

A blue-tinted background featuring a stethoscope and a calendar page. The calendar shows the number '19' and the day 'Friday' in English, along with other languages like 'Vendredi', 'Viernes', 'Piatek', and 'Пятница'.

# Clinical

# Year in Review



## ATS 2021

[conference.thoracic.org](https://conference.thoracic.org)

**MODERATORS**

---

**Patricia A. Kritek, MD, EdM**

Department of Medicine  
Division of Pulmonary, Critical Care and Sleep Medicine  
University of Washington School of Medicine  
Seattle, WA

**Jose L. Gomez-Villalobos, MD, MS, ATSF**

Yale School of Medicine  
Department of Medicine, Pulmonary, Critical Care and Sleep Section  
New Haven, CT

**Rupal J. Shah, MD, MSCE**

Department of Medicine  
Division of Pulmonary, Allergy, Critical Care and Sleep Medicine  
University of California San Francisco  
San Francisco, CA

---

**A21****Lung Cancer****Palliative Care and Communication in PCCMS****Medical Education****ARDS**

*This session and the International Conference are supported by independent medical educational grants from **AstraZeneca LP, Pfizer, Inc., Merck & Co.***

**B21****COPD****Mycobacterial Diseases****Novel Therapeutics for Infection**

*This session and the International Conference are supported by an independent medical educational grant from **AstraZeneca LP.***

**C21****Cognitive and Neurologic Effects of Critical Illness****Critical Care****ECMO****Sleep Medicine**

*This session and the International Conference are supported by an independent medical educational grant from **Jazz Pharmaceuticals, Inc.***

**D21****Asthma****Interstitial Lung Disease****Health Disparities in Pulmonary, Critical Care and  
Sleep Medicine****Pulmonary Rehabilitation**

*This session and the International Conference are supported by independent medical educational grants from **Boehringer Ingelheim Pharmaceuticals, Inc., Genentech, Inc., GlaxoSmithKline, Merck & Co.***

## LUNG CANCER

**Mathew Triplette, MD, MPH**

Fred Hutchinson Cancer Research Center and University of Washington  
Clinical Research Division; Division of Pulmonary, Critical Care and Sleep Medicine  
Seattle, WA

### LUNG CANCER SCREENING

US Preventive Services Task Force, Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, Caughey AB, Davis EM, Donahue KE, Doubeni CA, Kubik M, Landefeld CS, Li L, Ogedegbe G, Owens DK, Pbert L, Silverstein M, Stevermer J, Tseng CW, Wong JB. **Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement.** *JAMA.* 2021 Mar 9; 325(10): 962-970.

#### Summary

This is an updated recommendation statement on lung cancer screening from the United States Preventive Services Task Force. It is the first update on the initial recommendation for screening provided in 2013. After a review of the evidence, including the Netherlands-Leuven Longkanker Screenings Onderzoek (NELSON) trial, the USPSTF concludes with moderate certainty that annual screening for lung cancer with a low dose chest CT has a moderate net benefit for persons at high-risk for lung cancer (grade B recommendation). This statement extends the recommendation to a larger group of “high-risk” patients; adults aged 50 to 80 years old who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years. This recommendation was based on a systematic review of the evidence as well as collaborative modeling studies from the Cancer Intervention and Surveillance Modeling Network (CISNET) to determine the optimal age range, screening interval, and relative benefits and harms of different screening strategies.

#### Comments

1. CISNET modeling analyses demonstrate that these recommendations compared to prior USPSTF guidelines would be associated with a reduction of lung cancer mortality from 13.0% vs. 9.8%.
2. Models examined varying screening intervals but the USPSTF continues to recommend annual screening for eligible participants.
3. The statement acknowledges disparities in screening eligibility which may be improved by these recommendations, particularly among Black persons who are at higher risk for lung cancer with lower smoking history.
4. These recommendations may double the eligible U.S. screening population; however, the statement acknowledges the overall low uptake of screening among currently eligible participants.

5. The recommendation statement continues to acknowledge the importance of shared decision making and smoking cessation in the practice of lung cancer screening

### LUNG CANCER MORTALITY

Howlader N, Forjaz G, Mooradian MJ, Meza R, Kong CY, Cronin KA, Mariotto AB, Lowy DR, Feuer EJ. **The Effect of Advances in Lung Cancer Treatment on Population Mortality.** *N Engl J Med.* 2020 Aug 13;383(7): 640-649.

#### Summary

This study sought to determine mortality trends in lung cancer and specific lung cancer subtypes. Authors used data from the Surveillance, Epidemiology and End Results (SEER) registry to evaluate population-level trends in areas covering 28% of the U.S. population in both cancer incidence and survival according to lung cancer subtype, sex and year. Incidence-based mortality from non-small cell lung cancer (NSCLC), the most common subtype accounting for 76% of all lung cancers, decreased 6.3% annually between 2013 and 2016; incidence over that time decreased 3.1% annually. Improvements in survival were similar among racial, ethnic and sex groups. For small cell lung cancer (SCLC), incidence-based mortality and incidence declined by a similar percentage (3-5% annually), with a lack of improvement in lung cancer-specific survival independent of the lower incidence. Overall reduction in mortality from lung cancer in the U.S. was considered attributable to a rapid decline in NSCLC mortality.

#### Comments

1. Lung cancer as an overall cause of death in the United States is decreasing.
2. The reduction in lung cancer mortality appears to be attributable to both declining incidence of all lung cancer subtypes and mortality reduction in patients with NSCLC.
3. Trends in survival were similar between men and women and across racial and ethnic groups assessed by the study authors, though non-Hispanic Black men and women continue to have overall lower survival.
4. The implication of this study is that improvements in treatments for NSCLC, including targeted radiation, immunotherapy and targeted molecular therapy have improved survival in NSCLC.
5. There have been no major advances in SCLC therapy over the study time period which may account for the static mortality rates in this population.

## LUNG CANCER TREATMENT

Wu YL, Tsuboi, M, He J, John T, Grohe C, Majem M, Goldman JW, Laktionov K, Kim S-W, Kato T, Vu H-V, Lu S, Lee K-Y, Akewanlop C, Yu C-J, de Marinis F, Bonanno L, Domine M, Shepherd FA, Zeng L, Hodge R, Atasoy A, Rukazenkov Y, Herbst RS, for the ADAURA Investigators. **Osimertinib in Resected EGFR-mutated Non-Small-Cell Lung Cancer.** *N Engl J Med.* 2020 Oct 29; 383(18): 1711-1723.

### Summary

Based on last year's landmark study, the tyrosine kinase inhibitor Osimertinib has become the standard of care for advanced EGFR-mutated non-small-cell lung cancer (NSCLC). However, the impact of Osimertinib as adjuvant therapy for EGFR-mutated early stage NSCLC was unknown. This was a phase 3 randomized clinical trial of Osimertinib vs. placebo for three years in a cohort of patients with stage IB, II or IIIA disease evaluating disease-free survival. The primary end-point was disease-free survival in the stage II and IIIA group. The trial enrolled 682 patients across multiple sites. The investigators found a substantial difference in disease-free survival at 24 months favoring the Osimertinib group. Ninety percent of patients with stage II and IIIA disease in the Osimertinib group were alive and disease free at 24 months (95% CI 84-93%) compared to 44% of those in the placebo group (95% CI 37-51%). This represents an overall hazard ratio of disease recurrence or death of 0.17 (95% CI 0.11-0.26).

### Comments

1. This represents a practice-changing finding, as the majority of EGFR-mutated NSCLC at local stages was treated with traditional strategies with no adjuvant targeted therapy.
2. The majority of enrolled patients were treated appropriately according to standard of care; all patients underwent surgical resection and administration of adjuvant chemotherapy were made independent of trial assignment.
3. In the overall population, including stage IB disease, 89% of patients in the Osimertinib group were alive and disease free at 24-months compared to 52% of those in the placebo group.
4. The majority of outcomes represented disease recurrence; only 29 patients died (9 in the Osimertinib group and 20 in the placebo group) in the course of the trial.
5. There were no major safety concerns noted in the Osimertinib treatment group over the course of the trial.

Hong DS, Fakih MG, Strickler JH, Desai J, Durm GA, Shapiro GI, Falchook GS, Price TJ, Sacher A, Denlinger CS, Bang Y-J, Dy GK, Krauss JC, Kuboki Y, Kuo JC, Coveler AL, Park K, Kim TW, Barlesi F, Munster PN, Ramalingam SS, Burns TF, Meric-Bernstam F, Henary H, Ngang J, Ngarmchamnanrith G, Kim J, Houk BE, Canon J, Lipford JR, Friberg G, Lito P, Govindan R, Li RT. **KRAS Inhibition with Sotorasib in Advanced Solid Tumors.** *N Engl J Med.* 2020 Sep 24; 383(13): 1207-1217.

### Summary

Despite molecular testing for the KRAS mutation, which is present in 13% of all non-small-cell lung cancers, there have been no approved therapies targeting this mutation. This was a phase 1 open-label clinical trial of sotorasib, a small molecule that selectively and irreversibly targets KRASG12C. This trial enrolled 129 patients with advanced NSCLC, colorectal cancer and other KRAS-expressing tumors. Fifty-nine of the patients had NSCLC. The majority of patients had received other advanced therapies for metastatic disease; 75% of the NSCLC subgroup had received at least 2 lines of previous therapy. In the NSCLC group, 32% of patients had a complete or partial treatment response, and 88% had a minimum of disease control over a median follow-up of 11.7 months. The median progression free survival was 6.3 months. While no dose-limiting toxic effects were observed, almost all patients had a common adverse event (97%) and 11.6% were deemed to have grade III or IV treatment-related adverse events.

### Comments

1. Tumor response was much higher in the NSCLC group than other subgroups suggesting more utility of this molecule in NSCLC with the KRAS mutation than in colorectal cancer.
2. The treatment response of 32% of the NSCLC group compares to a general treatment response of 9-18% in this group with standard second or third line therapies.
3. Of the patients who had a response to treatment, the median duration of response was 10.9 months.
4. The most common severe treatment-related adverse events were elevations in liver enzymes, clinical hepatitis, diarrhea and anemia.
5. Further studies are planned evaluating sotorasib as monotherapy and in combination with other agents for patients with KRAS-mutated NSCLC.

## LUNG CANCER SCREENING

Taylor TD, Tong BC, Gao J, Henderson LM, Choudhury KR, Rubin GD. **Utilization of Lung Cancer Screening in the Medicare Fee-for-Service Population.** *Chest* 2020 Nov; 158(5): 2200-2210.

### Summary

The aim of this article was to evaluate the early uptake of lung cancer screening (LCS) following both United States Preventive Services Task Force (2013) and Centers for Medicare and Medicaid Services (2015) recommendations for annual LCS for a high-risk smoking population. This was a cross-sectional study which used all national Medicare fee-for-service claims during 2016 compared to the estimated screen-eligible population based on U.S. Census Bureau and Centers for Disease Control and Prevention Data. 103,892 Medicare beneficiaries received screening in 2016, estimated to represent only 4.1% (95% CI 3.9-4.3%) of the eligible population. The authors noted regional variation in LCS uptake (lowest in the Southern United States), as well as lower screening in nonwhite beneficiaries in all regions of the country. Black patients were approximately 40% as likely to receive screening as white patients.

### Comments

1. This study is consistent with others demonstrating poor early uptake of lung cancer screening.
2. There is variability in the estimate as the true denominator of eligible Medicare participants is unknown, but estimated here from broad regional national smoking and age data.
3. There was wide regional- and state-level variability in LCS uptake; for example, Massachusetts had a 15% screening rate while Tennessee had a 1.4% screening rate.
4. There was improvement in screening over time, with twice as many patients undergoing screening in December 2016 compared to January 2016.
5. It remains uncertain how much screening uptake has and will improve with sustained recommendations and advocacy for this preventive service.

## OTHER ARTICLES OF INTEREST

Drilon A, Oxnard GR, Tan DSW, Loong HHF, Johnson M, Gainor J, McCoach CE, Gautschi O, Besse B, Cho BC, Peled N, Weiss J, Kim Y-J, Ohe Y, Nishio M, Park K, Patel J, Seto T, Sakamoto T, Rosen E, Shah MH, Barlesi F, Cassier PA, Bazhenova L, De Braud F, Garralda E, Velcheti V, Satouchi M, Ohashi K, Pennell NA, Reckamp KL, Dy GK, Wolf J, Solomon B, Falchook G, Ebata K, Nguyen M, Nair B, Zhu EY, Yang L, Huang X, Olek E, Rothenberg SM, Goto K, Subbiah V. **Efficacy of Selpercatinib in RET Fusion-Positive Non-small-cell Lung Cancer.** *N Engl J Med.* 2020 Aug 27; 383(9): 813-824.

Faivre-Finn C, Vincente D, Kurata T, Planchard D, Paz-Ares L, Vansteenkiste JF, Spigel DR, Garassino MC, Reck M, Senan S, Naidoo J, Rimmer A, Wu Y-L, Gray JE,

Lee KH, Cho BC, Kato T, de Wit M, Newton M, Wang L, Thiyagarajah P, Antonia SJ. **Four-Year Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC—An Update from the PACIFIC Trial.** *J Thorac Oncol.* 2021 Jan 19; S1556-0864(21)00022-8.

Haaf KT, Bastani M, Cao P, Jeon J, Toumazis I, Han SS, Plevritis SK, Blom EF, Kong CY, Tammemagi MC, Feuer EJ, Meza R, de Koning HJ. **A Comparative Modeling Analysis of Risk-Based Lung Cancer Screening Strategies.** *J Natl Cancer Inst.* 2020 May 1; 112(5): 466-479.

Han SS, Chow E, Haaf KT, Toumazis I, Cao P, Bastani M, Tammemagi M, Jeon J, Feuer EJ, Meza R, Plevritis SK. **Disparities of National Lung Cancer Screening Guidelines in the US Population.** *J Natl Cancer Inst.* 2020 Nov 1; 112(11): 1136-1142.

Herbst RS, Giaccone G, de Marinis F, Reinmuth N, Vergnenegre A, Barrios CH, Morise M, Felip E, Andric Z, Geater S, Ozguroglu M, Zou W, Sandler A, Enquist I, Komatsubara K, Deng Y, Kuriki H, Wen X, McClelland M, Mocchi S, Jassem J, Spigel DR. **Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC.** *N Engl J Med.* 2020 Oct 1; 383(14):1328-1339.

Paik PK, Felip E, Veillon R, Sakai H, Cortot AB, Garassino MC, Mazieres J, Viteri S, Senellart H, Van Meerbeeck J, Raskin J, Reinmuth N, Conte P, Kowalski D, Cho BC, Patel JD, Horn L, Griesinger F, Han J-Y, Kim Y-C, Chang G-C, Tsai C-L, Yang JC, Chen Y-M, Smit EF, van der Wekken AJ, Kato T, Juraeva D, Stroh C, Bruns R, Straub J, Johne A, Scheele J, Heymach JV, Le X. **Tepotinib in Non-small-cell Lung Cancer with MET Exon 14 Skipping Mutations.** *N Engl J Med.* 2020 Sept 3; 383(10): 931-943.

Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, Zhou C, Reungwetwattana T, Cheng Y, Chewaskulyong B, Shah R, Cobo M, Lee KH, Cheema P, Tiseo M, John T, Lin M-C, Imamura F, Kurata T, Todd A, Hodge R, Saggese M, Rukazenzov Y, Soria J-C, FLAURA Investigators. **Overall Survival with Osimertinib in Untreated, EGFR-mutated Advanced NSCLC.** *N Engl J Med.* 2020 Jan 2; 382(1): 41-50.

Wolf J, Seto T, Han J-Y, Reguart N, Garon EB, Groen HJM, Tan DSW, Hida T, de Jonge M, Orlov SV, Smit EF, Souquet P-J, Vansteenkiste J, Hochmair M, Felip E, Nishio M, Thomas M, Ohashi K, Toyozawa R, Overbeck TR, de Marinis F, Kim T-M, Laack E, Robeva A, Mouhaer SL, Waldron-Lynch M, Sankaran B, Balbin OA, Cui X, Giovannini M, Akimov M, Heist RS. **GEOMETRY mono-1 Investigators. Capmatinib in MET Exon-14 Mutated or MET-Amplified Non-Small-Cell Lung Cancer.** *N Engl J Med.* 2020 Sep 3; 383(10): 944-957.

## PALLIATIVE CARE AND COMMUNICATION IN PCCMS

Anand S. Iyer, MD, MSPH

University of Alabama at Birmingham  
Division of Pulmonary, Allergy, and Critical Care Medicine  
Birmingham, AL

### PALLIATIVE CARE AND OUTCOMES ACROSS SERIOUS ILLNESSES

Quin KL, Stukel T, Stall NM, Huang A, Isenberg S, Tanisepuro P, Goldman R, Cram P, Kavalieratos D, Detsky AS, Bell CM. **Association Between Palliative Care and Healthcare Outcomes Among Adults with Terminal Non-Cancer Illness: Population Based Matched Cohort Study.** *BMJ* 2020; 370:m2257.

#### Summary

This population-based cohort study in Ontario, Canada investigated the association between palliative care in the last six months of life and end-of-life healthcare utilization in 113,530 older adults (age 83 years on average) who died from cancer and non-cancer serious illnesses between 2010-2015. Non-cancer serious illnesses included COPD, heart failure, cirrhosis, ESRD, stroke, and dementia. Palliative care was recorded by claims review and was defined as either specialist or generalist (delivered by non-palliative care specialists). Participants who received palliative care were propensity matched to those who did not. In participants dying from non-cancer serious illnesses, palliative care was associated with significant reductions in healthcare utilization: by 12%, 12%, and 41% reduction in emergency department visits, hospital admissions, and intensive care unit admissions, respectively. Palliative care was also associated with a 1.7 increased risk of dying at home and a reduction in burdensome end of life interventions. The findings extended to older adults with cancer but did not extend to those with dementia who lived in nursing homes, who were found to have increased rates of emergency department visits and hospitalizations after receiving palliative care.

#### Comments

1. This a well-designed, population-level, and propensity-matched study of palliative care and end of life healthcare utilization in older adults with terminal cancer and non-cancer serious illnesses, including COPD.
2. Palliative care was associated with statistically significant reductions in end-of-life healthcare utilization and increased odds of dying at home, which is the preferred location for most older adults.

3. The finding that palliative care was associated with an increased risk for healthcare utilization at the end of life among older adults with dementia who resided in nursing homes was surprising and warrants further investigation.
4. The study was conducted in Canada where palliative care is well-supported through public funding and may limit generalizability to systems with less seamless integration of palliative care across the continuum or rare uptake by non-specialist palliative care clinicians.
5. The results have important policy implications regarding the initiation of early palliative care across serious illnesses beyond cancer and timing before the very end of life.

### PALLIATIVE CARE IN COPD - LOW DOSE OPIOIDS

Verberkt CA, van den Beuken-van Everdingen MH, Schols JMGA, Hameleers N, Wouters EFM, Janssen DJA. **Effect of Sustained-Release Morphine for Refractory Breathlessness in Chronic Obstructive Pulmonary Disease on Health Status - A Randomized Clinical Trial.** *JAMA Intern Med* 2020; 180(10):1306-1314.

#### Summary

The Morphine for Treatment of Dyspnea in Patients with COPD (MORDYC) study was a randomized, double-blind, placebo-controlled trial of 4 weeks of oral sustained-release morphine versus placebo in 111 adults with COPD. Participants were recruited with stable COPD and refractory breathlessness [modified Medical Research Council Dyspnea Scale (mMRC) 2-4] despite optimized inhalers and pulmonary rehabilitation. One-fourth of eligible participants declined to participate. Primary outcomes were COPD Assessment Test (CAT) score and mean partial pressure of arterial carbon dioxide (PaCO<sub>2</sub>). After intention to treat analyses, participants randomized to intervention versus placebo had a statistically- and clinically- significant reduction in CAT score by 2.18 points (95% CI, -4.14 to -0.22 points) and no significant increase in PaCO<sub>2</sub>. In participants with mMRC 3-4, worst breathlessness in the prior 24 hours on a numerical rating scale (0-10) was significantly lower in the intervention compared to placebo group. Two-thirds of participants adhered to the intervention schedule, and only 9% withdrew due to adverse events. Nausea, vomiting, drowsiness, constipation, and sleeplessness were prevalent but did not significantly differ between groups.

Participants in the intervention compared to placebo group had a significant increase in constipation scores from baseline to follow-up.

### Comments

1. This was a large trial on the important palliative care topic of low-dose opioids in adults with COPD.
2. Participants who received sustained-release oral morphine compared to placebo had improved health status.
3. There were no significant differences in PaCO<sub>2</sub> between groups, which may help ease concerns among clinicians who may be concerned about respiratory depression and worsening hypercapnia in adults with COPD.
4. The reduction in CAT score of 2 points on average was on the lower end of clinical significance.
5. Over one-quarter of eligible participants declined to participate, and this required broadening of the inclusion criteria to include participants with less severe breathlessness (mMRC  $\geq 2$ ) than originally planned (mMRC 3-4), an adjustment that may have impacted study outcomes.

## EARLY PALLIATIVE CARE IN LUNG CANCER

Sullivan DR, Chan B, Lapidus JA, Ganzini L, Hansen L, Carney PA, Fromme EK, Marino M, Goldern SE, Vranas KC, Slatore CG. **Association of Early Palliative Care Use with Survival and Place of Death Among Patients with Advanced Lung Cancer Receiving Care in the Veterans Health Administration.** *JAMA Oncol* 2019; 5(12):1702-1709.

### Summary

This retrospective, population-based cohort study included 23,154 adults with advanced lung cancer in the Veterans Affairs health care system. The investigators examined the impact of specialist palliative care timing on survival and place of death. Overall, 98% were men and 89% had stage IV cancer. On average, 57% of study participants received specialist palliative care, though substantial geographic variation existed nationwide. Compared to no specialist palliative care, palliative care received 31 to 365 days after diagnosis was associated with a survival benefit (aHR, 0.47; 95% CI, 0.45-0.49), while palliative care 0-30 days after diagnosis was associated with decreased survival (aHR, 2.13; 95% CI, 1.97-2.30). These differences may in part be due to acuity of illness. In the 0-30 days group, 76% of palliative care encounters occurred in the inpatient setting compared to 50% in the 31-365 days group. The latter group may have been less seriously ill with more time to benefit from early palliative care as compared to the former who may have been more acutely ill in the inpatient setting. Specialist palliative care was also associated with a reduced risk of dying in the acute care setting (aOR, 0.57; 95% CI, 0.52-0.64).

### Comments

1. This was a large nationwide study across the Veterans Affairs healthcare system and provides further support for the benefit

of early specialist palliative care in patients with advanced cancer.

2. Early specialist palliative care was associated with increased survival and reduced risk of dying in the hospital among Veterans with advanced cancer.
3. There was a high uptake of palliative care at 57% of the cohort nationwide, though substantial geographic variation existed.
4. Though the study sample was large, 98% of participants were men, which may limit generalizability.
5. Survival is just one of the many outcomes that palliative care has positively impacted in serious illness, such as place of death, quality of life, mood, and caregiver burden.

## INTENSIVIST COMMUNICATION STYLES AND PROGNOSIS IN THE ICU

Oppenheim IM, Lee EM, Vasher ST, Zaeh SE, Hart JL, Turnbull AE. **Effect of Intensivist Communication in a Simulated Setting on Interpretation of Prognosis Among Family Members of Patients at High Risk of Intensive Care Unit Admission: A Randomized Trial.** *JAMA Netw Open* 2020; 3(4):e201945.

### Summary

This web-based, parallel-group randomized trial included a national sample of 302 adult family members of people with COPD on supplemental oxygen. The study was conducted outside the ICU and explored surrogate-intensivist discordance on prognosis based on intensivist communication style. Participants were randomized to view one of four videos of communication styles in which an intensivist simulated an ICU family meeting and responded to the following scripted surrogate question on prognosis, "What do you think is most likely to happen?". Simulated intensivist styles were direct (control) or one of three indirect responses: indirect and comparative to other patients, indirect and descriptive of deterioration, and redirecting to values and goals. Participants gauged what the simulated doctor thought was their hypothetical loved one's chance of survival from 0% (no chance of survival) to 100% (absolute survival) and what surrogates thought was the chance of survival. Compared to a direct response, participants perceived an indirect or redirecting response as more optimistic. Their own prognosis estimates were also more optimistic with a redirecting response. Three-fourths of family members were confident on prognosis regardless of response style. When trying to convey a poor prognosis, simple, direct responses may minimize differences in belief between intensivists and surrogates.

### Comments

1. This was an elegant web-based and simulated randomized trial of surrogate-intensivist discordance on prognosis based on intensivist communication style.
2. The majority (3/4) of surrogates were confident about prognosis regardless of direct or indirect intensivist communication

styles, stressing the importance of following up to gauge family understanding.

3. Indirect or redirecting responses were perceived by surrogates as being more optimistic than direct responses, while simple and direct responses may minimize surrogate-intensivist difference in beliefs about prognosis.
4. The simulated design with videos minimized the potential influence of conducting the study during the acute stresses of the ICU, but that could also impact practical interpretation.
5. The study included predominately White participants, which may limit generalizability to Black surrogates who could have different perspectives on prognosis.

## VALUES-BASED COMMUNICATION IN THE ICU

Scheunemann LP, Ernecoff NC, Buddadhumaruk P, Carson SS, Hough CL, Curtis JR, Anderson WG, Steingrub J, Lo B, Matthay M, Arnold RM, White DB.

**Clinician-Family Communication About Patients' Values and Preferences in Intensive Care Units.** *JAMA Intern Med* 2019;179(5):676-684.

### Summary

Shared decision making in the ICU using values-based discussions is a patient-centered approach that integrates patients' values (e.g., what makes life worth living) and preferences about life-extending treatments into ICU decisions and plans. This secondary analysis of a prospective, multicenter cohort study included 249 family conferences between ICU clinicians and surrogates of incapacitated, critically ill adults. Investigators thematically analyzed audio-recorded transcripts of clinician-family conferences for statements on patients' values and preferences and how these exchanges were deliberately applied to ICU treatment planning. Conferences included 450 surrogates and 141 clinicians. In 244 of the 249 clinician-surrogate conferences which discussed goals of care or prognosis, 25% had no information exchanged or deliberated on patients' values or preferences. In 68% of conferences, there was exchange of information about patients' values and preferences, but only 44% deliberated how these values applied to treatment decisions in the ICU. Only 36% of conferences discussed aspects of patients' spirituality or functional status, and surrogates provided substituted judgment in 14% of conferences. Values-based discussions between ICU clinicians and surrogates are infrequent and rarely integrated in a deliberate fashion into treatment decisions. Interventions may be needed that improve clinician communication about values and surrogate preparation for these discussions.

### Comments

1. This was a very large qualitative study of family meetings in the ICU and included data from multiple centers across the country.
2. One quarter of goals of care conferences in the ICU between clinicians and surrogates lacked discussions and deliberations on patients' values and preferences for treatments, and two-

thirds of these conversations did not include discussions on patients' functional status or spirituality.

3. Only a single clinician-surrogate conference per patient was recorded, which risks missing the growth and evolution that happens with ongoing family discussions over time.
4. Values-based discussions about the end of life are an important procedure in the ICU that are rarely conducted.
5. Interventions that train clinicians on frameworks of shared decision making in the ICU and how to have detailed and deliberate values-based conversations with surrogates are needed.

## OTHER ARTICLES OF INTEREST

### PALLIATIVE AND END OF LIFE CARE

Cross SH, Ely EW, Kavalieratos D. **Place of Death for Individuals with Chronic Lung Disease: Trends and Associated Factors From 2003 to 2017 in the United States.** *Chest* 2020; 158(2):670-680.

Sullivan DR, Kim H, Gozalo PL, Bunker J, Teno JM. **Trends in Noninvasive and Invasive Mechanical Ventilation Among Medicare Beneficiaries at the End of Life.** *JAMA Intern Med* 2021; 181(1):93-102.

Luckett T, San Martin A, Currow DC, Johnson MJ, Barnes-Harris MMM, Phillips JL. **A Systematic Review and Meta-Analysis of Studies Comparing Burden from Lung Cancer and Chronic Obstructive Pulmonary Disease.** *Palliative Med* 2020; 34(10): 1291-1304.

Broese JM, de Heij AH, Janssen DJ, Skora JA, Kerstjens HA, Chavannes NH, Engels Y, van der Kleij RM. **Effectiveness and Implementation of Palliative Care Interventions for Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review.** *Palliat Med* 2021; 35(3):486-502.

Scheerens C, Faes K, Pype P, Beernaert K, Joos G, Derom E, Cohen J, Deliens L, Chambaere K. **Earlier Palliative Home Care is Associated with Patient-Centred Medical Resource Utilisation and Lower Costs in the Last 30 Days Before Death in COPD: A Population-Level Decedent Cohort Study.** *Eur Respir J* 2020;55(5):1901139.

Iyer AS, Goodrich CA, Dransfield MT, Alam SS, Brown CJ, Landefeld CS, Bakitas MA, Brown JR. **End-of-Life Spending and Healthcare Utilization Among Older Adults with Chronic Obstructive Pulmonary Disease.** *Am J Med* 2020;133(7):817-824.e1.

Lee JD, Jennerich AL, Engelberg RA, Downey L, Curtis JR, Khandelwal N. **The Type of Intensive Care Unit Matters: Variations in Palliative Care for Critically Ill Patients with Chronic, Life-Limiting Illness.** *J Palliat Med* 2020; Online ahead of print.



Rubin EB, Buehler A, and Halpern SD. **Seriously Ill Patients' Willingness to Trade Survival Time to Avoid High Treatment Intensity at the End of Life.** *JAMA Intern Med.* 2020; 180(6):907-909.

Ma J, Chi S, Buettner B, Pollard K, Muir M, Kolekar C, Al-Hammadi N, Cen L, Kollef, M, Dans M. **Early Palliative Care Consultation in the Medical ICU: A Cluster Randomized Crossover Trial.** *Crit Care Med* 2019;47(12):1707-1715.

## COMMUNICATION

Moale A, Teply ML, Tiange L, Singh AL, Basyal PS, Turnbull AE. **Intensivists' Religiosity and Perceived Conflict During a Simulated ICU Family Meeting.** *J Pain Symptom Manage* 2020; 59(3):687-693.

Khandelwal N, Long NC, Lee RY, McDermott CL, Engelberg RA, Curtis JR. **Pragmatic Methods to Avoid Intensive Care Unit Admission When It Does Not Align with Patient and Family Goals.** *Lancet Respir Med* 2019;7(7):613-625.

Suen AO, Butler RA, Arnold RM, Myers B, Witteman HO, Cox CE, McComb JG, Buddadhumaruk P, Shields AM, Morse N, Argenas A, White DB. **A Pilot Randomized Trial of an Interactive Web-based Tool to Support Surrogate Decision-makers in the ICU.** *Ann Am Thorac Soc* 2020; Online Ahead of Print.

Feder S, Smith D, Griffin H, Shreve ST, Kinder D, Kutney-Lee A, Ersek M. **"Why Couldn't I Go in To See Him?" Bereaved Families' Perceptions of End-of-Life Communication During COVID-19.** *J Am Geriatr Soc* 2021;69(3):587-592.

Kennedy NR, Steinberg A, Arnold RM, Doshi AA, White DB, DeLair W, Nigra K, Elmer J. **Perspectives on Telephone and Video Communication in the ICU during COVID-19.** *Ann Am Thorac Soc* 2020; Online Ahead of Print.

## MEDICAL EDUCATION

**Lekshmi Santhosh, MD, M.A.Ed**

University of California – San Francisco (UCSF)  
Division of Pulmonary/Critical Care Medicine, Department of Medicine  
San Francisco, CA

### CLINICAL TRAINING MODELS

Landrigan CP, Rahman SA, Sullivan JP, Vittinghoff E, Barger LK, Sanderson AL, ... Czeisler CA (2020). **Effect on patient safety of a resident physician schedule without 24-hour shifts.** *New England Journal of Medicine*, 382(26), 2514-2523.

#### Summary

In this multicenter, cluster-randomized, crossover trial, pediatric intensive care unit residents were randomized to extended-duration work schedules (24 hour + schedules, control group) vs. night-shift type schedules (<16 hours schedules, intervention group). The primary outcome was serious medical errors made by resident physicians, which were assessed via direct observation and chart review. Residents who were assigned to the intervention group made more serious errors than the control group, and the number of ICU patients cared for by each resident was higher in the intervention group.

#### Comments

1. Intervention schedule did successfully increase sleep hours and decrease number of work hours, yet intriguingly, the intervention schedule had more errors.
2. There are many potential reasons for the increased errors including increased handoffs, increased resident workload, differences in supervision, or differences in handoff processes.
3. Letters to the editor argued that this question should not be studied and that 24hour + shifts are fundamentally flawed, or that more standardized handoff processes are needed for complex ICU patients, or that rapid cycling between days and nights could have contributed to the errors.
4. This article adds further evidence – and controversy – to other trials focusing on duty hours such as FIRST and iCOMPARE, which found no significant differences with duty hours restrictions.

### MEDICAL EDUCATION ADAPTATIONS DURING COVID-19

Hester TB, Cartwright JD, DiGiovine DG, Karlic KJ, Kercheval JB, DiGiovine B, ... Iwashyna TJ. (2020). **Training and deployment of medical students as respiratory therapist extenders during COVID-19.** *ATS Scholar*, 1(2), 145-151.

#### Summary

During the COVID-19 surge, the University of Michigan rapidly implemented a model to train and deploy medical students in a novel role as a “respiratory therapist extender” (RTE) to address the critical shortage of respiratory therapists. 25 students participated in a hybrid virtual/in-person training curriculum focused on basics of respiratory care, documentation, equipment processing and preparation. Multiple RTEs reported to a single RT to extend their capacity.

#### Comments

1. The article provides a framework for extending key staff during a natural disaster.
2. The article carefully notes how to explicitly balance patient care needs with medical student autonomy and safety, and acknowledges potential power dynamics, peer pressure, and social coercion in this voluntary effort.
3. The curriculum was also unique in that RTs were brought in as co-creators early in the process.
4. The article highlights the lessons learned and barriers encountered in implementing a novel RT extender curriculum amidst a pandemic.
5. This article is just one example of a just-in-time novel curricular innovation that occurred early in the pandemic.

### DIVERSITY, EQUITY, AND INCLUSION

Gonzaga AMR, Appiah-Pippim J, Onumah CM, Yialamas MA. (2020). **A framework for inclusive graduate medical education recruitment strategies: meeting the ACGME standard for a diverse and inclusive workforce.** *Academic Medicine*, 95(5), 710-716.

#### Summary

Improving the diversity of training programs is critical to address health disparities and promote a more diverse and inclusive workforce. This article proposes a five-point inclusive recruitment framework for diversifying GME training programs. The first step emphasizes strong institutional support that explicitly sets diversity as a major priority. The other steps include seeking out candidates, implementing inclusive recruitment strategies, investing in the success of trainees, and building a more diverse pipeline. The article specifically addresses practical tips on how to implement a holistic review process.

## Comments

1. This article is an important and practical resource for medical education leaders describing how to implement a framework to improve recruitment in training programs.
2. This article focuses specifically on recruitment of GME trainees; however, similar approaches are needed at the student and faculty level including conversations about both recruitment and retention.
3. The details about implementation of a holistic review process provide a welcome framework for programs that have not previously implemented such measures in trainee selection.
4. Diversifying our work force, particularly within PCCSM, is an urgent need and this article gives practical tips that go beyond simple messages of support for diversity work.

## CLINICIAN WELL-BEING AND BURNOUT

Sharp M, Burkart KM, Adelman MH, Ashton RW, Daugherty Biddison L, Bosslet GT, Doyle ST, Eckmann T, Khurram S Khan, MM, Lenz PH, McCallister JW, O'Toole J, Rand CS, Riekert KA, Soffler MI, Winter GR, Zaeh S, Eakin MN, Consensus Expert Panel (CEP) Members (2021). **A National Survey of Burnout and Depression Among Fellows Training in Pulmonary and Critical Care Medicine: A Special Report by the Association of Pulmonary and Critical Care Medicine Program Directors.** *Chest*, 159(2), 733–742. <https://doi.org/10.1016/j.chest.2020.08.2117>

### Summary

This cross-sectional survey of PCCM fellows across the United States assessed burnout and depressive symptoms using standardized well-validated tools (the Maslach Burnout Index two-item measure and the two-item Primary Care Evaluation of Mental Disorders procedure). Multivariate logistic regression models assessed association between individual and institutional variables with burnout or depressive symptoms. 592/976 fellows completed the survey (51% response rate), and 55% of fellows showed signs of either burnout or depressive symptoms. Protective factors included a coverage/jeopardy system and access to mental health services whereas exacerbating factors included financial concerns, working more than 70 hours/week, and EMR documentation burdens.

### Comments

1. In a pre-COVID sample, a majority of fellows experienced symptoms of depression or burnout.
2. Recent literature has shown that COVID-19 has further exacerbated the stressors of critical care practitioners.
3. An urgent crisis exists to identify solutions for fellow well-being, now more than ever.
4. Concrete institutional strategies include implementing a coverage system, access to mental health resources, reducing EMR burden, addressing work hours, and addressing financial concerns.
5. Further research regarding interventions for burnout and depression must be studied and invested in.

## OTHER ARTICLES OF INTEREST

### CLINICAL TRAINING MODELS

Voduc N, Adamson R, Kashgari A, Fenton M, Porhownick N, Wojnar M, Sharma K, Gillson AM, Chung C, McConnell M. (2020). **Development of Learning Curves for Bronchoscopy: Results of a Multicenter Study of Pulmonary Trainees.** *Chest*, 158(6), 2485–2492. <https://doi.org/10.1016/j.chest.2020.06.046>

Mamede S, Hautz WE, Berendonk C, Hautz SC, Sauter TC, Rotgans J, ... Schmidt HG. (2020). **Think twice: effects on diagnostic accuracy of returning to the case to reflect upon the initial diagnosis.** *Academic medicine*, 95(8), 1223-1229.

Catalanotti JS, O'Connor AB, Kisielewski M, Chick DA, Fletcher KE. **Association Between Nocturnist Supervision and Perceived Overnight Supervision Adequacy Among Internal Medicine Residents in the US.** *JAMA*. 2020;323(14):1407–1409. doi:10.1001/jama.2020.0875

Clancy CB, Heath JK, Nandiwada DR, Aizenberg D, Kassutto S. (2020). **Development and Implementation of a Novel Learner-driven Precepting Model for Pulmonary Fellowship.** *ATS Scholar*, 1(2), 161-169.

### ADAPTATIONS FROM COVID

Lucey CR, Johnston SC. **The Transformational Effects of COVID-19 on Medical Education.** *JAMA*. 2020;324(11):1033–1034. doi:10.1001/jama.2020.14136

Huppert LA, Hsiao EC, Cho KC, Marquez C, Chaudhry RI, Frank J, ... Babik JM. (2020). **Virtual Interviews at Graduate Medical Education Training Programs: Determining Evidence-Based Best Practices.** *Academic medicine: journal of the Association of American Medical Colleges*.

Nas J, Thannhauser J, Vart P, et al. **Effect of Face-to-Face vs Virtual Reality Training on Cardiopulmonary Resuscitation Quality: A Randomized Clinical Trial.** *JAMA Cardiol*. 2020;5(3):328–335.

He S, Lai D, Mott S, Little A, Grock A, Haas MR, Chan TM. (2020). **Remote e-work and distance learning for academic medicine: best practices and opportunities for the future.** *Journal of Graduate Medical Education*, 12(3), 256-263.

### DIVERSITY/EQUITY/INCLUSION

Capers IV, Q. (2020). **How clinicians and educators can mitigate implicit bias in patient care and candidate selection in medical education.** *ATS Scholar*, 1(3), 211-217.

Heath JK, Clancy CB, Carillo-Perez A, Dine CJ. (2020). **Assessment of gender-based qualitative differences within trainee evaluations of faculty.** *Annals of the American Thoracic Society*, 17(5), 621-626.

Santhosh L, Babik JM. (2020). **Diversity in the Pulmonary and Critical Care Medicine Pipeline. Trends in Gender, Race, and Ethnicity among Applicants and Fellows.** *ATS Scholar*, 1(2), 152-160.

de Bourmont SS, Burra A, Nouri SS, et al. **Resident Physician Experiences With and Responses to Biased Patients.** *JAMA Netw Open*. 2020;3(11):e2021769. doi:10.1001/jamanetworkopen.2020.21769

### **CLINICIAN WELLBEING AND BURNOUT**

Marshall AL, Dyrbye LN, Shanafelt TD, Sinsky CA, Satele D, Trockel M, ... West CP. (2020). **Disparities in burnout and satisfaction with work-life integration in US physicians by gender and practice setting.** *Academic Medicine*, 95(9), 1435-1443.

Linzer M, Smith CD, Hingle S, et al. **Evaluation of Work Satisfaction, Stress, and Burnout Among US Internal Medicine Physicians and Trainees.** *JAMA Netw Open*. 2020;3(10):e2018758.

Zhou AY, Panagioti M, Esmail A, Agius R, Van Tongeren M, Bower P. **Factors Associated With Burnout and Stress in Trainee Physicians: A Systematic Review and Meta-analysis.** *JAMA Netw Open*. 2020;3(8):e2013761. doi:10.1001/jamanetworkopen.2020.13761

Azoulay E, De Waele J, Ferrer R, et al. **Symptoms of burnout in intensive care unit specialists facing the COVID-19 outbreak.** *Ann. Intensive Care* 10, 110 (2020). <https://doi.org/10.1186/s13613-020-00722-3>.

Lieuwe D.J. Bos, MD, PhD

Amsterdam University Medical Center  
Intensive Care and Respiratory Medicine  
Amsterdam, the Netherlands

## IMMUNOMODULATION OF ARDS NOT RELATED TO COVID-19

Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA, Aguilar G, Alba F, González-Higueras E, Conesa LA, Martín-Rodríguez C, Díaz-Domínguez FJ, Serna-Grande P, Rivas R, Ferreres J, Belda J, Capilla L, Tallet A, Añón JM, Fernández RL, González-Martín JM, Aguilar G, Alba F, Álvarez J, Ambrós A, Añón JM, Asensio MJ, Belda J, Blanco J, Blasco M, et al. **Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial.** *Lancet Respir Med.* 2020; 8 (3): 267-276

### Summary

In this randomized controlled, open-label trial, early administration of high dose dexamethasone was tested in patients with persistent, moderate-to-severe ARDS with a minimal PEEP requirement of 10 cmH<sub>2</sub>O. Patients were recruited from 17 hospitals in Spain. Dexamethasone was dosed at 20mg for five days followed by 10mg for five days. The primary endpoint was number of ventilator-free days. More than 1000 patients were screened of whom 277 out of a planned 314 patients (88%) were included. Inclusion was stopped due to slow recruitment. The most common risk factor for ARDS was pneumonia. The number of ventilator-free days was higher in the dexamethasone arm than in the control group with a mean difference of 4.8 days [95% CI 2.5 to 7.0]. Mortality at 60 days follow-up was also lower in the dexamethasone arm (mean difference: -15.3% [-25.9 to -4.9]). PaO<sub>2</sub>/FiO<sub>2</sub> and PaCO<sub>2</sub> improved faster in patients treated with corticosteroids. Patients who received dexamethasone more frequently experienced hyperglycemia, but had similar rates of infectious complications. The authors conclude that early administration of dexamethasone could reduce duration of mechanical ventilation and mortality in patients with persistent moderate-to-severe ARDS.

### Comments

1. The study selected for a very specific subgroup of ARDS patients as potential steroid sensitive pathologies were excluded and only patients who maintained a PaO<sub>2</sub>/FiO<sub>2</sub> below 200 for 24 hours at 10cmH<sub>2</sub>O PEEP were included.
2. The search for this specific subgroup of patients led to the exclusion of around 80% of screened patients and was reflected by a very low recruitment rate that ultimately led to stopping the study prematurely.

3. Patients with corticosteroid sensitive pathologies were excluded and since patients in the control group were also allowed to be treated with steroids, the results may be biased against dexamethasone use rather than in favor of it.
4. The effect estimate and confidence interval for ventilator-free days and mortality are convincing and provide a strong rationale for the administration of high dose dexamethasone to patients who fulfill the inclusion criteria of this study.
5. Although some common side effects of corticosteroid were monitored in the study, the major missing adverse event is ICU acquired weakness, which was not adequately monitored in the study.

## IMMUNOMODULATION OF ARDS DUE TO COVID-19

Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, Avezum A, Lopes RD, Bueno FR, Silva MVAO, Baldassare FP, Costa ELV, Moura RAB, Honorato MO, Costa AN, Damiani LP, Lisboa T, Kawano-Dourado L, Zampieri FG, Olivato GB, Righy C, Amendola CP, Roepke RML, Freitas DHM, Forte DN, Freitas FGR, Fernandes CCF, Melro LMG, Junior GFS, Morais DC, Zung S, Machado FR, Azevedo LCP; COALITION COVID-19 Brazil III Investigators. **Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial.** *JAMA.* 2020 Oct 6;324(13):1307-1316.

### Summary

In this randomized controlled, open-label trial, early administration of high dose dexamethasone was tested in patients with moderate-to-severe ARDS due to COVID-19. Patients were recruited from 41 hospitals in Brazil. Dexamethasone was dosed at 20mg for five days followed by 10mg for five days. The primary endpoint was number of ventilator-free days. More than 500 patients were screened of whom 299 out of a planned 350 patients (85%) were included. Inclusion was stopped due to efficacy of the RECOVERY trial. The number of ventilator-free days was higher in the dexamethasone arm than in the control group with a mean difference of 2.3 days [95% CI 0.2 to 4.4]. There were no differences in mortality and duration of mechanical ventilation in survivors. Subgroup analyses did not show any differences. Patients who received dexamethasone did not experience more hyperglycemia and had similar rates of infectious complications. The authors conclude that early administration of dexamethasone could reduce

duration of mechanical ventilation in patients with COVID-19 related moderate-to-severe ARDS.

### Comments

1. The study included an unselected group of patients with COVID-19 related ARDS requiring invasive mechanical ventilation.
2. The major limitation of the study is the open-label design and the lack of a placebo group, which is in line with the limitation of the DEXA-ARDS trial (previous article), the RECOVERY trial and REMAP-CAP.
3. The effect estimate and confidence interval for ventilator-free days is convincing and provides a strong rationale for the administration of corticosteroids to patients who fulfill the inclusion criteria of this study.
4. Together with the results of RECOVERY and REMAP-CAP, in combination with a meta-analysis that was published simultaneously, corticosteroids are now standard of care for acute respiratory failure due to COVID-19 but questions remain on the type of drug and dosing.
5. The study is the starting point for a randomized controlled trial testing moderate dose versus high dose steroids in COVID-19 related ARDS, possibly involving specific immunomodulatory drugs as a third arm.

### UNDERSTANDING ANGIOPATHY IN COVID-19

Patel BV, Arachchilage DJ, Ridge CA, Bianchi P, Doyle JF, Garfield B, Ledot S, Morgan C, Passariello M, Price S, Singh S, Thakuria L, Trenfield S, Trimlett R, Weaver C, Wort SJ, Xu T, Padley SPG, Devaraj A, Desai SR. **Pulmonary Angiopathy in Severe COVID-19: Physiologic, Imaging, and Hematologic Observations.** *Am J Respir Crit Care Med.* 2020 Sep 1;202(5):690-699.

#### Summary

In this observational cohort study of 39 consecutive patients with COVID-19 related ARDS, coagulopathy was evaluated using physiological, biomarker and imaging data. All patients had respiratory physiology measurements and underwent thromboelastography (TEG). Dual energy CT (DECT) analysis was used for quantification of morphological CT patterns and perfusion defects. Half the patients were on ECMO. Patients had low PaO<sub>2</sub>/FiO<sub>2</sub>, low compliance and high ventilatory ratios, indicative of severe lung injury. C-reactive protein was high, with a mean value of 300 mg/L. Patients with more parenchymal consolidation had a lower compliance. Around one-third of patients had arterial filling defects consistent with pulmonary embolism, but two-thirds had dilated peripheral vessels in at least two lobes. All 18 patients who underwent DECT had perfusion defects, with a mean involvement of around 50% of the lung. Most patients showed hypercoagulability and absent fibrinolysis on TEG resulting in high D-dimers. The authors conclude that widespread pulmonary angiopathy is seen in severe COVID-19 pneumonia.

### Comments

1. In this relatively small study, a very specific subset of severely ill patients with COVID-19 related ARDS were included, half of whom required ECMO.
2. Perfusion defects were common and were not limited to areas with pulmonary embolism which suggests that microthrombosis is a common phenomenon in COVID-19 related ARDS.
3. A likely pathophysiological explanation is found in the observed hypercoagulability and absent fibrinolysis, but it remains unclear by what mechanism this is driven primarily.
4. Angiopathy is a common finding in ARDS due to other causes as well and this study cannot conclude any differences in the prevalence of these findings from other causes of ARDS, certainly given the particular selection criteria in a tertiary referral center for ECMO.
5. Larger validation studies with integration of imaging with a larger panel of biomarkers are needed to point towards the etiology of angiopathy in ARDS in general, and COVID-19 specifically.

### HETEROGENEITY IN RESPIRATORY PHYSIOLOGY IN ARDS

Panwar R, Madotto F, Laffey JG, van Haren FMP. **Compliance Phenotypes in Early Acute Respiratory Distress Syndrome before the COVID-19 Pandemic.** *Am J Respir Crit Care Med.* 2020 Nov 1;202(9):1244-1252. doi: 10.1164/rccm.202005-2046OC. PMID: 32805143; PMCID: PMC7605177.

#### Summary

At the beginning of the COVID-19 pandemic, several authors have speculated that COVID-19 related ARDS presents with distinct “compliance phenotypes”. In this post-hoc analysis of a large multi-national observational cohort study conducted before the emerging of SARS-CoV2, the authors set out to evaluate if these phenotypes are novel or predate COVID-19. 1117 patients with ARDS who were ventilated with controlled modes of ventilation were included. Median compliance was 30 mL/cmH<sub>2</sub>O. A minority (12%) had preserved compliance above 50 mL/cmH<sub>2</sub>O (“High elastance”; “H phenotype”) while 74% had a compliance below 40 mL/cmH<sub>2</sub>O (“Low elastance”; “L phenotype”). The association between compliance and PaO<sub>2</sub>/FiO<sub>2</sub> was very weak with an adjusted R<sup>2</sup> of 0.0001. Patients with a lower compliance had a higher hospital mortality (“L” 32% vs. “H” 45%; adjusted odds ratio per mL/cmH<sub>2</sub>O increase, 0.988; 95% confidence interval, 0.979-0.996). The relationship between compliance and worse outcome did not show a threshold and no distinct response phenotypes could be identified. These results were not sensitive to any subgroup analyses. The authors conclude that a significant proportion of ARDS patients with preserved compliance had moderate to severe hypoxemia and that a lower compliance was independently associated with higher mortality.

### Comments

1. Small case series led to the speculation that there are distinct compliance phenotypes in COVID-19 and that this is unique to this cause of ARDS.
2. The major strength of this study is that it is a large multi-national observational cohort study, which limits selection bias as much as possible.
3. The large sample size and hypothesis driven data collection allowed for more precise inference on the relation between commonly encountered respiratory variables: PaO<sub>2</sub>/FiO<sub>2</sub> and compliance.
4. The lack of a transition point for the relation between compliance and outcome suggests that any cut-off is arbitrary and therefore likely of little clinical utility.
5. The results of this study exemplify a rapid and evidence-based remedy to premature phenotyping of critical illness, which is prone to cognitive biases.

### THE BEST SUPPORTIVE THERAPIES FOR ARDS

Sachin Sud, Jan O Friedrich, Neill KJ Adhikari, Eddy Fan, Niall D Ferguson, Gordon Guyatt, Maureen O Meade.

**Comparative Effectiveness of Protective Ventilation Strategies for Moderate and Severe ARDS: Network Meta-Analysis.** *Am J Respir Crit Care Med.* 2021 Jan 6. doi: 10.1164/rccm.202008-3039OC. Online ahead of print. PMID: 33406009

### Summary

In this network meta-analysis, the authors systematically collected data from all 34 available randomized controlled trials on ventilator and supportive therapies for ARDS. These include size of tidal volume, PEEP strategy, prone positioning, veno-venous extra-corporeal oxygenation (vv-ECMO) and high frequency oscillation (HFO). Network analysis allows for a head-to-head comparison of each intervention, even when they are never compared in a single study, by creating a network through which interventions are linked and can be compared. Low tidal volume ventilation was found to be an effective intervention, with a high confidence of being superior to high tidal volume ventilation (the least effective intervention). Addition of prone-positioning to low tidal volume ventilation was found to be the best strategy within the network. There was high statistical confidence that vv-ECMO is a good strategy, with similar performance to low tidal volume ventilation in the prone position. A high PEEP, low tidal volume strategy performed better than high tidal volume ventilation, but not better than a low tidal volume strategy with lower PEEP levels. Sensitivity analyses did not show any large changes in the results.

### Comments

1. Network meta-analysis can teach us about the relative performance of treatment strategies, even when strategies are not compared head-to-head.
2. The major strength of this study is that it provides an unbiased overview of the available evidence and that multiple sensitivity analyses yield similar results, which should increase our confidence in the presented results.
3. The major limitation of any study-level meta-analysis is the disregard to heterogeneity at the individual patient level, and it is likely that different strategies will be more or less effective in different patients.
4. The identification of low tidal volume ventilation in prone position as most effective strategy is not surprising but should serve as a gentle reminder that we likely underuse this low cost, yet highly effective intervention.
5. The statistical confidence for the identification of vv-ECMO as an effective strategy is an overestimation as only patients with very severe ARDS were included in the studies that were used in the network analysis, and therefore conclusions should be reserved for this group only.

**Jessica Bon, MD, MS, ATSF**

University of Pittsburgh; VA Pittsburgh Healthcare System  
Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine  
Pittsburgh, PA

## TREATMENT OF COPD

Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, Trivedi R, Rose ES, Ballal S, McLaren J, Darken P, Aurivillius M, Reisner C, Dorinsky P, for the ETHOS Investigators. **Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD.** *NEJM* 2020; 383: 35-48.

### Summary

The ETHOS trial studied the impact of triple therapy (budesonide/glycopyrrolate/formoterol) at two ICS dose levels on COPD exacerbation rates. Patients with moderate-to-very-severe COPD and at least one exacerbation in the past year were randomized 1:1:1:1 to receive twice daily triple therapy, which included an inhaled ICS at two doses (budesonide 320 versus 160 mcg), or one of two dual therapies (LABA/LAMA or ICS/LABA). Eligible patients were 40 to 80 years of age, had at least a ten pack-year smoking history, used a minimum of two maintenance therapies at the time of screening, had an FEV1/FVC less than 0.7 with a post-bronchodilator FEV1% predicted of 25 to 65%, had a score of at least 10 on the COPD Assessment Test, and had at least one documented moderate or severe COPD exacerbation if FEV1 was < 50% predicted or at least two moderate or one severe COPD exacerbation if FEV1 was  $\geq$  50% predicted. The primary end point of annual rate of moderate or severe COPD exacerbations was assessed over a 52-week study period. Investigators found that triple therapy at either ICS dose resulted in a lower rate of moderate or severe COPD exacerbations compared to LABA/LAMA or ICS/LABA alone.

### Comments

1. The ETHOS study adds to growing evidence suggesting that triple therapy with an ICS/LABA/LAMA in patients with moderate to very severe COPD results in lower rates of moderate to severe exacerbations compared to dual therapy with either an ICS/LABA or LABA/LAMA.
2. Both triple therapy regimens reduced the annual rate of moderate or severe exacerbations compared to dual-therapy regimens regardless of eosinophil count (< 150 cells or  $\geq$  150 cells per cubic millimeter), bronchodilator response at screening, or use of inhaled glucocorticoids at screening.
3. Rates of moderate or severe exacerbations, time to first moderate or severe exacerbation, and time to death from any cause were similar in patients receiving a triple therapy regimen that included a higher dose ICS (budesonide 320 mcg) compared to a triple therapy regimen that included standard dose ICS (budesonide 160 mcg), although time to death from any cause was longer in the triple therapy 320 mcg

budesonide group compared to the LABA/LAMA (glycopyrrolate-formoterol) group.

4. Although prior studies have suggested that the risk of pneumonia is less with budesonide therapy, the ETHOS trial reported an incidence of pneumonia ranging from 3.5 to 4.5% in groups receiving inhaled budesonide compared to only 2.3% in LABA/LAMA group.

Mathioudakis AG, Bikov A, Foden P, Lahousse L, Brusselle G, Singh D, Vestbo J. **Change in blood eosinophils following treatment with inhaled corticosteroids may predict long-term clinical response in COPD.** *European Respiratory Journal* 2020; 55: 1902119 [https://doi.org/10.1183/13993003.02119-2019].

### Summary

ISOLDE, a 3-year double-blind trial comparing twice daily fluticasone propionate to placebo, showed that ICS did not affect FEV1 decline rate but decreased exacerbations and slowed health status decline in patients with moderate-to-severe COPD. In this post hoc analysis of ISOLDE, investigators evaluated whether eosinophil change after ICS initiation, eosinophils while not receiving either oral or inhaled corticosteroids, and eosinophils while receiving ICS predict the impact of ICS on FEV1, exacerbations, and health status over time. In subjects with eosinophil suppression of  $\geq$  100 cells per microliter, ICS decelerated FEV1 decline, whereas in those with an eosinophil rise of  $\geq$  100 cells per microliter, ICS accelerated lung function decline. Higher eosinophils while not on corticosteroids was associated with greater ICS treatment efficacy whereas high eosinophils while on ICS treatment was associated with accelerated FEV1 decline. In subjects with eosinophil suppression of  $\geq$  200 cells per microliter and eosinophil rise of  $\geq$  200 cells per microliter with ICS, exacerbations were decreased by 33% and increased by 80%, respectively. ICS did not impact FEV1 decline or exacerbations in subjects with unchanged eosinophils with ICS treatment. Finally, ICS slowed health status decline in those with higher eosinophils in the absence of ICS.

### Comments

1. This study suggests that eosinophils may serve as a therapeutic biomarker for ICS response in patients with moderate-to-severe COPD.
2. The authors suggest that the acceleration of FEV1 decline and increased exacerbation frequency with ICS in subjects demonstrating a rise in eosinophils with treatment may indicate that a subgroup of patients exist who lack benefit from ICS



but are still susceptible to their harmful immunosuppressive effects leading to increased respiratory infections and subsequent lung function decline.

- Of note, ISOLDE recruited subjects with moderate-to-severe COPD but did not require an acute exacerbation history for study inclusion, thus limiting the generalizability of the current analysis.
- While the findings of this post hoc analysis are intriguing, future prospective studies examining the role of eosinophils in monitoring ICS treatment response in patients with indications for ICS therapy are necessary.

## COPD RISK

Smith BM, Kirby M, Hoffman EA, Kronmal RA, Aaron SD, Allen NB, Bertoni A, Coxson HO, Cooper C, Couper DJ, Criner G, Dransfield MT, Han MK, Hansel NN, Jacobs DR, Kaufman JD, Lin C-L, Manichaikul A, Martinez FJ, Michos ED, Oelsner EC, Paine R, Watson KE, Benedetti A, Tan WC, Bourbeau J, Woodruff PG, Barr RG; for the MESA Lung, CanCOLD, and SPIROMICS Investigators. **Association of dysanapsis with chronic obstructive pulmonary disease among older adults.** *JAMA* 2020; 323(22): 2268-2280.

### Summary

COPD may develop from either accelerated lung function decline or low maximally attained lung function early in life. Dysanapsis refers to a mismatch between airway caliber to lung size, is thought to develop in early life, and may contribute to COPD susceptibility. In this analysis of two community-based cohorts (MESA Lung, CanCOLD) and one case-control study (SPIROMICS), investigators sought to determine if dysanapsis quantified by CT as the ratio of mean airway lumen diameter to total lung volume (airway to lung ratio) accounts for a significant proportion of the variation of FEV1/FVC ratio and is associated with incident COPD. Investigators also assessed whether individuals with established COPD and lower airway to lung ratio have a slower lung function decline compared to those with higher airway to lung ratio. MESA Lung and CanCOLD participants in the lowest quartile of airway to lung ratio had higher COPD incidence than participants in the highest quartile, although FEV1 decline was similar between quartiles in both cohorts. In SPIROMICS participants with COPD, those in the lowest airway to lung ratio quartile had an FEV1 decline similar to MESA Lung participants whereas those in the highest quartile had greater FEV1 decline compared to MESA Lung.

### Comments

- This study suggests that dysanapsis, which likely occurs early in life, may be an important risk factor for COPD, particularly in those without a significant smoking history or evidence of accelerated lung function decline.
- The airway to lung ratio accounted for a greater proportion of FEV1 to FVC ratio variation than other common COPD risk factors, including smoking, occupational and environmental pollutants, and asthma.

- Individuals with COPD and the highest quartile of airway to lung ratio had greater decline in FEV1 than those in the lowest quartile, supporting two major pathways of COPD development in susceptible individuals.

## HEALTH DISPARITIES IN COPD

Ejike CO, Woo H, Galiatsatos P, Paulin LM, Krishnan JA, Cooper CB, Couper DJ, Kanner RE, Bowler RP, Hoffman EA, Comellas AP, Criner GJ, Barr RG, Martinez FJ, Han MK, Martinez CH, Ortega VE, Parekh TM, Christenson SA, Thakur N, Baugh A, Belz DC, Raju S, Gassett AJ, Kaufman JD, Putcha N, Hansel NN. **Contribution of individual and neighborhood factors to racial disparities in respiratory outcomes.** *American Journal of Respiratory and Critical Care Medicine* 2020; in press.

### Summary

Studies show that US Black individuals have greater lung function impairment and worse COPD-related clinical outcomes compared to non-Hispanic whites, even after adjustment for certain individual socioeconomic status (SES) factors. In this study, investigators assessed independent and joint effects of individual and neighborhood SES on racial disparities in COPD, a relatively unexplored area, by assessing whether Black individuals have worse COPD outcomes compared to White individuals and, if so, to what extent these disparities are explained by individual and neighborhood SES in the SPIROMICS cohort. Participants included current and former smokers age 40-80 both with and without airflow obstruction. Merged neighborhood level data from the 2010 U.S. Census Bureau American Community Survey and data from the ancillary study SPIROMICS AIR were used to determine individual and neighborhood-level risk factors in SPIROMICS participants. In adjusted (age, gender, smoking status, pack-years, BMI, depression, marital and COPD status) analyses, Black participants had worse respiratory symptoms and quality of life, lower functional capacity, higher rates of hospitalization with severe exacerbations, and worse airway and emphysema CT metrics compared to white participants. Differences in outcomes were attenuated, but remained significant, after accounting for both individual and neighborhood SES.

### Comments

- Racial differences in COPD exist and may be explained by disparities in individual and neighborhood socioeconomic status.
- In this study, individual SES factors contributed 12% to 35% to the racial disparities in clinical outcomes while neighborhood-level SES factors contributed 26% to 54%.
- The combination of individual and neighborhood-level SES factors explained 33% to 69% of the race-outcome disparities in the SPIROMICS cohort.
- A further understanding of additional risk factors contributing to worse outcomes in Black individuals with COPD is critical to achieving health equity in the care of individuals with COPD.

## OTHER ARTICLES OF INTEREST

Moll M, Sakornsakolpat P, Shrine N, Hobbs BD, DeMeo DL, John C, Guyatt AL, McGeachie MJ, Gharib SA, Obeidat M, Lahousse L, Wijnant SRA, Brusselle G, Meyers DA, Bleecker ER, Li X, Tal-Singer R, Manichaikul A, Rich SS, Won S, Kim WJ, Do AR, Washko GR, Barr RG, Psaty BM, Bartz TM, Hansel NN, Barnes K, Hokanson JE, Crapo JD, Lynch D, Bakke P, Gulsvik A, Hall IP, Wain L, International COPD Genetics Consortium, SpiroMeta Consortium, Weiss ST, Silverman EK, Dudbridge F, Tobin MD, Cho MH. **Chronic obstructive pulmonary disease and related phenotypes: polygenic risk scores in population-based and case-control cohorts.** *Lancet Respiratory Medicine* 2020; 8: 696-708.

Lindenauer PK, Stefan MS, Pekow PS, Mazor KM, Priya A, Spitzer KA, Lagu TC, Pack QR, Pinto-Plata VM, ZuWallack R. **Association between initiation of pulmonary rehabilitation after hospitalization for COPD and 1-year survival among Medicare beneficiaries.** *JAMA* 2020; 323(18): 1813-1823.

Lacasse Y, Series F, Corbeil F, Baltzan M, Paradis B, Simao P, Fernandez AA, Esteban C, Guimaraes M, Bourbeau J, Aaron SD, Bernard S, Maltais F, for the INOX Trial Group. **Randomized trial of nocturnal oxygen in chronic obstructive pulmonary disease.** *The New England Journal of Medicine* 2020; 383: 1129-1138.

Schultze A, Walker AJ, MacKenna B, Morton CE, Bhaskaran K, Brown JP, Rentsch CT, Williamson E, Drysdale H, Croker R, Bacon S, Hulme W, Bates C, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J, McDonald HI, Tomlinson L, Mathur R, Wing K, Wong AYS, Forbes H, Parry J, Hester F, Harper S, Evans SJW, Quint J, Smeeth L, Douglas IJ, Goldacre B, for the OpenSAFELY Collaborative. **Risk of COVID-19 related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform.** *Lancet Respiratory Medicine* 2020; 8: 1106-1120.

Martinez FJ, Rabe KF, Ferguson GT, Wedzicha JA, Singh D, Wang C, Rossman K, Rose ES, Trivedi R, Ballal S, Darken P, Aurivillius M, Reisner C, Dorinsky P, on behalf of the ETHOS investigators. **Reduced all-cause mortality in the ETHOS trial of budesonide/glycopyrrolate/formoterol for chronic obstructive pulmonary disease.** *American Journal of Respiratory and Critical Care Medicine* 2021; 203(5): 553-564.

## MYCOBACTERIAL DISEASES

Keira Cohen, MD

Johns Hopkins University School of Medicine  
Division of Pulmonary and Critical Care Medicine  
Baltimore, MD

## TUBERCULOSIS TRANSMISSION

Martinez L, Cords O, Horsburgh CR, Andrews JR; Pediatric TB Contact Studies Consortium. **The risk of tuberculosis in children after close exposure: a systematic review and individual-participant meta-analysis.** *Lancet.* 2020 Mar 21;395(10228):973-984.

## Summary

While TB is a leading cause of pediatric morbidity and mortality globally, assessment of TB disease risk in children after TB exposure had not been recently quantified. This systematic review and meta-analysis assessed the contemporary risk of TB in TB-exposed children by analyzing publications from 1998 to 2018, which included 46 cohort studies conducted in 34 countries. Over 130,000 TB-exposed children were identified and followed for a minimum of 6 months (429,538 person-years) to identify TB cases and assess risk factors. A total of 1299 prevalent cases (identified within the first 90 days) and 999 incident cases (identified after the first 90 days) were found. If not treated with preventative therapy, 6.5% of TB-exposed children with latent TB at baseline were diagnosed with TB within 90 days of enrollment. A U-shaped curve of age-based risk was identified, with the highest cumulative incidence observed in ages under <5 years or >15 years. The 2-year cumulative risk of TB in children under age 5 with latent TB who were not treated with preventative therapy was 19%. The protective efficacy of preventative therapies for incident TB disease was 63% in all children and 91% in children with latent TB infection.

## Comments

1. In the largest study of TB-exposed children, children under age five with a positive TST or IGRA at baseline were at highest risk of progressing from TB infection to TB disease within 2 years if not treated with preventative treatment (19%).
2. The majority of TB cases in TB-exposed children occurred within 90 days of enrollment, thus efforts at early case finding and early intervention will be required to reduce risks of pediatric TB disease following exposure.
3. TB preventative therapies were effective at reducing TB cases following exposure for children living in both low-incidence and high-incidence TB settings.
4. BCG vaccination was protective against all forms of TB in children under 5 years of age, but not in older children.

## BCG TO PREVENT INFECTIONS IN THE ELDERLY

Giamarellos-Bourboulis EJ, Tsilika M, Moorlag S, Antonakos N, Kotsaki A, Domínguez-Andrés J, Kyriazopoulou E, Gkavogianni T, Adami ME, Damoraki G, Koufargyris P, Karageorgos A, Bolanou A, Koenen H, van Crevel R, Droggiti DI, Renieris G, Papadopoulos A, Netea MG. **Activate: Randomized Clinical Trial of BCG Vaccination against Infection in the Elderly.** *Cell.* 2020 Oct 15;183(2):315-323.e9.

## Summary

Beyond prevention of severe TB in endemic settings, the bacille Calmette-Guerin (BCG) vaccine may offer non-specific protection against other infections. In ACTIVATE, hospitalized elderly patients received either a single dose of BCG or placebo vaccination in a double-blind manner at hospital discharge. 202 participants were randomized 1:1 and followed for 12 months to identify new all-cause infections. Due to COVID-19 and the pressing need to better understand BCG protection, an interim analysis was performed with 78 placebo and 72 BCG-vaccinated participants who had completed 12 months of observation. With a primary endpoint of time to first new infection, BCG lengthened the median time to new infection: 11 weeks (placebo) vs. 16 weeks (BCG). During the study period, at least one new infection was identified in 42.3% of placebo and only 25.0% of BCG-vaccinated participants, a 45% risk reduction ( $p = 0.039$ ) with BCG. In particular, BCG reduced respiratory viral infections from 17.9% in the placebo group to 4.2% in the BCG group ( $p = 0.013$ ). The frequency of serious adverse events was not different between the two groups. A subgroup of 57 participants for whom immune responses were analyzed pre- and 3 months post-vaccination revealed BCG-induced immune responses consistent with induction of trained immunity.

## Comments

1. BCG is a potent inducer of “trained immunity,” which is a phenomenon of epigenetic and transcriptional reprogramming of innate immune cells such that they exhibit enhanced antimicrobial defenses against heterologous (other) infections.
2. In this phase three, double-blind placebo-controlled study of the elderly, BCG vaccination increased the time to first infection and significantly decreased the incidence of all-cause infections.

3. The majority of the protective effect of BCG could be attributed to decreased respiratory tract infections, particularly viral infections, in the BCG-vaccinated group.
4. While the study population was small and excluded immunosuppressed persons, adverse events from BCG vaccination of an elderly population was not observed.
5. Over 20 clinical trials are currently underway to evaluate if BCG vaccination provides protection against COVID-19.

## TREATMENT OF LATENT TB INFECTION IN HIV

Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N, Jean Juste MA, Lama JR, Valencia J, Omoz-Oarhe A, Supparatpinyo K, Masheto G, Mohapi L, da Silva Escada RO, Mawlana S, Banda P, Severe P, Hakim J, Kanyama C, Langat D, Moran L, Andersen J, Fletcher CV, Nuermberger E, Chaisson RE; BRIEF TB/A5279 Study Team. **One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis.** *N Engl J Med.* 2019 Mar 14;380(11):1001-1011.

### Summary

Isoniazid preventative treatment reduces the risk of tuberculosis and death in HIV. However, its prolonged course length is often an implementation barrier, largely due to concerns for toxicity and adherence. BRIEF TB/A5279 (Brief Rifapentine-Isoniazid Efficacy for TB Prevention) was a randomized, open-label, phase 3 noninferiority trial that compared the efficacy and safety of 1-month of daily rifapentine plus isoniazid to 9-months of isoniazid monotherapy in adults and adolescents with HIV with either evidence of latent TB infection or living in areas of high TB prevalence. 3000 participants were enrolled from 45 sites in 10 countries and randomized 1:1 to the 1-month or 9-month regimens. At study entry, the median CD4+ count was 470 cells per cubic mm, and 50% of participants were not receiving antiretroviral therapy. The combined primary endpoint--a diagnosis of active TB, or death from either confirmed TB or an unknown cause--was identified in 2% of participants in the 1-month group and 2% of participants in the 9-month group. Serious adverse events were identified in 6% and 7% of the participants in the 1-month and 9-month groups, respectively. Treatment completion was significantly higher in the 1-month group (97%) in comparison to the 9-month group (90%).

### Comments

1. In this study of HIV-infected adolescents and adults, one month of daily rifapentine plus isoniazid was non-inferior to 9 months of daily isoniazid alone for the prevention of TB disease.
2. A large fraction of participants (68%) had a negative tuberculin skin test at baseline, thus this trial may have been biased toward non-inferiority.
3. Only a small number of participants had a baseline a CD4+ count less than 250 (13%), thus assessment of inferiority

- or noninferiority was not able to be established for this risk group.
4. The frequency of adverse events was similar in both study groups, but treatment was more frequently discontinued or held in the 9-month group.
5. Treatment completion was higher in the 1-month treatment group.

## TREATMENT OF DRUG-RESISTANT TB

Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, Mendel CM, Egizi E, Moreira J, Timm J, McHugh TD, Wills GH, Bateson A, Hunt R, Van Niekerk C, Li M, Olugbosi M, Spigelman M; Nix-TB Trial Team.

**Treatment of Highly Drug-Resistant Pulmonary Tuberculosis.** *N Engl J Med.* 2020 Mar 5;382(10):893-902.

### Summary

Treatment of extensively-drug resistant (XDR) TB and MDR-TB is often challenging due to prolonged course lengths, need for parenteral drug administration, toxicities, and poor efficacy. Bedaquiline, pretomanid and linezolid (BPaL) is an all oral regimen for TB treatment that has previously performed favorably in shorter Phase 2 studies. Nix-TB was an open-label, single group study that evaluated the safety and efficacy of 26 weeks of BPaL in patients with XDR-TB and MDR-TB not previously responsive to treatment. The primary endpoint was defined as unfavorable outcome due to bacteriologic or clinical treatment failure or relapse within 6 months of treatment completion. A total of 109 adult and adolescent participants (71 with XDR-TB and 38 with MDR-TB) were enrolled from three sites in South Africa and treated with BPaL for 26-39 weeks. Six months after BPaL completion, unfavorable outcomes were observed in 11 patients (10%), whereas 98 (90%) had a favorable outcome. Favorable outcomes occurred in MDR and XDR patients with similar frequency. Typical linezolid toxicities of peripheral neuropathy and myelosuppression were observed in 81%, and 48% of participants, respectively, and treatment interruptions or dose reductions of linezolid were common.

### Comments

1. Approved in 2012 and 2019, respectively, bedaquiline and pretomanid are the two most recently FDA approved drugs for drug-resistant TB.
2. In this open-label, single group trial, remarkably favorable outcomes in patients with XDR and complicated MDR-TB were observed with 26 weeks of BPaL, an all oral TB regimen.
3. 51% of participants were HIV-infected, with similar efficacy and safety observed in HIV-infected and HIV-uninfected individuals.
4. Due to toxicities, only 15% of participants completed 26 weeks of linezolid at the intended dose (total daily dose of 1200mg) without interruptions or dose reductions.

5. Another clinical trial, ZeNix, which investigates BPAL regimens with lower doses and shorter durations of linezolid, is currently ongoing.

Nunn AJ, Phillips PPJ, Meredith SK, Chiang CY, Conradie F, Dalai D, van Deun A, Dat PT, Lan N, Master I, Mebrahtu T, Meressa D, Moodliar R, Ngubane N, Sanders K, Squire SB, Torrea G, Tsogt B, Rusen ID; STREAM Study Collaborators. **A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis.** *N Engl J Med.* 2019 Mar 28;380(13):1201-1213.

### Summary

While MDR-TB treatment often requires prolonged course lengths, an observational cohort study in Bangladesh of uncomplicated MDR-TB (MDR-TB with retained susceptibility to quinolones and second-line injectables) previously reported remarkable cure rates (87.9%) with a short regimen of only 9 to 11 months (van Deun et al, AJRCCM, 2011). The STREAM study (Standard Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB) was a randomized, phase 3 noninferiority trial that compared the efficacy and safety of a short regimen (9 to 11 months) to a longer regimen (20 months; in accordance to the 2011 WHO guidelines) in adults with rifampin-resistant uncomplicated pulmonary TB. Participants were randomized 2:1 to the shorter vs. longer regimen, and the primary outcome was favorable outcome at 132 weeks. A total of 424 participants were randomized, and 383 were included in the modified-intention-to-treat analysis. The shorter regimen was found to be non-inferior, with a favorable outcome reported in 78.8% (shorter) vs. 79.8% (longer), a 1.0% difference (95% CI: -7.5 to 9.5,  $p=0.02$ ). Adverse events and death occurred at similar frequencies in both groups with grade 3-5 adverse events observed in 48.2% (shorter) vs. 45.4% (longer), and death reported in 8.5% (shorter) and 6.4% (longer).

### Comments

1. In STREAM, the short (9 to 11 month) regimen for uncomplicated rifampin-resistant-TB included 40 weeks of moxifloxacin, clofazimine, ethambutol and pyrazinamide, supplemented by an initial intensive phase (length 16 to 24 weeks, as determined by smear conversion) with isoniazid, prothionamide and intravenous kanamycin.
2. The previously studied Bangladesh regimen and short regimen in STREAM differed only in the substitution of high dose moxifloxacin for gatifloxacin.
3. In this trial, in both the modified intention-to-treat and per-protocol analyses, a short, standardized regimen for treatment of rifampin-resistant TB was non-inferior to a longer regimen at achieving a favorable treatment outcome.
4. Despite shorter duration of drugs exposures, adverse events were not curtailed in the shorter treatment group, which reported a higher frequency of greater cardiac disorders and QT prolongation.
5. The ongoing STREAM trial stage 2 will also investigate the comparators with bedaquiline-containing regimens.

## OTHER ARTICLES OF INTEREST

### MYCOBACTERIAL TREATMENT GUIDELINES

Daley CL, Iaccarino JM, Lange C, Cambau E, Wallace RJ, Andrejak C, Böttger EC, Brozek J, Griffith DE, Guglielmetti L, Huitt GA, Knight SL, Leitman P, Marras TK, Olivier KN, Santin M, Stout JE, Tortoli E, van Ingen J, Wagner D, Winthrop KL. **Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline.** *Clin Infect Dis.* 2020 Aug 14;71(4):905-913.

Nahid P, Mase SR, Migliori GB, Sotgiu G, Bothamley GH, Brozek JL, Cattamanchi A, Cegielski JP, Chen L, Daley CL, Dalton TL, Duarte R, Fregonese F, Horsburgh CR Jr, Ahmad Khan F, Kheir F, Lan Z, Lardizabal A, Lauzardo M, Mangan JM, Marks SM, McKenna L, Menzies D, Mitnick CD, Nilsen DM, Parvez F, Peloquin CA, Raftery A, Schaaf HS, Shah NS, Starke JR, Wilson JW, Wortham JM, Chorba T, Seaworth B. **Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline.** *Am J Respir Crit Care Med.* 2019 Nov 15;200(10):e93-e142.

Sterling TR, Njie G, Zenner D, Cohn DL, Reves R, Ahmed A, Menzies D, Horsburgh CR Jr, Crane CM, Burgos M, LoBue P, Winston CA, Belknap R. **Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020.** *MMWR Recomm Rep.* 2020 Feb 14;69(1):1-11.

### TUBERCULOSIS DIAGNOSTICS

Gupta RK, Turner CT, Venturini C, Esmail H, Rangaka MX, Copas A, Lipman M, Abubakar I, Noursadeghi M. Concise whole blood transcriptional signatures for incipient tuberculosis: a systematic review and patient-level pooled meta-analysis. *Lancet Respir Med.* 2020 Apr;8(4):395-406.

Broger T, Nicol MP, Sigal GB, Gotuzzo E, Zimmer AJ, Surtie S, Caceres-Nakiche T, Mantsoki A, Reipold EI, Székely R, Tsionsky M, van Heerden J, Plisova T, Chikamatsu K, Lowary TL, Pinter A, Mitarai S, Moreau E, Schumacher SG, Denking CM. Diagnostic accuracy of 3 urine lipoarabinomannan tuberculosis assays in HIV-negative outpatients. *J Clin Invest.* 2020 Nov 2;130(11):5756-5764.

### THERAPIES FOR TB PREVENTION

Tait DR, Hatherill M, Van Der Meeren O, Ginsberg AM, Van Brakel E, Salaun B, Scriba TJ, Akite EJ, Ayles HM, Bollaerts A, Demoitié MA, Diacon A, Evans TG, Gillard P, Hellström E, Innes JC, Lempicki M, Malahleha M, Martinson N, Mesia Vela D, Muyoyeta M, Nduba V, Pascal

TG, Tameris M, Thienemann F, Wilkinson RJ, Roman F. **Final Analysis of a Trial of M72/AS01E Vaccine to Prevent Tuberculosis.** *N Engl J Med.* 2019 Dec 19;381(25):2429-2439.

Gupta A, Montepiedra G, Aaron L, Theron G, McCarthy K, Bradford S, Chipato T, Vhembo T, Stranix-Chibanda L, Onyango-Makumbi C, Masheto GR, Violari A, Mmbaga BT, Aurpibul L, Bhosale R, Mave V, Rouzier V, Hesseling A, Shin K, Zimmer B, Costello D, Sterling TR, Chakhtoura N, Jean-Philippe P, Weinberg A; IMPAACT P1078 TB APPRISE Study Team. **Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women.** *N Engl J Med.* 2019 Oct 3;381(14):1333-1346.

Ganmaa D, Uyanga B, Zhou X, Gantsetseg G, Delgerekh B, Enkhmaa D, Khulan D, Ariunzaya S, Sumiya E, Bolortuya B, Yanjmaa J, Enkhtsetseg T, Munkhaya A, Tunsag M, Khudyakov P, Seddon JA, Marais BJ, Batbayar O, Erdenetuya G, Amarsaikhan B, Spiegelman D, Tsoimon J, Martineau AR. **Vitamin D Supplements for Prevention of Tuberculosis Infection and Disease.** *N Engl J Med.* 2020 Jul 23;383(4):359-368.

## TREATMENT OF TB DISEASE

Dooley KE, Miyahara S, von Groote-Bidlingmaier F, Sun X, Hafner R, Rosenkranz SL, Ignatius EH, Nuermberger EL, Moran L, Donahue K, Swindells S, Vanker N, Diacon AH; A5312 Study Team. **Early Bactericidal Activity of Different Isoniazid Doses for Drug Resistant TB (INHindsight): A Randomized Open-label Clinical Trial.** *Am J Respir Crit Care Med.* 2020 Jan 16;201(11):1416-24.

Lan Z, Ahmad N, Baghaei P, Barkane L, Benedetti A, Brode SK, Brust JCM, Campbell JR, Chang VWL, Falzon D, Guglielmetti L, Isaakidis P, Kempker RR, Kipiani M, Kuksa L, Lange C, Laniado-Laborín R, Nahid P, Rodrigues D, Singla R, Udawadia ZF, Menzies D; Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment 2017. **Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis.** *Lancet Respir Med.* 2020 Apr;8(4):383-394.

## NONTUBERCULOUS MYCOBACTERIA

Dedrick RM, Guerrero-Bustamante CA, Garlena RA, Russell DA, Ford K, Harris K, Gilmour KC, Soothill J, Jacobs-Sera D, Schooley RT, Hatfull GF, Spencer H. **Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*.** *Nat Med.* 2019 May;25(5):730-733.

Winthrop KL, Flume PA, Thomson R, Mange KC, Yuen DW, Ciesielska M, Morimoto K, Ruoss SJ, Codecasa LR, Yim JJ, Marras TK, van Ingen J, Wallace RJ Jr, Brown-Elliott BA, Coulter C, Griffith DE; INS-312 Study Group. **Amikacin Liposome Inhalation Suspension for MAC Lung Disease: A 12-Month Open-Label Extension Study.** *Ann Am Thorac Soc.* 2020 Dec 16.

Phillips RO, Robert J, Abass KM, Thompson W, Sarfo FS, Wilson T, Sarpong G, Gateau T, Chauty A, Omollo R, Ochieng Otieno M, Egondi TW, Ampadu EO, Agossadou D, Marion E, Ganlonon L, Wansbrough-Jones M, Grosset J, Macdonald JM, Treadwell T, Saunderson P, Paintsil A, Lehman L, Frimpong M, Sarpong NF, Saizonou R, Tiendrebeogo A, Ohene SA, Stienstra Y, Asiedu KB, van der Werf TS; study team. **Rifampicin and clarithromycin (extended release) versus rifampicin and streptomycin for limited Buruli ulcer lesions: a randomised, open-label, non-inferiority phase 3 trial.** *Lancet.* 2020 Apr 18;395(10232):1259-1267.

Kim HJ, Kwak N, Hong H, Kang N, Im Y, Jhun BW, Yim JJ. **BACES Score for Predicting Mortality in Nontuberculous Mycobacterial Pulmonary Disease.** *Am J Respir Crit Care Med.* 2021 Jan 15;203(2):230-236.

Namkoong H, Omae Y, Asakura T, Ishii M, Suzuki S, Morimoto K, Kawai Y, Emoto K, Oler AJ, Szymanski EP, Yoshida M, Matsuda S, Yagi K, Hase I, Nishimura T, Sasaki Y, Asami T, Shiomi T, Matsubara H, Shimada H, Hamamoto J, Jhun BW, Kim SY, Huh HJ, Won HH, Ato M, Kosaki K, Betsuyaku T, Fukunaga K, Kurashima A, Tettelin H, Yanai H, Mahasirimongkol S, Olivier KN, Hoshino Y, Koh WJ, Holland SM, Tokunaga K, Hasegawa N. **Genome-wide association study in patients with pulmonary *Mycobacterium avium* complex disease.** *Eur Respir J.* 2021 Feb 4:1902269.

## NOVEL THERAPEUTICS FOR INFECTION

Katherine B. Hisert, MD, PhD

National Jewish Health  
Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine  
Denver, CO

## NOVEL THERAPIES TARGETING IRON DEPENDENT PATHOGENS

Wunderink RG, Matsunaga Y, Ariyasu M, Clevenbergh P, Echols R, Kaye KS, Kollef M, Menon A, Pogue JM, Schorr AF, Timset J, Zeitlinger M, Nagata TD. **Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial.** *Lancet Infect Dis.* 2021 Feb;21(2):213-225.

## Summary

Cefiderocol, a first-in-class, novel anti-bacterial agent composed of a siderophore conjugated to a cephalosporin, uses bacteria's iron uptake pathways to deliver high concentrations of a cephalosporin directly into the bacterial cytoplasm. Cefiderocol thus demonstrates efficacy against iron-dependent bacteria, specifically many Gram-negative rods, including many strains with mechanisms of multi-drug resistance (MDR). The FDA initially approved cefiderocol for the treatment of complicated urinary tract infections, but clinicians have been eager to utilize cefiderocol for treatment of other complex infections with MDR organisms including hospital-acquired bacterial pneumonia (HABP) and ventilator associated pneumonia (VAP). This article summarizes findings off the APEKS-NP study, which led the FDA to approve cefiderocol for HABP and VAP in late 2020. APEKS-NP was a randomized, double blinded, phase 3 non-inferiority trial of cefiderocol vs high dose, extended infusion meropenem for adults with nosocomial pneumonia. The study was carried out at 76 centers in 17 countries in Europe, Asia, and the USA, with a primary endpoint of all-cause mortality at day 14 in the modified intention to treat population. The researchers found that cefiderocol was non-inferior to high dose, extended infusion meropenem, with similar tolerability and safety.

## Comments

1. Most participants in this study were severely ill with ~70% of subjects in the intensive care unit and the majority of participants culturing *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* as their baseline organisms.
2. Subgroup analyses of all-cause mortality at days 14 and 28 suggested that cefiderocol's efficacy and non-inferiority

- extended across subgroups investigated, including age, renal function, clinical diagnosis, ventilation status, disease severity, APACHE II score, baseline pathogens, and pathogen groups.
3. This study is amplified by a parallel study reported in the same edition of *Lancet Infectious Diseases*, CREDIBLE-CR, which was a randomized, open-label, multi-center, parallel-group, pathogen-focused, descriptive, phase 3 study which investigated the safety and efficacy of Cefiderocol in nosocomial pneumonia, bloodstream infections, or complicated urinary tract infections (UTI) with evidence of a carbapenem-resistant Gram-negative pathogen.
  4. Ongoing clinical trials using intravenous and inhaled gallium nitrate for treatment of iron dependent pathogens, including Gram-negative bacteria, nontuberculous *Mycobacterium*, and fungi, further highlight the potential for leveraging microbial iron acquisition and dependence as novel strategies for infection eradication or control.

## PHAGE THERAPY FOR RECALCITRANT CHRONIC INFECTIONS

Dedrick RM, Guerrero-Bustamante CA, Garlena RA, Russell DA, Ford K, Harris K, Gilmour KC, Soothill J, Jacobs-Sera D, Schooley RT, Hatfull GF, Spencer H. **Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*.** *Nat Med.* 2019 May;25(5):730-733.

## Summary

Infections caused by slow growing organisms, such as nontuberculous mycobacteria (NTM), as well as those caused by multidrug resistance organisms, are especially difficult to treat, often requiring multiple antimicrobial agents for weeks to months duration. Effective treatment can be limited by patient intolerance of optimal drug regimens. This case report describes intravenous administration of mycobacteriophages as salvage therapy for a patient with disseminated NTM infection who was unable to tolerate a conventional antibiotic regimen. The patient was a 15-year-old female with severe cystic fibrosis lung disease complicated by airway infection with *Pseudomonas aeruginosa* and *Mycobacterium abscessus* subspecies *massiliense* who underwent uncomplicated bilateral orthotopic lung transplant. Following transplant, she received immunosuppression and anti-NTM antibiotics; however, antibiotics had to be discontinued due to severe side effects. Shortly thereafter, the patient developed disseminated *M. abscessus* infection, with

lesions in her lung, liver, bone (sternal wound), and skin. Screening of a panel of phages identified 3 phages that specifically lysed the patient's *M. abscessus* isolate. This phage cocktail was delivered intravenously twice a day, and by 6 weeks later, the patient demonstrated marked clinical improvement, as well as resolution of lesions seen previously on PET scan.

### Comments

1. This case report highlights the potential efficacy and tolerability of phage therapy when conventional antibiotics are either no longer effective or no longer tolerated.
2. There are approximately 30 clinical trials registered through [clinicaltrials.gov](https://clinicaltrials.gov) to assess safety and efficacy of phage therapy, predominantly for treatment of lung and urinary tract infections, to alter the gut microbiome, as well as to treat infections of wounds, burns, and prosthetic joints.
3. Although phage therapy was effective in this patient, it remains unclear if intravenous phage can reach and lyse their targets if bacteria are intracellular, if bacteria exist in biofilms, or if the lung is congested by viscous mucous and immune debris.
4. With long term phage therapy, efficacy may be limited if the patient develops neutralizing antibodies to the phage, or if bacteria mutate receptors such that the phage cannot longer recognize or bind the bacterial surface.

## THERAPIES THAT SHIFT THE IMMUNE RESPONSE TO BETTER TARGET THE PATHOGEN

Tsai M, Thauland TJ, Huang AY, Bun C, Fitzwater S, Krogstad P, Douine ED, Nelwson SF, Lee H, Garcia-Lloret MI, Butte MJ. **Disseminated coccidioidomycosis treated with interferon- $\gamma$  and dupilumab.** *N Engl J Med.* 2020 June 11; 382(24):2337-2343.

### Summary

The observation that infectious diseases often have highly variable manifestations supports the hypothesis that differences in host immune responses may contribute to the heterogeneity of disease pathophysiology. Immunomodulation has thus been proposed as an adjunctive anti-microbial strategy for a number of diseases. This case report describes effective use of immunomodulation to treat recalcitrant, disseminated coccidioidomycosis in a young child. The child had no known illnesses or common immunodeficiencies; however, conventional antifungals did not halt progression of disease. Phenotyping of the child's immune cells revealed an inappropriate skewing of his CD4+ T cells to a Th2 phenotype, whereas a robust Th1 response is required to clear coccidioidomycosis. DNA analyses revealed no known mutations in genes involved in the IL-12 or IFN- $\gamma$  pathways. *In vitro* experiments demonstrated that exogenous IFN- $\gamma$  could shift the child's CD4+ T cells to a Th1 phenotype, and thus the child's anti-fungal regimen was thus augmented with subcutaneous IFN- $\gamma$ . Disease slowed, but unfortunately continued to progress. The clinical team then administered dupilumab, a monoclonal

antibody that blocks the alpha chain common to the IL-4 and IL-13 receptors. This caused a shift to a predominant Th1 response. The child showed dramatic clinical improvement and ultimately disease resolution.

### Comments

1. Although it is highly labor intensive to phenotype the immune cells of a patient, this case report reveals that personalized medicine can identify unusual immune abnormalities that can be corrected with immune modulating medications.
2. This case report highlights the importance of not only stimulating cells toward the correct immune phenotype (in this case, with IFN gamma), but also blocking inappropriate immune signals (in this case, IL-4) that may be shifting cells towards a non-curative or non-resolving phenotype.
3. Many immune modulating medications are already FDA approved for the treatment of various rheumatologic, allergic, and immunologic diseases, and thus many therapeutic options are potentially available to shift the immune response to better fight infectious diseases.
4. Immune modulation is being assessed as therapy for a number of pathogens and infectious diseases that persist despite multiple anti-microbials agents, including sepsis and infections with mycobacterial species.

## ANTIFUNGAL THERAPIES

Alkhazraji S, Gebremariam T, Alqarihi A, Gu Y, Mamouei Z, Singh S, Wiederhold N, Shaw KJ, Ibrahim AS.

**Fosmanogepix (APX001) is effective in the treatment of immunocompromised mice infected with invasive pulmonary Scedosporiosis or disseminated Fusariosis.** *Antimicrob Agents Chemother.* 2020 Feb 21; 64(3): e01735-19.

### Summary

There remains a need for additional antifungal therapies, both for better treatment of invasive fungi seen in immunocompromised individuals, and because many currently available antifungal agents have numerous drug interactions and limiting side effects. Fortunately, there are a number of new compounds in the clinical trial pipeline, many of which are first-in-class. This article describes pre-clinical studies in mice using fosmanogepix (APX001), a first-in-class drug which targets the fungal Gwt1 enzyme that is required for localization of GPI-anchored mannoproteins. Mice were immunocompromised with cyclophosphamide and cortisone, and then infected intratracheally with *Scedosporium apiospermum* or intravenously with *Fusarium solani*. Oral treatment with different doses of fosmanogepix, amphotericin, voriconazole or posaconazole was initiated 16 hours after infection and maintained for 7-8 days. Survival of mice, as well as tissue fungal burden (lung, kidney, brain) and tissue histology (kidney, brain) were then evaluated. Fosmanogepix was found to be as effective, or more effective, than the currently prescribed antifungal agents at mitigating tissue damage, attenuating tissue fungal burden, and improving survival



### Comments

1. Fosmanogepix was administered with 1-aminobenzotriazole (ABT) to enhance its serum half-life, resulting in exposures of ~200 to 280 microgram x h/ml, which are equivalent to exposures achieved in human phase 1 clinical trials
2. The level of immunosuppression achieved in this study ensured pancytopenia for at least 9 days (as opposed to earlier studies of fosmanogepix in which neutrophil nadir occurred on the day of infection, and then neutrophil counts recovered.)
3. Fosmanogepix has shown efficacy in several other mouse and rabbit models of fungal infections, including intra-abdominal candidiasis, Candida endophthalmitis and meningoencephalitis, and *Rhizopus arrhizus* pulmonary mucormycosis
4. A phase 2, open-label clinical trial is ongoing to evaluate the safety and efficacy of fosmanogepix in the treatment of patients with invasive mold infections caused by aspergillus species or rare molds.

### COVID THERAPIES: SOME NOVEL, SOME FAMILIAR

Wahl A, Gralinski LE, Johnson CE, Yao W, Kovarova M, Dinnon KH 3rd, Liu H, Madden VJ, Krzystek HM, De C, White KK, Gully K, Shafer A, Zaman T, Leist SR, Grant PO, Bluemling GR, Kolykhalov AA, Natchus MG, Askin FB, Painter G, Browne EP, Jones CD, Pickles EJ, Baric RS, Garcia JV. **SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801.** *Nature*. 2021 Mar; 591(7850):451-457.

#### Summary

Therapeutic strategies aimed at preventing severe COVID19 disease have focused on limiting the ability of the virus to replicate and dampening the exaggerated immune response the results in ARDS. There have been several promising new therapies in the first category, including anti-viral agents and monoclonal antibodies. The article by Wahl et al demonstrates that a novel ribonucleoside analog prodrug EIDD-2801, also known as molnupiravir, exerts antiviral effects against several pulmonary coronavirus in vivo. The authors used immunodeficient mice implanted with human lung tissue to create a model in which mice could be infected with SARS-CoV, MERS-CoV, and SARS-CoV-2, as well as two SARS-like bat coronaviruses that have potential to emerge as human pathogens. This model replicates most features of COVID-19 disease in human lungs. EIDD-2801, given prophylactically (before infection) or therapeutically (after infection), decreased viral titers and reduced lung damage. Clinical trials have demonstrated safety of molnupiravir in humans, and an ongoing phase 2a randomized, double blind, placebo-controlled trial recently found that molnupiravir could reduce time to viral PCR negativity when given therapeutically to adults with signs or symptoms of COVID19 within 7 days of confirmed SARS-CoV-2 infections.

### Comments

1. Molnupiravir appears to exert antiviral activity against a variety of coronavirus isolates, thus possibly having relevance not only in the current pandemic, but potentially for future novel viral threats.
2. The mouse data suggest multiple potential applications of this oral, easily administered agent in humans: both prophylactic use, as well as therapeutic use for those already infected.
3. Although early, clinical trial data suggest that molnupiravir may decrease viral shedding and transmission, as well as possibly prevent development of severe disease, when given to individuals with mild COVID19 disease.
4. Molnupiravir is one of many novel agents in development that aims to limit the replication of virus in the host, and the emerging data from a number of studies suggest that we may soon have multiple options for limiting severe pulmonary disease caused by respiratory viruses.

### OTHER ARTICLES OF INTEREST

#### NOVEL THERAPIES TARGETING IRON DEPENDENT PATHOGENS

Parsels KA, Mastro KA, Steele JM, Thomas SJ, Kufel WC. **Cefiderocol: a novel siderophore cephalosporin for multidrug-resistant Gram-negative bacterial infections.** *J Antimicrob Chemother*. 2021, Feb 3.

Goss CH, Kaneko Y, Khuu L, Anderson GD, Ravishankar S, Aitken ML, Lechtzin N, Zhou G, Czyn DM, McLean K, Olakanmi O, Shuman HA, Teresi M, Wilhelm E, Caldwell E, Salipante SJ, Hornick DB, Siehnel RJ, Becker L, Britigan BE, Singh PK. **Gallium disrupts bacterial iron metabolism and has therapeutic effects in mice and humans with lung infections.** *Sci Transl Med*. 2018 Sep 26;10(460).

Bastos RW, Rossato L, Valero C, Lagrou K, Colombo AL, Goldman GH. **Potential of gallium as an antifungal agent.** *Front Cell Infect Microbiol*. 2019 Dec 11; 9:414.

Parquet MDC, Savage KA, Allan DS, Ang MTC, Chen W, Logan SM, Holbein BE. **Antibiotic-resistant *Acinetobacter baumannii* is susceptible to the novel iron-sequestering anti-infective DIBI in vitro and in experimental pneumonia in mice.** *Antimicrob Agents Chemother*. 2019 Aug 23; 63(9): e00855-19.

#### PHAGE THERAPY FOR RECALCITRANT CHRONIC INFECTIONS

Kakasis A, Panitsa G. **Bacteriophage therapy as an alternative treatment of human infections. A comprehensive review.** *Int J Antimicrob Agents*. 2019 Jan; 53(1):16-21.

Chan BK, Stanley G, Modak M, Koff JL, Turner PE. **Bacteriophage therapy for infections in CF.** *Pediatr Pulmonol.* 2021 Feb;56 Suppl 1: S4-S9.

Gilbey T, Ho J, Cooley LA, Fabijan AP, Iredell JR. **Adjunctive bacteriophage therapy for prosthetic valve endocarditis due to *Staphylococcus aureus*.** *Med J Aust.* 2019 Aug;211(3):142-143

Engeman E, Freyberger HE, Corey BW, Ward AM, He Y, Nikolich MP, Filippov AA, Tyner SD, Jacobs AC. **Synergistic killing and re-sensitization of *Pseudomonas aeruginosa* to antibiotics by phage-antibiotic combination treatment.** *Pharmaceuticals (Basel).* 2021 Feb 25; 14(3): 184.

## THERAPIES THAT SHIFT THE IMMUNE RESPONSE TO BETTER TARGET THE PATHOGEN

Waterer G. **Beyond antibiotics for pulmonary nontuberculous mycobacterial disease.** *Curr Opin Pulm Med.* 2020 May; 26(3): 260-266.

Benmerzoug S, Marinho FV, Rose S, Mackowiak C, Gosset D, Sedda D, Poisson E, Uyttenhove C, Van Snick J, Jacobs M, Garcia I, Ryffel B, Quesniaux VFJ. **GM-CSF targeted immunomodulation affects host response to *M. tuberculosis* infection.** *Sci Rep.* 2018 June 5; 8(1): 8652.

Hotchkiss RS, Opal SM. **Activating immunity to fight a foe – a new path.** *N Engl J Med.* 2020 Mar 26;382(13):1270-1272.

## ANTIFUNGAL THERAPIES

Rauseo AM, Coler-Reilly A, Larson L, Spec A. **Hope on the horizon: novel fungal treatments in development.** *Open Forum Infect Dis.* 2020 Jan 12; 7(2).

Shaw KJ, Ibrahim AS. **Fosmanogepix: a review of the first-in-class broad spectrum agent for the treatment of invasive fungal infections.** *J Fungi (Basel).* 2020 Oct 22; 6(4): 239.

## COVID THERAPIES: SOME NOVEL, SOME FAMILIAR

Tuccori M, Ferraro S, Convertino I, Cappello E, Valdiserra G, Blandizzi C, Maggi F, Focosi D. **Anti-SARS-CoV-2 neutralizing monoclonal antibodies: clinical pipeline.** *MAbs.* Jan-Dec 2020; 12(1):1854149.

Painter WP, Holman W, Bush JA, Almazedi F, Malik H, Eraut NCJE, Morin MH, Szewczyk LJ, Painter GR. **Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2.** *Antimicrob Agents Chemother.* 2021 Mar 1; AAC.02428-20.

## COGNITIVE AND NEUROLOGIC EFFECTS OF CRITICAL ILLNESS

Aluko A. Hope, MD, MSCE

Oregon Health and Sciences University  
Department of Medicine, Division of Pulmonary/Critical Care  
Portland, Oregon

### SEDATION IN ICU

Olsen HT, Nedergaard HK, Strøm T, Oxlund J, Wian KA, Ytrebø LM, Kroken BA, Chew M, Korkmaz S, Lauridsen JT, Toft P. **Nonsedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients.** *N Engl J Med.* 2020 Mar 19;382(12):1103-1111.

#### Summary

This clinical trial aimed to determine whether, in adults with acute respiratory failure requiring invasive mechanical ventilation, a strategy of no-sedation would be associated with improved survival when compared with light sedation & daily sedation interruption. 710 adults across eight centers in Denmark, Norway and Sweden were randomized. Patients who had medical conditions that were likely to need continuous sedation, including those patients with severe hypoxemia, were excluded. The primary outcome of interest was 90-day all-cause mortality and they explored multiple secondary outcomes. Although 38% of the non-sedation group were treated with a sedative during their ICU stay, on average the patients in the no-sedation group were more arousable and lightly sedated on each ICU day 1-7. 90-day mortality (42.4% in the non-sedation group and 37.0% in the sedation group,  $p=0.65$ ) was not statistically significantly different between the two groups and there were few notable differences in secondary outcomes such as time on mechanical ventilation, length of ICU or hospital stay. The non-sedation group did have 1 more day free of delirium or coma on average and had fewer thromboembolic events than the sedation group.

#### Comments

1. This was a large clinical trial during which the investigators were not blinded to treatment allocation.
2. Recruitment for the trial took over 3.5 years and 54% of the screened adults with acute respiratory failure were not eligible for inclusion into the study.
3. The randomized sample in this trial appears older than most other sedation trials in the ICU given that the median age of the no-sedation and sedation groups were 72 and 70, respectively.
4. Importantly, there were no clinical or statistically significant differences noted in adverse event with either sedation strategy.
5. Future analyses from this larger study should explore the long-term cognitive impact of these sedation strategies.

### ACUTE BRAIN DYSFUNCTION AND SEVERE SARS COV-2

Pun BT, Badenes R, Heras La Calle G, Orun OM, Chen W, Raman R, Simpson BK, Wilson-Linville S, Hinojal Olmedillo B, Vallejo de la Cueva A, van der Jagt M, Navarro Casado R, Leal Sanz P, Orhun G, Ferrer Gómez C, Núñez Vázquez K, Piñero Otero P, Taccone FS, Gallego Curto E, Caricato A, Woien H, Lacave G, O'Neal HR Jr, Peterson SJ, Brummel NE, Girard TD, Ely EW, Pandharipande PP; COVID-19 Intensive Care International Study Group. **Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study.** *Lancet Respir Med.* 2021 Mar;9(3):239-250.

#### Summary

This study aimed to examine the prevalence and risk factors of acute brain dysfunction (delirium and/or coma) in adults who were critically ill due to infection from SARS CoV-2. Relevant risk factors of interest included patient level factors as well as ICU care practices previously associated with improvement in acute brain dysfunction. 69 sites from around the world (50% of which were in Spain, 94% were academic teaching hospitals), all of whom were routinely assessing for delirium in the ICU, participated in this study by providing de-identified data on patient demographics, sedation, ICU care processes and short-term patient outcomes. In this cohort of severely ill adults with COVID-19 hospitalized before April 28th, 2020, there were high rates of coma (81.6%) and delirium (54.9%) and prolonged duration of acute brain dysfunction median (interquartile range) days were 12.0 (7.0-18.0). Across these sites, there were low rates of adherences to standard of care practices such as spontaneous awakening trials (23.8%), spontaneous breathing (22.8%) and avoidance of benzodiazepines (52.4%). Importantly, despite low rates of in-person or virtual family visits (17%), family visitation was associated with lower risk of transitioning to delirium the next day Odds Ratio 0.73 (95% Confidence Interval 0.63-0.84).

#### Comments

1. This is the largest prospective cohort study to capture acute brain dysfunction in adults critically ill with SARS CoV-2 during the early part of the 2020 pandemic year.
2. The prevalence and duration of acute brain dysfunction in this cohort of adults with severe COVID-19 were much higher than seen in recent observational and treatment interventions in non-COVID-19 critically ill adults prior to the pandemic.

3. During this early phase of the pandemic, the low rates of compliance with standard of care ABCDEF bundle may have contributed to the high prevalence of acute brain dysfunction seen in these sites.
4. Since acute brain dysfunction is an important predictor of long-term cognitive impairment after acute illness across multiple studies, research on the long-term impact of severe illness from SARS-CoV-2 on cognition will be a pressing public health challenge.
5. Strategies to facilitate improved compliance with sedation and family engagement care practices in severely ill adults with SARS CoV-1 may be worth testing towards improving long term outcomes in adult survivors of SARS CoV2.

## POST-ACUTE SEQUELAE OF SARSCOV-2 INFECTION

The Writing Committee for the COMEBAC Study Group. **Four-Month Clinical Status of a Cohort of Patients After Hospitalization for COVID-19.** *JAMA*. Published online March 17, 2021.

### Summary

These investigators from one large tertiary care university hospital in France aimed to describe the clinical status in adults who were hospitalized with severe SARS CoV-2 4-months after hospital discharge. They offered telephone symptom assessment and invited those patients who were treated in an Intensive Care Unit or who reported at least 1 sign or symptom consistent with post-acute sequelae of COVID-19 for an in-person detailed assessment. They completed telephone surveys in 478 of 834 eligible survivors and then consented 177 of the 294 eligible survivors for a clinic assessment. 51% of the survivors evaluated via telephone reported at least 1 new post-COVID-19 symptom. The most common symptoms were fatigue (31%), cognitive difficulties (21%), and dyspnea (16%). In addition, neurologic and cognitive assessments were performed as part of the detailed in-person assessment and 38.4% of adults assessed met criteria for cognitive impairment.

### Comments

1. The study suggests that both subjective cognitive difficulties and objective cognitive impairment may be prevalent in survivors of severe SARS CoV-2 infection
2. The study is limited by the fact that there were no data available on the patients' pre-COVID-19 cognitive function.
3. Since only about 57% of the eligible survivors were consented for telephone survey, enrolled participants may not be representative of all adult survivors of severe SARS CoV-2.
4. Since there is no comparison group of adults not infected with SARS CoV2, these data cannot disentangle post COVID-19 effects from post-hospitalization and pandemic effects.
5. The after-care infra-structure in hospital systems are well suited to provide important insights into the post-acute sequelae of COVID-19.

## SEDATION IN ACUTE RESPIRATORY FAILURE

Hughes CG, Mailloux PT, Devlin JW, Swan JT, Sanders RD, Anzueto A, Jackson JC, Hoskins AS, Pun BT, Orun OM, Raman R, Stollings JL, Kiehl AL, Duprey MS, Bui LN, O'Neal HR Jr, Snyder A, Gropper MA, Guntupalli KK, Stashenko GJ, Patel MB, Brummel NE, Girard TD, Dittus RS, Bernard GR, Ely EW, Pandharipande PP; MENDS2 Study Investigators. **Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis.** *N Engl J Med*. 2021

### Summary

In a multicenter, double-blind trial, these investigators randomly assigned mechanically ventilated adults with sepsis to receive dexmedetomidine or propofol, with doses adjusted by bedside nurses to achieve light sedation according to the Richmond Agitation–Sedation Scale. The primary end point was number days alive without delirium or coma over the 14-day intervention period. Secondary end points included ventilator-free days at 28 days, 90-day mortality and global cognition assessed via Telephone Interview for Cognitive Status (TICS) at 6-months. They randomized 432 adults, ensured a high rate of compliance in the ABCDEF bundle of care practices across both treatment groups. The median (interquartile range) of the RASS score as assessed by the research team was  $-2$  ( $-3$  to  $-1$ .) while patients were receiving a trial drug. They found no statistically significant differences in the delirium-coma free days between the two groups (adjusted median in dexmedetomidine group was 10.7 days (95% confidence interval 8.5 to 12.5) and in the propofol group 10.8 days (95% CI, 8.7 to 12.6)  $P=0.79$ ). About 25% of the survivors had TICS score consistent with cognitive impairment and there were no differences in this outcome by treatment assignment.

### Comments

1. An important strength of this study was that the study protocol attempted to keep the allocation blinded from the investigators; Whether this was achieved or not is not highlighted.
2. The study had difficulty recruiting patients; the multiple exclusions along with the high rate of refusal may suggest that the study population is not very generalizable to all critically ill adults with sepsis requiring invasive mechanical ventilation.
3. A strength of this trial is the high level of compliance with the ABCDEF bundle which are clinical interventions that have been associated with morbidity and mortality outcomes.
4. The fact that there were no differences in 6-month cognitive outcome by treatment group may suggest that the target sedation during hospital care may be more important than what sedative agent is used for explaining long-term cognitive impairment in acute illness survivors.

## CRITICAL CARE

Kathryn A. Hibbert, MD

Massachusetts General Hospital and Harvard Medical School  
Division of Pulmonary and Critical and Department of Medicine  
Boston, MA

## OXYGEN TARGETS IN THE ICU

Schjorring OL, Klitgaard TL, Perner A, Wetterslev J, Lange T, Siegemund M, Backlund M, Keus F, Laake JH, Morgan M, Thormar KM, Rosborg SA, Bisgaard J, Erntgaard AES, Lynnerup A-SH, Pedersen RL, Crescioli E, Gielstrup TC, Behzadi MT, Poulsen LM, Estrup S, Laigaard JP, Andersen C, Mortensen CB, Brand BA, White J, Jarnvig IL, Moller MH, Quist L, Bestle MH, Schonemann-Lund M, Kamper MK, Hindborg M, Hollinger A, Gebhard CE, Zellweger N, Meyhoff CS, Jhort M, Bech LK, Grofte, Bundgaard H, Ostergaard LHM, Thyo MS, Hildebrandt T, Uslu B, Solling CG, Moller-Nielsen N, Brochner AC, Borup M, Okkonen M, Dieperink W, Pedersen UG, Andreasen AS, Buus L, Aslam TN, Winding RR, Schefold JC, Thorup SB, Iversen SA, Engstrom J, Kjaer M-BN, Rasmussen BS, for the HOT-ICU Investigators. **Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure.** *New England Journal of Medicine.* <https://doi.org/10.1056/NEJMoa2032510>

## Summary

There has been a longstanding interest in the optimal target for oxygenation in critically ill patients. Prior studies have both shown a potential harm from higher oxygenation targets, putatively due to increased oxidative stress and lung injury, and suggested a harm from lower oxygenation targets due to decreased oxygen delivery and tissue ischemia. This multicenter international trial randomized 2928 patients with hypoxemic respiratory failure to a higher oxygen target (PaO<sub>2</sub> 90mmHg) or a lower oxygen target (PaO<sub>2</sub> 60mmHg). 90-day mortality was high in the study but was comparable between the two groups (42.4% in the higher-oxygenation group and 42.9% in the lower-oxygenation group, p = 0.64). Similarly, there were not significant differences in the secondary outcomes of including ischemic events, percentage of life support free days, and percentage of days that patients were alive after hospital discharge at 90 day follow up. Notably, there was good separation between the groups by PaO<sub>2</sub>, FiO<sub>2</sub> delivered and SaO<sub>2</sub>.

## Comments

1. This study contributes to a growing but conflicting literature on oxygen targets in critically ill patients and demonstrated no mortality benefit and no increased incidence of ischemic events in the lower-oxygenation group.

2. Unlike other recent trials of oxygen targets in the ICU, this study included only patients with hypoxemic respiratory failure and included patients who were not mechanically ventilated.
3. The mortality in this trial was high compared to some other trials, which may have been due to the high proportion of patients with medical reasons for admission and the severity of their respiratory failure, and which may limit the applicability of these findings to lower risk populations.
4. The optimal oxygen target for an individual patient, and for critically ill patients as a cohort, remains unknown but this very large trial provides some reassurance that lower oxygenation targets are safe.

## SEDATION IN THE ICU

Hughes CG, Mailloux PT, Devlin JW, Swan JT, Sanders RD, Anzueto A, Jackson JC, Hoskins AS, Pun BT, Orun OM, Raman R, Stollings JL, Kiehl AL, Duprey MS, Bui LN, O'Neal HR, Snyder A, Gropper MA, Guntupalli KK, Stashenko GJ, Patel MB, Brummel NE, Girard TD, Dittus RS, Bernard GR, Ely EW, Pandharipande PP for the MENDS2 Study Investigators. **Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis.** *N Engl J Med* 2021, Advance Online Publication DOI: 10.1056/NEJMoa2024922

## Summary

The Society of Critical Care medicine recommends sedation with either dexmedetomidine or propofol to achieve light levels of sedation in mechanically ventilated patients who require continuous sedation. There has been much interest in dexmedetomidine's unique anti-inflammatory properties, and trials comparing dexmedetomidine with benzodiazepines that showed an improvement in outcomes including delirium and duration of mechanical ventilation in the dexmedetomidine group. This randomized, multi-center noninferiority trial compared propofol and dexmedetomidine in 432 patients with suspected or known infections who were mechanically ventilated. There was no difference in days alive without delirium or coma within the 14-day intervention period between the propofol and dexmedetomidine groups (adjusted median 10.7 days, 95% CI 8.5-12.5 versus 10.8 days, 95% CI 8.7-12.6; p = 0.79). There were also no differences between the propofol or dexmedetomidine groups in number of ventilator-free days at 28 days (adjusted median 24 versus 23.7; OR 0.98, 95 CI 0.63-

1.51) or death at 90 days (39% versus 38%; HR 1.06, 95%CI 0.74-1.52). There were no meaningful differences in other secondary endpoints, though it was notable that across both groups there was clinically important cognitive dysfunction in approximately 25% of patients.

### Comments

1. This randomized trial supports the current guidelines that recommend either dexmedetomidine or propofol for critically ill patients requiring continuous sedation.
2. Although there are some data to support a uniquely anti-inflammatory effect of dexmedetomidine, there was no benefit in this cohort of patients with sepsis, who would be expected to benefit most compared to other critically ill patients.
3. Choice of sedative does not appear to modify outcomes, including clinically important cognitive outcomes, and more research is needed on mitigation strategies to improve post-critical care quality of life.

## ACUTE KIDNEY INJURY IN THE ICU

The STARTT-AKI Investigators for the Canadian Critical Care Trials Group, The Australian and New Zealand Clinical Trials Group, the United Kingdom Critical Care Research Group, The Canadian Nephrology Trials Network, and the Irish Critical Care Trials Group. **Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury.** *N Engl J Med* 2020; 383:240-251

DOI: 10.1056/NEJMoa2000741

### Summary

Although acute kidney injury is common in critically ill patients, the optimal timing of renal-replacement therapy initiation is unknown and one prior study suggested a mortality benefit with an early initiation strategy. The timing of initiation may not only be clinically important but also has a potential impact on the cost of critical care, staffing requirements, and ICU capacity. This large multi-center international trial of 3021 patients randomized critically ill patients with severe AKI to accelerated initiation (within 12 hours of randomization) versus standard initiation, which was only recommended if there was an acute indication for renal-replacement including metabolic disarray, volume overload causing hypoxemia or persistent AKI for more than 72 hours. Importantly, patients were not included in the trial if there was not clinical equipoise about timing of renal-replacement therapy, e.g. if the patient had an acute indication for renal-replacement. There was no significant difference in mortality between the groups (43.9% in the accelerated group versus 43.7% in the standard group, RR 1.0 and 95% CI 0.93-1.09; adjusted odds ratio 1.05 and 95% CI 0.90 to 1.23). There was an increased incidence of adverse events (especially hypotension and hypophosphatemia) in the accelerated group but no difference in serious adverse events. Notably, more patients in the accelerated group were started on renal replacement therapy than in the standard group (96.8%

versus 61.8%) and a greater proportion of patients in the accelerated group remained on renal-replacement therapy at 90 days (10.4% versus 6%, RR 1.74 and 95% CI 1.24-2.43).

### Comments

1. This large trial examining timing of initiation of renal replacement therapy did not show any benefit to early (accelerated) initiation in critically ill patients with severe acute kidney injury.
2. Because patients were not included in the trial if there was not clinical equipoise, these results are not applicable to critically ill patients with an acute indication for renal replacement therapy.
3. A significant proportion of patients in the standard therapy group did not ultimately require renal-replacement therapy, suggesting that a standard approach results in less resource utilization and may expose patients to fewer interventions.
4. Although there was not a significant difference in serious adverse events or major adverse kidney events between the two groups, a greater proportion of patients in the accelerated group were on renal-replacement therapy at 90 days compared to the standard group, raising a concern about renal-replacement associated kidney injury and / or delay in return of kidney function.

## DISPARITIES IN CRITICAL CARE

Ashana DC, Anesi GL, Liu VX, Escobar GJ, Chesley C, Eneanya ND, Weissman GE, Miller WD, Harhay MO, Halpern SD. **Equitably Allocating Resources During Crises: Racial Differences in Mortality Prediction Models.** *Am J Respir Crit Care Med* 2021, Online Publication Ahead of Print <https://doi.org/10.1164/rccm.202012-4383OC>

### Summary

Clinical illness severity scores have long been used not only to risk stratify individual patients but also in clinical trial design and development of guidelines for resource allocation in public health crises such as the ongoing COVID-19 pandemic. Recently, there is increasing recognition of the degree to which systemic inequities based on race are incorporated into medical care, including in predictive tools such as estimated glomerular filtration rate. This retrospective cohort study examined the impact of race on Sequential Organ Failure Assessment (SOFA) and Laboratory-based Acute Physiology Score, version 2 (LAPS2) scores in 113,158 patients across 27 hospitals who were diagnosed with sepsis or acute respiratory failure. In this patient cohort, of which 24.4% were Black, LAPS2 demonstrated higher discrimination for in-hospital mortality than did SOFA (AUC = 0.76; 95% CI 0.76-0.77 versus AUC = 0.68; 95% CI 0.68-0.69) as well as better calibration. However, both scores underestimated in-hospital mortality for White patients and over-estimated in-hospital mortality for Black patients. Based on one model of crisis standards of care, this resulted in 81.6% of Black patients being placed in a

lower priority crisis standard of care category and 9.5% of all Black patients being excluded from receiving the highest prioritization. Excluding creatinine from the SOFA scored reduced racial miscalibration.

### Comments

1. In this large, racially diverse cohort of patients with sepsis and acute respiratory failure, SOFA was a poor predictor of mortality and both SOFA and LAPS2 underestimated mortality in White patients and overestimated mortality in Black patients.
2. These data contribute to the growing understanding that creatinine may not be sufficiently accurate in understanding glomerular filtration rate in diverse populations and more research is needed to identify better measures of renal function available in an acute setting.
3. This study did not include patients who identified as Asian, Native American, Hawaiian, Pacific Islander, mixed race or other race and it is unknown whether SOFA scores in these patients would result in miscategorization.
4. When developing crisis standards of care, understanding the limitations of clinical scoring tools is necessary to avoid incorporating systemic bias into scarce resource allocation.

## OTHER ARTICLES OF INTEREST

### OXYGEN TARGETS IN THE ICU

The ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group.

**Conservative Oxygen Therapy during Mechanical Ventilation in the ICU.** *N Engl J Med* 2020; 382: 989-98

Barrot L, Asfar P, Mauny F, Winiszewski H, Montini F, Badie J, Quenot J-P, Pili-Floury S, Bouhemad B, Louis G, Souweine B, Colange O, Pottecher J, Levy B, Puyraveau M, Vettoretti L, Constantin J-M, Capellier G for the LOCO Investigators and REVA Research Network. **Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome.** *N Engl J Med* 2020; 382:999-1008

### SEDATION IN THE ICU

Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, Stiles RA, Dittus RS, Bernard GR, Ely EW. **Effect of Sedation with Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients: The MEDS Randomized Controlled Trial.** *JAMA* 2007; 298: 2644-2653

Pun BT, Badenes R, La Calle GH, Orun OM, Chen W, Raman R, Simpson B-GK, Wilson-Linville S, hinojal Olmedillo B, Vallejo de la Cueva A, van der Jagt M, Navarro Casado R, Leal Sanz P, Orhun G, Ferrer Gomez C, Nunez Vazquez K, Pineiro Otero P, Silvio Taccone F, Gallego Curto E, Caricato A, Woien H, Lacave G,

O'Neal HR, Peterson SJ, Brummel NE, Girard TD, Ely EW, Panharipande PP for the COVID Intensive Care International Study Group. **Prevalence and Risk Factors for Delirium in Critically Ill Patients with COVID-19 (COVID-D): a Multicentre Cohort Study.** *Lancet Respir Med* 2021; 9: 239-250

### ACUTE KIDNEY INJURY IN THE ICU

Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstadt H, Boanta A, Gerb J, Meersch M. **Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Morality in Critically Ill Patients with Acute Kidney Injury: The ELAIN Randomized Clinical Trial.** *JAMA* 2016; 315:2190-2199

Wong F, Pappas SC, Curry MP, Reddy KR, Rubin RA, Porayko MK, Gonzalez SA, Mumtaz K, Lim N, Simonetto DA, Sharma P, Sanyal AJ, Mayo MJ, Frederick RT, Escalante S, Jamil K for the CONFIRM Study Investigators. **Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome.** *N Engl J Med* 2021; 384: 818-828

### DISPARITIES IN CRITICAL CARE

Sarkar R, Martin C, Mattie H, Wawira Gochoya J, Stone DJ, Celi LA. **Performance of Intensive Care Unit Severity Scoring Systems Across Different Ethnicities in the USA: A Retrospective Observational Study.** *The Lancet Digital Health* 2021; 3: e241-e249

Sjoding MW, Dickson RP, Iwashyna TJ, Gay SE, Valley TS. **Racial Bias in Pulse Oximetry Measurement.** *N Engl J Med* 2020; 383: 25

## ECMO

Brijesh Patel, MRCP FRCA FFICM PhD

Imperial College London  
Anaesthesia, Pain Medicine, and Intensive Care  
London, United Kingdom

## GENERAL ECMO MANAGEMENT

Cavayas YA, Munshi L, Del Sorbo L, Fa, E. **The Early Change in PaCO<sub>2</sub> After Extracorporeal Membrane Oxygenation Initiation is Associated with Neurological Complications.** *Am J Resp Crit Care* 2020, 1525–1535 (2020).

## Summary

This is a large retrospective analysis of 11,972 adult patients entered in the ELSO Registry between January 2012 and December 2017. The aim was to ascertain if relative early changes in PaCO<sub>2</sub> (RelΔCO<sub>2</sub> - between pre-ECMO and at 24 hours post-initiation of ECMO) was associated with a primary outcome of neurological complications (clinical brain death, clinical seizures, EEG-proven seizures, central nervous system infarction, and central nervous system hemorrhage) and a secondary outcome of mortality. The primary composite outcome of neurological complications occurred in 6.9%, including seizures (1.1%), ischemic stroke (1.9%), intracranial hemorrhage (3.5%), and brain death (1.6%). The overall ICU mortality was 39.7%. A U-shaped relationship between the RelΔCO<sub>2</sub> and the incidence of neurological complications. Patients with a RelΔCO<sub>2</sub> drop >50% had a significantly increased incidence of neurological complications compared with patients with a RelΔCO<sub>2</sub> drop <50% (9.8% vs. 6.4%; P<0.001). A RelΔCO<sub>2</sub> drop <50% was documented in 1,719 patients (19%). These data recommend the frequent ABG monitoring and the use of modest sweep gas flow rates initially to limit the magnitude of the correction in PaCO<sub>2</sub> in the first 24 hours to prevent neurological complications in patients with respiratory failure supported with ECMO.

## Comments

1. An analysis of the Extracorporeal Life Support Organization (ELSO) Registry suggested that a higher pre-ECMO PaCO<sub>2</sub> was associated with increased mortality in patients receiving ECMO.
2. This is a large analysis of the ELSO registry spanning a recent period of veno-venous ECMO application.
3. A greater than 50% decrease in PaCO<sub>2</sub> in the first 24 hours was independently associated with an increased incidence of neurological complications.
4. Personalized changes in sweep gas flow rates should be used initially to limit the magnitude of the correction in PaCO<sub>2</sub> in the first 24 hours.
5. Further studies are needed to develop simple point of care approaches to monitor and personalize the management of PaCO<sub>2</sub> to reduce risk of neurological complications.

## ECMO FOR COVID-19

Barbaro RP, et al. **Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry.** *Lancet* 396, 1071–1078 (2020).

## Summary

This study analyzed ELSO Registry data to report the epidemiology, treatment, outcomes, and hospital characteristics of patients receiving ECMO with a confirmed diagnosis of COVID-19. To estimate the relative risks between potential risk factors and mortality, a Cox proportional hazards model for the primary outcome of death was applied. Increasing age was associated with a higher risk of in-hospital mortality for those 70 years or older relative to patients aged 16–39 years (HR 3.07, 95% CI 1.58–5.95); and higher PaO<sub>2</sub>:FiO<sub>2</sub> was associated with lower mortality (HR 0.68 per doubling, 95% CI 0.57–0.81). Patients with acute kidney injury, chronic respiratory insufficiency, an immunocompromised state, or a pre-ECMO cardiac arrest had an associated higher risk of mortality. Temporary circulatory support (venoarterial ECMO support) was significantly associated with in-hospital mortality (HR 1.89, 95% CI 1.20–2.97). In patients with COVID-19 supported with ECMO, both estimated mortality 90 days after ECMO initiation and mortality in those who achieved a final disposition of death or discharge were less than 40%. These results are consistent with previously reported survival rates in acute hypoxemic respiratory failure, supporting current recommendations that centers experienced in ECMO should consider its use in refractory COVID-19-related respiratory failure.

## Comments

1. The application of ECMO in a novel disease requires evaluation.
2. ELSO registry data was analyzed to understand the patient and treatment related factors that determine patient outcomes and if they are different to pre-COVID application.
3. Identified risk factors were age, immunocompromised state, chronic respiratory disease, pre-ECMO cardiac arrest, degree of hypoxemia, presence of acute kidney injury, and use of ECMO for temporary circulatory support (venoarterial ECMO support vs venovenous ECMO support).
4. Strengths of this study include the breadth of international participation and its use of experienced and trained Extracorporeal Life Support Organization site data managers to collect data.
5. This study of patients with COVID-19 who received ECMO in more than 200 hospitals in 36 countries provides a generalizable estimate of ECMO mortality and supports existing recommendations to consider use of ECMO in refractory COVID-



19-related respiratory failure when performed in experienced centers.

Shaefi S. et al. **Extracorporeal membrane oxygenation in patients with severe respiratory failure from COVID-19.** *Intens Care Med* 47, 208–221 (2021).

### Summary

The potential efficacy and safety of ECMO in critically ill adults with severe respiratory failure from COVID-19 remains unknown. This study emulated a target trial comparing patients with PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 100 mmHg while receiving invasive mechanical ventilation categorized as having initiated or not initiated ECMO in the first 7 days of ICU admission. The primary analysis compares survival with confounding variables adjusted using a multivariable Cox model. Two additional analyses were done using alternative PaO<sub>2</sub>/FiO<sub>2</sub> thresholds (<80 and <150 mmHg) to define eligibility. Among 5122 patients screened, 1297 were eligible for inclusion in the target trial on at least one of the seven days following ICU admission, 130 (10%) of whom received ECMO and 1167 (90%) of whom did not. In the primary analysis, patients who received ECMO had a lower risk of death compared to those who did not (adjusted HR 0.55; 95% CI 0.41–0.74). The estimated 60-day mortality was 35.3% (95% CI 27.2–43.5%) in the ECMO-treated patients and 47.9% (95% CI 44.9–50.8%) in the ECMO non-treated patients (risk difference 12.5%; 95% CI 4–21%). Interpretations were unchanged across all three sensitivity analyses, as well as analyses using alternative PaO<sub>2</sub>/FiO<sub>2</sub> thresholds to define eligibility.

### Comments

1. It is unlikely that a prospective randomized controlled trial for ECMO will occur during pandemic times and hence, the efficacy of ECMO in COVID-19 will remain unknown.
2. This study emulated a trial by matching patients that received ECMO and those that did not within the first 7 days of mechanical ventilation
3. The study aimed to match (as best as possible) the groups between ECMO and non-ECMO and showed a reduced mortality with ECMO application.
4. There is considerable risk for residual confounding as there were differences between the ECMO and non-ECMO groups which cannot statistically be resolved (e.g., the ECMO group had a higher application of adjunctive therapies and were nearly a decade younger).
5. This study cannot replace a prospective clinical study but gives added reassurance of the potential similar outcomes in COVID-19 to other pre-COVID etiologies of ARDS and that previous prospective ECMO studies could indeed be applied to Covid-19 management.

## OUTCOMES FOR VENOVENOUS ECMO

Combes A. et al. **ECMO for severe ARDS: systematic review and individual patient data meta-analysis.** *Intens Care Med* 46, 2048–2057 (2020).

### Summary

This systematic review and subsequent meta-analysis used individual patient data from randomized controlled trials (RCTs) comparing ECMO to conventional management in patients with severe ARDS. From the 1179 references identified by the search strategy, two randomized controlled trials fulfilled eligibility criteria—CESAR and EOLIA. The primary objective was to evaluate the effect of ECMO on 90-day mortality. Secondary objectives included the evaluation of ECMO for other clinical outcomes. The statistical analysis was performed for each outcome of interest using individual patient data. An intention to-treat analysis was used for all outcomes, whereby all patients were analyzed in the groups to which they were randomized. The two trials provided individual patient data for all randomized patients (429 overall, 180 in CESAR and 249 in EOLIA). The main disorder leading to study entry was severe hypoxia and the main cause of ARDS was pneumonia (> 60% of the patients) and 39% had 3 or more organs failing at randomization. The ECMO-group showed a 90-day mortality of 36% whereas the control group mortality was 48% (relative risk, 0.75, 95% confidence interval 0.6–0.94;  $p = 0.013$ ). The mortality of patients with only one or two organs failing at randomization was almost halved with ECMO (22% vs. 41%).

### Comments

1. Meta-analyses of individual patient data can also explore outcomes in important subgroups and suggest which population may derive the greatest benefit of a specific intervention, which is very limited in aggregated data meta-analyses.
2. This is a robust patient level data meta-analysis of the two most robust RCTs analyzing the utility of ECMO.
3. Beyond mortality, duration and severity of organ failures also favored ECMO, and these results were highly consistent between the two studies.
4. These results extend the conclusions of a post-hoc Bayesian analysis of EOLIA indicating a very high probability of ECMO success in severe ARDS patients, ranging from 88 to 99% depending on the chosen priors.
5. The only caveat is that the two studies were performed over a decade apart across which critical care outcomes may have changed due to generalized improvements in care and other interventions (e.g., prone position).

## OUTCOMES FOR VENOARTERIAL ECMO

Bréchet N. et al. **Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: a retrospective, multicentre, international cohort study.** *Lancet* 396, 545–552 (2020).

### Summary

This is a retrospective, international multi-center study comparing outcomes of patients who received VA-ECMO for refractory sepsis-induced cardiogenic shock. Data from patients with septic shock receiving VAECMO were collected between January 2008, and March 2018, at five university hospital ECMO centers. Criteria used for cardiogenic shock leading to VAECMO initiation included left ventricular ejection fraction (LVEF) 35% or less or cardiac index 3 L/min per m<sup>2</sup> or less; lactatemia at least 4 mmol/L; and inotropic score at least 75 µg/kg per min. Data from patients with severe septic shock who did not receive ECMO were collected from three databases that provided daily monitoring of patient's hemodynamic status. A propensity scoreweighted analysis was done for treatmenteffect estimation. ECMO was used early (1·1 days [SD 0·9]) after shock onset. Probability of survival at 90 days was markedly higher in patients receiving ECMO than in controls (60% vs 25%, RR for mortality 0·54, 95% CI 0·40–0·70; p<0·0001). Difference in survival persisted after propensity score weighting of patients according to their baseline severity and potential confounders (51% vs 14%, RR for mortality 0·57, 95% CI 0·35–0·93; p=0·0029). Patients receiving ECMO had significantly faster lactate clearance and decrease in inotrope score than did controls.

### Comments

1. There are no robust RCTs in the use of VA ECMO in cardiogenic shock induced by sepsis.
2. This is a propensity matched retrospective study examining outcomes for VA ECMO for sepsis induced cardiogenic shock.
3. This study was conducted over 10 years and so practice change may be a confounder.
4. The application of VA ECMO improved physiological indices.
5. These data showcase the importance of future prospective clinical trials although potential for cross-over seems high in any RCT.

## OTHER ARTICLES OF INTEREST

Millar JE. et al. **Combined Mesenchymal Stromal Cell Therapy and ECMO in ARDS: A Controlled Experimental Study in Sheep.** *Am J Resp Crit Care* 0, 383–392 (2020)

Sorbo LD. et al. **Effect of Driving Pressure Change During Extracorporeal Membrane Oxygenation in Adults With Acute Respiratory Distress Syndrome: A Randomized Crossover Physiologic Study\*.** *Crit Care Med* 48, 1771–1778 (2020)

Schmidt M. et al. **Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study.** *Lancet Respir Medicine* (2020) doi:10.1016/s2213-2600(20)30328-3

Wang R. et al. **Mechanical Ventilation Strategy Guided by Transpulmonary Pressure in Severe Acute Respiratory Distress Syndrome Treated With Venovenous Extracorporeal Membrane Oxygenation.** *Crit Care Med Publish Ahead of Print*, 1280–1288 (2020).

Lebreton G. et al. **Longitudinal Cytokine Profiling in Severe COVID-19 Patients on ECMO and Haemoadsorption.** *Am J Resp Crit Care* (2021) doi:10.1164/rccm.202011-4140le.

**SLEEP MEDICINE****Anna M. May, MD, MS**

VA Northeast Ohio Healthcare System, Case Western Reserve University  
 Division of Pulmonary, Critical Care, & Sleep Medicine  
 Cleveland, OH

**SLEEP APNEA: TREATMENT**

Op de Beeck S, Wellman A, Dieltjens M, Strohl KP, Willemen M, Van de Heyning PH, Verbraecken JA, Vanderveken OM, Sands SA. **Endotypic Mechanisms of Successful Hypoglossal Nerve Stimulation for Obstructive Sleep Apnea.** *Am J Respir Crit Care Med* 2020; 203:746–755.

**Summary**

Hypoglossal nerve stimulation (HNS) is an FDA-approved salvage therapy for OSA patients that are either unwilling or unable to use PAP therapy. HNS leads on incomplete response in about a third of patients. Therefore, additional refinement of patient selection based on endotypes may forestall surgery on those unlikely to benefit. This secondary analysis of the STAR trial evaluated polysomnographs for sleep apnea endotypes: loop gain, collapsibility (Vpassive), muscle compensation, and arousal threshold. Unexpectedly, response to HNS (AHI < 10 after 12 months) was associated with higher arousal threshold and worse collapsibility at baseline as well as higher muscle compensation (particularly in those with mild collapsibility). Nonresponders had a fourfold higher predicted AHI than responders when these endotypic traits were used to predict treatment effect (no validation group used for this analysis).

**Comments**

1. This result was quite surprising since the putative mechanism of HNS action was improving critical closing pressure.
2. The hypothesis that lower pharyngeal collapsibility is secondary primarily to non-anatomical factors needs additional study.
3. Higher arousal threshold is a common factor of success for both NHS and oral appliance therapy; however, these two therapies diverge on how muscle compensation affects therapy response with higher compensation predicting response to oral appliance.
4. This study highlights the needs to further endotypic examination of all sleep apnea therapies and a reconsideration of the relative influence of various endotypic factors on therapy efficacy.
5. Endotypic examination of therapy may identify those that are likely to be responders early and save the healthcare system and patients both time and money; however, results need to be replicated and validated in external data.

**SLEEP APNEA: HEALTH DISPARITIES**

Borker PV, Carmona E, Essien UR, Saeed GJ, Nouraiie SM, Bakker JP, Stitt CJ, Aloia MS, Patel SR. **Neighborhoods with Greater Prevalence of Minority Residents Have Lower CPAP Adherence.** *Am J Respir Crit Care Med* 2021; doi:10.1164/rccm.202009-3685OC.

**Summary**

Positive airway pressure is the more common treatment for sleep apnea, but adherence is poor. The interrelationship between race and individual and neighborhood factors that affect adherence have been incompletely characterized. Using a nationwide sample of people starting on positive airway pressure (11/2015-10/2018), this study found decreases in adherence in neighborhoods with either a higher percentage Black (absolute difference -1.3%) or Hispanic (absolute difference -1.2%) residents. Race was moderately associated with education and poverty measures. However, the association remained after adjustment for these variables. Adherence decline in the first 90 days was found in neighborhoods with high percentage of Black or Hispanic residents.

**Comments**

1. Positive airway pressure adherence, the go-to treatment for sleep apnea, is important and challenging to achieve in many patients.
2. Recognition of sleep apnea is lower for Black and Latinx sleep apnea patients; in addition, neighborhoods with high percentage of Black or Hispanic residents had higher drop-off in adherence over the first 90 days of therapy.
3. Mechanisms of decreased uptake of PAP therapy in minority communities needs more study.
4. Use of positive airway pressure has been associated with improvement in quality of life and sleepiness.
5. Identification of effective strategies to improve adherence in marginalized populations are sorely needed.

## PATIENT MANAGEMENT: TELEMEDICINE

Murase K, Tanizawa K, Minami T, Matsumoto T, Tachikawa R, Takahashi N, Tsuda T, Toyama Y, Ohi M, Akahoshi T, Tomita Y, Narui K, Nakamura H, Ohdaira T, Yoshimine H, Tsuboi T, Yamashiro Y, Ando S, Kasai T, Kita H, Tatsumi K, Burioka N, Tomii K, Kondoh Y, Takeyama H, Handa T, Hamada S, Oga T, Nakayama T, et al. **A Randomized Controlled Trial of Telemedicine for Long-Term Sleep Apnea Continuous Positive Airway Pressure Management.** *Ann Am Thorac Soc* 2020; 17:329–337.

### Summary

The pandemic has accelerated the trend toward telemedicine. Long-term, close follow-up with positive airway pressure (PAP) patients may improve adherence based on experience in the Japanese health system. This randomized three-arm trial evaluated PAP adherence with (1) supportive telemedicine with face-to-face follow-up every 3 months, (2) face-to-face follow-up every 3 months, and (3) monthly face-to-face follow-up for 6 months of follow-up. Seventeen Japanese sleep centers and clinics recruited adult participants who were on PAP therapy for more than 3 months. The telemonitoring group had monthly remote PAP adherence checks and coaching from their providers if not adherent (use  $\geq 4$  hours/night  $\geq 70\%$  nights). The other two groups did not have access to remote PAP adherence data other than during face-to-face visits. The telemonitoring intervention and 3-month visits were noninferior to the standard monthly visits. Clinic visits every 3 months was inferior to either of the other two arms in terms of maintaining adherence with decreased adherence in 33.1% in the 3-month group, 25.5% in the telemonitoring group, and 22.4% in the 1-month face-to-face visit group. There was differential effect based on baseline adherence with those that were nonadherent becoming more adherent in the telemonitoring and 1-month follow-up arms. The telemonitoring and 3-month follow-up arms had higher patient satisfaction.

### Comments

1. Even after the first 90-days, adherence can continue to improve with supportive interventions.
2. The telemonitoring had more people with improved adherence at 6 months while the 1-month follow-up arm had more individuals without adherence change.
3. Additional work on the effectiveness of automated interventions or automatic alerts for falls in adherence may provide more targeted interventions with reduced cost.
4. If all patients currently in standard follow-up in Japan were transitioned to telemedicine follow-up as in this study, there would be a 17% annual cost reduction for OSA management.
5. Longer-term investigations of such interventions are needed since previous work suggests a steady decline in adherence over time.

## HYPERSOMNOLENCE: DIAGNOSIS

Plante DT, Cook JD, Prairie ML. **Multimodal assessment increases objective identification of hypersomnolence in patients referred for multiple sleep latency testing.** *Journal of Clinical Sleep Medicine* 2020; doi:10.5664/jcsm.8470.

### Summary

After adequate exclusion of other potential causes of hypersomnolence, multiple sleep latency testing is currently the modality of choice for identification and subtyping of organic hypersomnolence disorders. However, this modality is limited by waning test-retest reliability in those without type I narcolepsy (with cataplexy or low orexin levels). Both mean sleep latency and sleep onset REM periods may vary from test to test. This study assessed 75 people with no identifiable etiology for hypersomnolence with a battery of tests including polysomnography and multiple sleep latency testing; a psychomotor vigilance task which requires sustained attention and response; and the pupillographic sleepiness test, an assessment of drowsiness based on pupil diameter changes in darkness secondary to decreased awake signals from the locus coeruleus. The use of multimodal assessment more than doubled identification of objective measures of hypersomnolence (25.3% vs 56%). No measure had high sensitivity, but the combination of measures identified all participants with multiple sleep latencies of  $\leq 10$  min.

### Comments

1. Hypersomnia as a symptom is multi-faceted and hypersomnolence disorders are not a monolith. These entities are, therefore, unlikely to be adequately described by a single testing regime.
2. Additional testing may uncover pathologic sleepiness even when multiple sleep testing yields normal results.
3. Narrow definition of hypersomnolence disorders may be preventing people with objective evidence of hypersomnia from obtaining treatment.
4. Investigation into the relative sensitivity and specificity of the multiple proposed hypersomnolence protocols is needed.
5. Additional study of hypersomnolence endotypes may inform diagnostic and therapeutic algorithms.

## INSOMNIA: EPIDEMIOLOGY

Morin CM, Jarrin DC, Ivers H, Mérette C, LeBlanc M, Savard J. **Incidence, Persistence, and Remission Rates of Insomnia Over 5 Years.** *JAMA Netw Open* 2020;3:e2018782.

### Summary

Insomnia is common and negatively affects productivity, quality of life, and medical comorbidity. The natural course of insomnia is not well characterized. This study followed 3073 adults over 5 years via a yearly telephone survey. Development of insomnia was relatively

common among good sleepers (13.9%). However, remission was common. Only 37.5% of people with insomnia symptoms reported persistent symptoms at 5 years without remission in the interim, this includes both people who have insomnia syndrome (59.1%) for those with subsyndromal insomnia (26.5%). Those with subsyndromal insomnia were much more likely to improve (35.3% over 5 years) than worsen (13.8% over 5 years) at any given year. For those with insomnia syndrome, however, were likely to remain in that category (66.2% per year). Surprisingly, no evidence for differential remission between age groups was found.

### Comments

1. Both self-limited and chronic insomnia are common.
2. The more severe the insomnia based on reported symptoms and functional impact, the more likely it is to be persistent.
3. This study did not assess for insomnia subtype: sleep initiation, maintenance, or early waking, which may have different underlying etiologies.
4. Long-term trajectories after treatment either with medication or cognitive behavioral therapy for insomnia are unknown. Rates of insomnia development or persistence with treatment for this study are not presented.
5. Identification of predictors of insomnia development or worsening as well as more prone to insomnia remission would be helpful in targeting therapy to those that are more likely to have a higher burden of this disease.

## OTHER ARTICLES OF INTEREST

### SLEEP AND COVID

Blume C, Schmidt MH, Cajochen C. **Effects of the COVID-19 lockdown on human sleep and rest-activity rhythms.** *Current Biology* 2020;30:R795–R797.

Cade BE, Dashti HS, Hassan SM, Redline S, Karlson EW. **Sleep Apnea and COVID-19 Mortality and Hospitalization.** *Am J Respir Crit Care Med* 2020;202:1462–1464.

Cellini N, Canale N, Mioni G, Costa S. **Changes in sleep pattern, sense of time and digital media use during COVID-19 lockdown in Italy.** *Journal of Sleep Research* 2020;29:e13074.

### INSOMNIA

Ekholm B, Spulber S, Adler M. **A randomized controlled study of weighted chain blankets for insomnia in psychiatric disorders.** *Journal of Clinical Sleep Medicine* 16:1567–1577.

Jaiswal SJ, Quer G, Galarnyk M, Steinhubl SR, Topol EJ, Owens RL. **Association of Sleep Duration and Variability With Body Mass Index: Sleep Measurements**

**in a Large US Population of Wearable Sensor Users.** *JAMA Internal Medicine* 2020;180:1694–1696.

Wong J, Murray Horwitz M, Bertisch SM, Herzig SJ, Buysse DJ, Toh S. **Trends in Dispensing of Zolpidem and Low-Dose Trazodone Among Commercially Insured Adults in the United States, 2011-2018.** *JAMA* 2020;324:2211–2213.

### HYPERSOMNIA

Barateau L, Lopez R, Chenini S, Rattu A-L, Scholz S, Lotierzo M, Cristol J-P, Jaussent I, Dauvilliers Y. **Association of CSF orexin-A levels and nocturnal sleep stability in patients with hypersomnolence.** *Neurology* 2020;95:e2900–e2911.

Kaplan S, Braverman DL, Frishman I, Bartov N. **Pregnancy and Fetal Outcomes Following Exposure to Modafinil and Armodafinil During Pregnancy.** *JAMA Internal Medicine* 2021;181:275–277.

Kolla BP, Jahani Kondori M, Silber MH, Samman H, Dhankikar S, Mansukhani MP. **Advance taper of antidepressants prior to multiple sleep latency testing increases the number of sleep-onset rapid eye movement periods and reduces mean sleep latency.** *Journal of Clinical Sleep Medicine* 16:1921–1927.

Lividini A, Pizza F, Filardi M, Vandi S, Ingravallo F, Antelmi E, Bruni O, Cosentino FII, Ferri R, Guarneri B, Marelli S, Ferini-Strambi L, Romigi A, Bonanni E, Maestri M, Terzaghi M, Manni R, Plazzi G. **Narcolepsy type 1 features across the life span: age impact on clinical and polysomnographic phenotype.** *Journal of Clinical Sleep Medicine* 2021;doi:10.5664/jcsm.9198.

### SLEEP APNEA

Giatti S, Santos RB, Aiello AN, Silva WA, Parise BK, Souza SP, Pio-Abreu A, Bortolotto LA, Lotufo PA, Bensenor IM, Drager LF. Association of Sodium with Obstructive Sleep Apnea. The ELSA-Brasil Study. *Annals ATS* 2020;18:502–510.

Hukins C, Duce B. **Asset life span in a government funded CPAP device program.** *Journal of Clinical Sleep Medicine* 2021;17:375–380.

Ibrahim B, de Freitas Mendonca MI, Gombar S, Callahan A, Jung K, Capasso R. **Association of Systemic Diseases With Surgical Treatment for Obstructive Sleep Apnea Compared With Continuous Positive Airway Pressure.** *JAMA Otolaryngol Head Neck Surg* 2021; doi:10.1001/jamaoto.2020.5179.

Ioachimescu OC, Allam JS, Samarghandi A, Anand N, Fields BG, Dholakia SA, Venkateshiah SB, Eisenstein R, Ciavatta M-M, Collop NA. **Performance of peripheral arterial tonometry-based testing for the diagnosis of**

**obstructive sleep apnea in a large sleep clinic cohort.**

*Journal of Clinical Sleep Medicine* 16:1663–1674.

Jhuang Y-H, Chung C-H, Wang I-D, Peng C-K, Meng E, Chien W-C, Chang P-Y. **Association of Obstructive Sleep Apnea With the Risk of Male Infertility in Taiwan.** *JAMA Netw Open* 2021;4:e2031846.

Li S, Xu L, Dong X, Zhang X, Keenan BT, Han F, Bi T, Chang Y, Yu Y, Zhou B, Pack AI, Kuna ST. **Home sleep apnea testing of adults with chronic heart failure.** *Journal of Clinical Sleep Medicine* 0:jcsm.9224.

Ng SSS, Wong VWS, Wong GLH, Chu WCW, Chan T-O, To K-W, Ko FWS, Chan K-P, Hui DS. **Continuous Positive Airway Pressure Does Not Improve Nonalcoholic Fatty Liver Disease in Patients with Obstructive Sleep Apnea. A Randomized Clinical Trial.** *Am J Respir Crit Care Med* 2020;203:493–501.

Pinilla L, Santamaria-Martos F, Benítez ID, Zapater A, Targa A, Mediano O, Masa JF, Masdeu MJ, Minguez O, Aguilà M, Barbé F, Sánchez-de-la-Torre M, Spanish Sleep Network. **Association of Obstructive Sleep Apnea with the Aging Process.** *Ann Am Thorac Soc* 2021; doi:10.1513/AnnalsATS.202007-771OC.

Zapater A, Sánchez-de-la-Torre M, Benítez ID, Targa A, Bertran S, Torres G, Aldomà A, De Batlle J, Abad J, Duran-Cantolla J, Cabriada-Nuño V, Mediano O, Masdeu MJ, Muñoz C, Masa JF, De la Peña M, Mayos M, Coloma R, Montserrat JM, Chiner E, Minguez O, Pascual L, Cortijo A, Martínez D, Dalmases M, McEvoy RD, Barbé F, Sánchez-de-la-Torre A, Abad L, et al. **The Effect of Sleep Apnea on Cardiovascular Events in Different Acute Coronary Syndrome Phenotypes.** *Am J Respir Crit Care Med* 2020;202:1698–1706.

**PHENOTYPING AND MACHINE LEARNING**

Azarbarzin A, Sands SA, Younes M, Taranto-Montemurro L, Sofer T, Vena D, Alex RM, Kim S-W, Gottlieb DJ, White DP, Redline S, Wellman A. **The Sleep Apnea-specific Pulse Rate Response Predicts Cardiovascular Morbidity and Mortality.** *Am J Respir Crit Care Med* 2021; doi:10.1164/rccm.202010-3900OC.

Borker PV, Reid M, Sofer T, Butler MP, Azarbarzin A, Wang H, Wellman A, Sands SA, Redline S. **NREM Apnea and Hypopnea Duration Varies Across Population Groups and Physiologic Traits.** *Am J Respir Crit Care Med* 2020; doi:10.1164/rccm.202005-1808OC.

Budhiraja R, Javaheri S, Parthasarathy S, Berry RB, Quan SF. **Incidence of hypertension in obstructive sleep apnea using hypopneas defined by a 3 percent oxygen desaturation or arousal but not by only 4 percent oxygen desaturation.** *J Clin Sleep Med* 2020;doi:10.5664/jcsm.8684.

Cimr D, Studnicka F, Fujita H, Tomaskova H, Cimler R, Kuhnova J, Slegl J. **Computer aided detection of breathing disorder from ballistocardiography signal using convolutional neural network.** *Information Sciences* 2020;541:207–217.

Feng K, Qin H, Wu S, Pan W, Liu G. **A Sleep Apnea Detection Method Based on Unsupervised Feature Learning and Single-Lead Electrocardiogram.** *IEEE Transactions on Instrumentation and Measurement* 2021;70:1–12.

**ASTHMA****Jose L. Gomez-Villalobos, MD, MS, ATSF**

Yale School of Medicine

Department of Medicine, Pulmonary, Critical Care and Sleep Section

New Haven, CT

**BIOMARKERS FOR PREDICTION OF EXACERBATIONS IN MILD ASTHMA**

Pavord ID, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, Harrison T, Houghton C, Oldfield K, Papi A, Williams M, Weatherall M, Beasley R; Novel START Study Team. **Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial.** *Lancet Respir Med.* 2020 Jul;8(7):671-680.

**Summary**

Blood eosinophils and fraction of exhaled nitric oxide (FeNO) are used to guide therapeutic selection in moderate and severe asthma. However, the association between these biomarkers and disease outcomes in mild asthma is less clear. This multicenter study evaluated the association between blood eosinophils and FeNO in patients who participated in a previously reported 52-week randomized, open-label trial comparing three interventions: as-needed salbutamol, maintenance budesonide plus as-needed salbutamol, or as-needed budesonide-formoterol. Blood eosinophils were measured only at baseline, while FeNO was measured at baseline, week 12 and week 52. The primary outcome was the annual rate of asthma exacerbations per patient. The study found that baseline blood eosinophil counts were associated with risk of exacerbations, particularly in the group receiving as-needed salbutamol. Furthermore, maintenance budesonide decreased rates of exacerbations in subjects with high blood eosinophils. Surprisingly, in subjects using as needed budesonide-formoterol, blood eosinophil counts did not predict rates of exacerbations. On the other hand, FeNO levels did not predict exacerbations in this study.

**Comments**

1. Patients with low FeNO (<20 ppb) had higher rates of smoking compared to those with high FeNO (>50 ppb). Consistent with previous reports of cigarette smoke suppression of FeNO.
2. In patients using as-needed salbutamol, higher levels of blood eosinophils were associated with higher rates of severe asthma exacerbations.
3. Maintenance inhaled budesonide prevented exacerbations in patients with high blood eosinophils, when compared with as-needed salbutamol. However, this effect was not seen when patients with low blood eosinophil counts were compared.
4. Patients with low blood eosinophils (<150 cells/microliter) may not benefit from maintenance inhaled corticosteroids (ICS).

**BIOMARKER-BASED ADJUSTMENT OF CORTICOSTEROID THERAPY IN SEVERE ASTHMA**

Heaney LG, Busby J, Hanratty CE, Djukanovic R, Woodcock A, Walker SM, Hardman TC, Arron JR, Choy DF, Bradding P, Brightling CE, Chaudhuri R, Cowan DC, Mansur AH, Fowler SJ, Niven RM, Howarth PH, Lordan JL, Menzies-Gow A, Harrison TW, Robinson DS, Holweg CTJ, Matthews JG, Pavord ID; investigators for the MRC Refractory Asthma Stratification Programme. **Composite type-2 biomarker strategy versus a symptom-risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multicentre, single-blind, parallel group, randomized controlled trial.** *Lancet Respir Med.* 2021 Jan;9(1):57-68.

**Summary**

Asthma guidelines rely heavily on symptoms and recommend increasing doses of corticosteroids in patients with decreased asthma control to prevent exacerbations and improve disease control. However, not all the components of asthma pathogenesis are steroid-sensitive, therefore it is important to identify strategies to help guide therapeutic adjustments. This multicenter study compared a composite biomarker-based approach with a symptom-based approach to adjust corticosteroids. The composite biomarker included blood eosinophil count, serum periostin, and FeNO, while the symptom-based approach also included lung function and recent exacerbation history. The primary endpoint was the number of patients with corticosteroid dose reduction at week 48. Prespecified analyses included intention-to-treat (ITT) and per-protocol (PP). While there were no differences in the primary endpoint in the ITT analysis, the PP analysis demonstrated that patients on the composite biomarker strategy arm used lower doses of corticosteroids at week 48, compared to those in the symptom-based approach. To contextualize this finding, it is important to highlight that there was significant attrition in this study, with the PP population representing 40% of the ITT population. The main reason driving patient loss was the lack of compliance with treatment advisories during the study, and the most common reason for the lack of compliance was patient's choice. Patients who did not follow treatment advisories had higher rates of exacerbations. These findings illustrate challenges in the implementation of interventions to de-escalate corticosteroids in patients with severe asthma and highlight the need to improve our

understanding of factors leading to lack of adherence to treatment recommendations.

### Comments

1. It is unknown whether a biomarker-based strategy vs. symptom-based strategy leads to a significant decrease in rates of corticosteroid use in severe asthma.
2. The PP population was only 40% of the ITT population in this trial.
3. In the PP population, patients in the composite biomarker achieved lower doses of corticosteroids at study completion.
4. Patients with decreased adherence to study advisories had higher rates of asthma exacerbations.

## BRONCHIAL THERMOPLASTY

Goorsenberg AWM, d'Hooghe JNS, Srikanthan K, Ten Hacken NHT, Weersink EJM, Roelofs JJTH, Kemp SV, Bel EH, Shah PL, Annema JT, Bonta PI; TASMA research group. **Bronchial Thermoplasty Induced Airway Smooth Muscle Reduction and Clinical Response in Severe Asthma. The TASMA Randomized Trial.** *Am J Respir Crit Care Med.* 2021 Jan 15;203(2):175-184.

### Summary

Previous studies have shown improvement in asthma control and quality of life with bronchial thermoplasty (BT), a non-pharmacologic treatment in severe asthma. Although the proposed mechanism is radiofrequency ablation of smooth muscle, our understanding of the anatomical correlates of this treatment is limited. This study applied an innovative design to study whether treatment with BT was associated with a reduction in airway smooth muscle. (ASM) This was achieved with airway biopsies before thermoplasty and with sparing of the right middle lobe to use as control during the study. Patients were randomized into immediate BT and delayed BT (6 months later). The study's primary endpoint was the reduction of ASM in the immediate treatment group. Patients in the immediate treatment group had a reduction in ASM compared to those in the delayed BT group. When all the participants were considered, BT treated segments showed reduced ASM in comparison with pre-BT airway biopsies. However, changes in ASM were not associated with asthma control or asthma quality of life after BT. Despite the lack of association between these features, the whole group showed improvements in asthma control and quality of life following BT. Despite detailed characterization of patients in this elegant study, it is still unclear which patients may derive the greatest benefit from BT.

### Comments

1. BT is associated with a reduction in ASM.
2. Changes in ASM are not associated with improvements in asthma control or asthma quality of life.
3. Patients with improved asthma control questionnaires (ACQ-6) and asthma quality of life questionnaires (AQLQ) after BT had higher blood eosinophil count and IgE at baseline.
4. It is unknown which asthma features predict response to BT.

## OTHER ARTICLES OF INTEREST

### Guidelines

Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC), Cloutier MM, Baptist AP, Blake KV, Brooks EG, Bryant-Stephens T, DiMango E, Dixon AE, Elward KS, Hartert T, Krishnan JA, Lemanske RF Jr, Ouellette DR, Pace WD, Schatz M, Skolnik NS, Stout JW, Teach SJ, Umscheid CA, Walsh CG. 2020 **Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group.** *J Allergy Clin Immunol.* 2020 Dec;146(6):1217-1270.

### Therapeutics

Corren J, Chen S, Callan L, Gil EG. **The effect of tezepelumab on hospitalizations and emergency department visits in patients with severe asthma.** *Ann Allergy Asthma Immunol.* 2020 Aug;125(2):211-214.

Psallidas I, Backer V, Kuna P, Palmér R, Necander S, Aurell M, Korsback K, Taib Z, Hashemi M, Gustafson P, Asimus S, Delaney S, Pardali K, Jiang F, Almquist J, Jackson S, Coffman RL, Keeling D, Sethi T. **A Phase 2a, Double-Blind, Placebo-controlled Randomized Trial of Inhaled TLR9 Agonist AZD1419 in Asthma.** *Am J Respir Crit Care Med.* 2021 Feb 1;203(3):296-306.

Brightling CE, Gaga M, Inoue H, Li J, Maspero J, Wenzel S, Maitra S, Lawrence D, Brockhaus F, Lehmann T, Brindicci C, Knorr B, Bleeker ER. **Effectiveness of fevipiprant in reducing exacerbations in patients with severe asthma (LUSTER-1 and LUSTER-2): two phase 3 randomised controlled trials.** *Lancet Respir Med.* 2021 Jan;9(1):43-56.

### Bronchial Thermoplasty

Hall CS, Quirk JD, Goss CW, Lew D, Kozlowski J, Thomen RP, Woods JC, Tustison NJ, Mugler JP 3rd, Gallagher L, Koch T, Schechtman KB, Ruset IC, Hersman FW, Castro M. **Single-Session Bronchial Thermoplasty Guided by 129Xe Magnetic Resonance Imaging. A Pilot Randomized Controlled Clinical Trial.** *Am J Respir Crit Care Med.* 2020 Aug 15;202(4):524-534.



**COVID-19 and Asthma**

Schultze A, Walker AJ, MacKenna B, Morton CE, Bhaskaran K, Brown JP, Rentsch CT, Williamson E, Drysdale H, Croker R, Bacon S, Hulme W, Bates C, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J, McDonald HI, Tomlinson L, Mathur R, Wing K, Wong AYS, Forbes H, Parry J, Hester F, Harper S, Evans SJW, Quint J, Smeeth L, Douglas IJ, Goldacre B; OpenSAFELY Collaborative. **Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform.** *Lancet Respir Med.* 2020 Nov;8(11):1106-1120.

## INTERSTITIAL LUNG DISEASE

Julie Morisset, MD

Centre Hospitalier de l'Université de Montréal  
Département de médecine  
Montreal, QC, Canada

### DIAGNOSIS OF INTERSTITIAL LUNG DISEASE

Raghu G, Wilson KC, Bargagli E, Bendstrup E, Chami HA, Chua AT, et al. **Diagnosis of hypersensitivity pneumonitis in adults: An official ATS/JRS/ALAT clinical practice guideline.** *American Journal of Respiratory and Critical Care Medicine*. Vol. 202, 2020. 36–69 p.

#### Summary

The diagnosis of hypersensitivity pneumonitis lacked clinical practice guidelines resulting in poor agreement for HP diagnosis across centers. The American Thoracic Society, the Japanese Respiratory Society and the Asociación Latinoamericana del Torax created a working group of experts that lead to the publication of collaborative guidelines for the diagnosis of HP. Through systematic reviews and evidence discussion, the multidisciplinary committee of experts made recommendations for 6 questions using the GRADE approach. Key recommendations include: 1) emphasis for clinicians to consider HP as a potential diagnosis in all patients with newly found ILD 2) new classification of HP (2 clinical phenotypes: nonfibrotic HP and fibrotic HP) based on the absence or presence of radiological or histopathological features of fibrosis 3) diagnostic algorithm (with level of confidence) incorporating imaging, exposure assessment, BAL lymphocytosis and histopathological findings 4) BAL with cellular analysis is suggested for patients with newly ILD whose differential diagnosis include nonfibrotic and fibrotic HP 5) confident diagnosis of HP can be established in patients with identified exposure, typical radiological pattern and BAL lymphocytosis without any additional testing 6) patients with other combination of exposure history, radiological pattern and BAL results should be discussed in multidisciplinary discussion to assess the need for histopathological sampling.

#### Comments

1. Hypersensitivity pneumonitis should be considered in the differential diagnosis of every patient with newly identified ILD.
2. HP is classified as either nonfibrotic or fibrotic HP according to the absence or presence of radiological and/or histopathological evidence of fibrosis.

3. The diagnosis of HP requires the integration of clinical, radiological and histopathological domains and is ideally considered in the settings of multidisciplinary discussion.

### FAMILIAL INTERSTITIAL LUNG DISEASE

Hunninghake GM, Quesada-Arias LD, Carmichael NE, Martinez Manzano JM, Poli De Frías S, Baumgartner MA, et al. **Interstitial Lung Disease in Relatives of Patients with Pulmonary Fibrosis.** *Am J Respir Crit Care Med*. 2020 May;201(10):1240–8.

#### Summary

This study aimed to identify the prevalence of interstitial lung abnormalities (ILA) and interstitial lung disease (ILD) among relatives of patients with familial pulmonary fibrosis (FPF) and sporadic idiopathic pulmonary fibrosis (IPF). First degree relatives of patients with pulmonary fibrosis were invited to participate in a 2-year protocol including various clinical assessments. The authors found that among the 105 relatives enrolled in their study, 33 (31%) had ILA and of those 19 (58%) also met the diagnostic criteria for ILD. There was no significant difference in the prevalence of ILA prevalence in relatives of patients with FPF or sporadic IPF. The presence of ILD in relatives was associated with shorter telomere lengths and MUC5B promoter polymorphism (rs35705950).

#### Comments

1. First degree relatives of patients with PPF and sporadic IPF have a high prevalence of ILA and ILD.
2. Sporadic IPF may be a misnomer as some patients do have undiagnosed family members with ILA and ILD.
3. Screening family members of patients with pulmonary fibrosis could represent an effective method to identify early ILD.

Salisbury ML, Hewlett JC, Ding G, Markin CR, Douglas K, Mason W, et al. **Development and Progression of Radiologic Abnormalities in Individuals at Risk for Familial Interstitial Lung Disease.** *Am J Respir Crit Care Med*. 2020 May;201(10):1230–9.

#### Summary

This study aimed to identify risk factors for interstitial lung abnormalities (ILA) and progression to interstitial lung disease (ILD) in a cohort of first-degree relatives of patients with familial interstitial pneumonia (family with

at least 2 relatives with ILD, one of which needs to have diagnosis of idiopathic fibrosis (IPF)). The longitudinal study enrolled 336 asymptomatic relatives from 157 families. Subjects underwent initial testing (questionnaire, blood draw, high-resolution CT (HRCT) and pulmonary function tests) at enrollment, yearly health questionnaire and repeat HRCT scan 5 years after enrollment. 23% of the relatives were found to have ILA on their initial HRCT. Older age, positive smoking history, shorter telomere length and self-reported exposure to aluminum smelting, birds, lead and mold was associated with presence of ILA. During the 5-year follow up, a majority of patients with early-mild ILA (63%) had evidence of radiological progression. However, less than 10% of patients without ILA on initial HRCT went on to develop ILA.

### Comments

1. Prevalence of ILA is high in first degree relatives of patients with familial interstitial pneumonia.
2. ILA prevalence increases with older age, smoking history and short telomere length.
3. Modifiable environmental risk factors: exposure to aluminum smelting, lead, mold and birds are associated to ILA in high-risk individuals.
4. HRCT-based screening should be considered in relatives of patients with familial interstitial pneumonia.

## TREATMENT OF INTERSTITIAL LUNG DISEASE

Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, et al. **Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial.** *Lancet Respir Med.* 2020 May;8(5):453–60.

### Summary

The INBUILD trial was a prospective, randomized, double-blind, placebo controlled, parallel group trial of nintedanib in patients with progressive interstitial lung disease (ILD). In a previous publication, nintedanib was shown to slow the rate of forced vital capacity (FVC) decline at 1 year when compared to placebo. This study aimed to establish the effect of nintedanib in subgroups based on ILD diagnosis. Patients were categorized into 5 diagnosis groups: hypersensitivity pneumonitis, autoimmune ILDs, idiopathic non-specific interstitial pneumonia (INSIP), unclassifiable idiopathic interstitial pneumonia (IIP) and other ILDs (sarcoidosis, exposure-related ILDs). The influence of each of these diagnosis on nintedanib treatment was analyzed. The authors showed the effect of nintedanib versus placebo on reducing FVC decline at 1 year was consistent across the five groups in the overall population ( $p=0.41$  for treatment by subgroup by time interaction). Similar results were observed across subgroups based on ILD diagnosis both in patients

with UIP-like fibrotic pattern and in patients with other radiological pattern on HRCT.

### Comments

1. Nintedanib was previously shown to reduced FVC decline at 1 year in patient with progressive fibrosing ILD.
2. The INBUILD trial was not designed or powered to evaluate the benefit of nintedanib in specific diagnostic subgroups.
3. This additional analysis suggest nintedanib reduces the rate of FVC decline irrespectively of the underlying ILD diagnosis.

## POST COVID 19 INTERSTITIAL LUNG DISEASE

Myall KJ, Mukherjee B, Castanheira AM, Lam JL, Benedetti G, Mak SM, et al. **Persistent Post-COVID-19 Inflammatory Interstitial Lung Disease: An Observational Study of Corticosteroid Treatment.** *Ann Am Thorac Soc.* 2021 Jan;

### Summary

This study aimed to determine the incidence of persistent interstitial lung disease (ILD) after SARS-CoV2 and describe its natural history when treated with prednisolone. Four weeks after discharge, 837 patients, who had been admitted to Guy's and St Thomas' NHS Foundation Trust with a SARS-CoV2 pneumonia, were screened by phone interview for persistent pulmonary symptoms. Of those, 325 (39%) were found to have ongoing symptoms and were offered additional investigations. Fifty-nine patients had post-COVID interstitial changes, the majority having imaging features suggestive of organizing pneumonia (59%). Thirty patients with post COVID ILD, persistent symptoms and physiological impairment on lung function received oral corticosteroid treatment. Prednisolone was started at doses of 0.5 mg /kg and rapidly weaned over 3 weeks. Following treatment, all patients experienced improvement in breathlessness and on average had improvement in both FVC (9.6%  $\pm$ 13.6%) and TLCO (31.49%  $\pm$ 27.7%). Control CT also demonstrated radiological improvement.

### Comments

1. Persistent pulmonary symptoms are common after SARS-CoV2 pneumonia.
2. Organizing pneumonia is the most frequent form of post COVID ILD.
3. 3-week treatment course of oral prednisolone was associated with improvement in symptoms, lung function and imaging features.

## OTHER ARTICLES OF INTEREST

Invernizzi R, Wu BG, Barnett J, Ghai P, Kingston S, Hewitt RJ, et al. **The Respiratory Microbiome in Chronic Hypersensitivity Pneumonitis Is Distinct from That of Idiopathic Pulmonary Fibrosis.** *Am J Respir Crit Care Med.* 2021 Feb;203(3):339–47.

- Lee JS, La J, Aziz S, Dobrinskikh E, Brownell R, Jones KD, et al. **Molecular Markers of Telomere Dysfunction and Senescence are Common Findings in the Usual Interstitial Pneumonia Pattern of Lung Fibrosis.** *Histopathology*. 2021 Jan;
- Richeldi L, Scholand MB, Lynch DA, Colby T V, Myers JL, Groshong SD, et al. **Utility of a Molecular Classifier as a Complement to High-Resolution Computed Tomography to Identify Usual Interstitial Pneumonia.** *Am J Respir Crit Care Med*. 2021 Jan;203(2):211–20.
- Nasser M, Larrieu S, Si-Mohamed S, Ahmad K, Bousset L, Brevet M, et al. **Progressive fibrosing interstitial lung disease: a clinical cohort (the PROGRESS study).** *Eur Respir J*. 2021 Feb;57(2).
- Cutting C, Bowman WS, Dao N, Pugashetti JV, Garcia CK, Oldham JM, et al. **Family History of Pulmonary Fibrosis Predicts Worse Survival in Patients With Interstitial Lung Disease.** *Chest*. 2021 Jan;
- Kreuter M, Bradley SJ, Lee JS, Tzouveleakis A, Oldham JM, Molyneaux PL, et al. **Monocyte Count as a Prognostic Biomarker in Patients with Idiopathic Pulmonary Fibrosis.** *Am J Respir Crit Care Med*. 2021 Jan;
- Drake TM, Docherty AB, Harrison EM, Quint JK, Adamali H, Agnew S, et al. **Outcome of Hospitalization for COVID-19 in Patients with Interstitial Lung Disease. An International Multicenter Study.** *Am J Respir Crit Care Med*. 2020 Dec;202(12):1656–65.
- Esposito AJ, Menon AA, Ghosh AJ, Putman RK, Fredenburgh LE, El-Chemaly SY, et al. **Increased Odds of Death for Patients with Interstitial Lung Disease and COVID-19: A Case-Control Study.** *American journal of respiratory and critical care medicine*. Vol. 202, 2020. p. 1710–3.
- Moor CC, Mostard RLM, Grutters JC, Bresser P, Aerts JGJ V, Chavannes NH, et al. **Home Monitoring in Patients with Idiopathic Pulmonary Fibrosis. A Randomized Controlled Trial.** *Am J Respir Crit Care Med*. 2020 Aug;202(3):393–401.
- Assayag D, Morisset J, Johannson KA, Wells AU, Walsh SLF. **Patient gender bias on the diagnosis of idiopathic pulmonary fibrosis.** *Thorax*. 2020 May;75(5):407–12.
- Cottin V, Richeldi L, Rosas I, Otaola M, Song JW, Tomassetti S, et al. **Nintedanib and immunomodulatory therapies in progressive fibrosing interstitial lung diseases.** *Respir Res*. 2021 Mar;22(1):84.
- Justet A, Klay D, Porcher R, Cottin V, Ahmad K, Molina Molina M, et al. **Safety and efficacy of pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis and carrying a telomere-related gene mutation.** *The European respiratory journal*. Vol. 57, England; 2021.
- Highland KB, Distler O, Kuwana M, Allanore Y, Assassi S, Azuma A, et al. **Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSICIS trial.** *Lancet Respir Med*. 2021 Jan;9(1):96–106.
- Khanna D, Lin CJF, Furst DE, Goldin J, Kim G, Kuwana M, et al. **Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial.** *Lancet Respir Med*. 2020 Oct;8(10):963–74.

## HEALTH DISPARITIES IN PULMONARY, CRITICAL CARE AND SLEEP MEDICINE

**Stephanie Lovinsky-Desir, MD, MS**

Columbia University Irving Medical Center  
Department of Pediatrics – Pulmonary Division  
New York, NY

### CRITICAL CARE OUTCOMES

Danziger J, Ángel Armengol de la Hoz M, Li W, Komorowski M, Deliberato RO, Rush BNM, Mukamal KJ, Celi L, Badawi O. **Temporal Trends in Critical Care Outcomes in U.S. Minority-Serving Hospitals.** *Am J Respir Crit Care Med.* 2020; 201(6): 681-687

#### Summary

Recognizing the improvements in critical care over the last decade, Danziger and colleagues sought to understand if related improvements in health outcomes extended to critical care patients treated in predominately minority serving hospitals compared to non-minority serving hospitals. Minority serving hospitals were defined as those with an ICU census of African American or Hispanic patients greater than twice the regional population mean based on 2010 U.S. Census data. The analytic cohort included 1,039,595 individuals from 208 US hospitals from 2006–2016 with data extracted from the Philips Healthcare Electronic ICU Research Institute Database. Ten percent of the cohort received care in minority-serving hospitals. A quarter (25%) of all African American patients in the cohort and nearly half (48%) of all Hispanic patients received care in minority serving hospitals. Across all ethnic groups, hospital mortality was proportionately higher in minority serving hospitals than non-minority serving hospitals. While non-minority serving hospitals experienced a steady decline in mortality rate (2% per year) and length of ICU and hospital stay, improved outcomes were not observed in minority serving hospitals. African American patients had 3% reduction in mortality per year when cared for in non-minority serving hospitals, yet no improvement in mortality at minority serving hospitals.

#### Comments

1. While advances in medical technology have resulted in improved critical care outcomes in the U.S., patients who receive care in minority serving hospitals, especially African American patients, have not experienced improved mortality or lengths of stay in the last 10 years.
2. A large proportion of African American and Hispanic patients received care in only 7% of the hospitals surveyed, minority-serving hospitals.
3. Patients cared for in minority serving-hospitals tended to be younger and had fewer co-morbidities yet had higher severity of acute illness and mortality.

4. Selection bias could have resulted in under or over estimation of the true association given that the sample only represented hospitals that utilized the electronic ICU platform.
5. Additional support and resources are needed for hospitals that serve large proportions of minority patients to help improve disparities in critical care outcomes.

### ASTHMA MORBIDITY

Nardone A, Casey JA, Morello-Frosch R, Mujahid M, Balmes JR, Thakur N. **Associations between historical residential redlining and current age-adjusted rates of emergency department visits due to asthma across eight cities in California: an ecological study.** *Lancet Planet Health.* 2020; 4(1): e24-e31.

#### Summary

Nardone and colleagues evaluated the impact of historical redlining of cities in California on current asthma burden in 2011–2013. Redlining refers to the historical, government-sponsored practice of categorizing neighborhoods on the basis of racial demographics and perceived risk for mortgage investment. In addition to denying wealth-generating opportunities, the long-standing effects of redlining have perpetuated racial segregation and dictated where highways and toxic-hazard sites were placed. Using census tract-level data, the authors characterized neighborhoods into the 4 categories of risk defined by Home Owner's Loan Corporation (HOLC) redline maps (A=best, B=still desirable, C=declining, and D=hazardous). The percentage of non-Hispanic Black and Hispanic residents increased with increase in risk grade from "A" to "D". Poverty rate was 3.3 times higher in the highest risk (redlined) "D" tracts compared to the lowest risk "A" tracts with 52% of the population in redlined tracts living below 2 times the federal poverty level. Redlined "D" tracts had nearly twice as much diesel particle emissions compared "A" tracts. Asthma related emergency department (ED) visits were 2.4 times higher in "D"-rated tracts than "A"-rated tracts. HOLC risk grade was a significant predictor of rates of asthma-related ED visits after controlling for census tract poverty level and air pollution measures.

**Comments**

1. ED visits for asthma were significantly higher in residential census-tracts that were historically redlined compared to lower risk neighborhoods.
2. In addition to exacerbating racial segregation, redlining likely contributed to increased concentration of poverty and traffic related air pollution in specific communities, all of which are known risk factors for asthma.
3. Individual-level factors such as socio-demographic characteristics and smoking status were not assessed thus; the study could be subject to ecological fallacy (i.e. inference made about individuals based on aggregated data).
4. Strategies that focus on addressing generational poverty and air quality particularly in racially segregated communities could contribute to reducing disparities in asthma burden.

**LUNG CANCER TREATMENT**

Blom EF, Ten Haaf K, Arenberg DA, de Koning HJ. **Disparities in Receiving Guideline-Concordant Treatment for Lung Cancer in the United States.** *Ann Am Thorac Soc.* 2020. 17(2): 186-194.

**Summary**

Blom and colleagues collected data from 441,812 patients with lung cancer in U.S. hospitals from 2010-2014 using the U.S. National Cancer database. Their objective was to determine if racial, ethnic, and age disparities existed with adherence to National Comprehensive Cancer Network Guidelines for the management of lung cancer. Models were adjusted for race, ethnicity, age, sex, health insurance, comorbidity score, facility type, stage at diagnosis and histology. Overall, 62.1% of patients received guideline-concordant treatment, 16.3% received less intensive treatment and 21.6% received no treatment. The rate of guideline-concordant treatment was highest for localized non-small cell lung cancer (L-NSCLC, 76.3%) that is most likely to be curative, and lowest for advance-NSCLC (A-NSCLC, 50%). The odds of receiving guideline-concordant treatment was significantly lower for patients  $\geq 80$  years versus  $< 50$  years of age (aOR = 0.06; 95% CI = 0.05–0.06). Across all subgroups of lung cancer, compared to non-Hispanic White patients, non-Hispanic Black patients had 23% lower odds (aOR = 0.78; 95% CI = 0.76–0.80) and Hispanic patients had 6% lower odds (aOR = 0.94; 95% CI = 0.90–0.98) of guideline-concordant treatment, while non-Hispanic Asian patients were more likely to receive guideline-concordant treatment (OR = 1.09; 95%CI = 1.04–1.15).

**Comments**

1. Elderly patients and non-Hispanic Black patients were less likely to receive guideline-concordant treatment for all types lung cancer, while guideline-concordant treatment varied among non-Hispanic Asian and Hispanic patients depending on the type of lung cancer.
2. The highest rates of no treatment were observed among those with the most advanced diseases: A-NSCLC (31.4%), extensive disease small-cell lung cancer (21.8%).

3. The stage at diagnosis stratified by race and ethnicity was not presented, thus we can not discern if minoritized patients were more likely to present with advanced forms of lung cancer, contributing to lower guideline-concordant treatment.
4. Factors like mistrust of the medical system by Black patients could explain some of the disparities in treatment; thus highlighting the need for continued efforts to improve trust and communication between the healthcare providers and historically minoritized patients.

**CHRONIC OBSTRUCTIVE PULMONARY DISEASE OUTCOMES**

Ejike CO, Woo H, Galiatsatos P, Paulin LM, Krishnan JA, Cooper CB, Couper DJ, Kanner RE, Bowler RP, Hoffman EA, Comellas AP, Criner GJ, Barr RG, Martinez FJ, Han MK, Martinez CH, Ortega VE, Parekh TM, Christenson SA, Thakur N, Baugh A, Belz DC, Raju S, Gassett AJ, Kaufman JD, Putcha N, Hansel NN. **Contribution of Individual and Neighborhood Factors to Racial Disparities in Respiratory Outcomes.** *Am J Respir Crit Care Med.* 2020. Online ahead of print. doi: 10.1164/rccm.202002-0253OC.

**Summary**

Ejike and colleagues examined independent and joint effects of both individual and neighborhood-level socioeconomic status (SES) on racial disparities in COPD. Data were collected from 2,649 participants in the multi-center SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) of individuals at risk for and with COPD enrolled from 2010-2015. Census tract-level neighborhood variables included poverty and educational attainment data from the 2010 US census, food access data from the USDA, and the area deprivation index, a validated geospatial index of socioeconomic disadvantage. Outcomes included respiratory specific quality of life, exercise capacity, dyspnea scale, exacerbation risk and CT scan outcomes. Black participants were more likely to be current smokers but had less pack-year history than White participants. Black participants were also more likely to live in high poverty neighborhoods with higher deprivation scores. In unadjusted models, Black participants had worse quality of life, worse CT scan metrics, and more severe exacerbations compared to White participants. In mediation analysis, 12-35% of the racial disparities in COPD outcomes were attributed to individual-level SES and 26-54% attributed to neighborhood-level SES. Up to 69% of the disparity in outcomes between Black and White individuals was explained by individual and neighborhood-level SES combined.

**Comments**

1. The investigators examined a broad range of COPD-related outcomes and demonstrated that Black individuals at risk for and with COPD fared worse than White individuals across all indicators.
2. Most of the disparity in respiratory related outcomes between Black and White participants was explained by a combination

of individual and neighborhood-level socio-demographic factors.

3. The cross-sectional study design limited the ability to infer causation, although it is very likely that poor SES factors preceded and contributed to the factors that lead to COPD and related outcomes.
4. Addressing both individual and neighborhood-level SES factors could have a significant impact on narrowing the gap between COPD outcomes between Black and White individuals.

## OTHER ARTICLES OF INTEREST

### ASTHMA

Sullivan K, Thakur N. **Structural and Social Determinants of Health in Asthma in Developed Economies: a Scoping Review of Literature Published Between 2014 and 2019.** *Curr Allergy Asthma Rep.* 2020;20(2):5.

Ogbogu PU, Capers Q 4th, Apter AJ. **Disparities in Asthma and Allergy Care: What Can We Do?** *J Allergy Clin Immunol Pract.* 2021;9(2):663-669.

Marquez-Velarde G. **The paradox does not fit all: Racial disparities in asthma among Mexican Americans in the U.S.** *PLoS One.* 2020;15(11):e0242855.

### COPD

Galiatsatos P, Woo H, Paulin LM, Kind A, Putcha N, Gassett AJ, Cooper CB, Dransfield MT, Parekh TM, Oates GR, Barr RG, Comellas AP, Han MK, Peters SP, Krishnan JA, Labaki WW, McCormack MC, Kaufman JD, Hansel NN. **The Association Between Neighborhood Socioeconomic Disadvantage and Chronic Obstructive Pulmonary Disease.** *Int J Chron Obstruct Pulmon Dis.* 2020;15:981-993.

Spitzer KA, Stefan MS, Priya A, Pack QR, Pekow PS, Lagu T, Mazor KM, Pinto-Plata VM, ZuWallack RL, Lindenauer PK. **A Geographic Analysis of Racial Disparities in Use of Pulmonary Rehabilitation After Hospitalization for COPD Exacerbation.** *Chest.* 2020;157(5):1130-1137.

Pekmezaris R, Kozikowski A, Pascarelli B, Wolf-Klein G, Boye-Codjoe E, Jacome S, Madera D, Tsang D, Guerrero B, Medina R, Polo J, Williams M, Hajizadeh N. **A Telehealth-Delivered Pulmonary Rehabilitation Intervention in Underserved Hispanic and African American Patients With Chronic Obstructive Pulmonary Disease: A Community-Based Participatory Research Approach.** *JMIR Form Res.* 2020;4(1):e13197.

### COVID

Thakur N, Lovinsky-Desir S, Bime C, Wisnivesky JP, Celedón JC. **The Structural and Social Determinants of the Racial/Ethnic Disparities in the U.S. COVID-19 Pandemic. What's Our Role?** *Am J Respir Crit Care Med.* 2020;202(7):943-949.

Galiatsatos P, Kachalia A, Belcher HME, Hughes MT, Kahn J, Rushton CH, Suarez JI, Biddison LD, Golden SH. **Health equity and distributive justice considerations in critical care resource allocation.** *Lancet Respir Med.* 2020;8(8):758-760.

Kanter GP, Segal AG, Groeneveld PW. **Income Disparities In Access To Critical Care Services.** *Health Aff.* 2020;39(8):1362-1367.

### CYSTIC FIBROSIS

McGarry ME, McColley SA. **Cystic fibrosis patients of minority race and ethnicity less likely eligible for CFTR modulators based on CFTR genotype.** *Pediatr Pulmonol.* 2021 Jan 20. Online ahead of print.

### LUNG CANCER

Rivera MP, Katki HA, Tanner NT, Triplett M, Sakoda LC, Wiener RS, Cardarelli R, Carter-Harris L, Crothers K, Fathi JT, Ford ME, Smith R, Winn RA, Wisnivesky JP, Henderson LM, Aldrich MC. **Addressing Disparities in Lung Cancer Screening Eligibility and Healthcare Access. An Official American Thoracic Society Statement.** *Am J Respir Crit Care Med.* 2020;202(7):e95-e112.

Adie Y, Kats DJ, Tlimat A, Perzynski A, Dalton J, Gunzler D, Tarabichi Y. **Neighborhood Disadvantage and Lung Cancer Incidence in Ever-Smokers at a Safety Net Health-Care System: A Retrospective Study.** *Chest.* 2020;157(4):1021-1029.

Pinsky PF, Lau YK, Doubeni CA. **Potential Disparities by Sex and Race-ethnicity in Lung Cancer Screening Eligibility Rates.** *Chest.* 2021;S0012-3692(21)00232-4.

### CRITICAL CARE/SEPSIS

Galiatsatos P, Follin A, Alghanim F, Sherry M, Sylvester C, Daniel Y, Chanmugam A, Townsend J, Saria S, Kind AJ, Chen E. **The Association Between Neighborhood Socioeconomic Disadvantage and Readmissions for Patients Hospitalized With Sepsis.** *Crit Care Med.* 2020;48(6):808-814.

Lizza BD, Betthausen KD, Juang PH, Hampton NB, Lyons PG, Kollef MH, Micek ST. **Racial Disparities in Readmissions Following Initial Hospitalization for Sepsis.** *Crit Care Med.* 2021;49(3):e258-e268.

**SLEEP**

Jackson CL, Walker JR, Brown MK, Das R, Jones NL. **A workshop report on the causes and consequences of sleep health disparities.** *Sleep.* 2020;43(8):zsaa037.

Billings ME, Cohen RT, Baldwin CM, Johnson DA, Palen BN, Parthasarathy S, Patel SR, Russell M, Tapia IE, Williamson AA, Sharma S. **Disparities in Sleep Health and Potential Intervention Models: A Focused Review.** *Chest.* 2021;159(3):1232-1240.

Gaston SA, Nguyen-Rodriguez S, Aiello AE, McGrath J, Jackson WB 2nd, Nápoles A, Pérez-Stable EJ, Jackson CL. **Hispanic/Latino heritage group disparities in sleep and the sleep-cardiovascular health relationship by housing tenure status in the United States.** *Sleep Health.* 2020; 6(4):451-462.

Troxel WM, Haas A, Ghosh-Dastidar B, Holliday SB, Richardson AS, Schwartz H, Gary-Webb TL, Hale L, Buysse DJ, Buman MP, Dubowitz T. Broken Windows, Broken Zzs: **Poor Housing and Neighborhood Conditions Are Associated with Objective Measures of Sleep Health.** *J Urban Health.* 2020; 97(2):230-238.

Ruthberg J, Summerville L, Cai Y, Boas S, Otteson T, Kumar A. **Utilization of surgical treatment for sleep apnea: A study of health disparities.** *Am J Otolaryngol.* 2020;41(6):102670.



## PULMONARY REHABILITATION

Pat Camp, PhD, PT

University of British Columbia  
Department of Physical Therapy

### SURVIVAL BENEFIT OF PULMONARY REHABILITATION

Lindenauer PK, Stefan MS, Pekow PS, Mazor KM, Priya A, Spitzer KA, Lagu TC, Pack QR, Pinto-Plata VM, ZuWallack R. **Association between initiation of pulmonary rehabilitation after hospitalization for COPD and 1-year survival among Medicare beneficiaries.** *JAMA* 2020; 323(18):1813-1823.

#### Summary

The purpose of this research study was to investigate the association between the initiation of pulmonary rehabilitation (PR) within 90 days of discharge from hospital after an acute exacerbation of chronic obstructive pulmonary disease (AECOPD), and survival. This study was undertaken as previous studies of health outcomes related to early PR after AECOPD had small sample sizes in select research populations. Medicare beneficiaries (age 66 and older, n=2710) with a previous AECOPD-related hospitalization and PR within 90 days of discharge were matched 1:1 with a control group who did not attend PR, using a propensity model. Those who initiated post-AECOPD PR were more likely to be younger, White and male, and lived closer to a PR facility. They also had fewer comorbidities, were less frail, and more likely to have no previous year admissions for AECOPD. However, they were more likely to be receiving supplemental oxygen prior to hospitalization. Participation in PR after an AECOPD discharge from hospital was significantly associated with decreased risk of mortality (hazard ratio 0.63, 95% CI, 0.57 to 0.69), with more sessions attended resulting in a lower risk of death. This article reinforces the necessity of PR after serious AECOPD.

#### Comments

1. PR within 90 days after discharge from hospital after an acute exacerbation of COPD is associated with a significantly reduced mortality rate.
2. A dose-response relationship was demonstrated, with every 3 additional sessions associated with lower mortality (hazard ratio 0.91, 95% CI 0.85, 0.98).
3. The higher proportion of younger, White men with fewer comorbidities and less frailty who accessed PR after discharge reinforces the problem of less access to PR in underserved populations.
4. The findings of this study support those reported in the 2016 Cochrane systematic review by Puhan et al. on pulmonary rehabilitation following exacerbations of COPD.

### PULMONARY REHABILITATION USING MINIMAL EQUIPMENT

Patel S, Palmer MD, Nolan CM, Barker RE, Walsh JA, Wynne SC, Jones SE, Shannon H, Hopkinson NS, Swee Chin Kon, S, Gao W, Maddocks M, Man WDC. **Supervised pulmonary rehabilitation using minimal or specialist equipment in COPD: a propensity-matched analysis.** *Thorax* 2021; 76:264-271..

#### Summary

The benefits of pulmonary rehabilitation (PR) are well-established, but many foundational studies were conducted in high-resource settings. The purpose of this study was to determine if PR conducted using minimal equipment would provide similar benefits as PR using specialist exercise equipment. The investigators compared the outcomes of 318 people with COPD who completed a minimal equipment PR program (PR-min: walking track, hand weights, and elastic bands) with 318 people who completed a PR program in a hospital setting (PR-gym: treadmills, cycle ergometers, and strength machines). Participants were matched on several variables, including age, sex, lung function and comorbidities, using propensity-match scores. All participants were supervised by highly-qualified rehabilitation professionals and received an individualized exercise program based on validated exercise testing. Although the PR-min group had a lower percentage of people completing the program compared to the PR-gym group (64% compared to 73%, respectively; p=0.014), both groups had clinically similar improvements in the incremental shuttle walk test (PR-min = 56.6m, PR-gym = 59.7m; p=0.63), and overall quality of life as measured by the Chronic Respiratory Questionnaire (p=0.62). The non-inferiority analysis confirmed that both programs yielded similar results in these outcomes, suggesting that PR using minimal equipment is non-inferior (provides similar benefits) as higher resource programs.

#### Comments

1. A well-supervised pulmonary rehabilitation program using minimal equipment provided similar exercise performance and overall quality of life improvements as a pulmonary rehabilitation program using typical gym exercise equipment.
2. A lower percentage of people in the rehabilitation program using minimal equipment completed the program, leading to questions related to differences in other characteristics, such as access or socioeconomic status, between the groups.
3. Further investigation into other outcomes such as patient satisfaction and improvements in muscle function are required (see next paper by Nyberg et al. regarding muscle function and exercise bands).

- The long-term benefits of pulmonary rehabilitation using minimal equipment are unknown as is whether patients who attend minimal resource programs continue to maintain their exercise behavior.
- The results from this study support increasing access to pulmonary rehabilitation by creating programs in community settings using minimal equipment resources.

## RESISTANCE TRAINING IN PULMONARY REHABILITATION

Nyberg A, Martin M, Saey D, Milad N, Patoine D, Morissette MC, Auger D, Per S, Maltais F. **Effects of low-load/high-repetition resistance training on exercise capacity, health status, and limb muscle adaptation in patients with severe COPD: a randomized controlled trial.** *Chest online* January 30, 2021.

### Summary

The purpose of this study was to determine if single-limb low load, high repetition resistance training (LLHR-RT) using exercise bands results in physiological adaptations and changes in exercise capacity, health status and muscle function compared to two-limb LLHR-RT. Thirty-three patients with stable COPD were randomized to either the single-limb or two-limb LLHR-RT program, which occurred for one hour, three times per week for eight weeks. The exercise program was identical, except that the exercise was either performed with one arm/leg, then the other, or both simultaneously. The training was individualized based on an objective test and progressed weekly. After eight weeks, both groups had similar improvements from baseline in muscle endurance, six minute walk distance (6MWD), and health status. Both groups had similar improvements in 6MWD and training volume. The per-protocol analysis revealed almost three times more participants in the single-limb group achieved the minimal clinical important difference (MCID) for the 6MWD compared to the two-limb group and had lower mean dyspnea levels during training. In summary, LLHR-RT is feasible in patients with COPD and achieves benefits using simple equipment. Single-limb training enables more people to reach the 6MWD MCID and is associated with lower dyspnea levels.

### Comments

- Individuals with severe COPD and dyspnea may find traditional muscle training regimens too difficult, and there is a need to develop and evaluate muscle training programs that are feasible in all pulmonary rehabilitation settings.
- A single-limb, low-load high-repetition muscle endurance training program for upper and lower extremities produced similar benefits in 6MWD (between group differences 14m, 95% CI -12 to 39), COPD Assessment Test score (between group differences -1.6, 95% CI -5.1 to 2.0), muscle endurance, and physiological muscle adaptations, as a program where both limbs are exercising simultaneously.
- The single limb program achieved a mean improvement in 6MWD that exceeded the MCID (+40m), had a reduced exertional dyspnea ( $p=0.01$ ) and the per-protocol analysis revealed that three times more participants in the single limb group achieved the MCID in walking distance.

- These improvements occurred via an individualized program based on objective exercise testing and using minimal resource equipment (exercise bands), enabling implementation in all pulmonary rehabilitation settings.

## IMPROVING UPTAKE OF POST-AECOPD PULMONARY REHABILITATION

Barker RE, Kon SS, Clarke SF, Wenneberg J, Nolan CM, Patel S, Walsh JA, Polgar O, Maddocks M, Farquhar M, Hopkinson NS, Bell D, Wedzicha JA, Man WD. **COPD discharge bundle and pulmonary rehabilitation referral and uptake following hospitalisation for acute exacerbation of COPD.** *Thorax* 2021 Mar 2. doi: 10.1136/thoraxjnl-2020-215464.

### Summary

Although pulmonary rehabilitation (PR) after discharge from hospital for an AECOPD shows benefit, few patients complete programs. The investigators conducted a parallel, two-group, mixed methods RCT to test the hypothesis if patients hospitalized with an AECOPD learned about PR before discharge, they would be more likely to attend. Hospitalized patients with an AECOPD ( $n=196$ ) were randomized to a group which received an AECOPD discharge bundle, or the group which received the discharge bundle plus viewed a video on PR after an AECOPD hospitalization. After 90 days post-discharge, there was no difference between intervention and control groups in overall uptake of PR (34% and 41%, respectively,  $p=0.37$ ), health status as measured by the COPD Assessment Test ( $p=0.21$ ), or 4 meter gait speed ( $p=0.57$ ). The qualitative interviews ( $n=15$ ) conducted at 90 days revealed that many participants did not recall seeing the video, raising issues of timing. Those that did felt the content was excellent, but did not feel well enough to attend PR, or conversely thought their current level of activity was adequate. This well-designed study, with the added strength of qualitative data, reinforces the continued need for development of strategies to improve the uptake of PR after a severe AECOPD.

### Comments

- Viewing a patient education video prior to discharge did not improve uptake to PR, health status or gait speed.
- The timing of when to provide patient education regarding referral to PR with a severe AECOPD remains unclear.
- An education video, co-designed with patients, was met with positive reviews by patients.
- Other strategies, such as reinforcement of the importance of PR after AECOPD by all members of the health care team, automatic referrals and follow-up, rehabilitation while in the hospital and other transition programs, may be required.
- There was substantial difficulty in recruiting participants (46% of those eligible) and significant loss to follow-up in both the experimental and control groups (43% and 39%, respectively), highlighting the challenges of conducting PR research with this population.

## REHABILITATION NEEDS OF PEOPLE WITH LONG COVID

Ladds E, Rushforth A, Wieringa S, Taylor S, Rayner C, Husain L, Greenhalgh T. **Persistent symptoms after Covid-19: qualitative study of 114 “long Covid” patients and draft quality principles for services.** *BMC Health Services Research* 2020; 20: 1144.

### Summary

The purpose of this qualitative study, which included patient partners as co-researchers, was to explore how people with Long COVID in the United Kingdom experience their illness; what services they accessed (or tried to) and their experience of those services; and their recommendations for improving the management of their condition. One hundred and fourteen people with Long COVID participated in either an individual interview or focus group, which were transcribed and analyzed for common themes using several sociological theories of illness as guides. Eighty percent were female, and 45% were health care professionals. Ninety-six percent were not hospitalized. Participants reported “a serious, uncertain, and confusing illness” with fluctuating symptoms. Pain, fatigue, and “brain fog” were commonly reported. Participants had difficulty accessing services due to the lack of a clearly-defined pathway to available care, and often a perception that their symptoms were not severe or were only “anxiety”. Participants with strong relationships with their care provider reported better access to Long COVID care. Participants identified several principles for Long COVID care, which included multi-disciplinary rehabilitation, and highlighted the discordance between the published literature which at the time reported a low prevalence of ongoing symptoms, and their lived experience of Long COVID illness.

### Comments

1. Many patients who had COVID-19 continue to experience disabling symptoms weeks after the acute infection has passed, termed Long COVID by patient groups.
2. The lived experience of Long COVID is confusing and uncertain for many patients, which was exacerbated by the expectation to prove the legitimacy of their symptoms.
3. Participants with Long COVID in this study report difficulty with accessing services, and confusion within the health care system regarding appropriate pathways for ongoing care after the acute infectious period has passed.
4. Participants identified six principles of Long COVID care which can guide rehabilitation professionals as they plan for future services: 1) access to appropriate care; 2) minimizing the burden of illness on patients; 3) identification of who is clinically responsible for the patient and ensuring continuity of care; 4) multi-disciplinary rehabilitation services; 5) evidence-based standards of care; and 6) further development of the knowledge base and clinical services.

## OTHER ARTICLES OF INTEREST

### ACUTE EXACERBATIONS OF COPD

Granados-Santiago M, Valenza MC, Lopez-Lopez L, Prados-Roman E, Rodriguez-Torres J, Cabrera-Martos I. **Shared decision-making and patient engagement program during acute exacerbation of COPD hospitalization: a randomized control trial.** *Patient Educ Couns* 2020; 103: 702-708.

### COVID-19

Carfi A, Bernabei R, Landi F; **Gemelli Against COVID-19 Post-Acute Care Study Group.** **Persistent symptoms in patients after acute COVID-19.** *JAMA* 2020; 324(6): 603-605.

Klok FA, Boon GJAM, Barco S, Endres M, Geelhoed JJM, Knauss S, Rezek SA, Spruit MA, Vehreschild J, Siegerink B. **The Post-COVID-19 Functional Status (PCFS) Scale: a tool to measure functional status over time after COVID-19.** *Eur Respir J* 2020; 56(1): 2001494.

### INTERSTITIAL LUNG DISEASE

Schneeberger T, Leitl D, Gloeckl R, Jarosch I, Reimann D, Hitzl W, Koczulla R, Kenn K. **Acute effects of supplemental oxygen therapy using different nasal cannulas on walking capacity in patients with idiopathic pulmonary fibrosis: a randomised crossover trial.** *ERJ Open Res* 2020; 6(3): 00197-2020.

Tikellis G, Tong A, Lee JYT, Corte TJ, Hey-Cunningham AJ, Bartlett M, Crawford T, Glaspole I, Price J, Maloney J, Holland AE. **Top 10 research priorities for people living with pulmonary fibrosis, their caregivers, healthcare professionals and researchers.** *Thorax* 2020; Dec 4; thoraxjnl-2020-215731.

Yohannes AM. **Depression and anxiety in patients with interstitial lung disease.** *Expert Rev Respir Med* 2020;14(9): 859-862.

### PHYSICAL ACTIVITY IN COPD

#### Four papers to read together:

- 1) Koolen EH, van Hees HW, van Lummel RC, Dekhuijzen R, Djamin RS, Spruit MA, van 't Hul AJ. **“Can do” versus “do do””: a novel concept to better understand physical functioning in patients with chronic obstructive pulmonary disease.** *J Clin Med* 2019;8:340.
- 2) Sievi NA, Brack T, Brutsche MH, Frey M, Irani S, Leuppi JD, Thurnheer R, Kohler M, Clarenbach CF. **“Can do, don't do” are not the lazy ones: a longitudinal study on physical functioning in patients with COPD.** *Respir Res* 2020;21:27.
- 3) van 't Hul AJA, Koolen EHN, van Hees HWJ, van den Borst BB, Spruit MAM. **The ‘can do, do do’ concept in COPD; quadrant interpretation, affiliation and tracking longitudinal changes.** *Respir Res* 2020; 21(1):112.

4) Sievi NA, Kohler M, Clarenbach CF. **Respond to the letter to the editor by Van't et al. regarding the published manuscript "can do, don't do" are not the lazy ones: a longitudinal study on physical functioning in patients with COPD** by Sievi et al. *Respir Res* 2020; 21 (1): 114.

Blondeel A, Demeyer H, Janssens W, Troosters T. **Accuracy of consumer-based activity trackers as measuring tool and coaching device in patients with COPD and healthy controls.** *PLoS One* 2020; 15(8) : e0236676.

Garcia-Aymerich J, Puhan MA, Corriol-Rohou S, de Jong C, Demeyer H, Dobbels F, Erzen D, Frei A, Gimeno-Santos E, Hopkinson NS, Ivanoff N, Karlsson N, Louvaris Z, Polkey MI, Rabinovich RA, Scuri M, Tabberer M, Vogiatzis I, Troosters T, PROactive consortium. **Validity and responsiveness of the daily- and clinical visit-PROactive Physical Activity in COPD (D-PPAC and C-PPAC) instruments.** *Thorax* 2021 Jan 21; thoraxjnl-2020-214554.

## PULMONARY REHABILITATION THROUGHOUT THE WORLD

Bickton FM, Fombe C, Chisati E, Rylance J. **Evidence for pulmonary rehabilitation in chronic respiratory diseases in sub-Saharan Africa: a systematic review.** *Int J Tuberc Lung Dis* 2020; 24(10): 991-999.

Galiatsatos P, Woo H, Paulin LM, Kind A, Putcha N, Gassett AJ, Cooper CB, Dransfield MT, Parekh TM, Oates GR, Barr RG, Comellas AP, Han MK, Peters SP, Krishnan JA, Labaki WW, McCormack MC, Kaufman JC, Hansel NN. **The association between neighborhood socioeconomic disadvantage and chronic obstructive pulmonary disease.** *Int J Chron Obstruct Pulmon Dis* 2020;15: 981-993.

Jayamaha AR, Perera CH, Orme MW, Jones AV, Wijayasiri UKDC, Amarasekara TD, Karunatilake RS, Fernando A, Seneviratne ALP, Barton A, Jones R, Yusuf ZK, Miah RB, Malcolm D, Matheson JA, Free RC, Manise A, Steiner MC, Wimalasekera SW, Singh SJ. **Protocol for the cultural adaptation of pulmonary rehabilitation and subsequent testing in a randomised controlled feasibility trial for adults with chronic obstructive pulmonary disease in Sri Lanka.** *BMJ Open* 2020; 10: e041677.

## STRATEGIES TO ENHANCE THE BENEFITS OF PULMONARY REHABILITATION

Pavitt MJ, Tanner RJ, Lewis A, Buttery S, Mehta B, Jefford H, Curtis KJ, Banya WAS, Husain S, Satkunam K, Shrikrishna D, Man W, Polkey MI, Hopkinson NS. **Oral nitrate supplementation to enhance pulmonary rehabilitation in COPD: ON-EPIC a multicentre, double-blind, placebo-controlled, randomised parallel group study.** *Thorax* 2020; 75(7): 547-555.

Yeh GY, Litrownik D, Wayne PM, Beach D, Klings ES, Nieva HR, Pinheiro A, Davis RB, Moy ML. **BEAM study (Breathing, Education, Awareness, Movement): a randomised controlled feasibility trial of tai chi exercise in patients with COPD.** *BMJ Open Respir Res* 2020; 7(1): e000697.



**ATS 2021**

[conference.thoracic.org](https://conference.thoracic.org)