American Thoracic Society International Conference

CLINICAL YEAR IN REVIEW

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May 18 - May 23
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TOPICS

A1 Sunday, May 20

B1 Monday, May 21

*This session and the International Conference are supported by educational grants from **AstraZeneca LP, GlaxoSmithKline.***

All CME sessions have been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) and are free of the control of commercial interests.

C1 Tuesday, May 22

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D1 Wednesday, May 23

INTERSTITIAL LUNG DISEASE

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DIAGNOSIS OF INTERSTITIAL LUNG DISEASE

Brownell R, Moua T, Henry TS, Elicker BM, White D, Vittinghoff E, Jones KD, Urisman A, Aravena C, Johannson KA, Golden JA, King TE, Jr., Wolters PJ, Collard HR, Ley B. **The use of pretest probability increases the value of high-resolution CT in diagnosing usual interstitial pneumonia**. *Thorax* 2017; 72: 424-429.

Summary

Although patients with a "possible UIP" or "inconsistent with UIP" HRCT pattern may have underlying histopathological UIP, many do not undergo surgical lung biopsy and cannot be diagnosed with confidence. This study sought to determine the test characteristics of non-definitive HRCT patterns in identifying histological UIP, and to determine the added discriminative value of other clinical and radiological variables. Multivariate models were derived in a biopsy proven cohort of well-characterized ILD patients (n=385), then externally validated in a separate cohort (n=166). The positive predictive value (PPV) of a "possible UIP" HRCT for histopathological UIP depends on the pre-test probability (e.g. population prevalence) of histopathological UIP. In cohorts with low prevalence of histopathological UIP (<70%), a possible UIP HRCT does not achieve a PPV high enough to obviate the need for lung biopsy to establish a confident diagnosis, whereas with higher prevalence (>/=70%), possible UIP demonstrates a PPV>90%. The addition of age, sex and extent of traction bronchiectasis, "the UIP score", sufficiently increases the PPV of a possible UIP HRCT to predict histopathological UIP, even in low prevalence populations. No combination of variables increases the PPV of an "inconsistent with UIP" HRCT pattern sufficiently high to predict histopathological UIP.

Comments

1. The positive predictive value of a diagnostic test is highly dependent on the population prevalence of the diagnosis of interest.
2. The UIP score, combining a possible UIP HRCT, age, sex and traction bronchiectasis score, provides a sufficiently high PPV across a range of population prevalence, to predict histopathological UIP.
3. No combination of variables can further refine an "inconsistent with UIP" pattern to predict histopathological UIP with sufficient confidence.
4. In appropriate clinical and research contexts, application of the UIP score may identify patients with IPF, without the need for surgical lung biopsy.

ACCURACY OF IPF DIAGNOSIS

Walsh SLF, Maher TM, Kolb M, Poletti V, Nusser R, Richeldi L, Vancheri C, Wilsher ML, Antoniou KM, Behr J, Bendstrup E, Brown K, Calandriello L, Corte TJ, Cottin V, Crestani B, Flaherty K, Glaspole I, Grutters J, Inoue Y, Kokosi M, Kondoh Y, Kouranos V, Kreuter M, Johannson K, Judge E, Ley B, Margaritopoulos G, Martinez FJ, Molina-Molina M, Morais A, Nunes H, Raghu G, Ryerson CJ, Selman M, Spagnolo P, Taniguchi H, Tomassetti S, Valeyre D, Wijsenbeek M, Wuyts W, Hansell D, Wells A. **Diagnostic accuracy of a clinical diagnosis of idiopathic pulmonary fibrosis: an international case-cohort study**. *Eur Respir J* 2017; 50.

Summary

Multidisciplinary team discussion (MDT) is the recommended gold standard for establishing a diagnosis of IPF, yet this specialized format is not widely available to all clinicians. This study compared IPF diagnoses made by academic (university) physicians, non-academic physicians, and an international panel of IPF experts through the use of an online format to present 60 real-life clinical cases of fibrotic ILD. 404 physicians, representing 57 countries, completed the survey. For each clinical scenario, participants provided their leading diagnoses with likelihoods for each diagnosis (considered confident if ≥ 70%). Using longitudinal follow-up data, prognostic accuracy was estimated, assuming that IPF outcomes are worse than those for non-IPF ILDs. Both the expert group and academic physicians diagnosed IPF more frequently (p=0.005 and p=0.008) and more often with high confidence (p=0.002 and p=0.001) than non-academic physicians. Academic physicians with >20 years' experience demonstrated prognostic accuracy for a diagnosis of IPF equivalent to that of international experts, regardless of access to MDT. Non-academic physicians with >20 years' experience that attended a weekly MDT demonstrated prognostic accuracy nearly as high as the expert group (C-index 0.72, IQR 0.70-0.72; p=0.052). Academic status, clinical experience, and access to MDT enable physicians to differentiate between IPF and non-IPF diagnoses.

Comments

1. Academic physicians with >20 years' experience can differentiate IPF from non-IPF diagnoses as well as IPF experts.
2. Non-academic physicians with >20 years' experience and regular (i.e. weekly) access to MDT perform nearly as well as IPF experts in differentiating IPF from non-IPF diagnoses.

3. Regular participation in MDT may improve diagnostic accuracy for IPF; therefore efforts should be made to broaden access to MDT, beyond specialized academic centers.

BIOMARKERS OF DISEASE PROGRESSION IN IPF

Maher TM, Oballa E, Simpson JK, Porte J, Habgood A, Fahy WA, Flynn A, Molyneaux PL, Braybrooke R, Divyateja H, Parfrey H, Rassl D, Russell AM, Saini G, Renzoni EA, Duggan AM, Hubbard R, Wells AU, Lukey PT, Marshall RP, Jenkins RG. **An epithelial biomarker signature for idiopathic pulmonary fibrosis: an analysis from the multicentre PROFILE cohort study**. *Lancet Respir Med* 2017; 5: 946-955.

Summary

IPF is a complex disease with a heterogeneous disease course, and few therapeutic options. The aim of this study was to identify potential serum biomarkers to predict disease course in IPF. This elegant study applied a two-stage discovery and validation protocol to a prospective, multicenter cohort of IPF patients. This cohort was derived from the PROFILE study and was well-characterized with longitudinal follow-up. From 123 candidate biomarkers, three demonstrated strong performance characteristics in predicting clinical outcomes, all with biologic plausibility in IPF. In both the discovery (n=106) and validation (n=206) analyses, baseline levels of surfactant protein D (SP-D) (46.6 ng/mL vs 34.6 ng/mL, p=0.0018) and CA19-9 (53.7 U/mL vs 22.2 U/mL; p<0.0001) were significantly higher in patients with progressive disease compared to stable disease. Rising concentrations of CA-125 over 3 months differentiated patients with progressive vs. stable disease at 1 year (1.26, 95%CI 1.05-1.1, p=0.015), and were associated with overall mortality (HR 2.542, 95% CI 1.493-4.328, p=0.00059). These novel findings provide insight into the pathobiology of IPF, while identifying potential biomarkers for application in clinical trials of therapeutics, both for cohort enrichment and to assess response to therapy.

Comments

1. CA19-9 and CA-125 are secreted by the metaplastic epithelium in fibrotic lesions in IPF.
2. SP-D and CA19-9 may be informative baseline biomarkers to stratify patients at risk for progressive disease.
3. CA-125 levels are elevated at baseline in progressive disease, increase over follow-up time, and predict mortality.
4. SP-D, CA19-9 and CA-125 appear to reflect an epithelial signature that identifies progressive IPF.

DIAGNOSIS OF CHRONIC HYPERSENSITIVITY PNEUMONITIS

Morisset J, Johannson KA, Jones KD, Wolters PJ, Collard HR, Walsh SLF, Ley B. Identification of Diagnostic Criteria for Chronic Hypersensitivity Pneumonitis: **An International Modified Delphi Survey**. *Am J Respir Crit Care Med* 2017. Nov 27. doi: 10.1164/rccm.201710-1986OC.

Summary

There are no widely accepted criteria to establish a diagnosis of chronic hypersensitivity pneumonitis (cHP), making it challenging for both clinical and research purposes. Using qualitative methodology, 45 clinicians with expertise in ILD, representing 14 countries, participated in 3 rounds of a modified Delphi survey with the goal of achieving consensus on items important in diagnosing cHP. Eighteen of 40 items reached consensus as important for the diagnosis of cHP. The items considered most important included identifying a causative agent, a temporal relationship between exposure and disease, mosaic attenuation on chest imaging, and poorly formed non-necrotizing granulomas on histopathology. When presented with clinical scenarios, cHP could be diagnosed with high confidence in the presence of combinations of specific items. These data inform the clinical, radiological and histological variables that international experts agree are important in the diagnosis of cHP. This is a first step towards establishing international consensus guidelines to characterize this disease.

Comments

1. 18 items were identified as being important to diagnose cHP.
2. The most important items were a positive exposure history, temporal relationship between exposure and disease, mosaic attenuation on HRCT and poorly formed, non-necrotizing granulomas on pathology.
3. Combinations of variables can establish a highly confident diagnosis of cHP.
4. Qualitative methodologies such as the Delphi have the potential to provide important insights in complex disease entities, such as cHP.

TREATMENT OF INTERSTITIAL LUNG DISEASE

Sullivan KM, Goldmuntz EA, Keyes-Elstein L, McSweeney PA, Pinckney A, Welch B, Mayes MD, Nash RA, Crofford LJ, Eggleston B, Castina S, Griffith LM, Goldstein JS, Wallace D, Craciunescu O, Khanna D, Folz RJ, Goldin J, St Clair EW, Seibold JR, Phillips K, Mineishi S, Simms RW, Ballen K, Wener MH, Georges GE, Heimfeld S, Hosing C, Forman S, Kafaja S, Silver RM, Griffing L, Storek J, LeClercq S, Brasington R, Csuka ME, Bredeson C, Keever-Taylor C, Domsic RT, Kahaleh MB, Medsger T, Furst DE. **Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma**. *N Engl J Med* 2018; 378: 35-47.

Summary

Systemic sclerosis (SSc) can be devastating, with the majority of patients having pulmonary involvement, the leading cause of death in SSc. This multicenter, randomized open-label phase 2 trial enrolled patients with SSc for less than 5 years, and either pulmonary or renal involvement. 36 patients were randomized to undergo myeloablative autologous hematopoietic stem cell transplantation (HSCT), and 39 patients were randomized to receive monthly intravenous cyclophosphamide for 12 months. 100% of the patients in the HSCT group and 95%

of patients in the cyclophosphamide group had active interstitial lung disease with either an FVC or DLCO <70% predicted. The primary endpoint, measured at 54 months, was a global rank composite score that compared patients to each other, based on a hierarchy of disease outcomes. In intention to treat and per-protocol analyses, HSCT was superior to cyclophosphamide based on the global rank composite score (p=0.01 and p=0.04, respectively). At 72 months, event free survival (survival without respiratory, renal or cardiac failure) and overall survival was higher in the HSCT group compared to cyclophosphamide (74% vs. 47%; p=0.03 and 85% vs. 51%; p=0.02, respectively). Fewer patients in the HSCT group (9% vs 44%) had initiated disease-modifying anti-rheumatic drugs by 54 months. Treatment-related mortality was higher in the HSCT group at 54 months (3%) and 72 months (6%), compared to 0% in the cyclophosphamide group.

Comments

1. Myeloablative autologous HSCT was superior to cyclophosphamide in patients with severe SSc, based on a global rank composite score assessed at 54 months.
2. HSCT led to improved event-free and overall survival compared to cyclophosphamide, demonstrating sustained clinical benefit over 72 months.
3. Treatment-related mortality was higher in the HSCT group than the cyclophosphamide group, but lower than in previously published studies of HSCT for SSc.
4. Myeloablative autologous HSCT improves clinical outcomes compared to cyclophosphamide, in severe SSc patients with pulmonary or renal involvement.

OTHER ARTICLES OF INTEREST

CHARACTERIZATION AND DIAGNOSIS OF INTERSTITIAL LUNG DISEASE

Griese M, Seidl E, Hengst M, Reu S, Rock H, Anthony G, Kiper N, Emiralioglu N, Snijders D, Goldbeck L, Leidl R, Ley-Zaporozhan J, Kruger-Stollfuss I, Kammer B, Wesselak T, Eismann C, Schams A, Neuner D, MacLean M, Nicholson AG, Lauren M, Clement A, Epaud R, de Blic J, Ashworth M, Aurora P, Calder A, Wetzke M, Kappler M, Cunningham S, Schwerk N, Bush A. **International management platform for children's interstitial lung disease (chILD-EU)**. *Thorax* 2017. Mar;73(3):231-239. doi: 10.1136/thoraxjnl-2017-210519

Ryerson CJ, Corte TJ, Lee JS, Richeldi L, Walsh SLF, Myers JL, Behr J, Cottin V, Danoff SK, Flaherty KR, Lederer DJ, Lynch DA, Martinez FJ, Raghu G, Travis WD, Udwadia Z, Wells AU, Collard HR. **A Standardized Diagnostic Ontology for Fibrotic Interstitial Lung Disease. An International Working Group Perspective**. *Am J Respir Crit Care Med* 2017; 196: 1249-1254.

Hetzel J, Maldonado F, Ravaglia C, Wells AU, Colby TV, Tomassetti S, Ryu JH, Fruchter O, Piciucchi S, Dubini A, Cavazza A, Chilosi M, Sverzellati N, Valeyre D, Leduc D, Walsh SLF, Gasparini S, Hetzel M, Hagmeyer L, Haentschel M, Eberhardt R, Darwiche K, Yarmus LB, Torrego A, Krishna G, Shah PL, Annema JT, Herth FJF, Poletti V. **Transbronchial Cryobiopsies for the Diagnosis of Diffuse Parenchymal Lung Diseases: Expert Statement from the Cryobiopsy Working Group on Safety and Utility and a Call for Standardization of the Procedure.** *Respiration* 2018. Jan 9. doi: 10.1159/000484055.

PATHOBIOLOGY AND GENETICS OF INTERSTITIAL LUNG DISEASE

Juge PA, Borie R, Kannengiesser C, Gazal S, Revy P, Wemeau-Stervinou L, Debray MP, Ottaviani S, Marchand-Adam S, Nathan N, Thabut G, Richez C, Nunes H, Callebaut I, Justet A, Leulliot N, Bonnefond A, Salgado D, Richette P, Desvignes JP, Liote H, Froguel P, Allanore Y, Sand O, Dromer C, Flipo RM, Clement A, Beroud C, Sibilia J, Coustet B, Cottin V, Boissier MC, Wallaert B, Schaeverbeke T, Dastot le Moal F, Frazier A, Menard C, Soubrier M, Saidenberg N, Valeyre D, Amselem S, Boileau C, Crestani B, Dieude P. **Shared genetic predisposition in rheumatoid arthritis-interstitial lung disease and familial pulmonary fibrosis**. *Eur Respir J* 2017; 49.

Armstrong HF, Podolanczuk AJ, Barr RG, Oelsner EC, Kawut SM, Hoffman EA, Tracy R, Kaminski N, McClelland RL, Lederer DJ. **Serum Matrix Metalloproteinase-7, Respiratory Symptoms, and Mortality in Community-Dwelling Adults. MESA (Multi-Ethnic Study of Atherosclerosis)**. *Am J Respir Crit Care Med* 2017; 196: 1311-1317.

Ley B, Newton CA, Arnould I, Elicker BM, Henry TS, Vittinghoff E, Golden JA, Jones KD, Batra K, Torrealba J, Garcia CK, Wolters PJ. **The MUC5B promoter polymorphism and telomere length in patients with chronic hypersensitivity pneumonitis: an observational cohort-control study.** *Lancet Respir Med* 2017; 5: 639-647.

Kitsios GD, Rojas M, Kass DJ, Fitch A, Sembrat JC, Qin S, Veraldi KL, Gibson KF, Lindell K, Pilewski JM, Methe B, Li K, McDyer J, McVerry BJ, Morris A. **Microbiome in lung explants of idiopathic pulmonary fibrosis: a case-control study in patients with end-stage fibrosis**. *Thorax* 2017. Aug 11. pii: thoraxjnl-2017-210537. doi: 10.1136/thoraxjnl-2017-210537.

Allen RJ, Porte J, Braybrooke R, Flores C, Fingerlin TE, Oldham JM, Guillen-Guio B, Ma SF, Okamoto T, John AE, Obeidat M, Yang IV, Henry A, Hubbard RB, Navaratnam V, Saini G, Thompson N, Booth HL, Hart SP, Hill MR, Hirani N, Maher TM, McAnulty RJ, Millar AB, Molyneaux PL, Parfrey H, Rassl DM, Whyte MKB, Fahy WA, Marshall RP, Oballa E, Bosse Y, Nickle DC, Sin DD, Timens W, Shrine N, Sayers I, Hall IP, Noth I, Schwartz DA, Tobin MD, Wain LV, Jenkins RG. **Genetic variants associated with susceptibility to idiopathic pulmonary fibrosis in people of European ancestry: a genome-wide association study**. *Lancet Respir Med* 2017; 5: 869-880.

ENVIRONMENTAL DETERMINANTS OF INTERSTITIAL LUNG DISEASE

Sese L, Nunes H, Cottin V, Sanyal S, Didier M, Carton Z, Israel-Biet D, Crestani B, Cadranel J, Wallaert B, Tazi A, Maitre B, Prevot G, Marchand-Adam S, Guillot-Dudoret S, Nardi A, Dury S, Giraud V, Gondouin A, Juvin K, Borie R, Wislez M, Valeyre D, Annesi-Maesano I. **Role of atmospheric pollution on the natural history of idiopathic pulmonary fibrosis**. *Thorax* 10 August 2017. doi: 10.1136/thoraxjnl-2017-209967

Delaunay M, Cadranel J, Lusque A, Meyer N, Gounant V, Moro-Sibilot D, Michot JM, Raimbourg J, Girard N, Guisier F, Planchard D, Metivier AC, Tomasini P, Dansin E, Perol M, Campana M, Gautschi O, Fruh M, Fumet JD, Audigier-Valette C, Couraud S, Dalle S, Leccia MT, Jaffro M, Collot S, Prevot G, Milia J, Mazieres J. **Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients**. *Eur Respir J* 2017 Aug 10;50(2)

RISK PREDICTION AND CLINICAL OUTCOMES IN INTERSTITIAL LUNG DISEASE

Herazo-Maya JD, Sun J, Molyneaux PL, Li Q, Villalba JA, Tzouvelekis A, Lynn H, Juan-Guardela BM, Risquez C, Osorio JC, Yan X, Michel G, Aurelien N, Lindell KO, Klesen MJ, Moffatt MF, Cookson WO, Zhang Y, Garcia JGN, Noth I, Prasse A, Bar-Joseph Z, Gibson KF, Zhao H, Herzog EL, Rosas IO, Maher TM, Kaminski N. **Validation of a 52-gene risk profile for outcome prediction in patients with idiopathic pulmonary fibrosis: an international, multicentre, cohort study**. *Lancet Respir Med* 2017; 5: 857-868.

Cottin V, Hansell DM, Sverzellati N, Weycker D, Antoniou KM, Atwood M, Oster G, Kirchgaessler KU, Collard HR, Wells AU. **Effect of Emphysema Extent on Serial Lung Function in Patients with Idiopathic Pulmonary Fibrosis**. *Am J Respir Crit Care Med* 2017; 196: 1162-1171.

Johannson KA, Vittinghoff E, Morisset J, Lee JS, Balmes JR, Collard HR. **Home monitoring improves endpoint efficiency in idiopathic pulmonary fibrosis**. *Eur Respir J* 2017 Jul 5;50(1).

TREATMENT OF INTERSTITIAL LUNG DISEASE

Kreuter M, Spagnolo P, Wuyts W, Renzoni E, Koschel D, Bonella F, Maher TM, Kolb M, Weycker D, Kirchgassler KU, Costabel U. **Antacid Therapy and Disease Progression in Patients with Idiopathic Pulmonary Fibrosis Who Received Pirfenidone**. *Respiration* 2017; 93: 415-423.

Birring SS, Wijsenbeek MS, Agrawal S, van den Berg JWK, Stone H, Maher TM, Tutuncu A, Morice AH. **A novel formulation of inhaled sodium cromoglicate (PA101) in idiopathic pulmonary fibrosis and chronic cough: a randomised, double-blind, proof-of-concept, phase 2 trial**. *Lancet Respir Med* 2017; 5: 806-815.

Kolb M, Richeldi L, Behr J, Maher TM, Tang W, Stowasser S, Hallmann C, du Bois RM. **Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume.** *Thorax* 2017; 72: 340-346.

Ley B, Swigris J, Day BM, Stauffer JL, Raimundo K, Chou W, Collard HR. **Pirfenidone Reduces Respiratory-related Hospitalizations in Idiopathic Pulmonary Fibrosis**. *Am J Respir Crit Care Med* 2017; 196: 756-761.

PULMONARY REHABILITATION

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ONLINE VERSUS CONVENTIONAL SUPERVISED PULMONARY REHABILITATION

Bourne S, DeVos R, North M, Chauhan A, Green B, Brown T, Cornelius V, Wilkinson T. **Online versus face-to-face pulmonary rehabilitation for patients with chronic obstructive pulmonary disease: randomised controlled trial**. *BMJ Open*. 2017;7(7):e014580.

Summary

The traditional model of pulmonary rehabilitation (PR) is a face-to-face structured program of exercise-training and education undertaken in a supervised center-based setting. Although it is highly effective at reducing symptom burden by increasing exercise tolerance, improving health-related quality of life and reducing exertional breathlessness, impact is limited by issues around accessibility, uptake and completion rates. This single-center non-inferiority, assessor-blinded, randomized controlled trial compared the efficacy and safety of an internet-based application (myPR) with a face-to-face outpatient PR program in patients with COPD. 90 participants were randomized 2:1 to either myPR or face-to-face PR. myPR comprised an incremental program of 10 exercises plus educational videos to be accessed at least five times per week for 6 weeks. Face-to-face PR consisted of same 10 exercises and educational content as myPR, two supervised sessions for 6 weeks. Primary outcome measures were 6 minute walk distance (6MWD) and the COPD Assessment Test (CAT). Adjusted mean difference for 6MWD was 23.8 meters with lower 95% CI above non-inferiority threshold. Adjusted mean difference in CAT was -1.0 with upper 95% CI below the non-inferiority threshold. No adverse effects were recorded with myPR.

Comments

1. For all clinical measures, online myPR was "non-inferior to usual care", suggesting a potential opportunity to increase capacity, reduce costs, and broaden availability of PR to groups without access to conventional PR.
2. The study population was highly selective: 1) ability to operate a web platform; 2) no recent exacerbation; 3) no oxygen desaturation; 4) well-preserved timed up and go time; 5) mild to moderate COPD.
3. Face-to-face PR consisted of 10 exercise stations designed to match myPR content with minimal aerobic exercise component – therefore "usual care" content would not meet recommendations of international PR guidelines.
4. Face-to-face PR showed benefits significantly lower than would be expected, providing further evidence that "usual care" was sub-optimal.
5. Adherence with myPR reduced with time (mean 3.9 falling to 2.5 sessions per week from week 1 to week 6) with only 22% of intervention group adhering to the recommended 5 sessions per week at week 6.

STRUCTURED HOME-BASED SELF-MANAGEMENT VERSUS CONVENTIONAL SUPERVISED PULMONARY REHABILITATION

Horton EJ, Mitchell KE, Johnson-Warrington V, Apps LD, Sewell L, Morgan M, Taylor RS, Singh SJ. **Comparison of a structured home-based rehabilitation programme with conventional supervised pulmonary rehabilitation: a randomised non-inferiority trial**. *Thorax*. 2018;73(1):29-36.

Summary

Home-based pulmonary rehabilitation (PR) may offer an alternative model to traditional center-based supervised PR. However previous trials have either been small-scale, included supplementation with a center-based component and home specialist exercise equipment, required familiarity with the internet or technology, or consisted of substantial staff supervision (home visits, telephone monitoring). This single-center, non-inferiority, assessor-blinded, randomized controlled trial compared supported but unsupervised home PR (n=142) with twice-weekly, supervised hospital-based PR (n=145) for 7-weeks in participants with COPD. Home-based PR was facilitated by a standardized manual (SPACE for COPD – a Self-management Programme of Activity, Coping and Education), an initial introductory session at the hospital with a healthcare professional trained in motivational interviewing and 2 standardized telephone calls. The exercise component was based on a progressive daily walking program. Primary outcome was the Dyspnea domain of the CRQ-SR at 7 weeks. Secondary outcomes included other domains of the Chronic Respiratory Questionnaire-Self-Report (CRQ-SR), exercise capacity, anxiety and depression and self-efficacy scores. Significant gains were seen in CRQ-Dyspnea (and most other outcomes) in both

groups, numerically favoring supervised center-based PR. There was inconclusive evidence that standardized unsupervised home-based PR was non-inferior or equivalent to supervised center-based PR.

Comments

1. This study tested an intervention that required less direct or indirect supervision than previous trials of home-based PR, facilitated by a manual that may be better applicable to patients with COPD than internet or technology-based solutions.
2. Of 527 eligible participants, 240 declined either because they wanted center-based PR or did not want any form of PR at all.
3. Home-based PR produced clinically significant changes in CRQ-D and endurance shuttle walk at 7 weeks.
4. 41% and 35% did not complete the 7-week assessment in the center-based and home-based PR groups respectively.
5. The non-inferiority margin was generous and set at the minimum clinically important difference (MCID) rather than the more common half MCID.

PEDOMETER STEP COUNT TARGETS AS AN ADJUNCT TO PULMONARY REHABILITATION

Nolan CM, Maddocks M, Canavan JL, Jones SE, Delogu V, Kaliaraju D, Banya W, Kon SS, Polkey MI, Man WD. **Pedometer Step Count Targets during Pulmonary Rehabilitation in Chronic Obstructive Pulmonary Disease. A Randomized Controlled Trial**. *Am J Respir Crit Care Med*. 2017;195(10):1344-52.

Summary

Increasing physical activity levels is a key therapeutic aim in COPD as inactivity is associated with adverse prognosis including mortality and exacerbations. Although there is strong evidence supporting the benefits of pulmonary rehabilitation (PR) on exercise capacity, the effects on physical activity are modest and inconsistent. In this assessor-blinded randomized controlled trial, 152 participants with COPD were assigned to either a twice weekly supervised hospital-based PR program for 8 weeks (control) or intervention (PR plus pedometer-directed step targets, reviewed weekly for 8 weeks, and then unsupervised for 6 months) and followed for 6 months after initial PR. The primary outcome was accelerometer-measured time spent in at least moderate intensity physical activity (time expending ≥3METS) at 8 weeks. Secondary outcomes included daily step count, exercise capacity and health-related quality of life at 8 weeks and 6 months. Despite both groups showing significant improvements in exercise capacity and health related quality of life, no between group differences in physical activity or exercise outcomes were observed at 8 weeks or 6 months. Findings were replicated in a sensitivity analysis of those with low baseline physical activity levels.

Comments

1. This is the largest randomized controlled trial to study the use of pedometers as an adjunct to PR, and does not support the routine addition of pedometers to PR.
2. Accelerometer-measured time spent in at least moderate intensity activity provided an objective measurement of physical activity, but clinical relevance and appropriateness of this outcome for patients with COPD is uncertain.
3. The intervention relied on pedometer feedback and had only a "light-touch" behavioral component.
4. The addition of the pedometer step count targets blunted short-term improvements in some domains of health related quality of life with PR and survey feedback on the pedometer was mixed.

INSPIRATORY MUSCLE TRAINING AS AN ADJUNCT TO PULMONARY REHABILITATION

Schultz K, Jelusic D, Wittmann M, Kramer B, Huber V, Fuchs S, Lehbert N, Wingart S, Stojanovic D, Gohl O, Alma HJ, de Jong C, van der Molen T, Faller H, Schuler M. **Inspiratory muscle training does not improve clinical outcomes in 3-week COPD rehabilitation: results from a randomised controlled trial.** *Eur Respir J*. 2018; 51(1). pii: 1702000.

Summary

The value of inspiratory muscle training (IMT) in COPD, particularly as an adjunct to pulmonary rehabilitation (PR), remains unclear. Proponents are supported by the observation that inspiratory muscle dysfunction is common in patients with COPD, which may contribute to dyspnea and reduced exercise tolerance. However opponents refer to the finding that inspiratory muscle strength is normal when the effects of hyperinflation on the muscle length-tension relationship are considered. In this single-center randomized controlled trial, 602 patients received three-weeks of inpatient PR and were randomized to receive in addition either highly intensive IMT (intervention) or sham IMT (control). IMT training occurred 7 times per week with initial training load 30% of maximal inspiratory pressure (PImax) and progressively increased to at least 60%. Primary outcome was PImax; secondary outcomes were six minute walk distance (6MWD), lung function and disease-specific health related quality of life (HrQoL). The intervention group showed greater improvements in PImax and forced inspiratory volume in 1 second than controls. All other outcomes improved significantly in both groups, but there were no between-group differences in 6MWD and HrQoL.

Comments

1. This is the largest randomized sham controlled trial to study the use of IMT as an adjunct to PR.
2. There was greater improvement in PImax, the primary outcome, with the intervention, but it is unclear whether the observed between-group differences were clinically significant or relevant.

3. Despite improvement in PImax, no additional improvement in other outcomes of relevance (6MWD, HrQoL) was observed when comparing active with sham IMT, providing evidence to defer the routine addition of IMT to PR.
4. Although the duration of PR intervention was short, the frequency was intensive and the observed improvements in 6MWD and HrQoL were substantial.

BENEFITS OF LONG-TERM PULMONARY REHABILITATION MAINTENANCE

Guell MR, Cejudo P, Ortega F, Puy MC, Rodriguez-Trigo G, Pijoan JI, Martinez-Indart L, Gorostiza A, Bdeir K, Celli B, Galdiz JN. **Benefits of Long-Term Pulmonary Rehabilitation Maintenance Program in Patients with Severe Chronic Obstructive Pulmonary Disease. Three-Year Follow-up**. *Am J Respir Crit Care Med.* 2017;195(5):622-9.

Summary

Although the positive effects of pulmonary rehabilitation (PR) are well recognized, the benefits wane with time. Guidelines recommend exercise-based maintenance programs after PR, but the evidence supporting this approach is limited and inconsistent. In this multi-center, randomized controlled trial, after an initial 8-weeks of outpatient PR, 138 patients with moderate to severe COPD (mean FEV1 34% predicted) were randomized to receive either a three-year maintenance program or simple advice about home exercise with minimal supervision (control group). The intervention consisted of a home program that included chest physiotherapy, upper limb training and 30 minutes of leg training at least three times a week. Cycle ergometers were provided. Furthermore, the intervention group attended supervised training sessions and received telephone calls on alternate weeks. The primary outcome was the composite prognostic BODE index. Other outcomes included the six minute walk distance (6MWD) and generic and disease-specific health related quality of life (HrQoL). The intervention produced a better maintenance of 6MWD and BODE index over the course of 24 (but not 36) months compared with usual care, but no differences in HrQoL were observed.

Comments

1. This trial demonstrates the feasibility of a maintenance strategy in achieving sustained health benefits after PR, and provides the longest follow-up of any published clinical trial of maintenance intervention following PR.
2. The maintenance intervention was focused primarily on exercise-training, and may not be generalizable to different healthcare systems (provision of cycle ergometer, supervised training and telephone calls alternate weeks for three years).
3. The power calculation stipulated 75 patients per arm would be required but only 34 and 31 patients completed the program in the intervention and control group respectively, and imputation for missing data was not performed.
4. Data on mortality, hospitalization, healthcare resource usage and cost-benefit analysis were not reported.
5. There was a less formal measurement of adherence in the control group compared to the intervention group.

OTHER ARTICLES OF INTEREST

PULMONARY REHABILITATION MECHANISMS

Herigstad M, Faull OK, Hayen A, Evans E, Hardinge FM, Wiech K, et al. **Treating breathlessness via the brain: changes in brain activity over a course of pulmonary rehabilitation**. *Eur Respir J.* 2017; 50(3). pii: 1701029. doi: 10.1183/13993003.01029-2017.

DELIVERING PULMONARY REHABILITATION

Chaplin E, Hewitt S, Apps L, Bankart J, Pulikottil-Jacob R, Boyce S, et al. **Interactive web-based pulmonary rehabilitation programme: a randomised controlled feasibility trial.** *BMJ Open*. 2017;7(3):e013682.

Tsai LL, McNamara RJ, Moddel C, Alison JA, McKenzie DK, McKeough ZJ. **Home-based telerehabilitation via real-time videoconferencing improves endurance exercise capacity in patients with COPD: The randomized controlled TeleR Study.** *Respirology*. 2017;22(4):699-707.

Holland AE, Mahal A, Hill CJ, Lee AL, Burge AT, Cox NS, et al. Hom**e-based rehabilitation for COPD using minimal resources: a randomised, controlled equivalence trial.** *Thorax*. 2017;72(1):57-65.

PULMONARY REHABILITATION IN NON-COPD

Dowman LM, McDonald CF, Hill CJ, Lee AL, Barker K, Boote C, et al. **The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial.** *Thorax*. 2017;72(7):610-9.

Mandal S, Suh ES, Harding R, Vaughan-France A, Ramsay M, Connolly B, et al. **Nutrition and Exercise Rehabilitation in Obesity hypoventilation syndrome (NERO): a pilot randomised controlled trial**. *Thorax*. 2018;73(1):62-9.

ADJUNCTS TO PULMONARY REHABILITATION

Beaumont M, Mialon P, Le Ber C, Le Mevel P, Peran L, Meurisse O, et al. **Effects of inspiratory muscle training on dyspnoea in severe COPD patients during pulmonary rehabilitation: controlled randomised trial**. *Eur Respir J.* 2018;51(1). pii: 1701107. doi: 10.1183/13993003.01107-2017.

Gloeckl R, Jarosch I, Bengsch U, Claus M, Schneeberger T, Andrianopoulos V, et al. **What's the secret behind the benefits of whole-body vibration training in patients with COPD? A randomized, controlled trial**. *Respir Med.* 2017;126:17-24.

Farver-Vestergaard I, O'Toole MS, O'Connor M, Lokke A, Bendstrup E, Basdeo SA, et al. **Mindfulness-based cognitive therapy in COPD: a cluster randomised controlled trial**. *Eur Respir J*. 2018;51(2). pii: 1702082. doi: 10.1183/13993003.02082-2017.

Vitacca M, Kaymaz D, Lanini B, Vagheggini G, Ergun P, Gigliotti F, et al. **Non-invasive ventilation during cycle exercise training in patients with chronic respiratory failure on long-term ventilatory support: A randomized controlled trial**. *Respirology*. 2018;23(2):182-9.

PULMONARY REHABILITATION IN ACUTE SETTING

Fuller LM, Button B, Tarrant B, Steward R, Bennett L, Snell G, et al. **Longer Versus Shorter Duration of Supervised Rehabilitation After Lung Transplantation: A Randomized Trial**. *Arch Phys Med Rehabil*. 2017;98(2):220-6 e3.

McDowell K, O'Neill B, Blackwood B, Clarke C, Gardner E, Johnston P, et al. **Effectiveness of an exercise programme on physical function in patients discharged from hospital following critical illness: a randomised controlled trial (the REVIVE trial)**. *Thorax*. 2017;72(7):594-5.

Torres-Sanchez I, Valenza MC, Cabrera-Martos I, Lopez-Torres I, Benitez-Feliponi A, Conde-Valero A. **Effects of an Exercise Intervention in Frail Older Patients with Chronic Obstructive Pulmonary Disease Hospitalized due to an Exacerbation: A Randomized Controlled Trial**. *COPD*. 2017;14(1):37-42.

PHYSICAL ACTIVITY

Demeyer H, Louvaris Z, Frei A, Rabinovich RA, de Jong C, Gimeno-Santos E, et al. **Physical activity is increased by a 12-week semiautomated telecoaching programme in patients with COPD: a multicentre randomised controlled trial**. *Thorax.* 2017;72(5):415-23.

Spina G, Spruit MA, Alison J, Benzo RP, Calverley PMA, Clarenbach CF, et al. **Analysis of nocturnal actigraphic sleep measures in patients with COPD and their association with daytime physical activity**. *Thorax*. 2017;72(8):694-701.

LUNG TRANSPLANTATION

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PRIMARY GRAFT DYSFUNCTION AFTER TRANSPLANTATION: DEFINITION AND GRADING

Snell GI, Yusen RD, Weill D, Strueber M, Garrity E, Reed A, Pelaez A, Whelan TP, Perch M, Bag R, Budev M, Corris PA, Crespo MM, Witt C, Cantu E, Christie JD. Report of the ISHLT **Working Group on Primary Lung Graft Dysfunction, part I: Definition and grading-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation**. *J Heart Lung Transplant*. 2017 Oct;36(10):1097-1103.

Summary

Primary graft dysfunction (PGD) is defined as acute lung injury after implantation. In 2005, the ISHLT Working Group (2005 WGC) provided the standard PGD definition/grading to facilitate future research. A decade later, 2016 ISHLT PGD Working Group Consensus (2016 WGC) refines the definition/grading of PGD as it has evolved into an important clinical endpoint in studies. The PGD definition has 1) predictive validity in the ability to discriminate mortality and BOS, 2) convergent and divergent validity for concurrent lung injury biomarkers, and 3) PGD 3 appears to be the driver of these differences. The 2016 WGC felt insufficient evidence exists for a separate PGD grade for transplant type or to change the PGD grading according to specific recipient complications. The optimal time to start PGD grading (Time 0) should be following pulmonary arterial cross clamp release at the point of reperfusion. No changes were made to the grading time points of T0, T24, T48, and T72.The T24 time point was the most complete and allows for best assessment of the effect of perioperative PGD management. PGD 3 present at later times (T48 and T72) appears to have the impact on long-term outcomes. The definition of PGD grade 0 was updated, as an absence of pulmonary edema on X-ray imaging with any P/F ratio.

Comments

1. The 2016 ISHLT Working Group on PGD definition and grading has taken the next step in clarifying and acknowledging gaps in the 2005 PGD grading including the need for further research into condensing or collapsing lower PGD grades (PGD Grade 0 and Grade 1) into one grade since recent investigations have shown no significant difference in 30 day, 90 day and 1 yr mortality risks irrespective if taken at T0, T24 or T72.
2. The 2016 WGC notes that bronchiolitis obliterans syndrome (BOS) phenotype of chronic lung allograft rejection (CLAD) is associated with PGD, but currently several different phenotypes with no defined mechanisms of PGD that may be linked to the development of a particular CLAD phenotype.
3. Increasing utilization of post-operative extracorporeal membrane oxygenation (ECMO) support in cases of severe PGD will impact the PGD 3 rates for registry reporting and clinical trials, and its use should be recorded and accounted for in reporting and analyses, especially in cases in which PGD grading is "ungradable" due to clear chest CXR and ECMO is intended for non-hypoxemic reasons to help further define mortality and outcomes associated with this subset of severe PGD.

PRIMARY GRAFT DYSFUNCTION AFTER TRANSPLANTATION: EPIDEMIOLOGY, RISK FACTORS, AND OUTCOMES

Diamond JM, Arcasoy S, Kennedy CC, Eberlein M, Singer JP, Patterson GM, Edelman JD, Dhillon G, Pena T, Kawut SM, Lee JC, Girgis R, Dark J, Thabut G. **Report of the International Society for Heart and Lung Transplantation Working Group on Primary Lung Graft Dysfunction, part II: Epidemiology, risk factors, and outcomes-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation**. *J Heart Lung Transplant*. 2017 Oct;36(10):1104-1113.

Summary

In the decade since the 2005 ISHLT Working Group (2005 WGC), a number of studies have expanded our knowledge regarding donor and recipient risk factors (RF) for developing PGD. The 2016 ISHLT PGD Working Group Consensus (2016 WGC) provides a review of physical and biochemical/ genetic RF for the development of PGD. Based on the level of evidence available, donor smoking is a definite RF for PGD. Additionally, donor gender, donor-recipient gender mismatch, and race are RF for PGD. Insights into donor biologic risk factors for PGD are emerging including donor polymorphisms associated with increased risk of PGD. Operative risk factors including prior cardiac surgery (excluding pleurodesis), or transplant type did not increase PGD risk. Independent RF increasing the risk for PGD include cardiopulmonary bypass, delayed chest closure, large volume intraoperative transfusions, prolonged ischemic time and increasing reperfusion Fi02. Short-term mortality and morbidity is the highest for PGD 3 at all timepoints. PGD is associated with a worse survival at T72. The presence of early PGD is associated with increased

duration of mechanical ventilation, ICU, and hospital length of stay, resource utilization, hospital costs and the development of BOS phenotype of CLAD. The overall risk for mortality after re-transplantation was significantly worse for PGD patients versus CLAD patients.

Comments

1. The 2016 Working Group Consensus statement on PGD risk factors provides an expansive review of donor risk factors that may impact the development of PGD from retrospective standard criteria donor cohorts but it bears noting the contemporary donor demographics and profiles are changing and the criteria are moving towards using a more liberal donor criteria in an effort to expand the donor pool. These "further" extended criteria donors may give rise to a new set of risk factors leading to the development of PGD.
2. It is still unclear if there is a differential effect of intraoperative veno-arterial ECMO vs CPB as a RF for the development of PGD, but as this practice increases, factors including intraoperative blood transfusions, and the recipient illness severity including the presence of pulmonary hypertension and alterations hemodynamic issues and extended criteria donors may continue to be significant RFs for the development of PGD and not the use of intraoperative ECMO or CPB.
3. There is no association of PGD and acute cellular rejection but an association with the development of de novo donor specific antibodies after PGD Grade 2 or Grade 3 at T48 during the initial hospitalization for transplant has been noted.

PRIMARY GRAFT DYSFUNCTION AFTER TRANSPLANTATION: PREVENTION AND TREATMENT

Van Raemdonck D, Hartwig MG, Hertz MI, Davis RD, Cypel M, Hayes D Jr, Ivulich S, Kukreja J, Lease ED, Loor G, Mercier O, Paoletti L, Parmar J, Rampolla R, Wille K, Walia R, Keshavjee S. **Report of the ISHLT Working Group on primary lung graft dysfunction Part IV: Prevention and treatment: A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation**. *J Heart Lung Transplant*. 2017 Oct;36(10):1121-1136.

Summary

The 2016 WGC updates the 2005 WGC reviews the most up to date evidence for reducing the incidence of PGD and for attenuating its severity. Strategies to prevent or minimize PGD that were included (1) optimizing donor and recipient selection, donor-recipient matching (DRM) and management of donors and recipients pre-operatively (2) improving lung preservation and storage techniques and (3) improving lung implantation and reperfusion. Presently, donor evaluation is a subjective assessment with minimal objective data available, but the evolution of biomarkers correlating with donor lung injury and EVLP reassessment will help to better differentiate allografts that should be declined or treated first prior to retrieval or during EVLP reconditioning. The mainstay of PGD management post implantation remains supportive care including lung protective ventilation in conjunction with fluid restriction and the use of venous – venous ECMO for support for severe PGD but noting these patients have a lower long-term survival than patients without PGD. Several novel therapies have emerged in the treatment of PGD including the instillation of surfactant, complement inhibition, platelet-activating factor antagonists, platelet and neutrophil traps, stem cells and plasmapheresis. Early re-transplantation for PGD remains particularly hazardous, and this should remain an option of last resort for the treatment of PGD due to poor outcomes.

Comments

1. The emerging role for biomarkers to help assess the degree of lung injury and use of EVLP for the same role raises the question if these biomarkers have the same characteristics during in vivo perfusion compared to ex-vivo or EVLP reperfusion.
2. Novel pharmacological treatments currently being tested in acute respiratory distress syndrome may have a therapeutic potential in the treatment of PGD by reducing alveolar fluid and restoring the endothelial-epithelial barrier.

AIRWAY COMPLICATIONS AFTER TRANSPLANTATION

Crespo MM, McCarthy DP, Hopkins PM, Clark SC, Budev M, Bermudez CA, Benden C, Eghtesady P, Lease E, Leard L, D'Cunha J, Wigfield CH, Cypel M, Diamond JM, Yun JJ, Yarmus L, Machuzak M, Klepetko W, Verleden G, Hoetzenecker K, Dellgren G, Mulligan M. **ISHLT Consensus Statement on Adult and Pediatric Airway Complications after Lung Transplantation: Definitions, Grading System and Therapeutics**. *J Heart Lung Transplant*. 2018 Feb 7. pii: S1053-2498(18)31349-4.

Summary

Airway complications (AC) are a major cause of morbidity and mortality post-transplant. The major AC lack a universal definition and lack a standardized grading system. Several classification systems have been proposed, none have been accepted as a "gold standard" by the transplant community. The International Society of Heart and Lung Transplantation (ISHLT) Working Group on AC, developed definitions of the common adult and pediatric AC (ischemia, necrosis, dehiscence, stenosis, and malacia) and created an associated grading system to facilitate precise communication in the identification and to better define successful or failures of treatment interventions. The grading system is based on the first bronchoscopy findings within 2-3 weeks post lung transplant and can be used on follow up bronchoscopies through the trajectory of healing or after an intervention. An AC is identified based on the pathophysiologic change using the standardized defined terms and with the aid of the endoscopic visual atlas. Each complication is graded based on the location within the tracheobronchial tree and the severity or extent of the abnormality. Recommendations for specific time-points (T

points) of airway assessment need to be flexible enough to take into account the variation in time to first bronchoscopy inspection and subsequent evaluation of allograft function among transplant centers. The consensus statement did address the endoscopic medical and surgical management of each AC noting that evidence for management is limited in most cases to case series and few randomized trials and can vary from patient to patient.

Comments

1. Similar to prior ISHLT consensus definitions of antibody mediated rejection and primary graft dysfunction, this is a universal definition of particular airway complications and a grading system which will standardize the subjective to a more objective way to communicate AC and the impact of treatment will likely evolve as we gain more insight over time.
2. The proposed grading system is based on an initial bronchoscopy at 2-3 weeks after transplant and may impact the timing of initial bronchoscopies in a transplant programs who do not routinely perform bronchoscopic exams until clinically indicated.
3. The subsequent natural progression of this initial effort of the ISHLT AC Working Group is to establish an International AC Registry to collect data to further define the true incidence of AC, further study risk factors for AC in the donors and recipients, and assess the impact of treatment interventions.
4. As the use of EVLP increases and cold ischemic times may be extended, especially in the extended criteria donors, the impact on airway healing and complications is unknown and needs further research.
5. AC are unique to each patient and the treatments highlighted in the consensus document provide an overview of potential treatment options available at this time but the future holds promise for novel therapies including biodegradable stents, and 3D printing technology to make patient specific silicone airway stents.

EXPANDING THE LUNG DONOR POOL: HEPATITIS C VIREMIC DONORS

Abdelbasit A, Hirji A, Halloran K, Weinkauf J, Kapasi A, Lien D, Nagendran J, Doucette K. **Lung Transplantation from Hepatitis C Viremic Donors to Uninfected Recipients.** *Am J Respir Crit Care Med*. 2018 Feb 7. doi: 10.1164/rccm.201712-2614LE. [Epub ahead of print]

Summary

The limited number of donors is the major factor contributing to waitlist mortality. The recent opioid crisis has led to an increasing number of hepatitis C virus (HCV) positive donors who could be considered as potential organ donors. The current practice of using HCV infected donor lungs has not been broadly adopted by transplant centers. The development of direct acting antivirals (DAAs) have now made HCV curable, possibly making the utilization of HCV positive donors a way to expand the donor pool. This is a single center case series describing the outcomes of lung transplantation from five HCV viremic donors (n=3 genotype 1a, n= 1genotype 1b, n= 1 genotype 2) to negative recipients. The donors all had varying HCV RNA viral loads at the time of transplant from 645 IU/ml to 2.1 IU/ml with two of the cases placed on ex vivo perfusion. Three recipients received basiliximab induction therapy and all received maintenance immunosuppression with tacrolimus, mycophenolate, and prednisone. HCV RNA was detected on days ranging from 1-16. Four patients (genotype 1) received sofosbuvir/ledipasvir and the remaining genotype 2 patient received sofosbuvir/velpatasvir for 12 weeks. DAA therapy was initiated post-transplant from days 24 to 94 days when able to take oral medications and deemed clinically stable. No attributable side effects due to DAA therapy were noted and all patients were discharged home and alive at 9-12 months post-transplant.

Comments

1. There are several limitations to this work including the small sample size, and a limited description of the timing of DAA therapy initiation, but in all of the cases DAA therapy was initiated after the HCV viral load had been rising and not when HCV viral load was first detected or in the operating room upon implantation of the HCV + organs.
2. Although none of the recipients developed HCV or DAA related adverse effects, all of the patients had complicated postoperative courses which may be related to the recipients' pre transplant condition (LAS ranged from 33.2-58.4) and possible intraoperative issues unrelated to the donors or DAA therapy, which likely impacted the timing of administration of the DAA therapy.
3. While more experience is needed with use of HCV viremic donors and the optimal timing for DAA therapy after implantation, this small case series is the first case series that suggests that early outcomes of using HCV viremic organs for HCV negative recipients treated with DAA therapy after 24 days post-transplant with no early mortality noted.
4. Further work is need regarding 1) the newer pan-genotypic DAA agents although one patient with genotype 2 did receive a newer pangenotypic again with no issues, 2) the safety and feasibility of using DAA when patients are unable to take oral medications, and 3) which second line agents are appropriate if the initial to initial DAA therapies were to fail.
5. Currently the cost, insurance coverage and availability of DAA therapy for donor derived HCV infection in lung transplant recipients in the United States has not been clearly addressed and will need to be part of the discussion as we as a transplant community consider using HCV viremic organs in the future.

OTHER ARTICLES OF INTEREST

PRIMARY GRAFT DYSFUNCTION

Gelman AE, Fisher AJ, Huang HJ, Baz MA, Shaver CM, Egan TM, Mulligan MS. **Report of the ISHLT Working Group on Primary Lung Graft Dysfunction Part III: Mechanisms: A 2016 Consensus Group Statement of the International Society for Heart and Lung Transplantation**. *J Heart Lung Transplant.* 2017 Oct;36(10):1114-1120.

Cantu E, Diamond JM, Suzuki Y, Lasky J, Schaufler C, Lim B, Shah R, Porteous M, Lederer DJ, Kawut SM, Palmer SM, Snyder LD, Hartwig MG, Lama VN, Bhorade S, Bermudez C, Crespo M, McDyer J, Wille K, Orens J, Shah PD, Weinacker A, Weill D, Wilkes D, Roe D, Hage C, Ware LB, Bellamy SL, Christie JD; **Lung Transplant Outcomes Group. Quantitative Evidence for Revising the Definition of Primary Graft Dysfunction after Lung Transplant**. *Am J Respir Crit Care Med*. 2018 Jan 15;197(2):235-243.

Porteous MK, Lee JC, Lederer DJ, Palmer SM, Cantu E, Shah RJ, Bellamy SL, Lama VN, Bhorade SM, Crespo MM, McDyer JF, Wille KM, Localio AR, Orens JB, Shah PD, Weinacker AB, Arcasoy S, Wilkes DS, Ware LB, Christie JD, Kawut SM, Diamond JM; **Lung Transplant Outcomes Group. Clinical Risk Factors and Prognostic Model for Primary Graft Dysfunction after Lung Transplantation in Patients with Pulmonary Hypertension**. *Ann Am Thorac Soc.* 2017 Oct;14(10):1514-1522.

Belhaj A, Boven C, Dewachter L, Ruiz Patino M, Sokolow Y, Rondelet B. **Influence of Donor Lung Surfactant-A and -B Protein Expression on the Development of Primary Graft Dysfunction After Lung Transplantation: A Pilot Study**. *Ann Transplant*. 2017 Jun 16;22:361-369.

Aigner C, Slama A, Barta M, Mitterbauer A, Lang G, Taghavi S, Matilla J, Ullrich R, Krenn K, Jaksch P, Markstaller K, Klepetko W. **Treatment of primary graft dysfunction after lung transplantation with orally inhaled AP301: A prospective, randomized pilot study**. *J Heart Lung Transplant*. 2017 Sep 30. pii: S1053-2498(17)32036-3.

AIRWAY COMPLICATIONS

Olland A, Reeb J, Puyraveau M, Hirschi S, Seitlinger J, Santelmo N, Collange O, Mertes PM, Kessler R, Falcoz PE, Massard G. **Bronchial complications after lung transplantation are associated with primary lung graft dysfunction and surgical technique**. *J Heart Lung Transplant*. 2017 Feb;36(2):157-165.

TELOMERE LENGTH AND LUNG TRANSPLANTATION

Faust HE, Golden JA, Rajalingam R, Wang AS, Green G, Hays SR, Kukreja J, Singer JP, Wolters PJ, Greenland JR. **Short lung transplant donor telomere length is associated with decreased CLAD-free survival**. *Thorax*. 2017 Nov;72(11):1052-1054.

HEPATITIS C DONORS AND LUNG TRANSPLANT

Khan B, Singer LG, Lilly LB, Chaparro C, Martinu T, Juvet S, Pipkin M, Waddell TK, Keshavjee S, Humar A, Cypel M. **Successful Lung Transplantation From Hepatitis C Positive Donor to Seronegative Recipient**. *Am J Transplant*. 2017 Apr;17(4):1129-1131.

Theodoropoulos N, Whitson BA, Martin SI, Pouch S, Pope-Harman A. **Successful treatment of donor-derived hepatitis C infection in a lung transplant recipient**. *Transpl Infect Dis*. 2017 Apr;19(2).

HEALTH RELATED QUALITY OF LIFE AND LUNG TRANSPLANTATION

Kolaitis NA, Soong A, Shrestha P, Zhuo H, Neuhaus J, Katz PP, Greenland JR, Golden J, Leard LE, Shah RJ, Hays SR, Kukreja J, Kleinhenz ME, Blanc PD, Singer JP. I**mprovement in patient-reported outcomes after lung transplantation is not impacted by the use of extracorporeal membrane oxygenation as a bridge to transplantation.** *J Thorac Cardiovasc Surg*. 2018 Feb 22

Singer JP, KatzPP, Soong A, Shrestha P, Huang D, Ho J, Mindo M, Greenland JR, Hays SR, Golden J, Kukreja J, Kleinhenz ME, Shah RJ, Blanc PD. **Effect of Lung Transplantation on Health-Related Quality of Life in the Era of the Lung Allocation Score: A U.S. Prospective Cohort Study**. *Am J Transplant*. 2017 May;17(5):1334-1345.

INTERVENTIONAL PULMONOLOGY

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MEDIASTINAL STAGING OF NSCLC

O'Connell OJ, Almeida FA, Simoff MJ, Yarmus L, Lazarus R, Young B, Chen Y, Semaan R, Saettele TM, Cicenia J, Bedi H, Kliment C, Li L, Sethi S, Diaz-Mendoza J, Feller-Kopman D, Song J, Gildea T, Lee H, Grosu HB, Machuzak M, Rodriguez-Vial M, Eapen GA, Jimenez CA, Casal RF, Ost DE. **A Prediction Model to Help with the Assessment of Adenopathy in Lung Cancer: HAL**. *Am J Respir Crit Care Med*. 2017 Jun 15;195(12):1651-1660.

Summary

Mediastinal staging of NSCLC in patients without extra-thoracic disease is a critical process which determines treatment options and prognosis. This article aimed to develop a prediction model to determine when invasive mediastinal sampling would be required. Using the ACQUIRE registry the authors analyzed patients undergoing mediastinal staging of NSCLC using CT, PET-CT and EBUS-TBNA. All EBUS-TBNA procedures were performed in a standard manner, with sampling of N3 followed by N2 and then N1 nodes. All lymph nodes measuring 0.5 cm or larger by EBUS were sampled, irrespective of CT and PET results. EBUS results were taken as the final accurate nodal stage.

A cohort of 633 patients was used to derive the model and had a 25% prevalence of malignant N2/3 disease. In the multivariate model, younger age, central location, adenocarcinoma histology, and higher PET-CT N stage were associated with a higher probability of N2/3 disease. The HAL (Help with the Assessment of Adenopathy in Lung Cancer) model was validated in 722 patients from 3 centers, although the prevalence of N2/3 disease in these 3 centers varied (28%, 45% and 56%). The model performed well, with good discrimination (AUC ROC, 0.85), but requires local calibration. The HAL model may improve clinical decision making in determining the presence of N2/3 disease by EBUS.

Comments

1. The HAL model is an excellent example of using data captured by a registry to develop new clinical tools and complies with TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis).
2. Using a 10% cutoff for positive EBUS, the HAL model suggests that only patients with lymph nodes <1cm and negative on PET should avoid invasive mediastinal staging.
3. Using the same cut off as above, the HAL model suggests invasive staging with EBUS should be considered in the following: 1) most patients with enlarged mediastinal (N2/N3) lymph nodes on chest CT scan; 2) virtually all patients with hypermetabolic N2/N3 nodes on PET/CT scan; 3) most patients with centrally located tumors; and 4) most patients with adenocarcinoma histology.
4. The HAL model reinforces current ACCP guidance on importance of invasive mediastinal staging in patients with stage 1-IIIA NSCLC.
5. A potentially important role for the HAL model may be in determining who should undergo mediastinoscopy after negative EBUS.

ENDOBRONCHIAL VALVES FOR EMPHYSEMA

Kemp SV, Slebos DJ, Kirk A, Kornaszewska M, Carron K, Ek L, Broman G, Hillerdal G, Mal H, Pison C, Briault A, Downer N, Darwiche K, Rao J, Hübner RH, Ruwwe-Glosenkamp C, Trosini-Desert V, Eberhardt R, Herth FJ, Derom E, Malfait T, Shah PL, Garner JL, Ten Hacken NH, Fallouh H, Leroy S, Marquette CH; TRANSFORM Study Team. **A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM)**. *Am J Respir Crit Care Med.* 2017 Dec 15;196(12):1535-1543

Summary

It has previously been shown that placement of endobronchial valves (EBV) in patients with severe emphysema can achieve atelectasis and lung volume reduction if there is no collateral ventilation between the target and an ipsilateral lobe. This has been shown to improve lung function, exercise tolerance and quality of life. The TRANSFORM trial is the first multi-center RCT to confirm these findings. 97 participants with heterogeneous emphysema (>10% difference in destruction scores between ipsilateral lobes) and absence of collateral ventilation were recruited at 17 sites in Europe between 2014 and 2016. Inclusion criteria were FEV1 15-45% despite optimal medical therapy, RV>180% and a 6 minute walk distance (6MWD) of between 150 and 450m. All patients underwent Chartis assessment to check for collateral ventilation prior to randomization. Patients

without collateral ventilation were randomized 2:1 to either EBV or standard of care (SoC).

At 3 months post procedure, 55.4% in the EBV group and 6.5% in the SoC group had a 12% improvement in FEV1. These differences were maintained at 6 months. There were also statistically and clinically significant improvements in the EBV group compared to the SoC group for 6MWD, SGRQ with a decrease in RV and BODE index. The median hospital stay for the EBV group was 4 days and pneumothorax occurred in 29% of patients who underwent EBV.

Comments

1. The TRANSFORM trial confirms the important role of endobronchial valves in the treatment of severe emphysema with hyperinflation who remain symptomatic despite maximal medical therapy.
2. 273 subjects were screened in order to recruit 97 eligible patients. Thus, selection of patients who can benefit from EBV therapy should mirror the clinical trial inclusion criteria and require a Chartis assessment to exclude collateral ventilation.
3. The change in BODE index in the EBV group of -1.8 may suggest a significant decrease in mortality although this will need to be clarified with longer follow-up.
4. Although not mandated in the trial, patients should undergo pulmonary rehabilitation prior to EBV treatment.
5. Lung volume reduction is an underutilized treatment for patients with severe COPD and hyperinflation.

NAVIGATIONAL BRONCHOSCOPY

Khandhar SJ, Bowling MR, Flandes J, Gildea TR, Hood KL, Krimsky WS, Minnich DJ, Murgu SD, Pritchett M, Toloza EM, Wahidi MM, Wolvers JJ, Folch EE; **NAVIGATE Study Investigators. Electromagnetic navigation bronchoscopy to access lung lesions in 1,000 subjects: first results of the prospective, multicenter NAVIGATE study**. *BMC Pulm Med*. 2017 Apr 11;17(1):59

Summary

NAVIGATE is a large multi-center prospective cohort study of electromagnetic navigation bronchoscopy (ENB) using the SuperDimension system. These results were a pre-specified analysis at 1 month after the procedure. 1000 participants were enrolled across 29 sites in the U.S. and Europe. Lesions were in the peripheral/middle lung thirds in 93%, approximately 50% were >20 mm, and 48% had a bronchus sign. Radial EBUS was used in 54%, fluoroscopy in 90%, general anesthesia in 80% and ROSE in 66%. 45% of patients had COPD. Navigation was completed in 964 subjects (1,129 lesions) and tissue was obtained in 94% (910/964). ENB samples were reported as malignant in 417/910 (46%). 13% of samples were considered inconclusive. 80% of samples of those submitted were adequate for genetic testing. The ENB-related pneumothorax rate was 5% (49/1,000). The short follow-up means that it was not possible to derive a sensitivity for the technique.

Comments

1. This is a large international prospective cohort study which demonstrates that navigational bronchoscopy is a safe procedure but practice is variable between institutions.
2. The pre-specified analysis at 1 month allowed assessment of safety and found rates of pneumothorax (5%), hemorrhage and respiratory failure were low.
3. It is not possible to determine sensitivity of the procedure since follow up has not been long enough to establish whether negative ENB results are true or false negatives.
4. In NAVIGATE, 36% of patients had stage III or IV lung cancer and in these patients, sampling the lymph nodes via EBUS-TBNA will provide valuable diagnostic and staging information precluding the need for navigational bronchoscopy in a significant proportion.
5. Molecular testing of samples was surprisingly variable and when requested was successful in 80% of patients which is lower than would be expected for CT guided biopsy or EBUS-TBNA.

CRYOBIOPSY FOR INTERSTITIAL LUNG DISEASE

Hetzel J, Maldonado F, Ravaglia C, Wells AU, Colby TV, Tomassetti S, Ryu JH, Fruchter O, Piciucchi S, Dubini A, Cavazza A, Chilosi M, Sverzellati N, Valeyre D, Leduc D, Walsh SLF, Gasparini S, Hetzel M, Hagmeyer L, Haentschel M, Eberhardt R, Darwiche K, Yarmus LB, Torrego A, Krishna G, Shah PL, Annema JT, Herth FJF, Poletti V. **Transbronchial Cryobiopsies for the Diagnosis of Diffuse Parenchymal Lung Diseases: Expert Statement from the Cryobiopsy Working Group on Safety and Utility and a Call for Standardization of the Procedure**. *Respiration.* 2018 Jan 9

Summary

Transbronchial cryobiopsy (TBCB) has emerged as an important diagnostic tool for the evaluation of interstitial lung disease. Up to 40% of patients with IPF may require pathological confirmation and TBCB may be a safer alternative to surgical lung biopsy (SLB). However, safety and yield from TBCB still remain a concern which this consensus review paper aimed to address. Patients should be assessed for risk for exacerbation of ILD e.g. recent onset of patchy ground glass and functional deterioration. Approximately 20% of TBCB specimens will not provide a specific diagnosis. In order to maximize yield, a sample size of 5 mm in diameter should be obtained and tissue should be manipulated as little as possible e.g. thawing the cryoprobe tip in hand warm water to facilitate specimen removal. The major risks after TBCB are pneumothorax and bleeding. Abnormal clotting, anticoagulant therapy, treatment with antiplatelet drugs and thrombocytopenia with platelets <50x109 /L should be considered contraindications. Pulmonary hypertension, TLCO <35% and FVC<50% may be considered as relative contraindications. The authors recommend TBCBs be performed in intubated patients under deep sedation or general anesthesia. An endobronchial blocker or a Fogarty balloon may

be used prophylactically in order to control bleeding. It is recommended that 3–5 biopsies are obtained 1 cm from the visceral pleura under fluoroscopic guidance. TBCBs should be performed in the operating room or bronchoscopy suite with full anesthesia support with the option to admit the patient to the intensive care unit and escalate care if needed.

Comments

1. Transbronchial cryoscopic lung biopsy has become an option for the histological diagnosis of interstitial lung disease as an alternative to surgery but practice internationally is variable.
2. This article provides a consensus on the current best practice for cryobiopsy but prospective studies and registry data are still required.
3. The result from TBCB should not be analyzed in isolation and is best interpreted by a multi-disciplinary board with expertise in the management of interstitial lung disease.
4. Complications from TBCB can occur frequently and may be life-threatening and therefore the procedure should only be undertaken by experienced IP centers with appropriate equipment and expertise to manage pneumothorax and airway haemorrhage.

BRONCHIAL THERMOPLASTY

Chupp G, Laviolette M, Cohn L, McEvoy C, Bansal S, Shifren A, Khatri S, Grubb GM, McMullen E, Strauven R, Kline JN; Other members of the PAS2 Study Group. **Long-term outcomes of bronchial thermoplasty in subjects with severe asthma: a comparison of 3-year follow-up results from two prospective multicentre studies**. *Eur Respir J*. 2017 Aug 31;50(2)

Summary

Bronchial thermoplasty is an endoscopic therapy for asthma that delivers radiofrequency energy to the airways of asthmatic subjects. The AIR2 trial was a randomized sham-controlled trial of thermoplasty in patients with severe asthma which demonstrated that thermoplasty improved quality of life scores and reduced exacerbations. This article describes the results from the PAS2 study which was a prospective cohort study designed to demonstrate the short- and long-term efficacy and safety profile of thermoplasty in routine clinical practice. 279 patients from 2011 and 2015 were treated in 27 centers in the U.S. and Canada. Subjects were enrolled if their asthma was inadequately controlled despite optimized treatment with ICS and LABA therapy. Bronchoplasty was carried out using the Alair system over 3 procedures: RLL in the first session, LLL during the 2nd session and finally both upper lobes. PAS2 subjects were 45.9 years old (5 years older than AIR2), and also had asthma for longer, had a higher BMI and took higher doses of ICS than AIR2 participants. More PAS2 subjects had experienced severe exacerbations (74% versus 52%) and hospitalizations (15.3% versus 4.2%) in the 12 months prior to bronchial thermoplasty. At 3 years of follow-up, the proportion of PAS2 participants with hospitalizations reduced significantly by 40%. In addition, PAS2 subjects were able to reduce their dose of ICS and use of oral corticosteroids from 18.9% to 10.2%. During the 3rd year of follow-up 40% of PAS2 subjects experienced at least one exacerbation compared to 74% in the 12 months prior to treatment.

Comments

1. Despite the PAS2 cohort having more severe asthma than the AIR2 trial participants, similar benefits from bronchial thermoplasty were seen, importantly demonstrating the utility of the procedure in routine clinical practice.
2. In the PAS2 study during the treatment phase, 13.2% of subjects experienced peri-procedural adverse events requiring hospitalization or prolongation of hospitalization and this risk should be communicated to patients undergoing the procedure
3. Enrolment in the PAS2 trial was slow with only a few patients per center per year being treated on average.
4. Studies are ongoing to further clarify the mechanism that underpins the efficacy of bronchial thermoplasty.
5. The study shows that bronchial thermoplasty is an important treatment option for patients with severe asthma uncontrolled by standard pharmacological therapies.

OTHER ARTICLES OF INTEREST

Tyan C, Patel P, Czarnecka K, Gompelmann D, Eberhardt R, Fortin M, MacEachern P, Hergott CA, Dumoulin E, Tremblay A, Kemp SV, Shah PL, Herth FJF, Yasufuku K. **Flexible 19-Gauge Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration Needle: First Experience.** *Respiration*. 2017;94(1):52-57

Furukawa BS, Pastis NJ, Tanner NT, Chen A, Silvestri GA. **Comparing Pulmonary Nodule Location During Electromagnetic Bronchoscopy With Predicted Location on the Basis of Two Virtual Airway Maps at Different Phases of Respiration**. *Chest*. 2018 Jan;153(1):181-186

Lee HJ, Labaki W, Yu DH, Salwen B, Gilbert C, Schneider ALC, Ortiz R, Feller-Kopman D, Arias S, Yarmus L. **Airway stent complications: the role of follow-up bronchoscopy as a surveillance method**. *J Thorac Dis*. 2017 Nov;9(11):4651-4659

Scholten EL, Semaan R, Illei P, Mallow C, Arias S, Feller-Kopman D, Oakjones-Burgess K, Frimpong B, Ortiz R, Lee H, Yarmus L. **Stylet Use Does Not Improve Diagnostic Outcomes in Endobronchial Ultrasonographic Transbronchial Needle Aspiration: A Randomized Clinical Trial**. *Chest*. 2017 Mar;151(3):636-642

Amini S, Peiman S, Khatuni M, Ghalamkari M, Rahimi B. **The Effect of Dextromethorphan Premedication on Cough and Patient Tolerance During Flexible Bronchoscopy: A Randomized, Double-blind, Placebo-controlled Tria**l. *J Bronchology Interv Pulmonol*. 2017 Oct;24(4):263-267

COPD

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TREATMENT OF EARLY COPD

Zhou Y, Zhong NS, Li X, Chen S, Zheng J, Zhao D, Yao W, Zhi R, Wei L, He B, Zhang X, Yang C, Li Y, Li F, Du J, Gui J, Hu B, Bai C, Huang P, Chen G, Xu Y, Wang C, Liang B, Li Y, Hu G, Tan H, Ye X, Ma X, Chen Y, Hu X, Tian J, Zhu X, Shi Z, Du X, Li M, Liu S, Yu R, Zhao J, Ma Q, Xie C, Li X, Chen T, Lin Y, Zeng L, Ye C, Ye W, Luo X, Zeng L, Yu S, Guan WJ, Ran P. **Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease**. *N Engl J Med* 2017; 377:923-935.

Summary

Although the majority of individuals with COPD have mild to moderate lung function impairment, there are sparse data to inform management of this group of patients, especially those without respiratory symptoms. Small trials and post hoc analyses have suggested a benefit of tiotropium over placebo on lung function decline, COPD exacerbation risk, and health status in this population. To prospectively determine the effect of tiotropium in patients with mild to moderate COPD, the Tie-COPD study recruited 841 GOLD stage 1 or 2 COPD patients from community screening at 24 centers in mainland China. Participants were randomized in double-blinded fashion to two-years of tiotropium versus placebo, with the primary end point of between-group difference in change from baseline to two year pre-bronchodilator FEV1. The majority of participants were male, with 21% having never smoked, 41% currently smoking, and 73% with minimal symptoms (CAT score <10). After two years, tiotropium was associated with 157 ml higher pre-bronchodilator FEV1 ($p<0.001$). Secondary endpoints including post-bronchodilator annual FEV1 decline, COPD exacerbation rates, and COPD-specific quality of life were improved with tiotropium. In subgroup analysis of participants with CAT score <10, similar benefits of tiotropium were observed on lung function and exacerbation measures

Comments

1. Although there were fewer participants with exacerbations in Tie-COPD compared to the subgroup of moderate COPD from UPLIFT, the beneficial reduction in exacerbation risk with tiotropium observed with Tie-COPD exceeded that seen in UPLIFT.
2. The benefit of tiotropium on lung function and exacerbation rates in mild COPD with minimal or no symptoms is not conclusive as these findings were from subgroup analyses.
3. The durable effects of tiotropium on rate of FEV1 decline over time is less clear, as FEV1 declines were largely similar between tiotropium and placebo groups after 6 months and extended follow-up one year after stopping tiotropium or placebo showed no difference in lung function measures between groups, suggesting a lack of modification of disease progression.
4. There were no differences in adverse events between tiotropium and placebo groups, with overall similar drop-out rates.
5. The Tie-COPD study highlights the need for additional large scale, long-term studies of maintenance inhaler therapies in mild COPD with minimal symptoms to fully inform the timing of disease treatment and appropriate screening approaches in order to improve health outcomes.

FIXED TRIPLE THERAPY VERSUS LAMA

Vestbo J, Papi A, Corradi M, Blazhko V, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, Singh D. **Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial**. *Lancet* 2017; 389: 1919-1929.

Summary

Inhaled “triple therapy” with ICS (inhaled corticosteroid), LABA (long-acting beta agonist), and LAMA (long-acting muscarinic antagonist) is recommended for COPD patients with ongoing exacerbations despite LAMA monotherapy, LABA/LAMA, or LABA/ICS dual therapy. These recommendations are based largely on expert consensus from few studies. Recent developments in inhaler design now incorporate triple therapy into one device (“fixed triple”). The TRINITY study compared treatment with beclometasone/formoterol/glycopyrronium (fixed triple) to tiotropium monotherapy, and beclometasone/fluticasone plus tiotropium (open triple). The 2691 participants had FEV1 <50% predicted, at least one moderate to severe exacerbation in the prior year, and CAT score ≥10. The primary endpoint was moderate to severe COPD exacerbation rate after 52 weeks. Compared with tiotropium, fixed triple was associated with 20% reduction in exacerbation rate ($p=0.0025$),

with similar exacerbation reduction with open triple versus tiotropium (21%; p=0.01). In secondary analyses, exacerbation reduction with open and fixed triple therapy compared to tiotropium was statistically significant in participants with ≥2% or 200 absolute eosinophils, with no evidence of benefit in low eosinophil participants. Fixed triple was superior to tiotropium (61 ml; p<0.001) and non-inferior to open triple (-3 ml; p=0.85) in adjusted mean change in FEV1 over study duration. Pneumonia incidence was 1-2% across treatment groups.

Comments

1. The results of TRINITY, combined with the results of the TRILOGY study of fixed triple versus ICS/LABA, support the effectiveness of triple therapy in exacerbation reduction compared with LAMA or LABA/ICS regimens. Additional studies comparing fixed triple regimens to LABA/LAMA and LABA/ICS are forthcoming.
2. The incidence of exacerbation in TRINITY was low (0.45-0.57/year), making these results more applicable to GOLD-B COPD (high symptoms, low exacerbation risk) where LAMA, LABA, or LABA/LAMA are currently recommended.
3. Fixed and open triple regimens had similar impact on COPD outcomes, but the study design incorporating double-dummy placebo inhalers does not permit assessment of potential benefits of single versus multiple inhalation devices.
4. Although greater exacerbation reduction with triple therapy over LAMA was observed in participants with higher eosinophil counts, this study is not designed to determine which components of triple therapy (LABA, ICS, or both) may be contributing to this observation.
5. Excellent medication adherence (>94% in all treatment groups), glycopyrronium dose higher than approved U.S. dosing, and tolerance of a tiotropium-only run-in period may affect the reproducibility of these results in general U.S. populations.

FIXED TRIPLE THERAPY VERSUS LABA/ICS

Lipson DA, Barnacle H, Birk R, Brealey N, Locantore N, Lomas DA, Ludwig-Sengpiel A, Mohindra R, Tabberer M, Zhu CQ, Pascoe SJ. **FULFIL Trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease**. *Am J Respir Crit Care Med* 2017; 196: 438-446.

Summary

As discussed with the TRINITY study, the role of triple therapy (ICS/LAMA/LABA) compared with dual therapies in COPD has not been rigorously evaluated. To further understand the potential impact of triple therapy versus LABA/ICS in COPD, the FULFIL study compared closed triple therapy (fluticasone/umeclidinium/vilanterol) with twice-daily ICS/LABA (budesonide/formoterol) for 24 weeks (N=1810) with an extended substudy to 52 weeks (N=430). The study recruited symptomatic COPD patients (CAT ≥10) with severe airflow obstruction (FEV1<50%) or symptomatic patients with FEV1 50-80% and frequent exacerbations. At baseline, 44% were smokers with 66% having cardiovascular risk factors. The co-primary endpoints included 24-week change from baseline in FEV1 and St. George's Respiratory Questionnaire total score. After 24 weeks, fixed triple was associated with 171 ml greater improvement in FEV1 compared with LABA/ICS (p<0.001). The SGRQ total score was 2.2 units lower in fixed triple compared with LABA/ICS (p<0.001). In the extended substudy, similar effects were seen in FEV1 and SGRQ, with only FEV1 effects remaining significant. The annualized rates of COPD exacerbations were low (0.22 and 0.34 for fixed triple and LABA/ICS, respectively), representing a 35% relative reduction in exacerbations with triple therapy (p=0.002). Pneumonia incidence was 1-2% across treatment groups.

Comments

1. The FULFIL study offers evidence of benefit of fixed triple therapy over LABA/ICS in improving lung function, with unclear clinical benefit in quality of life (SGRG MCID of 4 units not reached).
2. Because FULFIL included different ICS and LABA molecules administered via different inhaler devices (Ellipta versus Turbuhaler), it is uncertain if beneficial effects of fixed triple are related to regimen intensity, drug, or delivery device.
3. Similar to TRILOGY, the low rates of exacerbations in FULFIL led to a cohort more similar to GOLD-B disease, suggesting benefit in groups with less frequent exacerbations.
4. The updated 2018 GOLD guidelines included the results of FULFIL and TRINITY in discussions, but these findings did not change the current recommendations regarding timing of LABA/ICS and triple therapy for GOLD-C/D patients.
5. Few exclusion criteria and continuation of pre-study maintenance medications until randomization reflected a quasi-pragmatic trial design, better reflecting real-world clinical practice.

EOSINOPHILIC COPD TREATMENT

Pavord ID, Chanez P, Criner GJ, Kerstjens HAM, Korn S, Lugogo N, Martinot JB, Sagara H, Albers FC, Bradford ES, Harris SS, Mayer B, Rubin DB, Yancey SW, Sciurba FC. **Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease**. *N Engl J Med* 2017; 377: 1613-1629.

Summary

Eosinophilia may inform increased COPD exacerbation risk. Mepolizumab, a monoclonal antibody that blocks interleukin-5, has demonstrated effectiveness in reducing exacerbations in severe eosinophilic asthma. METREX and METREO were two phase 3 studies of mepolizumab in COPD patients on triple therapy, with FEV1 20-80% predicted and ≥2 moderate or ≥1 severe exacerbation in prior year. METREX stratified participants by eosinophilic phenotype (eosinophil count ≥150 at screening or ≥300 in prior year) prior to randomizing to 100 mg mepolizumab or placebo monthly for 52 weeks. METREO randomized only eosinophilic participants to placebo, 100 mg, or 300

mg monthly injections. For both studies, the primary endpoint was annual rate of moderate or severe exacerbations. In METREX, the eosinophilic phenotype treated with mepolizumab had an 18% reduction in exacerbation rates versus placebo (1.40 vs. 1.71 exacerbations/year; p=0.04). There was no difference in the overall METREX population comparing mepolizumab to placebo (1.49 vs. 1.52 exacerbations/year; p>0.99). In METREO, mepolizumab reduced exacerbations by 20% (100 mg) and 14% (300 mg) compared to placebo, yet failed to reach statistical significance (p=0.07 and 0.14, respectively). In pre-specified meta-analysis, exacerbation reduction was greater with mepolizumab versus placebo among participants with higher screening blood eosinophils.

Comments

1. Although statistically significant exacerbation reductions were not consistently seen across both METREX and METREO, both interventions were associated with an 18-20% exacerbation reduction with treatment, with longer time to first exacerbation and dose-response relationship with eosinophilia, suggesting possible therapeutic benefit.
2. Exacerbation rates in the placebo groups of METREX and METREO differed substantially, potentially influencing the observed effect of mepolizumab in the two studies.
3. This study highlights the importance of eosinophil level as a potential biomarker for personalized injectable therapy for COPD, moving beyond its evolving role in informing ICS responsiveness.
4. The optimal threshold to define elevated eosinophils in COPD remains unknown, with thresholds of 2%, 4%, 150 cells, and 300 cells reported to be of value in studies. Additional biomarkers may prove more sensitive at predictive response to anti-eosinophil therapy.
5. Several studies of benralizumab, an anti-interleukin-5 receptor antibody, on COPD exacerbation reduction will be forthcoming, advancing our understanding of the role of other eosinophil-targeted therapies in COPD.

NON-INVASIVE VENTILATION IN COPD

Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, Dowson L, Duffy N, Gibson GJ, Hughes PD, Hurst JR, Lewis KE, Mukherjee R, Nickol A, Oscroft N, Patout M, Pepperell J, Smith I, Stradling JR, Wedzicha JA, Polkey MI, Elliott MW, Hart N. **Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial**. *JAMA* 2017; 317: 2177-2186.

Summary

Non-invasive positive pressure ventilation (NPPV) is standard of care in COPD patients with acute hypercapnic respiratory failure, but benefits of NPPV in chronic hypercapnia is less clear. To address this, Murphy and colleagues recruited 116 patients with severe COPD (mean FEV1 23% predicted) with persistent hypercapnia (PaCO2>53 mm Hg) two to four weeks after COPD exacerbation requiring hospitalization with acute NPPV. Participants were randomized to home NPPV plus home oxygen (NPPV+HO) vs supplemental oxygen alone (HO alone) for one year, with the primary endpoint of time to readmission or death. NPPV was delivered via ventilator with high-pressure strategy (average inspiratory 24 and expiratory 4 cm H20) with supplemental oxygen in both interventions averaging 1.0 L/min. The median time to hospitalization or death was 4.3 months in NPPV+HO versus 1.4 months in HO alone (HR 0.49; 95% CI 0.31-0.77; p=0.002). 12-month risk of readmission or death was 63% in NPPV+HO compared with 80% in HO alone [absolute reduction 17% (95% CI 0.1%-34%)]. Benefit with NPPV+HO was largely derived from readmission reduction, as mortality did not differ between NPPV+HO and HO alone (28% vs. 32%; p=0.26). COPD exacerbation rates were reduced with NPPV+HO compared with HO alone (3.8 vs. 5.1 exacerbations/year; p=0.02).

Comments

1. These results highlight the importance of timely assessment for persistent hypercapnia after hospital discharge for COPD exacerbation, with consideration of NPPV to reduce readmissions in those with chronic hypercapnia. Barriers exist to prescribing ventilators for home NPPV in some U.S. payer systems.
2. Reduction in nocturnal transcutaneous carbon dioxide levels were observed through the 12 months of study in NPPV+HO, but did not differ with HO carbon dioxide levels after 6 months, potentially impacted by high numbers of crossovers from HO to NPPV+HO after experiencing the primary outcome.
3. Adherence to home NPPV (7.6 hr/night at 12 months), requirement for persistent hypercapnia (elevated PaCO2 at least two weeks after hospitalization), high inspiratory pressure protocol, and more severe COPD at enrollment likely explain the observed benefit with NPPV not seen in other randomized studies in post-exacerbation COPD patients.
4. Highlighting the severity of COPD in this study, only 6% of screened participants were eligible for study with one-third of screen fails due to inability to wean from acute NPPV, death prior to screening, or inability to provide consent.
5. Participants did not undergo overnight polysomnogram to exclude COPD with concurrent obstructive sleep apnea (overlap syndrome), making it difficult to ascertain if benefits with NPPV were related to treatment of overlap syndrome.

COPD NATIONAL ACTION PLAN

National Heart, Lung, and Blood Institute. **COPD National Action Plan**, 2017. https://www.nhlbi.nih.gov/health-pro/resources/lung/copd-national-action-plan. Accessed February 1, 2018.

Summary

Released in May 2017, the COPD National Action Plan represents a coordinated, multi-faceted blueprint to address the COPD epidemic in the United States. Developed by the

National Institutes of Health, federal partners, and external stakeholders (e.g., patients, caregivers, health care providers, researchers, industry sponsors), the action plan outlines five goals to increase COPD awareness and minimize the burden of COPD: 1) empower people with COPD, their families, and caregivers to recognize and reduce the burden of COPD; 2) improve the prevention, diagnosis, treatment, and management of COPD by improving quality of care delivered across the health care continuum; 3) collect, analyze, report, and disseminate COPD-related public health data that drive change and track progress; 4) increase and sustain research to better understand the prevention, pathogenesis, diagnosis, treatment, and management of COPD; 5) translate national policy, educational, and program recommendations into research and public health care actions. By outlining specific strategies to accomplish each of the five goals, the COPD Action Plan provides a framework for all who are interested in COPD to engage in approaches to raise awareness about COPD and support activities that will combat the unmet needs related to COPD.

Comments

1. The ATS Public Advisory Roundtable (PAR), comprising 15 member organizations representing individuals affected by pulmonary, critical care, and sleep problems, along with the ATS Patient Information Series are well suited to address the empowerment goal of the COPD Action Plan.
2. Pulmonary rehabilitation has demonstrated efficacy in improving outcomes in COPD, yet remains under-utilized. Improving access to quality pulmonary rehabilitation throughout the United States is a key component to the COPD Action Plan.
3. The electronic health record has the potential to support the needs of clinicians, researchers, payers, and other stakeholders in COPD (the third action plan goal), but requires harmonization of discrete data elements such as lung function measures across multiple platforms.
4. COPD is the third leading cause of death in the United States, yet ranks 154 out of 282 funded research/disease areas by the NIH in 2016.
5. ATS members should become involved in taking ownership of some portion of the COPD National Action Plan.

OTHER ARTICLES OF INTEREST

TREATMENT

Calverley PMA, Anderson JA, Brook RD, Crim C, Gallot N, Kilbride S, Martinez FJ, Yates J, Newby DE, Vestbo J, Wise R, Celli BR, Investigators S. **Fluticasone Furoate, Vilanterol, and Lung Function Decline in Patients with Moderate Chronic Obstructive Pulmonary Disease and Heightened Cardiovascular Risk**. *Am J Respir Crit Care Med* 2018; 197: 47-55.

Wang MT, Liou JT, Lin CW, Tsai CL, Wang YH, Hsu YJ, Lai JH. **Association of Cardiovascular Risk With Inhaled Long-Acting Bronchodilators in Patients With Chronic Obstructive Pulmonary Disease: A Nested Case-Control Study**. *JAMA Intern Med 2018*. Published online ahead of print (2018 Jan 2).

Roche N, Chapman KR, Vogelmeier CF, Herth FJF, Thach C, Fogel R, Olsson P, Patalano F, Banerji D, Wedzicha JA. **Blood Eosinophils and Response to Maintenance Chronic Obstructive Pulmonary Disease Treatment**. Data from the FLAME Trial. *Am J Respir Crit Care Me*d 2017; 195: 1189-1197.

EXACERBATIONS

Echevarria C, Steer J, Heslop-Marshall K, Stenton SC, Hickey PM, Hughes R, Wijesinghe M, Harrison RN,Steen N, Simpson AJ, Gibson GJ, Bourke SC. **The PEARL score predicts 90-day readmission or death after hospitalisation for acute exacerbation of COPD**. *Thorax* 2017; 72: 686-693.

Stolz D, Hirsch HH, Schilter D, Louis R, Rakic J, Boeck L, Papakonstantinou E, Schindler C, Grize L, Tamm M. **Intensified Therapy with Inhaled Corticosteroids and LABA at the Onset of URTI to Prevent COPD Exacerbations- A Multicentre, Randomised, Double-blind, Placebo-controlled Trial**. *Am J Respir Crit Care Med* 2017. Published online ahead of print (2017 Dec 21).

Han MK, Quibrera PM, Carretta EE, Barr RG, Bleecker ER, Bowler RP, Cooper CB, Comellas A, Couper DJ, Curtis JL, Criner G, Dransfield MT, Hansel NN, Hoffman EA, Kanner RE, Krishnan JA, Martinez CH, Pirozzi CB, O'Neal WK, Rennard S, Tashkin DP, Wedzicha JA, Woodruff P, Paine R, 3rd, Martinez FJ, investigators S. **Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort**. *Lancet Respir Med* 2017; 5: 619-626.

Loh CH, Peters SP, Lovings TM, Ohar JA. **Suboptimal Inspiratory Flow Rates Are Associated with Chronic Obstructive Pulmonary Disease and All-Cause Readmissions**. *Ann Am Thorac Soc* 2017; 14: 1305-1311.

EPIDEMIOLOGY

Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, Morozoff C, Shirude S, Naghavi M, Mokdad AH, Murray CJL. **Trends and Patterns of Differences in Chronic Respiratory Disease Mortality Among US Counties, 1980-2014**. *JAMA* 2017; 318: 1136-1149.

Lindenauer PK, Dharmarajan K, Qin L, Lin Z, Gershon AS, Krumholz HM. **Risk Trajectories of Readmission and Death in the First Year Following Hospitalization for COPD.** *Am J Respir Crit Care Med 201***7**. Published online ahead of print (2017 Dec 5).

Colak Y, Afzal S, Nordestgaard BG, Vestbo J, Lange P. **Prognosis of asymptomatic and symptomatic, undiagnosed COPD in the general population in Denmark: a prospective cohort study**. *Lancet Respir Med* 2017; 5: 426-434.

Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. **Combined Impact of Smoking and Early-Life Exposures on Adult Lung Function Trajectories**. *Am J Respir Crit Care Med* 2017; 196: 1021-1030.

MECHANISM

Kesimer M, Ford AA, Ceppe A, Radicioni G, Cao R, Davis CW, Doerschuk CM, Alexis NE, Anderson WH, Henderson AG, Barr RG, Bleecker ER, Christenson SA, Cooper CB, Han MK, Hansel NN, Hastie AT, Hoffman EA, Kanner RE, Martinez F, Paine R, 3rd, Woodruff PG, O'Neal WK, Boucher RC. **Airway Mucin Concentration as a Marker of Chronic Bronchitis**. *N Engl J Med* 2017; 377: 911-922.

Hastie AT, Martinez FJ, Curtis JL, Doerschuk CM, Hansel NN, Christenson S, Putcha N, Ortega VE, Li X, Barr RG, Carretta EE, Couper DJ, Cooper CB, Hoffman EA, Kanner RE, Kleerup E, O'Neal WK, Paine R, 3rd, Peters SP, Alexis NE, Woodruff PG, Han MK, Meyers DA, Bleecker ER, SPIROMICS investigators. **Association of sputum and blood eosinophil concentrations with clinical measures of COPD severity: an analysis of the SPIROMICS cohort.** *Lancet Respir Med* 2017; 5: 956-967.

GUIDELINES

Wedzicha JA, Calverley PMA, Albert RK, Anzueto A, Criner GJ, Hurst JR, Miravitlles M, Papi A, Rabe KF, Rigau D, Sliwinski P, Tonia T, Vestbo J, Wilson KC, Krishnan JA. **Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline**. *Eur Respir J* 2017; 50: 1602265.

Wedzicha JA, Miravitlles M, Hurst JR, Calverley PM, Albert RK, Anzueto A, Criner GJ, Papi A, Rabe KF, Rigau D, Sliwinski P, Tonia T, Vestbo J, Wilson KC, Krishnan. **Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline**. *Eur Respir J* 2017; 49: 1600791.

ASTHMA

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DIAGNOSIS OF ASTHMA

Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemière C, Field SK, McIvor RA, Hernandez P, Mayers I, Mulpuru S, Alvarez GG, Pakhale S, Mallick R, Boulet L-P, for the Canadian Respiratory Research Network. **Reevaluation of diagnosis in adults with physician-diagnosed asthma**. *JAMA* 2017; 317: 269-79.

Summary

Confirmation of a new diagnosis of asthma and stepping down the intensity of therapy after symptomatic improvement are guideline recommendations that can be challenging in routine clinical practice. The goal of this study was to determine the rate at which asthma could be ruled out in a randomly selected adult population with newly diagnosed asthma within the last 5 years. Screening for participation was performed by a random phone survey over 3 years in 10 of Canada's largest cities and surrounding suburban areas. 613 participants completed four study visits, designed for survey completion, spirometry and a structured withdrawal of asthma medications with serial methacholine challenge testing if the diagnosis had not been confirmed at the prior visit; these subjects were also followed for 12 months. The main result was that asthma was ruled out in 203 of 613 study participants (33.1%; 95%CI, 29.4%-36.8%). Baseline demographics such as age, sex, race and BMI were not different between participants confirming or ruling out their diagnosis. Of the participants in whom asthma was ruled out, there was a lower rate of performing spirometry at the time of diagnosis, and a lower rate of continuation of asthma medications at the time of study enrollment.

Comments

1. The phone screen required contact of nearly 17,000 households, with approximately 3,000 not completing questionnaires.
2. Patients with more severe disease may not be represented; 22 with maintenance oral steroids were excluded and 88 eligible subjects dropped out prior to study completion.
3. The rate of remission is thought to be lower in newly diagnosed adults relative to children; eleven percent of subjects in this study had spirometry at the time of diagnosis and were subsequently ruled out in this study.
4. Misdiagnosis was more likely in a primary care setting, compared to subjects seen by an asthma specialist.

RISKS OF FREQUENT EXACERBATIONS

Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, Castro M, Peters SP, Phipatanakul W, Aujla S, Bacharier LB, Bleecker ER, Comhair SAA, Coverstone A, DeBoer M, Erzurum SC, Fain SB, Fajt M, Fitzpatrick AM, Gaffin J, Gaston B, Hastie AT, Hawkins GA, Holguin F, Irani A-M, Israel E, Levy BD, Ly N, Meyers DA, Moore WC, Myers R, Opina MTD, Peters MC, Schiebler ML, Sorkness RL, Teague WG, Wenzel SE, Woodruff PG, Mauger DT, Fahy JV, Jarjour NN; for the National Heart, Lung, and Blood Institute's Severe Asthma Research Program-3 Investigators. **Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations**. *Am J Respir Crit Care Med* 2017; 195: 302–13.

Summary

Factors related to proneness to asthma exacerbations have been less well established than in COPD. This study evaluated these factors at the baseline visit for 709 participants of the Severe Asthma Research Program. Sixty percent of the cohort had severe disease and 25% were children. Exacerbation frequency was established by overlapping survey questions at baseline using a consensus definition of three or more days of burst, systemic corticosteroid use for worsening asthma symptoms. Forty percent of the cohort had no exacerbations in the prior year, 35% had one to two, and 25% had three or more exacerbations. The multivariable model showed that obesity, blood eosinophils, bronchodilator responsiveness, chronic sinusitis and reflux were independent risk factors after adjustment for age, sex, race, socioeconomic status and severity. This model was replicated in the combined SARP 1&2 cohort.

Comments

1. Two discordant groups are worth noting: 37% of the patients with no exacerbations at baseline met criteria for severe asthma, and 26% of adults with an FEV1 < 60% predicted had no exacerbations.
2. The rates of exacerbations between adults and children with severe asthma were not different.

3. More aggressive treatment of obesity, sinusitis and/or reflux may impact exacerbation frequency for patients with severe asthma.
4. The limitations of a 12 month recall warrant confirmation by a longitudinal follow up.

TREATMENT OF ASTHMA

Corren J, Parnes JR, Wang L, Mo M, Roseti SL, Griffiths JM, van der Merwe R. **Tezepelumab in adults with uncontrolled asthma**. *N Engl J Med* 2017; 377: 936-46.

Summary

Thymic stromal lymphopoietin (TSLP) is an epithelial derived cytokine thought to be critical to the development of Type 2 allergic airway inflammation. This is a 52 week Phase 2 trial of anti-TSLP (tezepelumab) to evaluate its safety and efficacy using several doses in patients with moderate to severe asthma and at least 1 severe exacerbation in three prior 12 months, as a baseline ACQ score > 1.5. 584 patients underwent randomization to three different doses or placebo. The exacerbation rate was 0.67/yr in the placebo group and 0.19 – 0.26 in the three tezepelumab groups. Subset analysis suggested similar benefits in patients with blood eosinophils above or below 250 cells/μL. Adverse events were similar across the groups.

Comments

1. This is the first Phase 2 asthma study of a therapeutic directed at an epithelial derived cytokine.
2. Biomarker analyses showed reductions in blood eosinophils, exhaled nitric oxide and IgE, suggesting there may be combined advantage to upstream targeting.

Cahill KN, Katz HR, Cui J, Lai J, Kazani S, Crosby-Thompson A, Garofalo D, Castro M, Jarjour N, DiMango E, Erzurum S, Trevor JL, Shenoy K, Chinchilli VM, Wechsler ME, Laidlaw TM, Boyce JA, Israel E. **KIT inhibition by imatinib in patients with severe refractory asthma**. N *Engl J Med* 2017; 376: 1911-20.

Summary

Mast cells are fundamental to asthma pathophysiology but have not previously been targeted for therapy. Relative to other leukocytes, they are more likely to retain expression of c-KIT after maturation and deposition to the subepithelial space. 62 patients with severe asthma and a baseline ACQ score greater than 1.5 underwent a 24-week Phase 2 trial of imatinib vs placebo. Imatinib increased the mean (±SD) methacholine PC20 doubling dose to a greater extent than placebo (1.73±0.60 vs 1.07±0.60, p = 0.048). Serum tryptase levels were reduced, although the baseline tryptase level did not predict a treatment response. The main side effects related to hypophosphatemia, which could be corrected with supplementation.

Comments

1. Exploratory analysis suggested that responses to treatment were inversely correlated to blood eosinophil counts.
2. Airway biopsy analysis suggested a reduction in the number of tissue mast cells.

LUNG CANCER

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IMMUNOTHERAPY AS ADJUVANT TREATMENT FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLCA)

Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Yokoi T, Chiappori A, Lee KH, de Wit M, Cho BC, Bourhaba M, Quantin X, Tokito T, Mekhail T, Planchard D, Kim YC, Karapetis CS, Hiret S, Ostoros G, Kubota K, Gray JE, Paz-Ares L, de Castro Carpeño J, Wadsworth C, Melillo G, Jiang H, Huang Y, Dennis PA, Özgüroğlu M; PACIFIC Investigators. **Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer**. *N Engl J Med*. 2017 Nov 16;377(20):1919-1929.

Summary

Recent studies have investigated the role of immune checkpoint blockade to restore T cell-mediated antitumor immunity in advanced NSCLCa. Durvalumab is a monoclonal antibody against programmed death ligand 1 (PD-L1). The multicenter, randomized, double-blind, phase 3 PACIFIC trial tested whether adjuvant therapy with durvalumab, as compared with placebo, could prolong progression-free survival among patients with unresectable Stage III NSCLCa who had not progressed after at least two cycles of concurrent platinum-based chemotherapy and radiation. There was no requirement for tumor expression of PD-L1. Participants (n=709: 473 durvalumab, 236 placebo) received the study drug within 6 weeks after radiation, and the study drug was continued for up to a year or until disease progression, unacceptable toxicity, or change in treatment regimen. Median progression-free survival was significantly longer with durvalumab vs placebo: 16.8 [13.0-18.1] vs 5.6 [4.6-7.8] months; HR for disease progression or death = 0.52 [0.42-0.65], P<0.001. Improved progression-free survival was observed in all subgroup analyses, including by PD-L1 tumor expression level. Durvalumab also increased median time to death or distant metastasis (23.2 [23.2 - not reached] durvalumab vs 14.6 [10.6-18.6] months placebo; HR=0.52 [0.39-0.69]; P<0.001). Adverse events were common in both arms, with immune-mediated adverse events occurring more often with durvalumab (24.2% vs 8.1% any grade; 3.4% vs 2.6% grade 3 or 4).

Comments

1. Despite the fact that roughly 40% of participants (39.3% durvalumab, 44.3% placebo, p=NS) had tumor cell PD-L1 expression <25%, durvalumab was effective at prolonging progression-free survival overall and in all subgroups, regardless of PD-L1 expression level.
2. Prognosis remains poor with standard concurrent platinum-based chemoradiation therapy for locally advanced, unresectable NSCLCa; this study could represent a paradigm shift in which adjuvant therapy with durvalumab becomes the standard of care.
3. The overall survival analysis, a more objective measure, from this study is still pending; however, the blinding of study investigators for outcome ascertainment to study arm is reassuring.
4. This study reports a pre-planned interim analysis, which may overestimate the magnitude of treatment effect.

ADVERSE EFFECTS OF IMMUNOTHERAPY WITH IMMUNE CHECKPOINT BLOCKERS

Pillai RN, Behera M, Owonikoko TK, Kamphorst AO, Pakkala S, Belani CP, Khuri FR, Ahmed R, Ramalingam SS. **Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer: A systematic analysis of the literature**. *Cancer*. 2018 Jan 15;124(2):271-277.

Summary

Given the emerging role of immune checkpoint blockade in NSCLCa treatment, it is critical to understand their toxicity profile. Pillai and colleagues performed a comprehensive systematic review of studies that reported adverse effects of monoclonal antibodies against programmed cell death protein 1 (PD-1; i.e., nivolumab, pembrolizumab) and programmed death ligand 1 (PD-L1; i.e., atezolizumab, durvalumab, avelumab) when used as monotherapy for NSCLCa, identifying 23 relevant studies with a total of 5744 patients, 3284 in the PD-1 group and 2460 in the PD-L1 group. Adverse effects occurred in roughly two-thirds of patients and were similar for PD-1 and PD-L1 (64% [63%-66%] vs 66% [65%-69%]; P=0.8), with fatigue being the most commonly reported adverse effect. There was no difference in frequency of Grades 3-5 toxicities. By contrast, immune-related adverse events (IRAE, i.e., toxicities mediated by an autoimmune mechanism, such

as pneumonitis, colitis, thyroid disorders, or inflammatory conditions of any organ system) and pneumonitis in particular were more common in PD-1 vs PD-L1 treated patients (IRAE: 16% [14-17%] vs 11% [10-13%], P=.07; pneumonitis (4% [3-5%] vs 2% [1-3%], P=0.01).

Comments

1. This study only examined trials of PD-1 and PD-L1 monotherapy for NSCLCa; toxicity may be higher when used in combination with other chemotherapeutic agents or radiation therapy.
2. This comprehensive systematic review included data from abstracts, which may include preliminary data that has not undergone as rigorous a peer review process as full publications; thus point estimates of adverse effects may change when complete data from these studies are available.
3. Other studies (see Haratani et al in other articles of interest) suggest that patients who experience IRAE related to PD-1 therapy are more likely to experience progression-free survival than those who do not experience treatment-related IRAE.
4. The Thoracic Oncology Assembly of the ATS is currently developing a research statement to identify gaps in knowledge and future research directions related to development, diagnosis, and management of pneumonitis related to immunotherapy among NSCLCa patients.

TARGETED THERAPY FOR ADVANCED EGFR-POSITIVE NON-SMALL CELL LUNG CANCER

Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, Okamoto I, Zhou C, Cho BC, Cheng Y, Cho EK, Voon PJ, Planchard D, Su WC, Gray JE, Lee SM, Hodge R, Marotti M, Rukazenkov Y, Ramalingam SS; FLAURA Investigators. **Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer**. *N Engl J Med*. 2018 Jan 11;378(2):113-125.

Summary

The standard of care for advanced NSCLCa tumors expressing epidermal growth factor receptor (EGFR) mutations is treatment with EGFR-tyrosine kinase inhibitors (TKI) such as gefitinib and erlotinib, which have superior response rate and survival outcomes compared with cytotoxic chemotherapy. However patients with a second EGFR mutation, most commonly T790M, may acquire resistance to first generation EGFR-TKIs. Third-generation EGFR-TKIs (e.g., osimertinib) selectively inhibit both the original sensitizing and T790M mutations and have shown efficacy as a second-line agent after disease progression on earlier generation EGFR-TKIs. The multicenter, double-blinded, randomized phase 3 FLAURA trial compared osimertinib (n=279) to first-generation EGFR-TKI (gefitinib or erlotinib; n=277) for untreated patients with advanced local or metastatic EGFR+ (exon 19 deletion or L858R) NSCLCa. Median duration of treatment was 16.2 months (range 0.1-27.4) osimertinib and 11.5 months (range 0-26.2) first generation EGFR-TKI. Osimertinib increased progression-free survival relative to first-generation EGFR-TKI treatment (median 18.9 [15.2-21.4] vs 10.2 [9.6-11.1] months; HR for disease progression or death, 0.46 [0.37-0.57]; P<0.001), including fewer cases of central nervous system progression (6% vs 15%), with similar findings across all pre-specified subgroups. Osimertinib-treated patients experienced fewer serious adverse events (Grade 3-5: 34% osimertinib vs. 45% first-generation EGFR-TKI). Rare but serious adverse events included interstitial lung disease and QT prolongation.

Comments

1. The FLAURA trial establishes osimertinib as an efficacious first-line treatment for advanced NSCLCa, with a comparable or superior safety profile to first-line EGFR-TKIs.
2. This paper represents an interim analysis for the effect on overall survival and could not conclusively comment on this endpoint, although the authors highlight the early separation in Kaplan-Meier curves for overall survival favoring osimertinib.
3. It is unknown whether resistance to osimertinib will develop and limit effectiveness as a first line therapy, similar to the experience with first-generation EGFR-TKIs.

LUNG CANCER SCREENING: PATIENT SELECTION AND COST EFFECTIVENESS

Jemal A, Fedewa SA. **Lung Cancer Screening With Low-Dose Computed Tomography in the United States-2010 to 2015**. *JAMA Oncol*. 2017 Sep 1;3(9):1278-1281.

Summary

Lung cancer screening with low-dose CT (LDCT) was shown in the National Lung Screening Trial (NLST), published in 2011, to decrease lung cancer death by 20% among high risk smokers. In response, multiple organizations including the U.S. Preventive Services Task Force (USPSTF) recommended annual LDCT screening for older individuals (USPSTF: age 55-80) with a heavy smoking history (at least 30 pack-years, either still smoking or quit within the past 15 years). Jemal and Fedewa used national data from the population-based National Health Information Survey to estimate rates of LDCT lung cancer screening in the U.S. in 2010 vs 2015. Based on USPSTF criteria, approximately 8.5 million individuals would have met eligibility for LDCT screening in 2010 (although this is before LDCT screening was recommended), compared with 6.8 million individuals in 2015. However, based on responses to the National Health Information Survey, only a small fraction of individuals received LDCT screening within the prior year, with no significant change before vs after publication of the NLST and guidelines recommending LDCT screening: 3.3% [95% CI 2.3-4.7%] in 2010 vs 3.9% [2.4-6.2%] in 2015, p=0.60.

Comments

1. This study suggests marked underuse of LDCT screening among eligible individuals, representing a missed opportunity to prevent lung cancer deaths among high-risk individuals.
2. This study is limited by reliance on patient self-report of LDCT screening, which may result in inaccurate estimates of actual utilization; other studies (see Wiener et al in other articles of interest) suggest that patients are not always aware that a CT is intended for lung cancer screening.
3. New interventions often take years to disseminate into practice; this study may have been conducted too close to release of the USPSTF guidelines (December 2013) and Medicare coverage policy (February 2015) to have captured the ultimate effect of these policy changes.
4. However, claims data from 2017 also suggests similarly low uptake of LDCT screening among eligible individuals (see Green AK, Bach P. Ann Intern Med. 2018 Feb 6;168(3):223-224.).
5. Further research is needed to determine how best to extend the reach and uptake of LDCT lung cancer screening.

Kumar V, Cohen JT, van Klaveren D, Soeteman DI, Wong JB, Neumann PJ, Kent DM. **Risk-Targeted Lung Cancer Screening: A Cost-Effectiveness Analysis**. *Ann Intern Med*. 2018 Feb 6;168(3):161-169.

Summary

Among patients eligible for low-dose CT (LDCT) lung cancer screening, expected benefits and harms vary dramatically, with patients at the highest risk of lung cancer experiencing greater effectiveness (lower number needed to screen to prevent one lung cancer death) and efficiency (fewer false positive results per lung cancer death prevented). Accordingly, some experts advocate for risk-based screening, with screening eligibility determined by the individual's predicted risk of developing or dying of lung cancer. Kumar and colleagues conducted a cost-effectiveness analysis of risk-based screening with LDCT vs chest x-ray using data from the National Lung Screening Trial. Although LDCT screening conferred a greater benefit in terms of lung cancer deaths prevented in higher risk deciles (9.5 vs 1.2 per 10,000 person-years in decile 10 vs 1), this translated into only a small increase in quality-adjusted life years (QALYs) gained (0.028 vs 0.011 in decile 10 vs 1), because participants in higher risk quintiles were older, had more comorbidities, and were more likely to die of other causes. There was little benefit to risk-based screening in terms of cost-effectiveness given that the small gain in QALYs in higher risk deciles was offset by increased costs of more invasive procedures to evaluate screening findings (incremental cost-effectiveness ratio: $53,000 vs $75,000 per QALY for decile 10 vs 1).

Comments

1. Lung cancer screening was cost-effective in all risk deciles using the commonly accepted willingness to pay threshold of $100,000 per QALY gained, although incremental cost-effectiveness ratio was 30% lower in the highest risk decile.
2. This study challenges previous assumptions that the short-term gains of risk-based LDCT screening in maximizing lung cancer deaths prevented would translate into long-term gains in QALYs and highlights the important effect of older age and smoking-related comorbid illnesses in patients at highest risk of lung cancer death.
3. Given the slow dissemination of LDCT screening into clinical practice (see Jemal et al), this study suggests there may be little benefit of changing from the current age and smoking history cut-offs recommended to determine LDCT screening eligibility, which may be more straightforward to implement, compared to a risk-based approach to determine screening eligibility.

OTHER ARTICLES OF INTEREST

TARGETED TREATMENT AND IMMUNOTHERAPY FOR ADVANCED NON-SMALL CELL LUNG CANCER

Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, Ou SI, Pérol M, Dziadziuszko R, Rosell R, Zeaiter A, Mitry E, Golding S, Balas B, Noe J, Morcos PN, Mok T; ALEX Trial Investigators. **Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer**. *N Engl J Med*. 2017 Aug 31;377(9):829-838.

Brahmer JR, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Zhang J, Lubiniecki GM, Deitz AC, Rangwala R, Reck M. **Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial**. *Lancet Oncol*. 2017 Dec;18(12):1600-1609.

Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, Kaneda H, Hasegawa Y, Tanaka K, Takeda M, Nakagawa K. **Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non-Small-Cell Lung Cancer**. *JAMA Oncol*. 2017 Sep 21. doi: 10.1001/jamaoncol.2017.2925. [Epub ahead of print]

Herbst RS, Morgensztern D, Boshoff C. **The biology and management of non-small cell lung cancer**. *Nature*. 2018 Jan 24;553(7689):446-454.

Lindeman NI, Cagle PT, Aisner DL, Arcila ME, Beasley MB, Bernicker E, Colasacco C, Dacic S, Hirsch FR, Kerr K, Kwiatkowski DJ, Ladanyi M, Nowak JA, Sholl L, Temple-Smolkin R, Solomon B, Souter LH, Thunnissen E, Tsao MS, Ventura CB, Wynes MW, Yatabe Y. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: **Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology**. *J Thorac Oncol*. 2018 Jan 23. pii: S1556-0864(17)33071-X. doi: 10.1016/j.jtho.2017.12.001. [Epub ahead of print]

LUNG CANCER SCREENING: GUIDELINES AND IMPLEMENTATION ISSUES

Mazzone PJ, Silvestri GA, Patel S, Kanne JP, Kinsinger LS, Wiener RS, Soo Hoo G, Detterbeck FC. **Screening for Lung Cancer: CHEST Guideline and Expert Panel Report**. *Chest*. 2018 Jan 24. pii: S0012-3692(18)30094-1. doi: 10.1016/j.chest.2018.01.016. [Epub ahead of print]

Gould MK, Sakoda LC, Ritzwoller DP, Simoff MJ, Neslund-Dudas CM, Kushi LH, Carter-Harris L, Feigelson HS, Minowada G, Doria-Rose VP. **Monitoring Lung Cancer Screening Use and Outcomes at Four Cancer Research Network Sites**. *Ann Am Thorac Soc*. 2017 Dec;14(12):1827-1835.

Wiener RS, Koppelman E, Bolton R, Lasser KE, Borrelli B, Au DH, Slatore CG, Clark JA, Kathuria H. **Patient and clinician perspectives on shared decision-making in early-adopting lung cancer screening programs: A qualitative study**. *J Gen Intern Med.* 2018 Feb 21. doi: 10.1007/s11606-018-4350-9. [Epub ahead of print].

Crosbie PA, Balata H, Evison M, Atack M, Bayliss-Brideaux V, Colligan D, Duerden R, Eaglesfield J, Edwards T, Elton P, Foster J, Greaves M, Hayler G, Higgins C, Howells J, Irion K, Karunaratne D, Kelly J, King Z, Manson S, Mellor S, Miller D, Myerscough A, Newton T, O'Leary M, Pearson R, Pickford J, Sawyer R, Screaton NJ, Sharman A, Simmons M, Smith E, Taylor B, Taylor S, Walsham A, Watts A, Whittaker J, Yarnell L, Threlfall A, Barber PV, Tonge J, Booton R. **Implementing lung cancer screening: baseline results from a community-based 'Lung Health Check' pilot in deprived areas of Manchester**. *Thorax.* 2018 Feb 13. pii: thoraxjnl-2017-211377. doi: 10.1136/thoraxjnl-2017-211377. [Epub ahead of print]

EVALUATION OF INCIDENTALLY DETECTED PULMONARY NODULES

Tanner NT, Porter A, Gould MK, Li XJ, Vachani A, Silvestri GA. **Physician Assessment of Pretest Probability of Malignancy and Adherence With Guidelines for Pulmonary Nodule Evaluation**. *Chest*. 2017 Aug;152(2):263-270.

MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, Mehta AC, Ohno Y, Powell CA, Prokop M, Rubin GD, Schaefer-Prokop CM, Travis WD, Van Schil PE, Bankier AA. **Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017**. *Radiology*. 2017 Jul;284(1):228-243.

STAGING OF LUNG CANCER

Chansky K, Detterbeck FC, Nicholson AG, Rusch VW, Vallières E, Groome P, Kennedy C, Krasnik M, Peake M, Shemanski L, Bolejack V, Crowley JJ, Asamura H, Rami-Porta R; IASLC Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions. **The IASLC Lung Cancer Staging Project: External Validation of the Revision of the TNM Stage Groupings in the Eighth Edition of the TNM Classification of Lung Cancer**. *J Thorac Oncol.* 2017 Jul;12(7):1109-1121.

SURGICAL TREATMENT OF LUNG CANCER

Yang CJ, Wang H, Kumar A, Wang X, Hartwig MG, D'Amico TA, Berry MF. **Impact of Timing of Lobectomy on Survival for Clinical Stage IA Lung Squamous Cell Carcinoma**. *Chest*. 2017 Dec;152(6):1239-1250.

Ezer N, Kale M, Sigel K, Lakha S, Mhango G, Goodman E, Nicastri D, Swanson S, Neugut A, Wisnivesky JP. **Outcomes after Video-assisted Thoracoscopic Lobectomy versus Open Lobectomy for Early-Stage Lung Cancer in Older Adults**. *Ann Am Thorac Soc*. 2018 Jan;15(1):76-82.

BIOMARKERS FOR EARLY DETECTION OF LUNG CANCER – POLICY STATEMENT

Mazzone PJ, Sears CR, Arenberg DA, Gaga M, Gould MK, Massion PP, Nair VS, Powell CA, Silvestri GA, Vachani A, Wiener RS; ATS Assembly on Thoracic Oncology. **Evaluating Molecular Biomarkers for the Early Detection of Lung Cancer: When Is a Biomarker Ready for Clinical Use? An Official American Thoracic Society Policy Statement.** *Am J Respir Crit Care Med*. 2017 Oct 1;196(7):e15-e29.

LUNG CANCER PREVENTION – FUTURE DIRECTIONS?

Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ; CANTOS Trial Group. **Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial**. *Lancet*. 2017 Oct 21;390(10105):1833-1842.

MANAGEMENT OF PLEURAL DISEASES

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INDWELLING PLEURAL CATHETER VS TALC PLEURODESIS FOR MALIGNANT PLEURAL EFFUSION

Thomas R, Fysh ETH, Smith NA, Lee P, Kwan BCH, Yap E, Horwood FC, Piccolo F, Lam DCL, Garske LA, Shrestha R, Kosky C, Read CA, Murray K, Lee YCG. **Effect of an indwelling pleural catheter vs talc pleurodesis on hospitalization days in patients with malignant pleural effusion: The AMPLE randomized clinical trial**. *JAMA* 2017; 318: 1903-12.

Summary

While many studies comparing indwelling pleural catheter (IPC) and talc pleurodesis in patients with malignant pleural effusion (MPE) have suggested equipoise, this important study was the first to use the primary endpoint of days spent in hospital, an endpoint of interest to patients with a limited lifespan. The AMPLE (Australasian Malignant Pleural Effusion) clinical trial was open-label and randomized, with patients drawn from 9 centers in Australia and Asia who were followed for up to 12 months. Patients with symptomatic MPE were randomized to IPC (n=74) or talc pleurodesis (n=72), performed using the protocols at each center. Overall, patients with IPC spent fewer days in hospital (median, 10 days) than did those with talc pleurodesis (12 days) (p=0.03). The difference due to effusion-related causes was mainly seen for the initial admission (1 day vs 3 days), as expected given that the IPC was inserted as an outpatient or overnight stay procedure. Importantly, fewer patients in the IPC group required additional interventions for further drainage (3 vs 16 patients; p=0.001). As in earlier studies, there was no difference in other secondary measures such as breathlessness, quality of life, or survival.

Comments

1. Compared to talc pleurodesis, IPC offers advantages as demonstrated in this study, mainly a shorter overall time in hospital and a need for fewer additional interventions for pleural drainage.
2. Although the actual difference in hospital time may seem small (10 vs 12 days), this may represent a meaningful difference to patients with a limited lifespan, as suggested when expressed as a percentage of remaining lifespan (6.2 vs 11.1%).
3. Although cost was not analyzed because of the differences in the participating centers, a shorter hospital time may represent a significant cost savings, especially if the IPC drainage is handled by family members instead of visiting nurses.
4. The technique for handling the IPC and the talc pleurodesis were left to the participating centers and thus, it is difficult to compare the approaches with those at one's own institution.
5. The shorter length of hospital stay was also observed in patients with mesothelioma, who, given the high incidence of mesothelioma in Australia, represented more than 25% of the patients with MPE in this study.

INDWELLING PLEURAL CATHETER: HOW OFTEN TO DRAIN?

Wahidi MM, Reddy C, Yarmus L, Feller-Kopman D, Musani A, Shepherd RW, Lee H, Bechara R, Lamb C, Shofer S, Mahmood K, Michaud G, Puchalski J, Rafeq S, Cattaneo SM, Mullon J, Leh S, Mayse M, Thomas SM, Peterson B, Light RW. **Randomized trial of pleural fluid drainage frequency in patients with malignant pleural effusions. The ASAP trial**. *Am J Respir Crit Care Med* 2017; 195:1050-7.

Summary

The approach to drainage of malignant pleural effusions via indwelling pleural catheters (IPC) has been empiric, often based on symptoms. It is not known whether a more aggressive drainage would encourage autopleurodesis (the spontaneous cessation of fluid drainage not due to catheter blockage), and thus allow earlier removal of the IPC. In this prospective trial, patients with IPC for drainage of malignant pleural effusions were randomized to daily or every other day drainage (n=73, daily; n=76, every other day). The drainage in each group was to a maximum of 1 liter. Over the study period of 12 weeks, the group with daily drainage had a higher rate of autopleurodesis (47% vs 24%, p=0.003) and a more rapid autopleurodesis (54 days vs 90 days) than did the every other day drainage group. There were no differences in adverse events, quality of life and satisfaction of the patients with the catheter. Cost was not evaluated. The results of this study give patients and clinicians insight into different ways to manage pleural fluid drainage to accomplish autopleurodesis. If this is a goal of the patient, then daily drainage offers benefits.

Comments

1. Daily fluid drainage via an indwelling pleural catheter increases the rate of autopleurodesis compared to every other day drainage.
2. Despite more frequent manipulation of the catheter for drainage, infections and other complications were no different in the two groups.
3. The reason for the enhanced autopleurodesis was not identified, and it was not clear whether the important factor was the daily drainage or the drainage of more fluid (max 1L per day vs 1L every other day).
4. Patients with trapped lung were excluded from this study and thus, it is not known how they would respond.
5. Other means to achieve autopleurodesis are being investigated, including other approaches to drainage (AMPLE-2 study of daily vs symptom-driven drainage), alteration of the catheter (e.g. impregnation with silver nitrate) or introduction of a pleurodesis agent (e.g. IPC plus talc - see next article by Bhatnagar et al, 2018).

INDWELLING PLEURAL CATHETER COMBINED WITH TALC

Bhatnagar R, Keenan EK, Morley AJ, Kahan BC, Stanton AE, Haris M, Harrison RN, Mustafa RA, Bishop LJ, Ahmed L, West A, Holme J, Evison M, Munavvar M, Sivasothy P, Herre J, Cooper D, Roberts M, Guhan A, Hooper C, Walters J, Saba TS, Chakrabarti B, Gunatilake S, Psallidas I, Walker SP, Bibby AC, Smith S, Stadon LJ, Zahan-Evans NJ, Lee YCG, Harvey JE, Rahman NM. Miller RF, Maskell NA. **Outpatient talc via indwelling pleural catheter for malignant effusions**. *N Engl J Med* (in press)

Summary

Whereas IPC and talc have been viewed as alternative approaches to MPE, here the two have been combined and compared to IPC alone. In this IPC-Plus trial, 154 patients with an IPC underwent maximal drainage at day 0 and 10 and drainage in the intervening 10 days to achieve optimal pleural fluid removal and lung reinflation; if at least 75% of the lung was apposed to the chest wall on CXR (or similarly on ultrasound), the patients were then randomized to receive 4 g talc in 50 mL of saline (Steritalc, Novatech SA, France, size graded) or 50 mL of saline alone via the IPC. IPC drainage continued at least twice per week during the study. Over 35 days, the likelihood of pleurodesis was more than double in the IPC-talc group than in the IPC alone group (30/69, 43.5% vs 16/70, 22.9%, p=0.008). The benefit was still observed at 70 days. In addition, the IPC-talc group had better quality of life measures and fewer symptoms. There were no significant differences in time spent in hospital or mortality, or adverse events such as catheter blockage.

Comments

1. Intrapleural talc given to outpatients via an indwelling pleural catheter is effective in producing a pleurodesis without adding complications and without causing catheter blockage.
2. When studied prospectively, IPC alone induced pleurodesis in 23% at 35 days and 27% at 70 days, a lower rate than reported in many retrospective studies.
3. The talc used in this study is graded to remove the smallest particles and has been shown to be safer than ungraded talc; of note, this size graded talc has recently been made available for use in the U.S.
4. For those who are now placing IPC for patients with MPE, talc can now be added for patients without trapped lung with significant improvement in rate of pleurodesis and also quality of life and symptom measures.

NEEDLE ASPIRATION VS CHEST TUBE FOR SPONTANEOUS PNEUMOTHORAX

Thelle A, Gjerdevik M, SueChu M, Hagen OM, Bakke P. **Randomised comparison of needle aspiration and chest tube drainage in spontaneous pneumothora**x. *Eur Respir J* 2017 49:1-9.

Summary

Official guidelines differ on the initial approach to spontaneous pneumothorax (PTX): the British Thoracic Society advocates needle aspiration, the ACCP advocates chest tube drainage. In this prospective, randomized trial, patients presenting to 3 Norwegian hospitals with symptomatic spontaneous pneumothorax (PTX) were managed initially with either needle aspiration (NA) or with chest tube drainage (CTD). All were admitted to hospital for oxygen (3L/min), observation and management. For the NA group (n=64), a 16G catheter was inserted in the second intercostal space and attached to a 3-way stopcock; air was aspirated up to a maximum of 3.5L. Two efforts at aspiration were allowed; if they failed, the patient underwent CTD. For the CTD group (n=63), a 14-20 F chest tube was inserted and placed to water seal. Overall, those randomized to NA had greater immediate success and a shorter time in hospital than those randomized to CTD: immediate success 68.8% vs 31.8%, ($p<0.001$) and hospital stay 2.4 days vs 4.6 days, ($p<0.001$). Complications were found only in the CTD group, including bleeding, wound infection, subcutaneous emphysema and empyema. The shorter hospital stay in the NA group was observed in both those with primary spontaneous PTX and in secondary PTX.

Comments

1. Needle aspiration is effective in the initial approach to spontaneous PTX and may allow outpatient management of some PTX.

2. Long-term response in these patients was not studied and thus, the use of needle aspiration or chest tube for preventing recurrence was not addressed.
3. The similar benefit in those thought to have no lung disease (primary) compared to those with lung disease (secondary) suggests that these entities are not significantly different and that all PTX derives from lung abnormalities.
4. The results seen with the chest tube arm appear worse than expected, perhaps due to a larger tube and placement by "junior doctors on call."
5. Further studies are needed to confirm these findings and to clarify the optimal approach to management of PTX.

PROPHYLACTIC RADIATION TO PROCEDURE TRACTS IN MESOTHELIOMA

Clive AO, Taylor H, Dobson L, Wilson P, de Winton E, Panakis N, Pepperell J, Howell T, Stewart SA, Penz E, Jordan N, Morley AJ, Zahan-Evans N, Smith S, Batchelor TJP, Marchbank A, Bishop L, Ionescu AA, Bayne M, Cooper S, Kerry A, Jenkins P, Toy E, Vigneswaran V, Gildersleve J, Ahmed M, McDonald F, Button M, Lewanski C, Comins C, Dakshinamoorthy M, Lee YCG, Rahman NM, Maskell NA. **Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled trial**. *Lancet Oncol.* 2016: 17:1094-1104.

Summary

Mesothelioma can migrate along procedure tracts, potentially causing painful procedure-tract metastases. There is conflicting evidence whether prophylactic radiation can prevent this complication. This prospective, randomized and adequately powered trial has been eagerly awaited. Patients with mesothelioma and recent procedure (e.g. VATS, thoracotomy, pleuroscopy, chest tube placement, IPC) were randomized to receive prophylactic radiation of 21 Gy in three fractions within 42 days of the procedure or deferred radiotherapy if metastases developed. There were no differences between the incidence of procedure-tract metastasis in the prophylactic radiotherapy group (9/102, 8.8%) vs the delayed radiotherapy group (16/101, 15.8%) (p=0.14). There was no difference in the time to development (179 vs 224 days, p=0.34). Nor were there differences in chest pain, quality of life, median overall survival, or cost. Of the metastases that did develop, few were painful (8/25, 32%), with no difference in the two groups. The overall conclusion is that prophylactic radiotherapy is not beneficial; the recommendation to avoid prophylactic radiotherapy has been included in recent BTS guidelines. Further studies may be warranted in subgroups that showed a suggestion of benefit: those with epithelioid tumors and those who did not receive chemotherapy.

Comments

1. This large randomized trial is reassuring that prophylactic radiation is not needed and is no better than close observation with radiotherapy in the small number that develop metastases.
2. Even when procedure-tract metastases develop, they are not commonly painful.
3. Concern about these metastases should not dissuade clinicians from performing necessary invasive procedures.
4. Indwelling pleural catheters were not harmed by the radiotherapy.

OTHER ARTICLES OF INTEREST

MORE ON MALIGNANT EFFUSIONS

Mishra EK, Clive AO, Wills GH, Davies HE, Stanton AE, Al-Aloul M, Hart-Thomas A, Pepperell J, Evison M, Saba T, Harrison RN, Guhan A, Callister ME, Sathyamurthy R, Rehal S, Corcoran JP, Hallifax R, Psallidas I, Russell N, Shaw R, Dobson M, Wrightson JM, West A, Lee YCG, Nunn AJ, Miller RF, Maskell NA, Rahman NM. **Randomized controlled trial of urokinase versus placebo for nondraining malignant pleural effusion**. *Am J Respir Crit Care Med* 2018;197:502-8.

Olfert JA, Penz ED, Manns BJ, Mishra EK, Davies HE, Miller RF, Luengo-Fernandez R, Gao S, Rahman NM. **Cost-effectiveness of indwelling pleural catheter compared with talc in malignant pleural effusion**. *Respirology* 2017;22:764-770.

Psallidas I, Yousuf A, Talwar A, Hallifax RJ, Mishra EK, Corcoran JP, Ali N, Rahman NM. **Assessment of patient-reported outcome measures in pleural interventions**. *BMJ Open Respir Res* 2017;4:e000171.

Porcel JM, Pardina M, Bielsa S, González A, Light RW. **Derivation and validation of a CT scan scoring system for discriminating malignant from benign pleural effusion**s. *Chest* 2015 Feb;147(2):513-519.

BENIGN EFFUSIONS

Patil M, Dhillon SS, Attwood K, Saoud M, Alraiyes AH, Harris K. **Management of benign pleural effusions using indwelling pleural catheters: A systematic review and meta-analysis**. *Chest* 2017 Mar;151(3):626-635.

Sehgal IS, Dhooria S, Aggarwal AN, Behera D, Agarwal R. **Diagnostic performance of Xpert MTB/RIF in tuberculous pleural effusion: Systematic review and meta-analysis**. *J Clin Microbiol* 2016;54:1133-6.

Popowicz N, Bintcliffe O, De Fonseka D, Blyth KG, Smith NA, Piccolo F, Martin G, Wong D, Edey A, Maskell N, Lee YCG. **Dose de-escalation of intrapleural tissue plasminogen activator therapy for pleural infection. The alteplase dose assessment for pleural infection therapy project**. *Ann Am Thorac Soc* 2017;14:929-936.

Porcel JM, Pardina M, Alemán C, Pallisa E, Light RW, Bielsa S. **Computed tomography scoring system for discriminating between parapneumonic effusions eventually drained and those cured only with antibiotics**. *Respirology* 2017;22:1199-1204.

PROGNOSIS OF PLEURAL EFFUSIONS

Morales-Rull JL, Bielsa S, Conde-Martel A, Aramburu-Bodas O, Llàcer P, Quesada MA, Suárez-Pedreira I, Manzano L, Barquero MM, Porcel JM; RICA Investigators group. **Pleural effusions in acute decompensated heart failure: Prevalence and prognostic implications**. *Eur J Intern Med* 2018 Epub ahead of print.

Zhou X, Zhang Z, Zhai Z, Zhang Y, Miao R, Yang Y, Xie W, Wan J, Wang C. **Pleural effusions as a predictive parameter for poor prognosis for patients with acute pulmonary thromboembolism**. *J Thromb Thrombolysis* 2016;42:432-40.

Walker SP, Morley AJ, Stadon L, De Fonseka D, Arnold DT, Medford ARL, Maskell NA. **Nonmalignant pleural effusions: A prospective study of 356 consecutive unselected patients**. *Chest* 2017;151:1099-1105.

Wang CM, Ling ZG, Wu YB, Cai SQ, Tang ZM, Wu C, Chen YQ. **Prognostic value of pleural lavage cytology in patients with lung cancer resection: An updated meta-analysis.** *PLoS One* 2016;11:e0157518.

PLEURAL MANOMETRY

Grabczak EM, Krenke R, Zielinska-Krawczyk M, Light RW. **Pleural manometry in patients with pleural diseases - the usefulness in clinical practic**e. *Respir Med* 2018 Jan 31. pii: S0954-6111(18)30023-4

MESOTHELIOMA

Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, Molinier O, Corre R, Monnet I, Gounant V, Rivière F, Janicot H, Gervais R, Locher C, Milleron B, Tran Q, Lebitasy MP, Morin F, Creveuil C, Parienti JJ, Scherpereel A; French Cooperative Thoracic Intergroup (IFCT). **Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial**. *Lancet* 2016;387:e24.

Woolhouse I, Bishop L, Darlison L, De Fonseka D, Edey A, Edwards J, Faivre-Finn C, Fennell DA, Holmes S, Kerr KM, Nakas A, Peel T, Rahman NM, Slade M, Steele J, Tsim S, Maskell NA. **British Thoracic Society guideline for the investigation and management of malignant pleural mesothelioma**. *Thorax* 2018;73(Suppl 1):i1-i30

Arnold DT, De Fonseka D, Hamilton FW, Rahman NM, Maskell NA. **Prognostication and monitoring of mesothelioma using biomarkers: a systematic review**. *Br J Cancer* 2017;116:731-741.

GENOMICS AND PRECISION MEDICINE IN LUNG DISEASE

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GENOME-WIDE ASSOCIATION STUDY (GWAS) OF GENERAL POPULATIONS REVEAL A RISK PROFILE OF 97 GENETIC VARIANTS ASSOCIATED WITH LUNG FUNCTION

Wain LV, Shrine N, Artigas MS, et al. **Genome-wide association analyses for lung function and chronic obstructive pulmonary disease identify new loci and potential druggable targets**. *Nat Genet* 2017;49(3):416-425.

Summary

An understanding of the genetic factors that cause COPD could facilitate the development of multi-gene risk profiles which could inform on disease risk, prevention, and target drug identification. Genome-wide association studies (GWAS) take advantage of genotyping "chips" which cover 100,000's to millions genetic variants in a group of individuals for genome-wide studies to discover variants in genes associated with risk for diseases such as COPD. Multiple prior GWAS for COPD and lung function have been limited by sample size yet have identified several variants which cumulatively account for a small proportion of the heritability of COPD. This genetic study scanned over 27 million variants from whole-genome data in several, large general populations to perform genome-wide association studies (GWAS) in two stages. The first stage was variant discovery in 48,943 individuals selected from the extremes of lung function from the U.K. BioBank followed by a second, confirmatory stage with meta-analysis in an additional 95,375 individuals from U.K. Biobank, SpiroMeta consortium, and the U.K. Households Longitudinal Study. These stages revealed 43 new genetic variant signals for lung function which were estimated to account for four percent of the heritability of FEV1, three percent of the heritability of FVC, and five percent of the heritability of FEV1/FVC ratio. These signals were combined with 54 known lung function variants from prior GWAS resulting in a risk profile consisting of a total 97 variant signals which accounted for 10 percent of the heritability of FEV1, six percent of the heritability of FVC, and 14 percent of the heritability of FEV1/FVC ratio. 95 of these variant signals were evaluated in 20,086 COPD cases and 215,630 controls, including populations ascertained for a significant cigarette smoking history and COPD (COPDGene, ECLIPSE, National Emphysema Treatment Trial [NETT], a Norway COPD cohort [GenKols]) and general populations with COPD or control status determined by a combination of spirometry and electronic medical record data (Normative Aging Study [NAS], deCODE COPD, U.K. BioBank, BioMe, and DiscovEHR). This resulted in a 95-variant weighted risk score which was significantly associated with COPD with a 1.24 increase odds of COPD for every six variant alleles in an individual subject (OR=1.24, p=5.05x10-49). Individuals with risk scores in the top decile had a greater than 3-fold risk for moderate to severe COPD compared to those in the lowest decile (OR=3.7).

Comments

1. This large GWAS for lung function demonstrates the power of leveraging different general population and COPD cohorts from a variety of sources to develop a cumulative genetic risk score strongly associated with COPD and accounting for 48% of the population attributable risk.
2. The genetic risk score was developed based on discovery stage using a large general population sample that was not ascertained for a history of cigarette smoking which facilitated the discovery of genes that contribute to lung function impairment in the presence or absence of cigarette smoking (autoimmune and lung development pathways). Thus, this approach did not capture all genetic variants associated with COPD in the setting of the critical gene-by-environment interaction with cigarette smoke.
3. The gene pathways represented by this genetic risk score are within biologic pathways which drive baseline lung function and risk for impairment in general populations but also implicate genes that are targeted by currently available FDA-approved drugs (CHRM3 is a gene which encodes the muscarinic acetylcholine receptor M3, among others).
4. This genetic variant risk score was determined and validated in primarily European descent White populations and might not directly apply to other racial or ethnic groups from different ancestries where the risk variants could have differing allele frequencies.

A LARGE GWAS FOR MODERATE TO SEVERE COPD IDENTIFIES A NOVEL GENE VARIANT AND AN ALPHA1 ANTITRYPSIN GENE VARIANT FOR THE DEVELOPMENT OF COPD RISK PROFILES

Busch R, Hobbs BD, Zhou J, et al. **Genetic Association and Risk Scores in a Chronic Obstructive Pulmonary Disease Meta-analysis of 16,707 Subjects**. *Am J Respir Cell Mol Biol*. Jul 2017;57(1):35-46.

Summary

The heritability of COPD cannot be fully attributed to variants which attain the strict thresholds of genome-wide significance in GWAS. Earlier studies have been limited by sample size, restricting the power of these studies, or have consisted of large general populations which might not adequately account for important tobacco smoke exposure, a critical gene-environment interaction for COPD pathogenesis. This genetic study scanned the genomes of over 16,707 subjects with moderate to severe COPD and controls from eight cohorts primarily ascertained for a significant cigarette smoking history to perform GWAS for COPD risk. This GWAS in 9,221 moderate to severe COPD cases and 7,486 controls confirmed COPD associations with variants in six genomic regions from prior studies (TGFB2, FAM13A, HHIP, nicotine receptor gene region [CHRNA3/CHRNA5/IREB2], RIN3) while identifying two novel variants on chromosome 5q23 and 14q32 significantly associated with COPD below the genome-wide significance threshold ($p \leq 5.0 \times 10^{-8}$). The variant on chromosome 14q32 was approximately 200,000 bases away from the gene encoding alpha1-antitrypsin and likely resulted from the strong effects of the PI Z variant on alpha1-antitrypsin deficiency and COPD risk. 12 of 23 gene variants known to be associated with lung function in prior general population studies were also associated with COPD risk with nominal significance ($p<0.05$). Combined risk scores using seven risk variants for COPD (COPD7 score: TGFB2, FAM13A, HHIP, CHRNA3, RIN3, CYP2A6, MMP12) or these COPD risk variants plus 23 lung function variants from general populations (LUNG30 score) were constructed based on this and prior GWAS. In an independent COPD case-control cohort, higher risk scores reflecting a higher number of risk variant alleles were incrementally associated with lower FEV1 and higher COPD risk. Despite these associations, these scores did not account for a significant percentage of the observed COPD risk.

Comments

1. This is one of the largest GWAS of moderate to severe COPD which confirmed the role of genetic variants uniquely associated with COPD in the setting of cigarette smoke exposure and lung function in general populations in cumulatively determining COPD risk.
2. The risk scores developed in this study (COPD7 and LUNG30) demonstrate a promising approach for COPD risk prediction and for understanding the mechanisms underlying severe COPD.
3. These risk scores were only able to predict a small percentage of the observed COPD risk likely due to limitations in sample size and the inability of GWAS to account for complex, environmental risk factors, including tobacco smoke exposure critical to altering gene expression and causing COPD.
4. The risk score used in this model were generated using risk variants identified before the most recent U.K. BioBank GWAS published which identified 43 additional variants associated with lung function in general populations resulting in a 95-variant risk score which was much more strongly associated with COPD risk.
5. While this study included African Americans from COPDGene (821 cases and 1,749 controls), the remainder of the population primarily consisted of European descent White cohorts which limits the interpretation of these findings in African descent populations where the allele frequencies of risk variants could differ or additional unique genetic risk factors could play a role.

LARGEST GWAS TO DATE FOR IDIOPATHIC PULMONARY FIBROSIS IDENTIFIES A NOVEL RISK LOCUS, A DRUGGABLE TARGET

Allen RJ, Porte J, Braybrooke R, et al. **Genetic variants associated with susceptibility to idiopathic pulmonary fibrosis in people of European ancestry: a genome-wide association study**. *Lancet Resp Med* 2017;5(11):869-880.

Summary

GWAS performed in cohorts ascertained for idiopathic pulmonary fibrosis (IPF) cases has reported variants in genes related to lung defense (mucin 5B gene, MUC5B), telomere maintenance (telomerase reverse transcriptase gene, TERT), and cell-to-cell adhesion (desmoplakin, DSP, and dipeptidyl peptidase 9 genes, DPP9). Some of these IPF-associate genetic variants have been associated with disease progression, but cumulatively account for approximately 30 percent of the genetic risk for this disease. This GWAS is the largest performed for IPF and brought together 2,760 IPF cases and 8,561 controls for GWAS performed in two stages. In the first stage, GWAS was performed in samples from 602 IPF patients in nine U.K.-based medical centers combined with 3,366 controls from the U.K. BioBank followed by a second, confirmatory stage in 2,158 IPF cases and 5,195 controls from two U.S.-based cohorts from the Colorado and Chicago consortia. In the first stage, over 13 million variants were analyzed resulting in the identification of 44 genetic signals of which 27 were available in the second stage cohorts for analysis. A meta-analysis of the combined two U.S. cohorts identified genetic variants in three genes that remained significant at the genome-wide multiple testing threshold ($p<5 \times 10^{-8}$): DSP, MUC5B, and a novel locus on AKAP13, a gene encoding A-kinase anchoring protein 13. The AKAP13 variant was associated with mRNA expression of AKAP13 in non-diseased lung tissue expression databases further implicating altered expression as a possible pathogen IPF mechanism. This was substantiated in lung tissue samples from IPF patients which showed that AKAP13 mRNA expression was 1.4 times higher compared to control lung tissue. Genetic signals in seven prior genes were confirmed to be associated with IPF in stage 1 samples with at least nominal significance; including MUC5B, DSP, TERT, DPP9, TOLLIP, and FAM13A.

Comments

1. This large GWAS of IPF cases and controls is the largest for IPF and confirmed seven previously known genetic variants for IPF risk while identifying a novel genetic signal at the A-kinase anchoring protein (AKAP13) gene.
2. This large GWAS identified a novel gene locus which has not been previously implicated in IPF pathogenesis but regulates a pharmacologically modifiable molecular pathway: 11 proteins were found to interact with AKAP13, some of which were targets for existing drugs (aspirin, dextromethorphan) or compounds under development.
3. The potential biologic role of AKAP13 in IPF pathogenesis was further confirmed using RNA expression data in complementary studies in lung tissue samples.
4. This study was limited to European Whites with IPF and, thus, might not be directly translatable to other interstitial lung diseases or other racial and ethnic groups where IPF is less common or where these genetic variants might have different allele frequencies.

GWAS DEMONSTRATES SHARED RISK VARIANTS FOR ASTHMA, ALLERGIC RHINITIS, AND ECZEMA

Ferreira MA, Vonk JM, Baurecht H, et al. **Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology**. *Nat Genet* 2017;49(12):1752-1757.

Summary

Asthma, allergic rhinitis, and eczema commonly coexist in the same individual, but the common genetic risk factors underlying this observation are largely unknown. This large GWAS scanned over 8 million variants in 180,129 cases with allergy-related diseases (asthma, allergic rhinitis, and eczema) and 180,709 controls from 13 study cohorts of European White descent, including general populations such as 23andMe (N=118,269) and the U.K. BioBank (N=138,354). This GWAS identified 136 variants within 99 genomic regions (50 known and 49 novel regions) independently associated with allergic disease at the genome-wide significance threshold ($p<3x10-8$). 130 of these 136 sentinel variants from this study had similar frequencies between those who only reported having either asthma (N=12,268), allergic rhinitis (N=33,305), or eczema (N=6,276). Thus, there was no evidence that these variants differentially affected one allergic disease versus another. In subsequent studies using a tissue-specific expression database, these investigators demonstrated that these variants were in genes specifically expressed in the lung and in whole blood. Additional analyses using the Encyclopedia of DNA Elements (ENCODE) project database and a biologic pathway GeneNetwork analysis demonstrated that these genes were enriched for biologic pathways related to T and B cell activation, B cell proliferation and isotype switching, and IL-2 and IL-4 production. These complex genomics analyses confirmed that genetic risk variants shared between asthma, allergic rhinitis, and eczema operate to a large extent by regulating the expression of genes in pathways related to lymphocyte mediated immunity, induction of cell death, lipid phosphorylation, and NK cell differentiation. In addition, data from the BIOS consortium also demonstrated that a significant percentage of the genes found using this GWAS (27 percent) occurred near gene methylation sites that significantly correlated with mRNA expression.

Comments

1. This large GWAS of asthma and collateral atopic disease resulted in a large sample size from a variety of general population samples that confirmed 50 known genomic risk regions while facilitating the discovery of a large number of new risk variants for three genetically correlated allergic diseases.
2. This GWAS is the largest to identify common genetic variants co-inherited in asthma, allergic rhinitis, and eczema which could, in part, explain why these three conditions co-exist.
3. The top 136 genetic associations found in this GWAS resulted in a heritability estimate of 3.2 percent for asthma, 3.8 percent for hay fever, 1.2 percent for eczema and, thus, accounted for one-fifth, one-sixth, and one-tenth of the overall heritability for each disease, respectively, which remains a small proportion.
4. The genetic variants found in this GWAS were significantly associated with allergic disease at the whole-genome threshold and were functionally validated using complex gene expression database and pathway analyses.
5. The limitations of this large GWAS were that the use of general populations resulted in allergic disease diagnoses based on self-report or physician report (ICD-9 codes) which could result in misdiagnoses and that the top novel variant associations were not confirmed or replicated in an independent cohort. Thus, additional replication in cohorts with objectively confirmed asthma diagnoses will be necessary prior to translating these findings into clinical use.
6. This GWAS found a significant percentage of genes adjacent to methylation sites that influenced mRNA expression, independent of the sentinel risk variant, which raises the possibility that environmental exposures, such as cigarette smoke, could alter DNA methylation to influence risk gene expression and asthma risk.
7. The findings of this study in European Whites might not apply to the genetic risk for allergic disease in other racial and ethnic groups where these genetic variants might have different allele frequencies or where ethnic-specific genetic factors might play a role.

EMR-BASED GWAS FOR ASTHMA CONFIRMS PRIOR GENE DETERMINANTS AND DISCOVERIES NOVEL DETERMINANTS FOR ASTHMA RISK

Almoguera B, Vazquez L, Mentch F, et al. **Identification of Four Novel Loci in Asthma in European American and African American Populations**. *Am J Respir Crit Care Med* 2017;195(4):456-463.

Summary

The discovery of novel genes using GWAS has been fueled by the lower costs of higher-throughput DNA genotyping and next-generation sequencing. This expansion of avail-

able genetic data in a greater number of individuals has occurred in parallel with the rapid adoption of the electronic medical record (EMR) to track medical diagnoses and as a massive source of clinical data. Almoguera and colleagues from the eMERGE network (Electronic Medical Records and Genomics Network) performed a large GWAS to identify genetic variants associated with physician-diagnosed asthma. The EMR-based diagnosis of asthma was based on a novel phenotyping algorithm which was used to mine the EMR of more than 57,000 patients to identify 21,644 physician-diagnosed asthma cases and controls (7,397 African Americans and 14,247 European Americans based on groupings of genetic ancestry). This algorithm diagnosed asthma based on ICD-9 code, medication prescription data, and EMR mention of "asthma" or "wheezing." This algorithm had a positive predictive value of 97 percent for cases and 99 percent for controls based on a random manual chart review. This GWAS identified three novel genetic regions with biologically plausible gene variants associated with asthma risk while confirming a previously replicated variant on chromosome 5q22 adjacent to a gene which regulates allergic inflammation (TSLP). All four regions had associations which reached the genome-wide level of statistical significance ($p \leq 5.0 \times 10^{-8}$) in either European or African American samples, but not both, demonstrating the importance of having an ethnically diverse sample to find population-specific asthma risk variants. In addition, multiple regions previously associated with asthma (including all reported variants on chromosome 17q12-21, the most replicated asthma risk locus) had associations which reached nominal significance ($p < 5 \times 10^{-3}$) further validating an EMR-based approach to identify asthma risk variants using a well-powered GWAS.

Comments

1. This GWAS is the largest based on EMR-based asthma diagnoses and demonstrates the potential for gene discovery through the integration of high-throughput genetic data with massive EMR clinical databases filtered using appropriate diagnostic algorithms.
2. For this GWAS, it was advantageous to include ethnically diverse cohorts for novel asthma variant discovery; however, this eMERGE cohort was stratified into two genetically defined populations based on genetic ancestry groupings which did not account for the cultural and environmental differences between different U.S. ethnic groups which could influence asthma risk and severity.
3. The ability to recapitulate prior genetic risk associations with asthma clearly showcases the promise of EMR-based genetic studies in facilitating novel variant discovery while demonstrating that published asthma risk variants found in well-designed study cohorts are valid biomarkers for asthma risk in a real-world setting.
4. The novel variants identified in this GWAS will have to be further confirmed and characterized in additional cohorts with objectively diagnosed asthma subjects.
5. Additional refinement of algorithms for mining EMR data using lung function or additional "free text" data with natural language processing could improve the accuracy of an asthma diagnosis for future EMR-based genetic studies.
6. This study is timely as the Precision Medicine Initiative (PMI) previously allocated $215 million for whole-genome sequencing in more than one million Americans from large EMR networks to advance precision medicine research.

LARGE GWAS FOR LUNG CANCER DISCOVERS TEN NEW RISK VARIANTS AND EMPHASIZES THE IMPORTANCE OF NICOTINE ADDICTION PATHWAYS

McKay JD, Hung RJ, Han Y, et al. **Large-scale association analysis identifies new lung cancer susceptibility loci and heterogeneity in genetic susceptibility across histological subtypes**. *Nat Genet* 2017;49(7):1126-1132.

Summary

Tobacco smoke is the main risk factor for lung cancer; however, lung cancer has been estimated to have a heritability of 18 percent. Prior GWAS have identified several risk variants for lung cancer, but the genetic variants discovered to date only account for a small percentage of the observed heritability of this disease. This GWAS evaluated over 10 million variants in 14,803 lung cancer cases and 12,262 controls of European ancestry and combined these data with prior lung cancer GWAS using meta-analysis resulting in a total of 29,266 cases and 56,240 controls. These data were complemented by mRNA expression data from 1,425 normal lung tissue samples. Variants in 18 genomic regions was associated with lung cancer at the genome-wide threshold ($p < 5.0 \times 10^{-8}$), of which 10 were novel regions, not found in prior GWAS for lung cancer. Four of these novel genomic regions were associated with lung cancer overall without heterogeneity among subtypes while six were associated with adenocarcinoma. A novel region associated with lung cancer overall on chromosome 8p21 had multiple independent signals in the gene encoding a nicotinic receptor (CHRNA2) providing novel evidence for this locus as a determinant for smoking addiction behavior and the gene encoding EPHX2 which regulates xenobiotic metabolism. Variants in three of the regions associated with adenocarcinoma were adjacent to genes related to telomere regulation on chromosomes 10q24, 20q13, and 5p15 (TERT), of which TERT has been previously implicated in lung cancer GWAS. The strongest variant association in this GWAS was the confirmation of the gene encoding another nicotinic receptor, CHRNA5 (association $p = 10^{-103}$), further demonstrating the importance of genes related to nicotine addiction. The variants identified in this GWAS appeared to account for 12 percent of the familial relative risk for lung cancer, of which 3.5 percent were attributed to the novel loci identified.

Comments

1. This GWAS is among the most comprehensive for lung cancer and histologic subtypes which identified eight new loci while confirming ten previously discovered loci for lung cancer.
2. This genetic study demonstrated that there are common genetic risk factors for all lung cancers overall, but that there are also genetic risk factors that differ between different histologic subtypes.
3. This GWAS further confirms the importance of genes which regulate the nicotine addiction pathway in the genetic architecture underlying lung cancer since three genes were found (CHRNA5, CHRNA2, CYP2A6) related to this pathway, one of which was novel (CHRNA2).
4. Despite the large size of this GWAS, the genes identified only accounted for a small proportion of the observed heritability of lung cancer risk suggesting that additional genetic and environmental risk factors not accounted for in this study might be at play.
5. The findings of this study in European Whites might not apply to other racial and ethnic groups where these genetic variants might have different allele frequencies or where ethnic-specific genetic factors might play a role.
6. Gene mRNA expression data was used as supportive evidence for the novel genomic regions discovered with this GWAS (novel genes such as RNASET2, SECISBP2L, and NRG1) but does not preclude the need for additional, independent replication to confirm all novel findings.

OTHER ARTICLES OF INTEREST

ASTHMA GWAS

White MJ, Risse-Adams O, Goddard P, et al. **Novel genetic risk factors for asthma in African American children: Precision Medicine and the SAGE II Study**. *Immunogenetics* 2016;68(6-7):391-400.

Yan Q, Brehm J, Pino-Yanes M, et al. **A meta-analysis of genome-wide association studies of asthma in Puerto Ricans**. *Eur Resp J* 2017;49(5).

Ober C. **Asthma Genetics in the Post-GWAS Era**. *Ann Am Thorac Soc* 2016;13 Suppl 1:S85-90.

EPIGENETICS

Morrow JD, Glass K, Cho MH, et al. **Human Lung DNA Methylation Quantitative Trait Loci Colocalize with COPD Genome-wide Association Loci**. *Am J Respir Crit Care Med*. 2018. In Press.

Yang IV, Pedersen BS, Liu AH, et al. **The nasal methylome and childhood atopic asthma**. *J Allergy Clin Immunol* 2017;139(5):1478-1488.

ENVIRONMENT, INNATE IMMUNITY, AND ASTHMA RISK

Stein MM, Hrusch CL, Gozdz J, et al. **Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children**. *N Engl J Med* 2016;375(5):411-421.

GENETIC RISK PROFILE FOR OUTCOMES IN IPF

Herazo-Maya JD, Sun J, Molyneaux PL, et al. **Validation of a 52-gene risk profile for outcome prediction in patients with idiopathic pulmonary fibrosis: an international, multicentre, cohort study**. *Lancet Respir Med* 2017;5(11):857-868.

OVERLAP OF GENETIC RISK FACTORS BETWEEN PULMONARY DISEASES

Hobbs BD, de Jong K, Lamontagne M, et al. **Genetic loci associated with chronic obstructive pulmonary disease overlap with loci for lung function and pulmonary fibrosis.** *Nat Genet* 2017;49(3):426-432.

Claar DD, Larkin EK, Bastarache L, et al. **A Phenome-Wide Association Study Identifies a Novel Asthma Risk Locus Near TERC**. *Am J Respir Crit Care Med* 2016;193(1):98-100.

ALPHA1-ANTITRYPSIN DEFICIENCY

Foreman MG, Wilson C, DeMeo DL, et al. **Alpha-1 Antitrypsin PiMZ Genotype Is Associated with Chronic Obstructive Pulmonary Disease in Two Racial Groups**. *Ann Am Thorac Soc* 2017;14(8):1280-1287.

ARDS

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VENTILATOR MANAGEMENT IN ARDS

Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators. **Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial**. *JAMA* 2017;318(14):1335-1345

Summary

Although the benefits of positive end expiratory pressure (PEEP) on lung recruitment in ARDS have been known since the initial description of the syndrome, the optimal level of PEEP remains controversial. Prior studies have compared higher PEEP to lower PEEP strategies with conflicting results related to mortality and organ failure. This multicenter randomized trial examines the potential role in ARDS of the "open lung strategy" consisting of a recruitment maneuver followed by the use of optimal PEEP levels as determined by the static respiratory system compliance during a decremental PEEP titration. The investigators randomized 1013 patients with moderate to severe ARDS to either the open lung strategy or a low-PEEP strategy and compared 28 day mortality (primary outcome) and additional clinically relevant secondary endpoints. All study participants received lung protective ventilation while subjects in the open lung arm received neuromuscular blockers more frequently. Subjects in the open lung arm experienced higher 28 day mortality (55%) compared to subjects in the low-PEEP arm (49%) and after adjustment for relevant covariates, the risk of mortality persisted (HR 1.22). Further, subjects who received open lung ventilation experienced increased need for vasopressors, higher rates of pneumothorax requiring drainage and higher rates of death with barotrauma.

Comments

1. In contrast to previous studies which compared enhanced recruitment to minimal recruitment strategies, this study demonstrated that the open lung approach increases mortality in patients with moderate to severe ARDS.
2. Subjects in the open lung arm experienced more frequent barotrauma including pneumothorax requiring drainage, a finding not seen in prior studies which have examined enhanced lung recruitment in ARDS.
3. The differences in PEEP levels (3.5 cm H2O) and driving pressures (1.5 cm H2O) between the open lung and control arms were modest.
4. The recruitment maneuver used in the open lung strategy utilized higher pressures and lasted longer than similar maneuvers in previous clinical trials which did not show differences in barotrauma or mortality.
5. Patients receiving the open lung strategy more frequently required initiation and uptitration of vasopressors in the first hour after the strategy was employed.

GLOBAL HETEROGENEITY IN THE SEVERITY, MANAGEMENT AND OUTCOMES OF ARDS

Laffey JG, Madotto F, Bellani G, Pham T, Fan E, Brochard L, Amin P, Arabi Y, Bajwa EK, Bruhn A, Cerny V, Clarkson K, Heunks L, Kurahashi K, Laake JH, Lorente JA, McNamee L, Nin N, Palo JE, Piquilloud L, Qiu H, Jimenez JIS, Esteban A, McAuley DF, van Haren F, Ranieri M, Rubenfeld G, Wrigge H, Slutsky AS, Pesenti A on behalf of the LUNG SAFE Investigators and the ESICM Trials Group. **Geo-Economic Variations in Epidemiology, Patterns of Care, and Outcomes in Patients With Acute Respiratory Distress Syndrome: Insights From the LUNG SAFE Prospective Cohort Study**. *Lancet Respir Med* 2017;5:627-38.

Summary

Geographic and economic heterogeneity have been identified in the incidence, management and outcomes of a variety of diseases; however, the impact of location and socio-economic status on these features of ARDS has not been described. The LUNG SAFE study was a prospective, cross-sectional observational study of 459 ICUs in 50 countries which examined the global incidence and outcomes of ARDS as well as clinician recognition and management patterns. The current study is a planned secondary analysis of the LUNG SAFE dataset designed to examine potential differences in ARDS risk factors, severity, management and outcomes across countries of different geographic and economic classes. The investigators grouped ICUs based on their location and their country's World Bank economic classification into three groups: high income European countries (Europe-High), high-income

countries from the rest of the world (rWORLD-High) and middle income countries (Middle). Patients in the rWORLD-High group were less likely to have severe ARDS but more likely to have higher non-pulmonary baseline SOFA scores. Clinicians in rWORLD-High ICUs were less likely to recognize ARDS (54% vs. 64%[Europe-High] vs. 66%[Middle]) but were also less likely to use tidal volumes > 8ml/kg (33% vs. 38%[Europe-High] vs. 39%[Middle]) and less likely to use an FiO2 > 0.6 than clinicians in Europe-High ICUs. After multivariate adjustment, care in rWORLD-High ICUs is associated with shorter duration of mechanical ventilation, shorter ICU length of stay and lower ICU and in-hospital mortality rates. Further, regardless of location, a country's gross domestic product is independently and inversely associated with ARDS mortality.

Comments

1. While important differences in baseline characteristics exist between the geo-economic groups, clinically relevant outcomes differ between the groups after adjustment.
2. Heterogeneity in practice including the use of tidal volumes > 8ml/kg, FiO2 > 0.6, neuromuscular blockade and prone positioning exists between geo-economical groups suggesting variable implementation of evidence based best practices by group.
3. The association between national gross domestic product and ARDS mortality is not explained by ICU resource availability as physician-to-bed and nurse-to-bed ratios differ little between high income and middle income countries and neither ratio was independently associated with ARDS mortality.
4. Although the use of injurious tidal volumes varied by geo-economic group, their frequency of use (33-39%) remains unacceptably high in all ICUs.
5. The potential impact of differences in ventilator weaning practices on clinical outcomes cannot be ascertained by the data available from the LUNG SAFE study.

IDENTIFYING THE ROLE OF ECMO IN ARDS

Schmidt M, Schellongowski P, Patroniti N, Taccone FS, Miranda DR, Reuter J, Prodanovic H, Pierrot M, Dorget A, Park S, Balik M, Demoule A, Crippa IA, Mercat A, Wohlfarth P, Sonneville R, Combes A for the International ECMO Network (ECMOnet), the REVA Research Network and the IDEA Study Group. **Six-Month Outcome of Immunocompromised Severe ARDS Patients Rescued by ECMO: An International Multicenter Retrospective Study.** *Am J Respir Crit Care Med* 2018 Jan 3 (Epub ahead of print).

Summary

Survival rates among immunocompromised patients who develop critical illness are improving while, independently, the use of extracorporeal membrane oxygenation (ECMO) is increasingly common. These simultaneous trends have led to an increased willingness to perform ECMO in immunocompromised patients; however, the outcomes of this high-risk population have been previously unexplored. This retrospective cohort study examines the outcomes of immunocompromised patients that received ECMO for moderate to severe ARDS and identifies pre-ECMO risk factors of 6 month morality in this population. Data from 10 international, high-volume ECMO centers between 2008 and 2015 were used for the analysis and immunocompromised status was defined as having one of the following conditions: hematologic malignancy, active solid tumor, solid-organ transplant, acquired immunodeficiency syndrome (AIDS), or long-term or high dose corticosteroid or immunosuppressant use. Six month survival was only 30% in the entire immunocompromised cohort and patients with hematologic malignancy experienced significantly lower survival rates than patients with other diagnoses (p=0.02). When compared to a risk-matched cohort of non-immunocompromised patients, the presence of an immunocompromising condition was independently associated with death (OR 5.72). In the immunocompromised population, increasing age, PCO2 and driving pressure as well as lower pre-ECMO platelet count were all independently associated with increased odds of death while a shorter duration of the immunocompromised state (< 30 days from diagnosis to need for ECMO) was associated with markedly reduced odds of death (OR 0.364). ECMO-related hemorrhages (36%), ventilator-associated pneumonias (50%), and cannula infections (10%) were common complications in immunocompromised patients.

Comments

1. The six month survival rate is very poor for immunocompromised patients who receive ECMO for ARDS.
2. Hematologic malignancy is associated with the lowest survival rates (20%) irrespective of whether or not a patient has undergone hematopoietic stem cell transplantation.
3. Patients who have only recently become immunocompromised (within 30 days of ARDS) have greater odds of surviving ECMO and could be potentially reasonable candidates for its use.
4. Infectious complications of ECMO are common in immunocompromised patients and the potential role of prophylactic antibiotics in this population remains unknown.
5. This study can be used to inform the complex medical, ethical, and economic decision-making that often occurs in this severely ill population.

LONG-TERM SEQUELAE OF ARDS SURVIVAL

Kamdar BB, Huang M, Dinglas VD, Colantuoni E, von Wachter TM, Hopkins RO, Needham DM. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network. **Joblessness and Lost Earnings after Acute Respiratory Distress Syndrome in a 1-Year National Multicenter Study**. *Am J Respir Crit Care Med* 2017;196(8):1012-1020.

Summary

ARDS survivors commonly experience long-term physical, cognitive, and psychiatric sequelae after hospital discharge. These complications can limit their functional status and may impact a survivor's ability to work. This analysis is part of the ALTOS study which longitudinally followed ARDS survivors from four different multicenter RCTs performed by the ARDS network and examined the rate of incident unemployment as well as the resultant financial and insurance repercussions. Of the 922 ARDS survivors who consented to follow up, 386 (42%) reported working full or part-time prior to their hospitalization with ARDS. Among these previously employed survivors, 189 (49%) were jobless at 6 months and 166 (44%) were jobless at 12 months. Of the 257 eligible patients who ever returned to work within the first 12 months after discharge, 111 (43%) worked less hours than before admission, 69 (27%) reported reduced effectiveness at work and 62 (24%) subsequently lost their jobs. Multivariate regression analysis demonstrated that being an older, non-white survivor and having a prolonged length of stay were independently associated with higher odds of delayed return to work. Using data from the U.S. Bureau of Labor Statistics, the investigators estimated that 271 (71%) of previously employed survivors lost an average of approximately $27,000 in wages in the 12 months after ARDS survival representing an estimated 60% of their pre-ARDS annual income. Jobless survivors experienced a 14% reduction in private insurance coverage and a 16% increase in Medicare and Medicaid coverage whereas employed survivors experienced no significant changes in insurance coverage.

Comments

1. ARDS survivors are at high risk for incident joblessness and substantial loss of wages.
2. Among previously employed survivors who never returned to work, 58% received disability suggesting that the physical, cognitive and psychiatric sequelae of ARDS may have contributed to their joblessness.
3. Although there was no age difference in the return to work among whites, older non-whites experienced delays in returning to work.
4. In addition to lost workplace productivity, ARDS results in a substantial increase in the use of government-funded insurance.
5. Future investigations should explore the role of occupational rehabilitation programs in this vulnerable population.

TOWARDS PRECISION MEDICINE IN THE MANAGEMENT OF ARDS

Famous KR, Delucchi K, Ware LB, Kangelaris KN, Liu KD, Thompson BT, Calfee CS for the Acute Respiratory Distress Syndrome Network. **Acute Respiratory Distress Syndrome Subphenotypes Respond Differently to Randomized Fluid Management Strategy**. *Am J Respir Crit Care Med* 2017;195(3):331-338.

Summary

Recent investigations have identified two distinct subphenotypes of ARDS stratified by a spectrum of laboratory and clinical data using latent class analysis. Subphenotype 1 is characterized by comparatively lower levels of inflammatory mediators and less severe clinical derangement as compared to subphenotype 2 and a three variable panel (IL-6, soluble TNFr-1, and vasopressor need) has been shown to reliably distinguish between phenotypes with a high degree of accuracy. In the current study, the investigators examined whether these subphenotypes can be validated in additional patient populations and whether subphenotype is associated with response to clinical interventions. By analyzing clinical data and plasma samples from the 1,000 patients enrolled in the ARDSnet FACTT trial, the investigators were once again able to classify patients into two distinct subphenotypes that were nearly identical to the previously identified subphenotypes. Patients in subphenotype 1 (n=727) experienced a lower 90 day mortality rate (22% vs. 45%, $p<0.0001$) and more ventilator-free days (19 vs. 3, $p<0.0001$) than patients in subphenotype 2 (n = 273). Intriguingly, the response to fluid management strategy varied by subphenotype with a conservative fluid strategy resulting in a higher mortality in the subphenotype 1 group (24% vs 17%) but a lower mortality in the subphenotype 2 group (39% vs 49%, p value 0.009 for the interaction).

Comments

1. Despite a common clinical definition, subphenotypes of ARDS exist and experience different clinical outcomes.
2. Although the FACTT trial demonstrated no overall difference in mortality between fluid management strategies, the current study suggests the possibility of differing and counterbalancing outcomes in each subphenotype.
3. Prospective validation of the divergent clinical responses observed in this study is required before their implications on clinical practice can be fully understood.
4. Rapid point-of-care testing to identify subphenotypes early in the course of disease is a critical requirement for the real-time application of these findings in clinical care.

OTHER ARTICLES OF INTEREST

ARDS VENTILATOR MANAGEMENT CLINICAL PRACTICE GUIDELINES

Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, Adhikari NKJ, Amato MBP, Branson R, Brower RG, Ferguson ND, Gajic O, Gattinoni L, Hess D, Mancebo J, Meade MO, McAuley DF, Pesenti A, Ranieri VM, Rubenfeld GD, Rubin E, Seckel M, Slutsky AS, Talmor D, Thompson BT, Wunsch H, Uleryk E, Brozek J, Brochard LJ on behalf of the American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical

Care Medicine. **An Official American Thoracic Society/ European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome**. *Am J Respir Crit Care Med* 2017;195(9):1253-1263.

ARDS VENTILATOR MANAGEMENT META-ANALYSES

Walkey A, Del Sorbo L, Hodgson CL, Adhikari NKJ, Wunsch H, Meade MO, Uleryk E, Hess D, Talmor DS, Thompson BT, Brower RG, Fan E. **Higher PEEP versus Lower PEEP Strategies for Patients with Acute Respiratory Distress Syndrome**. **A Systematic Review and Meta-Analysis.** *Annals of the American Thoracic Society*. 2017 14(Suppl 4):S297-S303.

Munshi L, Del Sorbo L, Adhikari NKJ, Hodgson CL, Wunsch H, Meade MO, Uleryk E, Mancebo J, Pesenti A, Ranieri VM, Fan E. **Prone Position for Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis**. *Annals of the American Thoracic Society*. 2017 14(Suppl 4):S280-S288.

Walkey AJ, Goligher EC, Del Sorbo L, Hodgson CL, Adhikari NKJ, Wunsch H, Meade MO, Uleryk E, Hess D, Talmor DS, Thompson BT, Brower RG, Fan E. **Low Tidal Volume versus Non-Volume-Limited Strategies for Patients with Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis**. *Annals of the American Thoracic Society*. 2017 14(Suppl 4):S271-S279.

Goligher EC, Hodgson CL, Adhikari NKJ, Meade MO, Wunsch H, Uleryk E, Gajic O, Amato MPB, Ferguson ND, Rubenfeld GD, Fan E. **Lung Recruitment Maneuvers for Adult Patients with Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis**. *Annals of the American Thoracic Society*. 2017 14(Suppl 4):S301-S311.

Goligher EC, Munshi L, Adhikari NKJ, Meade MO, Hodgson CL, Wunsch H, Uleryk E, Gajic O, Amato MPB, Ferguson ND, Rubenfeld GD, Fan E. High Frequency Oscillation for **Adult Patients with Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis**. *Annals of the American Thoracic Society*. 2017 14(Suppl 4):S289-S296.

HIGH FREQUENCY OSCILLATOR USE IN ARDS

Meade MO, Young D, Hanna S, Zhou Q, Bachman TE, Bollen C, Slutsky AS, Lamb SE, Adhikari NKJ, Mentzelopoulos SD, Cook DJ, Sud S, Brower RG, Thompson BT, Shah S, Stenzler A, Guyatt G, Ferguson ND. **Severity of Hypoxemia and Effect of High-Frequency Oscillatory Ventilation in Acute Respiratory Distress Syndrome**. *Am J Respir Crit Care Med* 2017;196(6):727-733.

NON-INVASIVE VENTILATION IN ARDS

Bellani G, Laffey JG, Pham T, Madotto F, Fan E, Brochard L, Esteban A, Gattinoni L, Bumbasirevic V, Piquilloud L, van Haren F, Larsson A, McAuley DF, Bauer PR, Arabi YM, Ranieri M, Antonelli M, Rubenfeld GD, Thompson BT, Wrigge H, Slutsky AS, Pesenti A. **Noninvasive Ventilation of Patients with Acute Respiratory Distress Syndrome. Insights from the LUNG SAFE Study**. *Am J Respir Crit Care Med*. 2017;195(1):67-77.

EARLY TREATMENT AND PREVENTION OF ARDS

Festic E, Carr GE, Cartin-Ceba R, Hinds RF, Banner-Goodspeed V, Bansal V, Asuni AT, Talmor D, Rajagopalan G, Frank RD, Gajic O, Matthay MA, Levitt JE. **Randomized Clinical Trial of a Combination of an Inhaled Corticosteroid and Beta Agonist in Patients at Risk of Developing the Acute Respiratory Distress Syndrome.** *Crit Care Med* 2017;45:798-805.

CYSTIC FIBROSIS

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TEZACAFTOR/IVACAFTOR: A NEW CFTR MODULATOR FOR INDIVIDUALS HOMOZYGOUS FOR F508DEL

Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, Wang LT, Ingenito EP, McKee C, Lu Y, Lekstrom-Himes J, Elborn JS. **Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del.** *N Engl J Med*. 2017;377(21):2013-2023.

Summary

Cystic fibrosis transmembrane conductance regulator (CFTR) modulators target the underlying cause of disease in individuals with cystic fibrosis (CF). Ivacaftor, a CFTR potentiator (increases the probability of the chloride channel opening), was approved in 2012 for certain genetic mutations. Lumacaftor, a CFTR corrector (improves processing and trafficking of the CFTR protein), was approved in 2015 in combination with Ivacaftor for individuals homozygous for F508del. The latest CFTR modulator to be approved is Tezacaftor/Ivacaftor in 2018. Tezacaftor is the second CFTR corrector.

Tezacaftor/Ivacaftor versus placebo was evaluated for 24 weeks in approximately 500 individuals with CF ages 12 years and older. Inclusion criteria included individuals homozygous for the F508del mutation, with a baseline FEV1 between 40-90% predicted. The primary outcome was change in lung function: the absolute and relative changes in percentage of predicted FEV1 for Tezacaftor/Ivacaftor over placebo were 4.0% and 6.8% respectively ($p<0.001$). The rate of pulmonary exacerbations was 35% lower in the Tezacaftor/Ivacaftor group versus placebo ($p=0.005$). Sweat chloride decreased by approximately 10.1 mmol per liter with use of Tezacaftor/Ivacaftor. The incidence of adverse events was similar between the two groups, but fewer patients in the Tezacaftor/Ivacaftor arm had respiratory adverse events.

Comments

1. This study demonstrates a 4% absolute increase in lung function in individuals homozygous for F508del who took Tezacaftor/Ivacaftor for 24 weeks, which is similar to the effect seen with Lumacaftor/Ivacaftor.
2. There was a 35% reduction in incidence of pulmonary exacerbations, which is an important outcome as pulmonary exacerbations are associated with lung function loss, a more rapid decline in lung function, decreased quality of life, and death.
3. The side effect profile of Tezacaftor/Ivacaftor is an improvement over Lumacaftor/Ivacaftor, and does not cause significant respiratory adverse events (approximately 20% of individuals do not tolerate Lumacaftor/Ivacaftor secondary to bronchospasm).
4. Tezacaftor/Ivacaftor has less drug-drug interactions than Lumacaftor/Ivacaftor with other medications frequently used in CF, which will simplify future therapeutic plans.
5. There was improvement in the respiratory domain of the CFQ-R, a symptom questionnaire, which showed individuals had improved quality of life on Tezacaftor/Ivacaftor.

TEZACAFTOR/IVACAFTOR: EXPANSION OF THE NUMBER OF INDIVIDUALS ELIGIBLE FOR A CFTR MODULATOR

Rowe SM, Daines C, Ringshausen FC, Kerem E, Wilson J, Tullis E, Nair N, Simard C, Han L, Ingenito EP, McKee C, Lekstrom-Himes J, Davies JC. **Tezacaftor-Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis**. *N Engl J Med*. 2017;377(21):2024-2035.

Summary

In this trial, Tezacaftor/Ivacaftor, Ivacaftor monotherapy, or placebo was evaluated for 24 weeks in approximately 248 individuals with CF, ages 12 years and older. Inclusion criteria included individuals who were heterozygous for F508del and also had a second CFTR mutation associated with residual CFTR function. Individuals were randomized to one of 6 sequences, involving two 8-week interventions separated by an 8-week washout. They received either Tezacaftor/Ivacaftor, Ivacaftor monotherapy, or placebo. The primary endpoint was absolute change in percentage of predicted FEV1 from baseline. The absolute change in FEV1 % predicted was 6.8% predicted for the Tezacaftor/Ivacaftor group, and 4.7% predicted in the Ivacaftor group ($p<0.001$ for both groups compared to placebo). In addition, the difference in improvement in FEV1 between Tezacaftor/Ivacaftor compared to Ivacaftor alone was statistically significant ($p<0.001$). CFQ-R respiratory domain score improved in both interventional arms, showing quality of life was improved in patients on Tezacaftor/Ivacaftor or Ivacaftor monotherapy. Overall, Tezacaftor/Ivacaftor

was shown to be safe, with no treatment discontinuations or significant adverse events.

Comments

1. Approximately 5% of individuals with CF have a residual function mutation.
2. Mutations that were eligible for this clinical trial were identified based on clinical phenotype, in vitro data, and clinical case reports.
3. The trial design innovatively combined multiple rare mutations into one single phenotypic group, as large clinical trials on rare mutations is not possible due to a small number of people with each individual mutation.
4. The results of this trial are important for individuals with the specified mutations that are already on Ivacaftor, as the combination of Tezacaftor/Ivacaftor provides additional benefit over Ivacaftor alone.
5. In February of 2018, the FDA approved Tezacaftor/Ivacaftor for 26 mutations that are classified as residual function mutations.

SURVIVAL IN CANADIAN AND UNITED STATES CF PATIENTS

Stephenson AL, Sykes J, Stanojevic S, Quon BS, Marshall BC, Petren K, Ostrenga J, Fink AK, Elbert A, Goss CH. **Survival Comparison of Patients With Cystic Fibrosis in Canada and the United States: A Population-Based Cohort Study**. *Ann Intern Med*. 2017;166(8):537-546.

Summary

In 2011, the median survival for CF patients in the United States (U.S.) CF Foundation Patient Registry (CFFPR) was 36.8 years, and in the Canadian Cystic Fibrosis Registry (CCFR) was 48.5 years. However, direct comparison of these two registries is challenging due to different methodologies, data processing, and ascertainment bias. This study used a standardized approach to survival analysis, in order to establish the true difference in survival in CF patients between the two nations. Investigators established a unified method to analyze each variable recorded in both registries. Results showed that approximately 45,500 and 6,000 individuals were followed in the CFFPR and CCFR, respectively, between 1999-2013. The median age of survival was 10 years higher in Canada than in the U.S. (50.9 years versus 40.6 years). The adjusted risk of death was 34% lower in Canada than in the U.S. (HR 0.66). There was a higher proportion of patients receiving lung transplants in Canada as compared to the U.S. (10.3% vs. 6.5%, respectively). Differences in survival did change based on insurance status of U.S. patients.

Comments

1. Median survival increased in both countries over time, but diverged in 1995 and 2005, which may be secondary to differences in nutritional support, lung transplant practices, and health care plans.
2. Implementation in the early 1970s of aggressive nutritional support and high-fat diets by Canada may have led to a reduced risk of death in early adulthood of CF patients in Canada; however, the U.S. did not adopt this diet until 5-10 years later which may be partially responsible for the divergence of the survival curve in 1995.
3. In 2005, the Lung Allocation Score (LAS) was implemented in the U.S. which changed the way lungs were allocated to individuals with CF that are in need of lung transplantation (Canada does not use the LAS), and several studies show that the LAS has decreased the number of U.S. CF patients transplanted and actually increased the risk of death after transplant.
4. The survival advantage seen in Canada may be partially secondary to the fact that a higher proportion of patients in Canada (10.3%) underwent lung transplantation compared to the U.S. (6.5%), and a higher number of U.S. deaths occurred in individuals who had not undergone lung transplantation compared to Canadian deaths.
5. Of note, there was no difference in risk of death between individuals in Canada (universal health plan) and in individuals in the U.S. that have private insurance, suggesting that differences in health care plans may explain part of the survival gap found in this study.

STANDARDIZING TREATMENT OF PULMONARY EXACERBATIONS

Sanders DB, Solomon GM, Beckett VV, West NE, Daines CL, Heltshe SL, VanDevanter DR, Spahr JE, Gibson RL, Nick JA, Marshall BC, Flume PA, Goss CH, STOP Study Group. **Standardized Treatment of Pulmonary Exacerbations (STOP) study: Observations at the initiation of intravenous antibiotics for cystic fibrosis pulmonary exacerbations**. *J Cyst Fibros*. 2017;16(5):592-599.

West NE, Beckett VV, Jain R, Sanders DB, Nick JA, Heltshe SL, Dasenbrook EC, VanDevanter DR, Solomon GM, Goss CH, Flume PA, STOP Investigators. **Standardized Treatment of Pulmonary Exacerbations (STOP) study: Physician treatment practices and outcomes for individuals with cystic fibrosis with pulmonary Exacerbations**. *J Cyst Fibros*. 2017;16(5):600-606.

Summary

CF individuals suffer from recurrent pulmonary exacerbations (PEx), generally described as worsening signs and symptoms that are treated with antibiotics. PEx are associated with increased morbidity and often unrecovered lung function loss, yet treatment practices vary widely as there is a paucity of evidence to base guidelines upon. The Standardized Treatment of Pulmonary Exacerbations (STOP) study was an observational study in 220 individuals hospitalized with intravenous (IV) antibiotics, performed to characterize PEx and physician treatment practices. Initial results showed that 85% of patients experienced symptoms for >7 days before admission, 43% had received IV antibiotics within the previous 6 months, and 48% failed oral and/or inhaled antibiotics before IV antibiotics were

started. The mean absolute decrease in FEV1 from the best 12-month FEV1 was 13.6% predicted. The mean duration of IV antibiotics was 15.9 days. The mean absolute increase in FEV1 from admission was 9% at end of IV antibiotic treatment, and 7% at day 28. Only 39% fully recovered lost lung function, and only 65% recovered at least 90% of lost lung function. Despite this, treatment was declared successful by 84% of treating physicians. Physicians surveyed demonstrated willingness to participate in most hypothetical interventional studies of PEx.

Comments

1. The CF Foundation convened a working group in 2009 that was tasked to conduct robust clinical trials and establish treatment guidelines for PEx.
2. A systematic review of PEx found insufficient evidence upon which to base recommendations surrounding treatment pf PEx [duration of antibiotic therapy, number of antibiotics to use, site of therapy (home versus hospital), and use of corticosteroids].
3. This STOP study was the first clinical study conducted, with the purpose of describing clinical characteristics of PEx, evaluating physician treatment practices, establishing the feasibility of future clinical trials, and identifying clinical endpoints to be used in clinical trials of PEx.
4. It is notable that despite patients falling short of previous baseline lung function after treatment, the majority of physicians characterized treatment as a success, suggesting an acceptance of a new (lower) baseline lung function.
5. The results of the STOP study were used to design STOP-2, an interventional clinical trial evaluating different durations of IV antibiotics, which is currently enrolling.

LCI AND MRI ARE COMPLEMENTARY IN ASSESSMENT OF LUNG DISEASE IN CHILDREN WITH CYSTIC FIBROSIS

Stahl M, Wielpütz MO, Graeber SY, Joachim C, Sommerburg O, Kauczor H-U, Puderbach M, Eichinger M, Mall MA. **Comparison of Lung Clearance Index and Magnetic Resonance Imaging for Assessment of Lung Disease in Children with Cystic Fibrosis**. *Am J Respir Crit Care Med*. 2017;195(3):349-359.

Summary

Recent studies have shown that progression of lung disease in children with CF occurs early, and noninvasive measurements are needed to better characterize lung damage and to guide clinical therapy. Since FEV1 is usually normal in early childhood, it is not helpful to detect the onset and early progression of lung disease. Previous studies have shown that magnetic resonance imaging (MRI) can detect early onset lung disease as well as response to antibiotic therapy for exacerbations in children with CF. The lung clearance index (LCI) has been shown to detect abnormal ventilation, but the relationship between MRI and LCI was unknown. In this study, LCI and MRI were performed in 97 clinically stable CF children and in a smaller number of patients at the time of PEx and after antibiotic therapy. Results showed that LCI had a strong correlation with the global MRI score (score of structural wall abnormalities, mucous plugging, and abnormal lung perfusion). Both were sensitive to detect different levels of disease severity, as well as a response to antibiotic therapy in PEx.

Comments

1. While FEV1 is used to monitor lung function and disease progression in older pediatric and adult CF patients, it is not helpful in young pediatric patients who either have normal FEV1 or are unable to perform spirometry correctly.
2. Chest computed tomography (CT) is widely used to detect structural abnormalities in CF lung disease, but frequent use is limited secondary to fears of accumulating radiation over the lifetime of an individual.
3. MRI offers a distinct advantage over CT scan for repeated measurements of structural lung disease, as MRI does not involve radiation.
4. This is the first study that examined the relationship between LCI and MRI to detect onset and early lung damage in CF, which showed that LCI correlates strongly with structural and perfusion abnormalities detected by MRI.
5. These results support the use of LCI and MRI for clinical monitoring as well as for use as endpoints in clinical trials in children with CF.

OTHER ARTICLES OF INTEREST

PULMONARY EXACERBATIONS

Lechtzin N, Mayer-Hamblett N, West NE, Allgood S, Wilhelm E, Khan U, Aitken ML, Ramsey BW, Boyle MP, Mogayzel PJ, Gibson RL, Orenstein D, Milla C, Clancy JP, Antony V, Goss CH, eICE Study Team. **Home Monitoring of Patients with Cystic Fibrosis to Identify and Treat Acute Pulmonary Exacerbations. eICE Study Results**. *Am J Respir Crit Care Med*. 2017;196(9):1144-1151.

Schechter MS, VanDevanter DR, Pasta DJ, Short SA, Morgan WJ, Konstan MW, Scientific Advisory Group and the Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. **Treatment Setting and Outcomes of Cystic Fibrosis Pulmonary Exacerbations**. *Ann Am Thorac Soc.* 2018;15(2):225-233.

Stanojevic S, McDonald A, Waters V, MacDonald S, Horton E, Tullis E, Ratjen F. **Effect of pulmonary exacerbations treated with oral antibiotics on clinical outcomes in cystic fibrosis**. *Thorax.* 2017;72(4):327.

VanDevanter DR, Heltshe SL, Spahr J, Beckett VV, Daines CL, Dasenbrook EC, Gibson RL, Jain R, Sanders DB, Goss CH, Flume PA, STOP Study Group. **Rationalizing endpoints for prospective studies of pulmonary exacerbation treatment response in cystic fibrosis**. *J Cyst Fibros.* 2017;16(5):607-615.

Heltshe SL, West NE, VanDevanter DR, Sanders DB, Beckett VV, Flume PA, Goss CH. **Study design considerations for the Standardized Treatment of Pulmonary Exacerbations 2 (STOP2): A trial to compare intrave-**

nous antibiotic treatment durations in CF. *Contemporary Clinical Trials*. 2018;64(Supplement C):35-40.

CFTR MODULATORS

Durmowicz AG, Lim R, Rogers H, Rosebraugh CJ, Chowdhury BA. **The U.S. Food and Drug Administration's Experience with Ivacaftor in Cystic Fibrosis. Establishing Efficacy Using In Vitro Data in Lieu of a Clinical Trial**. *Ann Am Thorac Soc*. 2018;15(1):1-2.

Milla CE, Ratjen F, Marigowda G, Liu F, Waltz D, Rosenfeld M. **Lumacaftor/Ivacaftor in Patients Aged 6–11 Years with Cystic Fibrosis and Homozygous for F508del-CFTR**. *Am J Respir Crit Care Med*. 2016;195(7):912-920.

Donaldson SH, Pilewski JM, Griese M, Cooke J, Viswanathan L, Tullis E, Davies JC, Lekstrom-Himes JA, Wang LT, VX11-661-101 Study Group. **Tezacaftor/Ivacaftor in Subjects with Cystic Fibrosis and F508del/F508del-CFTR or F508del/G551D-CFTR**. *Am J Respir Crit Care Med*. 2018;197(2):214-224.

Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, Huang X, Lubarsky B, Rubin J, Millar SJ, Pasta DJ, Mayer-Hamblett N, Goss CH, Morgan W, Sawicki GS. **Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study.** *Lancet Respir Med*. 2017;5(2):107-118.

Gelfond D, Heltshe S, Ma C, Rowe SM, Frederick C, Uluer A, Sicilian L, Konstan M, Tullis E, Roach RNC, Griffin K, Joseloff E, Borowitz D. **Impact of CFTR Modulation on Intestinal pH, Motility, and Clinical Outcomes in Patients With Cystic Fibrosis and the G551D Mutation**. *Clin Transl Gastroenterol*. 2017;8(3):e81.

Hisert KB, Heltshe SL, Pope C, Jorth P, Wu X, Edwards RM, Radey M, Accurso FJ, Wolter DJ, Cooke G, Adam RJ, Carter S, Grogan B, Launspach JL, Donnelly SC, Gallagher CG, Bruce JE, Stoltz DA, Welsh MJ, Hoffman LR, McKone EF, Singh PK. **Restoring Cystic Fibrosis Transmembrane Conductance Regulator Function Reduces Airway Bacteria and Inflammation in People with Cystic Fibrosis and Chronic Lung Infections**. *Am J Respir Crit Care Med*. 2017;195(12):1617-1628.

Heltshe SL, Rowe SM, Skalland M, Baines A, Jain M, GOAL Investigators of the Cystic Fibrosis Foundation Therapeutics Development Network. **Ivacaftor-treated CF Patients Derive Long-term Benefit Despite No Short-term Clinical Improvement**. *Am J Respir Crit Care Med.* December 2017 (Epub ahead of print).

Ratjen F, Hug C, Marigowda G, Tian S, Huang X, Stanojevic S, Milla CE, Robinson PD, Waltz D, Davies JC, VX14-809-109 investigator group. **Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial**. *Lancet Respir Med.* 2017;5(7):557-567.

CYSTIC FIBROSIS RELATED DIABETES

Terliesner N, Vogel M, Steighardt A, Gausche R, Henn C, Hentschel J, Kapellen T, Klamt S, Gebhardt J, Kiess W, Prenzel F. **Cystic-fibrosis related-diabetes (CFRD) is preceded by and associated with growth failure and deteriorating lung function**. *J Pediatr Endocrinol Metab.* 2017;30(8):815-821.

NON-TUBERCULOUS MYCOBACTERIA

Olivier KN, Griffith DE, Eagle G, McGinnis JP, Micioni L, Liu K, Daley CL, Winthrop KL, Ruoss S, Addrizzo-Harris DJ, Flume PA, Dorgan D, Salathe M, Brown-Elliott BA, Gupta R, Wallace RJ. **Randomized Trial of Liposomal Amikacin for Inhalation in Nontuberculous Mycobacterial Lung Disease.** *Am J Respir Crit Care Med*. 2016;195(6):814-823.

SLEEP DISORDERED BREATHING

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SCREENING FOR OBSTRUCTIVE SLEEP APNEA (OSA)

Jonas DE, Amick HR, Feltner C, Weber RP, Arvanitis M, Stine A, Lux L, Harris RP. **Screening for Obstructive Sleep Apnea in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force**. *JAMA* 2017; 317(4):415-433

Summary

Obstructive sleep apnea (OSA) is prevalent in the general population and has been associated with many adverse health outcomes. Screening for sleep apnea may help improve sleep quality and prevent or reduce these adverse events. This is a systemic review of 110 studies (N = 46,188), conducted to inform recommendations by the U.S. Preventive Services Task Force (USPSTF). The main aims of the study were: 1) To determine whether screening for OSA in adults who are asymptomatic or have unrecognized OSA symptoms improves health outcomes, 2) Evaluate the evidence for the accuracy of OSA screening tools and prediction rules, 3) Determine accuracy and reliability of diagnostic tests for OSA, 4) Evaluate whether therapies for OSA improve short term and long-term health outcomes, and 5) Determine if there is any harm in screening for and treatment of OSA. No studies were found that directly evaluated the benefits or harms of screening compared with no screening in the primary care population. The screening accuracy of the multivariable apnea prediction score followed by home portable monitor testing for detecting severe OSA syndrome was AUC 0.80 (95% CI, 0.78 to 0.82) and 0.83 (95% CI, 0.77 to 0.90), in 2 studies respectively, but these studies included mostly high-risk populations and those already with OSA. No studies prospectively determined the long-term health benefits of screening for OSA in the asymptomatic general population. Meta-analysis found that continuous positive airway pressure (CPAP) compared with sham was significantly associated with reductions of AHI, excessive sleepiness, diurnal systolic and diastolic blood pressure. CPAP was also associated with modest improvement in sleep-related quality of life. Mandibular advancement devices and weight loss programs were also associated with reduced AHI and excessive sleepiness; the effect sizes were smaller than those observed for CPAP. Trial evidence for most health outcomes was too limited to make conclusions (e.g., mortality, cardiovascular events, motor vehicle accidents). The study concluded that there is uncertainty about the clinical utility of all potential screening tools and evidence is limited on the effectiveness of CPAP on reducing mortality or other health outcomes.

Comments

1. More than anything else, this study highlights the paucity of sufficient evidence to make recommendations for or against screening in the asymptomatic primary care population.
2. It is important to recognize that OSA symptoms are often not routinely elicited by clinicians or spontaneously reported by patients leading to a misperception of the true prevalence of asymptomatic OSA in the population.
3. The guideline conclusions should be viewed as a call for evaluating patients, based on their individual characteristics and risks for sleep disturbance, including OSA, and an impetus for rigorous research in this area rather than discouraging further inquiry about sleep and sleep symptoms.
4. Improvement in sleep quality and subsequent quality of life as noted in PAP users is an important patient centered outcome and one goal of therapy than cannot be achieved if clinicians do not take the time to explore sleep related concerns with patients.

DIAGNOSTIC TESTING AND OSA

Corral J, Sanchez-Quiroga MA, Carmona-Bernal C, Sanchez-Armengol A, Sanchez de la Torre A, Duran-Cantolla J, Egea CJ, Salord N, Monasterio C, Teran J, Alonso-Alvarez ML, Muñoz-Mendez J, Arias EM, Cabello M, Montserrat JM, De la Peña M, Serrano JC, Barbe F, Masa JF; For the Spanish Sleep Network. **Conventional polysomnography is not necessary for the management of most patients with suspected obstructive sleep apnea: noninferiority, randomized controlled trial.** *Am J Respir Crit Car Med* 2017; 196: 1181–1190.

Summary

OSA is increasingly prevalent worldwide due to the aging of the population and a rise in obesity. It has been associated with significant morbidity and mortality. Traditionally in laboratory, observed polysomnography (PSG) is considered the gold standard of OSA diagnosis. However, given the global burden of disease and limited resources, sim-

pler, less expensive strategies are required for OSA diagnosis. This is a randomized controlled, multicenter, noninferiority trial, conducted in 12 tertiary sleep centers across Spain, comparing at home Type 3 (nasal pressure, oxygen saturation, thoracic and abdominal movement) respiratory polygraphy (HRP) to laboratory polysomnography (PSG) in subjects with suspicion for OSA and sleepiness (Epworth sleepiness scale [ESS] >10). Subjects with unstable cardiac conditions were excluded. The primary outcome for non-inferiority evaluation was change in ESS at 6-month follow-up. Both arms received auto continuous positive airway pressure (CPAP) treatment or sleep hygiene/diet education as clinically indicated. Other outcomes measured were quality-of-life questionnaires, 24-hour blood pressure monitoring, hospitalizations, 6-month PSG, and traffic accidents reported at 6 months. Cost effectiveness of the two strategies was calculated using direct study cost measurements and change in ESS as measure of effectiveness. In total, 430 patients were randomized. The HRP protocol was noninferior to PSG protocol as measured by change in ESS. Quality of life, blood pressure, CPAP adherence, and polysomnography were similar between protocols. Respiratory polygraphy (Type 3 device) was the most cost-effective protocol, primarily due to lower cost of testing. The authors conclude that for most symptomatic patients with suspicion for OSA, home testing is not inferior to PSG and is less costly.

Comments

1. This study's strengths include its intention-to-treat design, a range of severity of population with OSA, longer patient follow-up, and inclusion of cost data, measured throughout the study.
2. The study, however, did limit its inclusion criteria to symptomatic (ESS >10) individuals suspected of OSA, those with no significant medical comorbidities, and only evaluated CPAP as a therapeutic option. This limits generalizability of the study.
3. The study was conducted by trained personnel in sleep centers; in order for there to be a meaningful global impact, future evaluation of management pathways should determine whether similar success can be achieved by non-specialized personnel.
4. This study reinforces current clinical guideline recommendations for the use of Type 3 devices, and home sleep testing as an initial diagnostic pathway in symptomatic individuals with no medical comorbidities, referred to a sleep center for OSA diagnosis.

ASSOCIATION OF REM OSA WITH HEALTH OUTCOMES

Aurora RN, Crainiceanu C, Gottlieb D, Kim JS, Punjabi NM. **Obstructive Sleep Apnea during Rapid Eye Movement Sleep and Cardiovascular Disease**. *Am J Respir Crit Care Med* Published online: November 7, 2017 as DOI: https://doi.org/10.1164/rccm.2017061112OC

Summary

Rapid eye movement sleep (REM) accounts for 20-25% of total sleep time during which OSA events are usually more frequent, last longer, and are associated with more significant oxygen desaturations. Although the evidence is limited, REM sleep rated OSA has been associated with prevalent and incident hypertension and impaired glucose metabolism. The primary aim of this study was to determine the association between REM sleep-related OSA and a composite cardiovascular endpoint (occurrence of nonfatal or fatal CV events including myocardial infarction, coronary artery revascularization, congestive heart failure, and stroke) in a community-based cohort (derived from the Sleep Heart Health study) of middle-aged and older subjects with and without cardiovascular disease, followed for an average of 9.5 years. The study included 3,265 subjects (mean age 62±10.7 years, BMI 27.8±5.0 kg/m2, 63.1% women) with REM OSA and a NREM-AHI < 5.0 events/h. The composite endpoint was observed in 749 participants: 418 had coronary artery disease events, 233 had heart failure events, and 98 had strokes. The adjusted hazards ratios for the composite cardiovascular endpoint in all subjects with severe REM OSA (≥30 events/h; N=180) was 1.35 (95%: 0.98–1.85). Looking at participants with prevalent cardiovascular disease at baseline, the hazard ratio for the composite cardiovascular endpoint was 2.56 (95% CI, 1.46-4.47) for severe REM OSA compared to no OSA during REM sleep after adjusting for age, race, sex, body mass index, smoking status, diabetes and hypertension. The authors conclude that "severe OSA that occurs primarily during REM sleep is associated with higher incidence of a composite cardiovascular endpoint but in only those with prevalent cardiovascular disease."

Comments

1. The study has several strengths including a large sample size, reflective of a community base, use of polysomnography, and a long follow-up period.
2. The study highlights the importance of REM OSA and its association with cardiovascular outcomes in those with prevalent cardiac disease; it is possible that appropriate treatment of REM OSA may reduce risk of subsequent cardiovascular events in this population.
3. However, the studies on the impact of CPAP therapy on cardiovascular outcomes have been conflicted and most recently negative.
4. The lack of benefit noted for CPAP trials may be in part be due to the fact that most of the trials suffer from poor PAP adherence of 3 hours or less, and thus treatment exposure is not sufficiently long enough in duration to address REM OSA episodes.

CPAP THERAPY AND HEALTH OUTCOMES

Yu J, Zhou Z, McEvoy RD, Anderson CS, Rodgers A, Perkovic V, Neal B. **Association of Positive Airway Pressure With Cardiovascular Events and Death in Adults With Sleep Apnea: A Systematic Review and Meta-analysis.** *JAMA* 2017; 318(2):156-166.

Summary

Prospective observational studies have shown an association between OSA and cardiovascular events. Positive airway pressure (PAP) therapy has been shown to reduce hypertension and in some cohort studies improve cardiovascular outcomes and mortality. This study is a meta-analysis of 10 randomized clinical trials, including 7266 patients (5683 with OSA, 1583 with central sleep apnea, 80.5% men, mean body mass index 30.0) comparing PAP with sham PAP or no treatment. The main outcomes were a composite of acute coronary syndrome events, stroke, or vascular death (major adverse cardiovascular events); cause-specific vascular events; and death. There was no significant association of PAP on the composite outcome (relative risk, 0.77 [95% CI, 0.53-1.13]). There was also no significant association with individual components or all-cause mortality. Apnea severity, follow-up duration, or adherence to PAP did not affect outcomes (all P values > 0.13). The study concluded that the use of PAP was not associated with reduction of cardiovascular events or death in patients with OSA.

Comments

1. The results of this meta-analysis are largely driven by the negative SAVE study that examined the effects of PAP on secondary prevention of CV events. The main limitation of SAVE trial was the low mean number of hours of PAP (only 3.3 hours) and indeed a dose response improvement in cardiovascular outcomes was noted in a subsequent subgroup analysis of the SAVE data.
2. Conclusions about the mortality impact of CPAP may be limited by the inclusion of participants with heart failure and central apnea who arguably have a different pathophysiology than OSA and worse cardiac outcomes.
3. In this meta-analysis, the estimated relative risk for the association between CPAP and the composite outcome was 0.77, although not statistically significant, is similar in magnitude to the estimated risk reduction associated with anti-platelet therapy, statins and B blockers. This could be a clinically significant impact and warrants further study.
4. The authors conclusions may be premature; the article is important in highlighting the limitations of the existing literature on this topic.

IMPROVING CPAP ADHERENCE

Hwang D, Chang JW, Benjafield AV, Crocker ME, Kelly C, Becker KA, Kim JB, Woodrum RR, Liang J, Derose SF. **Effect of Telemedicine Education and Telemonitoring on Continuous Positive Airway Pressure Adherence. The Tele-OSA Randomized Trial**. *Am J Respir Crit Care Med*. 2018;197(1):117-126.

Summary

While PAP has been shown to be effective in improving symptoms of sleep apnea and quality of life, its downfall has always been poor patient adherence and tolerance. The Tele-OSA study was a four-arm, single center, single blinded, randomized, factorial-design clinical trial, including 1455 patients (51.0% women; age, 49 +/- 12 yr) suspected of OSA and eligible for home sleep apnea testing (HSAT). Prior to HSAT, subjects were randomized to 1) usual care alone, 2) usual care plus telemedicine web–based education (Tel-Ed), 3) usual care plus CPAP telemonitoring with automated feedback messaging based on usage data for 90 days (Tel-TM), or 4) usual care plus both Tel-Ed and Tel-TM (Tel-both). 556 (38.2% of all randomized patients; 71.7% of all patients with OSA) were eventually prescribed CPAP and followed for 90 days. The primary endpoint was 90-day CPAP usage. CPAP average daily use at 90 days was 3.86 +/- 2.5, 4.06 +/- 2.4, 4.46 +/- 2.2, and 4.86 +/- 2.3 hours in usual care, Tel-Ed, Tel-TM, and Tel-both groups. Usage was significantly higher in the Tel-TM and Tel-both groups versus usual care (P = 0.0002 for both) but not for Tel-Ed (P= 0.10). The authors concluded that "The use of CPAP telemonitoring with automated feedback messaging improved 90-day adherence in patients with OSA. Telemedicine-based education did not significantly improve CPAP adherence but did increase clinic attendance for OSA evaluation."

Comments

1. The combined CPAP telemonitoring and tele-education program on average increased adherence to 4.4 hours (from 3.8 hours). This additional hour may be clinically significant.
2. The advantage of this program is that it is completely automated and will not require significant personnel time beyond initial set up. However, the cost of acquiring and maintaining the software (both by provider and participant) may not make it a feasible option in underserved areas.
3. More than 70% of participants did not complete the web based educational program, it is possible that the educational component has a bigger impact than what was observed in this study.
4. Only participants with 1-week use and acceptance of CPAP continued with study interventions. This may have led to self-selection of a group of participants that are on average more motivated than the general CPAP user and limits generalizability.
5. This study only evaluated the success of tele-medicine over 90 days. It remains to be seen whether longer exposure to the program or periodic reminders of CPAP usage and performance will improve long term adherence.

NON-CPAP THERAPY FOR OSA

Carley DW, Prasad B, Reid KJ, Malkani R, Attarian H, Abbott SM, Vern B, Xie H, Yuan C, Zee PC. **Pharmacotherapy of Apnea by Cannabimimetic Enhancement, the PACE Clinical Trial: Effects of Dronabinol in Obstructive Sleep Apnea**. *Sleep*. 2018; 41(1). doi: 10.1093/sleep/zsx184.

Summary

PAP therapy, as the gold standard of OSA therapy, is limited by suboptimal adherence and tolerance. To date no medication has been approved for OSA therapy. This is a Phase II multisite, blinded, randomized placebo-controlled clinical trial of dronabinol in 73 adults with moderate or severe OSA. Participants were randomized to receive either placebo (N = 25), 2.5 mg dronabinol (N = 21), or 10 mg dronabinol (N = 27) daily, 1 hour before bedtime for 6 weeks. At baseline, overall apnea–hypopnea index (AHI) was 25.9 ± 11.3, Epworth Sleepiness Scale (ESS) score was 11.45 ± 3.8, maintenance of wakefulness test (MWT) mean latency was 19.2 ± 11.8 minutes, body mass index was 33.4 ± 5.4 kg/m2, and age was 53.6 ± 9.0 years. In comparison to placebo, dronabinol dose-dependently reduced AHI by 10.7 ± 4.4 (p = .02) and 12.9 ± 4.3 (p = .003) events/hour at doses of 2.5 and 10 mg/day, respectively. Dronabinol at 10 mg/day reduced ESS score by –3.8 ± 0.8 points from baseline (p < .0001) and by –2.3 ± 1.2 points in comparison to placebo (p = .05). MWT sleep latencies, sleep architecture, and overnight oxygenation parameters were unchanged from baseline in any treatment group. The medication was well tolerated. The findings from this study support further larger scale trials on impact of dronabinol on OSA therapy.

Comments

1. This is a phase II study, designed to look at safety, dose response, and then clinical efficacy of dronabinol as OSA therapy. As such it supports the need for larger multicenter, phase III studies to look at clinical efficacy across multiple health outcomes.
2. The changes in AHI from baseline were on average 8.5 events/hr on the highest dose of medication. This may not be a clinically significant reduction in those with moderate to severe OSA.
3. Only participants with moderate to severe OSA were included and it may be useful to determine the effectiveness and safety of therapy in those with mild OSA as well as a broader range of participants with OSA and comorbidities.
4. The impact of dronabinol on long term OSA health outcomes is yet to be determined; specifically, as the medication seems to improve AHI and sleep satisfaction but does not have a demonstrable impact on oxygen saturation/hypoxemia, arguably an important factor in the pathogenesis of the negative health outcomes of OSA.
5. If phase III studies continue to show a reasonable clinical benefit for dronabinol in OSA, its comparative effectiveness to CPAP, mandibular advancement devices, and surgical therapies needs to be determined.

OTHER ARTICLES OF INTEREST

Sharma RA, Varga AW, Bubu OM, Pirraglia E, Kam K, Parekh A, Wohlleber M, Miller MD, Andrade A, Lewis C, Tweardy S, Buj M, Yau PL, Sadda R, Mosconi L, Li Y, Butler T, Glodzik L, Fieremans E, Babb JS, Blennow K, Zetterberg H, Lu SE, Badia SG, Romero S, Rosenzweig I, Gosselin N, Jean-Louis G, Rapoport DM, de Leon MJ, Ayappa I, Osorio RS. **Obstructive Sleep Apnea Severity Affects Amyloid Burden in Cognitively Normal Elderly:A Longitudinal Study.** *Am J Respir Crit Care Med*. 2017 Nov 10. doi: 10.1164/rccm.201704-0704OC. [Epub ahead of print]

Loffler KA, Heeley E, Freed R, Anderson CS, Brockway B, Corbett A, Chang CL8, Douglas J, Ferrier K, Graham N, Hamilton GS, Hlavac M, McArdle N, McLachlan J, Mukherjee S, Naughton MT, Thien F, Young A, Grunstein RR, Palmer L, Woodman RJ, Hanly PJ, McEvoy RD; SAVE (Sleep Apnea Cardiovascular Endpoints) Investigators. **Effect of Obstructive Sleep Apnea Treatment on Renal Function in Patients with Cardiovascular Disease**. *Am J Respir Crit Care Me*d. 2017; 196(11):1456-1462.

Peppard PE, Hagen EW. **The Last 25 Years of Obstructive Sleep Apnea Epidemiology-and the Next 25?** *Am J Respir Crit Care Med*. 2018; 197(3):310-312.

Gurubhagavatula I, Sullivan S, Meoli A, Patil S, Olson R, Berneking M, Watson NF. **Management of obstructive sleep apnea in commercial motor vehicle operators: recommendations of the AASM Sleep and Transportation Safety Awareness Task Force**. *J Clin Sleep Med*. 2017; 13(5):745–758.

Patel S, Kon SSC, Nolan CM, Barker RE, Simonds AK, Morrell MJ, Man WD. **The Epworth Sleepiness Scale: Minimum Clinically Important Difference in Obstructive Sleep Apnea**. *Am J Respir Crit Care Med*. 2017 Sep 29. doi: 10.1164/rccm.201704-0672LE. [Epub ahead of print]

Leng Y, McEvoy CT, Allen IE, Yaffe K. **Association of Sleep-Disordered Breathing With Cognitive Function and Risk of Cognitive Impairment: A Systematic Review and Meta-analysis**. *JAMA* Neurol. 2017; 74(10):1237-1245.

Schwartz M, Acosta L, Hung YL, Padilla M, Enciso R. Effects of **CPAP and mandibular advancement device treatment in obstructive sleep apnea patients: a systematic review and meta-analysis**. *Sleep Breath*. 2017 Nov 11. doi: 10.1007/s11325-017-1590-6. [Epub ahead of print]

GENERAL CRITICAL CARE

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ADJUNCTIVE HYDROCORTISONE FOR SEPTIC SHOCK

Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, Billot L, Correa M, Glass P, Harward M, Joyce C, Li Q, McArthur C, Perner A, Rhodes A, Thompson K, Webb S, Myburgh J; ADRENAL Trial Investigators and the Austraia-New Zealand Intensive Care Society Clinical Trials Group. **Adjunctive Glucocorticoid Therapy in Patients with Septic Shock**. *N Engl J Med*. 2018. doi: 10.1056/NEJMoa1705835.

Summary

The role of adjunctive steroids in septic shock has been debated for decades. Prior studies of lower-dose hydrocortisone (200mg/day) showed earlier reversal of shock, but conflicting effects on mortality. Sepsis guidelines include a weak recommendation for hydrocortisone in patients with persistent shock despite adequate resuscitation and vasopressors. But, because of ongoing concerns regarding potential harms (e.g. infection), practice varies widely. This international, double-blind, randomized controlled trial compared 7-day hydrocortisone infusion to placebo in patients with vasopressor-dependent septic shock treated in an intensive care unit (ICU) and undergoing mechanical ventilation. The trial randomized 3,800 patients, with the primary outcome of 90-day mortality ascertained in 3,658. There was no difference in 90-day mortality in hydrocortisone (27.9%) vs. placebo groups (28.8%), p=0.5, and no difference in mortality for any of 6 pre-specified sub-groups (sex, medical vs surgical, illness severity, pulmonary vs non-pulmonary infection, severity of shock, or duration of shock pre-randomization). The hydrocortisone arm had faster time to shock resolution (3 vs. 4 days, p<0.001); faster time to extubation (6 vs. 7 days, p<0.001); shorter ICU length of stay (10 vs. 12 days, p<0.001); and fewer blood transfusions. There was no difference in new bacteremia or fungemia or hospital length of stay.

Comments

1. While mortality was indistinguishable, hydrocortisone infusion was associated with improvement of several secondary outcomes (time to shock reversal, time to extubation, ICU length of stay, and frequency of blood transfusion)—suggesting benefit of hydrocortisone.
2. However, the lack of difference in hospital length of stay raises the question—does this benefit result from truly more rapid stabilization, or just from buffing the numbers that reassure clinicians.
3. Data on quality-of-life at 6 months is still pending, and will be critically important to informing the use of hydrocortisone in septic shock.
4. In contrast to prior studies, this RCT delivered hydrocortisone by infusion, without fludrocortisone, without tapering, and without corticotropin testing.
5. The first interim analysis of this RCT suggested a mortality benefit to hydrocortisone (25.5% versus 31.6% 90-day mortality; odds ratio=0.73, p=0.03)—highlighting the importance of clearly pre-specified stopping criteria and large sample sizes for clinical trials.

ADJUNCTIVE VITAMIN C FOR SEPTIC SHOCK

Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. **Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study**. *Chest*. 2017. doi: 10.1016/j.chest.2016.11.036.

Summary

Vitamin deficiency is common in sepsis, and is associated with multi-organ failure and death. However, few studies have examined the benefit of vitamin repletion during critical illness. This single-center, pre-post study reports on the use of a metabolic resuscitation protocol (vitamin C 1.5g every 6 hours, hydrocortisone 50mg every 6 hours, and thiamine 200 mg every 12 hours) in severe sepsis and septic shock. The outcomes of 47 consecutive patients treated with the 3-drug regimen (January-July 2016) were compared to the outcomes of 47 historical patients not treated with vitamin C or thiamine (June-December 2015), who were matched by a propensity score that captured illness severity at ICU admission. All patients had clinically-identified severe sepsis and procalcitonin ≥ 2mg/ml; 47% in each group had septic shock. During the treatment period, patients received the 3-drug regimen. 28 (60%) historical patients received intravenous hydrocortisone alone, per the discretion of the treating physician. In-hospital mortality was 8.5% among treatment patients vs. 40.4% in matched historical controls. Median duration of vasopressors was 18.3 hours in treatment patients vs. 54.9 hours

in matched historical controls. Use of renal replacement therapy, change in SOFA score, and rate of procalcitonin clearance all favored the treatment patients.

Comments

1. While the study reports a remarkable 32% absolute risk reduction (87% relative risk reduction) for in-hospital mortality, the single-center design and lack of randomization, blinding, or concurrent controls increase the risk of false-positive results due to confounding and selection bias; the paper itself argues "additional studies are required to confirm our preliminary findings."
2. The benefit of this 3-drug regimen warrants evaluation in an RCT, with attention to the relative contributions of the 3 ingredients.
3. Until RCT data is available, the use of this 3-drug regimen remains highly controversial—with some arguing it is unethical to withhold an inexpensive, safe, and potentially beneficial therapy, and others arguing that it is unethical to assume the regimen is safe, let alone beneficial.
4. Vitamin C given in high doses may be converted to oxalate and cause renal stones, so thiamine was included in the regimen to decrease production of oxalate, with no immediate adverse effects identified in the 47 treatment patients.

MANAGEMENT OF VASODILATORY SHOCK

Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, Busse LW, Altaweel L, Albertson TE, Mackey C, McCurdy MT, Boldt DW, Chock S, Young PJ, Krell K, Wunderink RG, Ostermann M, Murugan R, Gong MN, Panwar R, Hästbacka J, Favory R, Venkatesh B, Thompson BT, Bellomo R, Jensen J, Kroll S, Chawla LS, Tidmarsh GF, Deane AM; ATHOS-3 Investigators. **Angiotensin II for the treatment of Vasodilatory Shock**. *N Engl J Med*. 2017; 377(5):419-430. doi: 10.1056/NEJMoa1704154.

Summary

Catecholamines (e.g. epinephrine, norepinephrine, dopamine) are the primary pharmacological treatment for shock. However, these agents can cause unwanted side effects, such as tachycardia, digital ischemia, and mesenteric ischemia. The ATHOS-3 trial was a multi-center, randomized, placebo-controlled trial of angiotensin II versus placebo in patients with vasodilatory shock already receiving high-dose vasopressors (≥0.2μg/kg/min of norepinephrine, or equivalent) for 6 to 48 hours. The primary end-point was blood-pressure response at 3 hours (defined as an increase of mean arterial pressure of ≥10mm Hg to at least 75 mm Hg, without an increase in the dose of background vasopressors). Among 321 patients who were randomized and received a study intervention, blood-pressure response was achieved in 69.9% of patients randomized to treatment vs. 23.4% of patients randomized to placebo. Mean improvement in organ failure at 48 hours (as measured by SOFA score) was greater in treatment vs placebo patients, p=0.01. 28-day mortality was 46% in treatment vs. 54% in placebo, p=0.12. Rates of serious adverse events were similar between treatment and placebo.

Comments

1. Because of this trial, the U.S. Food and Drug Administration approved angiotensin II (Giapreza) for use in septic and other vasodilatory shock in December 2017.
2. The FDA release comments that angiotensin group suffered more thrombotic phenomenon (12.9% vs 5%), but these were predominantly mild/moderate.
3. While this study demonstrates angiotensin II can increase blood pressure, it was not powered to detect benefit for patient-centered end-points, such as mortality or functional outcomes—which have not always tracked with initial organ failure measures.
4. 23 (7%) of patients who were randomized did not receive any study drug (most commonly due to rapid clinical improvement) and were excluded from the primary analysis, but results of sensitivity intention-to-treat analysis were similar (67.4% vs 23.8% with blood pressure response).

SEPSIS RESUSCIATION IN DEVELOPING COUNTRIES

Andrews B, Semler MW, Muchemwa L, Kelly P, Lakhi S, Heimburger DC, Mabula C, Bwalya M, Bernard GR. **Effect of an Early Resuscitation Protocol on In-hospital Mortality Among Adults with Sepsis and Hypotension: A Randomized Clinical Trial**. *JAMA.* 2017;318(13):1233-1240. doi: 10.1001/jama.2017.10913.

Summary

Sepsis mortality remains particularly high in developing countries. The benefit of an early resuscitation protocol is unclear, as the 2011 FEAST study showed increased mortality with fluid bolus in African children with sepsis. This SSSP2 trial randomized 212 adults presenting to a Zambian referral hospital with sepsis and hypotension (but without hypoxemia or severe tachypnea) to usual care versus an early resuscitation protocol for sepsis. The protocol included intravenous fluid bolus, dopamine to target mean arterial pressure ≥65 mm Hg, and blood transfusion for patients with hemoglobin ≤7 g/dL. Arterial oxygen saturation, respiratory rate, and jugular venous pressure were monitored, and fluid therapy was stopped if arterial oxygen saturation decreased by 3%, respiratory rate increased by 5, JVP reached 3cm above sternal angle, or after 4L had been given. 89.5% of patients were HIV positive, with a median CD4 count of 66/μL. The primary outcome of in-hospital mortality occurred in 48.1% randomized to resuscitation protocol vs. 33.0% in usual care (relative risk 1.46, p=0.03)—a number needed to harm of 7. Within 6 hours of presentation, the treatment arm received an average 3.5 L of intravenous fluid vs. 2.0L in usual care, p<0.001.

Comments

1. This important study highlights the importance of context, and the need to test interventions in the setting and with the populations where they will be used.
2. Due to resource limitations, fluids and vasopressors were not titrated to hemodynamic parameters and were not weight-based, but rather, were titrated to evidence of respiratory compromise.
3. Dopamine was used rather than norepinephrine because of safety concerns regarding peripheral infusion of norepinephrine
4. Only 1 patient in the study was admitted to an intensive care unit.
5. In the usual care arm, less than 50% of patients received any fluid bolus, <20% received blood, and <2% received a vasopressor.

PHARMACOLOGICAL TREATMENT OF DELIRIUM

Agar MR, Lawlor PG, Quinn S, Draper B, Caplan GA, Rowett D, Sanderson C, Hardy J, Le B, Eckermann S, McCaffrey N, Devilee L, Fazekas B, Hill M, Currow DC. **Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care: A Randomized Clinical Trial**. *JAMA Intern Med*. 2017. doi: 10.1001/jamainternmed.2016.7491.

Summary

Antipsychotics are widely used to treat distressing symptoms of delirium. However, there is little data to support this practice. Guidelines for management of delirium in the ICU state that atypical antipsychotics may reduce duration of delirium (based on low-quality evidence), but that there is no evidence that haloperidol reduces duration of delirium in adult ICU or nursing home patients. This double-blind randomized controlled trial, conducted in 11 Australian palliative care units, evaluated the efficacy of antipsychotic medications for treatment of delirium. 247 patients with life-limiting illness (88% with cancer) were randomized 1:1:1 to oral risperidone, haloperidol, or placebo for symptoms of delirium. All patients received supportive care, individualized treatment of delirium precipitants, and rescue midazolam for severe distress or for safety. Patients randomized to antipsychotics had worse symptom control—on average 0.48 units higher with risperidone (p=0.02) and 0.24 units higher with haloperidol (p=0.009) on the sum of the Nursing Delirium Screening Scale's behavioral, communication, and perceptual items (range, 0-6). Rescue midazolam use was significantly lower in the placebo versus antipsychotic arms (17.3% vs 34.7%, p=0.007). Median survival was 26 days in placebo, 17 days in risperidone arm, and 16 days in haloperidol arm (hazard ratio for death was 1.5 in patient randomized to antipsychotics).

Comments

1. While this study examined a non-ICU patient population, the findings of both worse symptom control and shorter time to death argue that prescribing antipsychotics for delirium in ICU patients may be both counter-productive and harmful.
2. This may be particularly relevant to patients in the ICU receiving palliation-targeted care.
3. Patients randomized to antipsychotics also experienced more extrapyramidal symptoms.

INTENSIVE CARE UNIT TRIAGE

Guidet B, Leblanc G, Simon T, Woimant M, Quenot JP, Ganansia O, Maignan M, Yordanov Y, Delerme S, Doumenc B, Fartoukh M, Charestan P, Trognon P, Galichon B, Javaud N, Patzak A, Garrouste-Orgeas M, Thomas C, Azerad S, Pateron D, Boumendil A; ICE-CUB 2 Study Network. **Effect of Systematic Intensive Care Unit Triage on Long-term Mortality Among Critically Ill Elderly Patients in France: A Randomized Clinical Trial**. *JAMA*. 2017;318(15):1450-1459. doi: 10.1001/jama.2017.13889.

Summary

There is little evidence to guide intensive care unit triage. This multi-center trial randomized 24 hospitals in France to a program for systematically increasing the rate of ICU admission for suitable elderly patients. 3,037 critically ill patients, aged 75+ years, with preserved functional status, not cachectic, and free of cancer were included in the study. Patients treated at hospitals randomized to the intervention were more likely to be admitted to an ICU (61% vs. 34%, relative risk 1.80, 95%CI: 1.66, 1.95). However, despite higher admission to an ICU, patients treated at intervention hospitals had a higher crude 6-month mortality (45% vs. 39%, relative risk 1.16, 95%CI: 1.07, 1.26). After adjusting for differences in baseline characteristics, patients treated at intervention hospitals were still more likely to be admitted to an ICU, but the difference in mortality was no longer statistically significant (relative risk 1.05, 95%CI: 0.96, 1.14). Patients at intervention hospitals were more likely to undergo invasive mechanical ventilation (42% vs. 31%, p<0.001).

Comments

1. This cluster-randomized study suggests that programs to promote systematic ICU admission are effective at increasing ICU admission, but not at decreasing 6-month mortality.
2. The recruitment rate was lower at control hospitals (26.7% vs 41.0%), and baseline characteristics (e.g. living situation, home support, admitting diagnosis, illness severity) were unbalanced, suggesting selection bias.
3. The trial was set in France, limiting applicability in other countries where ICU triage may differ.
4. Despite the methodological limitations (e.g. cluster randomization, differences in recruitment rates, differences in baseline characteristics), this study raises concern that admission to an intensive care unit and associated invasive treatment is potentially harmful for elderly patients.

OTHER ARTICLES OF INTEREST

MANAGEMENT OF SEPSIS AND SEPTIC SHOCK

Alam N, Oskam E, Stassen PM, Exter PV, van de Ven PM, Haak HR, Holleman F, Zanten AV, Leeuwen-Nguyen HV, Bon V, Duineveld BAM, Nannan Panday RS, Kramer MHH, Nanayakkara PWB; PHANTASi Trial Investigators and the ORCA (Onderzoeks Consortium Acute Geneeskunde) Research Consortium the Netherlands. **Prehospital antibiotics in the ambulance for sepsis: a multicenter, open label, randomized trial**. Lancet Resp Med. 2018;6(1):40-50. doi: 10.1016/S2213-2600(17)30469-1. Epub 2017 Nov 28.

PRISM Investigators, Rowan KM, Angus DC, Bailey M, Barnato AE, Bellomo R, Canter RR, Coats TJ, Delaney A, Gimbel E, Grieve RD, Harrison DA, Higgins AM, Howe B, Huang DT, Kellum JA, Mouncey PR, Music E, Peake SL, Pike F, Reade MC, Sadique MZ, Singer M, Yealy DM. **Early, Goal-Directed Therapy for Septic Shock - A Patient-Level Meta-Analysis**. N Engl J Med. 2017376(23):2223-2234. doi: 10.1056/NEJMoa1701380.

Vail E, Gershengorn HB, Hua M, Walkey AJ, Rubenfeld G, Wunsch H. **Association Between US Norepinephrine Shortage and Mortality Among Patients With Septic Shock**. JAMA. 2017;317(14):1433-1442. doi: 10.1001/jama.2017.2841.

METHOD OF INTUBATION

Lascarrou JB, Boisrame-Helms J, Bailly A, Le Thuaut A, Kamel T, Mercier E, Ricard JD, Lemiale V, Colin G, Mira JP, Meziani F, Messika J, Dequin PF, Boulain T, Azoulay E, Champigneulle B, Reignier J; Clinical Research in Intensive Care and Sepsis (CRICS) Group. **Video Laryngoscopy vs Direct Laryngoscopy on Successful First-Pass Orotracheal Intubation Among ICU Patients. A Randomized Clinical Trial**. JAMA. 2017;317(5):483-493. doi: 10.1001/jama.2016.20603.

NUTRITION

Reignier J, Boisramé-Helms J, Brisard L, Lascarrou JB, Ait Hssain A, Anguel N, Argaud L, Asehnoune K, Asfar P, Bellec F, Botoc V, Bretagnol A, Bui HN, Canet E, Da Silva D, Darmon M, Das V, Devaquet J, Djibre M, Ganster F, Garrouste-Orgeas M, Gaudry S, Gontier O, Guérin C, Guidet B, Guitton C, Herbrecht JE, Lacherade JC, Letocart P, Martino F, Maxime V, Mercier E, Mira JP, Nseir S, Piton G, Quenot JP, Richecoeur J, Rigaud JP, Robert R, Rolin N, Schwebel C41, Sirodot M, Tinturier F, Thévenin D, Giraudeau B, Le Gouge A; NUTRIREA-2 Trial Investigators; Clinical Research in Intensive Care and Sepsis (CRICS) group. **Enteral versus parenteral nutrition in ventilated adults with shock: a randomized, controlled, multicentre, parallel-group study (NUTREA-2).** Lancet. 2018;391(10116):133-143. doi: 10.1016/S0140-6736(17)32146-3.

Allingstrup MJ, Kondrup J, Wiis J, Claudius C, Pedersen UG, Hein-Rasmussen R, Bjerregaard MR, Steensen M, Jensen TH, Lange T, Madsen MB, Møller MH, Perner A. **Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial**. Intensive Care Med. 2017;43(11):1637-1647. doi: 10.1007/s00134-017-4880-3.

SEDATION

Chanques G, Conseil M, Roger C, Constantin JM, Prades A, Carr J, Muller L, Jung B, Belafia F, Cissé M, Delay JM, de Jong A, Lefrant JY, Futier E, Mercier G, Molinari N, Jaber S; SOS-Ventilation study investigators. **Immediate interruption of sedation compared with usual sedation care in critically ill postoperative patients (SOS-Ventilation): a randomised, parallel-group, clinical trial**. Lancet Respir Med. 2017;5(10):795-805. doi: 10.1016/S2213-2600(17)30304-1.

CONTRAST NEPHROPATHY PREVENTION

Nijssen EC, Rennenberg RJ, Nelemans PJ, Essers BA, Janssen MM, Vermeeren MA, Ommen VV, Wildberger JE. **Prophylactic hydration to protect renal function from intravascular Iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial**. Lancet. 2017;389(10076):1312-1322. doi: 10.1016/S0140-6736(17)30057-0.

PEDIATRIC CRITICAL CARE

Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, Meert KL, Browning B, Pemberton VL, Page K, Gildea MR, Scholefield BR, Shankaran S, Hutchison JS, Berger JT, Ofori-Amanfo G, Newth CJ, Topjian A, Bennett KS, Koch JD, Pham N, Chanani NK, Pineda JA, Harrison R, Dalton HJ, Alten J, Schleien CL, Goodman DM, Zimmerman JJ, Bhalala US, Schwarz AJ, Porter MB, Shah S, Fink EL, McQuillen P, Wu T, Skellett S, Thomas NJ, Nowak JE, Baines PB, Pappachan J, Mathur M, Lloyd E, van der Jagt EW, Dobyns EL, Meyer MT, Sanders RC Jr, Clark AE, Dean JM; THAPCA Trial Investigators. **Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children**. N Engl J Med. 2017; 376(4):318-329. doi: 10.1056/NEJMoa1610493.

Agus MS, Wypij D, Hirshberg EL, Srinivasan V, Faustino EV, Luckett PM, Alexander JL, Asaro LA, Curley MA, Steil GM, Nadkarni VM; HALF-PINT Study Investigators and the PALISI Network. **Tight Glycemic Control in Critically Ill Children**. N Engl J Med. 2017; 376(8):729-741. doi: 10.1056/NEJMoa1612348.

QUALITY IMPROVEMENT IN CRITICAL CARE

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IMPROVING ADHERENCE TO EVIDENCE-BASED PRACTICES

Barbash IJ, Pike F, Gunn SR, Seymour CW, Kahn JM. **Effects of Physician-targeted Pay for Performance on Use of Spontaneous Breathing Trials in Mechanically Ventilated Patients**. *Am J Respir Crit Care Med*. 2017;196(1):56-63.

Summary

Daily spontaneous breathing trials (SBT) are associated with decreased duration of mechanical ventilation and is widely recommended by professional societies. This before-after trial incentivized adherence to SBTs with a new payment-for-performance (P4P) strategy targeted at physicians in 3 hospitals if the rates of SBTs were over 90% on eligible ventilator-days. Eligibility for SBTs was determined on a daily basis by physicians and respiratory therapists. All ventilated days were included, but censored after 30 days to reduce the influence of chronic patients. The number of patients varied across hospitals (A: 4888, B: 311 and C: 2101), as did baseline adherence (A: 96.8%, B: 16.4% and C: 74.7%). At year 2, rates remained stable in Hospital A (97.7%), while it increased in both Hospitals B (93.7%, $p < 0.001$), and C (91.7%, $p < 0.01$). However, improvements were accompanied by increases in eligibility exclusion criteria (for example Hospital B: 39.8% to 69.1%, $p<0.001$). Interestingly, when analyzing the rates of SBTs over all ventilator-days (including those deemed ineligible) only Hospital B had an absolute increase in SBTs (9.9% to 28.9%, $p<0.01$). This suggests that improvements in Hospital C were due to changes in documentation practices, while C had a real increase in adherence.

Comments

1. The P4P strategy demonstrated improved adherence to SBTs in hospitals with baseline low rates.
2. However, improvements may be due to changes in documentation and not necessarily quality of care, suggesting that payers should be vigilant of other process metrics (such as exclusion criteria) when designing P4P programs.
3. As the most common patterns of eligibility exclusion were "Respiratory Instability" and "MD order/Other", both carrying potential for subjective interpretation, it is still possible that elements of gaming may have played a role in the high compliance rates.
4. Future studies should consider using objective eligibility criteria that are not dependent on clinician assessment, by using physiological parameters the possibility of "gaming" the system decreases and facilitates data collection.

EMOTIONAL INFLUENCE ON COGNITION AND TEAM PERFORMANCE

Riskin A, Erez A, Foulk TA, Riskin-Geuz KS, Ziv A, Sela R, et al. **Rudeness and Medical Team Performance.** *Pediatrics*. 2017;139(2).

Summary

Clinicians are frequently exposed to disrespectful behavior, which influences not only well-being, but also clinical performance. This simulation-based study investigated impact of exposure to "rudeness" from a patient's parent on team's performance, and the potential mitigating effect of 2 strategies, cognitive bias modification (CBM) and narrative writing (NW). CBM used a 20-minute computerized training to promote a positive response to ambiguous stimuli, while NW about previous experiences allows for better processing of the experience. 39 teams were randomized to control, rudeness, and rudeness with either CBM or NW. They worked in 5 different simulated scenarios, and were judged on 9 parameters by observers blinded to the interventions. Teams exposed to rudeness performed significantly worse than controls in the general teamwork score (4.4 vs 4.0, $p<0.05$) and across 6 of the other 8 domains of medical and teamwork performance. For example, therapeutic plan (4.2 vs 3.8, $p=0.01$) and helping scores (4.5 vs 4.0, $p<0.05$) were lower in participants exposed to rudeness. The effects of rudeness were mitigated by CBM where all scores were similar between CBM and control, but not by NW where all scores, but 1, remained significantly lower in teams exposed to rudeness.

Comments

1. Although this study is limited by its simulation design, it provides important information about clinical performance on clinical teams exposed to rudeness.
2. The finding that CBM, a strategy designed to change participant's response to ambiguous stimuli, could improve clinical performance suggests that individuals frequently exposed to disrespectful behavior could use a simple computer-led

intervention at the start of their clinical work to improve performance.
3. Another strong aspect of this study is that participants in the CBM arm continued to view the rude parents as rude, suggesting that their improved performance was mediated by improved resilience to emotional responses.
4. Interestingly the NW intervention led participants to see the parents as less rude, suggesting an empathetic effect that did not improve clinical performance.

MEDICAL ERROR SURVEILLANCE

Khan A, Coffey M, Litterer KP, Baird JD, Furtak SL, Garcia BM, et al. **Families as Partners in Hospital Error and Adverse Event Surveillance**. *JAMA pediatrics*. 2017;171(4):372-81.

Summary

Detection of medical errors forms the basis of patient-safety programs. Errors that lead to patient harm are considered adverse events (AE). Although daily prospective systematic surveillance for errors is a well-established methodology, it's not used outside of research because it is labor intensive and expensive. Therefore, hospitals usually resort to clinician volunteered incident reporting systems (IRS), which typically underestimate and miss important safety domains. Patients and families are not usually included in the detection of AE. This study reports a secondary analysis of the I-PASS communication trial in 4 pediatric hospitals, comparing AE rates reported by families via a family safety interview (FSI) to those gathered systematically using validated tools and to the clinician-based AE reporting system. Out of 989 parents in the original study, 746 consented to participate in this secondary analysis, and 717 completed FSIs. There were a total of 179 errors, including 113 AEs. Families identified 50 errors and 33 AEs, including 19 uniquely identified errors and 8 uniquely identified AEs. Among 3 sites with IRS, family-reported errors were 5-fold (95% CI, 1.9-13.0) higher than IRS. Higher parental education and age, and higher patient complexity and younger age were independent predictors of error detection by families.

Comments

1. Family reporting yields higher error and AE rates when compared to IRS and can be a potential tool to improve error surveillance in hospitals.
2. Although this strategy is still labor intensive, including the administration of the FSI and a chart review by independent clinicians, the yield of chart abstraction was high (50/97), or approximately 3 chart-reviews per hospital per month.
3. Many errors are still missed, but since domains of errors are frequently clustered, this strategy may still yield important information for local quality improvement and safety interventions.
4. The population was limited to pediatric, medical patients, and it is possible that these findings may not be generalizable to adult and/or surgical populations.

DELAYS IN ANTIMICROBIALS FOR SEPSIS

Leisman D, Huang V, Zhou Q, Gribben J, Bianculli A, Bernshteyn M, et al. **Delayed Second Dose Antibiotics for Patients Admitted From the Emergency Department With Sepsis: Prevalence, Risk Factors, and Outcomes**. *Crit Care Med*. 2017;45(6):956-65.

Summary

The association between delays in sepsis treatment and mortality is well established. Particularly, delays in initiating antimicrobials are associated with increases in mortality. Timely administration of subsequent doses of antimicrobials has received little attention, however delays are also potentially harmful due to subtherapeutic antimicrobial concentrations, which may increase resistance ratios. This single-center observational cohort investigated the frequency, determinants and outcomes associated with delays in the second dose of antimicrobials in patients with sepsis admitted through the emergency department (ED). The authors defined a priori major delays as greater than 25% of the recommended interval (e.g.: second dose in 8 hours for a recommended regimen of every 6 hours). 828 patients with sepsis were included and 272 (32.9%) had a major delay in antimicrobials. Risk factor for major delays included lower drug half-life (OR: 24h=1.0, 12h=6.9, 8h=23.7, 6h=71.9, $p<0.001$), boarding in ED (OR 2.6, $p<0.001$), compliance with 3-hour sepsis bundle (OR 1.5, $p=0.02$) and older age (OR 1.1 per 10 years, $p=0.045$). Exploratory analysis suggests that major delays were associated with increased mortality (OR 1.6, $p=0.046$).

Comments

1. Delays in administration of the second dose of antimicrobials for patients with sepsis were surprisingly frequent (roughly one third of patients).
2. This study provides insight on potentially modifiable factors, such as using drugs with longer half-life as first option and revisiting processes of care for patients boarded in the ED.
3. This study is limited by its single center nature, as it's likely that the estimate of delays will vary among different centers, however it brings to light a potentially modifiable and measurable step in the care of patients with sepsis.
4. The association with mortality should be interpreted with caution, as it is possible that residual confounding and selection bias may be partially responsible for these findings.

INTERDISCIPLINARY ROUNDS

Cao V, Tan LD, Horn F, Bland D, Giri P, Maken K, et al. **Patient-Centered Structured Interdisciplinary Bedside Rounds in the Medical ICU**. *Crit Care Med*. 2018;46(1):85-92.

Summary

Interdisciplinary rounds are a key component of ICU care. The inclusion of families during rounds is highly prevalent

in pediatric ICUs, but adult studies show mixed results in terms of family satisfaction and raise several concerns from clinicians, regarding teaching opportunities and time efficiency. In this single-center, parallel design study, patient-centered and structured rounds (PCSR) were implemented in one team in a medical ICU, while the other team continued to perform rounds as per attending physician preference. PCSR required the presence of all clinicians involved in patient care at the bedside, and defined clear roles and structure for presentation. Family members and patients were actively invited to participate on PCSR and ask questions. Clinicians were aware of the study, but blinded to the main outcome of interest (duration of rounds). PCSR increased attendance of family members (31% vs 10%, p<0.01) and bedside nurses (91% vs 61%, p<0.01), however rounding times per patient were shorter (16.9 min vs 22.4 min, p<0.01), due to decreases in resident's presentation and duration of interruptions. Teaching points were more frequent in PCSR (51% vs 34%, p<0.01) and residents, nurses and respiratory therapists discussed required items more frequently in PCSR.

Comments

1. Contrary to expectations, inclusion of families and applying structure to bedside rounds was time-efficient and did not interfere with teaching.
2. The study is limited by the single center nature, limited number of attending physicians and small number of family members during rounds (<30% in total), therefore it is not possible to generalize these findings.
3. It is remarkable that the time spent by nurses during rounds was very short (less than 1 minute), which limits generalizability to centers where nurses take a more central role during rounds.
4. There were very few families responding to the communication survey, limiting the ability of this study to understand the effects of family presence on rounds on their satisfaction with communication.

UNINTENDED CONSEQUENCES OF INTERVENTIONS

Kentish-Barnes N, Chevret S, Champigneulle B, Thirion M, Souppart V, Gilbert M, et al. **Effect of a condolence letter on grief symptoms among relatives of patients who died in the ICU: a randomized clinical trial**. Intensive Care Med. 2017;43(4):473-84.

Summary

A large number of bereaved family members of patients dying in the ICU experience symptoms of grief. Improving communication at the end-of-life may alleviate these symptoms, but there are no interventions targeting families after the death of a loved one. This randomized trial delivered a hand-written "condolence letter" to family members of patients dying in 22 French ICUs 15 days after the patient's death. Clinicians wrote the note within the first 3 days after death, based on guidelines that suggested informal letters and details about the person. Phone interviews were conducted with family members 30 days and 6 months after the patient's death by study personnel blinded to the intervention. Of 242 family members, 208 and 190 responded to the interviews and 30 days and 6 months, with similar loss to follow-up in both groups. There were no differences between groups at 30 days. At 6 months family members in the intervention group had more depression-related (36.6% vs 24.7%, p=0.05) and PTSD-related symptoms (52.4% vs 37.1%, p=0.03). The unintended consequences of the condolence letter persisted after multivariate adjustment.

Comments

1. 50% of family members were involved in the decisions to limit treatment, which may limit generalizability to centers where family involvement is either more or less prevalent.
2. This well developed, elegant and rational intervention did not improve outcomes, and led to worse symptoms of grief in those receiving the condolence letter.
3. Although this is not a quality improvement study, it informs on the unintended consequences of a well-intentioned and sound strategy and should raise clinician awareness when implementing interventions before empirically testing their effects.

OTHER ARTICLES OF INTEREST

Bloos F, Ruddel H, Thomas-Ruddel D, Schwarzkopf D, Pausch C, Harbarth S, et al. **Effect of a multifaceted educational intervention for anti-infectious measures on sepsis mortality: a cluster randomized tria**l. *Intensive Care Med.* 2017;43(11):1602-12.2.

Dykes PC, Rozenblum R, Dalal A, Massaro A, Chang F, Clements M, et al. **Prospective Evaluation of a Multifaceted Intervention to Improve Outcomes in Intensive Care: The Promoting Respect and Ongoing Safety Through Patient Engagement Communication and Technology Study**. *Crit Care Med*. 2017;45(8):e806-e13.3.

Kalfon P, Baumstarck K, Estagnasie P, Geantot MA, Berric A, Simon G, et al. **A tailored multicomponent program to reduce discomfort in critically ill patients: a cluster-randomized controlled trial**. *Intensive Care Med.* 2017;43(12):1829-40.4.

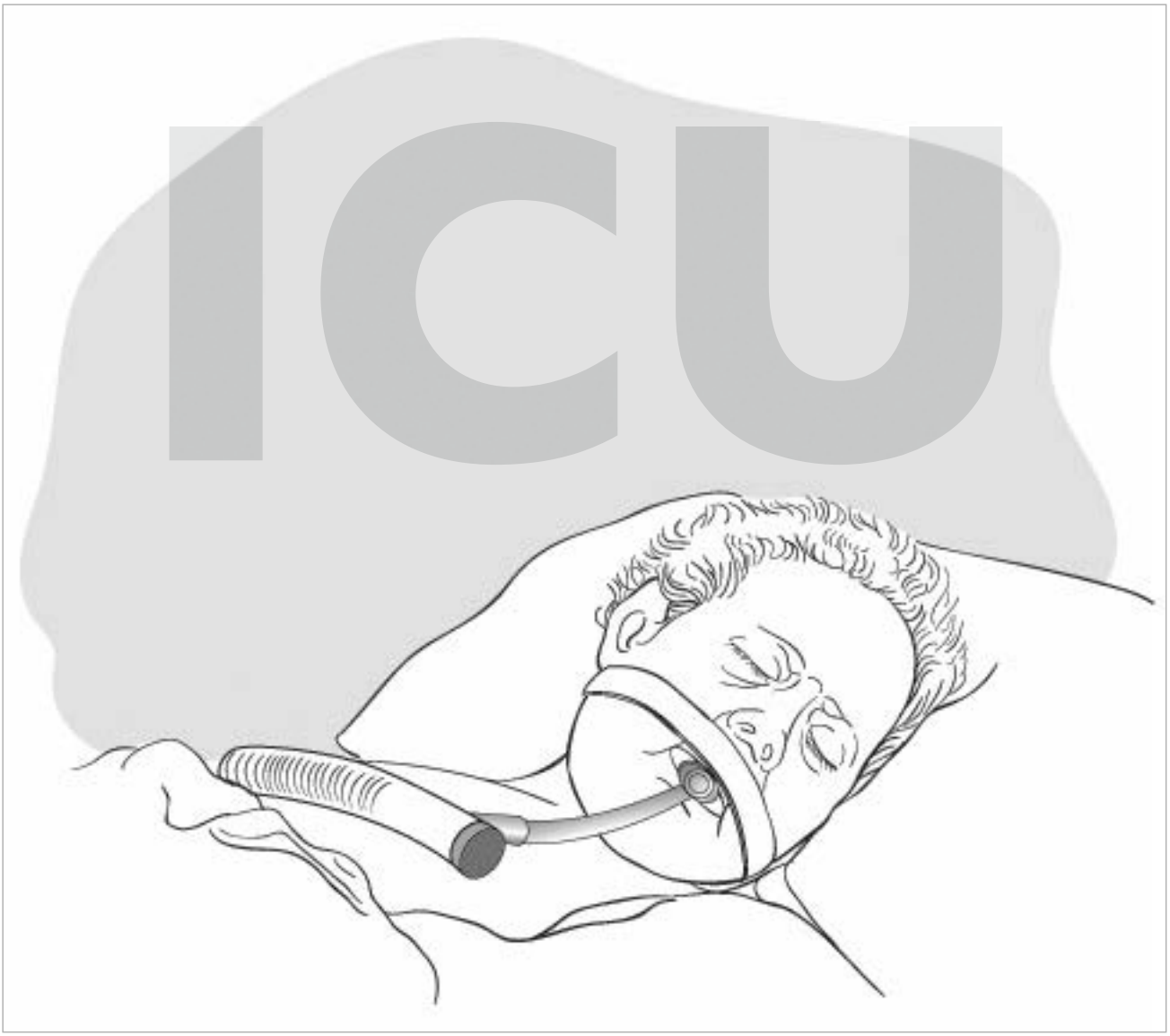
Peltan ID, Mitchell KH, Rudd KE, Mann BA, Carlbom DJ, Hough CL, et al. **Physician Variation in Time to Antimicrobial Treatment for Septic Patients Presenting to the Emergency Department**. *Crit Care Med.* 2017;45(6):1011-8.5.

Schwarzkopf D, Ruddel H, Thomas-Ruddel DO, Felfe J, Poidinger B, Matthaus-Kramer CT, et al. **Perceived Nonbeneficial Treatment of Patients, Burnout, and Intention to Leave the Job Among ICU Nurses and Junior and Senior Physicians**. *Crit Care Med.* 2017;45(3):e265-e73.6.

Stelfox HT, Leigh JP, Dodek PM, Turgeon AF, Forster AJ, Lamontagne F, et al. **A multi-center prospective cohort**

study of patient transfers from the intensive care unit to the hospital ward. *Intensive Care Med*. 2017;43(10):1485-94.7.

van der Kooi T, Sax H, Pittet D, van Dissel J, van Benthem B, Walder B, et al. **Prevention of hospital infections by intervention and training (PROHIBIT): results of a pan-European cluster-randomized multicentre study to reduce central venous catheter-related bloodstream infections.** *Intensive Care Med*. 2018;44(1):48-60.



HEALTH DISPARITIES

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AIR POLLUTION AND HEALTH DISPARITIES

Di Q, Wang Y, Zanobetti A, Wang Y, Koutrakis P, Choirat C, Dominici F, Schwartz JD. **Air Pollution and Mortality in the Medicare Population**. *N Engl J Med*. 2017 Jun 29;376(26):2513-2522.

Summary

Previous studies have shown that air pollution increases mortality. However, it is not clear whether cut-offs recommended by the current national air quality standards are sufficient to reduce this excess mortality. To address this question, the investigators used Medicare data to construct a cohort of over 460 million person-years in the U.S. between 2002 and 2012, and estimated the risk of death associated with exposure to higher concentrations of particulate matter with a mass median diameter under 2.5 μm (PM2.5) and ozone. They found that each 10 μg/m3 increase in PM2.5 was associated with 7.3% increase in all-cause mortality, and that each 10 ppb increase in ozone was linked to a 1.1% increase in mortality. Increases in mortality risk were more pronounced at pollution levels well below the recommendations from the National Ambient Air Quality Standards (12 μg/m3 for PM2.5 and 70 ppb for ozone). Furthermore, mortality risk associated with PM2.5 was higher among minorities (African-Americans, Hispanics, and Asians) compared to non-Hispanic whites, and among those of lower socioeconomic status.

Comments

1. Higher long-term exposure to PM2.5 and ozone levels was associated with increased all-cause mortality, with a more pronounced increase in risk from PM2.5 than ozone exposure.
2. These increases in mortality occurred at levels well below the minimum levels recommended by the U.S. Environmental Protection Agency (EPA).
3. Risk of mortality associated with PM2.5 was higher among racial/ethnic minorities (African-Americans, Hispanics, and Asians) and among those of low socioeconomic status.
4. Strengths included the extraordinary sample size, which allowed subgroup analysis by sex, racial/ethnic, and socioeconomic status.
5. Limitations included using data on adults 65 years of age or older, rather than a broader age range.

LUNG CANCER INCIDENCE AND SURVIVAL

Atkins GT, Kim T, Munson J. Residence in Rural Areas of the United States and Lung Cancer Mortality. **Disease Incidence, Treatment Disparities, and Stage-Specific Survival**. *Ann Am Thorac Soc*. 2017 Mar;14(3):403-411.

Summary

U.S. mortality from lung cancer is higher in rural areas; however, it is unclear whether that difference is explained by discrepancies in incidence, stage at diagnosis, or treatment received. To answer this question, researchers used data from the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, and analyzed data from over 348,000 patients diagnosed with lung cancer between 2000 and 2006. Each patient was classified into county rural-urban continuum areas (RUCA), which range from 1 (large metropolitan areas) to 9 (small rural areas distant from a metro area). The most rural areas had 90% higher mortality (67 vs. 35 per 100,000 population) and 75% higher incidence than the most urban areas (98 vs. 56 per 100,000), but also had 80% higher smoking prevalence (25% vs 14%). Stage at diagnosis was similar across areas, but stage I rural patients with NSCLC underwent fewer surgeries and had lower median survival (40 vs. 52 months, odds ratio of no treatment 1.40, $P<0.001$). Median survival for stages II-IV did not vary with rurality.

Comments

1. Lung cancer mortality increased from 62% in large metropolitan areas to 69% in the most rural areas.
2. Incidence of lung cancer was almost twice as high in small rural areas as in large metropolitan ones, largely explained by a similar difference in smoking rates.
3. Patients with stage I in rural areas underwent fewer surgeries and had lower median survival compared to large metropolitan areas (40 vs. 52 months), potentially identifying an area of intervention at an early stage that may yield improved survival.
4. Study limitations included lack of direct measures of comorbidities, insurance status, or health care access, as well as the lack of individual-level smoking history.

CYSTIC FIBROSIS IN HISPANICS

McGarry ME, Neuhaus JM, Nielson DW, Burchard E, Ly NP. **Pulmonary function disparities exist and persist in**

Hispanic patients with cystic fibrosis: A longitudinal analysis. *Pediatr Pulmonol*. 2017 Dec;52(12):1550-1557.

Summary

Life expectancy among patients with cystic fibrosis (CF) in the U.S. has continuously improved for many decades. However, Hispanic patients with CF have decreased life expectancy, compared to their non-Hispanic white (NHW) peers. In this study, the authors used CF Foundation Patient Registry data from 15,000 patients with CF ages 6-25 years, and used mixed linear models to evaluate lung function by race/ethnicity. They found that, on average, Hispanic patients had ~5.8% lower FEV1 than NHW patients (79.9% vs. 85.6%). Differences were significant after adjusting for multiple potential confounders, including age, sex, body mass index, pancreatic enzyme use, sweat chloride concentration, Pseudomonas and MRSA colonization, maternal education, insurance type, tobacco exposure, and age at diagnosis. There was no significant difference in FEV1 decline over time, but the difference was more pronounced among patients on pancreatic enzymes than among those not on enzymes (-6% vs -4.1%, P<0.001). There were no differences by CFTR mutation class or F508del status.

Comments

1. Using a large cohort of patients with CF, this study found a statistically and clinically significant gap in lung function between Hispanic and non-Hispanic white patients in the U.S.
2. This disparity in lung function was present early on, remained through at least 25 years of age, and was not explained by a dozen demographic and clinical characteristics that were included in the analysis.
3. The gap was more pronounced (~6% lower FEV1) among patients taking pancreatic enzymes than among those not on enzymes (~4% lower FEV1), suggesting nutritional status may play a role.
4. Given that Hispanic patients have lower lung volume and shorter life expectancy, it is critical to identify modifiable causes that may contribute to these disparities.
5. Study limitations included potential ethnicity misclassification, the choice of predictive equations, and the inability to extrapolate to the ~15-20% of patients with CF not included in the registry.

RACIAL DISPARITIES IN CHILDHOOD ASTHMA

Silber JH, Rosenbaum PR, Calhoun SR, Reiter JG, Hill AS, Guevara JP, Zorc JJ, Even-Shoshan O. **Racial Disparities in Medicaid Asthma Hospitalizations**. *Pediatric*s. 2017 Jan;139(1). pii: e20161221.

Summary

Asthma disproportionately affects some racial/ethnic minorities and those of lower socioeconomic status. However, it is a complex multifactorial disease, and it is difficult to disentangle how each risk factor contributes to asthma risk or severity. In this study, the authors evaluated differences in asthma hospitalizations between black and white children, using Medicaid claims data from 11,079 matched pairs of children. They found no differences in hospitalization rates, length of stay (LOS), revisits, readmissions, or mortality. Black children had higher rates of ICU admission (22.2% vs 17.5%, P<0.001), with a statistically significant but very small difference in ICU LOS (mean difference = 0.09 days, P<0.001). Of note, the matching algorithm produced pairs that were nearly identical in terms of sex distribution, age (mean and by groups), asthma severity groups, comorbidities (36 conditions including obesity, reflux, OSA, allergies, and respiratory infections), previous asthma encounters (including outpatient visits, ED visits, and hospitalizations), and mean predicted LOS, probability of ICU, and probability of return visits.

Comments

1. In a large Medicaid population, the authors found no differences between black and white children with asthma in terms of hospitalization rates, length of stay, return visits, readmissions, or mortality.
2. Black children were more likely to be admitted to the ICU (22.2% vs 17.5%) and had significantly longer length of ICU stay, although this difference was not likely to be clinically significant.
3. However, the matched analysis was based on pairs that were nearly identical for over 50 variables, including asthma severity, several variables closely related to the outcomes (such as mean number of previous ED visits and hospitalizations, predicted LOS, and predicted probabilities of ICU), and several conditions that may worsen asthma control (such as reflux, OSA, allergies, or obesity).
4. This analysis therefore is reassuring in that, considering two similar patients with asthma, race was not associated with worse asthma-related outcomes in children covered by Medicaid.
5. However, by matching on such an extensive array of patient characteristics, this analysis was designed to evaluate differences in practice or management style based on race; it should not be interpreted as evidence of an absence of racial disparities.

LGBT HEALTH

Fredriksen-Goldsen KI, Kim HJ, Shui C, Bryan AEB. **Chronic Health Conditions and Key Health Indicators Among Lesbian, Gay, and Bisexual Older US Adults, 2013-2014**. *Am J Public Health*. 2017 Aug;107(8):1332-1338.

Summary

Little population-based research on the long-term health status of sexual minorities has been conducted, in part due to lack of large-scale data on sexual orientation. There is recent evidence that lesbian, gay, and bisexual (LGB) adults may have higher rates of lung disease, cancer, and disability than heterosexual adults. In this study, the

authors evaluated health indicators among LGB individuals aged 50 years or older in the U.S., using data from the 2013-2014 National Health Interview Survey (NHIS); 2013 was the first year that NHIS assessed sexual orientation. They found that, compared to heterosexual women, lesbian/bisexual women had higher rates of asthma, strokes, heart attacks, arthritis, back pain, and a weakened immune system; lower rates of diabetes; and no differences in COPD, hypertension, obesity, or cancer. Compared to heterosexual men, gay/bisexual men had higher rates of angina, back pain, cancer, and a weak immune system; lower prevalence of obesity; and no differences for asthma, COPD, stroke, heart attacks, hypertension, or diabetes. Lesbian/bisexual women were more likely to report poor general health and disability; and gay/bisexual men were more likely to report mental distress and limitations with daily activities.

Comments

1. This population-based study using a sample representative of the U.S. population, found that LGB older adults have a significantly higher prevalence of several chronic conditions, including asthma, cardiovascular events, cancer, back pain, immune system problems, and disabilities.
2. Together with previous studies in younger adult populations, this study identifies LGB adults as a group at high risk for health disparities, which start in young adulthood and persist later in life.
3. Limitations of the study included a small number of some groups, particularly bisexual men and women, as well as limitations inherent to all survey studies, including the risk of bias or misclassification due to self-report of sexual orientation and outcomes.
4. Neither the NHIS, nor the National Health and Nutrition Examination Survey (NHANES), include questions regarding other sexual orientation minorities or gender identity options, such as transsexual individuals, who may be at even higher risk of health disparities.
5. As we improve our understanding of the health needs in LGBT+ populations, targeted prevention and intervention programs should be implemented.

ATS/NHLBI WORKSHOP ON RESPIRATORY HEALTH EQUALITY

Celedón JC, Burchard EG, Schraufnagel D, Castillo-Salgado C, Schenker M, Balmes J, Neptune E, Cummings KJ, Holguin F, Riekert KA, Wisnivesky JP, Garcia JGN, Roman J, Kittles R, Ortega VE, Redline S, Mathias R, Thomas A, Samet J, Ford JG; American Thoracic Society and the National Heart, Lung, and Blood Institute. **An American Thoracic Society/National Heart, Lung, and Blood Institute Workshop Report: Addressing Respiratory Health Equality in the United States**. *Ann Am Thorac Soc*. 2017 May;14(5):814-826

Summary

This publication contains the summary and recommendations from a joint ATS/NHLBI workshop to encourage and facilitate research on respiratory health disparities (RHD), held during ATS 2015. Main recommendations by topic:

1) Best practices to advance RHD research:
   - Characterize broad ethnic groups into more specific subgroups;
   - Consider using genetic ancestry in admixed populations;
   - Capture acculturation measures.
2) RHD risk factors:
   - Evaluate the interaction between air pollution and other risk factors;
   - Integrate the impact of new tobacco products like e-cigarettes and hookah;
   - Measure occupational and workplace risk factors;
   - Implement longitudinal studies of obesity and RHD.
3) Healthcare access and quality of care:
   - Conduct longitudinal studies of the impact of the Affordable Care Act among under-represented minorities (URMs);
   - Develop and test culturally-targeted interventions to improve adherence in URMs;
   - Design and evaluate interventions to address low health literacy.
4) Impact of personalized medicine on RHD:
   - Implement large pharmacogenetics studies in URMs;
   - Conduct birth cohort studies in URMs with long-term follow-up to develop genetic/epigenetic markers of disease risk and severity.
5) Design and methodology for RHD research:
   - Identify culturally appropriate recruitment strategies;
   - Reduce participant burden and foster trust by engaging participants as decision-makers;
   - Create training modules for RHD research.
6) Equity in the workforce:
   - Develop academic mentoring and support pipelines in URM communities from middle/high school, to college, to medical school;
   - Support junior URM faculty through new or improved funding mechanisms;
   - Institutional accountability for URM recruitment and retention;
   - Implement robust mentoring programs;
   - Include URM faculty in decision-making bodies at the ATS, NHLBI, and academic institutions.
7) Conclusions and future directions:
   - Respiratory health equality is a goal of the ATS and NHLBI, which will require concerted efforts by all stakeholders;
   - Addressing the above recommendations will help reduce RHD;
   - This workshop will hopefully motivate similar efforts to examine other causes of RHD, including sex, sexual orientation, and cognitive and physical disabilities.

OTHER ARTICLES OF INTEREST

Talwar A, Garcia JGN, Tsai H, Moreno M, Lahm T, Zamanian RT, Machado R, Kawut SM, Selej M, Mathai S, D'Anna LH, Sahni S, Rodriquez EJ, Channick R, Fagan K, Gray M, Armstrong J, Rodriguez Lopez J, de Jesus Perez V; Pulmonary Circulation Assembly. **Health Disparities in Patients with Pulmonary Arterial Hypertension: A Blueprint for Action. An Official ATS Statement.** *Am J Respir Crit Care Med*. 2017 Oct 15;196(8):e32-e47.

Makaroun LK, Brown RT, Diaz-Ramirez LG, Ahalt C, Boscardin WJ, Lang-Brown S, Lee S. **Wealth-Associated Disparities in Death and Disability in the United States and England**. *JAMA Intern Med*. 2017;177(12):1745–1753.

Sommers BD, Gawande AA, Baicker K. **Health Insurance Coverage and Health**. *N Engl J Med*. 2017 Nov 16;377(20):2000-2001.

Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, Morozoff C, Mackenbach JP, van Lenthe FJ, Mokdad AH, Murray CJL. **Inequalities in Life Expectancy Among US Counties, 1980 to 2014: Temporal Trends and Key Drivers**. *JAMA Intern Med*. 2017 Jul 1;177(7):1003-1011.

Gregoraci G, van Lenthe FJ, Artnik B, Bopp M, Deboosere P, Kovács K, Looman CWN, Martikainen P, Menvielle G, Peters F, Wojtyniak B, de Gelder R, Mackenbach JP; DEMETRIQ consortium. **Contribution of smoking to socioeconomic inequalities in mortality: a study of 14 European countries, 1990-2004**. *Tob Control*. 2017 May;26(3):260-268.

Richards TB, Henley SJ, Puckett MC, Weir HK, Huang B, Tucker TC, Allemani C. **Lung cancer survival in the United States by race and stage (2001-2009): Findings from the CONCORD-2 study**. *Cancer*. 2017 Dec 15;123 Suppl 24:5079-5099.

Soneji S, Tanner NT, Silvestri GA, Lathan CS, Black W. **Racial and Ethnic Disparities in Early-Stage Lung Cancer Survival**. *Chest.* 2017 Sep;152(3):587-597.

Child and Adolescent Health From 1990 to 2015: Findings from the Global Burden of Diseases, Injuries, and Risk Factors 2015 Study. *JAMA Pediatr*. 2017;171(6):573–592.

Stephenson AL, Sykes J, Stanojevic S, Quon BS, Marshall BC, Petren K, Ostrenga J, Fink AK, Elbert A, Goss CH. **Survival Comparison of Patients with Cystic Fibrosis in Canada and the United States: A Population-Based Cohort Study**. *Ann Intern Med*. 2017 Apr 18;166(8):537-546.

Alexander D, Currie J. **Is it who you are or where you live? Residential segregation and racial gaps in childhood asthma**. *J Health Econ*. 2017 Sep;55:186-200.

Keet CA, Keller JP, Peng RD. **Long-term Coarse PM Exposure is Associated with Asthma Among Children in Medicaid**. *Am J Respir Crit Care Med*. 2017 Dec 15.

Cardet JC, Louisias M, King TS, Castro M, Codispoti CD, Dunn R, Engle L, Giles BL, Holguin F, Lima JJ, Long D, Lugogo N, Nyenhuis S, Ortega VE, Ramratnam S, Wechsler ME, Israel E, Phipatanakul W. **Vitamin D Add-On Therapy Enhances Corticosteroid Disparities Working Group members on behalf of the AsthmaNet investigators. Income is an independent risk factor for worse asthma outcomes**. *J Allergy Clin Immunol*. 2018 Feb;141(2):754-760.e3.

Tøttenborg SS, Lange P, Thomsen RW, Nielsen H, Johnsen SP. **Reducing socioeconomic inequalities in COPD care in the hospital outpatient setting - A nationwide initiative.** *Respir Med*. 2017 Apr;125:19-23.

Townend J, Minelli C, Mortimer K, Obaseki DO, Al Ghobain M, Cherkaski H, Denguezli M, Gunesekera K, Hafizi H, Koul PA, Loh LC, Nejjari C, Patel J, Sooronbayev T, Buist SA, Burney PGJ. **The association between chronic airflow obstruction and poverty in 12 sites of the multinational BOLD study**. *Eur Respir J.* 2017 Jun 1;49(6). pii: 1601880.

NOSOCOMIAL PNEUMONIA

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NEW EUROPEAN GUIDELINES ON MANAGEMENT OF HAP AND VAP

Torres A, Niederman MS, Chastre J, et al. **International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia**. *Eur Respir J* 2017; 50: 1700582

Summary

The European Respiratory Society, European Society of Intensive Care Medicine, European Society of Clinical Microbiology and Infectious Diseases, and Asociación Latinoamericana del Tórax released updated guidelines on the management of HAP and VAP. Key recommendations include: 1) a weak suggestion to use quantitative BAL rather than endotracheal aspirates for diagnosis, 2) a weak suggestion to use narrow spectrum antibiotics for early VAP without septic shock or risk factors for MDR pathogens, 3) a strong recommendation to use combination therapy for VAP in the setting of prolonged hospitalization, septic shock, recent antibiotic exposure, known colonization with MDR pathogens, or high local rates of MDR pathogens, 4) a weak suggestion to set 7-8 days as the default treatment duration for HAP and VAP, 5) a strong recommendation that procalcitonin monitoring is not necessary if planning to treat for 7-8 days but could help shorten therapy for patients with special circumstances (e.g. severely immunocompromised, initially inappropriate antibiotics, highly resistant pathogens, etc.), and 6) a weak recommendation to use selective oral decontamination rather than selective digestive decontamination, although the panel decided not to issue a recommendation for or against the use of chlorhexidine for selective oral decontamination.

Comments

1. The American Thoracic Society and Infectious Disease Society of America released updated guidelines on managing HAP and VAP in 2016; comparing and contrasting the American and European guidelines helps to highlight areas of ongoing controversy and reasonable alternative ways of interpreting the HAP/VAP literature.
2. The suggestion to use quantitative BAL for diagnosis is based on a single RCT published almost 20 years ago that showed a decrease in antibiotic utilization and a possible mortality benefit (Ann Intern Med 2000;132:621-630); subsequent RCTs have not duplicated either finding and it is unclear if antibiotic utilization patterns from 20 years ago can inform current practice given the many changes in routine antibiotic choices, normative standards for duration of treatment, and antibiotic stewardship efforts.
3. Both the American and European guidelines favor the use of narrow spectrum treatments for patients without risk factors for antibiotic resistant pathogens but in practice, most patients with HAP and VAP have one or more risk factors for resistant pathogens; this mismatch points to our pressing need for better tools to identify patients with resistant isolates at the point-of-care.
4. The panel's recommendation against serial procalcitonin monitoring for patients slated to get 7 days of antibiotics is because most RCTs of procalcitonin monitoring only reduced duration of treatment to ~7 days; the most recent RCT, however, was able to decrease median duration of treatment for VAP in the procalcitonin arm to 4 days (Lancet Infect Dis 2016;16:819-827).
5. The panel's caution regarding oral care with chlorhexidine is based upon two meta-analyses (JAMA Internal Med 2014;174:751-761 and BMJ 2014;348:g2197) and an observational series (JAMA Internal Med 2016;176:1277-1283) suggesting that oral care with chlorhexidine may increase mortality rates in some patients.

PROCALCITONIN MONITORING

Schuetz P, Wirz Y, Sager R, et al. **Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis**. *Lancet Infect Dis*. 2018;18:95-107.

Summary

Suspected respiratory infections are a major driver of antibiotic utilization. Randomized controlled trials suggest that serial procalcitonin monitoring can shorten antibiotic treatment courses, but controversy remains over whether this strategy is entirely safe. The investigators of 26 randomized controlled trials pooled patient-level data to better assess the impact of procalcitonin protocols on 30-day mortality, length-of-stay, and antibiotic-related adverse events for patients with respiratory infections. The meta-analysis included 6,708 patients drawn from primary care (N=1,008), emergency departments (N=3,253), and intensive care units (N=2,447). There were 885 patients with hospital-acquired or ventilator-associated pneumonia.

Procalcitonin monitoring was associated with 2.4 fewer days of antibiotic utilization (95% CI -2.7 to -2.2 days). Mortality rates were significantly lower in patients randomized to procalcitonin protocols (8.6% vs 10%, adjusted odds ratio 0.83, 95% CI 0.70-0.99, P=0.04). Results were consistent in subgroup analyses restricted to ICU patients (adjusted odds ratio 0.84, 95% CI 0.69-1.02) and patients with ventilator-associated pneumonia (adjusted odds ratio 0.75, 95% CI 0.41-1.39). There were no significant differences between procalcitonin and control arms in hospital or ICU length-of-stay. There were significantly fewer antibiotic-related side-effects in patients randomized to procalcitonin (16% vs 22%, adjusted odds ratio 0.68, 95% CI 0.57-0.82, P<.0001).

Comments

1. The finding that procalcitonin monitoring was associated with lower mortality rates helps allay concerns that shortening antibiotic courses using procalcitonin levels as a guide may be harmful.
2. Although the meta-analysis included many patients from primary care and emergency department settings, the majority of the favorable mortality signal was driven by two large RCTs set in intensive care units (Lancet Infect Dis 2016;16:819-27 and JAMA Intern Med 2016;176:1266-76) suggesting that these results are applicable to critically ill patients.
3. Clinicians declined to follow procalcitonin-guided antibiotic stopping rules in more than 50% of patients in some of the larger ICU trials thus suggesting that one cannot follow procalcitonin stopping rules blindly; procalcitonin monitoring is an adjunct rather than a substitute for clinical judgement.
4. Some investigators question the utility of procalcitonin monitoring in the current era given that most of RCTs demonstrated a reduction in treatment courses to about 7 days and current guidelines now recommend 7 days as the default treatment course for all nosocomial pneumonias; the most recent RCT of procalcitonin monitoring, however, was able to decrease median duration of treatment for VAP in the procalcitonin arm to 4 days (Lancet Infect Dis 2016;16:819-827).
5. The applicability of this study to critically ill patients was affirmed by two additional meta-analyses that also reported shorter antibiotic courses without deleterious effects on length-of-stay or mortality in critically ill patients (Crit Care Med 2018;ePub ahead of print DOI 10.1097/CCM.0000000000002953 and Crit Care Med 2018;ePub ahead of print DOI 10.1097/CCM.0000000000002928).

NEW TREATMENT OPTIONS FOR NOSOCOMIAL PNEUMONIA

Torres A, Zhong N, Pachl J, et al. **Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial**. *Lancet Infect Dis*. 2017;ePub ahead of print.

Summary

The relentless rise in multidrug resistant pathogens compels an ongoing need for new agents active against antibiotic-resistant pathogens. This industry-funded, double-blinded, randomized controlled trial led the FDA to approve ceftazidime-avibactam as a viable new option to treat nosocomial pneumonia. Investigators randomized 879 patients with nosocomial pneumonia to ceftazidime-avibactam (2g IV q8h, 2-hour infusion) versus meropenem (1g IV q8h, 30min infusion). 726 patients were included in the clinically modified intention-to-treat population, including 246 with ventilator-associated pneumonia and 480 with non-ventilator-associated pneumonia. More than a quarter of microbiologically evaluable patients had isolates resistant to ceftazidime but susceptible to ceftazidime-avibactam. Clinical cure was achieved in 68.8% of patients randomized to ceftazidime-avibactam versus 73.0% of patients randomized to meropenem. Results were similar in the subset of patients with ventilator-associated pneumonia. These findings met the study's pre-specified threshold for non-inferiority and thus the investigators concluded that ceftazidime-avibactam is non-inferior to meropenem to treat nosocomial pneumonia caused by Gram-negative pathogens. There was no difference in all-cause mortality rates (9.4% for ceftazidime-avibactam vs 7.4% for meropenem) but ceftazidime-avibactam was associated with numerically more deaths due to disease progression (3.2% vs 2.0%, P=.38) and a significantly higher rate of serious adverse events (18.5% vs 13.4%, P=.05).

Comments

1. Studies demonstrating the utility of new antibiotics against nosocomial pneumonia are relatively rare; this investigation is a valuable demonstration that ceftazidime-avibactam is a viable option to treat nosocomial pneumonia.
2. The fact that over a quarter of evaluable patients had isolates resistant to ceftazidime but susceptible to ceftazidime-avibactam affirms the capacity of ceftazidime-avibactam to expand our therapeutic armamentarium against some drug-resistant isolates.
3. The slightly higher overall mortality rate, serious adverse event rate, and deaths due to progression of disease in patients randomized to ceftazidime-avibactam inject a note of caution; editorialists comment that ceftazidime-avibactam should probably be reserved as a second-line option for nosocomial pneumonia pending the availability of more safety data.
4. Ceftazidime-avibactam was administered as a 2-hour infusion whereas meropenem was administered over 30 minutes, a potential bias against meropenem; it is possible that more pronounced differences in clinical efficacy may have been seen if meropenem had been infused over a longer period (Lancet Infect Dis 2018;18:108-120).

NOSOCOMIAL PNEUMONIA IN NON-VENTILATED PATIENTS

Baker D, Quinn B. **Hospital Acquired Pneumonia Prevention Initiative-2: Incidence of nonventilator hospital-acquired pneumonia in the United States**. *Am J Infect Control*. 2018;46(1):2-7.

Summary

A CDC cross-sectional survey of the prevalence of healthcare-associated infections found that pneumonia was tied for first as the most common healthcare-associated infection and that almost two-thirds of cases were in non-ventilated patients (NEJM 2014;370:1198-208). The investigators in this industry-funded study sought to determine the incidence of non-ventilator HAP, whether and how incidence rates vary between hospitals, and the frequency of basic nursing practices that might prevent HAP. The study team retrospectively identified patients from 21 U.S. hospitals with ICD-9-CM discharge codes for pneumonia without a present-on-admission indicator. They reviewed patients' charts to apply CDC definitions for pneumonia and to assess nursing care in the 24 hours preceding pneumonia onset. There were 4,455 patients with ICD-9-CM discharge codes for pneumonia of whom 1,300 met CDC criteria. Of these, 71% were acquired outside of the ICU. Incidence rates across hospitals ranged from 0.04 to 1.11 cases per 100 patients. The crude mortality rate was 15.8%. The researchers reported that only 41% of patients received oral care at least 2 times in the 24 hours preceding their pneumonia, 65% had documentation of head-of-bed elevation, and 34% of patients were documented to get out of their beds at least twice (excluding those on bed rest).

Comments

1. Most studies on nosocomial pneumonia have focused almost exclusively on ventilated patients; this study adds to the growing recognition that we need to do more to track and prevent pneumonia in non-ventilated patients.
2. A strength of the study is that the investigators reviewed charts to confirm the diagnosis of pneumonia, a limitation is that they only reviewed charts of patients with diagnosis codes for pneumonia thus allowing for the possibility that some cases were not coded and were thus missed.
3. The preventative practices assessed by the investigators were reasonable but there are very little data on whether improving these processes can prevent non-ventilator pneumonia and improve outcomes; prevention studies of these strategies in ventilated patients have had mixed results and there are almost no rigorous studies evaluating the effectiveness of these measures in non-ventilated patients in acute care hospitals.
4. The accuracy of retrospective chart reviews to estimate the frequency of oral care, head-of-bed elevation, ambulation, and other preventative practices is unknown; documentation may be incomplete and could vary widely between nurses and hospitals.

THE IMPORTANCE OF VIRUSES IN HOSPITALIZED PATIENTS WITH PNEUMONIA

van Someren Greve F, Juffermans NP, Bos LDJ, et al. **Respiratory Viruses in Invasively Ventilated Critically Ill Patients-A Prospective Multicenter Observational Study**. *Crit Care Med*. 2018;46(1):29-36.

Summary

An increasing amount of literature attests to the frequent presence of respiratory viruses in hospitalized patients with both community-acquired and hospital-acquired pneumonia (e.g. J Clin Virology 2017;91:52-57 and Open Forum Infect Dis 2017;4:ofx006). The clinical significance of these viruses is unclear, however, because most studies have not included a control population to provide baseline data on the frequency of respiratory viruses in patients without suspected infections. Data of this nature are now furnished by Dutch investigators who prospectively sent nasopharyngeal swabs and tracheobronchial aspirates on all ventilated patients admitted to 5 ICUs. Both specimens were tested for 14 respiratory viruses using PCR. Of the 1,407 patients tested, 156 had suspected severe respiratory infections and the rest did not. Respiratory viruses were more common in those with suspected severe respiratory infections versus those without (28.8% vs 17.0%, P<.001). Rhinoviruses and human metapneumovirus in particular were more common in patients with severe respiratory infections versus those without. The presence of a respiratory virus was associated with trends towards better outcomes in patients with severe respiratory infections but not amongst those without severe respiratory infections. One third of viral infections were only detected via tracheal aspirates.

Comments

1. This study and others like it underscore the importance of testing patients with severe pneumonia, including nosocomial pneumonia, for respiratory viruses.
2. Misclassification bias may have led to underestimation of the morbidity attributable to respiratory viruses since viral infections may have contributed to acute illness in a large number of "control" patients, including those diagnosed with sepsis (respiratory viruses in 19%), cardiac arrest (respiratory viruses in 16%), COPD exacerbations (respiratory viruses in 64%), and congestive heart failure (respiratory viruses in 28%).
3. The study was conducted during a year with a mild influenza season; the frequency and morbidity of respiratory viruses may be more pronounced in more severe influenza seasons.
4. The finding that lower respiratory tract sampling uniquely identified many more patients with respiratory viruses relative to nasopharyngeal swabs echoes the results of other studies and bespeaks the importance of sending lower respiratory tract specimens when considering viral infections.
5. The small number of patients with severe respiratory infections may have limited power to detect associations with some viruses.

SELECTIVE DIGESTIVE DECONTAMINATION

Oostdijk EAN, Kesecioglu J, Schultz MJ, et al. Notice of Retraction and Replacement: Oostdijk et al. **Effects of Decontamination of the Oropharynx and Intestinal Tract on Antibiotic Resistance in ICUs: A Randomized Clinical Trial.** *JAMA*. 2014;312(14):1429-1437. JAMA. 2017;317(15):1583-1584.

Summary

Selective digestive decontamination remains an issue of intense controversy. It is one of the few VAP prevention strategies associated with lower mortality rates in critically ill patients. Only a fraction of ICUs worldwide use this strategy, however, due to ongoing concern that it will select for antibiotic resistant organisms and thus harm long term population-level outcomes. In 2014, researchers from the Netherlands reported the results of a cluster randomized crossover trial comparing the impact of 12 months of selective digestive decontamination (SDD) versus 12 months of selective oral decontamination (SOD) in 16 intensive care units on resistance rates and mortality. Resistance was tracked using perianal and respiratory surveillance cultures. 11,997 patients were enrolled. The investigators originally reported significantly lower rates of antibiotic-resistant gram-negative perianal colonization with SDD versus SOD but no difference in 28-day mortality rates (JAMA 2014;312:1429-1437). The study team subsequently discovered that they had mistakenly mixed up the SDD and SOD periods for one ICU during their original analysis. Upon correcting the error, they found that the signal towards significantly lower antibiotic-resistant colonization rates persisted but there was a significant mortality benefit in favor of SDD versus SOD (23.8% vs 25.7%, adjusted OR 0.85, 95% CI 0.77-0.93).

Comments

1. This is the largest study to date on selective digestive decontamination versus selective oral decontamination.
2. The mortality benefit seen in this trial is consistent with a previous large cluster randomized trial and multiple meta-analyses.
3. Overall antibiotic resistance rates in study units were low but investigators did note small but significant increases in the prevalence of aminoglycoside-resistant organisms in both the SDD and SOD arms over the course of the study; the rate of increase was numerically higher in the SDD arm but there was no significant difference in the slope of increase between the two groups.
4. Despite the mortality benefit associated with SDD in this study, commentators still wonder whether the findings from this study can be generalized to ICUs with higher baseline levels of antibiotic resistance, and whether antibiotic resistance might become more prevalent and problematic with longer term utilization of SDD.

OTHER ARTICLES OF INTEREST

PROLONGED INFUSIONS OF BETA-LACTAM ANTIBIOTICS MAY LOWER MORTALITY RATES

Vardakas KZ, Voulgaris GL, Maliaros A, Samonis G, Falagas ME. **Prolonged versus short-term intravenous infusion of antipseudomonal beta-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials.** *Lancet Infect Dis*. 2018;18(1):108-120.

NEBULIZED ANTIBIOTICS: CHALLENGING TO ADMINISTER CORRECTLY, LIMITED BENEFIT, POTENTIALLY HARMFUL

Sole-Lleonart C, Rouby JJ, Blot S, et al. **Nebulization of Antiinfective Agents in Invasively Mechanically Ventilated Adults: A Systematic Review and Meta-analysis**. *Anesthesiology*. 2017;126(5):890-908.

Rello J, Sole-Lleonart C, Rouby JJ, et al. **Use of nebulized antimicrobials for the treatment of respiratory infections in invasively mechanically ventilated adults: a position paper from the European Society of Clinical Microbiology and Infectious Diseases**. *Clin Microbiol Infect*. 2017;23(9):629-639.

VANCOMYCIN WITH PIPERACILLIN-TAZOBACTAM COMBINED INCREASES RISK OF ACUTE KIDNEY INJURY

Luther MK, Timbrook TT, Caffrey AR, Dosa D, Lodise TP, LaPlante KL. **Vancomycin Plus Piperacillin-Tazobactam and Acute Kidney Injury in Adults: A Systematic Review and Meta-Analysis**. *Crit Care Med*. 2018;46(1):12-20.

LATERAL TRENDELENBURG MAY LOWER VAP RATES BUT DIFFICULT TO MAINTAIN

Li Bassi G, Panigada M, Ranzani OT, et al. **Randomized, multicenter trial of lateral Trendelenburg versus semi-recumbent body position for the prevention of ventilator-associated pneumonia**. *Intensive Care Med.* 2017;43(11):1572-1584.

STRESS ULCER PROPHYLAXIS HAS LIMITED EFFECT ON BLEEDING RISK BUT MAY INCREASE PNEUMONIA RISK

Alhazzani W, Guyatt G, Alshahrani M, et al. **Withholding Pantoprazole for Stress Ulcer Prophylaxis in Critically Ill Patients: A Pilot Randomized Clinical Trial and Meta-Analysis**. *Crit Care Med*. 2017;45(7):1121-1129.

Huang HB, Jiang W, Wang CY, Qin HY, Du B. **Stress ulcer prophylaxis in intensive care unit patients receiving enteral nutrition: a systematic review and meta-analysis**. *Crit Care*. 2018;22(1):20.

TAPERED ENDOTRACHEAL TUBE CUFFS NO BETTER THAN STANDARD CUFFS FOR PREVENTING VAP

Jaillette E, Girault C, Brunin G, et al. **Impact of tapered-cuff tracheal tube on microaspiration of gastric contents in intubated critically ill patients: a multicenter cluster-randomized cross-over controlled trial**. *Intensive Care Med*. 2017;43(11):1562-1571.

Maertens B, Blot K, Blot S. **Prevention of Ventilator-Associated and Early Postoperative Pneumonia Through Tapered Endotracheal Tube Cuffs: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**. *Crit Care Med*. 2018;46(2):316-323.

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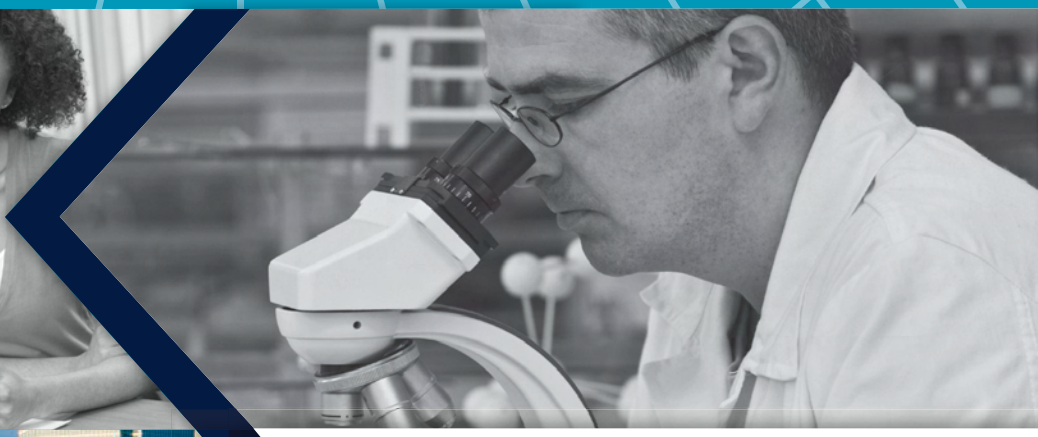

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