percent emphysema, airway wall thickness, and 6-minute-walk test. Using race-specific equations, African American individuals were calculated to have better lung function than non-Hispanic White individuals (FEV1, 76.8% vs. 71.8% predicted; P = 0.02). Using universally applied equations, African American individuals were calculated to have worse lung function. Prediction errors from linear regression were less for universally applied equations compared with race-specific equations when examining FEV1% predicted with the COPD Assessment Test (P < 0.01), St. George's Respiratory Questionnaire (P < 0.01), and airway wall thickness (P < 0.01). This study suggests that race-specific lung function equations may underestimate COPD severity in African American individuals.

Comments

1. African American individuals had lower percent predicted FEV1 when using race-specific versus universal equations.
2. The utility of FEV1 in predicting COPD severity and radiographic correlates of COPD was higher when using universally applied versus race-specific equations.
3. Race-specific lung function equations may underestimate COPD severity in African American individuals.

PULMONARY HEALTH POLICY EVALUATION

Lemire E, Samuels EA, Wang W, Haber A. **Unequal Housing Conditions And Code Enforcement Contribute To Asthma Disparities In Boston, Massachusetts.** *Health Aff (Millwood).* 2022 Apr;41(4):563-572. doi: 10.1377/hlthaff.2021.01403. PMID: 35377754.

Summary

Housing quality is a primary determinant of asthma disparities by race and class in the United States (US). The authors assessed how housing code enforcement systems in a US city addressed tenants' reports of asthma triggers (rodents, roaches, mold, and insufficient heat). After adjustment for income and neighborhood characteristics, racial demographics were significantly associated with trigger incidence. For each 10 percent decrease in neighborhood proportion of White residents, trigger incidence increased by 3.14 reports per thousand residents. These disparities persisted during the study period (2011-2021), and for mold, an established asthma trigger, racial disparities in reported exposure widened. The municipal response also demonstrated disparities: In neighborhoods with the fewest White residents compared to neighborhoods with the most, adjusted models showed a 17 percent (3.51 days) slower median time until cases (tenant requests for inspections to the Inspectional Services Department) were closed, a 14 percent higher probability of being flagged as overdue, and a 54.4 percent lower probability of a repair. We found that in Boston, current regulatory systems are insufficient to address disparities in healthy housing. To reduce asthma disparities, stronger inspectional standards and further enforcement policies to increase landlords' accountability and support tenants' rights to have repairs made are essential.

Comments

1. Asthma-inducing exposures to household triggers were different by race and class.
2. The median time to a definitive municipal response for addressing household triggers was longer in neighborhoods with the fewest White residents compared to neighborhoods with the most.
3. Given the established role of indoor air quality as a key factor in development and severity of asthma, these findings demonstrate that urban housing markets and associated code enforcement systems continue to drive asthma disparities.
4. As a primary determinant of a range of health outcomes, particularly respiratory health, the right to healthy housing must be upheld by stronger code enforcement and provision of high-quality public housing.

PULMONARY HEALTH POLICY EVALUATION

Asare S, Majmundar A, Westmaas JL, Bandi P, Xue Z, Jemal A, Nargis N. **Association of Cigarette Sales With Comprehensive Menthol Flavor Ban in Massachusetts.** *JAMA Intern Med*. 2022 Feb 1;182(2):231-234. doi: 10.1001/jamainternmed.2021.7333. PMID: 34982100; PMCID: PMC8728656.

Summary

In April 2021, the US Food and Drug Administration announced its intention to ban menthol flavors from cigarettes and cigars. Before this announcement, Massachusetts was the only state to implement a statewide comprehensive flavor ban on tobacco products in June 2020. The authors used a difference-in-differences design to examine temporal changes in cigarette sales in Massachusetts before (January 2017 to May 2020) and after (June 2020 to July 2021) the comprehensive flavor ban, in comparison with 27 states that did not enact similar bans. After the flavor ban, the adjusted 4-week sales of cigarettes in Massachusetts vs the comparison states decreased by 372.27 (95% CI, −428.90 to −315.64; P < .001) packs per 1000 people for menthol cigarettes but increased by 120.25 (95%CI, 72.61-167.88; P < .001) packs per 1000 people for nonflavored cigarettes. Overall, the adjusted 4-week sales of all cigarettes decreased by 282.65 (95%CI, −356.07 to −209.23; P < .001) packs per 1000 people in Massachusetts vs the comparison states.

Comments

1. Cigarettes are a leading cause of preventable death and disability.
2. In the United States, there are large socioeconomic disparities in the prevalence of cigarette smoking.
3. This study used causal inference methods to evaluate the effect of a policy regulating the sale of flavored tobacco products.
4. A state-wide ban on the sale of menthol flavored cigarettes and cigars led to a significant net reduction in cigarette sales.
5. Structural solutions are needed to mitigate health inequities and improve health.

BIASED DIAGNOSTIC HEURISTICS

Modra LJ, Higgins AM, Pilcher DV, Bailey MJ, Bellomo R. **Sex Differences in Mortality of ICU Patients According to Diagnosis-related Sex Balance**. *Am J Respir Crit Care Med*. 2022 Dec 1;206(11):1353-1360. doi: 10.1164/rccm.202203-0539OC. PMID: 35849500; PMCID: PMC9746862.

Summary

The authors examined the differences in hospital mortality of women and men admitted to adult ICUs in Australia and New Zealand. Between 2011 and 2020, there were 1.45 million eligible ICU admissions (42.1% women). There was no difference in the hospital mortality of women and men in the study population overall, after adjustment for illness severity, admission diagnosis, time in hospital before ICU admission, admission year and hospital site using a mixed effect logistic regression model. However, there was substantial variation in the adjusted hospital mortality of women compared to men across diagnostic groups of ICU patients. Among patients admitted following cardiac surgery, women were more likely to die than men (adjusted OR 1.63, 99% CI 1.45–1.82). Among patients admitted with metabolic, renal or hematologic disorders, men were more likely to die than women (adjusted OR 0.87, 99% CI 0.81-0.94). There was an association between sex balance (% female patients) within a diagnostic group and the mortality of women compared to men with that same diagnosis. In diagnoses with more men, women were relatively more likely to die; in diagnoses with more women, men were more likely to die – a finding that may be attributable to clinician cognitive bias.

Comments

1. ICU admission diagnosis is important when considering sex differences in outcomes from critical illness.
2. The most significant sex difference in mortality was in the cardiac surgery category (bypass graft and valvular heart surgery).
3. Patients presenting with illnesses less common for their sex tended to be sicker and more likely to die than the opposite sex.

4. This may represent a sex-based volume-outcome relationship that is mediated by clinician cognitive bias, in which clinicians treat patients with illnesses expected for their sex more promptly or effectively.

GLOBAL MEDICAL OXYGEN SECURITY

Simkovich SM, Underhill LJ, Kirby MA, Crocker ME, Goodman D, McCracken JP, Thompson LM, Diaz-Artiga A, Castañaza-Gonzalez A, Garg SS, Balakrishnan K, Thangavel G, Rosa G, Peel JL, Clasen TF, McCollum ED, Checkley W; HAPIN Investigators. **Resources and Geographic Access to Care for Severe Pediatric Pneumonia in Four Resource-limited Settings.** *Am J Respir Crit Care Med*. 2022 Jan 15;205(2):183-197. doi: 10.1164/rccm.202104-1013OC. PMID: 34662531; PMCID: PMC8787246.

Summary

Severe cases of pneumonia, such as those marked with clinical features of hypoxemia, carry the highest risk of morbidity and mortality. Early diagnosis and treatment of severe pneumonia are associated with reduced mortality. There are limited data on the geographic accessibility of facilities that are adequately resourced to care for severe pediatric pneumonia in low-and middle-income countries. This is the first study to characterize the geographic accessibility of adequately resourced healthcare facilities to manage severe pediatric pneumonia in low- and middle-income country settings. The authors found inconsistent levels of resources across facilities and significant heterogeneity in the availability of healthcare personnel, equipment, and medications in non-hospital facilities. Although most of the population at each site had access to a facility within 30 minutes of travel time, few healthcare facilities were adequately resourced to manage severe pneumonia. Expanding the availability of pulse oximetry devices to all facilities may be an effective approach to identify cases earlier and refer them for care in a timely manner.

Comments

1. Utilized the HAPIN (Household Air Pollution Intervention Network) trial infrastructure with sites in Guatemala, Peru, Rwanda, and India.
2. Conducted a survey of 350 public and private health facilities that queried the type of facility; hours of operation; availability of inpatient beds, healthcare personnel, equipment, medications, vaccines; and implementation of cold-chain protocols.
3. Used a consensus definition to identify facilities that were adequately resourced to manage severe pediatric pneumonia, which comprised being open daily and having overnight beds, an available physician, a pulse oximeter, supplemental oxygen, respiratory support devices (i.e., non-invasive or invasive mechanical ventilation), X-ray or ultrasound capacity, and antibiotics.
4. Of the facilities surveyed, 13% were adequately resourced to manage severe pneumonia, 37% had pulse oximeters, and 44% had supplemental oxygen, and mean travel time to an adequately resourced facility ranged from 31 to 99 minutes across sites.
5. This article demonstrates highlights an urgent need to ensure global medical oxygen security, and demonstrates the importance of mixed-methods and qualitative and research for understanding mechanisms of health care inequities.

OTHER ARTICLES OF INTEREST

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Cystic Fibrosis and Non-Cystic Fibrosis Bronchiectasis

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REAL-WORLD EXPERIENCE WITH ELEXACAFTOR/IVACAFTOR/TEZACAFTOR MIRRORS CLINICAL TRIAL EVIDENCE

Nichols, DP, Paynter, AC, Heltshe SL, Donaldson SH, Frederick CA, Freedman SD, Gelfond D, Hoffman, LR, Kelly A, Narkewicz MR, Pittman JE, Ratjen F, Rosenfeld M, Sagel SD, Schwarzenberg SJ, Singh PK, Solomon GM, Stalvey MS, Clancy JP, Kirby S, Van Dalfsen, JM, Kloster MH, Rowe SM, the Promise Study Group. **Clinical effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis a clinical trial.** *Am J Respir Crit Care Med.* 2022;205(5):529-39.

Summary

In controlled clinical trials, the triple CFTR modulator elexacaftor/tezacaftor/ivacaftor (ETI) resulted in dramatic improvements in FEV1, sweat chloride and respiratory symptoms in people with cystic fibrosis (PwCF) and an F508del allele. ETI has the potential to treat the majority of PwCF and its use has become widespread in many developed countries. The post-approval PROMISE study (Prospective Study to Evaluate Biological and Clinical Effects of Significantly Corrected CFTR Function) is being conducted at multiple US sites and aims to investigate the effectiveness of ETI in a real-world setting, out to 30 months. The primary outcomes are change in sweat chloride and percent-predicted FEV1 ($ppFEV_1$). This planned 6 month interim analysis found that among 487 PwCF ≥12 years with ≥ 1 F508del allele, $ppFEV_1$ improved 9.76% (95% CI 8.76 to 10.76), and sweat chloride decreased by 41.7mmol/L (95% CI, 43.8 to 39.6). Further, the cystic fibrosis questionnaire–revised respiratory domain (CFQ-R RD) score improved 20.4 points (95% CI, 18.3 to 22.5, MCID 4). Prespecified subgroup analysis stratified by baseline CFTR modulator use (none – 49%; ivacaftor – 7%; dual modulator – 44%) showed that improvements were most pronounced in modulator-naïve patients, but were substantial in all subgroups. No new safety signals were observed.

Comments

1. These data show improvements of a similar magnitude to the RCTs in a real-world setting and provide confidence in the generalizability of the RCT findings in a broader population, especially those with very mild or severe disease who were excluded from the clinical trials.
2. One third of patients had the maximum CFQ-R RD score at 6 months, suggesting resolution of chronic respiratory symptoms in many patients on ETI.
3. Despite encouragement to remain on usual therapy, by 6 months, the proportion using dornase alfa decreased by 6%, hypertonic saline by 9.8%, azithromycin by 9.1%, and inhaled antibiotics by 34%, showing the need for further evidence regarding safety of cessation of usual therapies.
4. Additional 18- and 30-month timepoints are planned and trial design includes several sub-studies investigating the microbiological and real-world extrapulmonary effects of ETI.

REDUCING TREATMENT BURDEN IN THOSE ON CFTR MODULATORS – SAFE IN THE SHORT TERM?

Mayer-Hamblett N, Ratjen F, Russell R, Donaldson SH, Riekert KA, Sawicki GS, Odem-Davis K, Young JK, Rosenbluth D, Taylor-Cousar JL, Goss CH, Retsch-Bogart G, Clancy JP, Genatossio A, O'Sullivan BP, Berlinski A, Millard SL, Omlor G, Wyatt CA, Moffett K, Nichols DP, Gifford AH; SIMPLIFY Study Group. **Discontinuation versus continuation of hypertonic saline or dornase alfa in modulator treated people with cystic fibrosis (SIMPLIFY): results from two parallel, multicentre, open-label, randomised, controlled, non-inferiority trials.** *Lancet Respir Med.* 2022:S2213-2600(22)00434-9.

Summary

Elexacaftor/tezacaftor/ivacaftor (ETI) substantially restores CFTR protein function and improves mucociliary clearance, thereby reducing sputum load. In PwCF on ETI, cessation of burdensome nebulized therapies has been observed in real-world trials and clinical practice, but whether it is safe to stop chronic therapies is unclear. The SIMPLIFY study aimed to assess the non-inferiority of ceasing either nebulized hypertonic saline or dornase alfa in those on ETI. Two parallel, multicentre, open-label, randomised, controlled trials were conducted at 80 US sites and included 594 participants ≥12years, on stable therapy with ETI plus ≥3% hypertonic saline and/or dornase alfa. Participants were randomly assigned to either continue or cease hypertonic saline or dornase alfa for 6 weeks. This non-inferiority trial examined whether there was more than a 3% difference in $ppFEV_1$ between groups (continue vs. cease) at 6 weeks. In the per protocol population, discontinuing treatment was non-inferior to continuing treatment in both the hypertonic saline trial (between-group difference in $ppFEV_1$ −0·32% [95% CI −1·25 to 0·60]) and dornase alfa trial (between-group difference in $ppFEV_1$ 0·35% [95% CI −0·45 to 1·14]).

Comments

1. Although promising, generalizability to clinical practice is limited as the trial was of short duration and the study population had near-normal lung function (mean $ppFEV_1$ of 97%) and minimal symptoms (mean CFQ-R RD >94, maximum possible score 100) at baseline.
2. Lung clearance index at 2·5% of the starting gas concentration ($LCI_{2·5}$) which is a more sensitive marker of lung function in people with mild disease was measured in 27% of the study population and no significant between- group difference was found at 6 weeks.
3. No serious adverse events were seen, however there were more respiratory adverse events in patients who discontinued mucoactive therapies (~2-fold increase in those who discontinued dornase alfa; ~1·5-fold in those who discontinued hypertonic saline), particularly in the small subgroup of patients with $ppFEV_1$ below 70.
4. The trial intentionally recruited a very adherent patient group, which does not reflect the real-world situation but strengthens the non-inferiority findings of the study.
5. This first, important study to examine discontinuation of mucoactive treatment in the CFTR modulator era shows that decreasing the burden of therapy by stopping either dornase alfa or hypertonic saline appears safe in a population with mild disease, at least in the short term – the results of HERO-2 and CF STORM are awaited.

PHAGE THERAPY FOR TREATMENT-REFRACTORY MYCOBACTERIAL INFECTIONS

Dedrick RM, Smith BE, Cristinziano M, Freeman KG, Jacobs-Sera D, Belessis Y, Whitney Brown A, Cohen KA, Davidson RM, van Duin D, Gainey A, Garcia CB, Robert George CR, Haidar G, Ip W, Iredell J, Khatami A, Little JS, Malmivaara K, McMullan BJ, Michalik DE, Moscatelli A, Nick JA, Tupayachi Ortiz MG, Polenakovik HM, Robinson PD, Skurnik M, Solomon DA, Soothill J, Spencer H, Wark P, Worth A, Schooley RT, Benson CA, Hatfull GF. **Phage therapy of mycobacterium infections: compassionate use of phages in 20 patients with drug-resistant mycobacterial disease.** *Clin Infect Dis.* 2023;76(1):103-112.

Summary

In patients with CF and bronchiectasis, non-tuberculous mycobacterial (NTM) infection is increasingly common and poses a significant treatment challenge due to intrinsic antibiotic resistance. Bacteriophage therapy is a novel treatment approach and case reports have suggested a good safety profile and microbiological efficacy. However, relatively few active lytic phages are available, the variation in phage susceptibility of mycobacterial isolates necessitates phage personalization, and the development of phage resistance or phage-neutralizing antibodies is of potential concern. Dedrick *et al.* present their experience of compassionate phage therapy in 20 patients with treatment-refractory NTM. Of 200 mycobacterial isolates received from culture-positive patients, lytic phage/s were identified for 55 patients. Patients eligible for treatment were those >5yrs with NTM-pulmonary disease or disseminated disease, with

failure or intolerance of antimycobacterial therapy. Ultimately, 20 patients received phage therapy (predominantly intravenously +_ aerosolized/topical) in combination with at least 2 appropriate antimycobacterial drugs for a planned duration of 6 months, although this was individualized depending on clinical and microbiological response. Favourable clinical or microbiological response was observed in 11 patients (of whom 5 had sustained negative mycobacterial cultures and 1 underwent successful lung transplantation); 5 had inconclusive results; 4 had no response. No phage-attributable adverse reactions were noted.

Comments

1. Of the 20 patients offered treatment, 17 had *M. abscessus* infection and 14 had underlying cystic fibrosis.
2. A favourable response was defined as mycobacterial smear and culture conversion to negative in at least 1 relevant specimen and clinical and/or radiographic improvement, or resolution of signs and symptoms of infection after at least 6–8 weeks of phage treatment.
3. No phage resistance was detected, even in 11 patients who received therapy with a single phage.
4. Neutralizing antibodies were identified in the sera of 8 patients after IV administration but did not always result in an unfavourable response.
5. This large case series demonstrates the potential of phage therapy for refractory NTM disease and highlights ongoing questions around pharmacodynamics, tissue penetration, optimal dose and route of administration for phage therapy.

NEBULIZED TOBRAMYCIN IN BRONCHIECTASIS

Guan WJ, Xu JF, Luo H, Xu XX, Song YL, Ma WL, Liang ZA, Liu XD, Zhang GJ, Zhang XJ, Li RK, Zhu SY, Zhang YJ, Cai XJ, Wei LP, Tian DB, Zhao H, Chen PY, Qu JM, Zhong NS; TORNASOL Study Group. **A double-blind randomized placebo-controlled phase 3 trial of tobramycin inhalation solution in adults with bronchiectasis with *Pseudomonas aeruginosa* infection.** *Chest.* 2023;163(1):64-76.

Summary

Inhaled antibiotics in patients with bronchiectasis have been shown to provide a modest reduction in exacerbation frequency in meta-analyses and are recommended in international guidelines for select patients with frequent exacerbations. However, individual RCT results have often not reached statistical significance for the clinical endpoints. The TORNASOL (Tobramycin in Bronchiectasis Colonized With Pseudomonas aeruginosa) study aimed to evaluate safety and efficacy of tobramycin inhalation solution (TIS) in adults with bronchiectasis and chronic *P. aeruginosa* infection. This 16-week multicentre study included 339 participants who received randomised treatment with either nebulized TIS or normal saline, for 2 cycles of 28 days on/28 days off. The coprimary end points were change in *P. aeruginosa* density and Quality-of-Life Bronchiectasis Respiratory Symptoms score (QoLB-RSS) on day 29, compared to baseline. On day 29, TIS significantly reduced *P. aeruginosa* density (adjusted mean difference 1.74 $\log_{10}$ colony-forming units/g; 95% CI 1.12-2.35) and improved QoLB-RSS (adjusted mean difference 7.91; 95% CI 5.72-10.11) which was statistically significant but fell short of the minimum clinically important difference of 8. TIS also resulted in improved sputum volume and purulence. Discontinuations due to adverse events were 6.2% and 2.8% in the TIS and control groups. Serious adverse events were comparable across groups.

Comments

1. TORNASOL represents that largest clinical trial of nebulized tobramycin conducted, however again does not provide definitive data around its clinical endpoint.
2. Generalizability is limited - the trial population were relatively younger Chinese patients with a median of 2 exacerbations in the preceding 2 years i.e., not the frequent exacerbator phenotype that would usually be considered for inhaled antibiotic therapy.
3. No differences in exacerbation frequency were seen in the trial population within the short duration of this trial.

4. Tobramycin-resistant strains were isolated in 5.4% of the TIS groups vs 0% of the control group at day 29.

THE FIRST LARGE CLINICAL TRIAL OF INHALED BRONCHODILATOR IN BRONCHIECTASIS

Jayaram L, Vandal AC, Chang CL, Lewis C, Tong C, Tuffery C, Bell J, Fergusson W, Jeon G, Milne D, Jones S, Karalus N, Hotu S, Wong C. Tiotropium treatment for bronchiectasis: a randomised, placebo-controlled, crossover trial. *Eur Respir J.* 2022;59(6):2102184.

Summary

The efficacy of bronchodilators in patients with bronchiectasis has not been studied in large clinical trials and although they are commonly prescribed, the routine use of bronchodilators is not supported by current bronchiectasis treatment guidelines. The antimuscarinic agent tiotropium results in bronchodilation and reduced submucosal gland secretion, providing a rationale for its use in bronchiectasis. This randomized, double-blind, placebo-controlled, crossover trial aimed to evaluate the effect of 6 months of inhaled tiotropium therapy on the rate of exacerbations. Ninety adults with bronchiectasis, airflow limitation and ≥1 exacerbation in the previous year were randomised. Smokers with a >20pack-year history and/or those with a primary diagnosis of asthma were not eligible. Results for the primary endpoint showed that tiotropium did not reduce exacerbations; exacerbation rate on tiotropium was 2.17/year vs. 2.27/year on placebo (rate ratio 0.96, 95% CI 0.72–1.27). Tiotropium improved FEV_1 by 58mL (95% CI 23–92mL) but did not improve symptoms, 6-minute walk distance, or change neutrophil or eosinophil counts in blood or sputum. Tiotropium was well tolerated.

Comments

1. At baseline, participants had mild symptoms and a normal/near normal exercise capacity, therefore the results cannot be generalized to very breathless bronchiectasis patients and it may be these patients who stand to benefit most.
2. Almost half of participants (47%) were on LABA or LABA/ICS throughout the trial, however due to small numbers, subgroup analysis was not able to be performed to delineate the effect of tiotropium when used alone vs. in combination.
3. The clinical relevance of a 58mL improvement in FEV_1 is uncertain; the MCID for FEV_1 in COPD is 100mL however the MCID for FEV_1 in bronchiectasis has not yet been determined.
4. This is the first large RCT of bronchodilator in patients with bronchiectasis and demonstrates that further studies are required to determine which phenotypes may benefit from tiotropium.

BRONCHIECTASIS – IT'S NOT ALL ABOUT NEUTROPHILS

Shoemark A, Shteinberg M, De Soyza A, Haworth CS, Richardson H, Gao Y, Perea L, Dicker AJ, Goeminne PC, Cant E, Polverino E, Altenburg J, Keir HR, Loebinger MR, Blasi F, Welte T, Sibila O, Aliberti S, Chalmers JD. Characterization of eosinophilic bronchiectasis: a European multicohort study. *Am J Respir Crit Care Med.* 2022;205(8):894-902.

Summary

A subset of patients with bronchiectasis and sputum eosinophilia has recently been recognised, but is not well characterized. It is unclear whether blood and sputum eosinophil counts are correlated and whether eosinophilia is useful prognostically in patients with bronchiectasis. To answer these questions, the authors used data from 5 existing bronchiectasis cohorts, and excluded those with asthma and allergic bronchopulmonary aspergillosis. In 2 independent UK cohorts (Dundee n=123, Newcastle n=112) a statistically significant correlation between blood and sputum eosinophil counts was found. Analysis of the sputum microbiome in a cohort of 198 patients from the UK, Spain and Italy showed that high blood eosinophil counts (BEC) ≥300 cells/µl were associated with *Streptococcus* and *Pseudomonas*-dominated microbiome profiles. Analysis of EMBARC FRIENDS (Facilitating Research into Existing National Datasets, n=951) cohort data showed no relationship between BEC and exacerbations. However, when the presence of infection was controlled (via post hoc analysis of data from the PROMIS- Inhaled Promixin in the Treatment of Non–Cystic Fibrosis Bronchiectasis trial– wherein all patients had chronic *Pseudomonas*) BEC >100 cells/µl was associated with shorter time to exacerbation (n =

144, BEC 100–299 cells/μl HR 2.38; 95% CI 1.33–4.25 and BEC ≥300 cells/μl HR 3.99; 95% CI 2.20–7.85).

Comments

1. The correlation between blood and sputum eosinophil counts was weak to moderate (r=0.31; P=0.0001) but of a similar strength to that which is accepted in COPD and asthma cohorts, therefore validating BEC as a surrogate of airway eosinophilia in bronchiectasis.
2. Across all the cohorts studied, eosinophilic bronchiectasis (BEC ?300 cells/μl) was relatively common, affecting ~20% of patients.
3. After controlling for the confounder of infection, high BEC predicted exacerbations, however whether this would be true in patients without or with pathogens other than pseudomonas is unclear; there is an incompletely understood interaction between inflammation, patient microbiology and outcomes.
4. Eosinophilia may represent a therapeutic target in bronchiectasis; the Phase 3 MAHALE Study (NCT05006573) will investigate the efficacy and safety of benralizumab in patients with bronchiectasis and eosinophilia and further characterize bronchiectasis endotypes.

OTHER ARTICLES OF INTEREST

GENOTYPE-AGNOSTIC TREATMENTS FOR ALL PATIENTS WITH CF

Amaral MD, Harrison PT. **Development of novel therapeutics for all individuals with CF (the future goes on).** *J Cyst Fibros*. 2023;22 Suppl 1:S45-S49.

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MANAGEMENT OF CF PULMONARY EXACERBATIONS

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ENDOTYPING & THE GUT-LUNG AXIS IN BRONCHIECTASIS
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