

# CYIR

Clinical Year  
in Review

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# Clinical Year in Review Bibliography

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*This session and the International Conference are supported by independent medical educational grants from Boehringer Ingelheim Pharmaceuticals, Inc., Merck & Co., Inc., and United Therapeutics Corporation. All CME sessions have been planned and implemented in accordance with the Accreditation Criteria of the Accreditation Council for Continuing Medical Education (ACCME®) and are free of the control of ineligible companies*

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## ARDS

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### THERAPEUTIC OPTIONS FOR COVID-19 ARDS

Misset B, Piagnerelli M, Hoste E, Dardenne N, Grimaldi D, Michaux I, De Waele E, Dumoulin A, Jorens PG, van der Hauwaert E, Vallot F, Lamote S, Swinnen W, De Schryver N, Fraipont V, de Mey N, Dauby N, Layios N, Mesland JB, Meyfroidt G, Moutschen M, Compennolle V, Gothot A, Desmecht D, Taveira da Silva Pereira MI, Garigliany M, Najdovski T, Bertrand A, Donneau AF, Laterre PF.

**Convalescent Plasma for Covid-19-Induced ARDS in Mechanically Ventilated Patients.** *N Engl J Med.* 2023 Oct 26;389(17):1590-1600

### Summary

Convalescent plasma may provide passive immunization and decrease viral load in patients with COVID-19. CONFIDENT was a multicenter, open label, randomized controlled trial conducted across 17 sites in Belgium involving mechanically ventilated adults with COVID-19 induced acute respiratory distress syndrome (ARDS). Patients were randomized to receive convalescent plasma with high neutralizing antibody titers against SARS-CoV-2 from recovered donors versus standard care. The study enrolled 475 patients (237 randomized to convalescent plasma and 238 to standard care) from September 2020 to March 2022. Randomization was stratified according to time from intubation (either  $\leq 48$  hours or  $>48$  to 120 hours). The convalescent plasma group had a significantly lower 28-day mortality compared to the standard group (35.4% vs. 45%,  $p=0.03$ ) Only 10% of patients were vaccinated against COVID-19. While other studies had investigated use of convalescent plasma in COVID-19, CONFIDENT is the first trial to focus on early treatment in mechanically ventilated patients and utilized plasma with high antibody titers. Notably, most of the study participants had early strains of COVID-19 and it is unclear how this therapy would be beneficial in future variants of COVID-19. Findings suggest that convalescent plasma may be a therapeutic consideration for patients requiring mechanical ventilation for COVID-19 ARDS.

### Comments

1. In prespecified analysis, this effect was mainly observed in the group that underwent randomization within 48 hours of intubation (32.7% in the convalescent plasma group vs. 46.8% in standard care group) and in patients with a higher SOFA score at study inclusion (44% in the convalescent plasma group vs. 55.9% in the standard care group).
2. Nearly all patients received steroids, and few received a second immunomodulator with no treatment related adverse events associated with convalescent plasma.
3. The median time from onset of symptoms to trial inclusion for the convalescent plasma group was 12 days (IQR 8-14).
4. A prior study noted a significant mortality benefit in patients who were mechanically ventilated with COVID-19 ARDS and hematologic cancer who received convalescent plasma (Thompson MA, Henderson JP, Shah PK, et al. Association of convalescent plasma therapy with survival in patients with hematologic cancers and COVID-19. *JAMA Oncol* 2021;7:1167-1175) and there may be a role for convalescent plasma therapy in ARDS in specific patient populations.
5. The trial was terminated early due to absence of new cases, however the study enrolled 95% of planned inclusions.

## THERAPEUTIC OPTIONS FOR COVID-19 ARDS

REMAP-CAP Investigators; Hills TE, Lorenzi E, Berry LR, Shyamsundar M, Al-Beidh F, Annane D, Arabi Y, Aryal D, Au C, Beane A, Bhimani Z, Bonten M, Bradbury CA, Brunkhorst FM, Burrell A, Buxton M, Calfee CS, Cecconi M, Cheng AC, Cove ME, Detry MA, Estcourt LJ, Fitzgerald M, Goligher EC, Goossens H, Green C, Haniffa R, Harrison DA, Hashmi M, Higgins AM, Huang DT, Ichihara N, Jayakumar D, Kruger PS, Lamontagne F, Lampro L, Lawler PR, Marshall JC, Mason AJ, McGlothlin A, McGuinness S, McQuilten ZK, McVerry BJ, Mouncey PR, Murthy S, Neal MD, Nichol AD, O'Kane CM, Parke RL, Parker JC, Rabindrarajan E, Reyes LF, Rowan KM, Saito H, Santos M, Saunders CT, Seymour CW, Shankar-Hari M, Sinha P, Thompson BT, Turgeon AF, Turner AM, van de Veerdonk F, Weis S, Young IS, Zarychanski R, Lewis RJ, McArthur CJ, Angus DC, Berry SM, Derde LPG, Webb SA, Gordon AC, McAuley DF. **Simvastatin in Critically Ill Patients with Covid-19.** *N Engl J Med.* 2023 Dec 21;389(25):2341-2354.

### Summary

Prior work has demonstrated that Simvastatin has anti-inflammatory properties and may be beneficial in ARDS and COVID-19. This was an open label, adaptive-platform, randomized controlled trial across 141 international sites conducted within the REMAP-CAP trial evaluating the use of daily high dose Simvastatin compared to no statin for either 28 days or ICU discharge in critically ill adult patients with COVID-19. A total of 2739 patients were randomized to the simvastatin domain through response-adaptive randomization with 841 in the control group and 1843 in the simvastatin group included for final analysis. There was a 95.5% posterior probability of superiority of simvastatin to standard care with respect to the primary outcome of organ support-free days through day 21 which did not meet the prespecified 99% threshold. The median duration of organ support-free days was 11 [IQR -1 to 17] in the simvastatin group and 7 [IQR -1 to 16] in the control group with a median adjusted OR of 1.15 (95% credible interval, 0.98 to 1.34). There were no statistically significant differences in secondary outcomes. Serious adverse events (elevated liver enzymes, pancreatitis, creatinine kinase) were higher in the intervention group compared to control group (3.1% vs 2%).

### Comments

1. Use of response-adaptive randomization in this trial may have impacted the ability to reach prespecified criteria.
2. Nearly all the enrolled patients were receiving respiratory support in the form of high-flow oxygen, non-invasive ventilation and invasive mechanical ventilation.
3. The study was stopped early due to the low likelihood of reaching prespecified criteria given decreasing numbers of patients with severe COVID-19.
4. The cohort was comprised almost entirely of a hypoinflammatory sub-phenotype of ARDS with increased benefit in subgroup analysis noted among patients with higher levels of CRP and ferritin which highlights the heterogeneity of ARDS and the need to identify which subgroups benefit from therapeutic strategies.
5. Subgroup analyses demonstrated a larger association of simvastatin with organ support-free days in patients who were not receiving mechanical ventilation at randomization with 37% of those in the simvastatin group progressing to mechanical ventilation, ECMO or death compared to 42.5% in the control group.

## ADDRESSING INEQUITY AND ADEQUATE REPRESENTATION OF MARGINALIZED COMMUNITIES IN ARDS RESEARCH

Papoutsis E, Kremmydas P, Tsolaki V, Kyriakoudi A, Routsis C, Kotanidou A, Siempos II. **Racial and ethnic minority participants in clinical trials of acute respiratory distress syndrome.** *Intensive Care Med.* 2023 Dec;49(12):1479-1488.

### Summary

There is an urgent need to ensure inclusion of racial and ethnic minorities in clinical trials as the benefit from development of therapeutic interventions and treatment depends largely on who is studied. This was a secondary analysis of 5375 patients with ARDS included in eight ARDS and PETAL network therapeutic trials published between 2000 and 2019 to evaluate inclusion of racial and ethnic minorities. The pooled prevalence of racial and ethnic minorities (Black, Hispanic or other race) was 30.4% across all eight trials and this representation did not change significantly over time ( $p=0.257$ ). The pooled 90-day mortality of racial and ethnic minority participants was 33% (95% CI 27.8-38.5%)

across all eight trials which is lower compared to prior trials. The authors restricted inclusion to 3244 participants with moderate to severe ARDS to account for the ROSE trial which only included such participants, and evaluated temporal trends of mortality. They found that the difference in mortality between racial minority participants and White participants decreased over time ( $p=0.021$ ). No significant difference was noted in secondary outcomes other than that the “Other race” participants had fewer ICU-free days compared to other groups. These results may not be generalizable to other clinical trials.

### Comments

1. The primary findings of similar mortality outcomes between White and non-White participants differs from other studies which reported higher mortality rates for Black and Hispanic patients with ARDS compared to White patients and this warrants future investigation to understand contributing factors.
2. The rigor and protocolization of clinical trials might mask unconscious biases and structural inequalities that could impact the care and clinical outcomes of racial and ethnic minorities.
3. Pooling of racial and ethnic groups in clinical trials highlight the challenges in understanding outcomes in the specific heterogeneous groups included.
4. The authors found no significant associations between race/ethnicity and mortality in any of the prespecified subgroup analyses including analysis of data from recent ARDS trials in 2021.

### A PROPOSED EXPANSION OF THE BERLIN DEFINITION OF ARDS

Matthay MA, Arabi Y, Arroliga AC, Bernard G, Bersten AD, Brochard LJ, Calfee CS, Combes A, Daniel BM, Ferguson ND, Gong MN, Gotts JE, Herridge MS, Laffey JG, Liu KD, Machado FR, Martin TR, McAuley DF, Mercat A, Moss M, Mularski RA, Pesenti A, Qiu H, Ramakrishnan N, Ranieri VM, Riviello ED, Rubin E, Slutsky AS, Thompson BT, Twagirumugabe T, Ware LB, Wick KD. **A New Global Definition of Acute Respiratory Distress Syndrome.** *Am J Respir Crit Care Med.* 2024 Jan 1;209(1):37-47.

### Summary

Since the revision of the ARDS criteria with the Berlin definition in 2012, several limitations of the definition have been noted including the lack of noninvasive pulse oximetric methods for evaluating oxygenation criteria, increasing use of high-flow nasal oxygen (HFNO) to treat acute hypoxemic respiratory failure as in the recent COVID-19 global pandemic and limited utility of the definition in resource-limited settings due to lack of available resources. A committee of 32 experts convened to propose a new global definition of ARDS to expand on the existing Berlin definition. This definition includes several important changes: 1) the inclusion of HFNO with oxygen delivery of  $\geq 30\text{L}/\text{min}$ , 2) addition of lung ultrasound as an alternative for imaging modality in the absence of chest radiograph and 3) alternative use of  $\text{SpO}_2/\text{FiO}_2$  to assess hypoxemia if arterial blood gas measurement ( $\text{PaO}_2$ ) is not available. The committee also recommended the creation of three categories of ARDS within the current definition: non-intubated ARDS including patients on HFNO or non-invasive ventilation at time of diagnosis, intubated ARDS and a modified definition for resource limited settings where a minimal flow rate of oxygen or positive end-expiratory pressure is not required as an adoption of the Kigali modification.

### Comments

1. The broadened definition has strong implications for inclusion of patients into clinical trials and will need attention to minimize heterogeneity from the inclusion of a large population of patients with acute respiratory failure who may fulfill the criteria in this definition.
2. There were no proposed changes to the diagnosis of ARDS in regard to time frame, association with predisposing risk factor or the severity cutoffs for  $\text{PaO}_2/\text{FiO}_2$  in intubated patients.
3. The inclusion of patients using high-flow nasal oxygen may allow for earlier recognition of ARDS and therefore increased ARDS prevalence.
4. With recent studies demonstrating striking inaccuracies in pulse oximetry readings among Black patients, the use of  $\text{SpO}_2$  as a surrogate for  $\text{PaO}_2$  may lead to a biased assessment and this further highlights the urgent need to minimize any associated racial bias with the use of pulse oximeter in patients with darker skin.

- While lung ultrasound is a promising tool especially in the absence of chest radiograph or chest CT, it will be crucial to ensure operators are appropriately trained in its use and interpretation of findings given lack of data on inter-rater agreement for lung ultrasound interpretation.

### DEVELOPMENT OF A LUNG ULTRASOUND SCORE FOR DIAGNOSIS OF ARDS

Smit MR, Hagens LA, Heijnen NFL, Pisani L, Cherpanath TGV, Dongelmans DA, de Grooth HS, Pierrakos C, Tuinman PR, Zimatore C, Paulus F, Schnabel RM, Schultz MJ, Bergmans DCJJ, Bos LDJ; DARTS Consortium members. **Lung Ultrasound Prediction Model for Acute Respiratory Distress Syndrome: A Multicenter Prospective Observational Study.** *Am J Respir Crit Care Med.* 2023 Jun 15;207(12):1591-1601.

#### Summary

This is a multi-center prospective observational study performed under the larger DART project conducted across two sites in Netherlands with a goal to derive and validate a lung ultrasound score (LUS-ARDS) for diagnosis of ARDS. Included patients were intubated less than 48 hours during screening and a 12-region LUS examination was performed on both the day of inclusion and 24 hours after inclusion. Expert panel classification of ARDS using features of Berlin definition (clinical and radiographic features) with application of an ARDS certainty score was used as the reference test. The score was developed from patients with an expert panel agreement label of “certain ARDS” or “certain no ARDS” in the derivation cohort. Overall, 453 patients were included for analysis including 324 to the derivation cohort and 129 to the validation cohort. The area under the ROC curve (AUROCC) of the LUS-ARDS score for diagnosis of ARDS was 0.90 (95% CI, 0.85-0.95) in the derivation cohort and 0.85 (95% CI, 0.77-0.93) in the validation cohort when patients with uncertain expert diagnosis labeled as “uncertain ARDS” were excluded. The AUROCC was 0.83 (95% CI, 0.77-0.88) in the derivation cohort and 0.80 (95% CI, 0.72-87) in the validation cohort when applied to all patients.

#### Comments

- The LUS-ARDS score demonstrated good diagnostic accuracy for ARDS in this study; however, the majority of patients had a pulmonary cause of ARDS, and it is unclear how this score would perform in different cohorts of ARDS patients.
- In sub-group analysis, the score showed high diagnostic accuracy with an AUROCC of 0.84 (95% CI, 0.79-89) when compared to 229 patients who had a chest CT available across both cohorts, comparable performance to ARDS diagnosis by independent evaluation of CXR by experts and improved the diagnostic accuracy in cases when a diagnosis of ARDS by the expert panel was uncertain.
- The score was calculated from a combined assessment of left and right LUS aeration scores based on the number and presence of B-lines in each region and the number of anterolateral regions with pleural line abnormalities.
- Patients could not receive the LUS initial test if missing multiple regions due certain scenarios (e.g., chest wounds, drains or subcutaneous emphysema) and this highlights the limitations of LUS performance.
- This study had 3 dedicated sonographers performing the tests and future research should focus on score validation with different operators in various settings to evaluate for interobserver variability.

**UPDATED ESCIM GUIDELINES ON MANAGEMENT OF ARDS**

Grasselli G, Calfee CS, Camporota L, Poole D, Amato MBP, Antonelli M, Arabi YM, Baroncelli F, Beitler JR, Bellani G, Bellingan G, Blackwood B, Bos LDJ, Brochard L, Brodie D, Burns KEA, Combes A, D'Arrigo S, De Backer D, Demoule A, Einav S, Fan E, Ferguson ND, Frat JP, Gattinoni L, Guérin C, Herridge MS, Hodgson C, Hough CL, Jaber S, Juffermans NP, Karagiannidis C, Kesecioglu J, Kwizera A, Laffey JG, Mancebo J, Matthay MA, McAuley DF, Mercat A, Meyer NJ, Moss M, Munshi L, Myatra SN, Ng Gong M, Papazian L, Patel BK, Pellegrini M, Perner A, Pesenti A, Piquilloud L, Qiu H, Ranieri MV, Riviello E, Slutsky AS, Stapleton RD, Summers C, Thompson TB, Valente Barbas CS, Villar J, Ware LB, Weiss B, Zampieri FG, Azoulay E, Cecconi M; European Society of Intensive Care Medicine Taskforce on ARDS. **ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies.** *Intensive Care Med.* 2023 Jul;49(7):727-759

**Summary**

ESICM released updated clinical practice guidelines focusing on ARDS definition, ARDS phenotyping and respiratory and non-respiratory support for patients with or at risk for ARDS. The panel noted the growing need to address the increasing use of HFNO in the definition of ARDS and interest in sub-phenotyping ARDS to reflect potential differential response to therapies. Key changes from the 2017 guidelines include specific recommendations for non-mechanically ventilated patients with AHRF (at risk for ARDS) where HFNO was noted to be superior to routine supplemental oxygen and should be utilized to prevent intubation in this population. Non-invasive ventilation (NIV) may be considered instead of HFNO to prevent re-intubation in patients with AHRF due to COVID-19. For intubated patients with ARDS, the panel continued to recommend use of low- tidal volume ventilation based on pathophysiologic rationale. However, the use of prolonged or brief high-pressure recruitment maneuvers and routine neuromuscular blockage use was no longer recommended. Other recommendations included early use of prone positioning in intubated patients with moderate to severe ARDS to reduce mortality, consideration of awake prone positioning in patients with COVID-19 related AHRF to reduce intubation and referral to ECMO centers for

consideration of VV-ECMO for select patients with severe ARDS.

**Comments**

1. The guidelines specifically highlight ARDS due to COVID-19 as a sub-type and this further emphasizes the challenges with making treatment recommendations while accounting for the heterogeneity of ARDS.
2. Notably, the panel stated that there was insufficient evidence to recommend a specific interface such as the helmet for non-invasive ventilation.
3. Despite recognition of the physiologic rationale for PEEP strategies, the panel had insufficient evidence to recommend a specific PEEP titration strategy (higher PEEP/FiO<sub>2</sub> vs. lower PEEP/FiO<sub>2</sub>).
4. Unlike the 2017 guidelines, the panel does not comment on the use of alternative ventilator strategies (e.g., high-frequency oscillatory ventilation).
5. Routine use of Extracorporeal carbon dioxide removal was not recommended in ARDS outside of clinical trials.

**UPDATED ATS GUIDELINES ON MANAGEMENT OF ARDS**

Qadir N, Sahetya S, Munshi L, Summers C, Abrams D, Beitler J, Bellani G, Brower RG, Burry L, Chen JT, Hodgson C, Hough CL, Lamontagne F, Law A, Papazian L, Pham T, Rubin E, Siuba M, Telias I, Patolia S, Chaudhuri D, Walkey A, Rochweg B, Fan E. **An Update on Management of Adult Patients with Acute Respiratory Distress Syndrome: An Official American Thoracic Society Clinical Practice Guideline.** *Am J Respir Crit Care Med.* 2024 Jan 1;209(1):24-36.

**Summary**

The ATS released guidelines with evidence-based practice recommendations for the management of ARDS in adult patients as an update to the 2017 guidelines. Strong recommendations for the use of low-tidal volume ventilation in all ARDS and prone positioning for severe ARDS remain from the 2017 guidelines. Compared to prior guidelines, the use of steroids and neuromuscular blockade (NMB) are both addressed in this update. Administration of corticosteroids for ARDS



is conditionally recommended for all patients with focus on the specific case of ARDS (e.g., COVID-19, community acquired pneumonia) and without specific guidance on timing, duration, dose or agent of choice. NMB is conditionally recommended in early severe ARDS and treatment is recommended for a maximum of 48 hours. Consistent with the ESCIM guidelines, VV-ECMO is recommended for select patients with severe ARDS after optimization of mechanical ventilation and adjunct therapy such as prone positioning and optimal ventilator management. Prolonged lung recruitment maneuvers are strongly discouraged. Opposed to the ESCIM guidelines, there is a brief comment on alternative ventilator strategies with a strong recommendation against the routine use of high-frequency oscillatory ventilation for moderate to severe ARDS.

### Comments

1. The conditional recommendation of steroids in patients with ARDS with a  $\text{PaO}_2/\text{FiO}_2 \leq 300$  is a significant practice change and may trigger routine steroid use in a large number of patients; two upcoming trials of steroids in ARDS (CORT-E2 and GuARDS) will further inform this recommendation.
2. Compared to the ESCIM guidelines, the ATS guidelines do not address the current ARDS definition or how to address management of non-intubated patients with acute hypoxemic respiratory failure or at risk of ARDS.
3. The ESCIM and ATS vary in their recommendation for the use of NMB in ARDS.
4. While the conditional recommendation for NMB use in severe ARDS was based on pooled data from seven randomized trials demonstrating a possible reduction in mortality with NMB use, there were variable sedation strategies in the different RCTs, and the mortality benefit was only noted when NMB was compared to deep sedation.
5. Conditional recommendation for a higher PEEP strategy in moderate to severe ARDS was based on a meta-analysis of 18 randomized trials in which higher PEEP was associated with lower mortality; however, the optimal strategy for consistent benefit is still uncertain.

### OTHER ARTICLES OF INTEREST

#### VENTILATOR MANAGEMENT IN ARDS

Jimenez JV, Munroe E, Weirauch AJ, Fiorino K, Culter CA, Nelson K, Labaki WW, Choi PJ, Co I, Standiford TJ, Prescott HC, Hyzy RC. **Electric impedance tomography-guided PEEP titration reduces mechanical power in ARDS: a randomized crossover pilot trial.** *Crit Care.* 2023 Jan 17;27(1):21.

Peltan ID, Knighton AJ, Barney BJ, Wolfe D, Jacobs JR, Klippel C, Allen L, Lanspa MJ, Leither LM, Brown SM, Srivastava R, Grissom CK. **Delivery of Lung-protective Ventilation for Acute Respiratory Distress Syndrome: A Hybrid Implementation-Effectiveness Trial.** *Ann Am Thorac Soc.* 2023 Mar;20(3):424-432.

Richard JC, Terzi N, Yonis H, Chorfa F, Wallet F, Dupuis C, Argaud L, Delannoy B, Thiery G, Pommier C, Abraham P, Muller M, Sigaud F, Rigault G, Joffredo E, Mezidi M, Souweine B, Baboi L, Serrier H, Rabilloud M, Bitker L; VT4COVID collaborators. **Ultra-low tidal volume ventilation for COVID-19-related ARDS in France (VT4COVID): a multicentre, open-label, parallel-group, randomised trial.** *Lancet Respir Med.* 2023 Nov;11(11):991-1002

#### PRONE POSITIONING DURING VV-ECMO IN SEVERE ARDS

Schmidt M, Hajage D, Lebreton G, Dres M, Guervilly C, Richard JC, Sonnevile R, Winiszewski H, Muller G, Beduneau G, Mercier E, Roze H, Lesouhaitier M, Terzi N, Thille AW, Laurent I, Kimmoun A, Combes A; PRONECMO Investigators, the REVA Network, and the International ECMO Network (ECMONet). **Prone Positioning During Extracorporeal Membrane Oxygenation in Patients With Severe ARDS: The PRONECMO Randomized Clinical Trial.** *JAMA.* 2023 Dec 26;330(24):2343-2353.

## EVALUATION OF THERAPIES FOR COVID-19 ARDS

Gorman EA, Rynne J, Gardiner HJ, Rostron AJ, Bannard-Smith J, Bentley AM, Brealey D, Campbell C, Curley G, Clarke M, Dushianthan A, Hopkins P, Jackson C, Kefela K, Krasnodembskaya A, Laffey JG, McDowell C, McFarland M, McFerran J, McGuigan P, Perkins GD, Silversides J, Smythe J, Thompson J, Tunnicliffe WS, Welters IDM, Amado-Rodríguez L, Albaiceta G, Williams B, Shankar-Hari M, McAuley DF, O'Kane CM. **Repair of Acute Respiratory Distress Syndrome in COVID-19 by Stromal Cells (REALIST-COVID Trial): A Multicenter, Randomized, Controlled Clinical Trial.** *Am J Respir Crit Care Med.* 2023 Aug 1;208(3):256-269.

LOVIT-COVID Investigators, on behalf of the Canadian Critical Care Trials Group, and the REMAP-CAP Investigators; Adhikari NKJ, Hashmi M, Tirupakuzhi Vijayaraghavan BK, Haniffa R, Beane A, Webb SA, Angus DC, Gordon AC, Cook DJ, Guyatt GH, Berry LR, Lorenzi E, Mouncey PR, Au C, Pinto R, Ménard J, Sprague S, Masse MH, Huang DT, Heyland DK, Nichol AD, McArthur CJ, de Man A, Al-Beidh F, Annane D, Anstey M, Arabi YM, Battista MC, Berry S, Bhimani Z, Bonten MJM, Bradbury CA, Brant EB, Brunkhorst FM, Burrell A, Buxton M, Cecconi M, Cheng AC, Cohen D, Cove ME, Day AG, Derde LPG, Detry MA, Estcourt LJ, Fagbodun EO, Fitzgerald M, Goossens H, Green C, Higgins AM, Hills TE, Ichihara N, Jayakumar D, Kanji S, Khoso MN, Lawler PR, Lewis RJ, Litton E, Marshall JC, McAuley DF, McGlothlin A, McGuinness SP, McQuilten ZK, McVerry BJ, Murthy S, Parke RL, Parker JC, Reyes LF, Rowan KM, Saito H, Salahuddin N, Santos MS, Saunders CT, Seymour CW, Shankar-Hari M, Tolppa T, Trapani T, Turgeon AF, Turner AM, Udy AA, van de Veerdonk FL, Zarychanski R, Lamontagne F. **Intravenous Vitamin C for Patients Hospitalized With COVID-19: Two Harmonized Randomized Clinical Trials.** *JAMA.* 2023 Nov 14;330(18):1745-1759.

## EFFECT OF STATINS ON MORTALITY IN ARDS PATIENTS WITH LOW CHOLESTEROL LEVELS

Pienkos SM, Moore AR, Guan J, Levitt JE, Matthay MA, Baron RM, Conlon J, McAuley DF, O'Kane CM, Rogers AJ. **Effect of total cholesterol and statin therapy on mortality in ARDS patients: a secondary analysis of the SAILS and HARP-2 trials.** *Crit Care.* 2023 Mar 28;27(1):126.

## LATENT CLASS ANALYSIS TO IDENTIFY INFLAMMATORY PHENOTYPES IN PATIENTS AT RISK OF ARDS

Redaelli S, von Wedel D, Fosset M, Suleiman A, Chen G, Alingrin J, Gong MN, Gajic O, Goodspeed V, Talmor D, Schaefer MS, Jung B. **Inflammatory subphenotypes in patients at risk of ARDS: evidence from the LIPS-A trial.** *Intensive Care Med.* 2023 Dec;49(12):1499-1507.

## Asthma

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### ASSOCIATION OF A HOUSING MOBILITY PROGRAM WITH CHILDHOOD ASTHMA SYMPTOMS AND EXACERBATIONS

Pollack CE, Roberts LC, Peng RD, Cimbalic P, Judy D, Balcer-Whaley S, Grant T, Rule A, Deluca S, Davis MF, Wright RJ, Keet CA, Matsui EC. **Association of a Housing Mobility Program With Childhood Asthma Symptoms and Exacerbations.** *JAMA.* 2023 May 16;329(19):1671-1681. doi: 10.1001/jama.2023.6488. PMID: 37191703; PMCID: PMC10189571.

#### Summary

Social determinants of health account for a substantial proportion of asthma morbidity in the US, of which Black individuals bear a disproportionate burden. Interventions aimed at individual- or household-level exposures have been only modestly successful. Pollack et al examined whether moving children from high- to low-poverty areas through a housing mobility program (BRHP) could reduce asthma morbidity, while attempting to understand possible mediating factors. Asthma morbidity outcomes were compared post/pre move and to a propensity-score matched non-interventional cohort (URECA). Relative to the period prior to the move, BRHP participants experienced a 54% reduction in the odds of experiencing a caregiver-reported exacerbation, and a 59% reduction in the odds of asthma symptom days, after adjustments and compared to the non-interventional URECA cohort. Similar reductions were seen regardless of prior housing assistance and were not attributable to controller therapy changes. The move was associated with greater perceived social cohesion, while perceived stress appeared as the major mediator of improved outcomes. Study limitations included its non-randomized design and restricted geographical representation. Cost effectiveness analyses remain to be conducted. This study demonstrates that policy decisions that target the social determinants of health can reduce asthma morbidity to degrees similar to asthma biologics.

#### Comments

1. A housing intervention that moved predominantly Black children living in high-poverty neighborhoods to low-poverty neighborhoods led to >50% reductions in asthma exacerbation rates.
2. Improvements in asthma exacerbation rates with the housing mobility program were concordant with improvement in asthma symptom days, and in the proportion of children who have exacerbation-prone asthma.
3. Results were significant after adjustment for covariates including seasonality, age, and sex and were not attributable to aging of the children, or regression to the mean in exacerbation rates.
4. Decreases in secondhand smoke exposure accounted for only a small proportion of the asthma outcome improvement, while reductions in pest allergen exposure, indoor particulate matter did not.

### RESPIRATORY SYNCYTIAL VIRUS INFECTION DURING INFANCY AND ASTHMA DURING CHILDHOOD IN THE USA (INSPIRE): A POPULATION-BASED, PROSPECTIVE BIRTH COHORT STUDY

Rosas-Salazar C, Chirkova T, Gebretsadik T, Chappell JD, Peebles RS Jr, Dupont WD, Jadhao SJ, Gergen PJ, Anderson LJ, Hartert TV. **Respiratory syncytial virus infection during infancy and asthma during childhood in the USA (INSPIRE): a population-based, prospective birth cohort study.** *Lancet.* 2023 May 20;401(10389):1669-1680. doi: 10.1016/S0140-6736(23)00811-5. Epub 2023 Apr 20. PMID: 37086744; PMCID: PMC10367596.

#### Summary

Respiratory syncytial virus (RSV) infects nearly all children by age 3 years, and RSV infection is a major cause of morbidity in infants. Many observational studies have reported the association between RSV bronchiolitis and childhood asthma, but only a minority

of RSV infections lead to bronchiolitis (~40%). Prior studies documenting this association were subject to ascertainment error (by including RSV hospitalizations, not just RSV infection, and the no-RSV group including mild RSV infections). In this article, the authors conducted a prospective population-based birth cohort study (INSPIRE) which ascertained RSV infection during infancy and identified RSV with molecular and serological techniques, and not just RSV hospitalizations. They found that proportion of children with 5-year asthma, ascertained through yearly parental contacts, was lower among those without vs. those with RSV infection during infancy (91/587[16%] vs. 139/670[21%], respectively), representing a 26% lower risk ( $p=0.014$ ). Sensitivity analyses showed similar results among those with RT-PCR-detected RSV infection and using different asthma definitions. All interaction analyses (e.g., by daycare attendance) were negative. These results suggest that RSV infection, not just bronchiolitis, is a risk factor for childhood asthma and justifies interventional studies (e.g., with newer prefusion RSV F-specific antibodies) to attempt to decrease childhood asthma morbidity.

#### Comments

1. Eligible children were healthy and born at term to distinguish eventual current asthma from respiratory diseases attributable to prematurity, and 6 months of younger at the start of their first RSV season for the catchment area of enrollment, study staff frequently contacted study participants' and approached them during unscheduled clinic visits parents to ascertain respiratory infections, and current asthma was defined by parental report or the prescription of asthma medicine, which is subject to classification bias.
2. Adjustment covariates included sex, race and ethnicity, breastfeeding status, day-care attendance during infancy or living with another child younger than 6 years, secondhand smoke exposure, and maternal asthma.
3. The authors had previously shown that host genetics do not influence the risk of RSV infection during childhood (as opposed to shared host genetics for RSV infection severity and asthma).
4. The association might be driven only by a decreased risk of non-atopic asthma, but sample sizes were too small to reliably confirm this result.
5. The authors estimated that 15% of 5-year childhood asthma cases were preventable by RSV infection avoidance, but residual

unmeasured confounding might have affected this estimated proportion.

#### **REDUCTION OF DAILY MAINTENANCE INHALED CORTICOSTEROIDS IN PATIENTS WITH SEVERE EOSINOPHILIC ASTHMA TREATED WITH BENRALIZUMAB (SHAMAL): A RANDOMISED, MULTICENTRE, OPEN LABEL, PHASE 4 STUDY**

Jackson DJ, Heaney LG, Humbert M, Kent BD, Shavit A, Hiljemark L, Olinger L, Cohen D, Menzies-Gow A, Korn S; SHAMAL Investigators. **Reduction of daily maintenance inhaled corticosteroids in patients with severe eosinophilic asthma treated with benralizumab (SHAMAL): a randomised, multicentre, open-label, phase 4 study.** *Lancet.* 2024 Jan 20;403(10423):271-281. doi: 10.1016/S0140-6736(23)02284-5. Epub 2023 Dec 7. PMID: 38071986.

#### Summary

Long-term high-dose inhaled corticosteroids (ICS) use leads to greater side effect rates vs. lower doses. Therefore, asthma guidelines recommend ICS dose reductions for biologic responders whose controller regimen includes high-dose ICS. No studies are available to inform on the safety or method for such ICS dose reductions. In this article, the authors tested whether participants with well-controlled asthma on the anti-IL5Ra biologic benralizumab plus maintenance high-dose ICS+formoterol could undergo ICS dose reductions and maintain asthma control vs. participants who continue maintenance high-dose ICS+formoterol. To do so, they conducted a phase 4, randomized, open-label, trial (SHAMAL) with participants assigned 3:1 to a reduction group (stepwise reductions in ICS dose, as tolerated, in the setting of maintenance and reliever therapy vs. a reference group continuing high-dose ICS+formoterol with as-needed albuterol). The investigators found that 92% of reduction group participants were able to reduce their ICS+formoterol maintenance dose. The reduction group had similar asthma control, asthma exacerbation rates, quality of life, and adverse event rates as the reference group. However, the reduction group experienced a mean 100mL FEV1 decrease and FENO increases vs. the reference group. This study suggests that asthma biologics can allow maintenance ICS dose reductions among patients with well-controlled asthma.

## Comments

1. The reduction group used <1/3 of the cumulative ICS dose used by the reference group, and 61% of the reduction group was able to reduce their regimen to as-needed ICS+formoterol only.
2. Most participants were exacerbation-free during the study period (87% vs. 88% in the reduction and reference groups, respectively).
3. This study was conducted during the COVID19 pandemic which likely contributed to the low rates of asthma exacerbations seen in both the reduction and reference groups.
4. Similar studies are needed to confirm this finding in biologics with different mechanisms of action.

## CLINICAL REMISSION IN SEVERE ASTHMA WITH BIOLOGIC THERAPY: AN ANALYSIS FROM THE UK SEVERE ASTHMA REGISTRY

McDowell PJ, McDowell R, Busby J, Eastwood MC, Patel PH, Jackson DJ, Mansur A, Patel M, Burhan H, Doe S, Chaudhuri R, Gore R, Dodd JW, Subramanian D, Brown T, Heaney LG; UK Severe Asthma Registry. **Clinical remission in severe asthma with biologic therapy: an analysis from the UK Severe Asthma Registry.** *Eur Respir J.* 2023 Dec 14;62(6):2300819. doi: 10.1183/13993003.00819-2023. PMID: 37857423; PMCID: PMC10719453.

## Summary

Biologics have dramatically improved asthma management, and on-biologic clinical remission is possible for many patients. No universally accepted definition of remission exists even though several have been proposed and tested. In this retrospective analysis of patients registered in the UK Severe Asthma Registry who met biologic criteria and were assessed at baseline and on annual review, the authors defined remission as Asthma Control Questionnaire-5 <1.5 (i.e., not uncontrolled), no oral corticosteroids for asthma, and FEV1 above the lower limit of normal or <100 mL less than baseline. With these criteria, 18.3% achieved remission, and remission was more common with older age, males, shorter disease duration, never smoking, nasal polyps, White race, lower BMI, and elevated T2 biomarkers. Greater symptom burden, and number of comorbidities and exacerbations associated with non-remission. Removing the lung function criterion only increased the remission prevalence to 21.2%. A stricter definition of symptom burden with ACQ $\leq$ 0.75 reduced it to 11.9%. Most of those without remission did not meet

multiple remission criteria. The real-world study design might overestimate remission due to regression to the mean. This study identifies symptom burden as the strongest driver of non-remission, possibly due to overlap with non-asthmatic comorbidities, which are unlikely to improve with biologics.

## Comments

1. The likelihood of remission decreased by 14% (95% CI 0.76–0.97) with every 10-year increase in disease duration, which the authors use to justify future studies to address whether earlier biologic initiation can improve long-term disease trajectories.
2. The receiver operating characteristic area under the curve score for predicting remission using the full adjusted model was 0.81, while the most predictive single characteristic was ACQ-5 at 0.71.
3. The only adjustment covariates included in multivariable models were time to first review and hospital, in order to prevent overadjustment bias which occurs when adjustments are made for variables that lie on the causal path between the exposure and outcome.
4. The odds of remission with biologics were 7.44 (95% CI 1.73–31.95)-fold higher among patients with elevated T2 biomarkers (i.e., FeNO>20ppb and blood eosinophils>150/uL), after adjustment.
5. Non-White race lost its significance as a predictor for non-remission when adjustment was made for hospital and baseline comorbidities.

## A NOVEL AIR TRAPPING SEGMENT SCORE IDENTIFIES OPPOSING EFFECTS OF OBESITY AND EOSINOPHILIA ON AIR TRAPPING IN ASTHMA

Leung C, Tang M, Huang BK, Fain SB, Hoffman EA, Choi J, Dunican EM, Mauger DT, Denlinger LC, Jarjour NN, Israel E, Levy BD, Wenzel SE, Sumino K, Hastie AT, Schirm J, McCulloch CE, Peters MC, Woodruff PG, Sorkness RL, Castro M, Fahy JV; NHLBI Severe Asthma Research Program (SARP). **A Novel Air Trapping Segment Score Identifies Opposing Effects of Obesity and Eosinophilia on Air Trapping in Asthma.** *Am J Respir Crit Care Med.* 2023 Dec 19. doi: 10.1164/rccm.202305-0802OC. Epub ahead of print. PMID: 38113166.

## Summary

Air trapping is the excessive retention of gas at expiration. While CT scans and pulmonary function tests detect air trapping, these measures provide whole lung averages which do not account for the heterogeneity of airway segment involvement noted for other asthmatic pathologic manifestations (e.g., mucus plugging). In this article, Leung et al used a novel bronchopulmonary segment level score to characterize clinical phenotypes of air trapping and their persistence over 3 years of follow up on 199 Severe Asthma Research Program-3 (SARP3) participants. While air trapping segment scores correlated with traditional measures of air trapping, most patients (91%) with limited air trapping would have been mislabeled as not having air trapping using a whole lung-averaged attenuation method. Widespread air trapping was associated with severe asthma, more frequent exacerbations, and worse lung function. Air trapping associated with non-obesity, driven by a reduced prevalence of air trapping in the lower lobes of obese individuals. Both sputum and blood eosinophil counts, and mucus plugging scores correlated with higher air trapping scores. Older age associated with worse air trapping segment scores. Air trapping persisted in the same airway segments over 3 years of follow up. This study highlights a potential clinically available asthma severity marker.

## Comments

1. The authors quantified air trapping as % voxels with an attenuation value  $< -856$  Hounsfield units at functional residual capacity (i.e., low attenuation areas, LAA856%), and a bronchopulmonary segment was labeled as air trapped if LAA856% was  $\geq 15$ , a threshold based on 95<sup>th</sup> percentile scores from healthy controls.
2. The authors correlated their novel airway segment scores with traditional measures of air trapping that included whole lung LAA856%, Jacobian mean index, anisotropic deformation index, disease probability measure for air trapping, expiratory-to-inspiratory ratio of mean lung density, and expiratory-to-inspiratory.
3. BMI was inversely associated with air trapping score.
4. Whether this air trapping segment score identifies a population with severe asthma distinct from those that can be identified by more readily available biomarkers (e.g., blood eosinophils) remains to be determined.

## PREVALENCE, DIAGNOSTIC UTILITY AND ASSOCIATED CHARACTERISTICS OF BRONCHODILATOR RESPONSIVENESS

Beasley R, Hughes R, Agusti A, Calverley P, Chipps B, Del Olmo R, Papi A, Price D, Reddel H, Müllerová H, Rapsomaniki E. **Prevalence, Diagnostic Utility and Associated Characteristics of Bronchodilator Responsiveness.** *Am J Respir Crit Care Med.* 2024 Feb 15;209(4):390-401. doi: 10.1164/rccm.202308-1436OC. PMID: 38029294; PMCID: PMC10878375.

## Summary

Bronchodilator response (BDR) is a diagnostic feature of asthma also known to be present among individuals with other airway diseases (i.e., COPD and asthma-COPD overlap [ACO]). The prevalence of BDR is unclear. A joint ERS/ATS taskforce defined BDR in 2005 as a change in FEV1 or FVC of  $\geq 12\%$  and  $\geq 200$  mL and replaced that definition in 2021 as a change in FEV1 or FVC of  $\geq 10\%$  predicted. In this article, the authors set out to determine the prevalence and diagnostic utility of BDR by comparing these two definitions using data from NOVELTY, an international, prospective, observational cohort of patients aged 12+ years with suspected or physician-diagnosed asthma or COPD, and categorized as having asthma, COPD or ACO. Spirometers were provided to all 253 sites. The authors found that the proportion of individuals with +BDR was only modestly lower using the 2021 vs. 2005 BDR criteria, and that those with asthma had a lower prevalence of +BDR vs. those with COPD and ACO. Results from this study question whether BDR should be an asthma diagnostic criterion, which would broaden patient inclusion into clinical trials, and calls for using BDR instead as a treatable trait.

## Comments

1. Only a minority of individuals with asthma have BDR, and BDR has poor discriminatory ability for distinguishing asthma from COPD or ACO regardless of BDR criteria used, and although higher BDR levels are more likely to be observed in asthma, most individuals with asthma do not exhibit high BDR levels.
2. The proportion of individuals with + BDR increases with worsening lung function (i.e., lower FEV1), worse physician assessed severity, higher intensity asthma controller therapy, and greater asthma morbidity.
3. The 2005 but not the 2021 BDR criteria associates with a higher likelihood of subsequent exacerbations, suggesting that clinical trials that use the 2005 BDR definition

as inclusion criterion enrich their cohorts with individuals more likely to exacerbate.

4. The two components of the 2021 definition led to contradictory results on the prevalence of +BDR in asthma vs. COPD (with the FEV1  $\geq$ 10% predicted component, 15% of asthma and 8% of

COPD had +BDR, while with the FVC  $\geq$ 10% predicted component, 9% of asthma and 15% of COPD had a +BDR).

5. The study was limited in that it included only a single BDR assessment, and is not generalizable to children younger than 12 years.

## Health Equity

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### CRITICAL CARE MEDICINE

Armstrong-Hough M, Lin P, Venkatesh S, Ghous M, Hough CL, Cook SH, Iwashyna TJ, Valley TS. **Ethnic Disparities in Deep Sedation of Patients with Acute Respiratory Distress Syndrome in the United States: Secondary Analysis of a Multicenter Randomized Trial.** *Ann Am Thorac Soc.* 2024 Feb 7. doi: 10.1513/AnnalsATS.202307-600OC. Epub ahead of print. PMID: 38324712.

#### Summary:

In this secondary analysis of the ROSE trial, Armstrong-Hough et al explore one potential mechanism for increased deaths among Hispanic patients with ARDS. The ROSE trial enrolled 1,006 participants across 48 hospitals to consider the value of early paralysis. The present analysis, by contrast, considered only the 263 participants cared for in a facility that cared for at least one Hispanic enrollee. Their multi-level, multivariable approach allowed adjustment not only for demographics and illness severity, but also hospital- and patient-level differences. In both their primary analysis, and a series of sensitivity tests—including amongst the entire control arm—Hispanic patients had significantly higher odds of deep sedation.

In the quest to better understand the disparities observed in one ethnic group Armstrong-Hough and colleagues have identified an important point of universal poor practice. While Hispanics are a diverse group for whom the literature increasingly encourages disaggregation, it is also true that, as here, structural inequities can tend to homogenize all towards poorer outcomes. Both demonstrate important dynamics in health equity research. Beyond that, this work moves us towards specific, intervenable hypotheses to address the observed disparities.

#### Comments

1. Despite representing guideline-discordant practice, use of deep sedation was common in ARDS care for all patients.

2. Hispanic-serving hospitals were more likely to treat participants with deep sedation, regardless of their particular race/ethnicity.
3. Even after accounting for these factors, Hispanic patients had approximately 5x the odds of deep sedation as compared with Non-Hispanic Whites.
4. Differences in language preference was hypothesized as an important mechanism, but will require a separate, dedicated study to assess.

### CHRONIC RESPIRATORY DISEASE

Pollack CE, Roberts LC, Peng RD, Cimboric P, Judy D, Balcer-Whaley S, Grant T, Rule A, Deluca S, Davis MF, Wright RJ, Keet CA, Matsui EC. **Association of a Housing Mobility Program With Childhood Asthma Symptoms and Exacerbations.** *JAMA.* 2023 May 16;329(19):1671-1681. doi: 10.1001/jama.2023.6488. PMID: 37191703; PMCID: PMC10189571.

#### Summary

In response to a federal housing discrimination lawsuit, the city of Baltimore has developed the Baltimore Regional Housing Program (BRHP), which uses vouchers and education programs to help disadvantaged residents relocate to better-resourced neighborhoods. Pollack et al take advantage of this important innovation to assess the impact of housing interventions on asthma control. The 5-year prospective cohort compared exacerbations and maximum symptom days between children with persistent asthma whose households were BRHP enrollees versus a propensity-matched sample from another cohort of persistent asthmatics from high poverty neighborhoods, these without support for relocation. Relocating to better neighborhoods through BRHP was associated with reduced treatment intensity, 59% lower odds of symptom days, and 54% reduced odds of exacerbation. Reductions in stress mediated a significant, but non-majority portion of these improvements.



This work represents a unique fusion of restorative justice in public policy, contemporary understandings of structural racism, and innovative trial design. It aligns well with prior evidence in other health concerns that neighborhood enrichment can improve outcomes. We should understand from these results that understanding racism and other social inequities are not only important as a matter of ethical principle, but as practical targets for intervention in healthcare.

### Comments

1. The genesis of the poor neighborhood conditions for study participants, and the impact of changing them suggest strongly that observed health disparities in asthma should be discussed in part as health inequities from discriminatory social policies.
2. One important priority is understanding which specific features of neighborhood transition were the most important drivers of improved disease control, or whether there is an emergent/gestalt effect of several differences.
3. Factoring the observed improvements into cost-benefit analyses of similar programs may make a more persuasive case for their expansion.

### PULMONARY FUNCTION TESTING

Bonner SN, Lagisetty K, Reddy RM, Engeda Y, Griggs JJ, Valley TS. **Clinical Implications of Removing Race-Corrected Pulmonary Function Tests for African American Patients Requiring Surgery for Lung Cancer.** *JAMA Surg.* 2023 Oct 1;158(10):1061-1068. doi: 10.1001/jamasurg.2023.3239. Erratum in: *JAMA Surg.* 2023 Oct 1;158(10):1116. PMID: 37585181; PMCID: PMC10433136.

#### Summary

Undertaken as a quality improvement project, Bonner et al analyzed the impact of the new ATS research statement favoring the GLI-Global multi-ethnic composite reference equations (hereafter and by convention called “race-neutral.”). In a critical part of their work, they randomized surgeons to a vignette about early-stage lung cancer management that used either the prior, race-specific or newly recommended race-neutral values. When presented with values derived from a race-neutral reference equation, surgeons were more likely to recommend wedge resection and less likely lobectomy. While risks of other peri-procedural complications was equivocal between the two interpretative strategies, there was a higher

perceived risk of death when evaluating race-neutral values.

Changing pulmonary function test interpretation via the use of race-neutral rather than race-specific reference equations is a very upstream intervention. The direct impact on equitable outcomes is hard to predict, likely context-dependent, and modifiable by implementation strategy. Dedicated work in each application is needed. Bonner’s work fills a critical gap in elucidating this point. Among much needed follow-up work, it begs one question in particular: Are the surgeons correct? Is the perceived higher mortality borne out in the data, or should greater preference for lobectomy always be treated as an unalloyed good?

### Comments

1. Paradoxically, this intervention meant to enhance health equity showed potential to worsen existing racial disparities in access to lobectomy as a curative treatment for early-stage lung cancer.
2. Given prior reports of increased in-hospital mortality among Black patients, efforts to consider perceived risk in the race-neutral system should be weighed alongside renewed efforts to understand observed peri-procedural risks.
3. Careful attention to implementation strategies is needed to prevent unintended health disparities; education may be particularly helpful in this instance.

### THORACIC ONCOLOGY

Núñez ER, Zhang S, Glickman ME, Qian SX, Boudreau JH, Lindenauer PK, Slatore CG, Miller DR, Caverly TJ, Wiener RS. What Goes into Patient Selection for Lung Cancer Screening? **Factors Associated with Clinician Judgments of Suitability for Screening.** *Am J Respir Crit Care Med.* 2024 Jan 15;209(2):197-205. doi: 10.1164/rccm.202301-0155OC. PMID: 37819144; PMCID: PMC10806423.

#### Summary

Lung cancer screening is an important intervention, the benefits of which only emerge with careful, appropriate patient selection. Núñez et al help assess our fidelity to this task with a 6-year retrospective examination of ineligibility determinations within the Veterans Health Administration. To assess likelihood of death in three years—one of the most important ineligibility criteria—they used a random forest model. The hierarchical

mixed model approach otherwise found that providers tended to over-estimate the importance of age and underestimate the importance of continued tobacco use. The most important factor explaining variability in determinations appeared to be the provider his or herself, rather than any quality of the case in question.

This study highlights many problems that may grow in importance in coming years. Age bias is less acknowledged but must be addressed as life expectancy and duration of active social participation extend. “Big data” techniques like random forest models and artificial intelligence can be powerfully harnessed to achieve new insights but are also susceptible to bias and require careful handling to avoid misinterpretation. Ultimately, too, in spite of these many innovations and decision supports, we find in these results the timeless question of how to improve physicians’ judgment.

### Comments

1. The risk of a patient being judged inappropriate ranged from <1% to 74% dependent on the assessing provider, more variability than was seen from any patient characteristic.
2. There were also important observed differences between facilities themselves in the likelihood a patient would be deemed ineligible.
3. Healthy elderly patients may disproportionately benefit from lung cancer screening.

### OTHER ARTICLES OF INTEREST

Rupsha Singh, Paul Juarez, Susan Redline, Anna Nápoles, Chandra Jackson, 0933 Sleep Specialists in Federally Qualified Health Centers: **A Gap in Sleep Health Care Potentially Contributing to Sleep Disparities.** *Sleep*, Volume 46, Issue Supplement\_1, May 2023, Pages A411–A412, <https://doi.org/10.1093/sleep/zsad077.0933>

Rupsha Singh, Raegan Atha, Kristina P Lenker, Susan L Calhoun, Jiangang Liao, Fan He, Alexandros N Vgontzas, Duanping Liao, Edward O Bixler, Chandra L Jackson, Julio Fernandez-Mendoza, Racial/ethnic disparities in the trajectories of insomnia symptoms from childhood to young adulthood, *Sleep*, 2024;,, zsa021, <https://doi.org/10.1093/sleep/zsae021>  
Hua JT, Zell-Baran LM, Moore CM, Rose CS. **Racial Differences in Respiratory Impairment, Pneumoconiosis, and Federal Compensation for Western U.S. Indigenous Coal Miners.** *Ann Am Thorac Soc.* 2023 Nov 2. doi: 10.1513/AnnalsATS.202305-496OC. Epub ahead of print. PMID: 37916934.

Limaye NP, Matias WR, Rozansky H, et al. **Limited English Proficiency and Sepsis Mortality by Race and Ethnicity.** *JAMA Netw Open.* 2024;7(1):e2350373. doi:10.1001/jamanetworkopen.2023.50373

Adegunsoye A, Freiheit E, White EN, et al. **Evaluation of Pulmonary Fibrosis Outcomes by Race and Ethnicity in US Adults.** *JAMA Netw Open.* 2023;6(3):e232427. doi:10.1001/jamanetworkopen.2023.2427

Koo MM, Mounce LTA, Rafiq M, Callister MEJ, Singh H, Abel GA, Lyratzopoulos G. **Guideline concordance for timely chest imaging after new presentations of dyspnoea or haemoptysis in primary care: a retrospective cohort study.** *Thorax.* 2024 Feb 15;79(3):236–244. doi: 10.1136/thorax-2022-219509. PMID: 37620048.

Mehta AB, Taylor JK, Day G, Lane TC, Douglas IS. **Disparities in Adult Patient Selection for Extracorporeal Membrane Oxygenation in the United States: A Population-Level Study.** *Ann Am Thorac Soc.* 2023 Aug;20(8):1166–1174. doi: 10.1513/AnnalsATS.202212-1029OC. PMID: 37021958; PMCID: PMC10405618.

# Lung Cancer

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## EPIDEMIOLOGY

Kratzer TB, Bandi P, Freedman ND, Smith RA, Travis WD, Jemal A, Siegel RL. **Lung cancer statistics, 2023.** *Cancer*. 2024 Jan 27. doi: 10.1002/cncr.35128. Epub ahead of print. PMID: 38279776.

## Summary

This article updates trends in lung cancer incidence and mortality across the United States using a combination of population registry data derived from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, the Centers for Disease Control and Prevention, and the North American Association of Central Cancer Registries. This data was updated through calendar year 2019. This demonstrates ongoing trends of a sustained decline in lung cancer incidence in both men and women, declining by 1.1-2.6% annually, reflecting decreases in population tobacco use. Lung cancer survival has increased more substantially, absolute gains in 2-year relative survival are approximately 1.4% annually. This likely reflects a combination of expanded access to care, improved advanced cancer therapies for non-small cell lung cancer, and a stage shift related to screening and earlier diagnosis. Both national and state registry data reveals significant disparities across states and racial-ethnic groups.

## Comments

1. This article provides insights into national and state-level trends in lung cancer data by combining Surveillance, Epidemiology, and End Results (SEER) registry data and National Program of Cancer Registries data as well as state-level registries.
2. Declines in lung cancer incidence have been seen since the 1990s in men, and the 2000s in women, reflecting differences in population-level smoking behavior.
3. Lung cancer incidence is the highest among American Indian/Alaska Natives compared to other racial or ethnic groups. There is wide variation in lung cancer incidence by race which largely reflects historic smoking prevalence.
4. There are significant trends in increased localized stage disease. Between 2013-2017, localized stage disease increased by 6.5% per year, which likely reflects efforts in lung cancer screening as well as expanded care access.
5. 5-year survival remains lower than other cancer types and is 27% among women and 19% among men; Beyond sex, the survival rate varies significantly by racial-ethnic group which reflects social determinants of health.

## SCREENING

Choi E, Ding VY, Luo SJ, Ten Haaf K, Wu JT, Aredo JV, Wilkens LR, Freedman ND, Backhus LM, Leung AN, Meza R, Lui NS, Haiman CA, Park SL, Le Marchand L, Neal JW, Cheng I, Wakelee HA, Tammemägi MC, Han SS. **Risk Model-Based Lung Cancer Screening and Racial and Ethnic Disparities in the US.** *JAMA Oncol*. 2023 Dec 1;9(12):1640-1648. doi: 10.1001/jamaoncol.2023.4447. PMID: 37883107; PMCID: PMC10603577.

## Summary

This is a retrospective analysis of prospectively collected data through the Multiethnic Cohort Study which enrolled participants aged 45-75 in California and Hawaii between 1993 and 1996. This study included the 105,261 participants who reported a smoking history on enrollment and had available self-reported data on race and ethnicity. Exposure data was defined from a questionnaire at study enrollment and all incident cancers were identified through linkage to the Surveillance, Epidemiology, and End Results (SEER) cancer registries through 2018 to determine incident lung cancer cases within 6 years of enrollment. The main outcomes included a comparison of screening eligibility among lung cancer cases between the United States Preventive Services Task Force (USPSTF) 2021 criteria and the PLCom2012 model (with a 6-year lung cancer risk threshold of  $\geq 1.3\%$ ) as well as a comparison of the eligibility to incidence ratio (E-I ratio) for racial and ethnic groups. The PLCom2012 model was recalibrated to the Multiethnic Cohort Study prior to use. Compared to USPSTF 2021 criteria, risk-based

screening had both higher sensitivity for lung cancer and lower disparities across racial and ethnic groups as summarized by the E-I ratio.

### Comments

1. This article expands on prior work demonstrating that risk-based lung cancer screening may be useful to improve screening efficiency and reduce disparities.
2. The original and publicly available PLCom2012 was recalibrated prior to use due to under-estimation of risk among Japanese American, Latinx and Native Hawaiian/Other Pacific Islander populations.
3. Disparities in the eligibility to incidence ratio (E-I) using USPSTF 2021 criteria were highest comparing Black/African Americans to White participants, with the E-I ratio 53% lower in Black/African Americans (9.5 vs. 20.3).
4. The difference in the E-I ratio was substantially reduced using risk-based screening between Black/African American and White individuals. (15.9 vs. 18.4).
5. In the cohort, risk-based screening showed a higher overall sensitivity for incident lung cancer (67.2%) than USPSTF 2021 criteria (57.7%).

### SCREENING

Rendle KA, Saia CA, Vachani A, Burnett-Hartman AN, Doria-Rose VP, Beucker S, Neslund-Dudas C, Oshiro C, Kim RY, Elston-Lafata J, Honda SA, Ritzwoller D, Wainwright JV, Mitra N, Greenlee RT. **Rates of Downstream Procedures and Complications Associated With Lung Cancer Screening in Routine Clinical Practice : A Retrospective Cohort Study.** *Ann Intern Med.* 2024 Jan;177(1):18-28. doi: 10.7326/M23-0653. Epub 2024 Jan 2. PMID: 38163370.

### Summary

This article presents findings on downstream procedures and procedural complications related to lung cancer screening in a real-world multisite screening cohort. This is a retrospective cohort study of the 5 sites of the Population-based Research to Optimize the Screening Process (PROSPR) Lung Consortium, integrating clinical screening data from 5 diverse health systems. Participants who were aged 55-80, underwent screening between 2014-2018 and had at least a year of follow-up data were included. Investigators used procedural codes to identify both

related diagnostic procedures and procedural harms. A total of 9266 PROSPR participants who underwent baseline lung cancer screening were included. 1472 of these screening exams had abnormal findings and 180 of these patients underwent an invasive diagnostic procedure. 30.6% of all participants who underwent an invasive procedure had a complication within 30 days, and most were defined as a “major” complication. Compared to the National Lung Screening Trial (NLST), PROSPR patients were more likely to be older, more racially diverse and had higher rates of comorbidities. Procedural rates were higher in the PROSPR cohort than NLST for all procedures with the exception of thoracotomy. Overall complication rates were twice as high (30.6% vs. 17.7%) comparing PROSPR to NLST.

### Comments

1. Procedures may be more common after lung cancer screening in clinical practice than in trial settings which may reflect both changes in diagnostic approaches and practice variation.
2. Procedural harms are more common in clinical practice than the NLST and this may largely reflect differences (including age, smoking status and comorbid conditions) in real-world screened patients.
3. The number of invasive procedures, specific invasive procedures used, and complications varied widely across the 5 sites which suggests wide variation in diagnostic workups, practices and administrative coding related to abnormal screening in clinical practice.
4. While the rate of procedural complications was still high in patients without lung cancer (21.7%), most procedures (67%) and complications (76%) occurred in patients ultimately diagnosed with lung cancer.
5. Studies are needed to inform best-practices and standardize diagnostic practice to reduce harms related to lung cancer screening.

### DIAGNOSIS

Mikhael PG, Wohlwend J, Yala A, Karstens L, Xiang J, Takigami AK, Bourgouin PP, Chan P, Mrah S, Amayri W, Juan YH, Yang CT, Wan YL, Lin G, Sequist LV, Fintelmann FJ, Barzilay R. Sybil: **A Validated Deep Learning Model to Predict Future Lung Cancer Risk From a Single Low-Dose Chest Computed Tomography.** *J Clin Oncol.* 2023 Apr 20;41(12):2191-2200. doi: 10.1200/JCO.22.01345. PMID: 36634294; PMCID: PMC1041960

## Summary

This article describes the development, training and validation of a deep learning model to predict both short- and long-term lung cancer risk on the basis of a single screening low dose chest CT. This model, Sybil, was developed using CT examinations from the National Lung Screening Trial (NLST) and designed to predict lung cancer within 1 and 6 years of an index CT. The model was designed to predict lung cancer using an agnostic approach through a deep learning model using 3D convolutional neural network architecture. 15,000 participants from NLST with over 44,000 exams were split between a training, development and test set with suspicious lesions on index CTs for participants lung cancer within 1 year annotated by two radiologists to train the model. The model was then validated in a set-aside group from NLST, a set of US clinical screens (13,309) and a set of clinical screens from Taiwan (12,480). The area under the receiver operator curves (AUC) for 1-year lung cancer prediction was 0.92 in NLST, and in the external cohorts: 0.86 in the US clinical cohort and 0.94 in the Taiwanese cohort.

## Comments

1. Most prior models of lung cancer risk, even when incorporating radiomic features, utilize semantic features of a nodule (such as spiculation) to predict lung cancer risk, as well as patient risk factors, rather than an agnostic deep learning approach.
2. While details are provided on the model development and calibration, it remains uncertain what CT features were most correlated with future lung cancer risk in the model.
3. The validation approach, using clinical screens and including a cohort with lower and never-smoking history (Taiwan) suggests this model may have broad applicability, at least in high-risk cohorts.
4. The authors argue that Sybil output could be utilized to ensure appropriate follow-up for screened patients at highest risk for short-term lung cancer diagnosis.
5. Future study is needed to validate this model in a prospective setting.

## TREATMENT

Altorki N, Wang X, Kozono D, Watt C, Landrenau R, Wigle D, Port J, Jones DR, Conti M, Ashrafi AS, Liberman M, Yasufuku K, Yang S, Mitchell JD, Pass H, Keenan R, Bauer T, Miller D, Kohman LJ, Stinchcombe TE, Vokes E. **Lobar or Sublobar Resection for Peripheral Stage IA Non-Small-Cell Lung Cancer.** *N Engl J Med.* 2023 Feb 9;388(6):489-498. doi: 10.1056/NEJMoa2212083. PMID: 36780674; PMCID: PMC10036605.

## Summary

This is a multicenter randomized controlled trial to evaluate the noninferiority of sublobar resection compared to lobectomy for early-stage non-small cell lung cancers (T1aN0). Over a 10-year period (2007-2017), 697 patients were randomized to receive either sublobar (n=340) or lobar (n=357) resection and were followed for long-term outcomes (median of 7 years) to assess disease-free survival. Randomization occurred intraoperatively and was not concealed from patients, providers or researchers. Sublobar resection included both non-anatomic wedge resection (59%) and anatomic segmental resection (38%), at the surgeon's discretion. The primary composite endpoint of disease-free survival (including disease recurrence or death) demonstrated noninferiority of sublobar resection (hazard ratio of 1.01, 95% confidence interval of 0.83-1.24) and the overall 5-year disease free survival was similar for sublobar resection (63.6%) and lobar resection (64.1%). Limited secondary outcomes are presented, aside from a small difference (2%) in post-operative lung function (forced expiratory volume in one second) favoring the sublobar group.

## Comments

1. This study provides compelling evidence that sublobar resection is not inferior to traditional standard of care (lobectomy) for earliest stage (<2cm) non-small cell lung cancer.
2. This study confirms the non-inferiority of an approach to T1aN0 non-small cell lung cancers that has become common in clinical practice with an increase in early diagnosis and screening.
3. All participants had intraoperative or pre-operative confirmation of node-negative disease which may limit this study in assessing whether invasive nodal staging is necessary for earliest stage non-small cell lung cancer.
4. Beyond lung function, this study does not report other relevant outcomes including peri-

operative complications, hospital stays and impact on long-term functional status.

5. This study, along with others (including a trial comparing radiation-based treatment for early non-small cell lung cancer) are essential to optimize approaches to early-stage lung cancer management.

## TREATMENT

Tsuboi M, Herbst RS, John T, Kato T, Majem M, Grohé C, Wang J, Goldman JW, Lu S, Su WC, de Marinis F, Shepherd FA, Lee KH, Le NT, Dechaphunkul A, Kowalski D, Poole L, Bolanos A, Rukazenkov Y, Wu YL; ADAURA Investigators. **Overall Survival with Osimertinib in Resected EGFR-Mutated NSCLC.** *N Engl J Med.* 2023 Jul 13;389(2):137-147. doi: 10.1056/NEJMoa2304594. PMID: 37272535.

### Summary

This study presents the updated, and final, planned analyses from the ADAURA trial. Between 2015-2019, the ADAURA trial enrolled 682 participants with stage IB to IIIA non-squamous non-small cell lung cancer who underwent surgical resection of the primary tumor with a confirmed EGFR mutation. In this double-blind trial, participants were randomized to receive either the tyrosine kinase inhibitor Osimertinib or placebo for up to 3 years, in addition to clinical prescribed standard of care including adjuvant chemotherapy. Initial interim analyses, published in 2020, demonstrated significant improvement in 2-year disease free survival in the Osimertinib arm in those with stage II-IIIa disease. In this updated and final analysis, the authors report 5-year follow-up on participants to compare overall survival. In the primary analytic group (stage II-IIIa), the 5-year overall survival was 85% in the Osimertinib group and 73% in this control group ( $p < 0.001$ ) with limited adverse events related to treatment. In secondary analyses, a survival benefit at 5-years was not significant for patients with stage IB, with overall deaths low in both arms (12% in placebo arm, 6% in Osimertinib arm).

### Comments

1. In the original ADAURA trial interim report at 2-years, the major of outcomes for the disease-free survival composite were relapses rather than death; this study provides more patient-centered data on benefit in overall survival.

2. Far more participants in the placebo group (54%) received subsequent anti-cancer treatments than the Osimertinib group, however survival was entirely established using an intention to treat protocol.
3. There were limited adverse events despite longer follow-up times in this updated analysis.
4. The benefit of adjuvant Osimertinib remains uncertain for patients with stage IB EGFR-mutated lung cancer.
5. This trial does not establish the optimal treatment regimen with Osimertinib, and there may be benefit for treatment beyond 3 years.

## OTHER ARTICLES OF INTEREST

### EPIDEMIOLOGY

Bonner SN, Curley R, Love K, Akande T, Akhtar A, Erhunmwunsee L. **Structural Racism and Lung Cancer Risk: A Scoping Review.** *JAMA Oncol.* 2024 Jan 1;10(1):122-128. doi: 10.1001/jamaoncol.2023.4897. PMID: 38032677.

### SCREENING

Wolf AMD, Oeffinger KC, Shih TY, Walter LC, Church TR, Fontham ETH, Elkin EB, Etzioni RD, Guerra CE, Perkins RB, Kondo KK, Kratzer TB, Manassaram-Baptiste D, Dahut WL, Smith RA. **Screening for lung cancer: 2023 guideline update from the American Cancer Society.** *CA Cancer J Clin.* 2024 Jan-Feb;74(1):50-81. doi: 10.3322/caac.21811. Epub 2023 Nov 1. PMID: 37909877.

Nadig TR, Thomas N, Nietert PJ, Lozier J, Tanner NT, Wang Memoli JS, Pastis NJ, Silvestri GA. **Guided Bronchoscopy for the Evaluation of Pulmonary Lesions: An Updated Meta-analysis.** *Chest.* 2023 Jun;163(6):1589-1598. doi: 10.1016/j.chest.2022.12.044. Epub 2023 Jan 11. PMID: 36640994.

Núñez ER, Zhang S, Glickman ME, Qian SX, Boudreau JH, Lindenauer PK, Slatore CG, Miller DR, Caverly TJ, Wiener RS. **What Goes into Patient Selection for Lung Cancer Screening? Factors Associated with Clinician Judgments of Suitability for Screening.** *Am J Respir Crit Care Med.* 2024 Jan 15;209(2):197-205. doi: 10.1164/rccm.202301-0155OC. PMID: 37819144; PMCID: PMC10806423.

Toumazis I, Cao P, de Nijs K, Bastani M, Munshi V, Hemmati M, Ten Haaf K, Jeon J, Tammemägi M, Gazelle GS, Feuer EJ, Kong CY, Meza R, de Koning HJ, Plevritis SK, Han SS. **Risk Model-Based Lung Cancer Screening : A Cost-Effectiveness Analysis.** *Ann Intern Med.* 2023

Mar;176(3):320-332. doi: 10.7326/M22-2216. Epub 2023 Feb 7. PMID: 36745885.

Silvestri GA, Goldman L, Tanner NT, Bureson J, Gould M, Kazerooni EA, Mazzone PJ, Rivera MP, Doria-Rose VP, Rosenthal LS, Simanowith M, Smith RA, Fedewa S.

**Outcomes From More Than 1 Million People Screened for Lung Cancer With Low-Dose CT Imaging.** *Chest.* 2023 Jul;164(1):241-251. doi: 10.1016/j.chest.2023.02.003. Epub 2023 Feb 10. PMID: 36773935; PMCID: PMC10331628.

Ahmed A, Hippe DS, Snidarich M, Crothers K, Triplette M. **Delays in Recommended Follow-Up after Positive Findings in Lung Cancer Screening.** *Ann Am Thorac Soc.* 2023 Aug;20(8):1175-1181. doi: 10.1513/AnnalsATS.202210-891OC. PMID: 36973008.

## DIAGNOSIS

Meernik C, Raveendran Y, Kolarova M, Rahman F, Olunuga E, Hammond E, Shivaramakrishnan A, Hendren S, Bosworth HB, Check DK, Green M, Strickler JH, Akinyemiju T. **Racial and ethnic disparities in genomic testing among lung cancer patients: a systematic review.** *J Natl Cancer Inst.* 2024 Feb 6:djae026. doi: 10.1093/jnci/djae026. Epub ahead of print. PMID: 38321254.

Fong KM, Rosenthal A, Giroux DJ, Nishimura KK, Erasmus J, Lievens Y, Marino M, Marom EM, Putora PM, Singh N, Suárez F, Rami-Porta R, Detterbeck F, Eberhardt WE, Asamura H; Members of the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Members of the Advisory Boards, and Participating Institutions of the Lung Cancer Domain. **The IASLC Lung Cancer Staging Project: Proposals for the Revision of the M Descriptors in the Forthcoming 9th edition of the TNM Classification of Lung Cancer.** *J Thorac Oncol.* 2024 Feb 4:S1556-0864(24)00060-1. doi: 10.1016/j.jtho.2024.01.019. Epub ahead of print. PMID: 38320664.

## TREATMENT

Heymach JV, Harpole D, Mitsudomi T, Taube JM, Galffy G, Hochmair M, Winder T, Zukov R, Garbaos G, Gao S,

Kuroda H, Ostoros G, Tran TV, You J, Lee KY, Antonuzzo L, Papai-Szekely Z, Akamatsu H, Biswas B, Spira A, Crawford J, Le HT, Aperghis M, Doherty GJ, Mann H, Fouad TM, Reck M; AEGEAN Investigators. **Perioperative Durvalumab for Resectable Non-Small-Cell Lung Cancer.** *N Engl J Med.* 2023 Nov 2;389(18):1672-1684. doi: 10.1056/NEJMoa2304875. Epub 2023 Oct 23. PMID: 37870974.

Provencio M, Nadal E, González-Larriba JL, Martínez-Martí A, Bernabé R, Bosch-Barrera J, Casal-Rubio J, Calvo V, Insa A, Ponce S, Reguart N, de Castro J, Mosquera J, Cobo M, Aguilar A, López Vivanco G, Camps C, López-Castro R, Morán T, Barneto I, Rodríguez-Abreu D, Serna-Blasco R, Benítez R, Aguado de la Rosa C, Palmero R, Hernando-Trancho F, Martín-López J, Cruz-Bermúdez A, Massuti B, Romero A. **Perioperative Nivolumab and Chemotherapy in Stage III Non-Small-Cell Lung Cancer.** *N Engl J Med.* 2023 Aug 10;389(6):504-513. doi: 10.1056/NEJMoa2215530. Epub 2023 Jun 28. PMID: 37379158.

West HJ, Kim JY. **Rapid Advances in Resectable Non-Small Cell Lung Cancer: A Narrative Review.** *JAMA Oncol.* 2024 Feb 1;10(2):249-255. doi: 10.1001/jamaoncol.2023.5276. PMID: 38153722.

## SURVIVORSHIP

Takemura N, Cheung DST, Fong DYT, Lee AWM, Lam TC, Ho JC, Kam TY, Chik JYK, Lin CC. **Effectiveness of Aerobic Exercise and Tai Chi Interventions on Sleep Quality in Patients With Advanced Lung Cancer: A Randomized Clinical Trial.** *JAMA Oncol.* 2024 Feb 1;10(2):176-184. doi: 10.1001/jamaoncol.2023.5248. PMID: 38060250; PMCID: PMC10704344.

Deboever N, Eisenberg M, Hofstetter WL, Mehran RJ, Rice DC, Roth J, Sepesi B, Swisher SG, Vaporciyan AA, Walsh GL, Antonoff MB, Rajaram R. **Financial Toxicity in Patients With Resected Lung Cancer.** *Ann Surg.* 2023 Dec 1;278(6):1038-1044. doi: 10.1097/SLA.0000000000005926. Epub 2023 May 30. PMID: 37249193.

## COPD

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### NEW THERAPIES IN COPD

Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Cole J, Bafadhel M, Christenson SA, Papi A, Singh D, Laws E, Mannent LP, Patel N, Staudinger HW, Yancopoulos GD, Mortensen ER, Akinlade B, Maloney J, Lu X, Bauer D, Bansal A, Robinson LB, Abdulai RM. **Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts.** *N Engl J Med.* 2023;389(3):205-214.

#### Summary

Clinical trials of biologics targeting the interleukin-5 pathway have produced mixed results with regards to exacerbation reduction in patients with COPD. Dupilumab is a fully human monoclonal antibody that inhibits both interleukin-4 and interleukin-13 signaling. BOREAS was a phase 3, multicenter, randomized, placebo-controlled trial designed to investigate the efficacy and safety of dupilumab (administered as 300 mg subcutaneously every 2 weeks) in COPD patients with type 2 inflammation defined as an absolute blood eosinophil count of at least 300/ $\mu$ L at the screening visit. Main inclusion criteria were a post-bronchodilator FEV<sub>1</sub> 30-70% predicted, a history of at least two moderate or one severe COPD exacerbation in the preceding year, receipt of triple inhaler therapy for at least 3 months before randomization and symptoms of chronic bronchitis for at least 3 months in the preceding year. Individuals with a current or past diagnosis of asthma were excluded. The annualized rate of moderate or severe COPD exacerbations during 52 weeks (primary outcome) was 0.78 with dupilumab and 1.10 with placebo (RR 0.70; 95% CI 0.58-0.86). The type and frequency of adverse events were similar in the two groups.

#### Comments

1. Compared to placebo, dupilumab also resulted in significantly greater improvements in lung function, respiratory symptoms and health-related quality of life, with differences observed within 4 weeks and maintained throughout 52 weeks.

2. The beneficial effects of dupilumab on exacerbation frequency and lung function were more pronounced in participants with a baseline fractional exhaled nitric oxide (FENO) level  $\geq$  20 ppb.
3. The efficacy of dupilumab in this COPD population may be explained by its broad effects on type 2 inflammation through inhibition of the interleukin-4 and interleukin-13 pathways, which likely decreases airway remodeling, goblet cell hyperplasia and mucus hypersecretion.
4. The efficacy of dupilumab in patients with lower absolute blood eosinophil counts or without symptoms of chronic bronchitis remains to be determined.
5. Further studies are needed to understand the effects of dupilumab on long-term clinical outcomes such as mortality and exacerbation frequency and lung function change beyond 52 weeks.

### NEW THERAPIES IN COPD

Anzueto A, Barjaktarevic IZ, Siler TM, Rheault T, Bengtsson T, Rickard K, Scierba F. **Ensifentrine, a Novel Phosphodiesterase 3 and 4 Inhibitor for the Treatment of Chronic Obstructive Pulmonary Disease: Randomized, Double-Blind, Placebo-controlled, Multicenter Phase III Trials (the ENHANCE Trials).** *Am J Respir Crit Care Med.* 2023;208(4):406-416.

#### Summary

COPD inhaled therapies have been limited to  $\beta_2$ -agonists, muscarinic antagonists and corticosteroids for the past several decades. Ensifentrine is a novel nebulized dual inhibitor of phosphodiesterase-3 and phosphodiesterase-4 with bronchodilator and anti-inflammatory effects. ENHANCE-1 and -2 were two phase 3, multicenter, randomized, placebo-controlled trials designed to evaluate the efficacy and safety of ensifentrine (administered as 3 mg twice daily through a nebulizer) in patients with COPD. Main inclusion criteria were a post-bronchodilator FEV<sub>1</sub> 30-70%



predicted, a mMRC dyspnea score  $\geq 2$  and receipt of either (a) no maintenance inhaler therapy (31% and 45% of participants in ENHANCE-1 and -2, respectively) or (b) a long-acting beta agonist (LABA) or a long-acting muscarinic antagonist (LAMA) with or without an inhaled corticosteroid (ICS). The primary endpoint of baseline-to-week 12 change in FEV<sub>1</sub> during the 12 hours after dosing (FEV<sub>1</sub> AUC<sub>0-12h</sub>) was higher in the ensifentrine group, with mean differences between ensifentrine and placebo of 87 mL (95% CI 55-119) in ENHANCE-1 and 94 mL (95% CI 65-124) in ENHANCE-2. Participants in the ensifentrine group also had significantly better Transition Dyspnea Index scores and lower COPD exacerbation rates at week 24 in both trials. Adverse events were similar in the ensifentrine and placebo groups.

### Comments

1. Ensifentrine-associated clinical benefits in the maintenance inhaler subgroups of LABA  $\pm$  ICS and LAMA  $\pm$  ICS were similar to those in the main analysis.
2. The COPD exacerbation reduction seen in the ensifentrine group is notable because most participants were on background maintenance inhaler therapy and the trials were not enriched for patients at high exacerbation risk.
3. Diarrhea, a common side effect of oral phosphodiesterase-4 inhibitors, occurred at similar and infrequent rates in the ensifentrine and placebo groups and was not temporally associated with dosing.
4. The consistency of symptom benefit associated with ensifentrine deserves further study as significant improvements in the Evaluating Respiratory Symptoms score, the St. George's Respiratory Questionnaire score and daily rescue medication use were observed in ENHANCE-1, but not in ENHANCE-2.
5. As patients on maintenance LABA + LAMA or LABA + LAMA + ICS were excluded, more data is needed to understand where ensifentrine fits in the COPD treatment algorithm.

### BLOOD EOSINOPHIL-GUIDED THERAPY FOR COPD EXACERBATIONS

Ramakrishnan S, Jeffers H, Langford-Wiley B, Davies J, Thulborn SJ, Mahdi M, A'Court C, Binnian I, Bright S, Cartwright S, Glover V, Law A, Fox R, Jones A, Davies C, Copping D, Russell RE, Bafadhel M. **Blood eosinophil-guided oral prednisolone for COPD exacerbations in primary care in the UK (STARR2): a non-inferiority, multicentre, double-blind, placebo-controlled, randomised controlled trial.** *Lancet Respir Med.* 2024;12(1):67-77.

### Summary

Systemic corticosteroids are currently recommended for the treatment of COPD exacerbations but can result in adverse events. A biomarker-based approach may help guide corticosteroid treatment decisions. STARR2 was a randomized, double-blind, placebo-controlled clinical trial designed to evaluate the efficacy of blood eosinophil-guided oral prednisolone treatment for COPD exacerbations in 14 UK primary care practices. In the blood eosinophil-guided treatment (BET) arm, participants received prednisolone 30 mg daily or matching placebo for 14 days if their blood eosinophil count at the time of exacerbation was  $\geq 2\%$  or  $< 2\%$ , respectively. In the standard care treatment (ST) arm, participants received prednisolone 30 mg daily for 14 days regardless of their blood eosinophil count. Participants in both arms were additionally prescribed a 7-day course of doxycycline. The primary outcome was treatment failure defined as the need for re-treatment of exacerbation, hospitalization for any cause or death within 30 days. Treatment failure occurred in 19% of exacerbations in the BET arm and 32% of exacerbations in the ST arm (relative risk: 0.60; 95% CI 0.33-1.04), indicating that BET was non-inferior to ST as the upper bound of the 95% CI was lower than the pre-determined non-inferiority margin of 1.105.

### Comments

1. Initially designed to show superiority, this study was converted to a non-inferiority trial following detection of an error in the randomization code.
2. The incidence of adverse events (including new glycosuria) was low and similar in the BET and ST arms.
3. In secondary analyses of exacerbations with a blood eosinophil count  $< 2\%$ , those treated with placebo (in the BET arm) were associated with fewer treatment failures than those treated with prednisolone (in the ST arm).
4. The efficacy of blood-eosinophil guided therapy with shorter courses of systemic

corticosteroids, as currently recommended by international COPD guidelines, remains to be determined.

5. The ease of implementation of point-of-care blood eosinophil count testing at the onset of COPD exacerbations in various primary care settings across the world is unclear.

2. The prognostic implications of mucus plugs that do not completely occlude the airways remain to be determined.
3. Whether CT-identified bronchiectasis is an effect modifier of the association between mucus plugs and mortality in patients with COPD deserves further study.
4. Based on the findings of this study and others, the standardization of airway mucus plug reporting and scoring should be explored for chest CTs obtained in clinical practice.

### PROGNOSTIC IMPLICATIONS OF MUCUS PLUGS IN COPD

Diaz AA, Orejas JL, Grumley S, Nath HP, Wang W, Dolliver WR, Yen A, Kligerman SJ, Jacobs K, Manapragada PP, Abozeed M, Aziz MU, Zahid M, Ahmed AN, Terry NL, San José Estépar R, Kim V, Make BJ, Han MK, Sonavane S, Washko GR, Cho M, San José Estépar R. **Airway-Occluding Mucus Plugs and Mortality in Patients With Chronic Obstructive Pulmonary Disease.** *JAMA.* 2023;329(21):1832-1839.

#### Summary

Mucus plugs are common in patients with COPD and adversely affect lung function, oxygen saturation, exercise capacity and health-related quality of life. However, the association between mucus plugs and mortality has not been investigated in COPD. In this analysis of the COPDGene study, baseline chest CTs of 4,363 participants with GOLD 1-4 COPD were examined for the presence of mucus plugs completely occluding the lumen of medium- and large-sized airways (2-10 mm in diameter). The association between extent of mucus plugging and all-cause mortality was tested using Cox proportional-hazard regression models adjusted for age, sex, race, BMI, smoking pack-years, smoking status, FEV<sub>1</sub> and quantitative CT measures of emphysema and airway wall thickness. The number of lung segments affected by mucus plugging was 0, 1-2 and  $\geq 3$  in 59.3%, 21.8% and 18.9% of participants, respectively. Median follow-up was 9.5 years during which 1,769 participants (40.6%) died. Compared to no occluding mucus plugs in any lung segment, mucus plugging in 1-2 lung segments (aHR 1.15; 95% CI 1.02-1.29) and in  $\geq 3$  lung segments (aHR 1.24; 95% CI 1.10-1.41) was independently associated with higher mortality. These associations were maintained after additional adjustments for coronary artery disease, chronic bronchitis and asthma.

#### Comments

1. Targeted therapies to decrease mucus plug burden are needed given our growing understanding of the deleterious clinical effects associated with these plugs in patients with COPD.

### NATURAL HISTORY OF SMOKING-RELATED LUNG DISEASE WITH PRESERVED SPIROMETRY

McKleroy W, Shing T, Anderson WH, Arjomandi M, Awan HA, Barjaktarevic I, Barr RG, Bleecker ER, Boscardin J, Bowler RP, Buhr RG, Criner GJ, Comellas AP, Curtis JL, Dransfield M, Doerschuk CM, Dolezal BA, Drummond MB, Han MK, Hansel NN, Helton K, Hoffman EA, Kaner RJ, Kanner RE, Krishnan JA, Lazarus SC, Martinez FJ, Ohar J, Ortega VE, Paine R 3rd, Peters SP, Reinhardt JM, Rennard S, Smith BM, Tashkin DP, Couper D, Cooper CB, Woodruff PG. **Longitudinal Follow-Up of Participants With Tobacco Exposure and Preserved Spirometry.** *JAMA.* 2023;330(5):442-453.

#### Summary

Although not currently classified as having COPD, individuals with tobacco exposure and preserved spirometry (TEPS) can experience a high burden of respiratory symptoms and exacerbations. The long-term clinical trajectory of these individuals remains to be defined. In this SPIROMICS analysis, participants with TEPS ( $\geq 20$  smoking pack-years; post-bronchodilator FEV<sub>1</sub>/FVC  $\geq 0.7$ ) were categorized as symptomatic or asymptomatic (CAT score  $\geq 10$  vs.  $< 10$ ) and were followed for a median time close to 6 years during which they underwent at least three spirometry measurements. FEV<sub>1</sub> decline was similar in participants with symptomatic (-31.3 mL/y) and asymptomatic (-38.8 mL/y) TEPS for a between-group difference of -7.5 mL/y (95% CI -16.6-1.6 mL/y). Similarly, there was no difference in cumulative COPD incidence between the two groups: 33.0% in symptomatic TEPS and 31.6% in asymptomatic TEPS (HR 1.05; 95% CI 0.76-1.46). Participants with symptomatic TEPS experienced more respiratory exacerbations than their asymptomatic counterparts: 0.23 vs 0.08 exacerbations per person-year (RR 2.38; 95% CI 1.71-3.31). Results were similar in sensitivity analyses that excluded participants with a self-reported history of childhood asthma and that classified participants based on the presence/absence

of chronic bronchitis and the presence/absence of dyspnea (mMRC  $\geq$  2).

### Comments

1. Respiratory exacerbations requiring ED visits or hospitalizations occurred in a higher proportion of participants with symptomatic TEPS (31.4%) than those with asymptomatic TEPS (6.3%) and, remarkably, those with asymptomatic mild-to-moderate COPD (21.2%).
2. This study enrolled older participants (mean age > 60 years) compared to other studies that found an association between non-obstructive respiratory symptoms and FEV<sub>1</sub> decline.
3. Longer durations of follow-up and accounting for non-smoking-related COPD risk factors should improve our understanding of the natural history of TEPS.
4. Beyond lung function trajectories, this study highlights the importance of patient-centered factors such as respiratory symptoms and exacerbations in smoking-related lung disease.
5. Identifying best clinical management strategies for symptomatic TEPS remains a priority given its high prevalence and association with respiratory exacerbations.

### OTHER ARTICLES OF INTEREST

#### EPIDEMIOLOGY

Boers E, Barrett M, Su JG, Benjafield AV, Sinha S, Kaye L, Zar HJ, Vuong V, Tellez D, Gondalia R, Rice MB, Nunez CM, Wedzicha JA, Malhotra A. **Global Burden of Chronic Obstructive Pulmonary Disease Through 2050.** *JAMA Netw Open.* 2023;6(12):e2346598.

#### SUSCEPTIBILITY TO COPD

Ritchie AI, Donaldson GC, Hoffman EA, Allinson JP, Bloom CI, Bolton CE, Choudhury G, Gerard SE, Guo J, Alves-Moreira L, McGarvey L, Sapey E, Stockley RA, Yip KP, Singh D, Wilkinson T, Fageras M, Ostridge K, Jöns O, Bucchioni E, Compton CH, Jones P, Mezzi K, Vestbo J, Calverley PMA, Wedzicha JA. **Structural Predictors of Lung Function Decline in Young Smokers with Normal Spirometry.** *Am J Respir Crit Care Med.* 2024; Epub ahead of print.

Çolak Y, Lange P, Vestbo J, Nordestgaard BG, Afzal S. **Susceptible Young Adults and Development of COPD**

**Later in Life.** *Am J Respir Crit Care Med.* 2024; Epub ahead of print.

#### RACE-SPECIFIC SPIROMETRY REFERENCE EQUATIONS AND COPD SEVERITY

Regan EA, Lowe ME, Make BJ, Curtis JL, Chen QG, Crooks JL, Wilson C, Oates GR, Gregg RW, Baldomero AK, Bhatt SP, Diaz AA, Benos PV, O'Brien JK, Young KA, Kinney GL, Conrad DJ, Lowe KE, DeMeo DL, Non A, Cho MH, Kallet J, Foreman MG, Westney GE, Hoth K, MacIntyre NR, Hanania NA, Wolfe A, Amaza H, Han M, Beaty TH, Hansel NN, McCormack MC, Balasubramanian A, Crapo JD, Silverman EK, Casaburi R, Wise RA. **Early Evidence of Chronic Obstructive Pulmonary Disease Obscured by Race-Specific Prediction Equations.** *Am J Respir Crit Care Med.* 2024;209(1):59-69.

#### EFFECTS OF INDOOR AND OUTDOOR AIR POLLUTION

Hansel NN, Woo H, Koehler K, Gassett A, Paulin LM, Alexis NE, Putcha N, Lorizio W, Fawzy A, Belz D, Sack C, Barr RG, Martinez FJ, Han MK, Woodruff P, Pirozzi C, Paine R 3rd, Barjaktarevic I, Cooper CB, Ortega V, Zusman M, Kaufman JD. **Indoor Pollution and Lung Function Decline in Current and Former Smokers: SPIROMICS AIR.** *Am J Respir Crit Care Med.* 2023;208(10):1042-1051.

Sin DD, Doiron D, Agusti A, Anzueto A, Barnes PJ, Celli BR, Criner GJ, Halpin D, Han MK, Martinez FJ, Montes de Oca M, Papi A, Pavord I, Roche N, Singh D, Stockley R, Lopez Varlera MV, Wedzicha J, Vogelmeier C, Bourbeau J; GOLD Scientific Committee. **Air pollution and COPD: GOLD 2023 committee report.** *Eur Respir J.* 2023;61(5):2202469.

#### MORTALITY

Labaki WW, Gu T, Murray S, Curtis JL, Wells JM, Bhatt SP, Bon J, Diaz AA, Hersh CP, Wan ES, Kim V, Beaty TH, Hokanson JE, Bowler RP, Arenberg DA, Kazerooni EA, Martinez FJ, Silverman EK, Crapo JD, Make BJ, Regan EA, Han MK. **Causes of and Clinical Features Associated with Death in Tobacco Cigarette Users by Lung Function Impairment.** *Am J Respir Crit Care Med.* 2023;208(4):451-460.

Whittaker H, Rothnie KJ, Quint JK. **Cause-specific mortality in COPD subpopulations: a cohort study of 339 647 people in England.** *Thorax.* 2024;79(3):202-208.

Kim T, Kim H, Kong S, Shin SH, Cho J, Kang D, Park HY. **Association Between Regular Moderate to Vigorous Physical Activity Initiation Following COPD Diagnosis and Mortality: An Emulated Target Trial Using Nationwide Cohort Data.** *Chest.* 2024;165(1):84-94.

#### BIOMARKERS OF RESPONSE TO THERAPY

Stolz D, Papakonstantinou E, Pascarella M, Jahn K, Siebeneichler A, Darie AM, Herrmann MJ, Strobel W, Salina A, Grize L, Savic Prince S, Tamm M. **Airway smooth muscle area to predict steroid responsiveness in COPD patients receiving triple therapy (HISTORIC): a randomised, placebo-controlled, double-blind, investigator-initiated trial.** *Eur Respir J.* 2023;62(1):2300218.

Faiz A, Mahbub RM, Boedijono FS, Tomassen MI, Kooistra W, Timens W, Nawijn M, Hansbro PM, Johansen MD, Pouwels SD, Heijink IH, Massip F, de Biase MS, Schwarz RF, Adcock IM, Chung KF, van der Does A, Hiemstra PS, Goulaouic H, Xing H, Abdulai R, de Rinaldis E, Cunoosamy D, Harel S, Lederer D, Nivens MC, Wark PA, Kerstjens HAM, Hylkema MN, Brandsma CA, van den Berge M. **IL-33 Expression Is Lower in Current Smokers at both Transcriptomic and Protein Levels.** *Am J Respir Crit Care Med.* 2023;208(10):1075-1087.

#### THERAPIES FOR PREVENTION OF COPD EXACERBATIONS

Feldman WB, Avorn J, Kesselheim AS, Gagne JJ. **Chronic Obstructive Pulmonary Disease Exacerbations and**

**Pneumonia Hospitalizations Among New Users of Combination Maintenance Inhalers.** *JAMA Intern Med.* 2023;183(7):685-695.

Allinson JP, Vlies BH, Brill SE, Law M, Burnside G, Finney LJ, Alves-Moreira L, Donaldson GC, Calverley PMA, Walker PP, Wedzicha JA. **A Double-Blind, Randomized, Placebo-controlled Trial of Long-Term Doxycycline Therapy on Exacerbation Rate in Patients with Stable Chronic Obstructive Pulmonary Disease.** *Am J Respir Crit Care Med.* 2023;208(5):549-558.

#### PULMONARY EMPHYSEMA SUBTYPES ON CT

Angelini ED, Yang J, Balte PP, Hoffman EA, Manichaikul AW, Sun Y, Shen W, Austin JHM, Allen NB, Bleecker ER, Bowler R, Cho MH, Cooper CS, Couper D, Dransfield MT, Garcia CK, Han MK, Hansel NN, Hughes E, Jacobs DR, Kasela S, Kaufman JD, Kim JS, Lappalainen T, Lima J, Malinsky D, Martinez FJ, Oelsner EC, Ortega VE, Paine R, Post W, Pottinger TD, Prince MR, Rich SS, Silverman EK, Smith BM, Swift AJ, Watson KE, Woodruff PG, Laine AF, Barr RG. **Pulmonary emphysema subtypes defined by unsupervised machine learning on CT scans.** *Thorax.* 2023;78(11):1067-1079.

#### LUNG VOLUME REDUCTION

Buttery SC, Banya W, Bilancia R, Boyd E, Buckley J, Greening NJ, Housley K, Jordan S, Kemp SV, Kirk AJB, Latimer L, Lau K, Lawson R, Lewis A, Moxham J, Rathinam S, Steiner MC, Tenconi S, Waller D, Shah PL, Hopkinson NS. **Lung volume reduction surgery versus endobronchial valves: a randomised controlled trial.** *Eur Respir J.* 2023;61(4):2202063.

## Critical Care

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### STEROIDS FOR SEVERE COMMUNITY-ACQUIRED PNEUMONIA

Dequin PF, Meziani F, Quenot JP, Kamel T, Ricard JD, Badie J, Reignier J, Heming N, Plantefève G, Souweine B, Voiriot G, Colin G, Frat JP, Mira JP, Barbarot N, François B, Louis G, Gibot S, Guitton C, Giacardi C, Hraiech S, Vimeux S, L'Her E, Faure H, Herbrecht JE, Bouisse C, Joret A, Terzi N, Gacouin A, Quentin C, Jourdain M, Leclerc M, Coffre C, Bourgoin H, Lengellé C, Caille-Fénérol C, Giraudeau B, Le Gouge A; CRICS-TriGGERSep Network. **Hydrocortisone in Severe Community-Acquired Pneumonia.** *N Engl J Med.* 2023 May 25;388(21):1931-1941.

#### Summary

In this multicenter, double-blind, randomized placebo-controlled trial (CAPE COD: **Community-Acquired Pneumonia: Evaluation of Corticosteroids**), adults admitted to the ICU for severe community-acquired pneumonia were randomized 1:1 (stratified by center and use/nonuse of mechanical ventilation at enrollment) to receive either intravenous hydrocortisone (200mg continuous intravenous infusion daily for either 4 or 7 days, as determined by clinical improvement, followed by tapering for a total of 8 or 14 days) or placebo across 31 centers in France, 2015-2020. Pneumonia was diagnosed by clinical and radiologic criteria, and considered "severe" if patients met at least one of four criteria: (1) receipt of invasive or noninvasive mechanical ventilation with PEEP  $\geq$ 5cm H<sub>2</sub>O; (2) receipt of FiO<sub>2</sub>  $\geq$ 50% through a high-flow nasal cannula with PaO<sub>2</sub>:FiO<sub>2</sub> <300; (3) receipt of a nonbreathing mask with estimated PaO<sub>2</sub>:FiO<sub>2</sub> <300; or (4) score >130 on the Pulmonary Severity Index. Patients with a do-not-intubate order, influenza, recent mechanical ventilation, other indication for corticosteroids, or septic shock were excluded. Of 795 patients analyzed, all-cause 28-day mortality (primary outcome) was lower in the hydrocortisone group (6.2% hydrocortisone, 11.9% control; absolute difference -5.6%; 95% CI -9.6 to -1.7; P = 0.006). Secondary outcomes were also lower in the hydrocortisone group (all-cause 90-day mortality, absolute difference -5.4%, -9.9 to -0.8; ventilation at 28 days among those not receiving mechanical ventilation at enrollment, HR 0.59, 0.40 to

0.86; vasopressors at 28 days among those not receiving vasopressors at enrollment, HR 0.59, 0.43 to 0.82). Rates of hospital-acquired infection and gastrointestinal bleeding were similar across groups, though the hydrocortisone group received higher median insulin doses during the first week of the trial.

#### Comments

1. Factors cited by the authors that may explain the discrepancy in results with prior studies include: shorter median time between ICU admission and administration of hydrocortisone or placebo (<15 hours, compared to up to 96 hours), higher enrollment of women (31%, with sex-based differences in response to glucocorticoids previously hypothesized), differences in steroids studied (i.e., balance in mineralocorticoid/glucocorticoid activity), exclusion of patients with septic shock, and high level of protocol adherence.
2. Initial enrollment targeted 1200 patients; trial was discontinued after the second interim analysis, which occurred after a prolonged suspension due to COVID-19.
3. Other than excluding influenza, microbiologic investigation was not standardized; no pathogen was identified in ~45% of patients.
4. Neuropsychologic or neuromuscular side effects of glucocorticoids were not specifically assessed.
5. Mortality observed in the control group (11.9%) was lower than anticipated (27%).

### INTUBATION FOR PATIENTS WITH COMA

Freund Y, Viglino D, Cachanado M, Cassard C, Montassier E, Douay B, Guenezan J, Le Borgne P, Yordanov Y, Severin A, Roussel M, Daniel M, Marteau A, Peschanski N, Teissandier D, Macrez R, Morere J, Chouihed T, Roux D, Adnet F, Bloom B, Chauvin A, Simon T. **Effect of Noninvasive Airway Management of Comatose Patients With Acute Poisoning: A Randomized Clinical Trial.** *JAMA.* 2023 Dec 19;330(23):2267-2274.

## Summary

In this multicenter, unblinded, randomized trial (**NICO: Noninvasive Airway Management of Comatose Poisoned Emergency Patients**), adults with coma secondary to suspected acute poisoning were randomized 1:1 (stratified by hospital and block balanced) to a strategy of withholding tracheal intubation (for up to 4 hours, unless emergency criteria met, e.g., seizure, respiratory distress, vomiting, shock) or routine practice (intubation at discretion of treating physician) across 20 emergency departments and 1 ICU in France, 2021-2023. Eligible patients had a clinical suspicion of acute poisoning and a Glasgow Coma Scale score <9 as assessed by treating physicians. Patients were excluded if they had an immediate need for tracheal intubation (defined by signs of respiratory distress, clinical suspicion of any brain injury, seizure, or shock), were intoxicated with a single reversible toxic agent (opioids or benzodiazepines) or if poisoning with cardiotoxic drugs was suspected. Of 225 patients analyzed (116 in intervention group with 16% intubated, 109 in control group with 58% intubated; median GCS score 6, main toxin was alcohol [67%]), the primary outcome, a hierarchical composite end point (in-hospital death, ICU length of stay, and hospital length of stay), was improved in the intervention arm (win ratio of 1.85; 95% CI 1.33-2.58;  $P < 0.001$ ). Patients in the intervention group also had lower rates of ICU admission (OR 0.23 [95% CI 0.12-0.44]), mechanical ventilation (OR 0.12 [0.06-0.24]), and adverse events from intubation (OR 0.37 [0.15-0.99]).

## Comments

1. Prior evidence to guide risks vs. benefits of intubation patients with a decreased level of consciousness at risk of aspiration had largely been observational or conducted in small subgroups; in this large randomized trial, withholding intubation appeared beneficial and did not lead to higher-risk intubations (among patients intubated, there were no differences between groups in adverse events, first pass failures, or differences in ICU/hospital length of stay).
2. In the absence of deaths during the trial, the composite primary outcome was driven by the reduction in ICU admission in the intervention group.
3. Trial was unblinded and is susceptible to a Hawthorne effect, i.e., enrollment in a trial could have influenced physician behavior and the decision to intubate.
4. The monitoring strategy for patients not intubated or in the conservative arm was not specified.

5. Findings may not be generalizable to populations at higher risk of emesis or aspiration, including pregnant patients or patients treated with gastric evacuation or activated charcoal (which was not administered to any patients in the trial).

## INTUBATION BY DIRECT VERSUS VIDEO LARYNGOSCOPY

Prekker ME, Driver BE, Trent SA, Resnick-Ault D, Seitz KP, Russell DW, Gaillard JP, Latimer AJ, Ghamande SA, Gibbs KW, Vonderhaar DJ, Whitson MR, Barnes CR, Walco JP, Douglas IS, Krishnamoorthy V, Dagan A, Bastman JJ, Lloyd BD, Gandotra S, Goranson JK, Mitchell SH, White HD, Palakshappa JA, Espinera A, Page DB, Joffe A, Hansen SJ, Hughes CG, George T, Herbert JT, Shapiro NI, Schauer SG, Long BJ, Imhoff B, Wang L, Rhoads JP, Womack KN, Janz DR, Self WH, Rice TW, Ginde AA, Casey JD, Semler MW; DEVICE Investigators and the Pragmatic Critical Care Research Group. **Video versus Direct Laryngoscopy for Tracheal Intubation of Critically Ill Adults.** *N Engl J Med.* 2023 Aug 3;389(5):418-429.

## Summary

In this pragmatic, multicenter, unblinded, randomized controlled trial (**DEVICE: Direct versus Video Laryngoscope**), adults undergoing orotracheal intubation in the emergency room or ICU were randomized 1:1 (stratified by trial site, permuted blocks of variable size) to intubation with video laryngoscope (VL, defined as laryngoscope with a camera and a video screen, of any brand) or direct laryngoscope (DL), across 11 medical centers (7 emergency departments, 10 ICUs) in the United States, March-November 2022. Patients were excluded if they had an immediate need for tracheal intubation that precluded randomization, or if the clinician performing the procedure determined that the use of a VL or DL on the first attempt was either necessary or contraindicated. Of the 1417 patients included in analysis (705 VL, 712 DL; 45.3% intubated for altered mental status, 69.7% intubated in the emergency room; 91.5% performed by emergency medicine resident or critical care fellow), successful intubation on the first attempt (primary outcome, defined as a single insertion of the laryngoscope blade followed by a single insertion of an endotracheal tube) was significantly higher in the VL group (85.1% vs. 70.8%, absolute risk difference 14.3%; 95% CI 9.9-18.7;  $P < 0.001$ ). There were no significant differences in severe complication during intubation, esophageal intubation, injury to teeth, or aspiration.

## Comments

1. A prior multicenter trial of VL vs. DL among 371 critically ill adults did not show difference in first-pass success rates (Lascarrou et al, MACMAN, 2017); adoption of VL in critically ill patients has since increased, particularly during the COVID-19 pandemic, and >90% of operators in the current study reported significant prior VL experience (>25% of their prior intubations were performed with VL).
2. Investigators planned to enroll 2000 patients; the trial was stopped for efficacy after interim analysis met the p-value threshold of <0.001 for difference between groups in primary outcome.
3. Prior to patient randomization, operators were asked to subjectively rate the anticipated difficulty of intubation; range in difficulty were similar across both groups (Easy: 33% VL, 31% DL; Moderate: 45% VL, 47% DL; Difficult: 10% VL, 9% DL).
4. The median number of prior intubations performed by operators was 50 in both groups; in subgroup analysis, the improvement in first attempt success with VL for operators with <25 prior intubations was a 26.1% absolute difference (95% CI 15.4 to 36.8) while the improvement in first attempt success with VL for more experienced operators was a 5.9% absolute difference (95% CI -4.1 to 16.0) (confidence intervals were not adjusted for multiple comparisons and analysis of interaction effect significance was not reported).
5. Findings may not be generalizable to other settings (e.g., in health systems without trainees, with greater DL experience relative to VL experience, and/or where anesthesiologists are primary operators of tracheal intubations outside of the operating room).

## TRAUMA-INDUCED COAGULOPATHY

PATCH-Trauma Investigators and the ANZICS Clinical Trials Group; Gruen RL, Mitra B, Bernard SA, McArthur CJ, Burns B, Gantner DC, Maegele M, Cameron PA, Dicker B, Forbes AB, Hurford S, Martin CA, Mazur SM, Medcalf RL, Murray LJ, Myles PS, Ng SJ, Pitt V, Rashford S, Reade MC, Swain AH, Trapani T, Young PJ. **Prehospital Tranexamic Acid for Severe Trauma.** *N Engl J Med.* 2023 Jul 13;389(2):127-136.

## Summary

In this pragmatic, multicenter, double-blinded, randomized, placebo-controlled trial (**PATCH-Trauma: Pre-hospital Antifibrinolytics for Traumatic Coagulopathy and Hemorrhage**), adults with major trauma who were at risk for trauma-induced coagulopathy (Coagulopathy of Severe Trauma score [COAST] >3) were randomized 1:1 (stratified by national or state jurisdiction and initial Glasgow Coma Scale) to receive tranexamic acid (TXA) or placebo, across 36 trauma centers in Australia, New Zealand, and Germany, 2014-2021. Patient risk of coagulopathy was screened at the trauma scene and considered eligible if TXA or placebo could be administered within 3 hours of injury (initial dose administered as a bolus prior to hospital arrival; 8-hour infusion initiated after hospital arrival); patients with known or suspected pregnancy or residents of a facility for older persons were excluded. Of 1300 patients included in intention-to-treat analysis (572 of 657 in TXA group and 559 of 643 in placebo group with outcome data available), there was no significant difference in the primary outcome of survival with a favorable functional outcome at 6 months as assessed by the Glasgow Outcome Scale-Extended (GOS-E  $\geq 5$  in 53.7% in TXA group, 53.5% in placebo group; absolute risk difference 0.2 percentage points; 95% CI -5.6 to 6.0). Mortality was significantly lower in the TXA group at 24 hours (9.7% vs. 14.1%; risk ratio 0.69; 95% CI 0.51 to 0.94) and at 28 days (17.3% vs. 21.8%; risk ratio 0.79; 95% CI 0.63 to 0.99) and numerically lower at 6 months (19.0% vs. 22.9%; risk ratio 0.83; 95% CI 0.61 to 1.03).

## Comments

1. While PATCH-Trauma confirms the survival benefit of TXA at 24-hours and 28-days (previously seen in CRASH-2), PATCH-Trauma extends our understanding of quality of life after trauma, and the lack of benefit in functional outcomes at 6 months suggests that patients survived at the cost of living with severe disability at 6 months; it remains unknown if many of the survivors will go on to recover over a longer period of time.
2. In contrast with prior studies, there was not a statistically significant increase in thrombotic complications in the TXA group (risk ratio 1.20, 95% CI 0.97-1.48)
3. Some aspects of the trial may bias observed effects toward the null, including protocol violations (17% of the patients assigned to receive placebo received tranexamic acid, and 21% assigned to receive tranexamic acid did not

receive the second dose) and loss to follow-up (13%); however, per-protocol analyses were similar to intention-to-treat analyses.

4. The survival benefit of TXA seen in PATCH is in contrast to other studies published in 2023 assessing other interventions for traumatic hemorrhage; PROCOAG (Bouzat et al, JAMA, 4-factor prothrombin complex concentrate), CRYOSTAT-2 (Davenport et al, JAMA, empiric high-dose cryoprecipitate), and UK-REBOA (Jansen et al, JAMA, resuscitative endovascular balloon occlusion of the aorta) did not find clinical benefit in patients with traumatic hemorrhage (and in some cases, found a signal for harm).

## PROPHYLAXIS FOR VENTILATOR-ASSOCIATED PNEUMONIA

Dahyot-Fizelier C, Lasocki S, Kerforne T, Perrigault PF, Geeraerts T, Asehnoune K, Cinotti R, Launey Y, Cottenceau V, Laffon M, Gaillard T, Boisson M, Aleyrat C, Frasca D, Mimoz O; PROPHY-VAP Study Group and the ATLANREA Study Group. **Ceftriaxone to prevent early ventilator-associated pneumonia in patients with acute brain injury: a multicentre, randomised, double-blind, placebo-controlled, assessor-masked superiority trial.** *Lancet Respir Med.* 2024 Jan 19:S2213-2600(23)00471-X.

### Summary

In this multicenter, double-blind, randomized placebo-controlled trial (**PROPHY-VAP**) adults with acute brain injury and GCS  $\leq 12$  who were expected to receive  $\geq 48$  hours of invasive mechanical ventilation were randomized 1:1 (stratified by center and severity of coma) to receive one dose of IV ceftriaxone 2g or placebo within the first 12 hours of tracheal intubation, across 8 hospitals in France, 2015-2020. Patients with a beta-lactam allergy, who had already received antibiotics at time of admission, were ventilated via tracheostomy, or who had coma due to infectious disease, cardiac arrest, or tumor were excluded. All patients received standard VAP prevention measures including head-of-bed elevation and mouth care; none received selective oropharyngeal or digestive tract decontamination. Ventilator-associated pneumonia (VAP) was defined by clinical, radiologic, and microbiologic criteria and were centrally adjudicated in a blinded fashion. Of the 319 patients included in analysis (162 in ceftriaxone group, 157 in placebo group), the primary outcome, incidence of early VAP (between day 2-7 of mechanical ventilation), was significantly lower in the ceftriaxone group (14% vs 32%; HR 0.60;

95% CI 0.38-0.95;  $p = 0.030$ ). The ceftriaxone group also had improved secondary endpoints, including all VAP (20% vs. 36%; HR 0.62; 95% CI 0.42-0.98), ventilator-free days (9 vs. 5 days,  $p=0.023$ ), antibiotic-free days (21 vs. 15 days,  $p<0.001$ ) and mortality at ICU discharge or day 28 (15% vs. 25%; HR 0.62; 95% CI 0.39-0.97). There were no differences in adverse effect or microbiologic impact.

### Comments

1. PROPHY-VAP builds upon the ANTHARTIC trial (Francois et al, NEJM 2019), which showed reduced early-onset VAP after 48 hours of amoxicillin/clavulanate among patients intubated after cardiac arrest, and SuDDICU (JAMA 2022), which showed no reduction in infection after four days of systemic antibiotic therapy among critically ill, intubated patients; however, in post-hoc analysis, SuDDICU found that selective digestive decontamination (SDD) reduced mortality and improved ventilator-free days in the subgroup with acute brain injury, who were hypothesized to be at higher risk for early VAP (specifically through progression of tracheal colonization to infection).
2. The authors suggest that a single dose of ceftriaxone may have a lower ecologic impact compared to other prophylactic regimens, as a single dose of ceftriaxone reduced overall antibiotic use (increased antibiotic-free days) without increasing rates of *C. difficile* or ESBL-producing organisms; PROPHY-VAP was not powered to assess for emergence of antibiotic-resistant pathogens and longer-term ecologic data is necessary.
3. The observed clinical benefits of reducing VAP seen in the secondary outcomes of PROPHY-VAP (e.g., 10% absolute reduction in mortality) are in sharp contrast with other studies (including ANTHARTIC) and should be considered hypothesis-generating; for example, AMIKINHAL (Ehrman et al, NEJM 2023) showed a reduction in VAP (primary outcome) without reduction in mortality in the group randomized to receive inhaled amikacin for 3 days.
4. The generalizability of the findings to settings with other microbiologic and drug-resistance patterns is unknown; for example, there was only 1 MRSA strain and 1 ESBL-producing Enterobacteriaceae strain identified in the entire cohort (both in placebo group); generalizability may also be limited by the large number of patients screened but excluded (2230 patients screened; over 1/3 of the 1885



excluded patients were excluded due to having already received an antibiotic).

- Studying VAP as a primary outcome in trials assessing antibiotic prophylaxis is controversial (Young, Crit Care Resusc, 2023); the diagnosis of VAP requires positive microbiology which is more difficult to detect following administration of antibiotics, leading to a risk of detection bias.

## PRE-PROCEDURE TRANSFUSION

van Baarle FLF, van de Weerd EK, van der Velden WJFM, Ruisertkamp RA, Tuinman PR, Ypma PF, van den Bergh WM, Demandt AMP, Kerver ED, Jansen AJG, Westerweel PE, Arbous SM, Determann RM, van Mook WNKA, Koeman M, Mäkelburg ABU, van Lienden KP, Binnekade JM, Biemond BJ, Vlaar APJ. **Platelet Transfusion before CVC Placement in Patients with Thrombocytopenia.** *N Engl J Med.* 2023 May 25;388(21):1956-1965.

### Summary

In this multicenter, open-label, randomized, controlled, non-inferiority trial (**PACER: Prophylactic Platelet Transfusion Prior to Central Venous Catheter (CVC) Placement in Patients with Thrombocytopenia**), patients with severe thrombocytopenia (platelet count 10,000-50,000/mm<sup>3</sup>) treated on a hematology ward or intensive care unit were randomized 1:1 (stratified by trial center and catheter type, i.e., dialysis versus regular catheter) to receive either one unit of prophylactic platelet transfusion or no platelet transfusion prior to ultrasound-guided CVC, across 10 hospitals in the Netherlands, 2016-2022. Patients who had received a therapeutic anticoagulant, had an INR  $\geq 1.5$  (subsequently revised to INR  $\geq 3$ ), or a had a history of a coagulation factor deficiency or bleeding risk were excluded. Patients with multiple CVC placement episodes could be re-included if prior randomization occurred >24 hours earlier. Investigators had estimated a 1% rate of grade 2-4 bleeding and pre-specified that an absolute increase of <2.5 percentage points of Grade 2-4 bleeding in the no-transfusion arm over the transfusion arm would be deemed noninferior, where Grade 2-4 bleeding is defined bleeding resulting in minor interventions, such as prolonged manual compression, up to bleeding associated with severe hemodynamic instability or death. Of 373 episodes of CVC placement among 338 patients (188 in transfusion group, 185 in no-transfusion group; median platelet count 30,000/mm<sup>3</sup>; median INR 1.1; 43% in ICU; 83% with standard CVC), the primary outcome of Grade 2-4 bleeding was lower in the transfusion group (4.8% vs.

11.9%; absolute risk difference 7.1; 90% CI 1.3-17.8). The no-transfusion group was more likely to receive platelets after CVC placement, but there were no significant differences in rate of red-cell transfusion within 24 hours, risk of Grade 3-4 bleeding, allergic transfusion reaction, or ICU or hospital mortality. The authors concluded that withholding prophylactic platelet transfusion did not meet the margin for noninferiority.

### Comments

- Current guidelines vary in platelet thresholds for transfusion prior to CVC placement; many (e.g., British Society of Hematology 2016 and American Society of Clinical Oncology 2017) recommend a platelet threshold >20,000/mm<sup>3</sup>, while others recommend a threshold of >50,000/mm<sup>3</sup> for “invasive procedures” or make no recommendation.
- Platelets were not transfused to a specific target, but median platelet counts were higher in the transfusion group at 1 hour (54,000 vs. 26,000) and 24 hours (36,000 vs. 26,000) after CVC placement.
- All operators of CVC placements were required to have placed at least 50 prior CVCs; nevertheless, despite high operator experience and ultrasound guidance, rates of Grade 2-3 bleeding in the control group were much higher than investigators anticipated.
- The study was not fully blinded, and observation of bleeding complications could have been susceptible to Hawthorne effect.
- Subgroup analysis (where confidence intervals were not adjusted for multiple comparisons and analysis of interaction effect significance was not reported) revealed effect estimates favoring transfusion with 95% confidence intervals not crossing 1 among patients receiving a subclavian line (but not internal jugular or femoral), a non-tunneled line (but not tunneled line), patients in the hematology ward (but not patients in the ICU); further work rigorously examining heterogeneity of treatment effect (including underlying etiology of thrombocytopenia, degree of thrombocytopenia, and variation in available post-procedure monitoring) is indicated.

## OTHER ARTICLES OF INTEREST

Balik M, Maly M, Brozek T, Rulisek J, Porizka M, Sachl R, Otahal M, Brestovansky P, Svobodova E, Flaksa M, Stach Z, Horejsek J, Volny L, Jurisinova I, Novotny A, Trachta P, Kunstyr J, Kopecky P, Tencer T, Pazout J, Belohlavek J, Duska F, Krajcova A, Waldauf P. **Propafenone versus amiodarone for supraventricular arrhythmias in septic shock: a randomised controlled trial.** *Intensive Care Med.* 2023 Nov;49(11):1283-1292.

Bosch NA, Myers LC, Jafarzadeh SR, Wunsch H, Stevens JP, Liu VX, Walkey AJ. **Temporal Trends in Use of Opioids for Patients with Acute Respiratory Failure following "Analgesia-First" Sedation Guidelines.** *Ann Am Thorac Soc.* 2024 Jan;21(1):179-183.

Carson JL, Brooks MM, Hébert PC, Goodman SG, Bertolet M, Glynn SA, Chaitman BR, Simon T, Lopes RD, Goldsweig AM, DeFilippis AP, Abbott JD, Potter BJ, Carrier FM, Rao SV, Cooper HA, Ghafghazi S, Fergusson DA, Kostis WJ, Noveck H, Kim S, Tessalee M, Ducrocq G, de Barros E Silva PGM, Triulzi DJ, Alswelter C, Menegus MA, Neary JD, Uhl L, Strom JB, Fordyce CB, Ferrari E, Silvain J, Wood FO, Daneault B, Polonsky TS, Senaratne M, Puymirat E, Bouleti C, Lattuca B, White HD, Kelsey SF, Steg PG, Alexander JH; MINT Investigators. **Restrictive or Liberal Transfusion Strategy in Myocardial Infarction and Anemia.** *N Engl J Med.* 2023 Dec 28;389(26):2446-2456.

Eastwood G, Nichol AD, Hodgson C, Parke RL, McGuinness S, Nielsen N, Bernard S, Skrifvars MB, Stub D, Taccone FS, Archer J, Kutsogiannis D, Dankiewicz J, Lilja G, Cronberg T, Kirkegaard H, Capellier G, Landoni G, Horn J, Olasveengen T, Arabi Y, Chia YW, Markota A, Hænggi M, Wise MP, Grejs AM, Christensen S, Munk-Andersen H, Granfeldt A, Andersen GØ, Qvigstad E, Flaa A, Thomas M, Sweet K, Bewley J, Bäcklund M, Tiainen M, Iten M, Levis A, Peck L, Walsham J, Deane A, Ghosh A, Annoni F, Chen Y, Knight D, Lesona E, Tlayjeh H, Svenšek F, McGuigan PJ, Cole J, Pogson D, Hilty MP, Düring JP, Bailey MJ, Paul E, Ady B, Ainscough K, Hunt A, Monahan S, Trapani T, Fahey C, Bellomo R; TAME Study Investigators. **Mild Hypercapnia or Normocapnia after Out-of-Hospital Cardiac Arrest.** *N Engl J Med.* 2023 Jul 6;389(1):45-57.

Ehrmann S, Barbier F, Demiselle J, Quenot JP, Herbrecht JE, Roux D, Lacherade JC, Landais M, Seguin P, Schnell D, Veinstein A, Gouin P, Lasocki S, Lu Q, Beduneau G, Ferrandiere M, Plantefève G, Dahyot-Fizelier C, Chebib N, Mercier E, Heuzé-Vourc'h N, Respaud R, Gregoire N, Garot D, Nay MA, Meziani F, Andreu P, Clere-Jehl R, Zucman N, Azaïs MA, Saint-Martin M, Gandonnière CS,

Benzekri D, Merdji H, Tavernier E; Reva and CRICS-TRIGGERSEP F-CRIN Research Networks. **Inhaled Amikacin to Prevent Ventilator-Associated Pneumonia.** *N Engl J Med.* 2023 Nov 30;389(22):2052-2062.

Goligher EC, Lawler PR, Jensen TP, Talisa V, Berry LR, Lorenzi E, McVerry BJ, Chang CH, Leifer E, Bradbury C, Berger J, Hunt BJ, Castellucci LA, Kornblith LZ, Gordon AC, McArthur C, Webb S, Hochman J, Neal MD, Zarychanski R, Berry S, Angus DC; REMAP-CAP, ATTACC, and ACTIV-4a Investigators. **Heterogeneous Treatment Effects of Therapeutic-Dose Heparin in Patients Hospitalized for COVID-19.** *JAMA.* 2023 Apr 4;329(13):1066-1077.

Gunst J, Debaveye Y, Güiza F, Dubois J, De Bruyn A, Dauwe D, De Troy E, Casaer MP, De Vlieger G, Haghedooren R, Jacobs B, Meyfroidt G, Ingels C, Muller J, Vlasselaers D, Desmet L, Mebis L, Wouters PJ, Stessel B, Geebelen L, Vandenbrande J, Brands M, Gruyters I, Geerts E, De Pauw I, Vermassen J, Peperstraete H, Hoste E, De Waele JJ, Herck I, Depuydt P, Wilmer A, Hermans G, Benoit DD, Van den Berghe G; TGC-Fast Collaborators. **Tight Blood-Glucose Control without Early Parenteral Nutrition in the ICU.** *N Engl J Med.* 2023 Sep 28;389(13):1180-1190.

Jivraj NK, Hill AD, Shieh MS, Hua M, Gershengorn HB, Ferrando-Vivas P, Harrison D, Rowan K, Lindenauer PK, Wunsch H. **Use of Mechanical Ventilation Across 3 Countries.** *JAMA Intern Med.* 2023 Aug 1;183(8):824-831. Kruser JM, Clapp JT, Arnold RM. **Reconsidering the Language of Serious Illness.** *JAMA.* 2023 Aug 15;330(7):587-588.

Law AC, Bosch NA, Song Y, Tale A, Yeh RW, Kahn JM, Stevens JP, Walkey AJ. **Patient Outcomes After Long-Term Acute Care Hospital Closures.** *JAMA Netw Open.* 2023 Nov 1;6(11):e2344377.

Mo Y, Booraphun S, Li AY, Domthong P, Kayastha G, Lau YH, Chetchotisakd P, Limmathurotsakul D, Tambyah PA, Cooper BS; REGARD-VAP investigators. **Individualised, short-course antibiotic treatment versus usual long-course treatment for ventilator-associated pneumonia (REGARD-VAP): a multicentre, individually randomised, open-label, non-inferiority trial.** *Lancet Respir Med.* 2024 Jan 22:S2213-2600(23)00418-6.

Pham T, Heunks L, Bellani G, Madotto F, Aragao I, Beduneau G, Goligher EC, Grasselli G, Laake JH, Mancebo J, Peñuelas O, Piquilloud L, Pesenti A, Wunsch H, van Haren F, Brochard L, Laffey JG; WEAN SAFE Investigators. **Weaning from mechanical ventilation in intensive care units across 50 countries (WEAN SAFE): a multicentre,**

prospective, observational cohort study. *Lancet Respir Med.* 2023 May;11(5):465-476.

Reignier J, Plantefeve G, Mira JP, Argaud L, Asfar P, Aissaoui N, Badie J, Botoc NV, Brisard L, Bui HN, Chatellier D, Chauvelot L, Combes A, Cracco C, Darmon M, Das V, Debarre M, Delbove A, Devaquet J, Dumont LM, Gontier O, Groyer S, Guérin L, Guidet B, Hourmant Y, Jaber S, Lambiotte F, Leroy C, Letocart P, Madeux B, Maizel J, Martinet O, Martino F, Maxime V, Mercier E, Nay MA, Nseir S, Oziel J, Picard W, Piton G, Quenot JP, Reizine F, Renault A, Richecoeur J, Rigaud JP, Schneider F, Silva D, Sirodot M, Souweine B, Tamion F, Terzi N, Thévenin D, Thiery G, Thieulot-Rolin N, Timsit JF, Tinturier F, Tirot P, Vanderlinden T, Vinatier I, Vinsonneau C, Voicu S, Lascarrou JB, Le Gouge A; NUTRIREA-3 Trial Investigators; Clinical Research in Intensive Care; Sepsis (CRICS-TRIGGERSEP)Group. **Low versus standard calorie and protein feeding in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group trial (NUTRIREA-3).** *Lancet Respir Med.* 2023 Jul;11(7):602-612.

Sarraj A, Hassan AE, Abraham MG, Ortega-Gutierrez S, Kasner SE, Hussain MS, Chen M, Blackburn S, Sitton CW, Churilov L, Sundararajan S, Hu YC, Herial NA, Jabbour P,

Gibson D, Wallace AN, Arenillas JF, Tsai JP, Budzik RF, Hicks WJ, Kozak O, Yan B, Cordato DJ, Manning NW, Parsons MW, Hanel RA, Aghaebrahim AN, Wu TY, Cardona-Portela P, Pérez de la Ossa N, Schaafsma JD, Blasco J, Sangha N, Warach S, Gandhi CD, Kleinig TJ, Sahlein D, Eljovich L, Tekle W, Samaniego EA, Maali L, Abdulrazzak MA, Psychogios MN, Shuaib A, Pujara DK, Shaker F, Johns H, Sharma G, Yogendrakumar V, Ng FC, Rahbar MH, Cai C, Lavori P, Hamilton S, Nguyen T, Fifi JT, Davis S, Wechsler L, Pereira VM, Lansberg MG, Hill MD, Grotta JC, Ribo M, Campbell BC, Albers GW; SELECT2 Investigators. **Trial of Endovascular Thrombectomy for Large Ischemic Strokes.** *N Engl J Med.* 2023 Apr 6;388(14):1259-1271.

Siegal DM, Belley-Côté EP, Lee SF, Hill S, D'Aragon F, Zarychanski R, Rochwerg B, Chassé M, Binnie A, Honarmand K, Lauzier F, Ball I, Al-Hazzani W, Archambault P, Duan E, Khwaja K, Lellouche F, Lysecki P, Marquis F, Naud JF, Shahin J, Shea J, Tsang JLY, Wang HT, Crowther M, Arnold DM, Di Sante E, Marfo G, Kovalova T, Fonguh S, Vincent J, Connolly SJ. **Small-Volume Blood Collection Tubes to Reduce Transfusions in Intensive Care: The STRATUS Randomized Clinical Trial.** *JAMA.* 2023 Nov 21;330(19):1872-1881.

# Global Lung Health

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## A COMPARISON OF HEALTH EFFECTS BETWEEN USE OF GAS vs ELECTRICITY, AND GAS vs WOOD/CHARCOAL FOR DOMESTIC COOKING AND HEATING

Puzzolo E, Fleeman N, Lorenzetti F, Rubinstein F, Li Y, Xing R, Shen G, Nix E, Maden M, Bresnahan R, Duarte R, Abebe L, Lewis J, Williams KN, Adahir-Rohani H, Pope D. **Estimated health effects from domestic use of gaseous fuels for cooking and heating in high-income, middle-income, and low-income countries: a systematic review and meta-analyses.** *Lancet Respir Med.* 2024 Feb 1:S2213-2600(23)00427-7. doi: 10.1016/S2213-2600(23)00427-7. Epub ahead of print. PMID: 38310914.

### Summary

This was a systematic review and meta-analysis to determine the differences in health effects between use of domestic gas vs electricity, and use of domestic gas vs wood/charcoal for cooking and heating. The studies included in this systematic review and meta-analysis comprised original studies and data from high income, middle income and low-income countries. Out of 48,130 records identified on WHO database, 1103 full text papers were assessed for eligibility. After a rigorous process based on strict inclusion and exclusion criteria, 116 papers were included in the meta-analysis. Compared with electricity, use of gas significantly increased risk of pneumonia (OR 1.26, 1.03 -1.53;  $p=0.025$ ) and chronic obstructive pulmonary disease (OR 1.15, 1.06-1.25;  $p=0.0011$ ). In addition, there was an increased risk of asthma in children though the results did not meet the predetermined level of statistical significance. Compared with use of polluting fuels such as wood or charcoal, use of domestic gas significantly lowered the risk of pneumonia (OR 0.54, 95% CI 0.38-0.77;  $p=0.0008$ ), wheeze (OR 0.42, 0.30 – 0.59;  $p<0.0001$ ), cough (OR 0.44, 0.32 – 0.62;  $p<0.0001$ ), breathlessness (OR 0.40, 0.21 - 0.76;  $p=0.0052$ ), chronic obstructive pulmonary disease (OR 0.37, 0.23-0.60;  $p<0.0001$ ), pulmonary function deficit

(OR 0.27, 0.17 – 0.44;  $p<0.0001$ ) and severe respiratory illness or death (OR 0.27, 0.11-0.63;  $p=0.0024$ ). Similar findings were observed in the risk of preterm birth (OR 0.66, 0.45-0.97;  $p=0.033$ ) and low birthweight (OR 0.70, 0.53-0.93;  $p=0.015$ )

### Comments

1. This study confirms the gains which could be achieved with switching to cleaner types of energy such as electricity for domestic cooking and heating in both high and low/middle income countries.
2. There is a significant reduction in risk of acute lower respiratory infections, chronic lung disease, adverse pregnancy outcomes and respiratory symptoms in populations that use domestic gas for domestic cooking or heating compared with those that use polluting fuels such as wood, charcoal or kerosene.
3. Using electricity instead of gas for domestic cooking and heating significantly reduces the risk of lower respiratory tract infections, chronic lung disease as well as respiratory symptoms and asthma in childhood.
4. There is an emerging concern about the risk of asthma and the use of domestic gas for cooking and heating, but more research is needed to clarify this observation.
5. The use of gas for domestic cooking and heating could be a transitional option in many developing countries in which constant electricity supply is still a huge challenge.

## A LONGITUDINAL EVALUATION OF INCIDENCES OF SEVERE INFANT PNEUMONIA IN BABIES BORN TO WOMEN IN FOUR LOW- AND MIDDLE-INCOME COUNTRIES USING A RANDOMIZED CONTROL TRIAL OF LIQUEFIED PETROLEUM GAS OR BIOMASS FOR COOKING.

McCollum ED, McCracken JP, Kirby MA, Grajeda LM, Hossen S, Moulton LH, Simkovich SM, Goodman-Palmer D, Rosa G, Mukeshimana A, Balakrishnan K, Thangavel G, Garg SS, Castañaza A, Thompson LM, Diaz-Artiga A, Papageorghiou AT, Davila-Roman VG, Underhill LJ, Hartinger SM, Williams KN, Nicolaou L, Chang HH, Lovvorn AE, Rosenthal JP, Pillarisetti A, Ye W, Naeher LP, Johnson MA, Waller LA, Jabbarzadeh S, Wang J, Chen Y, Steenland K, Clasen TF, Peel JL, Checkley W; HAPIN Investigators. **Liquefied Petroleum Gas or Biomass Cooking and Severe Infant Pneumonia.** *N Engl J Med.* 2024 Jan 4;390(1):32-43. doi: 10.1056/NEJMoa2305681. PMID: 38169488; PMCID: PMC10768798.

### Summary

This study was conducted to determine through a randomized trial, whether using Cookstoves with liquefied petroleum gas (LPG) had an impact on the risk of severe pneumonia and infections in infants born to pregnant women aged 18 - 34 years between 9 to 20 weeks gestation in 4 different countries in 4 continents- India, Guatemala, Peru and Rwanda. Out of 6447 women assessed for eligibility, 3195 were pregnant, underwent randomization, and met the eligibility criteria. They gave birth to 3061 infants which were divided into the intervention group and control group. A total of 175 episodes of severe pneumonia were identified during the first year of life with an incidence of 5.67 cases per 100 child years, 95% CI: 4.55-7.07 in intervention group and 6.06 per 100 child years, 95% CI of 4.81-7.62 in the control group.

### Comments

1. This study did not show any significant difference in the incidence of severe infant pneumonia in the babies of mothers who were assigned to use LPG cookstoves compared with those who continued to use biomass cookstoves.
2. Strategies to reduce the incidence of severe pneumonia in infants may require broader community interventions rather than household strategies alone.

3. This study was conducted during the COVID-19 pandemic, and it is possible that the mitigating interventions during the pandemic may have reduced both respiratory viral circulation and also pediatric hospitalization.
4. The rate of vaccinations in the population studied is high and this may help reduce the incidence of pneumonia in early infancy—further suggesting the role and impact of broader community interventions including vaccination against childhood infections.

## LONG-TERM OUTCOME OF TUBERCULOSIS AND COVID-19 COINFECTION

Global Tuberculosis Network and TB/COVID-19 Global Study Group; Casco N, Jorge AL, Palmero DJ, Alffenaar JW, Fox GJ, Ezz W, Cho JG, Denholm J, Skrahina A, Solodovnikova V, Arbex MA, Alves T, Rabahi MF, Pereira GR, Sales R, Silva DR, Saffie MM, Salinas NE, Miranda RC, Cisterna C, Concha C, Fernandez I, Villalón C, Vera CG, Tapia PG, Cancino V, Carbonell M, Cruz A, Muñoz E, Muñoz C, Navarro I, Pizarro R, Cristina Sánchez GP, Vergara Riquelme MS, Vilca E, Soto A, Flores X, Garavagno A, Bahamondes MH, Merino LM, Pradenas AM, Revillot ME, Rodriguez P, Salinas AS, Taiba C, Valdés JF, Subiabre JN, Ortega C, Palma S, Castillo PP, Pinto M, Bidegain FR, Venegas M, Yucra E, Li Y, Cruz A, Guelvez B, Victoria Plaza R, Tello Hoyos KY, Cardoso-Landivar J, Van Den Boom M, Andrzejak C, Blanc FX, Dourmane S, Froissart A, Izadifar A, Rivière F, Schlemmer F, Manika K, Diallo BD, Hassane-Harouna S, Artiles N, Mejia LA, Gupta N, Ish P, Mishra G, Patel JM, Singla R, Udwadia ZF, Alladio F, Angeli F, Calcagno A, Centis R, Codecasa LR, De Lauretis A, Esposito SMR, Formenti B, Gaviraghi A, Giacomet V, Goletti D, Gualano G, Matteelli A, Migliori GB, Motta I, Palmieri F, Pontali E, Prestileo T, Riccardi N, Saderi L, Saporiti M, Sotgiu G, Spanevello A, Stochino C, Tadolini M, Torre A, Villa S, Visca D, Kurhasani X, Furjani M, Rasheed N, Danila E, Diktanas S, Ridaura RL, Luna López FL, Torrico MM, Rendon A, Akkerman OW, Chizaram O, Al-Abri S, Alyaquobi F, Althohli K, Aguirre S, Teixeira RC, De Egea V, Irala S, Medina A, Sequera G, Sosa N, Vázquez F, Llanos-Tejada FK, Manga S, Villanueva-Villegas R, Araujo D, Sales Marques RD, Socaci A, Barkanova O, Bogorodskaya M, Borisov S, Mariandyshev A, Kaluzhenina A, Vukicevic TA, Stosic M, Beh D, Ng D, Ong CWM, Solovic I, Dheda K, Gina P,

Caminero JA, De Souza Galvão ML, Dominguez-Castellano A, García-García JM, Pinargote IM, Fernandez SQ, Sánchez-Montalvá A, Huguet ET, Murguiondo MZ, Bart PA, Mazza-Stalder J, D'Ambrosio L, Kamolwat P, Bakko F, Barnacle J, Bird S, Brown A, Chandran S, Killington K, Man K, Papineni P, Ritchie F, Tiberi S, Utjesanovic N, Zenner D, Hearn JL, Heysell S, Young L. **Long-term outcomes of the global tuberculosis and COVID-19 co-infection cohort.** *Eur Respir J.* 2023 Nov 29;62(5):2300925. doi: 10.1183/13993003.00925-2023. PMID: 37827576; PMCID: PMC10627308.

### Summary

This was a cohort study of patients affected with tuberculosis and coronavirus disease 2019 between 1 March 2020 and 30 September 2022 to determine the long-term outcomes. It was an international study in 174 centers in 31 countries. A total of 788 patients with COVID-19 and tuberculosis were recruited for the study. They were followed up until cured, death or end of cohort time. A survival analysis was performed to compare survival and mortality attributed to tuberculosis, COVID-19 or both. The results showed that survival was lower in patients who had a coinfection of tuberculosis and COVID-19 compared with those who were dying of either tuberculosis or COVID-19 alone. Higher age (HR: 1.05, 95% CI: 1.03–1.07), HIV infection (HR: 2.29 95% CI: 1.02–5.16) and invasive ventilation (HR: 4.28, 95% CI: 2.34–7.83) were significant risk factors for TB mortality. For COVID-19, the risk factors for death were higher age (HR: 1.03, 95% CI: 1.02–1.04), male sex (HR: 2.21, 95% CI: 1.24–3.91), oxygen requirement (HR: 7.93, 95% CI: 3.44–18.26) and invasive ventilation (HR: 2.19, 95% CI: 1.36–3.53).

### Comments

1. This study confirms that COVID-19 and tuberculosis coinfection may lead to severe acute illness and a high risk of mortality.
2. The findings show the overlap and similarities in the risk factors for TB mortality and the risk factors for COVID-19 mortality including older age, HIV infection and invasive ventilation.
3. It highlights the importance of early recognition and treatment of COVID-19 and tuberculosis to improve outcomes especially if ventilation is required.

4. Patients with tuberculosis who were diagnosed with COVID-19 infection at the end of TB treatment appeared to have poor prognosis and a higher likelihood of poor outcome or non-recovery from COVID-19-suggesting that pre-existing tuberculosis could lead to poor outcomes in COVID-19 infections.
5. There is need for long term follow up to establish strategies to deal with excess mortality associated with co-infection with these 2 diseases and to evaluate the need for pulmonary rehabilitation as an important aspect of postinfection treatments.

### ISOLATED SMALL AIRWAY OBSTRUCTION COULD PREDICT FUTURE CHRONIC OBSTRUCTIVE LUNG DISEASE

Knox-Brown B, Potts J, Santofimio VQ, Minelli C, Patel J, Abass NM, Agarwal D, Ahmed R, Mahesh PA, Bs J, Denguezli M, Franssen F, Gislason T, Janson C, Juvekar SK, Koul P, Malinowski A, Nafees AA, Nielsen R, Paraguas SNM, Buist S, Burney PG, Amaral AFS. **Isolated small airways obstruction predicts future chronic airflow obstruction: a multinational longitudinal study.** *BMJ Open Respir Res.* 2023 Nov;10(1):e002056. doi: 10.1136/bmjresp-2023-002056. PMID: 37989490; PMCID: PMC10660204.

### Summary

This study was aimed to determine whether isolated small airway obstruction is associated with development of chronic airway obstruction in the future. The authors used a longitudinal databank from the burden of obstructive lung disease (BOLD) study. The median follow-up time was 8.3 years. Isolated small airway obstruction was determined using the forced expiratory flow rate between 25% and 75% of the forced vital capacity below the lower limits of normal in the presence of a normal forced expiratory volume in 1 second to FVC ratio. The result showed chronic obstructive airway disease was more likely to develop in participants with baseline evidence of small airway obstruction-  $FEF_{25-75} < LLN$  (OR: 2.95, 95% CI: 1.02 - 8.54).

## Comments

1. Isolated small airway disease can predict the future development of chronic airway obstruction.
2. This study suggests that modifying risk factors leading to airway small airway disease could help in reducing the risk of developing COPD or chronic airway obstruction.
3. The findings raise awareness of clinicians regarding potential benefits of forced expiratory flow between the 25th and 75th percentile
4. More research is needed to understand these observations particularly the long-term impact of modifying risk factors for FEV<sub>25-75</sub> for reduction of risk of developing COPD in the future.

## LUNG FUNCTION AND HEALTH-RELATED QUALITY OF LIFE IN CHILDREN AFTER PULMONARY TUBERCULOSIS

Nkereuwem E, Agbla S, Sallahdeen A, Owolabi O, Sillah AK, Genekah M, Tunkara A, Kandeh S, Jawara M, Saidu L, Bush A, Togun T, Kampmann B. **Reduced lung function and health-related quality of life after treatment for pulmonary tuberculosis in Gambian children: a cross-sectional comparative study.** *Thorax*. 2023 Mar;78(3):281-287. doi: 10.1136/thorax-2022-219085. Epub 2022 Sep 15. PMID: 36109164; PMCID: PMC9985734.

### Summary

This was a cross-sectional comparative study to estimate the prevalence of lung function impairment and reduced health related quality of life in children after completion of pulmonary tuberculosis treatment. Children aged above 5 years and under 15 years with a diagnosis of pulmonary tuberculosis, who had completed treatment for at least 6 months, were recruited into the study. A comparison group of age-matched participants without a history of tuberculosis living in the same households as the cases were also recruited. Lung function measurements were done according to the ATS guidelines. Health-related quality of life was measured with pediatric quality of life scale (PedsQL V4.0). The median age at tuberculosis diagnosis was 6.5 years and median duration since completion of tuberculosis treatment was 19.2 months. The authors found that a higher proportion of post

tuberculosis children were stunted (height-for-age more than two standard deviations below the WHO median) compared with the comparison group (19.1% versus 6.6%,  $P = 0.032$ ). The mean values for FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC ratio were significantly lower in post tuberculosis cases compared with the comparison group. In addition, the proportion of children with impaired lung function was higher in post tuberculosis group compared with the comparison group (38.5% versus 17.4%,  $p=0.009$ ). Restrictive pattern was the most commonly noted lung pattern abnormality. Post tuberculosis cases had lower medium scores on the self-reported physical functioning scale of PedsQL compared with the comparison group (68.8% versus 81.3%,  $p=0.016$ )

## Comments

1. Pulmonary tuberculosis in children is associated with impaired lung function beyond 6 months after completion of treatment.
2. Tuberculosis also significantly impacts the health-related quality of life in children with tuberculosis.
3. Recognition and early treatment of tuberculosis in children may have a significant impact on the risk for development of chronic lung diseases.
4. A more holistic approach should be used to define and describe the outcomes of tuberculosis in children including evaluation of physical growth, quality of life and lung function.
5. More research is needed to determine the trajectory of lung function post tuberculosis in children longitudinally and to determine how much recovery can be achieved over time.

## THE BURDEN OF POST-TUBERCULOSIS LUNG DISEASE IN ADULTS

Ivanova O, Hoffmann VS, Lange C, Hoelscher M, Rachow A. **Post-tuberculosis lung impairment: systematic review and meta-analysis of spirometry data from 14 621 people.** *Eur Respir Rev*. 2023 Apr 19;32(168):220221. doi: 10.1183/16000617.0221-2022. PMID: 37076175; PMCID: PMC10113954.

### Summary

This was a systemic review and meta-analysis of several studies examining the burden of post tuberculosis lung

impairment. Out of the database of 1270 records, 54 articles published between 1971 and 2020 that were found eligible and included in the review. The included studies were case series and cohort studies as well as population-based surveys in which TB history was assessed as one of the risk factors for lung impairment. The combined estimated mean FEV1 for drug-susceptible tuberculosis was 76.6% (95% CI: 71.6–81.6) and estimated FVC was 81.8% (95% CI: 77.4–86.2). 22% had obstructive pattern of lung disease, 23% had restrictive pattern and 15% had a mixed impairment type. For patients with multidrug-resistant tuberculosis, 19% had obstructive lung disease, 22% had a restrictive lung pattern and 43% had a mixed impairment type of lung impairment. Overall, 10 to 15% of survivors had severe lung impairment.

### Comments

1. There is a significant burden of abnormal lung function among TB survivors.
2. All the types of lung impairment, including obstruction, restriction and mixed patterns are prevalent in former TB patients- this could indicate that there are additional cofactors that may be at play in the evolution of lung disease post tuberculosis including genetic background, comorbidities, environmental aspects and risk behaviors including smoking history.
3. Mixed type of impairment was dominant in patients with multidrug resistant TB—suggesting that delaying initiation of antimycobacterial treatment and less than optimal treatment efficacy may contribute to the chronicity and severity of lung disease post tuberculosis.
3. Early recognition and treatment of tuberculosis could potentially reduce the risk of development of post TB sequelae.
4. There is a strong need for longitudinal studies to provide more clarity and a better understanding of how post tuberculosis lung disease differs from smoking-related obstructive lung disease.

### OTHER ARTICLES OF INTEREST

Mortimer, K., Nantanda, R., Meghji, J., Vanker, A., Bush, A., Ndimande, N., ... & Masekela, R. (2021). **Africa's respiratory "big five"**. *Journal of the Pan African Thoracic Society*, 2(2), 64-72.

Mabille, D., Dirx, L., Thys, S., Vermeersch, M., Monteny, D., Govaerts, M., ... & Caljon, G. (2022). **Impact of pulmonary African trypanosomes on the immunology and function of the lung**. *Nature communications*, 13(1), 7083.

Bhakta NR, Bime C, Kaminsky DA, McCormack MC, Thakur N, Stanojevic S, Baugh AD, Braun L, Lovinsky-Desir S, Adamson R, Witonsky J, Wise RA, Levy SD, Brown R, Forno E, Cohen RT, Johnson M, Balmes J, Mageto Y, Lee CT, Masekela R, Weiner DJ, Irvin CG, Swenson ER, Rosenfeld M, Schwartzstein RM, Agrawal A, Neptune E, Wisnivesky JP, Ortega VE, Burney P. **Race and Ethnicity in Pulmonary Function Test Interpretation: An Official American Thoracic Society Statement**. *Am J Respir Crit Care Med*. 2023 Apr 15;207(8):978-995. doi: 10.1164/rccm.202302-0310ST. PMID: 36973004; PMCID: PMC10112445.

Zhao J, Fares J, George G, Maheu A, Loizidis G, Roman J, Kramer D, Li M, Summer R. **Racial and ethnic disparities in antifibrotic therapy in idiopathic pulmonary fibrosis**. *Respirology*. 2023 Nov;28(11):1036-1042. doi: 10.1111/resp.14563. Epub 2023 Aug 3. PMID: 37534632.



# Tuberculosis

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## TREATMENT FOR ACTIVE TUBERCULOSIS

Paton NI, Cousins C, Suresh C, Burhan E, Chew KL, Dalay VB, Lu Q, Kusmiati T, Balanag VM, Lee SL, Ruslami R, Pokharkar Y, Djaharuddin I, Sugiri JJR, Veto RS, Sekaggya-Wiltshire C, Avihingsanon A, Sarin R, Papineni P, Nunn AJ, Crook AM; TRUNCATE-TB Trial Team.

### Treatment Strategy for Rifampin-Susceptible

**Tuberculosis.** *N Engl J Med.* 2023 Mar 9;388(10):873-887. doi: 10.1056/NEJMoa2212537. Epub 2023 Feb 20. PMID: 36808186.

### Summary

In the wake of several recent studies showing favorable outcomes with shortened courses of treatment for drug-susceptible TB, the TRUNCATE investigators conducted an adaptive, open-label, non-inferiority trial at 5 sites across southeast Asia and Uganda. Participants with rifampin-susceptible TB were randomized to one of four investigational “intensified” regimens as compared to a standard 6-month regimen. The intensified regimens consisted of 8 weeks of treatment, with an additional 4 weeks of treatment (i.e., 12 weeks total) for participants with persistent clinical disease (symptoms and a positive sputum smear). The primary study outcome was a composite of death, ongoing treatment, or active disease at 96 weeks. With an intention-to-treat population of 674 participants, the primary outcome occurred in ~6% of participants randomized to a bedaquiline-linezolid regimen, which was non-inferior to the standard regimen. The mean duration of treatment in the bedaquiline-linezolid regimen was 85 days, which was 13.5 weeks shorter than the 180 days of treatment in the standard regimen.

### Comments

1. Participants randomized to shorter treatment regimens reported greater motivation to take treatment and more than 70% in these groups said they would recommend the alternative/intensified strategy to others.
2. Rates of acquired drug resistance were low across the trial arms, with only 2 cases of

acquired resistance in the bedaquiline-linezolid regimen.

3. Adherence to treatment regimens were higher than typically seen in real-world settings.
4. People with HIV were not included in the trial, and so trial results cannot be extrapolated to this important group.
5. Patients with a cavity exceeding 4cm diameter on chest radiograph were initially excluded from the trial and so few participants (2%) with extensive cavitary disease were included.

## TREATMENT FOR ACTIVE TUBERCULOSIS

Goodall RL, Meredith SK, Nunn AJ, Bayissa A, Bhatnagar AK, Bronson G, Chiang CY, Conradie F, Gurumurthy M, Kirenga B, Kiria N, Meressa D, Moodliar R, Narendran G, Ngubane N, Rassool M, Sanders K, Solanki R, Squire SB, Torrea G, Tsogt B, Tudor E, Van Deun A, Rusen ID; STREAM study collaborators. **Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial.** *Lancet.* 2022 Nov 26;400(10366):1858-1868. doi: 10.1016/S0140-6736(22)02078-5. Epub 2022 Nov 8. Erratum in: *Lancet.* 2022 Nov 19;400(10365):1766. PMID: 36368336; PMCID: PMC7614824.

### Summary

The STREAM-1 trial, which was published in 2019, found that a 9-month, 7-drug regimen (including 16-weeks of injected kanamycin) was non-inferior to a traditional 18-to-24-month regimen endorsed by the WHO in 2011 for the treatment of MDR-TB. With the STREAM-2 trial, the investigators conducted an open-label trial that compared the 9-month injectable-containing regimen from STREAM-1 (which had been endorsed by the WHO in 2016) to a 9-month all-oral regimen with bedaquiline and a 6-month bedaquiline regimen that included 8 weeks with a second-line injectable agent. The primary outcome was favorable status defined as negative *Mtb* cultures at 76 weeks without a preceding unfavorable outcome (death, bacteriologic failure or recurrence, or major treatment changes), at 76 weeks. Among 517 participants included in a modified intention-to-treat

analysis, both bedaquiline-containing regimens (6- and 9-months) were superior to the 9-month injectable-containing regimen, with the primary outcome occurring in 91% and 83% of those in the bedaquiline-based regimens as compared to ~70% in the 9-month injectable-containing regimen. Adverse events were similar across the study arms, with the exception of grade 3 or 4 hearing which was more common in the 9-month injectable-containing regimen.

### Comments

1. Rates of acquired phenotypic resistance were low across all study arms.
2. Approximately 15% of the study population were coinfecting with HIV, and people with HIV coinfection had better outcomes with the oral regimen (largely driven by fewer regimen changes after adverse events occurring early during treatment).
3. More than 1/3 of the study population had advanced radiographic disease, with subgroup analyses demonstrating improved outcomes for those with far advanced disease who received a bedaquiline-based oral regimen.
4. QTc prolongation, a concern for several of the drugs in the bedaquiline-containing regimens, was relatively uncommon, with QTc prolongation > 500ms occurring in 3-6% of participants.

### POST-TUBERCULOSIS LUNG DISEASE

Taylor J, Bastos ML, Lachapelle-Chisholm S, Mayo NE, Johnston J, Menzies D. **Residual respiratory disability after successful treatment of pulmonary tuberculosis: a systematic review and meta-analysis.** *EClinicalMedicine.* 2023 May 8;59:101979. doi: 10.1016/j.eclinm.2023.101979. PMID: 37205923; PMCID: PMC10189364.

#### Summary

Post-tuberculosis (TB) lung disease (PTLD) is increasingly recognized as a substantial contributor to the global burden of chronic lung disease. With this systematic review and meta-analysis, the authors identified 61 studies with 41,014 individuals who had successfully completed TB treatment and had an outcome measure of respiratory impairment. Among 42 studies with post-treatment spirometry, 59% of individuals had abnormal spirometry, including 18% with obstruction, 21% with restriction, and 13% with a mixed pattern. Among 13 studies with MRC scores, 73% of participants had a score of 1-2 and 25% had a score of 3-5. Only four studies reported on the incidence of

lung cancer, for which there was an incidence rate ratio of 4.0 (95% CI 2.1-7.6) with an incidence rate difference of 2.7 per 1000 person-years as compared to controls. Persistent cavitation, fibrosis, bronchiectasis, and aspergilloma were common post-TB pulmonary complications.

### Comments

1. Over half of TB survivors have evidence of chronic respiratory impairment after successful completion of TB treatment.
2. Impaired lung function was more common after treatment for MDR TB than drug-susceptible TB, with a nearly four-fold increase in the odds of abnormal spirometry after MDR TB.
3. Impaired lung function was less common after treatment for TB among people with HIV coinfection, with 28% of those with HIV coinfection having abnormal spirometry after TB treatment completion as compared to 83% of those without HIV coinfection.
4. Given limited availability of lung volume measurements (via body plethysmography and/or breath washout techniques) in settings with a high burden of TB, restrictive impairments were defined on spirometry alone as a FVC < 80% predicted or < LLN with a FEV1/FVC ≥ 70%.

### POST-TUBERCULOSIS LUNG DISEASE

Martinez L, Gray DM, Botha M, Nel M, Chaya S, Jacobs C, Workman L, Nicol MP, Zar HJ. **The Long-Term Impact of Early-Life Tuberculosis Disease on Child Health: A Prospective Birth Cohort Study.** *Am J Respir Crit Care Med.* 2023 Apr 15;207(8):1080-1088. doi: 10.1164/rccm.202208-1543OC. PMID: 36746196; PMCID: PMC10112440.

#### Summary

Although there is an expanding evidence base demonstrating a substantial burden of post-TB lung disease in adults, few studies have examined lung health among children treated for TB. With data from a South African birth cohort study with repeated visits throughout the first 5 years of life, the authors examined the association between early childhood TB and lung health. From 1,068 infants who had at least one relevant lung health measurement, 96 TB cases occurred during 7,815 years of follow-up (1,228 cases per 100,000 person-years). Children diagnosed and treated for TB had lower length- and weight-for-age z-scores and body mass index z-scores, in addition to reduced

measures of expiratory flow, higher FeNO, greater risk of wheezing, and lower tidal volume at 5 years of age.

### Comments

1. Despite completion of appropriate treatment, early childhood TB contributes to a substantial burden of respiratory impairment during childhood, and likely to lifelong respiratory impairment although further studies with extended follow-up duration will be needed to demonstrate longer term impacts.
2. Early childhood TB also contributes to reduced growth and decreased anthropometric measurements.
3. The greatest risk of poor lung health was seen for children who developed TB at younger ages (i.e., before 6 or 12 months), as compared to those who developed TB at older ages (i.e., 1-5 years).
4. The study cohort had low socioeconomic status, 22% of mothers had HIV (although only two infants), and 23% of mothers smoked during pregnancy.

## SPECTRUM OF TUBERCULOSIS INFECTION AND DISEASE

Horton KC, Richards AS, Emery JC, Esmail H, Houben RMGJ. **Reevaluating progression and pathways following *Mycobacterium tuberculosis* infection within the spectrum of tuberculosis.** Proc Natl Acad Sci U S A. 2023 Nov 21;120(47):e2221186120. doi: 10.1073/pnas.2221186120. Epub 2023 Nov 14. PMID: 37963250; PMCID: PMC10666121.

### Summary

Although TB has traditionally been conceived of as occurring either as latent TB infection or active TB disease, there is growing recognition that TB likely occurs across a broader spectrum of disease presentations including multiple intermediate disease states between the binary extremes of infection and symptomatic disease. Using data from natural history studies of TB, the authors used a Bayesian approach to calibrate a model of TB infection and disease, with estimations of TB incidence, pathways, and 10-year outcomes for a simulated cohort. The spectrum of TB disease states included: infection (positive immunologic test without bacteriologic or clinical disease), cleared (control or elimination of infection), recovered (control or elimination of infection after clinical disease), minimal disease (pathology without bacteriologic disease), subclinical disease (bacteriologic disease without clinical symptoms), and clinical disease (bacteriologic disease with symptoms). Over a 10-year

period following Mtb infection, one in 10 simulated individuals progressed to TB with either minimal, subclinical, or clinical disease, of whom two-third developed infectious disease (subclinical or clinical) and half progressed to clinical disease. Most progression to minimal and subclinical disease occurred within 2 years of infection, but half of clinical disease developed after 2 years.

### Comments

1. There is substantial heterogeneity in pathways following Mtb infection, ranging from clearance of infection to rapid progression to infectious disease.
2. The model estimated that 90% of individuals self-clear TB during the 10 years after infection.
3. Pathways of infection and disease may differ for individuals with comorbidities such as HIV coinfection, which were not accounted for in this model.
4. Subclinical disease, where bacteriologic disease is present without reported symptoms, may be a substantial contributor to transmission of TB on a population-level.

## NUTRITIONAL SUPPLEMENTATION TO PREVENT TB

Bhargava A, Bhargava M, Meher A, Benedetti A, Velayutham B, Sai Teja G, Watson B, Barik G, Pathak RR, Prasad R, Dayal R, Madhukeshwar AK, Chadha V, Pai M, Joshi R, Menzies D, Swaminathan S. **Nutritional supplementation to prevent tuberculosis incidence in household contacts of patients with pulmonary tuberculosis in India (RATIONS): a field-based, open-label, cluster-randomised, controlled trial.** Lancet. 2023 Aug 19;402(10402):627-640. doi: 10.1016/S0140-6736(23)01231-X. Epub 2023 Aug 8. PMID: 37567200.

### Summary

Undernutrition is a leading contributor to the global burden of TB and is a biological and social risk factor for TB incidence and mortality. With this open-label, cluster-randomized trial, household contacts of TB patients were randomly allocated to receive monthly food rations of 750 kcal and 23 grams of protein per day plus micronutrients. The primary study outcome was incident TB in household contacts. Among 10,345 household contacts, 34% had undernutrition at enrollment. After at least 2 years of follow-up, 1.7% of the intervention group and 2.6% of the control group developed TB. TB incidence in the intervention group had an adjusted incidence rate ratio of 0.61 (95% CI 0.43-0.85), reflecting a relative reduction of TB incidence

of 39% (and a 48% reduction among microbiologically confirmed disease).

### Comments

1. In order to prevent one case of incident TB, 30 households (with 111 household contacts) would need to receive nutritional supplementation.
2. The cost per adult contact for the intervention, which was continued for the 6-months during which the index case received TB treatment, was \$4.75 per month; support was extended for up to 12 months for household contacts with a BMI < 16 kg/m<sup>2</sup>.
3. The nutritional intervention had no significant effect on other common infections including malaria, diarrhea, respiratory infections, hospitalizations, and deaths related to febrile illness.
4. Nutritional support can be considered a form of host-directed therapy to reduce TB incidence, with “food as medicine” providing reductions comparable to that of global targets for TB vaccines.

## OTHER ARTICLES OF INTEREST

### TREATMENT FOR ACTIVE TB DISEASE

Jindani A, Atwine D, Grint D, Bah B, Adams J, Ticona ER, Shrestha B, Agizew T, Hamid S, Jamil B, Byamukama A, Kananura K, Mugisha Taremwa I, Bonnet M, Camara LM, Bah-Sow OY, Bah KS, Bah NM, Sow M, Ticona Huaroto CE, Mugruza Pineda R, Tandukar B, Raya BB, Shrestha N, Mathoma A, Mathebula-Modongo UP, Basotli J, Irfan M, Begum D, Muzammil A, Ahmed I, Hasan R, Burgos MV, Sultan F, Hassan M, Masood I, Robb C, Decker J, Grubnic S, Butcher PD, Witney A, Dhillon J, Munshi T, Fielding K, Harrison TS. **Four-Month High-Dose Rifampicin Regimens for Pulmonary Tuberculosis.** NEJM Evid. 2023 Sep;2(9):EVIDoa2300054. doi: 10.1056/EVIDoa2300054. Epub 2023 Aug 22. PMID: 38320155.

Haley CA, Schechter MC, Ashkin D, Peloquin CA, Peter Cegielski J, Andrino BB, Burgos M, Caloia LA, Chen L, Colon-Semidey A, DeSilva MB, Dhanireddy S, Dorman SE, Dworkin FF, Hammond-Epstein H, Easton AV, Gaensbauer JT, Ghassemieh B, Gomez ME, Horne D, Jasuja S, Jones BA, Kaplan LJ, Khan AE, Kracen E, Labuda S, Landers KM, Lardizabal AA, Lasley MT, Letzer DM, Lopes VK, Lubelchek RJ, Patricia Macias C, Mihalyov A, Misch EA, Murray JA, Narita M, Nilsen DM, Ninneman MJ, Ogawa L, Oladele A, Overman M, Ray SM, Ritger KA, Rowlinson MC, Sabuwala N, Schiller TM, Schwartz LE, Spitters C, Thomson DB, Tresgallo RR, Valois P, Goswami ND; BPaL Implementation Group. **Implementation of Bedaquiline, Pretomanid, and Linezolid in the United States: Experience Using a Novel All-Oral Treatment Regimen for Treatment of Rifampin-Resistant or Rifampin-Intolerant Tuberculosis Disease.** Clin Infect Dis. 2023 Oct 5;77(7):1053-1062. doi: 10.1093/cid/ciad312. PMID: 37249079.

Hasan T, Medcalf E, Nyang'wa BT, Egizi E, Berry C, Dodd M, Foraida S, Gegia M, Li M, Mirzayev F, Morgan H, Motta I, Nguyen L, Schumacher S, Schlub T, Fox G. **The safety and tolerability of linezolid in novel short-course regimens containing bedaquiline, pretomanid and linezolid to treat rifampicin-resistant tuberculosis: an individual patient data meta-analysis.** Clin Infect Dis. 2023 Oct 24:ciad653. doi: 10.1093/cid/ciad653. Epub ahead of print. PMID: 37874021.

### SCREENING FOR LATENT TB INFECTION

US Preventive Services Task Force; Mangione CM, Barry MJ, Nicholson WK, Cabana M, Chelmow D, Coker TR, Davis EM, Donahue KE, Jaén CR, Li L, Ogedegbe G, Rao G, Ruiz JM, Stevermer J, Underwood SM, Wong JB. **Screening for Latent Tuberculosis Infection in Adults: US Preventive Services Task Force Recommendation Statement.** JAMA. 2023 May 2;329(17):1487-1494. doi: 10.1001/jama.2023.4899. PMID: 37129649.

Zavala S, Winglee K, Ho CS, Pettit AC, Ahmed A, Katz DJ, Belknap RW, Stout JE. **Examining Test Cutoffs to Optimize Diagnosis of Latent Tuberculosis Infection in People Born Outside the United States.** Ann Am Thorac Soc. 2023 Sep;20(9):1258-1266. doi: 10.1513/AnnalsATS.202212-1005OC. PMID: 37159954.

### TB TRANSMISSION

Nelson KN, Churchyard G, Cobelens F, Hanekom WA, Hill PC, Lopman B, Mave V, Rangaka MX, Vekemans J, White RG, Wong EB, Martinez L, García-Basteiro AL. **Measuring**

**indirect transmission-reducing effects in tuberculosis vaccine efficacy trials: why and how?** *Lancet Microbe*. 2023 Aug;4(8):e651-e656. doi: 10.1016/S2666-5247(23)00112-X. Epub 2023 Jun 14. PMID: 37329893; PMCID: PMC10393779.

Marks GB, Ho J, Nguyen PTB, Nguyen TA, Boi KL, Tran KH, Nguyen SV, Nguyen NV, Nguyen HB, Nguyen LN, Garden FL, Fox GJ. **A Direct Measure of Tuberculosis Incidence - Effect of Community Screening.** *N Engl J Med*. 2022 Apr 7;386(14):1380-1382. doi: 10.1056/NEJMc2114176. PMID: 35388676.

Trevisi L, Brooks MB, Becerra MC, Calderón RI, Contreras CC, Galea JT, Jimenez J, Lecca LW, Yataco RM, Tovar X, Zhang Z, Murray MB, Huang CC. **Who Transmits Tuberculosis to Whom: A Cross-Sectional Analysis of a Cohort Study in Lima, Peru.** *Am J Respir Crit Care Med*. 2024 Feb 28. doi: 10.1164/rccm.202307-1217OC. Epub ahead of print. PMID: 38416532.

#### TB MENINGITIS

Manesh A, Gautam P, Kumar D SS, Mannam P, Jasper A, Gunasekaran K, Thomas NC, Benjamin RN, Inbaraj LR, Devasagayam E, George MM, Karthik R, Abraham OC, Vanjare HA, Sivadasan A, Appaswamy PT, Jonathan E, Michael JS, Samuel P, Varghese GM. **Effectiveness of Adjunctive High-Dose Infliximab Therapy to Improve Disability-Free Survival Among Patients With Severe**

**Central Nervous System Tuberculosis: A Matched Retrospective Cohort Study.** *Clin Infect Dis*. 2023 Nov 17;77(10):1460-1467. doi: 10.1093/cid/ciad401. PMID: 37405816.

Donovan J, Bang ND, Imran D, Nghia HDT, Burhan E, Huong DTT, Hiep NTT, Ngoc LHB, Thanh DV, Thanh NT, Wardhani ALS, Maharani K, Gasmara CP, Hanh NHH, Oanh PKN, Estiasari R, Thu DDA, Kusumaningrum A, Dung LT, Giang DC, Ha DTM, Lan NH, Chau NVV, Nguyet NTM, Geskus RB, Thuong NTT, Kestelyn E, Hamers RL, Phu NH, Thwaites GE; ACT HIV Investigators. **Adjunctive Dexamethasone for Tuberculous Meningitis in HIV-Positive Adults.** *N Engl J Med*. 2023 Oct 12;389(15):1357-1367. doi: 10.1056/NEJMoa2216218. PMID: 37819954; PMCID: PMC7615197.

#### MISCELLANEOUS

Migliori GB, Dowdy D, Denholm JT, D'Ambrosio L, Centis R. **The path to tuberculosis elimination: a renewed vision.** *Eur Respir J*. 2023 Jun 15;61(6):2300499. doi: 10.1183/13993003.00499-2023. PMID: 37080572.

Linde LR, Readhead A, Barry PM, Balmes JR, Lewnard JA. **Tuberculosis Diagnoses Following Wildfire Smoke Exposure in California.** *Am J Respir Crit Care Med*. 2023 Feb 1;207(3):336-345. doi: 10.1164/rccm.202203-0457OC. PMID: 36103611.

# Interstitial Lung Disease

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## TREATMENT OF COUGH IN IPF

Wu Z, Spencer LG, Banya W, Westoby J, Tudor VA, Rivera-Ortega P, et al. **Morphine for treatment of cough in idiopathic pulmonary fibrosis (PACIFY COUGH): a prospective, multicentre, randomised, double-blind, placebo-controlled, two-way crossover trial.** *The Lancet Respiratory Medicine*. 2024. Epub 20240115. doi: 10.1016/s2213-2600(23)00432-0. PubMed PMID: 38237620

### Summary

The PACIFY COUGH study, was a prospective, multicenter, randomized, double blind, placebo controlled, crossover trial. The objective was to examine the use of low-dose controlled-release morphine on cough frequency in patients with idiopathic pulmonary fibrosis (IPF). A total of 44 patients aged 40-90 with a diagnosis of IPF and self-reported cough were randomly assigned to twice daily placebo or controlled-release morphine 5 mg for 14 days, followed by a 7-day washout period and crossover. The primary endpoint was change in awake cough frequency (coughs per hour) measured using an ambulatory digital recording device with a lapel microphone and contact sensor. In the intention-to-treat primary analysis, controlled-release morphine reduced daytime cough frequency by 39%. Cough frequency went from 22 coughs per hour, to 13 coughs per hour ( $p < 0.0001$ ) on morphine treatment, while there was no difference in the placebo group (22 coughs per hour to 21 coughs per hour). Controlled-release morphine also improved all of the measured cough-related patient-reported outcomes, but did not improve breathlessness, depression or anxiety measures. Most common adverse events included constipation, and nausea.

### Comments

1. This study is the first to report benefit of morphine in cough related to IPF, a debilitating and refractory symptom of this disease.
2. Despite the small sample size of participants (44), morphine significantly reduced cough

frequency compared to placebo, and cough related patient-reported outcomes.

3. Treatment adherence was excellent, at 98% in both treatment and placebo groups.
4. Controlled-release morphine was safe, with few, expected adverse events.
5. Active smokers, patients with severe disease, and those with a recent acute exacerbation were excluded from the trial, which may limit generalizability of study findings to a broader IPF population.

## TREATMENT IN NON-IPF ILD

Mankikian J, Caille A, Reynaud-Gaubert M, Agier MS, Bermudez J, Bonniaud P, et al. **Rituximab and mycophenolate mofetil combination in patients with interstitial lung disease (EVER-ILD): a double-blind, randomised, placebo-controlled trial.** *The European Respiratory Journal*. 2023;61(6). Epub 2023/05/26. doi: 10.1183/13993003.02071-2022. PubMed PMID: 37230499.

### Summary

The EVER-ILD trial was a prospective, double-blind, randomized controlled trial of patients with non-specific interstitial pneumonia pattern (NSIP) and underlying diagnosis of a connective-tissue disease related ILD or idiopathic interstitial pneumonia. The objective of the trial was to determine the efficacy and safety of combining rituximab with mycophenolate (MMF) versus MMF alone in patients with NSIP. NSIP was determined based on a surgical lung biopsy or on radiological features compatible with NSIP. Adult patients were assigned to receive rituximab at a dose of 1000 mg or placebo on days 1 and 15, in addition to mycophenolate mofetil for 6 months. The primary endpoint was the change in forced vital capacity (FVC) from baseline to 6 months. There were 122 patients

randomized to receive at least one dose of rituximab or placebo. There was a significant difference in absolute change in FVC from baseline, favoring the rituximab + MMF group (between group difference in FVC% predicted 3.60,  $p=0.027$ ). In addition, progression-free survival was better in the rituximab + MMF group compared to the placebo + MMF group, with a hazard ratio for exacerbation or death of 0.47 ( $p=0.03$ ). There was no difference in adverse events between the groups.

### Comments

1. The EVER-ILD study is the first randomized trial assessing combination treatment with immunosuppression in patients with ILD and an NSIP pattern.
2. Although the benefit of combination therapy on FVC was small (3.6% predicted points), it corresponded to about 100 mL in FVC and this was on a short study period of 6 months.
3. The combination of rituximab and MMF was also associated with improved progression-free survival.
4. The main limitation concerns diagnosis of ILD with NSIP pattern: a formal diagnosis of NSIP requires histopathologic evaluation of a lung biopsy, which only 15 patients (12%) underwent.
5. This study reported no difference between arms in several secondary outcomes such as six minute walking distance, diffusion capacity, dyspnea, cough, or radiological fibrosis.

### TREATMENT IN NON-IPF ILD

Zhang D, Adegunsoye A, Oldham JM, Kozlitina J, Garcia N, Poonawalla M, et al. **Telomere length and immunosuppression in non-idiopathic pulmonary fibrosis interstitial lung disease.** *European Respiratory Journal*. 2023;62(5):2300441. doi: 10.1183/13993003.00441-2023.

### Summary

This was a retrospective, multicenter cohort analyses to explore the interaction between short leukocyte telomere length and immunosuppression (specifically azathioprine and mycophenolate) on 2-year transplant-free survival in patients with non-IPF ILD. Patients were included in the discovery and replication cohorts if they had a diagnosis of fibrotic hypersensitivity pneumonitis, unclassifiable ILD, or connective tissue disease-related ILD. Patients were grouped into those who were exposed to immunosuppression vs non exposed. Leukocyte telomere length (LTL) was measured by quantitative PCR and expressed as age-adjusted percentile of normal, then dichotomized into  $\geq 10$ th percentile vs  $< 10$ th percentile. There were 938 patients who met eligibility criteria, of which 40% were exposed to immunosuppression, and 22% had LTL  $< 10$ th percentile. Patients with fibrotic hypersensitivity pneumonitis and unclassifiable ILD and who had a  $< 10$ th percentile LTL had significantly reduced survival compared to non-exposed individuals, with a mortality hazard ratio of 4.9. This was seen in the discovery and replication cohorts. Immunosuppression was not associated with increased mortality in those with a LTL  $> 10$ th percentile. Trajectory of forced vital capacity over time did not differ between those exposed and non-exposed to immunosuppression. However, short LTL was associated with more rapid decline in lung function, independent of immunosuppression exposure.

### Comments

1. This study is important as it suggests that LTL might be a key clinical biomarker when making treatment decisions in patients with non-IPF ILD.
2. Short LTL was associated with a nearly 5-fold increased hazard of mortality in patients with unclassifiable ILD and hypersensitivity pneumonitis who received immunosuppression.
3. The potential for biases in this observational study were mitigated by treating exposure as a time-dependent covariate, and by using propensity score matching between exposed and non-exposed to immunosuppression.
4. This study was underpowered to detect a difference in the subgroup of patients with a

diagnosis of connective tissue disease related ILD, as few of these patients had a LTL <10th percentile.

## INTERSTITIAL LUNG ABNORMALITIES

Park S, Choe J, Hwang HJ, Noh HN, Jung YJ, Lee J-B, et al. **Long-Term Follow-Up of Interstitial Lung Abnormality: Implication in Follow-Up Strategy and Risk Thresholds.** *American Journal of Respiratory and Critical Care Medicine.* 2023;208(8):858-67. doi: 10.1164/rccm.202303-0410OC. PubMed PMID: 37590877.

### Summary

Interstitial lung abnormalities (ILA) are defined as incidental findings on CT chest; however, many will progress to a definite ILD. In those who have a high risk of progression, the optimal follow up strategies and timeline have not been established. This was a retrospective study of adult participants aged 50 years and older who had self-referred for a health screening program and underwent two CT chests within a 5-year interval. Progression of ILA over time was defined as an increase in lung areas affected by nondependent ground glass opacities, reticulations, bronchiectasis, or honeycombing. Out of 4659 participants screened, 305 met inclusion criteria of indeterminate or definitive ILA. Of those, 200 had consecutive CT scans with interval of less than 2 years and could be included in the radiologic analysis for ILA. ILA progression was observed in 81%, with a median time to ILA progression of 3.2 years. Of those, 17% progressed to a usual interstitial pneumonia pattern. Critically, values of 5% fibrotic ILA in any lung zone or 1% in the whole lung were determined as optimal thresholds for risk stratification of participants. Presence of honeycombing was another key risk factor for progression. Participants with both risk factors were at the highest risk of progression in the shortest timeline.

### Comments

1. This is one of the most comprehensive studies of radiologic longitudinal follow up of ILA.

2. A 3-year interval CT follow-up for ILA is likely adequate for most, considering the median timeline for progression of 3 years.
3. In patients with ILA who have both honeycombing, and extent of  $\geq 5\%$  in any lung zone (or 1% whole lung), a shorter follow up might be considered given the greater risk of progression.
4. This study population was self-referred for comprehensive health screening and might not be representative of a broader population.
5. A limitation of this study is that it does not integrate physiologic or clinical data with the radiology findings.

## COVID-19 AND ILD

Stewart I, Jacob J, George PM, Molyneaux PL, Porter JC, Allen RJ, et al. **Residual Lung Abnormalities after COVID-19 Hospitalization: Interim Analysis of the UKILD Post-COVID-19 Study.** *Am J Respir Crit Care Med.* 2023;207(6):693-703. doi: 10.1164/rccm.202203-0564OC. PubMed PMID: 36457159; PubMed Central PMCID: PMC10037479.

### Summary

This article reports the interim analysis of the UK Interstitial Lung Disease Consortium post-COVID-19 study. The objective of this post hospitalization longitudinal prospective study was to estimate the prevalence of residual lung abnormalities in people hospitalized with COVID-19. This interim cohort included 3,700 participants, of which 255 had clinically indicated linked CT scans of the chest within 240 days of discharge, and 209 were visually scored. The presence of residual lung abnormalities (specifically ground glass opacities, reticulations) was assessed on a lobar basis. Residual lung abnormalities greater than 10% of the lung were observed in 166 (79%) or participants. Interestingly, there were 33 participants who had a repeat CT subsequently, and 92% had persistent residual lung abnormalities. Key clinical risk factors for residual lung abnormalities included diffusion capacity  $\leq 80\%$ , abnormal chest radiograph, and severe illness on



admission requiring invasive support. Prevalence of residual lung abnormalities was estimated at 8.5% overall.

### Comments

1. This study demonstrates that residual lung abnormalities were identifiable on follow up CT chest in over 8% of patients within 8 months of discharge for COVID-19 hospitalization.
2. This study is the largest assessment of prevalence in hospitalized individuals.
3. Limitation of this study included the lack of systematic chest imaging post discharge, which may have led to underestimating the prevalence of residual abnormalities.
4. This was a planned interim analysis, and longer term follow up is needed to evaluate the evolution of these patients.

recommendation for the use of cyclophosphamide, rituximab, tocilizumab, nintedanib, and nintedanib plus mycophenolate. Finally, they made a strong recommendation for further research on the use of pirfenidone, and pirfenidone plus mycophenolate.

### Comments

1. This guideline document was developed in compliance with the National Academy of Medicine standards for trustworthy guidelines.
2. This was an international multidisciplinary committee that consisted of pulmonologists, rheumatologists, information scientist and two patients with the disease.
3. This guideline document was intended to provide rational decisions on management of SSc-ILD rather than to impose a standard of care.

## GUIDELINES IN SCLERODERMA-ILD

Raghu G, Montesi SB, Silver RM, Hossain T, Macrea M, Herman D, et al. **Treatment of Systemic Sclerosis-associated Interstitial Lung Disease: Evidence-based Recommendations. An Official American Thoracic Society Clinical Practice Guideline.** *Am J Respir Crit Care Med.* 2024;209(2):137-52. doi: 10.1164/rccm.202306-1113ST. PubMed PMID: 37772985; PubMed Central PMCID: PMC10806429.

### Summary

This international, multidisciplinary clinical guideline document made evidence-based recommendations for the treatment of scleroderma related interstitial lung disease. The expert committee panel defined progressive scleroderma related ILD if two out three criteria are met: worsening dyspnea or cough, evidence of physiologic progression, or radiologic disease progression. The expert panel also made recommendations on 6 individual therapies and 2 combinations therapies. For treatment of scleroderma related ILD, they made a strong recommendation for the use of mycophenolate, a conditional

## OTHER ARTICLES OF INTEREST

### ILD EPIDEMIOLOGY

McGroder CF, Hansen S, Hinckley Stukovsky K, Zhang D, Nath PH, Salvatore MM, et al. **Incidence of Interstitial Lung Abnormalities: The MESA Lung Study.** *The European Respiratory Journal.* 2023. Epub 20230518. doi: 10.1183/13993003.01950-2022. PubMed PMID: 37202153; PubMed Central PMCID: PMC10773573.

Jeganathan N, Sathananthan M. **Interstitial Lung Disease Cases, Prevalence Rates and Trends Among States in the United States.** *Chest.* 2024;165(2):389-95. doi: 10.1016/j.chest.2023.08.006.

### ILD DIAGNOSIS

Fortin M, Liberman M, Delage A, Dion G, Martel S, Rolland F, et al. **Transbronchial Lung Cryobiopsy and Surgical Lung Biopsy: A Prospective Multi-Centre Agreement Clinical Trial (CAN-ICE).** *American Journal of Respiratory and Critical Care Medicine.* 2023;207(12):1612-

9. doi: 10.1164/rccm.202209-1812OC. PubMed PMID: 36796092.

Moll M, Peljto AL, Kim JS, Xu H, Debban CL, Chen X, et al. **A Polygenic Risk Score for Idiopathic Pulmonary Fibrosis and Interstitial Lung Abnormalities.** *Am J Respir Crit Care Med.* 2023;208(7):791-801. doi: 10.1164/rccm.202212-2257OC. PubMed PMID: 37523715; PubMed Central PMCID: PMC10563194.

Desai SR, Sivarasan N, Johannson KA, George PM, Culver DA, Devaraj A, et al. **High-resolution CT phenotypes in pulmonary sarcoidosis: a multinational Delphi consensus study.** *The Lancet Respiratory Medicine.* doi: 10.1016/S2213-2600(23)00267-9.

Barnett JL, Maher TM, Quint JK, Adamson A, Wu Z, Smith DJF, et al. **Combination of BAL and Computed Tomography Differentiates Progressive and Non-progressive Fibrotic Lung Diseases.** *American Journal of Respiratory and Critical Care Medicine.* 2023;208(9):975-82. doi: 10.1164/rccm.202305-0796OC. PubMed PMID: 37672028.

Griese M, Schwerk N, Carlens J, Wetzke M, Emiralioğlu N, Kiper N, et al. **Minimal important difference in childhood interstitial lung diseases.** *Thorax.* 2023;78(5):476-83. doi: 10.1136/thorax-2022-219206.

## ILD TREATMENT

Pérez ERF, Crooks JL, Lynch DA, Humphries SM, Koelsch TL, Swigris JJ, et al. **Pirfenidone in fibrotic hypersensitivity pneumonitis: a double-blind, randomised clinical trial of efficacy and safety.** *Thorax.* 2023;78(11):1097-104. doi: 10.1136/thorax-2022-219795.

Maher TM, Tudor VA, Saunders P, Gibbons MA, Fletcher SV, Denton CP, et al. **Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial.** *The Lancet Respiratory Medicine.* 2023;11(1):45-54. Epub 2022/11/15. doi: 10.1016/s2213-2600(22)00359-9. PubMed PMID: 36375479.

Dempsey TM, Thao V, Helfinstine D, Sangaralingham L, Limper AH. **Comparing the Utilization of Antifibrotic Medications Based on Income Level.** *Chest.* 2024;165(1):146-9. doi: 10.1016/j.chest.2023.07.4215.

O'Dowd EL, Tietzova I, Bartlett E, Devaraj A, Biederer J, Brambilla M, et al. **ERS/ESTS/ESTRO/ESR/ESTI/EFOMP statement on management of incidental findings from low dose CT screening for lung cancer.** *The European Respiratory Journal.* 2023;62(4). Epub 20231019. doi: 10.1183/13993003.00533-2023. PubMed PMID: 37802631.

Maher TM, Ford P, Brown KK, Costabel U, Cottin V, Danoff SK, et al. **Ziritaxestat, a Novel Autotaxin Inhibitor, and Lung Function in Idiopathic Pulmonary Fibrosis: The ISABELA 1 and 2 Randomized Clinical Trials.** *Jama.* 2023;329(18):1567-78. doi: 10.1001/jama.2023.5355.

## ILD BURDEN AND PROGNOSIS

Pitre T, Lupas D, Ebeido I, Colak A, Modi M, Kachkovski GV, et al. **Prognostic factors associated with mortality in acute exacerbations of idiopathic pulmonary fibrosis: A systematic review and meta-analysis.** *Respir Med.* 2024;222:107515. Epub 20231226. doi: 10.1016/j.rmed.2023.107515. PubMed PMID: 38154738.

Guler SA, Marinescu DC, Cox G, Durand C, Fisher JH, Grant-Orser A, et al. **The clinical frailty scale for risk stratification in patients with fibrotic interstitial lung disease.** *Chest.* 2024. Epub 2024/03/01. doi: 10.1016/j.chest.2024.02.043. PubMed PMID: 38423280.

Saunders P, Wu Z, Fahy WA, Stewart ID, Saini G, Smith DJF, et al. **The Burden and Impact of Cough in Patients with Idiopathic Pulmonary Fibrosis: An Analysis of the Prospective Observational PROFILE Study.** *Annals of the American Thoracic Society.* 2023;20(9):1267-73. doi: 10.1513/AnnalsATS.202302-174OC. PubMed PMID: 37159951; PubMed Central PMCID: PMC10502892.

# Sepsis

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## TREATMENT HETEROGENEITY IN SEPSIS

Sinha P, Kerchberger VE, Willmore A, Chambers J, Zhuo H, Abbott J, Jones C, Wickersham N, Wu N, Neyton L, Langelier CR, Mick E, He J, Jauregui A, Churpek MM, Gomez AD, Hendrickson CM, Kangelaris KN, Sarma A, Leligdowicz A, Delucchi KL, Liu KD, Russell JA, Matthay MA, Walley KR, Ware LB, Calfee CS. **Identifying molecular phenotypes in sepsis: an analysis of two prospective observational cohorts and secondary analysis of two randomised controlled trials.** *Lancet Respir Med*, 2023;11(11):965-74.

### Summary

The underlying pathophysiological heterogeneity of critical care syndromes like sepsis and ARDS contributes to medical science's ongoing failure to identify targeted therapies. Past work using an unsupervised machine learning method called latent class analysis has reliably divided ARDS patients into "hyperinflammatory" and "hypoinflammatory" phenotypes exhibiting different outcome profiles and possibly different responses to potential therapies. In two cohorts of ICU sepsis patients (N=1140 and N=818), application of the statistical methods and data inputs (inflammation biomarkers plus limited clinical data) previously applied to ARDS independently recapitulated the hyper- and hypoinflammatory phenotypes in both sepsis cohorts. The hyperinflammatory phenotype characterized similar proportions of both sepsis cohorts (30% and 35%, respectively), and was associated with similarly elevated hospital mortality (43% and 45%) compared to the hypoinflammatory phenotype (17% and 20%). When septic shock patients enrolled in the VASST randomized controlled trial (vasopressin for septic shock) were retrospectively classified as hyper- or hypoinflammatory, no heterogeneity of treatment effect was seen. In contrast, hyperinflammatory phenotype

patients in the PROWESS-SHOCK trial seemed to benefit from activated protein C treatment compared to placebo (28-day mortality 33% vs 39%), while hypoinflammatory patients had higher 28-day mortality with active treatment (23% vs 17%,  $p=0.004$  for the interaction).

### Comments

1. Independent recapitulation in sepsis of hyperinflammatory and hypoinflammatory phenotypes previously derived in ARDS — and especially the phenotypes' stability when ARDS patients were excluded from the sepsis cohorts — suggests that shared biological phenotypes may underpin seemingly distinct critical care syndromes.
2. The two hyperinflammatory and hypoinflammatory phenotypes identified using proinflammatory protein biomarkers may capture different biological heterogeneity compared to other published sepsis phenotyping systems, including a four-group classification previously derived from clinical data and two- to four-group classifications derived from gene expression.
3. Post hoc analyses of the VASST and PROWESS-SHOCK trial were exploratory, and the findings suggesting heterogeneity in effect in the latter trial are strictly hypothesis generating.
4. Application of the hyper-/hypoinflammatory sepsis phenotypes (and other phenotyping systems) as "treatable traits" awaits development of clinical criteria or clinical assays that can assign phenotypes in real time at the bedside followed by phenotypes' prospective application as eligibility criteria in clinical trials.

## TREATMENT HETEROGENEITY IN SEPSIS

Hechtman RK, Kipnis P, Cano J, Seelye S, Liu VX, Prescott HC. **Heterogeneity of Benefit from Earlier Time-to-Antibiotics for Sepsis.** *Am J Respir Crit Care Med*, 2024. 2024 Apr 1;209(7):852-860. <https://pubmed.ncbi.nlm.nih.gov/38261986/>

### Summary

The 2021 Surviving Sepsis Campaign guidelines made antibiotic initiation goals contingent on illness severity (specifically shock) and sepsis probability. Among 273,255 patients hospitalized at 173 Kaiser Permanente or VA hospitals with community-acquired sepsis, Hechtman et al. investigated whether major benefits from earliest possible antibiotic initiation are restricted to patients with shock. Unsurprisingly, the 48% of patients receiving antibiotics within 3 hours of ED arrival exhibited an absolute 1.2% reduction in adjusted 30-day mortality (9% lower adjusted relative risk). Except possibly for decreasing benefit above age 70, relative mortality risk reductions from prompt antibiotics were fairly consistent across tested demographic, comorbidity, SIRS criteria, and organ failure subgroups. However, non-shock acute organ dysfunctions (hematologic, hepatic, or respiratory),  $\geq 3$  total acutely dysfunctional organ systems, and metastatic cancer were all associated with substantial absolute mortality reductions from prompt antibiotics on par with septic shock. Causal forest analysis — an innovative machine learning method robust to false discovery and capable of handling complex subgroup interactions — confirmed these findings, demonstrating acute hematologic, liver, and respiratory dysfunction, comorbid liver disease, and especially comorbid metastatic cancer were overrepresented to a similar degree as shock among patients deriving the greatest benefit from early antibiotics.

### Comments

1. Similar relative risk reduction mask important differences in absolute treatment benefit (absolute risk difference and number needed to treat) from prompt antibiotic initiation across subgroups of patients with sepsis.

2. Shock appears to be an insufficient single criterion to identify sepsis patients who obtain large absolute mortality benefit from prompt antibiotic initiation.
3. The effects of infection probability stratification methods — particularly different thresholds for distinguishing possible from probable infection — remain undefined, challenging both assessment and bedside application of the 2021 Surviving Sepsis antibiotic initiation guidelines.

## REAL-WORLD SEPSIS TREATMENT

Bosch NA, Teja B, Law AC, Pang B, Jafarzadeh SR, Walkey AJ. **Comparative Effectiveness of Fludrocortisone and Hydrocortisone vs Hydrocortisone Alone Among Patients with Septic Shock.** *JAMA Intern Med*, 2023;183(5):451-9.

### Summary

While guidelines recommend hydrocortisone for septic shock with “ongoing vasopressor requirement,” divergent trial results — especially the ADRENAL (no fludrocortisone, no benefit) and the APPROCCHSS (fludrocortisone co-treatment, improved 90-day mortality) trials — as well as some meta-analyses suggest that fludrocortisone co-treatment may be required for maximal benefit. This retrospective study of over 88,000 septic shock patients used administrative data from about 25% of U.S. hospitals to simulate a trial comparing effects of treatment with fludrocortisone plus hydrocortisone versus hydrocortisone alone on a composite outcome of in-hospital mortality or palliative discharge. The 2.6% of patients who received fludrocortisone had 3.7% (95% CI 1.5-5.7) lower adjusted absolute risk for the primary outcome as well as increased vasopressor-free and hospital-free days. Despite similar trends in sepsis mortality prior to the APPROCCHSS trial’s publication, “fludrocortisone adopter” hospitals after this trial (0.3% to 12.6% utilization) saw smaller increases in septic shock patients’ mortality after APPROCCHSS publication than hospitals that didn’t increase fludrocortisone use (adjusted difference-in-differences absolute mortality -2.0% (95% CI -3.9% to -0.2%). A negative control

outcome (blood transfusion) showed no significant association with fludrocortisone treatment in either the primary analysis or the difference-in-differences analysis.

### Comments

1. “Target trial emulation” substantially strengthened causal inference from this observational study via application of study design and statistical methods maximizing generalizability, minimizing confounding and indication, immortal time, selection, ascertainment, and other biases, and evaluating the sensitivity of study findings to differences in study design or analysis.
2. Study results are numerically consistent with a negative but underpowered septic shock study (COITSS) published in 2010 that enrolled 509 patients treated with hydrocortisone and found 42.9% hospital mortality among fludrocortisone-treated patients compared to 45.8% mortality among patients receiving placebo ( $p=0.50$ ).
3. A randomized trial comparing fludrocortisone/hydrocortisone to hydrocortisone alone powered to detect this study’s observed effect size will need to enroll approximately 11,500 patients.

### REAL-WORLD SEPSIS TREATMENT

Qian ET, Casey JD, Wright A, Wang L, Shotwell MS, Siemann JK, Dear ML, Stollings JL, Lloyd BD, Marvi TK, Seitz KP, Nelson GE, Wright PW, Siew ED, Dennis BM, Wrenn JO, Andereck JW, Han JH, Self WH, Semler MW, Rice TW, Vanderbilt Center for Learning Healthcare, Pragmatic Critical Care Research Group. **Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized with Acute Infection: The ACORN Randomized Clinical Trial.** *JAMA*, 2023;330(16):1557-67.

### Summary

In order to compare two antibiotics commonly employed in empiric regimens for sepsis and acute infection, the single-center ACORN trial randomized adult ED and MICU patients to cefepime or piperacillin-

tazobactam at the time their treating clinicians ordered either agent. Automated EMR-based alerts identified potentially eligible patients, and enrollment and randomization also occurred via the EMR if the treating clinician agreed a patient was eligible and that either tested antibiotic was an acceptable choice. Modified intention-to-treat analyses included 2511 (54% sepsis) patients. Median assigned antibiotic treatment duration was 3 days and about three-fourths of patients received vancomycin at baseline. There was no difference (OR 0.95, 95% CI 0.80-1.13) in the primary outcome, a 5-level ordinal outcome for renal function ranging from 0 (no new/worsening AKI) to 4 (death). Cefepime and piperacillin-tazobactam patients also had similar 28-day mortality (9% and 8%, respectively) and incidence of an outcome compositing persistent renal dysfunction, new renal replacement therapy, and death at 14 days (10% vs 9%). However, cefepime group patients had fewer days alive and free of coma or delirium through day 14 (mean difference 0.3 days, OR 0.79, 95% CI 0.65-0.95) and more prevalent delirium (21% vs 18%).

### Comments

1. Pragmatic embedded trials like ACORN allow learning health systems to answer common and meaningful comparative effectiveness questions rigorously, efficiently, and ethically by replacing arbitrary treatment decisions with randomized treatment assignment.
2. Using screening, enrollment and randomization embedded in routine care via the EMR, the ACORN trial individually randomized over 2500 patients in <11 months at a single center.
3. Trial results do not substantiate concerns for increased AKI risk with combination vancomycin/piperacillin-tazobactam treatment but do suggest cefepime increases risk for neurologic dysfunction, although between group differences were small.
4. Atypically low piperacillin/tazobactam doses and relatively rapid cefepime infusion (leading to exaggerated peak levels and increased blood/brain barrier penetrance) may have contributed to observed study findings.
5. Although piperacillin-tazobactam is a potent anaerobic antimicrobial while cefepime lacks

anaerobic activity, this trial has limited ability to determine whether unnecessary anaerobic therapy and associated disruption of the gut microbiome is harmful because many cefepime-assigned patients (47%) received metronidazole co-treatment.

## NOVEL AND EXPERIMENTAL SEPSIS THERAPIES

Liu S, Yao C, Xie J, Liu H, Wang H, Lin Z, Qin B, Wang D, Lu W, Ma X, Liu Y, Liu L, Zhang C, Xu L, Zheng R, Zhou F, Liu Z, Zhang G, Zhou L, Liu J, Fei A, Zhang G, Zhu Y, Qian K, Wang R, Liang Y, Duan M, Wu D, Sun R, Wang Y, Zhang X, Cao Q, Yang M, Jin M, Song Y, Huang L, Zhou F, Chen D, Liang Q, Qian C, Tang Z, Zhang Z, Feng Q, Peng Z, Sun R, Song Z, Sun Y, Chai Y, Zhou L, Cheng C, Li L, Yan X, Zhang J, Huang Y, Guo F, Li C, Yang Y, Shang H, Qiu H, Investigators E-S. **Effect of an Herbal-Based Injection on 28-Day Mortality in Patients With Sepsis: The EXIT-SEP Randomized Clinical Trial.** *JAMA Intern Med*, 2023;183(7):647-55.

### Summary

The efficacy and risks of natural products, supplements, and traditional medicines commonly employed in formal or informal settings for treatment of sepsis and infection are understudied. Xuebijing (血必净) is an extraction prepared from five botanical agents (e.g., *Angelica sinensis* roots) suggested to have pleiotropic anti-inflammatory and immunomodulatory effects and licensed by the Chinese National Medical Products Administration since 2004 as an intravenously administered sepsis therapy. However, few studies rigorously evaluating this agent have been reported in the English-language medical literature. The EXIT-SEP trial, conducted at 45 hospitals in China, randomized ICU patients meeting Sepsis-3 criteria to IV Xuebijing or placebo twice daily for 5 days. Patients with immunocompromise, “severe primary disease,” or more than moderately severe acute renal failure or liver failure were excluded. Treatment groups were well balanced with moderate illness severity (mean SOFA score 7.1 and mean APACHE II score 12.6). Mortality through day 28, the primary outcome, was significantly lower in patients treated with Xuebijing (19%) compared to placebo (26%,  $p < 0.001$ ). Xuebijing-treated patients also had more ventilator-free days and ICU-free days through day 28. Adverse events, including serious

adverse events, were distributed similarly between treatment groups.

### Comments

1. This large, multicenter, placebo-controlled study demonstrated lower sepsis mortality with a botanical preparation derived from 5 different Chinese traditional medicines.
2. Spectrographic analysis of Xuebijing demonstrated at least 104 distinct chemical compounds, with no information in the present study and limited data from past investigation to identify active compounds and their mechanisms of action.
3. Control group mortality was relatively high given the overall low illness severity of the study population, raising questions about study results’ generalizability outside of China.
4. FDA approval to market Xuebijing as a sepsis therapy in the U.S. would likely require a confirmatory trial conducted in a less homogeneous population (the study reported 97% of patients were of Han Chinese nationality) as well as evidence that the product to be marketed matches the product tested in trials and can be manufactured with a consistent composition.

## NOVEL AND EXPERIMENTAL SEPSIS THERAPIES

Whitehouse T, Hossain A, Perkins GD, Gordon AC, Bion J, Young D, McAuley D, Singer M, Lord J, Gates S, Veenith T, MacCallum NS, Yeung J, Innes R, Welters I, Boota N, Skilton E, Ghuman B, Hill M, Regan SE, Mistry D, Lall R, Collaborators S-L. **Landiolol and Organ Failure in Patients With Septic Shock: The STRESS-L Randomized Clinical Trial.** *JAMA*, 2023;330(17):1641-52.

### Summary

Although counterintuitive, adjunctive  $\beta$ -blockers may mitigate putative deleterious effects of endogenous and exogenous catecholamines in patients with septic shock. In fact, exploratory analysis of a 2013 pilot trial treating persistent septic shock with esmolol suggested a potentially substantial mortality benefit. The present

pragmatic phase 2B trial randomized tachycardic septic shock patients receiving  $\geq 0.1$  mcg/kg/min norepinephrine for 24-72 hours to treatment with open-label IV landiolol or usual care. Landiolol — a short-acting  $\beta_1$  receptor antagonist approximately 8-fold more selective than esmolol — was titrated to a target heart rate of 80-94 beats/min. Active treatment continued until subjects were off vasopressors for 12 hours. The DSMB stopped the trial after enrollment of 126 of 340 planned subjects because the trial was “unlikely to demonstrate benefit and because there was a signal for possible harm.” For the primary outcome of organ failure severity through day 14, mean SOFA scores in the landiolol and usual care groups ( $8.8 \pm 3.9$  vs  $8.1 \pm 3.2$ ,  $p=0.24$ ) were similar. However, compared to usual care, landiolol-treated patients exhibited numerically higher mortality at 28 days (37% vs 25%,  $p=0.16$ ) and 90 days (43% vs 29%,  $p=0.08$ ) and also suffered more serious adverse events (25% vs 6%,  $p=0.006$ ).

### Comments

1. The STRESS-L trial was stopped with less than 40% target enrollment due to concern for futility (despite no formal futility stopping rules) and for higher mortality among landiolol-treated patients.
2. While subjects' baseline illness severity was similar across treatment groups, the unusually low control group mortality for patients with persistent and fairly severe septic shock (mean baseline norepinephrine doses  $\geq 0.3$  mcg/kg/min) allows consideration that the mortality signal reflects a chance statistical aberration in an undersized study.
3. Increased post-randomization inotrope use among landiolol-treated patients raises the possibility that harm among patients with acute cardiac dysfunction outweighed benefit in patients without this sepsis complication since, unlike the 2013 pilot trial, the STRESS-L trial did not exclude patients with septic cardiomyopathy or systematically assess cardiac function after enrollment.

### OTHER ARTICLES OF INTEREST

#### PHOENIX CRITERIA FOR PEDIATRIC SEPSIS

Schlapbach LJ, Watson RS, Sorce LR, Argent AC, Menon K, Hall MW, Akech S, Albers DJ, Alpern ER, Balamuth F, Bembea M, Biban P, Carrol ED, Chiotos K, Chisti MJ, DeWitt PE, Evans I, Flauzino de Oliveira C, Horvat CM, Inwald D, Ishimine P, Jaramillo-Bustamante JC, Levin M, Lodha R, Martin B, Nadel S, Nakagawa S, Peters MJ, Randolph AG, Ranjit S, Rebull MN, Russell S, Scott HF, de Souza DC, Tissieres P, Weiss SL, Wiens MO, Wynn JL, Kisson N, Zimmerman JJ, Sanchez-Pinto LN, Bennett TD, Society of Critical Care Medicine Pediatric Sepsis Definition Task Force. **International Consensus Criteria for Pediatric Sepsis and Septic Shock.** *JAMA*, 2024;331(8):665-74.

Sanchez-Pinto LN, Bennett TD, DeWitt PE, Russell S, Rebull MN, Martin B, Akech S, Albers DJ, Alpern ER, Balamuth F, Bembea M, Chisti MJ, Evans I, Horvat CM, Jaramillo-Bustamante JC, Kisson N, Menon K, Scott HF, Weiss SL, Wiens MO, Zimmerman JJ, Argent AC, Sorce LR, Schlapbach LJ, Watson RS, Society of Critical Care Medicine Pediatric Sepsis Definition Task Force.

**Development and Validation of the Phoenix Criteria for Pediatric Sepsis and Septic Shock.** *JAMA*, 2024;331(8):675-86.

#### SEPSIS PHENOTYPES AND EFFECT HETEROGENEITY FOR CORE TREATMENTS

van Amstel RBE, Kennedy JN, Scicluna BP, Bos LDJ, Peters-Sengers H, Butler JM, Cano-Gamez E, Knight JC, Vlaar APJ, Cremer OL, Angus DC, van der Poll T, Seymour CW, van Vught LA, Consortium M. **Uncovering heterogeneity in sepsis: a comparative analysis of subphenotypes.** *Intensive Care Med*, 2023;49(11):1360-9.

Yang A, Kennedy JN, Reitz KM, Phillips G, Terry KM, Levy MM, Angus DC, Seymour CW. **Time to treatment and mortality for clinical sepsis subtypes.** *Crit Care*, 2023;27(1):236.

Donnelly JP, Seelye SM, Kipnis P, McGrath BM, Iwashyna TJ, Pogue J, Jones M, Liu VX, Prescott HC. **Impact of Reducing Time-to-Antibiotics on Sepsis Mortality, Antibiotic Use, and Adverse Events.** *Ann Am Thorac Soc*, 2024;21(1):94-101.

Pak TR, Young J, McKenna CS, Agan A, DelloStritto L, Filbin MR, Dutta S, Kadri SS, Septimus EJ, Rhee C, Klompas M. **Risk of Misleading Conclusions in Observational Studies of Time-to-Antibiotics and Mortality in Suspected Sepsis.** *Clin Infect Dis*, 2023;77(11):1534-43.

Khader A, Zelnick LR, Sathe NA, Kestenbaum BR, Himmelfarb J, Johnson NJ, Shapiro NI, Douglas IS, Hough CL, Bhatraju PK. **The Interaction of Acute Kidney Injury with Resuscitation Strategy in Sepsis: A Secondary Analysis of a Multicenter, Phase 3, Randomized Clinical Trial (CLOVERS).** *Am J Respir Crit Care Med*, 2023;208(12):1335-8.

#### EXAMINING EMERGING OR NOVEL SEPSIS THERAPIES

Patel JJ, Willoughby R, Peterson J, Carver T, Zelten J, Markiewicz A, Spiegelhoff K, Hipp LA, Canales B, Szabo A, Heyland DK, Stoppe C, Zielonka J, Freed JK. **High-Dose IV Hydroxocobalamin (Vitamin B12) in Septic Shock: A Double-Blind, Allocation-Concealed, Placebo-Controlled Single-Center Pilot Randomized Controlled Trial (The Intravenous Hydroxocobalamin in Septic Shock Trial).** *Chest*, 2023;163(2):303-12.

Ibarra-Estrada M, Kattan E, Aguilera-Gonzalez P, Sandoval-Plascencia L, Rico-Jauregui U, Gomez-Partida CA, Ortiz-Macias IX, Lopez-Pulgarin JA, Chavez-Pena Q, Mijangos-Mendez JC, Aguirre-Avalos G, Hernandez G. **Early adjunctive methylene blue in patients with septic shock: a randomized controlled trial.** *Crit Care*, 2023;27(1):110.

Moskowitz A, Berg KM, Grossestreuer AV, Balaji L, Liu X, Cocchi MN, Chase M, Gong MN, Gong J, Parikh SM, Ngo L, Berlin N, Donnino MW. **Thiamine for Renal Protection in Septic Shock (TRPSS): A Randomized, Placebo-controlled, Clinical Trial.** *Am J Respir Crit Care Med*, 2023;208(5):570-8.

Pereira AG, Costa NA, Amancio SCP, Okoshi MP, Zornoff LAM, Azevedo PS, Minicucci MF, de Paiva SAR, Polegato BF. **Effect of Thiamine on Clinical Outcomes in Septic Shock Patients: A Randomized, Double-Blinded Pilot Study.** *Am J Respir Crit Care Med*, 2023;208(5):616-8.

Francois B, Lambden S, Fivez T, Gibot S, Derive M, Grouin JM, Salcedo-Magguilli M, Lemarie J, De Schryver N, Jalkanen V, Hicheur T, Garaud JJ, Cuvier V, Ferrer R, Bestle M, Pettila V, Mira JP, Bouisse C, Mercier E, Vermassen J, Huberlant V, Vinatier I, Anguel N, Levy M, Laterre PF, ASTONISH Investigators. **Prospective evaluation of the efficacy, safety, and optimal biomarker enrichment strategy for nangibotide, a TREM-1 inhibitor, in patients with septic shock (ASTONISH): a double-blind, randomised, controlled, phase 2b trial.** *Lancet Respir Med*, 2023;11(10):894-904.

Pickkers P, Angus DC, Bass K, Bellomo R, van den Berg E, Bernholz J, Bestle MH, Doi K, Doig CJ, Ferrer R, Francois B, Gammelager H, Pedersen UG, Hoste E, Iversen S, Joannidis M, Kellum JA, Liu K, Meersch M, Mehta R, Millington S, Murray PT, Nichol A, Ostermann M, Pettila V, Solling C, Winkel M, Young PJ, Zarbock A, REVIVAL Investigators. **Phase-3 trial of recombinant human alkaline phosphatase for patients with sepsis-associated acute kidney injury (REVIVAL).** *Intensive Care Med*, 2024;50(1):68-78.

Monti G, Bradic N, Marzaroli M, Konkayev A, Fominskiy E, Kotani Y, Likhvantsev VV, Momesso E, Nogtev P, Lobreglio R, Redkin I, Toffoletto F, Bruni A, Baiardo Redaelli M, D'Andrea N, Paternoster G, Scandroglio AM, Gallicchio F, Ballestra M, Calabro MG, Cotoia A, Perone R, Cuffaro R, Montrucchio G, Pota V, Ananiadou S, Lembo R, Musu M, Rauch S, Galbiati C, Pinelli F, Pasin L, Guarracino F, Santarpino G, Agro FE, Bove T, Corradi F, Forfori F, Longhini F, Cecconi M, Landoni G, Bellomo R, Zangrillo A, MERCY Investigators. **Continuous vs Intermittent Meropenem Administration in Critically Ill Patients With Sepsis: The MERCY Randomized Clinical Trial.** *JAMA*, 2023;330(2):141-51.



Tita ATN, Carlo WA, McClure EM, Mwenechanya M, Chomba E, Hemingway-Foday JJ, Kavi A, Metgud MC, Goudar SS, Derman R, Lokangaka A, Tshefu A, Bauserman M, Bose C, Shivkumar P, Waikar M, Patel A, Hibberd PL, Nyongesa P, Esamai F, Ekhaguere OA, Bucher S, Jessani S, Tikmani SS, Saleem S, Goldenberg

RL, Billah SM, Lennox R, Haque R, Petri W, Figueroa L, Mazariegos M, Krebs NF, Moore JL, Nolen TL, Koso-Thomas M, A-PLUS Trial Group. **Azithromycin to Prevent Sepsis or Death in Women Planning a Vaginal Birth.** *N Engl J Med*, 2023;388(13):1161-70.

## Medical Education

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### WELLNESS

Wesslund HM, Payne JS, Baxter JD, Westmark DM, Bartels K, Bailey KL, Krutsinger DC. **Personal Financial Wellness Curricula for Medical Trainees: A Systematic Review.** *Acad Med.* 2023;98(5):636-643.

#### Summary

This systematic review article examined the impact of financial stress on physicians due to education debt and poor financial literacy. It reviewed thirteen studies on personal financial wellness curricula for medical trainees. Most of the curricula are focused on residents. The most frequently discussed topics included student loans, investment options, disability insurance, life insurance, retirement savings, budgeting, and general personal finance. The median time spent on finance topics was 3.5 hours, and delivery of the curriculum was conducted most often by physicians. They found improvements in financial literacy based on pre- and post-financial literacy evaluations. Only four studies assessed actual or planned financial behaviors and each of those noted post-course changes. One study assessed the well-being of the participants, which improved after the course. This review highlighted the need for further studies with concrete outcome measures, including behavior change and validated measures of wellness. Additionally, it emphasized the importance of teaching financial literacy to medical trainees.

#### Comments

1. The limited focus on medical students suggests a gap in early financial education.
2. The reliance on physicians for curriculum delivery highlights the need for expertise in financial education among medical educators.
3. Improvements in financial literacy and behavioral changes underscore the potential impact of financial education on reducing financial stress among medical trainees.
4. The call for more robust studies indicates the emerging recognition of financial wellness as a critical component of medical education.

5. The variety in curriculum delivery methods, including lectures and interactive discussions, points to a need for innovative approaches to financial education in medicine.

### ARTIFICIAL INTELLIGENCE

Klang E, Portugez S, Gross R, Kassif Lerner R, Brenner A, Gilboa M, Ortal T, Ron S, Robinzon V, Meiri H, Segal G. **Advantages and pitfalls in utilizing artificial intelligence for crafting medical examinations: a medical education pilot study with GPT-4.** *BMC Medical Education.* 2023;23(1):772.

#### Summary

This article evaluated the effectiveness of using GPT-4, an artificial intelligence (AI) model, to generate multiple-choice questions (MCQs) for medical exams. It involved creating a 210-question MCQ exam, with the questions assessed by specialist physicians for accuracy and appropriateness. Each reviewer was blinded to the source of the questions. The test domains included internal medicine, general surgery, obstetrics and gynecology, psychiatry, and pediatrics. The GPT-4 model used was not previously trained in the clinical disciplines included in the examination. Authors inserted a prompt to GPT-4 to rewrite MCQ tests based on a prior examination. The findings showed GPT-4 could rapidly produce a large set of questions, with only 0.5% requiring replacement due to incorrect answers. However, 15% of the questions needed revisions due to errors like outdated terminology, age, gender, or geographical inaccuracies, and methodological issues. Most problematic questions pertained to surgery compared to other medical disciplines. The study concluded that while GPT-4 can assist in creating MCQ exams, expert review remains crucial to ensure quality and accuracy.

#### Comments

1. This study demonstrates the potential of AI in automating aspects of medical education, highlighting efficiency gains.

2. However, this also reinforces the importance of human oversight in using AI tools to maintain question quality and relevance.
3. There are specific areas where AI-generated content may fall short, such as sensitivity to context and accuracy.
4. Further refinement and training of AI models are needed for specialized applications like medical exams.
5. The results also point to the broader implications of AI in educational content creation, including opportunities and limitations.

## DIVERSITY, EQUITY, AND INCLUSION

Olson EM, Sanborn DM, Dyster TG, Kelm DJ, Murray SG, Santhosh L, DesJardin JT. **Gender Disparities in Critical Care Procedure Training of Internal Medicine Residents.** *ATS Sch.* 2023;4(2):164-176.

### Summary

This article investigated gender disparities in critical care procedure training among internal medicine residents, focusing on two large academic residencies. Both programs had structured procedural rotations and critical care rotations in which procedure allocation was unstructured. The authors conducted a mixed methods observational study with the goal of exploring how gender influences procedural training and what factors promote or mitigate gender-based disparities. Interestingly, the results identified significant gender-based differences in the volume of procedures performed, particularly in ICU settings, where women residents were found to perform fewer procedures than their male counterparts. This disparity was not uniform across institutions, suggesting variability in training experiences and opportunities. Qualitative analysis from focus group discussions highlighted three themes: 1) procedural self-identity – perceptions about intrinsic procedural skillsets; 2) procedural self-advocacy – requirement of the learner to be proactive with procedural opportunities and be selected by supervisors for procedures; 3) team dynamics around procedural training – interactions with the learning environment leading to procedural acquisition. The study advocated for structured procedural training programs to mitigate these disparities and ensure equitable access to procedural training for all residents.

### Comments

1. This study highlights the importance of addressing implicit gender biases in medical training environments.
2. Women residents faced stereotype threat, which is the psychological experience of anxiety or concern in a situation where a person has the potential to confirm a negative stereotype about their social group, thus suggesting the importance of focused training sessions on this for women in medicine.
3. The unstructured environments such as the ICU results in uneven procedural distribution making procedures a scarce resource and allocation to those that are more aggressive and outspoken.
4. Required faculty supervision may allow those that are less confident in their procedural skills to ask for help rather than being embarrassed to seek help.
5. There seems to be institutional variability in addressing gender disparities, indicating a need for widespread policy changes.

## RECRUITMENT

Atwood DT, Chiel LE, Nelson BA, Casey AM. **Expectations versus reality: Understanding the accuracy of impressions made during virtual interviews of pediatric pulmonary fellowship programs.** *Pediatr Pulmonol.* 2023;58(1):306-314.

### Summary

This article explored the transition to virtual interviews for pediatric pulmonary fellowship programs due to the COVID-19 pandemic. It assessed whether the impressions formed about programs during these virtual interviews aligned with the actual experiences of fellows. Authors conducted a national survey study of first-year pediatric pulmonary fellows through the Pediatric Pulmonary Training Directors Association. The response rate was 44%. They found that most fellows (96%) were able to accurately gauge the programs during their virtual interviews, and their actual experiences matched their initial impressions closely. The only two factors that were statistically different between the virtual interview to fellowship experience were patient care related volume of “bread and butter” pediatric pulmonary cases and volume of tertiary care pediatric pulmonary patients. Despite the effectiveness of virtual interviews, a significant majority (87%) expressed a preference for including in-person interviews in future application cycles, with a tiered

approach—initial virtual interview followed by an optional in-person visit—being the most favored format.

### Comments

1. Impressions from virtual interviews are largely accurate including for the most important factors that applicants use for ranking pediatric pulmonary fellowship programs.
2. Despite that, most fellows still want some in-person aspect to the fellowship interview process.
3. Some features of fellowship training can be difficult to present virtually such as procedural training and certain program attributes like the “culture” of a program.
4. Programs should more accurately explain the patient exposure that fellows would encounter in their clinical training.
5. Innovative ways to bring applicants virtually into the hospital to experience what it would be like to train in their program should be considered.

## ULTRASOUND TRAINING

Adelman MH, Deshwal H, Pradhan D. **Critical Care Ultrasound Competency of Fellows and Faculty in Pulmonary and Critical Care Medicine: A Nationwide Survey.** *POCUS J.* 2023;8(2):202-211.

### Summary

This study explored the competency assessment standards in Critical Care Ultrasonography (CCUS) for trainees in pulmonary/critical care medicine fellowship programs across the United States. Through a cross-sectional nationwide electronic survey of program directors and fellows, authors found significant variation in how CCUS competency is assessed, with a notable lack of formal assessment for both fellows and faculty. Of note, the response rate for program directors was 27% and estimated to be 18% for fellows. The perceptions of faculty and fellows were generally concordant. The study highlighted that procedural guidance using CCUS is the area where fellows feel most competent, but there are lower rates of competency and interpretation of abdominal and lower extremity diagnostic venous ultrasonography. Only a minority felt faculty was competent in goal-directed cardiac echo, abdominal/kidney ultrasound, and lower extremity deep venous thrombosis studies, which can be a barrier to training fellows. Moreover, hands-on

workshops and directly supervised CCUS exams were perceived as more effective learning methods compared to unsupervised or self-directed learning. The study concluded that standardized competency assessment tools are urgently needed to address the variations and enhance CCUS training and competency evaluation in fellowship programs.

### Comments

1. The lack of standardized assessment for CCUS competency across programs points to a crucial gap in the uniformity of critical care education.
2. The high value placed on hands-on workshops and supervised exams underscores the importance of practical experience in mastering CCUS skills.
3. The disparity in assessing procedural vs. diagnostic competencies suggests a potential area for curriculum development within critical care training.
4. The article's findings on the effectiveness of different teaching methodologies could inform the development of more effective CCUS training programs.
5. The need for standardized competency assessment tools highlighted in the study could lead to a significant shift in how critical care ultrasonography training is approached and evaluated.

## OTHER ARTICLES OF INTEREST

### WELLNESS

Abahuje E, Smith KS, Amortegui D, Eng JS, Philbin SE, Verma R, Dastoor JD, Schlick C, Ma M, Mackiewicz NI, Choi JN, Greenberg J, Johnson J, Bilimoria KY, Hu Y. **See One, Do One, Improve One's Wellness: Resident Autonomy in US General Surgery Programs, A Mixed-Methods Study.** *Ann Surg.* 2023;278(6):1045-1052.

Mann A, Shah AN, Thibodeau PS, Dyrbye L, Syed A, Woodward MA, Thurmon K, Jones CD, Dunbar KS, Fainstad T. **Online Well-Being Group Coaching Program for Women Physician Trainees: A Randomized Clinical Trial.** *JAMA Netw Open.* 2023;6(10):e2335541.

Vaa Stelling BE, Andersen CA, Suarez DA, Nordhues HC, Hafferty FW, Beckman TJ, Sawatsky AP. **Fitting In While Standing Out: Professional Identity Formation, Imposter Syndrome, and Burnout in Early-Career Faculty Physicians.** *Acad Med.* 2023;98(4):514-520.

**ARTIFICIAL INTELLIGENCE**

Tolsgaard MG, Pusic MV, Sebok-Syer SS, Gin B, Svendsen MB, Syer MD, Brydges R, Cuddy MM, Boscardin CK. **The Fundamentals of Artificial Intelligence in Medical Education Research: AMEE Guide No. 156.** *Med Teach.* 2023;45(6):565-573.

Yaneva V, Baldwin P, Jurich DP, Swygert K, Clauser BE. **Examining ChatGPT Performance on USMLE Sample Items and Implications for Assessment.** *Acad Med.* 2024;99(2):192-197.

**DIVERSITY, EQUITY, AND INCLUSION**

James AK, Matthiesen MI, Jasrasaria R, Jowell AR, Kelly MS, Vyas DA, Zeidman JA, Burnett-Bowie SM. **An Anti-Racism and Equity Initiative Improves Residency Educational Conferences.** *J Grad Med Educ.* 2023;5(3):322-327.

Wei C, Bernstein SA, Gu A, Mehta A, Sharma D, Mortman R, Verduzco-Gutierrez M, Chretien KC. **Evaluating Diversity and Inclusion Content on Graduate Medical Education Websites.** *J Gen Intern Med.* 2023;38(3):582-585.

Manan MR, Nawaz I, Rahman S, Manan H. **Diversity, equity, and inclusion in medical education journals: An evaluation of editorial board composition.** *Med Teach.* 2024;46(2):280-288.

**RECRUITMENT**

Mahtani AU, Reinstein I, Marin M, Burk-Rafel J. **A New Tool for Holistic Residency Application Review: Using Natural Language Processing of Applicant Experiences**

**to Predict Interview Invitation.** *Acad Med.* 2023;98(9):1018-1021.

Bailey J, Desai B, Wang A, Sunwoo B, Kerr K, Mandel J, Crouch DR, Crotty Alexander LE. **Implementing Holistic Review Practices in a Pulmonary and Critical Care Fellowship.** *ATS Sch.* 2023;4(4):528-537.

**ULTRASOUND TRAINING**

Jedwab R, Boas S, Potashner D, Ostrovsky D, Wacht O, Taragin BH, Gat T, Dayan RR, Fuchs L. A. **Comparison of Online Self-Training and Standard Bedside Training in Lung Ultrasonography for Medical Students.** *Acad Med.* 2024;99(3):304-309.

Israel HP, Slade M, Gielissen K, Liu RB, Pisani MA, Chichra A. **A Tool to Assess Competence in Critical Care Ultrasound Based on Entrustable Professional Activities.** *ATS Sch.* 2023;4(1):61-75.

**SIMULATION-BASED EDUCATION**

Gerretsen ECF, Chen A, Annema JT, Groenier M, van der Heijden EHFM, van Mook WNKA, Smeenk FWJM. **Effectiveness of Flexible Bronchoscopy Simulation-Based Training: A Systematic Review.** *Chest.* 2023;164(4):952-962.

Cavaleri R, Withington A, Chalmers KJ, Blackstock F. **The Influence of Stress on Student Performance during Simulation-based Learning: A Pilot Randomized Trial.** *ATS Sch.* 2023;4(4):474-489.

Sadek O, Baldwin F, Gray R, Khayyat N, Fotis T. **Impact of Virtual and Augmented Reality on Quality of Medical Education During the COVID-19 Pandemic: A Systematic Review.** *J Grad Med Educ.* 2023;15(3):328-338.

## Occupational/Environmental Lung Disease

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### CARDIOPULMONARY DISEASE AND WILDFIRE SMOKE

Thurston, G., Wuyue, Y., and Luglio, D. **"An Evaluation of the Asthma Impact of the June 2023 New York City Wildfire Air Pollution Episode."** *American Journal of Respiratory and Critical Care Medicine* 208, no. 8 (October 15, 2023): 898–900. PMID: 37582196.

#### Summary

Thurston et al. examine the impact of the severe 2023 Canadian wildfire season on New York City's (NYC) air quality and health effects. Unusual weather patterns led to the southward transport of wildfire pollution, notably increasing fine particulate matter (PM<sub>2.5</sub>) levels in NYC in June 2023. Researchers analyzed its influence on respiratory emergency department (ED) visits. They observed a significant association between wildfire PM<sub>2.5</sub> and increased asthma-related ED visits, particularly among adults aged 18-64, while background PM<sub>2.5</sub> levels showed no significant link. However, no notable association was found between wildfire PM<sub>2.5</sub> and ED visits for other respiratory conditions. The exact mechanism behind this association remains unclear but could involve allergenic material in the plume and/or lung irritation from particulate matter. Elemental analysis revealed lower levels of oxidative stress-inducing metals (e.g., copper, sulfur) in wildfire particles compared to typical NYC PM<sub>2.5</sub>, along with indications of entrained soil PM<sub>2.5</sub> (e.g., potassium, calcium). The study acknowledges limitations like unmeasured factors and emphasizes the necessity for further research into additional health outcomes and the long-term effects of wildfire pollution.

#### Comments

1. This paper along with others is notable for its description of a healthcare outcome with precise measurement of wildfire smoke components.
2. There was an increase in acute asthma-related emergency department visits during and

immediately following a southward transport of wildfire pollution to New York City.

3. No relationship was found for all respiratory-related emergency room visits.
4. The wildfire smoke contained high levels of particulate matter and chemicals associated with entrained soil, while it contained low levels of other oxidative stress-inducing metals which are typically found in background air pollution in NYC.
5. The authors postulate that those with asthma may be particularly affected due to the airway irritation from the particulate matter and the allergenic component of the entrained soil.

### SILICOSIS IN ARTIFICIAL (ENGINEERED) STONE COUNTERTOP FABRICATORS

Fazio, Jane C., Sheiphali A. Gandhi, Jennifer Flattery, Amy Heinzerling, Nader Kamangar, Nawal Afif, Kristin J. Cummings, and Robert J. Harrison. **"Silicosis Among Immigrant Engineered Stone (Quartz) Countertop Fabrication Workers in California."** *JAMA Internal Medicine*, July 24, 2023. PMID: 37486642.

#### Summary

The case series by Fazio and Gandhi et al. investigates patients in California diagnosed with silicosis due to occupational exposure to dust from engineered stone countertops (also called artificial stone or quartz). In contrast to natural stone products, engineered stone contains more than 3 times the silica content (90% vs 3%-30%). At present, engineered stone is the most popular countertop material in the United States. The study includes 52 Californian patients, mostly young Latino immigrant men (98%), with a median age of 45 years at diagnosis. Nearly 58% experienced a delay in diagnosis, with 38% presenting with advanced disease (progressive massive fibrosis), and 19% succumbing to the condition (median age of death 46) at the time of study publication. 3 (6%) underwent lung transplant. Many patients continued to work with engineered stone after diagnosis. Usage of water suppression, exhaust ventilation, and respiratory protective equipment usage

was inconsistent. Clinical findings included respiratory symptoms, abnormal pulmonary function test results, and radiographic evidence of silicosis. Healthcare utilization was high, with many patients presenting to emergency departments and requiring hospitalization. The findings underscore the need for timely diagnosis, improved workplace safety measures, and enhanced medical surveillance programs to address silicosis among engineered stone countertop fabrication workers.

### Comments

1. The case series describes an outbreak of pneumoconiosis (silicosis) associated with fabrication of engineered stone countertops in California since 2019.
2. Thousands of workers across the United States and internationally work in the industry as engineered stone products have surpassed natural stone in the construction and renovation industry.
3. The patients are predominantly Latino men between age 30-50 with high rates of advanced disease (38%) lung transplant (6%), and mortality (19%).
4. The findings underscore the need for timely diagnosis, improved workplace safety measures, and enhanced medical surveillance programs to address silicosis among engineered stone countertop fabrication workers.

## TERRORISM AND INHALATIONAL DISASTERS

Amini, H., M. Solaymani-dodaran, M. Ghanei, J. Abolghasemi, M. Salesi, A. Vahedian azimi, and A. Sahebkar. "Standardised Mortality Ratios in People Exposed to Sulphur Mustard during the Iran-Iraq War: A Retrospective Study with 39-Year Follow-Up." *Public Health* 227 (February 1, 2024): 86–94. PMID: 38141270.

### Summary

Sulfur mustard (SM) emerged as a prevalent chemical warfare agent in the 20th century, notably utilized by various nations in conflicts spanning from World War I to the Iran-Iraq War. Despite its initial use by Germany in World War I, subsequent employment occurred in conflicts such as France in Morocco, Italy in Ethiopia,

Poland against Germany, Japan in China, and Egypt in Yemen. During the Iran-Iraq War (1980's), Iraqi forces extensively deployed SM against both military personnel and civilians, resulting in morbidity and mortality in Iran and Iraq. As an alkylating agent, SM induces a dose-dependent acute lung injury with tracheobronchitis, chemical pneumonitis, acute respiratory distress syndrome, and even death. Chronic respiratory complications include tracheal stenosis, bronchiectasis, and constrictive bronchiolitis. A study on 60,861 Iranian SM-exposed veterans revealed that while their overall mortality rate was lower than the general population (8.9% vs. 39.9%), they exhibited high rates of respiratory disease (53.4%), with mortality from respiratory disorders (defined by an abnormal spirometry) surpassing that of the general populace (SMR 1.59, 95% CI 1.46-1.73). This underscores the necessity of addressing the health needs of SM-exposed veterans and the wider population, emphasizing the persistent challenges posed by chemical warfare agents and the imperative of safeguarding against such threats.

### Comments

1. Amini et al. describe a large-scale registry of sulfur mustard (SM)-exposed Veterans following the Iran-Iraq war of the 1980's.
2. SM induces a dose-dependent acute lung injury with tracheobronchitis, chemical pneumonitis, acute respiratory distress syndrome, and even death. Chronic respiratory complications include tracheal stenosis, bronchiectasis, and constrictive bronchiolitis.
3. While the mortality rate was lower than the general population, SM-exposed Veterans demonstrated a higher likelihood of respiratory disorders.
4. This article is notable as the largest scale study of the long-term health effects of chemical warfare on Veterans.

## OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES AND SARCOIDOSIS

Levin, Albert M., Ruicong She, Yalei Chen, Indra Adrianto, Indrani Datta, Ian M. Loveless, Lori Garman, et al.

**“Identification of Environmental Exposures Associated with Risk of Sarcoidosis in African Americans.”** *Annals of the American Thoracic Society* 20, no. 9 (September 2023): 1274–82.

### Summary

Levin et al. aimed to identify environmental exposures associated with the risk of sarcoidosis in African Americans and those differing by self-identified race and genetic ancestry. The research involves 2,096 African American participants, both with and without sarcoidosis, from three studies. Seven clusters of environmental exposures were identified, with five associated with increased risk of sarcoidosis. The cluster with the strongest risk association is composed of metals, particularly aluminum. Investigators utilized African American ancestry as a surrogate for genetic susceptibility based on known increased rates of sarcoidosis in African American populations. Exposure effects differ by race, with European Americans showing no significant association with aluminum exposure. Among African Americans, the increased risk is dependent on genetic African ancestry. These findings suggest differences in environmental risk profiles between African Americans and European Americans, partially explaining racially disparate incidence rates of sarcoidosis. These findings begin to elucidate why previous exposure studies may have demonstrated tempered results as the exposure effect is pronounced in genetically predisposed individuals. Further investigation into gene-environment interactions may aid in understanding and addressing sarcoidosis susceptibility in minority populations.

### Comments

1. Five environmental exposures groups were associated with risk of sarcoidosis (farm animals, hospital, mold, musty odor, and metals).
2. Risk differed by African American and European American ancestry, most notably aluminum demonstrated in increased risk for African Americans but not European Americans.

3. Risk to metals also differed within the African American ancestry subgroup.
4. Further investigation into gene-environment interactions may aid in understanding and addressing sarcoidosis susceptibility in minority populations.

## INDOOR AIR POLLUTION AND RESPIRATORY HEALTH

Gruenwald, Talor, Brady A. Seals, Luke D. Knibbs, and H. Dean Hosgood. **“Population Attributable Fraction of Gas Stoves and Childhood Asthma in the United States.”** *International Journal of Environmental Research and Public Health* 20, no. 1 (January 2023): 75. PMID: 36612391.

### Summary

Indoor gas stove use for cooking is associated with an increased risk of current asthma among children and is prevalent in 35% of households in the United States (US). Gruenwald et al. used effect sizes from previous meta-analyses and data from the American Housing Survey, the researchers calculated the population attributable fraction (PAF; the amount of asthma that could be prevented by removal of exposure) for gas stove use and childhood asthma, both nationally and at the state level. The proportion of childhood asthma that could be theoretically prevented if gas stove use was not present was 12.7% nationwide. State-specific PAFs varied from 3% to 21.1% (Illinois = 21.1%; California = 20.1%; New York = 18.8%; Massachusetts = 15.4%; Pennsylvania = 13.5%). The study highlights the significant public health burden of gas stove use on childhood asthma and emphasizes the need for mitigation strategies. These strategies could include replacing gas cooking with cleaner alternatives like electric stoves or improving ventilation systems. The study suggests that such interventions could help reduce childhood asthma burden, particularly in states with high PAFs.

### Comments

1. Gruenwald et al. performed a meta-analysis to determine the burden of pediatric asthma due to indoor gas stove use in the United States along with data from the American Housing Survey.
2. The proportion of childhood asthma that could be theoretically prevented if gas stove use was not present was 12.7% nationwide.



3. The study highlights that there are preventive strategies that could decrease rates of pediatric asthma through improvement of indoor air pollution.

## OCCUPATIONAL EXPOSURE AND LUNG CANCER

Wan, Wenxin, Susan Peters, Lützen Portengen, Ann Olsson, Joachim Schüz, Wolfgang Ahrens, Miriam Schejbalova, et al. **“Occupational Benzene Exposure and Lung Cancer Risk: A Pooled Analysis of 14 Case-Control Studies.”** *American Journal of Respiratory and Critical Care Medicine* 209, no. 2 (January 15, 2024): 185–96. PMID: 37812782.

### Summary

Benzene, a volatile air pollutant mainly from human sources, has been regulated due to its carcinogenic properties. While its use has decreased in regulated regions since the 1980s, it remains prevalent, particularly in low- and middle-income countries. Occupational exposure occurs in various industries, including petroleum, chemical, and manufacturing. Previous studies have shown conflicting results regarding benzene's association with lung cancer, partly due to inconsistent adjustments for smoking and other occupational lung carcinogens. Wan et al. aimed to address these gaps by examining benzene exposure metrics and their association with lung cancer, stratified by smoking status and lung cancer subtype. They pooled data from 14 case-control studies across European countries and Canada. Exposure to benzene was assessed using a job-exposure matrix, adjusting for various confounding factors including smoking and other lung carcinogens. Results show a consistent association between benzene exposure and increased lung cancer risk, with higher exposure associated with higher risk. These associations remained robust after adjusting for confounders and in sensitivity analyses. Moreover, the association persisted across different lung cancer subtypes and smoking statuses, suggesting an independent effect of benzene on lung cancer risk. The findings highlight the importance of continued regulation and monitoring of benzene exposure in occupational settings, particularly in regions with less stringent regulations.

### Comments

1. Benzene is a known carcinogen though its relationship to lung cancer has been controversial due to inconsistent adjustments of smoking status and lung cancer subtype.
2. This study performed a pooled analysis of 14 international case-control studies and demonstrated a consistent dose-dependent relationship between occupational benzene exposure and lung cancer.
3. This along with other studies demonstrating increased risk of lung cancer due to occupational risk factors highlight the importance of a thorough history as part of a lung cancer screening risk assessment.

## OTHER ARTICLES OF INTEREST

### CARDIOPULMONARY DISEASE AND WILDFIRE SMOKE

Heaney, Alexandra, Jennifer D. Stowell, Jia Coco Liu, Rupa Basu, Miriam Marlier, and Patrick Kinney. **“Impacts of Fine Particulate Matter From Wildfire Smoke on Respiratory and Cardiovascular Health in California.”** *GeoHealth* 6, no. 6 (2022): e2021GH000578.

Meek, Haillie C. **“Notes from the Field: Asthma-Associated Emergency Department Visits During a Wildfire Smoke Event — New York, June 2023.”** *MMWR. Morbidity and Mortality Weekly Report* 72 (2023).

Moore, Linn E., Andre Oliveira, Raymond Zhang, Laleh Behjat, and Anne Hicks. **“Impacts of Wildfire Smoke and Air Pollution on a Pediatric Population with Asthma: A Population-Based Study.”** *International Journal of Environmental Research and Public Health* 20, no. 3 (January 20, 2023): 1937.

### SILICOSIS IN ARTIFICIAL STONE COUNTERTOP FABRICATORS

Hoy, Ryan F., Christina Dimitriadis, Michael Abramson, Deborah C. Glass, StellaMay Gwini, Fiona Hore-Lacy, Javier Jimenez-Martin, Karen Walker-Bone, and Malcolm R. Sim. **“Prevalence and Risk Factors for Silicosis among a Large Cohort of Stone Benchtop Industry Workers.”**

*Occupational and Environmental Medicine* 80, no. 8 (August 1, 2023): 439–46.

Hua, Jeremy Tang, Lauren Zell-Baran, Leonard H. T. Go, Mordechai R. Kramer, Johanna B. Van Bree, Daniel Chambers, David Deller, et al. **“Demographic, Exposure and Clinical Characteristics in a Multinational Registry of Engineered Stone Workers with Silicosis.”** *Occupational and Environmental Medicine*, May 3, 2022.

#### TERRORISM AND INHALATIONAL DISASTERS

Wang, Xinyu, Taylor A. Doherty, and Christine James. **“Military Burn Pit Exposure and Airway Disease: Implications for Our Veteran Population.”** *Annals of Allergy, Asthma & Immunology* 131, no. 6 (December 1, 2023): 720–25. <https://doi.org/10.1016/j.anai.2023.06.012>.

#### OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES AND SARCOIDOSIS

Huntley, Christopher C., Ketan Patel, Aishah Z. Mughal, Shirley Coelho, P. Sherwood Burge, Alice M. Turner, and Gareth I. Walters. **“Airborne Occupational Exposures Associated with Pulmonary Sarcoidosis: A Systematic Review and Meta-Analysis.”** *Occupational and Environmental Medicine* 80, no. 10 (October 1, 2023): 580–89.

Seedahmed, Mohamed I., Aaron D. Baugh, Mohamed T. Albirair, Yanting Luo, Jianhong Chen, Charles E. McCulloch, Mary A. Whooley, Laura L. Koth, and Mehrdad Arjomandi. **“Epidemiology of Sarcoidosis in U.S. Veterans from 2003 to 2019.”** *Annals of the American Thoracic Society* 20, no. 6 (June 2023): 797–806.

Seedahmed, Mohamed I., Mohamed T. Albirair, Mary A. Whooley, Laura L. Koth, Paul D. Blanc, and Mehrdad

Arjomandi. **“Screening for Exposure to Beryllium Among US Veterans With a Diagnosis of Sarcoidosis, 2002–2020.”** *CHEST* 164, no. 5 (November 1, 2023): 1253–56. <https://doi.org/10.1016/j.chest.2023.05.034>.

#### INDOOR AIR POLLUTION AND RESPIRATORY HEALTH

Gent, Janneane F., Theodore R. Holford, Michael B. Bracken, Julie M. Plano, Lisa A. McKay, Keli M. Sorrentino, Petros Koutrakis, and Brian P. Leaderer. **“Childhood Asthma and Household Exposures to Nitrogen Dioxide and Fine Particles: A Triple-Crossover Randomized Intervention Trial.”** *Journal of Asthma* 60, no. 4 (April 3, 2023): 744–53.

Hansel, Nadia N., Han Woo, Kirsten Koehler, Amanda Gassett, Laura M. Paulin, Neil E. Alexis, Nirupama Putcha, et al. **“Indoor Pollution and Lung Function Decline in Current and Former Smokers: SPIROMICS AIR.”** *American Journal of Respiratory and Critical Care Medicine* 208, no. 10 (November 15, 2023): 1042–51.

#### OCCUPATIONAL EXPOSURE AND LUNG CANCER

Markowitz, Steven B., and Brittany Dickens. **“Screening for Occupational Lung Cancer: An Unprecedented Opportunity.”** *Clinics in Chest Medicine, Advances in Occupational and Environmental Lung Diseases*, 41, no. 4 (December 1, 2020): 723–37.

Wang, Jianing, Yudiayang Ma, Linxi Tang, Dankang Li, Junqing Xie, Yu Sun, and Yaohua Tian. **“Long-Term Exposure to Low-Level Ambient Benzene and Mortality in a National English Cohort.”** *American Journal of Respiratory and Critical Care Medicine*, December 21, 2023.

## Tobacco Control

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### BEHAVIORAL APPROACHES TO CESSATION

Jenssen BP, Schnoll R, Beidas RS, Bekelman J, Bauer AM, Evers-Casey S, Fisher T, Scott C, Nicoloso J, Gabriel P, Asch DA, Bутtenheim AM, Chen J, Melo J, Grant D, Horst M, Oyer R, Shulman LN, Clifton ABW, Lieberman A, Salam T, Rendle KA, Chaiyachati KH, Shelton RC, Fayanju O, Wileyto EP, Ware S, Blumenthal D, Ragusano D, Leone FT. **Cluster Randomized Pragmatic Clinical Trial Testing Behavioral Economic Implementation Strategies to Improve Tobacco Treatment for Patients With Cancer Who Smoke.** *J Clin Oncol.* 2023 Oct 1;41(28):4511-4521. doi: 10.1200/JCO.23.00355. Epub 2023 Jul 19. PMID: 37467454; PMCID: PMC10552951.

#### Summary

Patients with cancer will benefit from treatment for tobacco dependence. What type of approaches to improve tobacco use treatment (TUT) within oncology centers be successful? This four-arm cluster-randomized pragmatic trial included 246 clinicians and 2,146 patients across 11 clinical sites to compare the efficacy of four different types of behavioral economics-informed nudges in the electronic health record based: 1) patient only, 2) clinician only, 3) clinician and patient or 4) usual care. The primary outcome was the proportion of patients with documented TUT referral or medication prescription. Intent-to-treat analysis observed a significant increase in TUT penetration in the clinician only nudge arm compared to usual care (36% vs. 14% respectively) but no increase for the patient only nudge arm compared to usual care (10% vs. 14% respectively). Advanced practice providers (APPs) had higher TUT engagement rates than physicians (48% vs. 31% respectively). There were no significant differences in results in the completer only model compared to the intent-to-treat analysis. There was no difference in engagement by patient race.

#### Comments

1. Patients with cancer are an important group to engage in tobacco dependence treatment efforts.

2. This study suggests that this low-cost behavioral approach appeared to be more effective for APPs than physicians in increasing tobacco use treatment engagement.
3. Roughly 17% of patient nudges were not read, indicating an opportunity for improvement in overcoming health care access related disparities in future engagement approaches.
4. Due to the stigma of smoking, the framing and presentation of patient nudges need to be carefully worded and designed to avoid negative reactions.
5. The use of behavioral interventions in the electronic health record to improve treatment of tobacco dependence may enhance the ability to share approaches between institutions.

### CLINICAL TRIAL DESIGN

Davis, J. M., Masclans, L., & Rose, J. E. (2023). **Adaptive Smoking Cessation Using Precessation Varenicline or Nicotine Patch: A Randomized Clinical Trial.** *JAMA Network Open*, 6(9), e2332214-e2332214.

#### Summary

Adaptive clinical trials are a newer approach within the smoking cessation literature. How does adaptive pharmacotherapy for smoking cessation compare with nonadaptive standard pharmacotherapy? This double-blinded stratified placebo-controlled randomized clinical trial included 188 participants (median 15 cigarettes/day) and compared an adaptive treatment strategy with a nonadaptive treatment strategy. Participants selected their starting medication (Varenicline or nicotine patches) or placebo (nonadaptive) four weeks prior to their target quit date. Two weeks after their quit date, Bupropion was added to the regimen of adaptive participants who did not decrease their daily cigarette intake by at least 50% and placebo bupropion was added to the regimen of those who did. The nonadaptive treatment arm selected either nicotine or varenicline to start 1 week prior their

quit date and all received placebo Bupropion two weeks after their quit date. After 12 weeks from the quit date, the intent-to-treat analysis observed biochemically verified 30-day continuous smoking abstinence in 24% of the adaptive group (23/95) and 9% in the standard treatment group (8/93). A larger reduction in smoking was observed in the adaptive Varenicline v. nonadaptive group than for nicotine patches, though sleep problems were more common in the varenicline group than nicotine patch group.

### Comments

1. Though patients with substance use were excluded, the generalizability of this study was aided by the minimal exclusion criteria (69% of screened participants were enrolled), resulting in a similar rate of psychiatric illness in the study population (31%) as the national average for smokers (35%).
2. The higher-than-expected percentage of participants lost to follow up (27%) were counted as nonabstinent, though the lost to follow up percentage was similar across groups.
3. While the adaptive pharmacotherapy approach appeared to be more effective than the standard approach, the study was designed to determine whether the use of varenicline 4 weeks prior to the desired quit date would be more beneficial than starting 1 week prior the quit date.
4. The statistically significant difference in the main outcome of this study was observed despite recruitment being limited to 188 of the intended 300 patients secondary to the COVID-19 pandemic.
5. Adaptive pharmacotherapy can be effective for smoking cessation treatment and should be considered as potential study design for future smoking cessation trials.

### STATE OF EDUCATIONAL EFFORTS

Melzer AC, Reese ZA, Mascarhenas L, Clancy CB, Deepak J, Gogineni H, Gesthalter Y, Hart JL. **Education for Tobacco Use Disorder Treatment: Current State, Evidence, and Unmet Needs.** *ATS Sch.* 2023 Oct 18;4(4):546-566. doi: 10.34197/ats-scholar.2022-0131RE. PMID: 38196686; PMCID: PMC10773493.

### Summary

Within the background of the undertreatment of

tobacco use disorder, Melzer and colleagues examined the current state of training for tobacco use disorder treatment (TUDT) during the continuum of medical education. This American Thoracic Society workgroup included pulmonary physicians, a pharmacist, a nurse, two trainees and experts in medical education. This narrative, nonsystematic review included 50 studies and was divided into two main sections 1) TUDT training practices and evidence 2) Professional testing and curriculum requirements. High functioning educational programs for TUDT were found to include longitudinal sessions and active learning components such as case-based discussions or standardized patient encounters. Unfortunately, these features were rarely implemented, and medical school students have reported 3 or fewer hours of TUDT training over the course of 4 years. In the residencies, fellowships and continuing medical education that followed, there was little formal training and little competency-based learning reported. Professional certification exams (e.g. internal medicine, pulmonary, advanced practice providers) minimally test topics of TUDT. Within this barren TUDT training landscape, the need for improvement is evident as surveys of pulmonary clinics observed as few as 21% of patients who currently used tobacco being counseled on cessation.

### Comments

1. Tobacco use disorder treatment education is desperately lacking in medical education.
2. Tobacco use disorder treatment cannot improve without training the next generation of providers.
3. This review uncovered a need for evaluation of the training of advanced practice providers and respiratory therapists in tobacco use treatment.
4. The approach of high functioning education programs needs to be evaluated for adoption into lower performing TUDT training program.
5. The importance of TUDT will need to be emphasized in standardized testing given the massive public health benefit possible from TUDT.

### NOVEL TREATMENT

Rigotti NA, Benowitz NL, Prochaska J, Leischow S, Nides M, Blumenstein B, Clarke A, Cain D, Jacobs C. **Cytisine for Smoking Cessation: A Randomized Clinical Trial.** *JAMA.* 2023 Jul 11;330(2):152-160. doi: 10.1001/jama.2023.10042. PMID: 37432430; PMCID: PMC10336611.

## Summary

The most recent FDA approved medication came in 2006. New, more effective smoking cessation medications are needed. Rigotti and colleagues evaluated the efficacy and tolerability of cystisine (three times daily), a nicotinic acetylcholine receptor binding plant-based alkaloid, for smoking cessation. In this double blind, placebo controlled randomized trial, 810 patients across multiple clinical sites were randomized to two durations of cystisine (6 or 12 weeks) vs. placebo. The primary outcome of the study was biochemically verified continuous smoking abstinence for the final 4 weeks of cystisine treatment vs. placebo and a secondary outcome extended 24 weeks from the end of treatment. The highest rate of abstinence was observed with the 12-week course of cystisine vs. placebo (33% vs. 7% respectively) from the primary outcome and 21% vs 5%, respectively, for the secondary outcome. While a slightly smaller rate of abstinence was observed for the 6-week treatment course (6 weeks cystisine followed by 6 weeks of placebo) compared to placebo (25% vs. 4%), the secondary outcome for the 6-week course had the smallest rate of abstinence (9% vs. 3%). While no drug related serious adverse events occurred, sleep related reports and nausea were present in <10% of patients.

## Comments

1. Combined with behavioral support, both the 12 week and 6-week cystisine courses (3 times daily dosing) appeared effective and safe for smoking cessation.
2. While cystisine is novel to the U.S. population, it has been used for decades in Central and Eastern Europe at a 6 times daily dosing schedule and has a similar mechanism to the current most effective existing treatment in the U.S. (varenicline)
3. Cystisine appeared to be well tolerated by participants with similar sleep related side effects as varenicline and predominantly mild adverse events.
4. Just over 80% of participants in the treatment groups were White, limiting generalizability to other racial and ethnic groups.
5. Future studies will need to determine the optimal dosing regimen (12 week vs. other lengths) of cystisine and possibility for combination therapy with existing agents for smoking cessation.

## VAPING IN SMOKING CESSATION

Auer, R., Schoeni, A., Humair, J.P., Jacot-Sadowski, I., Berlin, I., Stuber, M.J., Haller, M.L., Tango, R.C., Frei, A., Strassmann, A. and Bruggmann, P. **Electronic Nicotine-Delivery Systems for Smoking Cessation.** 2024. *New England Journal of Medicine*, 390(7), pp.601-610.

## Summary

Electronic cigarettes (EC) are effective at nicotine delivery. How does a refillable pen style EC compare with counseling for smoking cessation? In this multi-center, open label, randomized clinical trial in Switzerland, 622 participants were randomized to the intervention group and received a free refillable pen style EC along with 6 months of free e-liquids (nicotine concentrations from 0 up to 19.6 mg/ml). The control group (n=624) were given a voucher with which they could purchase nicotine replacement (NRT). Both the intervention and control groups received standard of care counseling for smoking cessation in person and by phone. The primary outcome was biochemically verified abstinence from tobacco smoking at 6 months. A greater proportion of the participants in the intervention group were abstinent from tobacco smoking at 6 month (26%) compared to the control group (16%). There were no substantial differences in serious adverse events, adverse events or symptoms (including cough) between the intervention and control groups. In the intervention group, 346/370 (94%) of patients with data on e-liquids were still using EC at 6 months with a median of 6 mg/ml [nicotine] (IQR of 3; 11) in the e-liquid and 84mg of nicotine use a week (IQR of 18; 154).

## Comments

1. Use of a pen style electronic cigarette with counseling appears superior to counseling with optional nicotine replacement therapy.
2. Nicotine concentrations in the trial ECs were lower than concentrations available in the U.S. and 64% (370/575) of the intervention group were using ECs at 6 months from their quit date.
3. There was no significant difference in adverse events or symptomatology between the intervention and control groups.
4. This study is ongoing and will have 12, 24 and 60 month follow up on cessation to review in the future.
5. Providers will need to determine for themselves whether a transition to ECs from combustibles represents a quit event (continued EC use condoned with an assessment of harm)

reduction) vs. a switch event (with cessation of EC use recommended due to the health risks of ECs).

## COUNTERING MISINFORMATION

Brown, J. L., Galiatsatos, P., & Neptune, E. (2023). **Banning Menthol Cigarette Manufacture and Sale in the United States: Countering Tobacco Industry-driven Misperceptions.** *Annals of the American Thoracic Society*, 20(6), 785-787.

### Summary

Misinformation on healthcare related topics is pervasive in modern society. In a perspective by Brown, Galiatsatos and Neptune, the authors provide a helpful guide to countering the false narratives surrounding the proposed ban on menthol cigarettes. While the authors reference the menthol ban in the U.S., the strategies outlined in the perspective can be helpful to members of the tobacco control field worldwide. The tobacco industry opposes the ban on menthol cigarettes by supporting several false claims. First, the claim that the ban would criminalize African Americans is countered by the fact that the FDA rule would not be enforced against possession by individuals, only the manufacture and sale of menthol cigarettes. There is also no current evidence that the menthol ban increases the market for illicit cigarettes. The claim that the ban restricts freedom to make individual choices (an often-used tactic to counter public health measures) is countered by the fact that the ban would provide positive health benefits to a community suffering from tobacco related disparities. Finally, the claim that the ban will have negative economic implications focuses only on retail stores and minimizes the estimated savings on healthcare costs, worker productivity and second-hand smoke exposure.

### Comments

1. Due in part to targeted advertisement by the tobacco industry, 85% of African American adults who smoke use menthol cigarettes.
2. Nicotine addiction from menthol cigarettes, not the menthol ban, threatens the freedom of choice of African Americans.
3. The menthol ban has the potential to lead to an estimated 15% decline in smoking by 2026, thereby reducing 11.3 million life-years lost by 2060.
4. Providers must be prepared to counter the false claims of the menthol ban being a

discriminatory, anti-African American policy that hurts local economies.

5. Engaging with leaders at the local, state and national level will be required to maximize the benefit of the menthol ban and minimize evasion by the tobacco industry.

## OTHER ARTICLES OF INTEREST

Caponnetto P, Campagna D, Ahluwalia JS, Russell C, Maglia M, Riel PM, Longo CF, Busa B, Polosa R. **Varenicline and counseling for vaping cessation: a double-blind, randomized, parallel-group, placebo-controlled trial.** *BMC Med.* 2023 Jul 5;21(1):220. doi: 10.1186/s12916-023-02919-2. PMID: 37403047; PMCID: PMC10321010.

World Health Organization. (2023). **WHO report on the global tobacco epidemic, 2023: protect people from tobacco smoke.** *World Health Organization.* <https://iris.who.int/handle/10665/372043>. License: CC BY-NC-SA 3.0 IGO

Nollen NL, Ahluwalia JS, Mayo MS, Ellerbeck EF, Leavens ELS, Salzman G, et al. **Multiple Pharmacotherapy Adaptations for Smoking Cessation Based on Treatment Response in Black Adults Who Smoke: A Randomized Clinical Trial.** *JAMA Network Open.* 2023;6(6):e2317895-e. doi: 10.1001/jamanetworkopen.2023.17895.

Orfin RH, Siddalingaiah S, Dontu V, Estrada B, Martinez C, Guerra D, Carrillo H, Cervantes-Díaz MJ, Rodríguez-Rojas DV, Rahman I, McIntosh S, Ossip DJ, Cupertino AP, Cartujano-Barrera F. **Development of a Vaping Cessation Text Messaging Intervention for Latino Young Adults: A Participatory Research Approach.** *Community Health Equity Res Policy.* 2024 Jan 5:2752535X231225928. doi: 10.1177/2752535X231225928. Epub ahead of print. PMID: 38183157.

Tan ASL, Hinds JT, Smith PH, Antin T, Lee JP, Ostroff JS, Patten C, Rose SW, Sheffer CE, Fagan P. **Incorporating Intersectionality as a Framework for Equity-Minded Tobacco Control Research: A Call for Collective Action Toward a Paradigm Shift.** *Nicotine Tob Res.* 2023 Jan 1;25(1):73-76. doi: 10.1093/ntr/ntac110. PMID: 35439321; PMCID: PMC9717371.

Friedman AS, Pesko MF. **Tobacco 21 Laws and Youth Tobacco Use: The Role of Policy Attributes.** *Am J*

*Public Health*. 2024 Jan;114(1):90-97. doi: 10.2105/AJPH.2023.307447. PMID: 38091563; PMCID: PMC10726938.

Grable JC, Lin JK, Peltzer K, Schultz R, Bugbee D, Pilipenko M, Levy SC, Hawkins S. **Integrating Tobacco Dependence Treatment into Hospital Practice Using the Rochester Model.** *J Multidiscip Healthc*. 2023 Apr 4;16:905-911. doi: 10.2147/JMDH.S400615. PMID: 37038455; PMCID: PMC10082598.

Richter KP, Catley D, Gajewski BJ, Faseru B, Shireman TI, Zhang C, Scheuermann TS, Mussulman LM, Nazir N, Hutcheson T, Shergina E, Ellerbeck EF. **The Effects**

**of Opt-out vs Opt-in Tobacco Treatment on Engagement, Cessation, and Costs: A Randomized Clinical Trial.** *JAMA Intern Med*. 2023 Apr 1;183(4):331-339. doi: 10.1001/jamainternmed.2022.7170. PMID: 36848129; PMCID: PMC9972241.

Chen R, Pierce JP, Leas EC, Benmarhnia T, Strong DR, White MM, Stone M, Trinidad DR, McMenamin SB, Messer K. **Effectiveness of e-cigarettes as aids for smoking cessation: evidence from the PATH Study cohort, 2017-2019.** *Tob Control*. 2023 Aug;32(e2):e145-e152. doi: 10.1136/tobaccocontrol-2021-056901. Epub 2022 Feb 7. PMID: 35131948; PMCID: PMC10423520.

## ECMO

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**EXTRACORPOREAL LIFE SUPPORT FOR CARDIOGENIC SHOCK**

Thiele H, Zeymer U, Akin I, Behnes M, Rassaf T, Mahabadi AA, Lehmann R, Eitel I, Graf T, Seidler T, Schuster A, Skurk C, Duerschmied D, Clemmensen P, Hennersdorf M, Fichtlscherer S, Voigt I, Seyfarth M, John S, Ewen S, Linke A, Tigges E, Nordbeck P, Bruch L, Jung C, Franz J, Lauten P, Goslar T, Feistritz HJ, Pöss J, Kirchhof E, Ouarrak T, Schneider S, Desch S, Freund A. **Extracorporeal Life Support in Infarct-Related Cardiogenic Shock.** *N Engl J Med.* 2023 Oct 5;389(14):1286–97.

**Summary:**

In this multicenter, open-label, randomized controlled trial, adults (18–80 years) with acute myocardial infarction complicated by cardiogenic shock with planned early revascularization, were randomized 1:1 to receive early extracorporeal life support (ECLS, i.e., venoarterial extracorporeal membrane oxygenation) or usual medical treatment alone, across 44 centers in Germany and Slovenia, between 2019 and 2022. Cardiogenic shock was defined as: (1) SBP <90mmHg for >30 minutes or catecholamines to maintain SBP >90mmHg; and (2) arterial lactate >3mmol/L; and (3) impaired organ perfusion (at least one of: altered mental status, cold/clammy skin and limbs, urine output <30ml/hr). Patients with >45 minutes of CPR prior to enrollment, a mechanical cause of cardiogenic shock or severe peripheral vascular disease preventing ECLS cannulation were excluded. Of 417 patients analyzed (209 in ECLS group, 208 in control), ECLS was initiated in 92% in the ECLS group and 12.5% in the control group. All-cause 30-day mortality (primary outcome) was similar in the two groups (47.8% ECLS, 49.0% control; relative risk, 0.98; 95% CI 0.80–1.19; P=0.81). Complication rates were higher in the ECLS group (moderate or severe bleeding: relative risk 2.44 [95%CI 1.50–3.95]; peripheral ischemic vascular complications warranting intervention: relative risk 2.86 [95%CI 1.31–6.25]).

**Comments**

1. To optimize group separation, investigators standardized criteria for escalating and deescalating treatments in both arms.
2. Blinding to intervention was not possible.
3. There is no signal for difference in the treatment groups in any of the prespecified subgroup analyses sex, age, diabetes, type of infarction, arterial lactate, cardiopulmonary resuscitation before randomization.
4. Observed mortality was higher compared to prior trials, likely due to the enrolled population; a quarter of patients were older than 70, median lactate was 6.9mmol/L, and a very high proportion (78%) of patients underwent CPR prior to randomization.
5. If any, cardiac benefit of ECLS may be balanced by device-related complication rates, as all-cause 30-day mortality was similar despite higher rates of bleeding, vascular complications, and time on mechanical ventilation.

**EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION**

Suverein MM, Delnoij TSR, Lorusso R, Brandon Bravo Bruinsma GJ, Otterspoor L, Elzo Kraemer CV, Vlaar APJ, van der Heijden JJ, Scholten E, den Uil C, Jansen T, van den Bogaard B, Kuijpers M, Lam KY, Montero Cabezas JM, Driessen AHG, Rittersma SZH, Heijnen BG, Dos Reis Miranda D, Bleeker G, de Metz J, Hermanides RS, Lopez Matta J, Eberl S, Donker DW, van Thiel RJ, Akin S, van Meer O, Henriques J, Bokhoven KC, Mandigers L, Bunge JH, Bol ME, Winkens B, Essers B, Weerwind PW, Maessen JG, van de Poll MCG. **Early Extracorporeal CPR for Refractory Out-of-Hospital Cardiac Arrest.** *N Engl J Med.* 2023 Jan 26;388(4):299–309.

**Summary**

This multicenter open label randomized controlled trial performed in The Netherlands from 2017 to 2021, included adult patients (18–70 years) who presented



refractory out-of-hospital cardiac arrest due to ventricular arrhythmia. Patients without return to spontaneous circulation 15 min after cardiopulmonary resuscitation (CPR) initiation were randomized to conventional CPR (control) or extracorporeal CPR (intervention) with an extracorporeal membrane oxygenation cannulation. Primary outcome was survival with favorable neurologic outcome (i.e. Cerebral Performance Category [CPC] <3) at 30 days. Of the 160 patients randomized, 26 (16%) were excluded at hospital admission as they actually did not present inclusion criteria. Primary outcome was met in 10 (26%) of the 64 patients randomized in the control group and in 14 (20%) of the 70 patients randomized in the intervention group. This difference did not reach statistical significance (OR=1.4 [95%CI 0.5;3.5]). Survival with CPC<3 was also similar at 3 months (OR=1.5 [95%CI 0.6;3.8]) and at 6 months (OR=1.3 [95%CI 0.5;3.3]) in the two groups. The mean number of serious adverse events including death before ICU admission, cardiogenic shock, multi-organ failure, major bleeding, post-anoxic encephalopathy, ECMO etc. was also similar in the two groups (1.0±0.6 in the control group and 1.4±0.9 in the intervention group).

### Comments

1. Though treatment could not be blinded, emergency medical service teams initially in charge of the patients and independent neurologists assessing CPC were unaware of the patients' group assignment.
2. Investigators underestimated the favorable outcomes in the control group as their sample size calculation was based on an 8% favorable outcome in the conventional CPR group (which finally reached 26%).
3. In both groups, 14% of the patients had return of spontaneous circulation (ROSC) before emergency department arrival.
4. In the eCPR group, 25% of the patients did not have initiation of eCPR due to logistic failure (4%), cessation of treatment (3%) or stable ROSC (19%).
5. Though a higher proportion of patients in the Extracorporeal CPR group survived until admission to the intensive care unit than conventional CPR, the survival until hospital discharge was similar in the two groups raising questions of the cost of the intervention in the absence of ultimate benefit.

### ECMO FOR ACUTE RESPIRATORY DISTRESS SYNDROME

Schmidt M, Hajage D, Lebreton G, Dres M, Guervilly C, Richard JC, Sonnevill R, Winiszewski H, Muller G, Beduneau G, Mercier E, Roze H, Lesouhaitier M, Terzi N, Thille AW, Laurent I, Kimmoun A, Combes A, PRONECMO Investigators, the REVA Network, and the International ECMO Network (ECMONet), Luyt CE, Hekimian G, Brechot N, Chommeloux J, Pineton De Chambrun M, Saura O, Levy D, Lefevre L, Assouline B, Bahroum P, Gautier M, Leprince P, Juvin C, Demondion P, Bergue E, Danial P, Al-kabani H, Bounader K, Schoell T, D'Allesandro C, Bureau C, Le Marec J, Mayaux J, Decavèle M, Demoule A, Deleris R, Nemlaghi S, Lecronier M, Capellier G, Piton G, Belon F, Vieille T, Lafay V, Manfait C, Taponnier R, Belin N, Gacouin A, Tadié JM, Papazian L, Hraiech S, Forel JM, Roch A, Adda M, Daviet F, Gragueb-Chatti I, Textoris L, Timsit JF, Bouadma L, De Montmollin E, Lamara F, Deiler V, Para M, Nataf P, Zmihi S, Wicky PH, Patrier J, Jaquet P, Levy B, Perez P, Thivilier C, Mattei M, Haddadi C, Kozutski M, Maureira P, Yonis H, Mezidi M, Chauvelot L, Danjou W, Dhelft F, Bitker L, Bettinger C, Bernon P, Jolly G, Carpentier D, Nay MA, Boulain T, Kamel T, Barbier F, Bretagnol A, Mathonnet A, Desgrouas M, Skarzynski M, Repousseau B, Sigaud F, Rigault G, Galerneau LM, Schwebel C, Candille C, Dartevell A, Bougnaud J, Turbil E, Ehrmann S, Garot D, Salmon C, Le Pape S, Arrivé F. **Prone Positioning During Extracorporeal Membrane Oxygenation in Patients With Severe ARDS: The PRONECMO Randomized Clinical Trial.** *JAMA.* 2023 Dec 26;330(24):2343.

### Summary

In this multicenter, open-label, randomized controlled trial performed in 14 ICUs in France in 2021, adults with severe acute respiratory distress syndrome (ARDS) treated with venovenous ECMO, were randomized (1:1) to receive prone positioning (intervention) or to supine positioning (control). The primary outcome was time to successful ECMO weaning. Patients in the prone ECMO group were treated with at least 4 sessions of 16 hours of proning within the 4 days following inclusion. Investigators screened 250 patients and randomized 170 of them: 86 in the intervention and 84 in the control group. Primary outcome was not different in the intervention group (44.2%) and in the control group (44.0%) with a risk difference of 0.1% [95% CI -14.9%;15.2%]. All secondary outcomes (i.e. respiratory system compliance improvement, days alive and free of kidney or cardiovascular failure, rate of pneumothorax, length of mechanical ventilation, length of stay in the ICU or in the hospital, all-cause mortality) were similar

in the two groups. However, the rate of cardiac arrest was lower in the intervention group (3.5%) than in the control group (11.1%) with an absolute risk difference of -9.6% [95%CI -19.0;-0.2%] and a relative risk of 0.27 [95% CI 0.08;0.92], P=0.05. The rate of all other adverse events was similar in the two groups.

### Comments

1. The study was planned before the COVID-19 pandemics for a 4 year inclusion period but was completed in 9 months due to the high number of patients with COVID-19 induced ARDS treated with venovenous ECMO.
2. Ventilation parameters were standardized in the two groups to ensure the only difference was the intervention.
3. Patients included in the study had severe respiratory failure with low baseline mean PaO<sub>2</sub>/FIO<sub>2</sub> of 67mmHg, low baseline mean pH of 7.31 and almost all had pre-cannulation prone positioning and continuous neuromuscular blockade.
4. Adherence to the protocol was excellent with all patients in the intervention group receiving at least 1 session of proning (80% of them receiving at least 4 prone positions sessions) and only 2.4% of the patients in the control group crossed-over to prone position for refractory hypoxemia.
5. More than 10% of the patients were still under ECMO at day 60 (7 patients in the intervention group and 13 patients in the control group).

### ECMO FOR ACUTE RESPIRATORY DISTRESS SYNDROME

Rudym D, Pham T, Rackley CR, Grasselli G, Anderson M, Baldwin MR, Beitler J, Agerstrand C, Serra A, Winston LA, Bonadonna D, Yip N, Emerson LJ, Dzierba A, Sonett J, Abrams D, Ferguson ND, Bacchetta M, Schmidt M, Brodie D, Luyt CE, Lebreton G, Leprince P, Brechot N, Franchineau G, Nieszkowska A, Hekimian G, Bacchetta M, Abrams D, Parekh M, Trindade A, Kida Y, Kyo M, Shimatani T, Shime N, Tanigawa K, Valchanov K, Fowles J, Anne, Meagher L, Papazian L, Hraiech S, Forel JM, Parke R, McCarthy L, Gilder E, McGeorge A, Pierard S, Jacquet LM, Van Caenegem O, Nair P, Reynolds C, Forrest P, Wai Ming C, Kong H, Harmon M, Bouadma L, Timsit JF, Sonnevile R, Dupont H, Nader J, Wasilewski M, Gilles D, Trojette F, Moubarak M, Caus T, Faraone E, Smith R.

**Mortality in Patients with Obesity and Acute Respiratory Distress Syndrome Receiving Extracorporeal Membrane Oxygenation: The Multicenter ECMO Obesity Study.** *Am J Respir Crit Care Med.* 2023 Sep 15;208(6):685–94.

### Summary

This retrospective cohort study combined observational data from 23 centers across 10 countries collected in adult patients with acute respiratory distress syndrome (ARDS) treated with ECMO. The main goal was to assess the association between obesity (defined as a body mass index  $\geq 30$  kg/m<sup>2</sup>) and mortality in this population. A total of 790 patients were included; 470 (59%) without and 320 (41%) with obesity. Patients with obesity had lower pre-ECMO PaO<sub>2</sub>:FIO<sub>2</sub> (mean $\pm$ SD; 64 $\pm$ 29 vs. 72 $\pm$ 31 mmHg, P=0.001) and higher pre-ECMO plateau pressure (median [IQR]; 32 [30;36] vs. 31 [28;35] cmH<sub>2</sub>O, P=0.001) than patients without obesity. Unadjusted mortality was lower in patients with obesity than in patients without obesity (24.1% vs. 35.3%, P<0.001) and multivariable analysis (adjusting for age, duration of mechanical ventilation before cannulation, pre-ECMO positive end-expiratory pressure, pH, PaO<sub>2</sub>:FIO<sub>2</sub>, use of neuromuscular blocking agents, prone positioning and renal replacement therapy) found that obesity was associated with a decreased ICU mortality: OR 0.63 [95%CI 0.43;0.93]. All sensitivity analysis comprising multivariable analysis with different covariates, a generalized additive model, and a propensity score matching analysis found similar results with a lower mortality in patients with obesity.

### Comments

1. Obesity is usually considered a relative contraindication to ECMO cannulation due to potential technical issues or anticipated poorer outcomes, but these results suggest clinicians should not refrain from using this treatment in patients with obesity.
2. This cohort included patients with extreme obesity as 24% of the whole cohort (60% of the patients with obesity) had a BMI  $\geq 35$  kg/m<sup>2</sup>.
3. The finding of improved survival in patients with obesity is reinforced by the consistent results of all the sensitivity analyses performed in this study.
4. The observational design of this studies allowed for inclusion of a population of patients less selected than those usually included in randomized controlled trials, but its interpretation is limited by unmeasured confounders.
5. Some previous studies found that advanced respiratory assessment with esophageal pressure allowing increasing positive end-expiratory pressure over usual ranges in patients with obesity could improve

oxygenation and avoid ECMO cannulation, but these pre-cannulation data was not available in this cohort

## TRANSFUSION DURING VENOVENOUS ECMO

Matteucci G, Schmidt M, Agerstrand C, Tabatabai A, Tuzzolino F, Giani M, Ramanan R, Grasselli G, Schellongowski P, Riera J, Hssain AA, Duburcq T, Gorjup V, De Pascale G, Buabbas S, Gannon WD, Jeon K, Trethowan B, Fanelli V, Chico JI, Balik M, Broman LM, Pesenti A, Combes A, Ranieri MV, Foti G, Buscher H, Tanaka K, Lorusso R, Arcadipane A, Brodie D, International ECMO Network (ECMONet). **Transfusion practice in patients receiving VV ECMO (PROTECMO): a prospective, multicentre, observational study.** *Lancet Respir Med.* 2023 Mar;11(3):245–55.

### Summary

This is a prospective international observational study performed in adult patients treated with venovenous ECMO for acute respiratory distress syndrome (ARDS) in 41 centres across 19 countries between 2018 and 2021. A total of 604 patients were included and 504 (83%) received packed red blood cells (PRBC) transfusion during their ICU stay. This corresponded to PRBC transfusion on 2432 (31%) of the 7944 days of ECMO collected. Mean haemoglobin concentration was 9.1g/dL (SD 1.2) during the ECMO run and mean haemoglobin concentration pre-transfusion was 8.1g/dL (SD 1.1). In multivariable analyses, a positive fluid balance, higher cardiovascular item of the SOFA score, higher pH, bleeding and ECMO circuit change were independently associated with PRBC transfusion. ICU survival was 59% (N=359) and in a multivariable analysis adjusting on baseline and daily covariates, PRBC transfusion reduced the risk of death only when haemoglobin concentration was less than 7g/dL with as hazard ratio of 0.15 [95%CI 0.03;0.74], P=0.019.

### Comments

1. Though historical ECMO practice suggested to maintain high concentrations of haemoglobin to optimize oxygen transport, most centers tolerated more profound anemia
2. Haemoglobin concentration decreased progressively following ECMO cannulation, but the rate of daily transfusion remained stable around 30%
3. There was important variability in transfusion threshold according to centres and patients' profile and PRBC transfusion were given in 21%

of the days when haemoglobin transfusion was  $\geq 10\text{g/dL}$

4. These results suggest that intensivists should not have a different threshold for transfusion in patients treated with ECMO than in other patients

## ANTIMICROBIAL PHARMACOKINETICS DURING ECMO

Shekar K, Abdul-Aziz MH, Cheng V, Burrows F, Buscher H, Cho YJ, Corley A, Diehl A, Gilder E, Jakob SM, Kim HS, Levkovich BJ, Lim SY, McGuinness S, Parke R, Pellegrino V, Que YA, Reynolds C, Rudham S, Wallis SC, Welch SA, Zacharias D, Fraser JF, Roberts JA. **Antimicrobial Exposures in Critically Ill Patients Receiving Extracorporeal Membrane Oxygenation.** *Am J Respir Crit Care Med.* 2023 Mar 15;207(6):704–20.

### Summary

This is a prospective open-labeled multicenter pharmacokinetics (PK) study performed in six ICU from 2012 to 2019 in adult receiving ECMO. The primary objective was to describe PKs of eleven antimicrobials (casprofungin, cefepime, ceftriaxone, ciprofloxacin, fluconazole, linezolid, meropenem, oseltamivir carboxylate, piperacillin, vancomycin, and voriconazole) and the secondary objective was to assess if these antimicrobials reached predefined effective and safe exposure. A total of 993 blood samples were collected in 85 patients (55% venovenous [VV] and 45% venoarterial [VA] or venoarterial-venovenous [VA-VV] ECMO recipients) and 38 (45%) of them received renal replacement therapy during the first PK sampling. A total of 126 concentrations profiles were included in the PK analysis and showed large variation between subjects (coefficients of variation  $\geq 30\%$ ) for all PKs parameters across all antimicrobials studied. This variation increased even more in samples collected during renal replacement therapy. In the 124 samples available for this specific analysis, 56% concentration profiles achieved predefined target concentration and exposure ranges. The rate of correct ranges did not differ among ECMO types (VV, VA, VA-VV) nor if samples were collected during renal replacement therapy or not.

### Comments

1. These results suggest that prediction of safe and effective exposure to most of the commonly used antimicrobials is challenging in

patients treated with ECMO and routine dosing should be performed.

2. The study is limited by the low sample size of some of the antimicrobials assessed
3. The great majority of the out-of-range concentrations (80%) are subtherapeutic exposing patients to treatment failure and antimicrobial resistance emergence
4. The variability in exposure and pharmacokinetics is even more important in patients receiving renal replacement therapy on top of ECMO with coefficients of variability ranging from 63 to 99%

### OTHER ARTICLES OF INTEREST

Zeymer U, Freund A, Hochadel M, Ostadal P, Belohlavek J, Rokyta R, Massberg S, Brunner S, Lüsebrink E, Flather M, Adlam D, Bogaerts K, Banning A, Sabaté M, Akin I, Jobs A, Schneider S, Desch S, Thiele H. **Venoarterial extracorporeal membrane oxygenation in patients with infarct-related cardiogenic shock: an individual patient data meta-analysis of randomised trials.** *The Lancet*. 2023 Oct 14;402(10410):1338–46.

Tran A, Fernando SM, Rochweg B, Barbaro RP, Hodgson CL, Munshi L, MacLaren G, Ramanathan K, Hough CL, Brochard LJ, Rowan KM, Ferguson ND, Combes A, Slutsky AS, Fan E, Brodie D. **Prognostic factors associated with mortality among patients receiving venovenous extracorporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis.** *Lancet Respir Med*. 2023 Mar;11(3):235–44.

Brusatori S, Zinnato C, Busana M, Romitti F, Gattarello S, Palumbo MM, Pozzi T, Steinberg I, Palermo P, Lazzari S, Maj R, Velati M, D'Albo R, Wassong J, Meissner K, Lombardo F, Herrmann P, Quintel M, Moerer O, Camporota L, Marini JJ, Meissner K, Gattinoni L. **High-versus Low-Flow Extracorporeal Respiratory Support in Experimental Hypoxemic Acute Lung Injury.** *Am J Respir Crit Care Med*. 2023 May 1;207(9):1183–93.

Lorusso R, De Piero ME, Mariani S, Di Mauro M, Folliguet T, Taccone FS, Camporota L, Swol J, Wiedemann D, Belliato M, Broman LM, Vuylsteke A, Kassif Y, Scandroglio AM, Fanelli V, Gaudard P, Ledot S, Barker J, Boeken U, Maier S, Kersten A, Meyns B, Pozzi M, Pedersen FM, Schellongowski P, Kirali K, Barrett N, Riera J, Mueller T, Belohlavek J, **EuroECMO-COVID Study Group. In-hospital and 6-month outcomes in patients with COVID-19 supported with extracorporeal membrane oxygenation (EuroECMO-COVID): a multicentre, prospective observational study.** *Lancet Respir Med*. 2023 Feb;11(2):151–62.

Chommeloux J, Valentin S, Winiszewski H, Adda M, Pineton De Chambrun M, Moyon Q, Mathian A, Capellier G, Guervilly C, Levy B, Jaquet P, Sonnevill R, Voiriot G, Demoule A, Boussouar S, Painvin B, Lebreton G, Combes A, Schmidt M. **One-Year Mental and Physical Health Assessment in Survivors after Extracorporeal Membrane Oxygenation for COVID-19-related Acute Respiratory Distress Syndrome.** *Am J Respir Crit Care Med*. 2023 Jan 15;207(2):150–9.

Pladet LCA, Barten JMM, Vernooij LM, Kraemer CVE, Bunge JJH, Scholten E, Monteni L, Kuijpers M, Donker DW, Cremer OL, Meuwese CL. **Prognostic models for mortality risk in patients requiring ECMO.** *Intensive Care Med*. 2023 Feb;49(2):131–41.

Mehta AB, Taylor JK, Day G, Lane TC, Douglas IS. **Disparities in Adult Patient Selection for Extracorporeal Membrane Oxygenation in the United States: A Population-Level Study.** *Annals ATS*. 2023 Aug;20(8):1166–74.

Fernando SM, MacLaren G, Barbaro RP, Mathew R, Munshi L, Madahar P, Fried JA, Ramanathan K, Lorusso R, Brodie D, McIsaac DI. **Age and associated outcomes among patients receiving venoarterial extracorporeal membrane oxygenation—analysis of the Extracorporeal Life Support Organization registry.** *Intensive Care Med*. 2023 Dec;49(12):1456–66.

Stephens AF, Šeman M, Diehl A, Pilcher D, Barbaro RP, Brodie D, Pellegrino V, Kaye DM, Gregory SD, Hodgson C, the Extracorporeal Life Support Organization Member Centres. **ECMO PAL: using deep neural networks for survival prediction in venoarterial extracorporeal membrane oxygenation.** *Intensive Care Med*. 2023 Sep;49(9):1090–9.

Zaaqoq AM, Griffie MJ, Kelly TL, Fanning JP, Heinsar S, Suen JY, Mariani S, Li Bassi G, Jacobs JP, White N, Fraser JF, Lorusso R, Peek GJ, Cho SM, COVID-19 Critical Care Consortium (COVID Critical). **Cerebrovascular Complications of COVID-19 on Venovenous Extracorporeal Membrane Oxygenation.** Crit Care Med. 2023 Aug 1;51(8):1043–53.

Shen BH, Law AC, Wilson KC. **Evidence Synthesis of Outcomes of Extracorporeal Membrane Oxygenation for**

**Life-Threatening Asthma Exacerbations.** CHEST Critical Care. 2024 Mar 1;2(1):100044.

Zakrajsek JK, Min SJ, Ho PM, Kiser TH, Kannappan A, Sottile PD, Allen RR, Althoff MD, Reynolds PM, Moss M, Burnham EL, Mikkelsen ME, Vandivier RW. **Extracorporeal Membrane Oxygenation for Refractory Asthma Exacerbations With Respiratory Failure.** Chest. 2023 Jan;163(1):38–51.

## Pulmonary Vascular Disease

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### RISK ASSESSMENT IN PAH AS SURROGATE TRIAL ENDPOINTS – STILL A GAP

Blette BS, Moutchia J, Al-Naamani N, Ventetuolo CE, Cheng C, Appleby D, Urbanowicz RJ, Fritz J, Mazurek JA, Li F, Kawut SM, Harhay MO. **Is low-risk status a surrogate outcome in pulmonary arterial hypertension? An analysis of three randomised trials.** *Lancet Respir Med.* 2023 Oct;11(10):873-882

#### Summary:

Hemodynamic or functional measures, particularly exercise capacity by the 6-minute walk distance (6MWD) test, are the main efficacy outcomes in trials including patients with pulmonary arterial hypertension (PAH). From evidence of various PAH registries, there is an increasingly strong recommendations to use multicomponent risk scores that combine hemodynamics, functional measures and other clinical and laboratory values into ordinal scales to guide PAH-treatment. This study aimed to determine whether PAH multicomponent risk scores were adequate surrogates for clinical worsening or mortality outcomes in PAH randomized clinical trials (RCT). Individual participant data provided by the FDA from 3 long-term event-driven RCTs (AMBITION, GRIPHON, SERAPHIN) that included data to calculate 5 commonly used multipoint risk scores (REVEAL 2.0, REVEAL Lite 2, COMPERA, COMPERA 2.0, non-invasive FPHR) at 12 or 16 weeks and 1–4 years follow-up were analyzed. The main outcome was time to clinical worsening defined as a composite endpoint-event including death and indicators of PAH-worsening. In contrary to recent guidelines and proposals to use established multicomponent risks scores as surrogate endpoints in RCTs or as targets in clinical management, the results of this metanalysis suggest that this could lead to erroneous conclusions about the effects of new PAH treatments on long-term outcome.

#### Comments

1. According to various registries, multicomponent risk scores have utility for the prediction of long-term outcomes in patients with PAH.
2. An ideal surrogate endpoint in a short-term therapeutic RCT would be one that would lead to long-term benefits in real life – e.g. improving patients to low risk multicomponent score in a RCT would be a surrogate and as such indicate also beneficial long-term outcome in real-life
3. According to this mediation and meta-analysis from three large long-term event driven studies (AMBITION, GRIPHON, and SERAPHIN), evidence for surrogacy for five popular multicomponent PAH risk scores (COMPERA, COMPERA 2.0, REVEAL 2.0, REVEAL Lite 2, and non-invasive FPHR) is weak to moderate, and therefore, using these risk scores as surrogates in future trials could lead to erroneous conclusions.
4. There is a pervasive fallacy that showing an impact of treatment on the potential surrogate and an association between the surrogate and outcome is sufficient to validate a surrogate endpoint.
5. Although the risk scores remain strong predictive tools and can be used as such, this approach should not be conflated with use as a validated surrogate endpoint

### SOTATERCEPT- A LIGHT AT THE HORIZON TO REVERSE PULMONARY VASCULAR REMODELING AND UNLOAD THE RIGHT HEART

Souza R, Badesch DB, Ghofrani HA, Gibbs JSR, Gomberg-Maitland M, McLaughlin VV, Preston IR, Waxman AB, Grünig E, Kopeć G, Meyer G, Olsson KM, Rosenkranz S, Lin J, Johnson-Levonas AO, de Oliveira Pena J, Humbert M, Hoeper MM. **Effects of sotatercept on haemodynamics and right heart function: analysis of the STELLAR trial.** *Eur Respir J.* 2023 Sep 21;62(3):2301107.

## Summary

Sotatercept, a first-in-class activin signaling inhibitor, demonstrated beneficial effects on 6-min walk distance (6MWD) and various additional efficacy endpoints in pre-treated patient with pulmonary arterial hypertension (PAH). This post-hoc analysis of the STELLAR study, which included 323 PAH-patients in functional class II or III, PVR  $\geq 400$  dyn·s·cm<sup>-5</sup> and 6MWD 150–500 m, extends the strong evidence of efficacy of Sotatercept in symptomatic, pretreated PAH-patients by demonstrating substantial improvements in hemodynamics. Right heart catheterization at 24 weeks revealed significant reduction from baseline in mean pulmonary artery pressure (PAP) of 13.9 mmHg with Sotatercept versus placebo, along with reduced right ventricular (RV) work and RV-power, improved cardiac efficiency, lowered mean right atrium pressure, and improved NT-proBNP levels. Echocardiography revealed a significant increase in TAPSE/systolic PAP ratio, reflecting improved RV–pulmonary artery (PA) coupling, increased RV-fractional area change and a decline in RV volumes such as degree of tricuspid regurgitation. Together with the clinical benefits observed with Sotatercept in the STELLAR trial, these results underscore the therapeutic relevance of reducing PAP in the management of patients with PAH.

## Comments

1. In pretreated patients with PAH in functional class II-III, Sotatercept ameliorated 6MWD and many other clinical measures of disease severity and thus holds promise to significantly improve quality of life and prognosis for many patients.
2. In the PULSAR (Phase II) and confirmatory STELLAR (Phase III) RCTs, Sotatercept, significantly decreased PVR driven by a decreased PAP, which was suggested to indicate regression of pulmonary vascular remodeling, however, of potential concern, without increasing the cardiac output.
3. The present post-hoc analysis of the STELLAR trial reveals that the PAP-decrease with Sotatercept vs. placebo is associated with improvements in PA-compliance (stroke volume/pulse pressure) and PA-elasticity (systolic PAP/stroke volume) reflecting improved pulmonary artery distensibility and reduced RV afterload.
4. Other indicators of improved RV-PA coupling were the increased TAPSE/systolic PAP and decreased RV work and RV power, indicating a reduction in the workload and energy

expenditure of the RV with enhanced cardiac efficiency.

5. In summary, these hemodynamic findings with Sotatercept vs. placebo may reflect partial reversal of remodeling of the pulmonary arteries, the proposed mechanism of action for Sotatercept, albeit this is not yet proven in humans and needs future research.

## DISEASE-TARGETING MEDICATION ALSO WORKS IN PULMONARY ARTERIAL HYPERTENSION WITH COMORBIDITIES, ALBEIT TO A LESSER EXTENT

Rosenkranz S, Pausch C, Coghlan JG, Huscher D, Pittrow D, Grünig E, Staehler G, Vizza CD, Gall H, Distler O, Delcroix M, Ghofrani HA, Ewert R, Kabitz HJ, Skowasch D, Behr J, Milger K, Halank M, Wilkens H, Seyfarth HJ, Held M, Scelsi L, Neurohr C, Vonk-Noordegraaf A, Ulrich S, Klose H, Claussen M, Eisenmann S, Schmidt KH, Remppis BA, Skride A, Jureviciene E, Gumbiene L, Miliauskas S, Löffler-Ragg J, Lange TJ, Olsson KM, Hoepfer MM, Opitz C. **Risk stratification and response to therapy in patients with pulmonary arterial hypertension and comorbidities: A COMPERA analysis.** *J Heart Lung Transplant.* 2023 Jan;42(1):102-114.

## Summary

Precapillary pulmonary hypertension in the absence of chronic thromboembolic or lung disease is frequently found in elderly dyspneic patients with comorbidities, including systemic hypertension, coronary heart disease, diabetes or obesity. These patients with comorbidities thus fulfill hemodynamic criteria of pulmonary arterial hypertension (PAH) and nowadays encompass the largest proportion of patients with idiopathic PAH (iPAH) in registries. However, their prognosis and response to therapy is less known due to underrepresentation in RCTs on PAH-drug efficacy. This article investigates 1120 iPAH patients from the COMPERA registry, 19% without, 57% with 1-2 and 24% with 3-4 comorbidities. It shows that patients with comorbidities benefit from PAH-medication in terms of improvements in functional class (FC), 6-minute walk distance (6MWD), BNP/NT-proBNP and mortality risk, albeit to a lesser extent than patients without comorbidities. The 4-strata risk assessment as proposed in the latest guidelines predicted outcome irrespective of the presence of comorbidities.

## Comments

1. According to this analysis from the COMPERA registry including 1120 patients with IPAH, 81% with at least one comorbidity, patients with comorbidities improved with PAH-targeted therapies.
2. The response to PAH-targeted therapies in regard to improvements in FC, 6MWD and BNP/NT-pro-BNP was lower in patients with IPAH with comorbidities compared to patients without comorbidities, and fewer patients with comorbidities reached a low risk status.
3. Prognostic 4-strata risk stratification as proposed by the current PH-Guidelines works in iPAH irrespective of comorbidities.
4. Survival was improved in patients without comorbidities compared to those with comorbidities, but this survival benefit was no longer present if adjusted for age.
5. Future studies on diagnosis and drug efficacy in iPAH should focus on optimal phenotyping of patients with iPAH in order to get insights into which patient groups respond to which therapies.

## EXERCISE LIMITATION REMAINS A RELEVANT PROBLEM AFTER SUCCESSFUL SURGICAL THERAPY OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Kianzad A, Baccelli A, Braams NJ, Andersen S, van Wezenbeek J, Wessels JN, Celant LR, Vos AE, Davies R, Lo Giudice F, Haji G, Rinaldo RF, Vigo B, Gopalan D, Symersky P, Winkelman JA, Boonstra A, Nossent EJ, Tim Marcus J, Vonk Noordegraaf A, Meijboom LJ, de Man FS, Andersen A, Howard LS, Bogaard HJ. **Long-term effects of pulmonary endarterectomy on pulmonary hemodynamics, cardiac function, and exercise capacity in chronic thromboembolic pulmonary hypertension.** *J Heart Lung Transplant.* 2023 Nov 23:S1053-2498(23)02130-7

### Summary

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by persistent occlusion of the pulmonary arteries by organized thromboembolic material and subsequent remodeling of the pulmonary vasculature, leading to increased vascular resistance (PVR). The therapy of choice in patients with surgically accessible forms is pulmonary endarterectomy (PEA). This data from two CTEPH cohorts in London and

Amsterdam including 118 operated CTEPH patients confirm the beneficial effects of PEA on exercise performance, pulmonary hemodynamics and right ventricular function after 6 month. However, 42% of patients had post-operative persistent PH and the proportion of patients with persistently impaired exercise capacity, defined as peakVO<sub>2</sub> <80% predicted, was high and even increased from 52% to 59% from 6 to 18 months. Persistent exercise intolerance was associated with older age, lower diffusion capacity for carbon monoxide (DLCO), lower 6MWD, worse hemodynamic profile, history of systemic hypertension and with a higher proportion of persistent PH. Low DLCO before PEA was associated with persistent PH and exercise limitation after PEA and may be considered as a surrogate marker of distal vasculopathy, not amenable to surgery.

## Comments

1. Surgical PEA is the treatment of choice in patients with accessible lesions and resulted in significant improvements in RV function, pulmonary hemodynamics and exercise capacity after 6 month, but persistent PH was frequent (42%).
2. Improvements in peak workload, oxygen pulse, VE/VCO<sub>2</sub> at gas exchange threshold further improved from 6 to 18 months after PEA, but persistent exercise intolerance was frequent (59% at 18 months), and correlated with lower baseline DLCO and SmvO<sub>2</sub>. PH persisted in half of the patients.
3. This long-term-data confirms that CTEPH has a mechanical component, which significantly improves with PEA, but many patients reveal a relevant distal vasculopathy, of which a low DLCO may be considered as a surrogate marker.
4. Many aspects of the frequently found impaired long-term exercise intolerance in CTEPH after PEA remain unclear. This includes the persistence of PH in only half of these patients. Apart from distal vasculopathy, other factors might be at play, resembling those implicated in the persistent exercise intolerance seen after acute PE, known as the post-PE syndrome, which still lacks a clear etiology.
5. This persistent exercise limitation after PEA calls for future research in this field in order to investigate which patients may benefit from training programs to address potential peripheral oxygen extraction limitation and which may benefit from specific medical



therapies to address distal vasculopathy. The study also emphasizes that CTEPH patients should be closely followed after PEA and potentially included into well designed studies looking at etiologies and potential treatments of addressing persistent exercise limitation.

### AN IMPORTANT LIGHT AT THE HORIZON TO TREAT PH IN ILD - BUT STILL NO HALT OF DISEASE PROGRESSION

Waxman A, Restrepo-Jaramillo R, Thenappan T, Engel P, Bajwa A, Ravichandran A, Feldman J, Hajari Case A, Argula RG, Tapson V, Smith P, Deng C, Shen E, Nathan SD. **Long-term inhaled treprostinil for pulmonary hypertension due to interstitial lung disease: INCREASE open-label extension study.** *Eur Respir J.* 2023 Jun 29;61(6):2202414.

#### Summary

This article shows data from 242 patients with pulmonary hypertension due to interstitial lung disease (PH-ILD) that participated in the open-label extension (OLE) of the INCREASE study, the first RCT revealing efficacy of inhaled treprostinil to improved 6-min walk distance (6MWD) vs. placebo at 16-weeks. At 52 and 108 weeks, 123 and 70 patients remained in the trial, all receiving inhaled treprostinil. The main reasons for study discontinuation were death (56), withdrawal by patients (41), adverse events (29) and others. Up to 52 weeks, patients who received placebo in the original trial did not catch up with patients who initially received inhaled treprostinil, but transiently improved 6MWD as well. Patients who received inhaled treprostinil versus placebo in the preceding RCT had a 31% lower relative risk of exacerbation of underlying lung disease in the OLE (hazard ratio 0.69(95%CI 0.49–0.97); $p=0.03$ ). These results support long-term efficacy of inhaled treprostinil in severely ill patients with PH-ILD with an acceptable safety profile and are consistent with the results observed in the preceding RCT.

#### Comments

1. According to registries and confirmed by the INCREASE trial, the development of PH in patients with ILD is associated with a poor prognosis.
2. In the INCREASE RCT, inhaled treprostinil revealed improvements in 6MWD, NT-proBNP and time to clinical worsening after 16 weeks,

demonstrating highly warranted therapeutic advancements for this devastating disease.

3. The presently discussed INCREASE OLE demonstrates minimal decline in 6MWD in those previously receiving inhaled treprostinil, whereas those crossing-over from the placebo arm transiently improved, but without reaching the same benefit as initially treated patients, albeit levels of NT-proBNP, clinical status and pulmonary haemodynamics ameliorated or remained stable.
4. Inhaled treprostinil improved FVC, sustainably in those initially on treprostinil, and promptly after initiation in those crossing-over from placebo, indicating an antifibrotic potential of treprostinil, or, hypothetically, an improved pulmonary compliance and blood flow resulting in increased respiratory muscle strength.
5. Of interest, this study also indicates improved prognosis with inhaled treprostinil in PH-ILD, as reflected by a longer event-free survival, reduced relative risk of exacerbation and, according to a related model analysis published by Nathan SD, Thorax (see below) a potential long-term survival benefit.

### CAN PARAMETERS OF RIGHT-VENTRICULAR PULMONARY ARTERIAL COUPLING BY ECHOCARDIOGRAPHY PREDICT PULMONARY HYPERTENSION IN HEART FAILURE WITH PRESERVED EJECTION FRACTION?

Chen ZW, Chung YW, Cheng JF, Huang CY, Chen SY, Lin LY, Lai HC, Wu CK. **Right Ventricular-Vascular Uncoupling Predicts Pulmonary Hypertension in Clinically Diagnosed Heart Failure With Preserved Ejection Fraction.** *J Am Heart Assoc.* 2024 Jan 2;13(1):e030025. doi: 10.1161/JAHA.123.030025. Epub 2023 Dec 29. PMID: 38156457; PMCID: PMC10863814.

#### Summary

Pulmonary hypertension (PH) is highly prevalent in patients with heart failure with preserved ejection fraction (HFpEF). PH in HFpEF is associated with adverse outcomes. This study aimed to determine echocardiographic parameters to predict the presence of PH in HFpEF. 113 patients with HFpEF were investigated simultaneously by echocardiography and right heart catheterization at rest and during stepwise

incremental supine cycle exercise. 68 patients had HFpEF with PH, 45 HFpEF without PH. Tricuspid annular plane systolic excursion (TAPSE)/pulmonary artery systolic pressure (PASP) and tricuspid annular systolic velocity (TAS')/PASP as markers of right-ventricular (RV) to pulmonary artery (PA)-coupling were lower in HFpEF-patients with PH and correlated with PAP- and Wedge-pressure increase during exercise. In receiver operating characteristic curve (ROC) analysis, the optimal cut-off points of TAPSE/PASP and TAS'/PASP to differentiate patients with HFpEF with PH from those without PH were  $\leq 0.62$  and  $\leq 0.47$ , respectively. Due to sensitivity and specificity of each parameter, the authors suggest to combine both. The data indicates that RV-PA coupling is closely correlated to abnormal resting and exercise hemodynamics in HFpEF and TAPSE/SPAP and TAS'/PASP is useful to predict PH in patients with HFpEF.

### Comments

1. HFpEF is clinically diagnosed in the presence of 3 criteria: (1) signs and symptoms of heart failure, (2) left ventricular ejection fraction  $\geq 50\%$ , and objective evidence of cardiac dysfunction including raised natriuretic peptide and echocardiography-derived structural heart disease or abnormal diastolic parameters.
2. Up to 80% of patients with HFpEF reveal PH, which is a marker of adverse prognosis and thus, early PH-detection to guide management and intensify therapy is desirable.
3. Of Interest, amongst patients with HFpEF with PH, 5 ( $\approx 8\%$ ) had precapillary PH with characteristics similar to PAH with cardiovascular risk factors/comorbidities, which suggest a continuum from HFpEF to HFpEF with PH to PAH with cardiovascular risk factors.
4. This study identified that echocardiographic markers of RV-PA coupling TAPSE/SPAP and TAS'/SPAP were closely associated with invasively assessed PAP and Wedge-pressure at rest and during exercise, and are relatively simple to measure.
5. The use of TAPSE/SPAP and TAS'/SPAP, or their combination, should be used for diagnostic purposes and not prognosis, and warrants future investigations.

### OTHER ARTICLES OF INTEREST

#### PAH Diagnosis, Characteristics and Pathophysiology

Arkani M, Kianzad A, Jansen S, Smit J, Post E, Ramaker J, Lagerweij T, In't Veld SGJG, Noske DP, Vonk Noordegraaf A, Wurdinger T, Best MG, Bogaard HJ. **Discrimination Between Pre- and Postcapillary Pulmonary Hypertension Using Platelet RNA.** *J Am Heart Assoc.* 2023 Jul 4;12(13):e028447. doi: 10.1161/JAHA.122.028447. Epub 2023 Jun 22. PMID: 37345802; PMCID: PMC10356096.

Janowski AM, Ravellette KS, Insel M, Garcia JGN, Rischard FP, Vanderpool RR. **Advanced hemodynamic and cluster analysis for identifying novel RV function subphenotypes in patients with pulmonary hypertension.** *J Heart Lung Transplant.* 2023 Dec 21:S1053-2498(23)02178-2. doi: 10.1016/j.healun.2023.12.009. Epub ahead of print. PMID: 38141893.

Sahay S, Lane J, Sharpe MG, Toth D, Paul D, Siuba MT, Tonelli AR. **Impact on Pulmonary Hypertension Hemodynamic Classification Based on the Methodology Used to Measure Pulmonary Artery Wedge Pressure and Cardiac Output.** *Ann Am Thorac Soc.* 2023 Dec;20(12):1752-1759. doi: 10.1513/AnnalsATS.202303-216OC. PMID: 37561068.

Müller J, Titz A, Schneider SR, Bauer M, Mayer L, Lüönd L, Ulrich T, Furian M, Forrer A, Schwarz EI, Bloch KE, Lichtblau M, Ulrich S. **The effect of high altitude (2500 m) on incremental cycling exercise in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: a randomised controlled cross-over trial.** *Eur Respir J.* 2024 Feb 29:2301001. doi: 10.1183/13993003.01001-2023. Epub ahead of print. PMID: 38423623.

Pienn M, Gertz RJ, Gerhardt F, Kröger JR, Zaytoun H, Reimer RP, Kaplan A, Wissmüller M, Kovacs G, Rosenkranz S, Olschewski H, Bunck AC. **CT-derived lung vessel morphology correlates with prognostic markers in precapillary pulmonary hypertension.** *J Heart Lung Transplant.* 2024 Jan;43(1):54-65. doi: 10.1016/j.healun.2023.08.013. Epub 2023 Aug 22. PMID: 37619642.

Harder EM, Divo MJ, Washko GR, Leopold JA, Rahaghi FN, Waxman AB. **Implications of Mean Pulmonary Arterial Wedge Pressure Trajectories in Pulmonary Arterial Hypertension.** *Am J Respir Crit Care Med.* 2024 Feb 1;209(3):316-324. doi: 10.1164/rccm.202306-1072OC. PMID: 37939220; PMCID: PMC10840771.

Martens P, Yu S, Larive B, Borlaug BA, Erzurum SC, Farha S, Finet JE, Grunig G, Hemnes AR, Hill NS, Horn EM, Jacob M, Kwon DH, Park MM, Rischard FP, Rosenzweig EB, Wilcox JD, Tang WHW; PVDOMICS Study Group. **Iron deficiency in pulmonary vascular disease: pathophysiological and clinical implications.** *Eur Heart J.* 2023 Jun 9;44(22):1979-1991. doi: 10.1093/eurheartj/ehad149. PMID: 36879444; PMCID: PMC10474927.

### PAH Risk Assessment and Prognosis

Boucly A, Tu L, Guignabert C, Rhodes C, De Groot P, Prévot G, Bergot E, Bourdin A, Beurnier A, Roche A, Jevnikar M, Jaïs X, Montani D, Wilkins MR, Humbert M, Sitbon O, Savale L. **Cytokines as prognostic biomarkers in pulmonary arterial hypertension.** *Eur Respir J.* 2023 Mar 23;61(3):2201232. doi: 10.1183/13993003.01232-2022. PMID: 36549710.

Harder EM, Divo MJ, Washko GR, Leopold JA, Rahaghi FN, Waxman AB. **Implications of Mean Pulmonary Arterial Wedge Pressure Trajectories in Pulmonary Arterial Hypertension.** *Am J Respir Crit Care Med.* 2024 Feb 1;209(3):316-324. doi: 10.1164/rccm.202306-1072OC. PMID: 37939220.

Celant LR, Wessels JN, Marcus JT, Meijboom LJ, Bogaard HJ, de Man FS, Vonk Noordegraaf A. **Toward the Implementation of Optimal Cardiac Magnetic Resonance Risk Stratification in Pulmonary Arterial Hypertension.** *Chest.* 2024 Jan;165(1):181-191. doi: 10.1016/j.chest.2023.07.028. Epub 2023 Jul 30. PMID: 37527773.

El-Kersh K, Zhao C, Elliott G, Farber HW, Gomberg-Maitland M, Selej M, Garcia-Ferrer J, Benza R. **Derivation of a Risk Score (REVEAL-ECHO) Based on Echocardiographic Parameters of Patients With Pulmonary Arterial Hypertension.** *Chest.* 2023 May;163(5):1232-1244. doi: 10.1016/j.chest.2022.12.045. Epub 2023 Jan 9. PMID: 36634897; PMCID: PMC10268808.

McLaughlin V, Alsumali A, Liu R, Klok R, Martinez EC, Nourhussein I, Bernotas D, Chevure J, Pausch C, De Oliveira Pena J, Lautsch D, Hoeper MM. **Population Health Model Predicting the Long-Term Impact of Sotatercept on Morbidity and Mortality in Patients with Pulmonary Arterial Hypertension (PAH).** *Adv Ther.* 2024 Jan;41(1):130-151. doi: 10.1007/s12325-023-02684-x. Epub 2023 Oct 18. PMID: 37851297; PMCID: PMC10796519.

Fauvel C, Liu Y, Correa-Jaque P, Kanwar MK, Vizza CD, Lin S, Benza RL. **Do Patients With Low-Risk Pulmonary Arterial Hypertension Really Benefit From Upfront Combination Therapy?: Insight From the AMBITION Trial.** *Chest.* 2023 Dec;164(6):1518-1530. doi: 10.1016/j.chest.2023.06.023. Epub 2023 Jun 24. PMID: 37356711; PMCID: PMC10716797.

Wang RS, Huang S, Waldo SW, Hess E, Gokhale M, Johnson SW, Zeder K, Choudhary G, Leopold JA, Oldham WM, Kovacs G, Freiberg MS, Tedford RJ, Maron BA, Brittain EL. **Elevated Pulmonary Arterial Compliance Is Associated with Survival in Pulmonary Hypertension: Results from a Novel Network Medicine Analysis.** *Am J Respir Crit Care Med.* 2023 Aug 1;208(3):312-321. doi: 10.1164/rccm.202211-2097OC. PMID: 37276608; PMCID: PMC10395727.

### PAH Treatment and Management

Morland K, Gerges C, Elwing J, Visovatti SH, Weatherald J, Gillmeyer KR, Sahay S, Mathai SC, Boucly A, Williams PG, Harikrishnan S, Minty EP, Hobohm L, Jose A, Badagliacca R, Lau EMT, Jing ZC, Vanderpool RR, Fauvel C, Leonidas Alves J Jr, Strange G, Pulido T, Qian J, Li M, Mercurio V, Zelt JGE, Moles VM, Cirulis MM, Nikkho SM, Benza RL, Elliott CG. **Real-world evidence to advance knowledge in pulmonary hypertension: Status, challenges, and opportunities. A consensus statement from the Pulmonary Vascular Research Institute's Innovative Drug Development Initiative's Real-world Evidence Working Group.** *Pulm Circ.* 2023 Dec 21;13(4):e12317. doi: 10.1002/pul2.12317. PMID: 38144948; PMCID: PMC10739115.

Johnson S, Sommer N, Cox-Flaherty K, Weissmann N, Ventetuolo CE, Maron BA. **Pulmonary Hypertension: A Contemporary Review.** *Am J Respir Crit Care Med.* 2023 Sep 1;208(5):528-548. doi: 10.1164/rccm.202302-0327SO. PMID: 37450768; PMCID: PMC10492255.

Humbert M, Sitbon O, Guignabert C, Savale L, Boucly A, Gallant-Dewavrin M, McLaughlin V, Hoeper MM, Weatherald J. **Treatment of pulmonary arterial hypertension: recent progress and a look to the future.** *Lancet Respir Med.* 2023 Sep;11(9):804-819. doi: 10.1016/S2213-2600(23)00264-3. Epub 2023 Aug 14. PMID: 37591298.

Schneider SR, Müller J, Bauer M, Mayer L, Lüönd L, Ulrich T, Furian M, Forrer A, Carta A, Schwarz EI, Bloch KE, Lichtblau M, Ulrich S. **Overnight exposure to high altitude in pulmonary hypertension: adverse events and effect of oxygen therapy.** *Eur Heart J.* 2024 Jan

27;45(4):309-311. doi: 10.1093/eurheartj/ehad789. PMID: 38079468; PMCID: PMC10821358.

Alabed S, Garg P, Alandejani F, Dwivedi K, Maiter A, Karunasaagarar K, Rajaram S, Hill C, Thomas S, Gossling R, Sharkey MJ, Salehi M, Wild JM, Watson L, Hameed A, Charalamopoulos A, Lu H, Rothman AMK, Thompson AAR, Elliot CA, Hamilton N, Johns CS, Armstrong I, Condliffe R, van der Geest RJ, Swift AJ, Kiely DG.

**Establishing minimally important differences for cardiac MRI end-points in pulmonary arterial hypertension.** *Eur Respir J.* 2023 Aug 3;62(2):2202225. doi: 10.1183/13993003.02225-2022. PMID: 37414419; PMCID: PMC10397469.

### PH Left Heart Disease

Chen ZW, Chung YW, Cheng JF, Huang CY, Chen SY, Lin LY, Lai HC, Wu CK. **Right Ventricular-Vascular Uncoupling Predicts Pulmonary Hypertension in Clinically Diagnosed Heart Failure With Preserved Ejection Fraction.** *J Am Heart Assoc.* 2024 Jan 2;13(1):e030025. doi: 10.1161/JAHA.123.030025. Epub 2023 Dec 29. PMID: 38156457.

Rako ZA, Kremer N, Yogeswaran A, Richter MJ, Tello K. **Adaptive versus maladaptive right ventricular remodelling.** *ESC Heart Fail.* 2023 Apr;10(2):762-775. doi: 10.1002/ehf2.14233. Epub 2022 Nov 23. PMID: 36419369; PMCID: PMC10053363.

Talha KM, Butler J, Greene SJ, Aggarwal R, Anker SD, Claggett BL, Solomon SD, McMurray JJV, Vaduganathan M, Fonarow GC. **Population-Level Implications of Sodium-Glucose Cotransporter-2 Inhibitors for Heart Failure With Preserved Ejection Fraction in the US.** *JAMA Cardiol.* 2023 Jan 1;8(1):66-73. doi: 10.1001/jamacardio.2022.4348. PMID: 36334258; PMCID: PMC9637275.

### PH Lung Diseases

Olsson KM, Corte TJ, Kamp JC, Montani D, Nathan SD, Neubert L, Price LC, Kiely DG. **Pulmonary hypertension associated with lung disease: new insights into pathomechanisms, diagnosis, and management.** *Lancet Respir Med.* 2023 Sep;11(9):820-835. doi: 10.1016/S2213-2600(23)00259-X. Epub 2023 Aug 14. PMID: 37591300.

Pienn M, Gertz RJ, Gerhardt F, Kröger JR, Zaytoun H, Reimer RP, Kaplan A, Wissmüller M, Kovacs G, Rosenkranz S, Olschewski H, Bunck AC. **CT-derived lung vessel morphology correlates with prognostic markers in precapillary pulmonary hypertension.** *J Heart Lung Transplant.* 2024 Jan;43(1):54-65. doi: 10.1016/j.healun.2023.08.013. Epub 2023 Aug 22. PMID: 37619642.

Nathan SD, Johri S, Joly JM, King CS, Raina A, McEvoy CA, Lee D, Shen E, Smith P, Deng C, Waxman AB. **Survival analysis from the INCREASE study in PH-ILD: evaluating the impact of treatment crossover on overall mortality.** *Thorax.* 2023 Nov 18;thorax-2023-220821. doi: 10.1136/thorax-2023-220821. Epub ahead of print. PMID: 37979971.

Weiss T, Near AM, Zhao X, Ramey DR, Banerji T, Xie H, Nathan SD. **Healthcare resource utilization in patients with pulmonary hypertension associated with chronic obstructive pulmonary disease (PH-COPD): a real-world data analysis.** *BMC Pulm Med.* 2023 Nov 21;23(1):455. doi: 10.1186/s12890-023-02698-9. PMID: 37990203; PMCID: PMC10664271.

### CTEPH

Agarwal MA, Dhaliwal JS, Yang EH, Aksoy O, Press M, Watson K, Ziaeeian B, Fonarow GC, Moriarty JM, Saggarr R, Channick R. **Sex Differences in Outcomes of Percutaneous Pulmonary Artery Thrombectomy in Patients With Pulmonary Embolism.** *Chest.* 2023 Jan;163(1):216-225. doi: 10.1016/j.chest.2022.07.020. Epub 2022 Aug 2. PMID: 35926721.

Jevnikar M, Solinas S, Brenot P, Lechartier B, Kularatne M, Montani D, Savale L, Garcia-Alonso C, Sitbon O, Beurnier A, Boucly A, Bulifon S, Seferian A, Roche A, Mercier O, Simonneau G, Fadel E, Humbert M, Jaïs X. **Sequential multimodal therapy in chronic thromboembolic pulmonary hypertension with mixed anatomical lesions: a proof of concept.** *Eur Respir J.* 2023 Nov 2;62(5):2300517. doi: 10.1183/13993003.00517-2023. PMID: 37802632.

### Pulmonary Embolism

van Es N, Takada T, Kraaijpoel N, Klok FA, Stals MAM, Büller HR, Courtney DM, Freund Y, Galipienzo J, Le Gal G, Ghanima W, Huisman MV, Kline JA, Moons KGM, Parpia S, Perrier A, Righini M, Robert-Ebadi H, Roy PM, Wells PS, de Wit K, van Smeden M, Geersing GJ. **Diagnostic management of acute pulmonary embolism: a**

prediction model based on a patient data meta-analysis. *Eur Heart J*. 2023 Aug 22;44(32):3073-3081. doi: 10.1093/eurheartj/ehad417. PMID: 37452732

Barco S, Mavromanoli AC, Kreitner KF, Bunck AC, Gertz RJ, Ley S, Valerio L, Klok FA, Gerhardt F, Rosenkranz S, Konstantinides SV. **Preexisting Chronic Thromboembolic Pulmonary Hypertension in Acute Pulmonary Embolism.** *Chest*. 2023 Apr;163(4):923-932. doi: 10.1016/j.chest.2022.11.045. Epub 2023 Jan 5. PMID: 36621756.

Jervan Ø, Haukeland-Parker S, Gleditsch J, Tavoly M, Klok FA, Steine K, Johannessen HH, Spruit MA, Atar D, Holst R, Astrup Dahm AE, Sirnes PA, Stavem K, Ghanima W. **The Effects of Exercise Training in Patients With Persistent**

**Dyspnea Following Pulmonary Embolism: A Randomized Controlled Trial.** *Chest*. 2023 Oct;164(4):981-991. doi: 10.1016/j.chest.2023.04.042. Epub 2023 May 5. PMID: 37149257.

Farmakis IT, Valerio L, Barco S, Christodoulou KC, Ewert R, Giannakoulas G, Held M, Hobohm L, Keller K, Wilkens H, Rosenkranz S, Konstantinides SV. **Functional capacity and dyspnea during follow-up after acute pulmonary embolism.** *J Thromb Haemost*. 2024 Jan;22(1):163-171. doi: 10.1016/j.jth.2023.08.024. Epub 2023 Aug 29. PMID: 37652350.

## Sleep Medicine

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### CENTRAL SLEEP APNEA

Bradley TD, Logan AG, Lorenzi Filho G, Kimoff RJ, Durán Cantolla J, Arzt M, Redolfi S, Parati G, Kasai T, Dunlap ME, Delgado D, Yatsu S, Bertolami A, Pedrosa R, Tomlinson G, Marin Trigo JM, Tantucci C, Floras JS; ADVENT-HF Investigators. **Adaptive servo-ventilation for sleep-disordered breathing in patients with heart failure with reduced ejection fraction (ADVENT-HF): a multicentre, multinational, parallel-group, open-label, phase 3 randomised controlled trial.** *Lancet Respir Med.* 2024 Feb;12(2):153-166. doi: 10.1016/S2213-2600(23)00374-0. Epub 2023 Dec 21. PMID: 38142697.

#### Summary:

Multicenter, multinational, parallel-group, open-label, phase 3 RCT of ASV in adults with ejection fraction  $\leq 45\%$  and co-existing moderate sleep-disordered breathing (SDB). SDB was stratified into predominantly non-sleepy obstructive sleep apnea (OSA) or central sleep apnea (CSA). Participants randomized to standard care or standard care plus ASV (1:1). Primary endpoint was cumulative incidence of composite of all-cause mortality, first admission to hospital for cardiovascular reason, new onset atrial fibrillation or flutter, and delivery of an appropriate cardioverter-defibrillator shock. All-cause mortality was a secondary endpoint. 1127 patients were screened, 731 (65%) randomized to standard care (n=375; mean AHI 42.8/h [SD 20.9]) or standard care plus ASV (n=356; 43.3/h [20.5]). In the ASV group, the mean AHI decreased to 2.8–3.7/h with associated improvements in sleep quality. Over 3.6 years (SD 1.6), ASV had no effect on primary outcome (180 events in the control vs 166 in ASV group; HR 0.95, 95% CI 0.77–1.18; p=0.67) or all-cause mortality (88 deaths in control vs. 76 in ASV group; 0.89, 0.66–1.21; p=0.47). For OSA patients, the HR for all-cause mortality

was 1.00 (0.68–1.46; p=0.98) and for CSA was 0.74 (0.44–1.23; p=0.25).

#### Comments

1. This long-awaited trial comes after the SERVE-HF concluded that ASV increased mortality without improving quality of life and should not be used in heart failure with reduced ejection fraction (HFrEF) patients with CSA.
2. The ADVENT-HF trial is similar in that it included HFrEF patients with CSA and employed ASV as the intervention, but it differed from the landmark SERVE-HF in that it included non-sleepy patients with OSA, an ASV device with a different algorithm with lower default end-expiratory (4 cmH<sub>2</sub>O) and minimum pressure support settings (0 cmH<sub>2</sub>O), and had more close monitoring (six-month intervals vs. yearly intervals) of subjects enrolled.
3. In patients with HFrEF and SDB, ASV had no effect on the primary composite outcome or mortality but eliminated sleep-disordered breathing safely and was associated with significant improvements in Minnesota Living with Heart Failure Questionnaire scores and Epworth Sleepiness Scale (ESS) scores consistently across OSA and CSA subgroups.
4. These novel findings argue that there might be a role for selective application of the ASV treatment strategy as adjunctive therapy for patients with HFrEF and sleep-disordered breathing, including CSA, to reduce symptom burden.
5. Unfortunately, enrollments ended prematurely because of COVID-19 related restrictions, and the trial was terminated early due to the ASV device being affected by a recall linked to disintegration of the motor sound-abatement material.

## OBSTRUCTIVE SLEEP APNEA- PHARMACOLOGIC TREATMENT

Schweitzer PK, Taranto-Montemurro L, Ojile JM, Thein SG, Drake CL, Rosenberg R, Corser B, Abaluck B, Sangal RB, Maynard J. **The Combination of Aroxybutynin and Atomoxetine in the Treatment of Obstructive Sleep Apnea (MARIPOSA): A Randomized Controlled Trial.** *Am J Respir Crit Care Med.* 2023 Dec 15;208(12):1316-1327. doi: 10.1164/rccm.202306-1036OC. Erratum in: *Am J Respir Crit Care Med.* 2024 Mar 15;209(6):767. Erratum in: *Am J Respir Crit Care Med.* 2024 Mar 15;209(6):767. PMID: 37812772; PMCID: PMC10765395.

### Summary

The aim of this study was to evaluate the efficacy and safety of AD109, a combination of the novel antimuscarinic agent aroxybutynin and the norepinephrine reuptake inhibitor atomoxetine, in the treatment of OSA. The MARIPOSA trial is a Phase II randomized, double-blind, placebo-controlled, parallel-group, 4-week trial comparing AD109 2.5/75 mg, AD109 5/75 mg, atomoxetine 75 mg alone, and placebo. Of 211 randomized patients, 181 were included in the prespecified efficacy analyses. Sleep was assessed by two baseline and two treatment polysomnograms. Apnea-hypopnea index (AHI) with a 4% desaturation criterion (AHI<sub>4</sub>; primary outcome) was reduced from a median (IQR) of 20.5 (12.3-27.2) to 10.8 (5.6-18.5) in the AD109 2.5/75 mg arm (-47.1%), from 19.4 (13.7-26.4) to 9.5 (6.1-19.3) in the AD109 5/75 mg arm (-42.9%; both  $P < 0.0001$  vs. placebo), and from 19.0 (11.8-28.8) to 11.8 (5.5-21.5) with atomoxetine alone (-38.8%;  $P < 0.01$  vs. placebo). AHI<sub>4</sub> decreased from 20.1 (11.9-25.9) to 16.3 (11.1-28.9) in the placebo arm. Subjectively, there was improvement in fatigue with AD109 2.5/75 mg ( $P < 0.05$  vs. placebo and atomoxetine). Atomoxetine taken alone decreased total sleep time ( $P < 0.05$  vs. AD109 and placebo). The most common adverse events were dry mouth, insomnia, and urinary hesitancy.

### Comments

1. There is currently no approved pharmacotherapy for OSA and the principal treatment option, continuous positive airway pressure (CPAP) therapy is not tolerated by

many, but recent studies had demonstrated improvement in OSA with combined antimuscarinic and noradrenergic drugs.

2. AD109 showed clinically meaningful improvement in OSA, suggesting that further development of the compound is warranted, two large ( $n = 1,300$ ) randomized, placebo-controlled Phase-3 studies with treatment durations of 6 months (NCT05813275) and 1 year (NCT05811247) are currently underway to evaluate the safety, tolerability, and efficacy of AD109 in all patients with OSA.
3. Although AD109 and atomoxetine monotherapy caused similar reductions in the AHI<sub>4</sub>, results suggest that atomoxetine by itself is not a viable treatment option for patients with OSA: atomoxetine significantly reduced total sleep time (TST) compared with both placebo and AD109, and this was associated with a trend toward deteriorating subjective sleep quality for atomoxetine, more frequent reports of insomnia and a higher rate of early terminations.
4. Atomoxetine with aroxybutynin exhibits a significant reduction in AHI<sub>3a</sub> (AHI with hypopneas defined by minimum 3% desaturation or arousal) compared with placebo, this reduction was not seen in atomoxetine alone.
5. Although AD109 may not achieve complete resolution of OSA in all patients, we should keep in mind that partial compliance with CPAP has similar implications.

## OBSTRUCTIVE SLEEP APNEA AND CARDIOVASCULAR OUTCOMES

Sánchez-de-la-Torre M, Gracia-Lavedan E, Benitez ID, Sánchez-de-la-Torre A, Moncusí-Moix A, Torres G, Loffler K, Woodman R, Adams R, Labarca G, Dreyse J, Eulenburg C, Thunström E, Glantz H, Peker Y, Anderson C, McEvoy D, Barbé F. **Adherence to CPAP Treatment and the Risk of Recurrent Cardiovascular Events: A Meta-Analysis.** *JAMA.* 2023 Oct 3;330(13):1255-1265. doi: 10.1001/jama.2023.17465. PMID: 37787793; PMCID: PMC10548300.

## Summary

This meta-analysis included qualitative and individual participant data (IPD) from RCTs addressing the therapeutic effect of CPAP on cardiovascular outcomes and mortality in adults with cardiovascular disease and OSA. IPD were requested from authors of the selected studies (SAVE [NCT00738179], ISAACC [NCT01335087], and RICCADSA [NCT00519597]). One-stage and 2-stage IPD meta-analyses were completed to estimate the effect of CPAP treatment on risk of recurrent major adverse cardiac and cerebrovascular events (MACCEs) using mixed-effect Cox regression models. Additionally, an on-treatment analysis with marginal structural Cox models using inverse probability of treatment weighting was fitted to assess the effect of good adherence to CPAP ( $\geq 4$  hours per day). A total of 4186 individual participants were evaluated (82.1% men; mean [SD] body mass index, 28.9 [4.5]; mean [SD] age, 61.2 [8.7] years; mean [SD] apnea-hypopnea index, 31.2 [17] events per hour; 71% with hypertension; 50.1% receiving CPAP [mean {SD} adherence, 3.1 {2.4} hours per day]; 49.9% not receiving CPAP [usual care], mean [SD] follow-up, 3.25 [1.8] years). The main outcome was defined as the first MACCE, which was similar for the CPAP and no CPAP groups (hazard ratio, 1.01 [95% CI, 0.87-1.17]). An on-treatment analysis by marginal structural model revealed a reduced risk of MACCEs associated with good adherence to CPAP (hazard ratio, 0.69 [95% CI, 0.52-0.92]).

## Comments

1. Individually, in the three previous clinical trials, a beneficial effect of CPAP treatment could not be demonstrated leading to questioning of the effect of CPAP on secondary cardiovascular disease prevention.
2. Among 4,168 patients with established CVD and OSA who were enrolled in RCTs evaluating the effects of CPAP, an intention-to-treat analysis showed no cardiovascular benefit of CPAP.
3. Thanks to the analysis of the combined data from these three large clinical trials, the authors demonstrated that adherence to CPAP was associated with a reduced MACCE recurrence risk, suggesting that treatment adherence is a key factor in secondary cardiovascular prevention in patients with OSA.

4. This trial suggests that CPAP effect is not neutral and, above all, is not cumulative.
5. Patient acceptance of CPAP therapy remains limited in clinical practice, especially among patients who do not derive overt symptomatic benefit such as reduced sleepiness.
- 6.

## OBESITY MEDICATIONS, OSA AND CARDIOVASCULAR RISK PREVENTION

O'Donnell C, Crilly S, O'Mahony A, O'Riordan B, Traynor M, Gitau R, McDonald K, Ledwidge M, O'Shea D, Murphy DJ, Dodd JD, Ryan S. **Continuous Positive Airway Pressure but Not GLP1-mediated Weight Loss Improves Early Cardiovascular Disease in Obstructive Sleep Apnea: A Randomized Proof-of-Concept Study.** *Ann Am Thorac Soc.* 2024 Mar;21(3):464-473. doi: 10.1513/AnnalsATS.202309-821OC. PMID: 38096106.

### Summary

The aim was to gain insights into the effect of CPAP on early atherosclerotic processes and to compare it with a glucagon-like peptide (GLP)-1-mediated weight loss regimen in patients with OSA. This is a randomized proof-of-concept study comparing CPAP, liraglutide (Lir), and both in combination for 24 weeks in 30 consecutive patients with OSA (AHI  $> 15$ /h; BMI 30-40 kg/m<sup>2</sup>; and no history of diabetes, heart failure, or unstable CV disease. In addition to extensive evaluation for CV risk factors and endothelial function at baseline and end of study, subjects underwent 18F-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography (18F-FDG PET-CT) for the measurement of aortic wall inflammation (target-to-background ratio) and coronary CT angiography for semiautomated coronary plaque analysis. CPAP alone and in combination resulted in greater reduction in AHI than Lir alone (mean difference, -45 and -43 events/h, respectively, vs. -12 events/h;  $P < 0.05$ ). Both Lir and combination treatment led to significant weight loss, but only CPAP alone resulted in significant decrease in vascular inflammation (aortic wall target-to-background ratio from  $2.03 \pm 0.34$  to  $1.84 \pm 0.43$ ;  $P = 0.010$ ), associated with an improvement in endothelial function and a decrease in C-reactive protein. Low-attenuation coronary artery plaque volume as a marker of unstable



plaque also decreased with CPAP (from  $571 \pm 490$  to  $334 \pm 185$  mm<sup>3</sup>) and with combination therapy (from  $401 \pm 145$  to  $278 \pm 126$  mm<sup>3</sup>) but not with Lir.

#### Comments:

1. Pharmacotherapy for obesity is being used increasingly based on advances in this field, definitive data regarding the optimal management of people with obesity and OSA are lacking.
2. These data suggest that CPAP therapy, but not GLP1-mediated weight loss, improves vascular inflammation and reduces unstable plaque volume in patients with OSA.
3. The findings support the potential benefit of CPAP therapy in modifying early CV disease but larger clinical trials are needed
4. The SURMOUNT- OSA trial (listed below) is evaluating the role of weight loss medications in the treatment of obese patients with OSA, including effect on cardiometabolic markers.
- 5.

#### OBESITY MEDICATIONS IN OSA TREATMENT

Malhotra, Atul and Bednarik, Josef and Chakladar, Sujatro and Dunn, Julia P. and Weaver, Terri and Grunstein, Ronald and Fietze, Ingo and Redline, Susan and Azarbarzin, Ali and Sands, Scott A. and Schwab, Richard J. and Bunck, Mathijs. **Tirzepatide for the Treatment of Obstructive Sleep Apnea: Rationale, Design, and Sample Baseline Characteristics of the SURMOUNT -OSA Phase 3 Trial.** Available at SSRN: <https://ssrn.com/abstract=4710000> or <http://dx.doi.org/10.2139/ssrn.4710000>

#### Summary

This is a randomized, placebo -controlled, 52-week phase 3 trial, investigating the efficacy and safety of tirzepatide for treatment of moderate to severe OSA (AHI  $\geq 15$ /h) in participants with obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) and established OSA diagnosis. There are 2 intervention specific appendices (ISAs): ISA-1 includes participants with no current OSA treatment, and ISA-2 includes participants using positive airway pressure (PAP) therapy. Overall, 469 participants have been randomized 1:1 to receive tirzepatide or placebo across

the master protocol (ISA-1, n=234; ISA-2, n=235). All participants are also receiving lifestyle intervention for weight reduction. The primary endpoint is difference in AHI between tirzepatide and placebo arms at week 52. Secondary endpoints include sleep apnea-specific hypoxic burden, functional outcomes, and cardiometabolic biomarkers. Participants are 30.3% females with a mean age of 49.7 years and BMI of 38.8 kg/m<sup>2</sup> (roughly evenly distributed with class 1, class 2, and class 3 obesity). Participants are from diverse racial and ethnic backgrounds (17.5% Asian, 5.2% Black, 8.1% American Indian/Alaska native, 36.2% Hispanic/Latino ethnicity). Most have severe OSA (mean AHI 50.1/h) with mild sleepiness (mean ESS 10.3). Baseline comorbidities were typical of this patient population (participants with diabetes were excluded) including prediabetes (61.7%), hypertension (76.3%), and dyslipidemia (83.4%).

#### Comments

1. Currently, no approved anti-obesity medication has demonstrated effectiveness in OSA management.
2. The SURMOUNT-OSA study is evaluating the efficacy and safety of tirzepatide for treatment of moderate to severe OSA in people with obesity.
3. The study will uniquely explore the effect of tirzepatide treatment in 2 standalone ISAs of participants with and without use of PAP therapy.
4. This study design is used to maximize generalizability in OSA management.
5. Cardiometabolic biomarkers information between ISAs will add to much needed data regarding cardiovascular prevention benefits of this long-acting glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 receptor agonist (tirzepatide).

## RESTLESS LEGS SYNDROME (RLS)

Bogan RK, Roy A, Kram J, Ojile J, Rosenberg R, Hudson JD, Scheuller HS, Winkelman JW, Charlesworth JD. **Efficacy and safety of tonic motor activation (TOMAC) for medication-refractory restless legs syndrome: a randomized clinical trial.** *Sleep.* 2023 Oct 11;46(10):zsad190. doi: 10.1093/sleep/zsad190. PMID: 37458698; PMCID: PMC10566236.

### Summary

RESTFUL was a multicenter, randomized, double-blind, sham-controlled trial in adults with medication-refractory moderate-to-severe primary RLS. Participants were randomized 1:1 to active or sham TOMAC for a double-blind, 4-week stage 1 and all received active TOMAC during open-label, 4-week stage 2. The primary endpoint was the Clinical Global Impressions-Improvement (CGI-I) responder rate at the end of stage 1. Key secondary endpoints included change to International RLS Study Group (IRLS) total score from study entry to the end of stage 1. A total of 133 participants were enrolled. CGI-I responder rate at the end of stage 1 was significantly greater for the active versus sham group (45% vs. 16%; Difference = 28%; 95% CI 14% to 43%;  $p = .00011$ ). At the end of stage 2, CGI-I responder rate further increased to 61% for the active group. IRLS change at the end of stage 1 improved for the active versus sham group (-7.2 vs. -3.8; difference = -3.4; 95% CI -1.4 to -5.4;  $p = .00093$ ). There were no severe or serious device-related adverse events (AEs). The most common AEs were mild discomfort and mild administration site irritation which resolved rapidly and reduced in prevalence over time.

### Comments

1. This study evaluated the efficacy and safety/tolerability of bilateral high-frequency tonic motor activation (TOMAC) in patients with medication-refractory restless legs syndrome (RLS).
2. TOMAC was safe, well tolerated, and reduced symptoms of RLS in medication-refractory patients by electrically stimulating specific fibers of the peroneal nerve to activate the tibialis anterior muscle.

3. TOMAC received marketing approval in 2023 and availability is anticipated in 2024.
4. There is a large and growing population of patient with medication-refractory RLS for whom TOMAC is a promising new treatment.

## NARCOLEPSY

Dauvilliers Y, Mignot E, Del Río Villegas R, Du Y, Hanson E, Inoue Y, Kadali H, Koundourakis E, Meyer S, Rogers R, Scammell TE, Sheikh SI, Swick T, Szakács Z, von Rosenstiel P, Wu J, Zeitz H, Murthy NV, Plazzi G, von Hehn C. **Oral Orexin Receptor 2 Agonist in Narcolepsy Type 1.** *N Engl J Med.* 2023 Jul 27;389(4):309-321. doi: 10.1056/NEJMoa2301940. PMID: 37494485.

### Summary

This is a Phase 2, randomized, placebo-controlled trial of the oral orexin receptor 2-selective agonist TAK-994 in patients with narcolepsy type 1. Patients were randomized to twice-daily oral TAK-994 (30 mg, 90 mg, or 180 mg) or placebo. Primary end point was mean change from baseline to week-8 in average sleep latency on the MWT. Secondary end points included change in ESS score and weekly cataplexy rate. Of 73 patients, 17 received TAK-994 30mg BID, 20 received 90mg BID, 19 received 180 mg BID, and 17 received placebo. The phase 2 trial and an extension trial were terminated early due to hepatic adverse events. Primary end-point data were available for 41 patients (56%). Least-squares (LS) mean changes to week 8 in average sleep latency on MWT were 23.9 minutes in the 30-mg group, 27.4 minutes in the 90-mg group, 32.6 minutes in the 180-mg group, and -2.5 minutes in the placebo group. Least-squares mean changes to week 8 in the ESS score were -12.2 in the 30-mg group, -13.5 in the 90-mg group, -15.1 in the 180-mg group, and -2.1 in the placebo group. Clinically important elevations in liver-enzymes occurred in 5 patients, and drug-induced liver injury in 3 patients.

### Comments

1. Narcolepsy type 1 is caused by severe loss or lack of brain orexin neuropeptides, this is the first trial to test a molecule that acts like a key similar to orexin and is given orally.

2. The phase 2 trial and an extension trial were terminated early owing to hepatic adverse events.
3. Primary end-point data were available for 41 patients (56%) and the orexin receptor 2 agonist TAK-994 demonstrates greater (and clinically quite significant and unprecedented) improvements on measures of sleepiness and cataplexy when compared to placebo over a period of 8 weeks but was associated with hepatotoxic effects.
4. Notably, currently available treatments for narcolepsy result in only partial reductions in symptoms.
5. This is a major step forward in the treatment of narcolepsy, more importantly a new agonist, with greater affinity for orexin 2 receptor and fewer side effects is under development.
- 6.

**Supine-isolated Sleep Apnea: A Clinical Trial.** *Ann Am Thorac Soc.* 2024 Feb;21(2):308-316. doi: 10.1513/AnnalsATS.202309-753OC. PMID: 38015501.

Peker Y, Celik Y, Behboudi A, Redline S, Lyu J, Wei Y, Gottlieb DJ, Jelic S. **CPAP may promote an endothelial inflammatory milieu in sleep apnoea after coronary revascularization.** *EBioMedicine.* 2024 Mar;101:105015. doi: 10.1016/j.ebiom.2024.105015. Epub 2024 Feb 24. PMID: 38403558.

Dedhia RC, Bliwise DL, Quyyumi AA, Thaler ER, Boon MS, Huntley CT, Seay EG, Tangutur A, Strollo PJ, Gurel N, Keenan BT. **Hypoglossal Nerve Stimulation and Cardiovascular Outcomes for Patients With Obstructive Sleep Apnea: A Randomized Clinical Trial.** *JAMA Otolaryngol Head Neck Surg.* 2024 Jan 1;150(1):39-48. doi: 10.1001/jamaoto.2023.3756. PMID: 38032624; PMCID: PMC10690581.

## OTHER ARTICLES OF INTEREST

### Insomnia

Kyle SD, Siriwardena AN, Espie CA, Yang Y, Petrou S, Ogburn E, Begum N, Maurer LF, Robinson B, Gardner C, Lee V, Armstrong S, Pattinson J, Mort S, Temple E, Harris V, Yu LM, Bower P, Aveyard P. **Clinical and cost-effectiveness of nurse-delivered sleep restriction therapy for insomnia in primary care (HABIT): a pragmatic, superiority, open-label, randomised controlled trial.** *Lancet.* 2023 Sep 16;402(10406):975-987. doi: 10.1016/S0140-6736(23)00683-9. Epub 2023 Aug 10. PMID: 37573859.

Ried K, Tamanna T, Matthews S, Sali A. **Medicinal cannabis improves sleep in adults with insomnia: a randomised double-blind placebo-controlled crossover study.** *J Sleep Res.* 2023 Jun;32(3):e13793. doi: 10.1111/jsr.13793. Epub 2022 Dec 20. PMID: 36539991.

### OSA

Rahimi MM, Vakulin A, McEvoy RD, Barnes M, Quinn SJ, Mercer JD, O'Grady A, Antic NA, Catcheside PG. **Comparative Effectiveness of Supine Avoidance versus Continuous Positive Airway Pressure for Treating**

### COMISA

Turner AD, Ong JC, Jones AL, Tu A, Salanitro M, Crawford MR. **Neurocognitive functioning in comorbid insomnia and sleep apnea patients is better after positive airway pressure therapy, but worse after cognitive behavioral therapy for insomnia: exploratory analysis of cognitive outcomes from the Multidisciplinary Approach to the Treatment of Insomnia and Comorbid Sleep Apnea study.** *Sleep.* 2023 Aug 14;46(8):zsad128. doi: 10.1093/sleep/zsad128. PMID: 37148183; PMCID: PMC10424173.

### Pediatric OSA

Redline S, Cook K, Chervin RD, Ishman S, Baldassari CM, Mitchell RB, Tapia IE, Amin R, Hassan F, Ibrahim S, Ross K, Elden LM, Kirkham EM, Zopf D, Shah J, Otteson T, Naqvi K, Owens J, Young L, Furth S, Connolly H, Clark CAC, Bakker JP, Garetz S, Radcliffe J, Taylor HG, Rosen CL, Wang R. **Pediatric Adenotonsillectomy Trial for Snoring (PATS) Study Team. Adenotonsillectomy for Snoring and Mild Sleep Apnea in Children: A Randomized Clinical Trial.** *JAMA.* 2023 Dec 5;330(21):2084-2095. doi: 10.1001/jama.2023.22114. PMID: 38051326; PMCID: PMC10698619.

## Restless Legs Syndrome

Riccardi S, Ferri R, Garbazza C, Miano S, Manconi M.

Pharmacological responsiveness of periodic limb movements in patients with restless legs syndrome: a

systematic review and meta-analysis. *J Clin Sleep Med.* 2023 Apr 1;19(4):811-822. doi: 10.5664/jcsm.10440. PMID: 36692194; PMCID: PMC10071388.