



# CYIR

Clinical Year in Review

 **ATS** 2022

# Clinical Year in Review Bibliography

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## Pulmonary Vascular Disease

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### COMBINATION THERAPY IN PULMONARY ARTERIAL HYPERTENSION

Chin KM, Sitbon O, Doelberg M, Feldman J, Gibbs JSR, Grünig E, Hoepfer MM, Martin N, Mathai SC, McLaughlin VV, Perchenet L, Poch D, Saggar R, Simonneau G, Galiè N.

#### Three- Versus Two-Drug Therapy for Patients With Newly Diagnosed Pulmonary Arterial Hypertension. *J Am Coll Cardiol.* 2021 Oct 5;78(14):1393-1403. doi:

10.1016/j.jacc.2021.07.057. PMID: 34593120.

#### Summary

Randomized clinical trials have demonstrated that combination therapy in incident or treatment-naïve patients with pulmonary arterial hypertension (PAH) alleviates symptoms and improves exercise tolerance and clinical outcomes. However, the benefit of initial triple over double therapy is less clear. TRITON, a multicenter, double-blind, randomized phase 3b study, evaluated initial triple (macitentan, tadalafil and selexipag) versus initial double (macitentan, tadalafil and placebo) in newly diagnosed, treatment naïve patients with PAH. The primary endpoint was change in pulmonary vascular resistance (PVR) at week 26. Both treatment strategies reduced PVR compared with baseline (by 54% and 52%, 95% CI 0.86-10.7, P=0.42). Six-minute walk distance (6MWD) and N-terminal pro-brain natriuretic peptide (BNP) improved, with no difference between groups. Exploratory analysis suggested a signal for reduced risk for disease progression in triple versus double therapy (HR 0.59, 95% CI 0.32-1.09). More patients experienced side effects on triple versus double therapy.

#### Comments

1. TRITON is the first randomized, placebo-controlled, head-to-head comparison, of initial triple oral combination therapy versus double oral combination therapy, in patients with newly diagnosed PAH.
2. Enrollment criteria ensured that patient population had moderate to severe disease, with the majority

categorized as WHO functional class III or IV, with intermediate- to high-risk clinical features, and PVR  $\geq 6$  Wood Units.

3. Upfront triple combination therapy did not improve the change in PVR at 26 weeks compared with dual combination therapy and had similar reductions improvements in NT-pro BNP and 6MWD.
4. Exploratory analysis suggested that triple therapy may decrease the risk for disease progression and first clinical events, such as hospitalizations for worsening PAH and death.
5. Although TRITON did not meet its primary endpoint, it is unlikely to close the door on future randomized clinical trials of initial triple combination therapy in intermediate- to high-risk patients.

### NEW THERAPIES IN PULMONARY ARTERIAL HYPERTENSION

Humbert M, McLaughlin V, Gibbs JSR, Gomberg-Maitland M, Hoepfer MM, Preston IR, Souza R, Waxman A, Escribano Subias P, Feldman J, Meyer G, Montani D, Olsson KM, Manimaran S, Barnes J, Linde PG, de Oliveira Pena J, Badesch DB; PULSAR Trial Investigators.

#### Sotatercept for the Treatment of Pulmonary Arterial Hypertension. *N Engl J Med.* 2021 Apr 1;384(13):1204-1215. doi: 10.1056/NEJMoa2024277. PMID: 33789009.

#### Summary

Novel therapies are needed to attenuate disease progression of PAH. Mutations in bone morphogenic protein (BMP) receptor type 2 (BMP2) play a role in the pathogenesis of PAH. BMP is a member of the transforming growth-factor (TGF)-beta family. Sotatercept is a first-in-class ligand trap for members of TGF-beta and restores balance between growth-promoting and growth-inhibiting BMP pathways, thereby having the potential to reverse the vascular remodeling in PAH. PULSAR, a multicenter, randomized, double-blind, phase 2 trial, evaluated the safety and

efficacy of subcutaneous sotatercept versus placebo on PAH patients who were receiving background therapy. Background therapy included monotherapy, double therapy or triple therapy with combinations of phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, endothelin-receptor antagonists, prostacyclin analogues, or prostacyclin-receptor agonists. Sotatercept at two doses (0.3mg/kg and 0.7mg/kg) was associated with significantly greater reduction in PVR from baseline to 24 weeks (least-squares difference of  $-145 \text{ dyn/sec/cm}^{-5}$ ,  $P=0.003$  and  $-239 \text{ dyn/sec/cm}^{-5}$ ,  $P<0.001$ , respectively). Additionally, sotatercept showed a significant improvement in 6MWD and NT-proBNP. Thrombocytopenia and increased hemoglobin level were the most common hematologic adverse events.

### Comments

1. Sotatercept could be a promising novel agent for PAH.
2. Sotatercept was shown to reduce PVR and improve 6MWD and NT-proBNP in patients receiving background therapy (majority on combination therapy, including >50% on triple therapy and >33% on prostacyclin infusion therapy).
3. Limitations of this trial were the relatively small sample size (106 patients), the lack of clinical outcomes such as mortality, and the short duration of follow-up.
4. A follow-up, phase 2 PULSAR, open-label extension interim results suggested that clinical efficacy is maintained across multiple endpoints for up to 48 weeks.
5. Ongoing phase 3 clinical trials will hopefully provide insight on clinical outcomes, such as time to clinical worsening, hospitalizations, and death.

### PULMONARY HYPERTENSION DUE TO INTERSTITIAL LUNG DISEASE

Waxman A, Restrepo-Jaramillo R, Thenappan T, Ravichandran A, Engel P, Bajwa A, Allen R, Feldman J, Argula R, Smith P, Rollins K, Deng C, Peterson L, Bell H, Tapson V, Nathan SD. **Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease.** *N Engl J Med.* 2021 Jan 28;384(4):325-334. doi: 10.1056/NEJMoa2008470. Epub 2021 Jan 13. PMID: 33440084.

### Summary

Most therapies approved for PAH that have been studied in pulmonary hypertension from interstitial lung disease (PH-ILD) have shown inconsistent results, no significant benefit or even harm. INCREASE, a multicenter, randomized, double-blind, placebo-controlled trial, studied the safety and efficacy of inhaled treprostinil in patients with PH-ILD. Most patients had idiopathic pulmonary fibrosis, connective tissue disease-ILD or combined pulmonary fibrosis and emphysema. Pulmonary hypertension was established by right heart catheterization and patients were not allowed on background PH therapy. Treprostinil demonstrated a significant least-squares mean difference in 6MWD at 16 weeks compared with placebo of 31m (95% CI 16.85-45.39,  $P<0.001$ ); the 6MWD increased by a mean 21m in the treprostinil group and decreased by 10m in the placebo group. Additionally, there was a 15% reduction in NT-proBNP with inhaled treprostinil. Clinical worsening (including hospitalizations for cardiopulmonary disease, a decrease of > 15% from baseline in 6MWD, death, and lung transplantation) occurred less in the treprostinil group (HR 0.61, 95% CI 0.40-0.92,  $P=0.04$ ). The most frequent adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue and diarrhea, and were similar in both groups. Lung function and oxygenation were not meaningfully affected.

### Comments

1. INCREASE is the first clinical trial with a significant impact in PH-ILD, showing an improvement of 31m (the minimal clinically important difference for 6MWD in pulmonary diseases is approximately 30m).
2. No evidence of worsening oxygenation was seen, which further allays historical concerns of ventilation-perfusion mismatching in group 3 PH.
3. No significant difference in patient-reported quality of life, as assessed with the SGRQ, between groups.
4. Limitations of the trial included short duration, premature discontinuation (21%), and lack of hemodynamic or echocardiographic outcomes.
5. Post-hoc analysis of the INCREASE data showed a decrease in disease progression (defined as at least 15% decline in 6MWD, cardiopulmonary hospitalization, lung transplantation, or death

during the study and a at least a 10% decline in FVC and exacerbations of underlying lung disease).

### **GUIDELINES FOR VENOUS THROMBOEMBOLIC DISEASE**

Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, Huisman MV, Kearon C, King CS, Knighton AJ, Lake E, Murin S, Vintch JRE, Wells PS, Moores LK. **Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report.** *Chest.* 2021 Dec;160(6):e545-e608. doi: 10.1016/j.chest.2021.07.055. Epub 2021 Aug 2. PMID: 34352278.

#### **Summary**

This is the 2nd update to the 9th edition of the CHEST Antithrombotic Therapy for VTE guidelines. It is endorsed by other important societies. Experts followed a PICO (Population, Intervention, Comparator, Outcome) framework. Strong or weak recommendations were generated based on high-, moderate-, and low-certainty evidence, using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology. The expert panel generated 29 guideline statements, 13 of which are graded as strong recommendations, covering decision to treat, interventional treatments, initiation phase, treatment phase, extended phase, and complications of VTE. Key recommendations included: 1) In acute PE associated with hypotension (SBP < 90 mm Hg) without a high bleeding risk, recommend treatment with systemic thrombolysis; 2) In acute PE who deteriorate (decrease in SBP, increase in HR, worsening gas exchange, signs of inadequate perfusion, worsening right ventricular function, or increasing cardiac biomarkers) after starting anticoagulation but have yet to develop hypotension and have acceptable bleeding risk, recommend treatment with systemic thrombolysis; 3) In acute PE associated with hypotension with a high bleeding risk, failed systemic thrombolysis or shock that is likely to cause death before systemic thrombolysis can take effect, if appropriate expertise and resources are available, recommend treatment with catheter-assisted thrombus removal; 4) In acute DVT of the leg tolerating anticoagulation, recommend against the use of an IVC filter; 5) In acute proximal DVT of the leg and contraindication to anticoagulation, recommend the use of an IVC filter; 6) In low-risk PE, recommend

outpatient treatment over hospitalization provided access to medications, ability to access outpatient care and home circumstances are adequate; 7) In acute VTE, recommend apixaban, dabigatran, edoxaban or rivaroxaban over VKA; 8) In acute VTE with associated cancer, recommend apixaban, edoxaban or rivaroxaban over LMWH; 9) In VTE with major or minor transient risk factor, recommend against extended-phase anticoagulation; 10) In VTE in the absence of transient provocation (unprovoked VTE or provoked by persistent risk factor), recommend extended-phase anticoagulation.

### **HEART FAILURE WITH PRESERVED EJECTION FRACTION**

Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiere-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M; EMPEROR-Preserved Trial Investigators. **Empagliflozin in Heart Failure with a Preserved Ejection Fraction.** *N Engl J Med.* 2021 Oct 14;385(16):1451-1461. doi: 10.1056/NEJMoa2107038. Epub 2021 Aug 27. PMID: 34449189.

#### **Summary**

Treatment options for patients with heart failure with preserved ejection fraction (HFpEF) are limited. Sodium glucose cotransporter 2 (SGLT2) inhibitors have been shown to reduce heart failure progression in patients with a reduced ejection fraction, but the effect in HFpEF are unclear. EMPEROR-Preserved, a multicenter, double-blind, randomized, placebo-controlled trial examined the effects of the SGLT2 inhibitor empagliflozin in 5988 HFpEF patients with NYHA FC II-IV chronic heart failure and a left ventricular ejection fraction > 40%. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure. During a median follow up of 26 months, a primary composite outcome event occurred significantly less in the empagliflozin group than in the placebo (HR 0.79, 95% CI 0.69-0.90, P<0.001). This effect was mainly related to a 29% lower risk of hospitalization for heart failure in the empagliflozin group. The benefit of empagliflozin

appeared similar in patients with and without diabetes. Uncomplicated genital and urinary tract infections and hypotension were more common in empagliflozin.

### Comments

1. Although SGLT2 inhibitors were introduced as type 2 diabetes medications, results of several RCT indicate a clear benefit in heart failure management, though the exact mechanism of benefit is unclear.
2. EMPEROR-Preserved demonstrated that empagliflozin improves heart failure outcomes in patients with HFpEF and EF > 40%, irrespective of diabetes status.
3. Benefit is primarily driven by a reduction in heart failure hospitalizations, not mortality.
4. Empagliflozin also slowed down the rate of decline in the eGFR and improved quality of life, as assessed with KCCQ.
5. Limitations of the trial included premature discontinuation (23%).

### Other Articles of Interest

#### Pulmonary Hypertension

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Guth S, D'Armini AM, Delcroix M, Nakayama K, Fadel E, Hoole SP, Jenkins DP, Kiely DG, Kim NH, Lang IM, Madani MM, Matsubara H, Ogawa A, Ota-Arakaki JS, Quarck R, Sadushi-Kolici R, Simonneau G, Wiedenroth CB, Yildizeli B, Mayer E, Pepke-Zaba J. **Current strategies for managing chronic thromboembolic pulmonary hypertension: results of the worldwide prospective CTEPH Registry.** *ERJ Open Res.* 2021 Aug 16;7(3):00850-2020. doi: 10.1183/23120541.00850-2020. PMID: 34409094; PMCID: PMC8365143.

Hoeper MM, Al-Hiti H, Benza RL, Chang SA, Corris PA, Gibbs JSR, Grünig E, Jansa P, Klinger JR, Langleben D, McLaughlin VV, Meyer GMB, Ota-Arakaki J, Peacock AJ, Pulido T, Rosenkranz S, Vizza CD, Vonk-Noordegraaf A, White RJ, Chang M, Kleinjung F, Meier C, Parascchin K, Ghofrani HA, Simonneau G; REPLACE investigators. **Switching to riociguat versus maintenance therapy with phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension (REPLACE): a multicentre, open-label, randomised controlled trial.** *Lancet Respir Med.* 2021 Jun;9(6):573-584. doi: 10.1016/S2213-2600(20)30532-4. Epub 2021 Mar 24. PMID: 33773120.

Grünig E, MacKenzie A, Peacock AJ, Eichstaedt CA, Benjamin N, Nechwatal R, Ulrich S, Saxer S, Bussotti M, Sommaruga M, Ghio S, Gumbiene L, Palevičiūtė E, Jurevičienė E, Cittadini A, Stanzola AA, Marra AM, Kovacs G, Olschewski H, Barberà JA, Blanco I, Spruit MA, Franssen FME, Vonk Noordegraaf A, Reis A, Santos M, Viamonte SG, Demeyer H, Delcroix M, Bossone E, Johnson M. **Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: results from a large European multicentre randomized controlled trial.** *Eur Heart J.* 2021 Jun 14;42(23):2284-2295. doi: 10.1093/eurheartj/ehaa696. PMID: 33232470.

#### Pulmonary Embolism

Jaureguizar A, Jiménez D, Bikdeli B, Ruiz-Artacho P, Muriel A, Tapson V, López-Reyes R, Valero B, Kenet G, Monreal M; Registro Informatizado de la Enfermedad TromboEmbólica Investigators. **Heart Rate and Mortality in Patients With Acute Symptomatic Pulmonary Embolism.** *Chest.* 2022 Feb;161(2):524-534. doi: 10.1016/j.chest.2021.08.059. Epub 2021 Aug 31. PMID: 34478718.

Lim P, Delmas C, Sanchez O, Meneveau N, Rosario R, Bouvaist H, Bernard A, Mansourati J, Couturaud F, Sebbane M, Coste P, Rohel G, Tardy B, Biendel C, Lairez O, Ivanes F, Gallet R, Dubois-Rande JL, Fard D, Chatelier G, Simon T, Paul M, Natella PA, Layese R, Bastuji-Garin S. **Diuretic vs. placebo in intermediate-risk acute pulmonary embolism: a randomized clinical trial.** *Eur Heart J Acute Cardiovasc Care.* 2022 Jan 12;11(1):2-9. doi: 10.1093/ehjacc/zuab082. PMID: 34632490.

D'Auria S, Sezer A, Thoma F, Sharbaugh M, McKibben J, Maholic R, Avgerinos ED, Rivera-Lebron BN, Toma C. **Outcomes of catheter-directed thrombolysis vs. standard medical therapy in patients with acute submassive pulmonary embolism.** *Pulm Circ.* 2020 Apr 8;10(1):2045894019898368. doi: 10.1177/2045894019898368. PMID: 32292583; PMCID: PMC7144676.

Avgerinos ED, Jaber W, Lacomis J, Markel K, McDaniel M, Rivera-Lebron BN, Ross CB, Sechrist J, Toma C, Chaer R; SUNSET sPE Collaborators. **Randomized Trial Comparing Standard Versus Ultrasound-Assisted Thrombolysis for Submassive Pulmonary Embolism: The SUNSET sPE Trial.** *JACC Cardiovasc Interv.* 2021 Jun 28;14(12):1364-1373. doi: 10.1016/j.jcin.2021.04.049. Erratum in: *JACC Cardiovasc Interv.* 2021 Oct 11;14(19):2194. PMID: 34167677.

Barco S, Schmidtmann I, Ageno W, Bauersachs RM, Becattini C, Bernardi E, Beyer-Westendorf J, Bonacchini L, Brachmann J, Christ M, Czihal M, Duerschmied D, Empen K, Espinola-Klein C, Ficker JH, Fonseca C, Genth-Zotz S, Jiménez D, Harjola VP, Held M, Iogna Prat L, Lange TJ, Manolis A, Meyer A, Mustonen P, Rauch-Kroehnert U, Ruiz-Artacho P, Schellong S, Schwaiblmair M, Stahrenberg R, Westerweel PE, Wild PS, Konstantinides SV, Lankeit M; HoT-PE Investigators. **Early discharge and home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban: an international multicentre single-arm clinical trial.** *Eur Heart J.* 2020 Jan 21;41(4):509-518. doi: 10.1093/eurheartj/ehz367. PMID: 31120118.

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Angel W, Sarosi MG, Qaqi O, Veerina K, Brown MA, Pollak JS. **Percutaneous mechanical thrombectomy in a real-world pulmonary embolism population: Interim results of the FLASH registry.** *Catheter Cardiovasc Interv.* 2022 Feb 3. doi: 10.1002/ccd.30091. Epub ahead of print. PMID: 35114059.

Klok FA, Ageno W, Ay C, Bäck M, Barco S, Bertolotti L, Becattini C, Carlsen J, Delcroix M, van Es N, Huisman MV, Jara-Palomares L, Konstantinides S, Lang I, Meyer G, Ní Áinle F, Rosenkranz S, Pruszczyk P. **Optimal follow-up after acute pulmonary embolism: a position paper of the European Society of Cardiology Working Group on Pulmonary Circulation and Right Ventricular Function, in collaboration with the European Society of Cardiology Working Group on Atherosclerosis and Vascular Biology, endorsed by the European Respiratory Society.** *Eur Heart J.* 2022 Jan 25;43(3):183-189. doi: 10.1093/eurheartj/ehab816. PMID: 34875048; PMCID: PMC8790766.

#### COVID VTE

ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators. **Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19.** *N Engl J Med.* 2021 Aug 26;385(9):790-802. doi: 10.1056/NEJMoa2105911. Epub 2021 Aug 4. PMID: 34351721; PMCID: PMC8362594.

REMAP-CAP Investigators; ACTIV-4a Investigators; ATTACC Investigators. **Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19.** *N Engl J Med.* 2021 Aug 26;385(9):777-789. doi: 10.1056/NEJMoa2103417. Epub 2021 Aug 4. PMID: 34351722; PMCID: PMC8362592.

Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, Huisman MV, Kearon C, King CS, Knighton AJ, Lake E, Murin S, Vintch JRE, Wells PS, Moores LK. **Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report.** *Chest.* 2021 Dec;160(6):e545-e608. doi: 10.1016/j.chest.2021.07.055. Epub 2021 Aug 2. PMID: 34352278.

# Interstitial Lung Disease

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## DIAGNOSIS OF UIP

Nandy S, Raphaely RA, Muniappan A, Shih, A, Roop BW et al **Diagnostic Accuracy of Endobronchial Optical Coherence Tomography for the Microscopic Diagnosis of Usual Interstitial Pneumonia.** *Am J Respir Crit Care Med.* 2021 Nov 15;204(10):1164-1179. doi: 10.1164/rccm.202104-0847OC.

## Summary

Diagnostic evaluation of patients with interstitial lung disease continues to be challenging, particularly in patients who may be high risk for surgical lung biopsy. Nandy et al evaluates the role of endobronchial optical coherence tomography (EB-OCT), a technique that allows imaging of the lung via a bronchoscope, for diagnosis of IPF. They enrolled 27 patients with unclassifiable ILD who were undergoing lung (surgical or transbronchial) biopsy for diagnosis. Prior to biopsy, they performed EB-OCT on at least 4 regions of interest, including subpleural lung, which were chosen based on imaging findings. Images were interpreted by a trained ILD pathologist, who was blinded to biopsy findings. Patients had mild-moderate disease (average FVC 76% predicted and DLCO 54% predicted). The average bronchoscopy time for EB-OCT was 9.5 minutes (SD 4.22 min). EB-OCT had a sensitivity and specificity of 100% for identifying histopathologic UIP pattern, using a gold standard of biopsy tissue (1 transbronchial, 26 surgical). The kappa between EB-OCT diagnoses and surgical lung biopsy diagnosis was also high ( $k=0.87$ ) in non UIP patterns, although study was not powered to evaluate sensitivity and specificity of non-UIP patterns. There were no adverse events during the EB-OCT.

## Comments

1. EB-OCT may represent a minimally invasive and safe way to differentiate between histopathologic patterns of ILD

2. Authors demonstrated that both pulmonologists and interpreting pathologists can be easily trained in this new diagnostic procedure.
3. There was excellent sensitivity and specificity for UIP and the clinical correlate, IPF.
4. Future studies should further evaluate the role of EB-OCT in a larger patient population, including non-UIP pattern ILD.

## TREATMENT OF IPF EXACERBATION

Naccache JM, Jouneau S, Didier M, Borie R, Cachando M, Bourdin A et al. **Cyclophosphamide added to glucocorticoids in acute exacerbation of idiopathic pulmonary fibrosis (EXAFIP): a randomized double-blind placebo-controlled, phase 3 trial.** *Lancet Respiratory Medicine* 2022; 10:26-34

## Summary

The role of systemic immunosuppression in exacerbations of IPF is unclear. This randomized controlled trial of cyclophosphamide added to glucocorticoids vs. glucocorticoids alone included 120 patients with exacerbations of IPF. Patients receiving mechanical ventilation, with an active infection, cancer, or awaiting lung transplant were excluded. All participants received methylprednisolone 10mg/kg/day x 3 days with a taper, and those in cyclophosphamide arm received a dose of 600mg/m<sup>2</sup> and umitrexan (to prevent hemorrhagic cystitis) on days 0, 15, 30 and 60. Mortality at 3 months was 45% in the cyclophosphamide group and 31% in the placebo arm ( $p=0.10$ ) and there was no difference in mortality at 1 year. The risk of death at 3 months was higher with severe IPF and lower with baseline antifibrotic therapy, regardless of treatment arm. There was no significant difference in adverse events, including infections, between the groups. In conclusion, there was no benefit to the addition of cyclophosphamide to high dose glucocorticoids in IPF exacerbation.

## Comments

1. This study demonstrates that it is feasible to conduct randomized controlled trials in the IPF exacerbation population
2. Mortality after IPF exacerbation is high, and addition of cyclophosphamide to high dose glucocorticoids had no benefit on outcomes
3. Antifibrotic therapy prior to exacerbation was associated with a lower risk of death.
4. Future study should evaluate the utility of glucocorticoids in IPF exacerbation.

## COVID-19 IN PATIENTS WITH ILD

Drake TM, Docherty AB, Harrison EM, Quint JK, Adamali H, Agnew S, Baby S et al **Outcome of Hospitalization for COVID-19 in Patients with Interstitial Lung Disease. An International Multicenter Study.** *Am J Respir Crit Care Med.* 2020 Dec 15;202(12):1656-1665. doi: 10.1164/rccm.202007-2794OC.

## Summary

Using a retrospective cohort design, authors evaluated outcomes of COVID-19 in patients with ILD early in the pandemic (March-May 2020). The authors utilized a 2:1 propensity score matching scheme to identify 322 patients hospitalized for COVID-19 during that time without respiratory comorbidities and matched them to 161 patients with ILD hospitalized for COVID-19. ILD was associated with a higher risk of death from COVID-19 (HR 1.6, 95% CI: 1.17-2.18, p=0.003). Of ILD sub-types, patients with IPF had the highest mortality (HR 1.74, 95% CI: 1.16-2.60, p=0.007). Obesity with ILD had an increased hazard of death compared to obesity alone (HR 2.27, 95% CI 1.39-3.71, p=0.001) as did male sex (adjusted HR for age and comorbidity: HR 1.98, 95% CI 1.14-3.43, p=0.015). Patients with lower lung function (FVC<80% predicted) also had a higher risk of mortality (HR 1.72, 95% CI, 1.05-2.83, p=0.032). There was high mortality in patients receiving enhanced respiratory support. There was no difference in outcomes in patients taking antifibrotics prior to hospitalization. There was also no difference between those who received corticosteroids during the hospitalization and those who did not.

## Comments

1. Outcomes for patients with ILD, particularly those with IPF, were worse than a group of propensity

- matched controls without chronic lung disease early in the pandemic.
2. Authors found that male sex and obesity significantly increased risk of death in the ILD population.
3. Given the high mortality of COVID-19 in ILD patients, it is extremely important that ILD patients receive vaccinations and boosters and have access to antiviral medications
4. Further work is needed on outcomes of COVID-19 in patients with ILD after vaccinations and widespread use of antiviral agents, as well as long-term morbidity and mortality outcomes for those who survive COVID-19 infection.

## TREATMENT OF IPF

Martinez FJ, Yow E, Flaherty KR et al **Effect of Antimicrobial Therapy on Respiratory Hospitalization or Death in Adults With Idiopathic Pulmonary Fibrosis: The Clean UP-IPF Randomized Clinical Trial.** *JAMA.* 2021;325(18):1841-1851. doi:10.1001/jama.2021.4956

## Summary

This is a pragmatic, randomized, unblinded clinical trial to evaluate whether the use of antibiotics reduces the risk of respiratory hospitalization or death in patients with IPF. 513 patients were enrolled. Patients and treating physicians were allowed to express a preference for antibiotic prior to enrollment. 272 chose trimethoprim/sulfamethoxazole plus folic acid, of which 128 received the drug and 114 received usual care. 241 patients chose doxycycline, of which 126 received the drug and 115 were randomized to usual care. There was no placebo drug. Treatment groups were well matched on clinical characteristics. At the first planned efficacy analysis (300 patients with 12 months of follow up), the study was stopped for futility. There was no significant difference in time to hospitalization, time to death, or a composite outcome of the two between usual care and antimicrobial group. There was also no difference in several HRQoL metrics, including dyspnea and cough. Unsurprisingly, there were increased adverse events in the microbial group, including GI side effects (doxycycline), rash and hyperkalemia (in the TMP/SMX arm). There was an increased number of respiratory serious adverse events in the antimicrobial arm (42 (16.5%) vs 26 (10%)) but no difference in occurrence of pneumonia.

**Comments**

1. This study demonstrates the feasibility of a pragmatic, open label approach to clinical trials in the IPF population.
2. There was no difference in outcomes in patients treated with antimicrobials compared to those who underwent usual care
3. Further work on the role of antimicrobial therapy in IPF is needed.

**TREATMENT OF COUGH IN IPF**

Martinez FJ, Wijssenbeek MS, Raghu G, Flaherty KR, Maher TM et al **Phase 2b Study of Inhaled RVT-1601 for Chronic Cough in Idiopathic Pulmonary Fibrosis: SCENIC Trial: Multi-Center, Randomized, Placebo-Controlled Study.**

*Am J Respir Crit Care Med.* 2022 Jan 20. doi: 10.1164/rccm.202106-1485OC. Online ahead of print

**Summary**

Chronic cough is one of the most disabling symptoms in ILD with few effective treatments. This multicenter, randomized, placebo-controlled phase 2b trial evaluated the efficacy and safety of RVT-1601 (nebulized cromolyn sodium) for treatment of chronic cough in patients with IPF. Patients were enrolled who had IPF with significant cough and FVC > 45% predicted. Patients were randomly assigned to receive study drug (10mg, 40mg, or 80mg) or placebo, nebulized three times per day. The study duration was 12 weeks with a 12 week open label extension. The primary outcome was least squares mean change in 24-hour average cough count. Enrollment was stopped after 108 patients due to pandemic (goal 180), and 61% of patients completed the study. Adherence was high, and demographics of placebo and treatment arms were similar. There was no significant change in the primary outcome from baseline in any of the arms. Serious adverse events were reported in 15% on study drug vs. 7% receiving placebo and were evenly distributed across all arms of the study drug. Only one was treatment-related, which was IPF progression. 8 deaths were reported in the study, 5/8 were related to hospitalization due to infection (perhaps COVID-19 given timing). Review by a Data Monitoring Committee concluded deaths were not related to the study drug.

**Comments**

1. This RCT of nebulized cromolyn sodium (RVT-1601) did not show an impact on objective measures of cough.
2. Study was terminated early because of the COVID-19 pandemic and did not meet enrollment goal
3. There were an increased number of adverse events in the treatment arm, including deaths, but analysis by an external safety monitor did not conclude there was significant harm from the study drug.
4. This study highlights the importance of studying chronic cough in IPF as it is one of the most debilitating symptoms of IPF.

**TREATMENT OF IPF**

Dempsey, TM, Payne S, Sangaralingham L, Yao X, Shah ND, Limper AH. **Adoption of the Antifibrotic Medications Pirfenidone and Nintedanib for Patients with Idiopathic Pulmonary Fibrosis.** *Ann Am Thorac Soc.* 2021 Jul;18(7):1121-1128. doi: 10.1513/AnnalsATS.202007-901OC.

**Summary**

This study evaluated the adoption, treatment duration, and cost of nintedanib and pirfenidone in patients with IPF. The authors used a database with deidentified administrative claims data for patients enrolled in private and Medicare Advantage health plans, using ICD codes to identify IPF. Codes were validated in a local cohort by chart and imaging review. Adult patients who filled a prescription for pirfenidone or nintedanib between 10/1/14 and 7/31/19 and had IPF diagnosis code were included. 8,095 of 10,996 patients (74%) with IPF were not on treatment. There were equal numbers on pirfenidone (13.2%) and nintedanib (13.2%) in the treated patients. Treated patients were younger (72 vs. 73.9,  $p < 0.0001$ ), male (30% vs. 21.9% women,  $p < 0.0001$ ), and had fewer comorbidities (3.9 vs. 4.9,  $p < 0.0001$ ). 90% of patients received prescriptions from a pulmonologist. 51.8% of untreated patients did not have a visit with a pulmonologist. The mean duration of time on treatment was 302 days. 43% of patients on therapy discontinued treatment. 37% of those who discontinued treatment died, mean time from treatment end until death was 505 days. The yearly cost for both medications was over \$106,000 with average monthly out of pocket cost of \$394.49 for pirfenidone and \$397.51 for nintedanib.

## Comments

1. Adoption of antifibrotics is low in a retrospective cohort study using insurance claims data with rates remaining at 21% in 2019, with no difference in prescribing patterns between nintedanib and pirfenidone.
2. The average duration of treatment was 302 days, which was not attributable to patient mortality as the average time between treatment end and death was 505 days
3. The annual cost of pirfenidone and nintedanib is over \$100,000 with about \$400/month in out of pocket costs for patients
4. 52% of untreated patients in this cohort did not see a pulmonologist.
5. Use of insurance claims data is a limitation, however, this study provides important information on real world prescribing practices of antifibrotic medications.

## OTHER ARTICLES OF INTEREST

### Diagnosis of ILD

Hunninghake GM, Goldin JG, Kadoch MA, Kropski JA, Rosas IO, et al. **Detection and Early Referral of Patients With Interstitial Lung Abnormalities: An Expert Survey Initiative.** *Chest.* 2022 Feb;161(2):470-482. doi: 10.1016/j.chest.2021.06.035. Epub 2021 Jun 29.

Teoh AKY, Holland AE, Morisset J, Flaherty KR et al **Essential Features of an ILD Multidisciplinary Meeting: An International Dephi Survey** *Ann Am Thorac Soc.* 2022 Jan;19(1):66-73. doi: 10.1513/AnnalsATS.202011-1421OC.

### Treatment of ILD

Assayag D, Garlick K, Johannson KA, Fell CD, Kolb et al **Treatment Initiation in Patients with ILD in Canada** *Ann Am Thorac Soc.* 2021 Oct;18(10):1661-1668. doi: 10.1513/AnnalsATS.202009-1122OC.

Behr JB, Prasse A, Kreuter M, Johow J, Rabe KF, Bonella F et al **Pirfenidone in patients with progressive fibrotic ILD other than IPF (RELIEF): a double-blind, randomized, placebo-controlled, phase 2b trial.** *Lancet Respir Med.* 2021 May;9(5):476-486. doi: 10.1016/S2213-2600(20)30554-3. Epub 2021 Mar 30.

Khanna D, Lin CJF, Furst DE, Wagner B, Zucchetto M, Raghu G, Martinez FJ, Goldin J Siegel J, Denton CP et al. **Long-Term Safety and Efficacy of Tocilizumab in Early Systemic Sclerosis-Interstitial Lung Disease: Open Lab Extension of a Phase 3 Randomized Controlled Trial** *Am J Respir Crit Care Med.* 2022 Mar 15;205(6):674-684. doi: 10.1164/rccm.202103-0714OC.

Lok SD, Wong AW, Khor YH, Ryerson CJ, Johannson KA; CARE-PF Investigators. **Malignancy Risk Associated With Mycophenolate Mofetil or Azathioprine in Patients With Fibrotic Interstitial Lung Disease.** *Chest.* 2021 Dec 16:S0012-3692(21)05085-6. doi: 10.1016/j.chest.2021.12.636. Epub ahead of print. PMID: 34921905.

Swaminatha A, Hellkamp AS, Neely ML, Bender S, Paoletti L et al **Disparities in Lung Transplant among Patients with Idiopathic Pulmonary Fibrosis: An Analysis of the IPF-PRO Registry** *Ann Am Thorac Soc.* 2022 Jan 24. doi: 10.1513/AnnalsATS.202105-5890C. Online ahead of print.

Tomassetti S, Ravagli C, Puglisi S, Ryu JH, Colby TV et al **Impact of Lung Biopsy Information on Treatment Strategy of Patients with Interstitial Lung Disease** *Ann Am Thorac Soc.* 2021 Nov 5. doi: 10.1513/AnnalsATS.202104-4660C. Online ahead of print

Waxman, A, Restrepo-Jaramillo R, Thenappan T, Ravichandran A, Engel P et al **Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease** *N Engl J Med* 2021; 384:325-334 DOI: 10.1056/NEJMoa2008470 \*Discussed in the Pulmonary Hypertension Year in Review

### Outcomes of ILD

Cutting CC, Bowman WS, Dao N, Pugashetti JV, Garcia CK, Oldham JM, Newton CA. **Family History of Pulmonary Fibrosis Predicts Worse Survival in Patients With Interstitial Lung Disease.** *Chest.* 2021 05; 159(5):1913-1921.

Johannson KA, Lethebe BC, Assaya D, Fisher, JH, Kolb M et al **Travel Distance to Subspecialty Clinic and Outcomes in Patients with Fibrotic Interstitial Lung Disease** *Ann Am Thorac Soc.* 2022 Jan;19(1):20-27. doi: 10.1513/AnnalsATS.202102-2160C.

Kaul B, Lee JS, Zhang N, Vittinghoff E, Sarmiento K et al **Epidemiology of Idiopathic Pulmonary Fibrosis among US Veterans, 2010-2019.** *Ann Am Thorac Soc.* 2022 Feb;19(2):196-203. doi: 10.1513/AnnalsATS.202103-295OC.

Nasser M, Larrieu S, Si-Mohamed S, Ahma K, Bousset L **Progressive fibrosing interstitial lung disease: a clinical cohort (the PROGRESS study)** *ERJ* 2021 Feb 11;57 (2): 2002718

Oldham JM, Lee CT, Wu Z, Bowman WS, Vu Pugashetti J, et al. **Lung function trajectory in progressive fibrosing interstitial lung disease.** *Eur Respir J.* 2021 Nov 04.

Simpson T, Barratt SL, Beirne P, Chaudhuri N, Crawshaw A et al **The Burden of Progressive Fibrotic Interstitial Lung Disease Across the UK** *ERJ* 2021 Jul 8;58

### COVID 19 in ILD

Lee H, Choi H, Yang B, Lee S, Park TS, Park DW, et al **Interstitial lung disease increases susceptibility to and severity of COVID-19** *ERJ* 2021; 58(6) PMID: 33888524

Myall KJ, Mukherjee B, Catanheira AM, Lam JL, Benedetti G et al **Persistent Post-COVID-19 Interstitial Lung Disease. An Observational Study of Corticosteroid Treatment.** *AATS* 2021 May; 18(5).

Wild JM, Porter JC, Molyneaux PL, George PM, Stewart I, et al. **Understanding the burden of interstitial lung disease post-COVID-19: the UK Interstitial Lung Disease-Long COVID Study (UKILD-Long COVID).** *BMJ Open Respir Res.* 2021 Sep;8(1):e001049. doi: 10.1136/bmjresp-2021-001049. PMID: 34556492; PMCID: PMC8461362.

## Lung Cancer

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### LUNG CANCER SCREENING

Meza R, Jeon J, Toumazis I, Ten Haaf K, Cao P, Bastani M, Han SS, Blom EF, Jonas DE, Feuer EJ, Plevritis SK, de Koning HJ, Kong CY. **Evaluation of the Benefits and Harms of Lung Cancer Screening With Low-Dose Computed Tomography: Modeling Study for the US Preventive Services Task Force.** *JAMA* 2021 Mar 9;325(10):988-997.

#### Summary

Meza et al used 4 lung cancer simulation models that predict age- and sex-specific lung cancer incidence and mortality according to an individual's smoking history, to assess the benefits and harms of lung cancer screening using 2 different screening strategies. The first screening strategy was based on risk factors and used criteria similar to the 2013 recommendation criteria. The second, a risk model-based strategy, evaluated eligibility criteria based on 3 multivariable risk prediction models to estimate lung cancer risk. The models were simplified to incorporate only smoking history, sex, and age but excluded other risk variables such as race, ethnicity, chronic obstructive pulmonary disease, family history, and personal history of cancer. Using these 2 strategies, Meza and colleagues identified a set of screening criteria estimated to be associated with a reduction in lung cancer mortality and an increase in life-years gained. The risk factor-based strategy identified as efficient was an approach that included beginning screening at age 50 or 55 years and stopping at age 80 years, with 20 pack-year smoking intensity minimum.

#### Comments

1. This study supports the new 2021 USPSTF recommendation of "annual screening for lung cancer with LDCT [low-dose CT] in adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years."

2. This study is an improvement over the analyses conducted in 2013 because the new risk factor-based strategy considers both lung cancer deaths averted as well as life-years gained and applies them to a 1960 cohort which is more similar to current population.
3. Compared to the 2013 criteria, the 2021 criteria are estimated to increase screening eligibility with a greater reduction in mortality and more life-years gained.
4. Full uptake and adherence were assumed for all scenarios in the evaluation while in practice, uptake is much lower e.g. 6-18%

### LUNG CANCER RISK FACTORS

Myers R, Brauer M, Dummer T, Atkar-Khattra S, Yee J, Melosky B, Ho C, McGuire AL, Sun S, Grant K, Lee A, Lee M, Yuchi W, Tammemagi M, Lam S. **High-Ambient Air Pollution Exposure Among Never Smokers Versus Ever Smokers With Lung Cancer.** *J Thorac Oncol.* 2021 Nov;16(11):1850-1858.

#### Summary

The proportion of patients with lung cancer who have never smoked is increasing in Asian countries and lung cancer in never smokers is now the 7th leading cause of cancer death worldwide in both sexes. This case series study compared the air pollution exposure in never smokers with lung cancer versus ever smokers with lung cancer, adjusting for sex, race/ethnicity, and additional factors. Patients were prospectively recruited from 2017-2019 in Vancouver. Street and city address or postal codes allow accurate linking of residential locations to satellite derived PM2.5 exposure data that were available from 1996 onward. Household exposure was obtained by questionnaire. In multivariable logistic regression analysis, there was a significant association with never-smoker lung cancer and being female (OR 4.01), Asian (OR 6.48) and greater exposure to air

pollution (OR 1.79). Exposure to ambient air pollution should be considered when evaluating risk for developing lung cancer.

### Comments

1. In this study, compared with ever smokers with lung cancer, never smokers with lung cancer were more likely females who were significantly younger with adenocarcinoma, more frequently East Asian, better educated, less likely to have COPD or a family history of lung cancer, and had higher exposure to outdoor PM<sub>2.5</sub> but lower exposure to second-hand smoke.
2. The Global Burden of Disease 2019 study revealed that the percent of the global lung cancers attributable to each risk factor is 62.4% for smoking, 5.8% for second-hand smoking, 15.3% for air pollution exposure, and 4% for household air pollution from use of solid fuels for cooking.
3. Residential radon exposure is also known to be associated with lung cancer in never smokers but varies from hour to hour and in the absence of direct measurements was not included in this study.
4. Never smokers with lung cancer in this study were more likely to live near truck routes where diesel fumes are concentrated
5. Although this study was able to estimate PM<sub>2.5</sub> exposure in the 20 years prior to lung cancer diagnosis, the etiologically relevant period for exposure is not known.

### MANAGEMENT OF EARLY STAGE LUNG CANCER

Lim E, Batchelor TJP, Dunning J, Shackcloth M et al.

**Video-assisted thoracoscopic or open lobectomy in early-stage lung cancer.** *NEJM Evidence* 2022; 1 (3)

### Summary

While surgery is established as the standard of care for early-stage lung cancer, previous trials of a video-assisted thoracoscopic (VATS) vs open approach have been inconclusive. In this U.K. multicenter pragmatic trial, 503 participants were randomly assigned to VATS (n=247) or open lobectomy (n=256). In the VATS group, there was one to four incisions without rib spreading while participants in the open surgery group underwent lobectomy through a single thoracotomy incision with

rib spreading. The primary outcome was physical function at 5 weeks as a measure of recovery using the European Organization for Research and Treatment of Cancer core health-related quality of life questionnaire (QLQ-C30). For this primary endpoint, participants allocated to VATS had significantly better physical functioning at 5 weeks (median score 73 vs 67 in open surgery group) and those undergoing VATS had less pain. Median length of stay was 1 day shorter for the VATS group (4 days vs 5 days for the open group). Oncological outcomes including number of lymph nodes harvested, R0 and upstaging rates, adjuvant chemotherapy rates and recurrence rates at 12 months were similar between the groups. In conclusion, VATS lobectomy results in better physical recovery at 5 weeks compared with open surgery.

### Comments

1. Lobectomy via VATS rather than open lobectomy led to a shorter length of stay with better physical function at 5 weeks.
2. From 6 months to 1 year after surgery, the benefit of VATS over open lobectomy were lost and the groups had similar physical function.
3. There was more bleeding and more patients with air leaks in the VATS group but these did not appear to impact patient outcomes.
4. Although a wound dressing sufficiently large to conceal a thoracotomy incision (regardless of actual access used) was applied, the dressing was removed on discharge and so the participants were not blinded for the primary endpoint.
5. Longer term oncological outcomes e.g. 5 year survival will be important and are awaited.

### MANAGEMENT OF EARLY STAGE NON-SMALL CELL LUNG CANCER

Felip E, Altorki N, Zhou C, Csőszi T, Vynnychenko I, Goloborodko O, Luft A, Akopov A, Martinez-Marti A, Kenmotsu H, Chen YM, Chella A, Sugawara S, Voong D, Wu F, Yi J, Deng Y, McClelland M, Bennett E, Gitlitz B, Wakelee H; IMpower010 Investigators. **Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIa non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial.** *Lancet*. 2021 Oct 9;398(10308):1344-1357.

## Summary

No new therapies have been approved over the past decade for patients with completely resected NSCLC without oncogenic drivers. Immune-checkpoint inhibitors are routinely used in patients with advanced lung cancer and this IMpower010 trial is the first positive trial of immunotherapy in the adjuvant setting. In this trial, 1,005 patients with completely resected stage IB–IIIA NSCLC were randomly assigned (1:1) to receive adjuvant atezolizumab (1200 mg every 21 days for 16 cycles or 1 year) or best supportive care, after adjuvant platinum-based chemotherapy. The primary end point was investigator-assessed disease-free survival (DFS) and was tested in a complex hierarchy. In the first analysis, atezolizumab prolonged DFS in the subpopulation of patients with stage II–IIIA NSCLC and PD-L1 expression on  $\geq 1\%$  tumor cells (HR 0.66, 95% CI 0.50–0.88;  $P = 0.0039$ ). In the second analysis, a lower level of benefit from atezolizumab was demonstrated among all patients in the stage II–IIIA population (HR 0.79, 95% CI 0.64–0.96;  $P = 0.02$ ), including  $\sim 45\%$  with PD-L1 expression on  $\leq 1\%$  of tumour cells. In the third analysis, in the intention-to-treat population that additionally included the patients with stage IB disease, the HR was 0.81, 95% CI 0.67–0.99 ( $P = 0.04$ ). Finally, a fourth analysis revealed no benefit with adjuvant atezolizumab for the secondary endpoint of overall survival (HR 1.07, 95% CI 0.80–1.42). The 3rd and 4th analyses are immature and will be updated.

## Comments

1. IMpower010 showed a disease-free survival benefit with atezolizumab versus best supportive care after adjuvant chemotherapy in patients with resected stage II–IIIA NSCLC, with particular benefit in the subgroup whose tumours expressed PD-L1  $\geq 1\%$
2. Although DFS is an accepted endpoint for drug approval, overall survival benefit should be the aim for adjuvant treatment and it is difficult to anticipate whether the DFS seen in this trial will translate into an OS benefit.
3. A post hoc exploratory analysis in the stage II–IIIA population of IMpower010 showed a positive correlation between the DFS benefit from atezolizumab and PD-L1 expression on tumor cells (PD-L1  $< 1\%$ : HR 0.97, 0.72–1.31; PD-L1 1–49%: HR 0.87, 0.60–1.26; and PD-L1  $\geq 50\%$ : HR 0.43, 0.27–0.66).

4. In IMpower010 8% of patients developed grade 3–4 immune-related adverse events and risk of chronic adverse events should be considered in shared decision-making.
5. Use of immunotherapy in the adjuvant setting raises questions about the efficacy of immunotherapy in patients who subsequently develop disease progression.

## MANAGEMENT OF ADVANCED NSCLC

Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, Italiano A, Schuler M, Borghaei H, Barlesi F, Kato T, Curioni-Fontecedro A, Sacher A, Spira A, Ramalingam SS, Takahashi T, Besse B, Anderson A, Ang A, Tran Q, Mather O, Henary H, Ngarmchamnanrith G, Friberg G, Velcheti V, Govindan R. **Sotorasib for Lung Cancers with KRAS p.G12C Mutation**. *N Engl J Med*. 2021 Jun 24;384(25):2371–2381.

## Summary

KRASG12C mutations can be found in approximately 13% of patients with NSCLC and are associated with poor prognosis. This phase II study, CodeBreak 100, demonstrates the efficacy of the novel KRASG12C specific inhibitor sotorasib. In this single-arm study, a total of 126 patients with disease progression on an anti-PD-1 or anti-PD-L1 antibody and/or platinum-based chemotherapy received a 960 mg daily dose of sotorasib until death, disease progression, unacceptable adverse events or withdrawal. Objective response rate was the primary end point. Secondary end points included duration of response, disease control (defined as complete response, partial response, or stable disease), progression-free survival, overall survival, and safety. An objective response was observed in 46 patients (37.1%, 95% CI 28.6–46.2%). Median duration of response was 11.1 months and responses were significant with a median 60% decrease in tumor burden from baseline. Median progression-free survival was 6.8 months, with a median overall survival of 12.5 months. Adverse events deemed to be treatment-related of any grade occurred in 69.8% of patients, including grade 3–4 events in 20.6%. CodeBreak 100 demonstrates the safety and efficacy of sotorasib in patients with pretreated advanced KRASG12C NSCLC and has resulted in FDA accelerated approval in May 2021.

## Comments

1. KRAS mutant lung cancers are common but have proved difficult to target and this is the first report of a novel agent with significant activity after disease progression on immunotherapy and/or chemotherapy.
2. Disease control occurred in 81% of patients and tumour shrinkage of any magnitude was observed in 82% of participants.
3. Although encouraging, the response rate (37%) is lower than for other personalized therapies in NSCLC e.g. EGFR-TKIs
4. A variety of resistance mechanisms are likely to exist that may limit efficacy including lesions that activate RAS by a non-G12C mechanism and KRAS amplification.
5. The efficacy of combinations of sotorasib with immune-checkpoint inhibitors and/or chemotherapy is to be determined, while newer generations of KRAS inhibitors are also in development

## OTHER ARTICLES OF INTEREST

### Epidemiology

Ganti AK, Klein AB, Cotarla I, Seal B, Chou E. **Update of Incidence, Prevalence, Survival, and Initial Treatment in Patients With Non-Small Cell Lung Cancer in the US.** *JAMA Oncol.* 2021 Dec 1;7(12):1824-1832.

Huang Y, Zhu M, Ji M, Fan J, Xie J, Wei X, Jiang X, Xu J, Chen L, Yin R, Wang Y, Dai J, Jin G, Xu L, Hu Z, Ma H, Shen H. **Air Pollution, Genetic Factors, and the Risk of Lung Cancer: A Prospective Study in the UK Biobank.** *Am J Respir Crit Care Med.* 2021 Oct 1;204(7):817-825.

### Screening

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

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Management of Advanced Non-Small Cell Lung Cancer  
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### Malignant Mesothelioma

Baas P, Scherpereel A, Nowak AK, Fujimoto N, Peters S, Tsao AS, Mansfield AS, Popat S, Jahan T, Antonia S, Oulkhair Y, Bautista Y, Cornelissen R, Greillier L, Grossi F, Kowalski D, Rodríguez-Cid J, Aanur P, Oukessou A, Baudelet C, Zalcman G. **First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial.** *Lancet.* 2021 Jan 30;397(10272):375-386.

# Pneumonia and Pulmonary Infections

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## DURATION OF ANTIBIOTIC TREATMENT IN ADULT PATIENTS WITH NON-SEVERE CAP

Dinh A et al. **Discontinuing  $\beta$ -Lactam Treatment After 3 Days for Patients with Community-Acquired Pneumonia in Non-Critical Care Wards (PTC): A Double-Blind, Randomised, Placebo-Controlled, Non-Inferiority Trial.** *Lancet* 2021. PMID: 33773631

### Summary

Clinical Question: Is a 3-day course of  $\beta$ -lactam therapy non inferior compared to an 8-day course for admitted patients with non-severe CAP?

Methods and design: Multi-center, double-blind, randomized, placebo-controlled non-inferiority trial comparing 3 days of  $\beta$ -lactam treatment to 8 days of  $\beta$ -lactam treatment in non-ICU patients admitted with CAP. Randomized adult patients ( $\geq 18$  years old) admitted to the hospital with CAP after 3 days of IV or oral  $\beta$ -lactam treatment.

Primary outcome: Cure at 15 days after start of antibiotic treatment.

Results: 706 patients assessed for eligibility; 396 excluded; 310 patients randomized to a placebo group or  $\beta$ -lactam group. 117 of 152 (77%) of patients in the 3 day  $\beta$ -lactam group, followed by 5 days of placebo (placebo) were cured whereas 102 of 151 (68%) of patients in the 8 day  $\beta$ -lactam group were cured. The difference was 9.42% (95 % CI -0.38 – 20.04) indicating non-inferiority. No differences in the secondary outcomes were recorded, including 30-day cure, all-cause mortality, frequency and severity of adverse events, length of hospital stay and recovery time.

### Comments

1. This RCT attempts to tackle a relevant clinical question: reducing antibiotic usage for CAP.
2. Primary and secondary outcomes of the study are patient-oriented.
3. Adherence to protocol and inclusion criteria reflects the fact that the study might be easily replicated in clinical practice

4. The study was performed in France where microbial resistance rates and patient-level characteristics may differ from an individual physician's practice population
5. European treatment guidelines used in the study differ from the U.S.

## DURATION OF ANTIBIOTIC TREATMENT IN PEDIATRIC PATIENTS WITH NON-HOSPITALIZED CAP

Pernica JM, Harman S, Kam AJ, et al. **Short-Course Antimicrobial Therapy for Pediatric Community-Acquired Pneumonia: The SAFER Randomized Clinical Trial.** *JAMA Pediatr.* 2021;175(5):475-482. doi:10.1001/jamapediatrics.2020.6735

### Summary

Clinical question: Is 5 days of high-dose amoxicillin for non-hospitalized CAP in pediatric community associated with non-inferior rates of clinical cure compared with 10 days of high-dose amoxicillin?

Methods and design: The SAFER (Short-Course Antimicrobial Therapy for Pediatric Respiratory Infections) study was a 2-center, parallel-group, non-inferiority randomized clinical trial. Patients were randomized to 5 days of high-dose amoxicillin therapy followed by 5 days of placebo (intervention group) vs 5 days of high-dose amoxicillin followed by a different formulation of 5 days of high-dose amoxicillin (control group).

Primary outcome: Clinical cure at 14 to 21 days.

Results: Among the 281 participants, the median age was 2.6 (interquartile range, 1.6-4.9) years (160 boys [57.7%] of 279 with sex listed). Clinical cure was observed in 101 of 114 children (88.6%) in the intervention group and in 99 of 109 (90.8%) in the control group in per-protocol analysis (risk difference, -0.016; 97.5% confidence limit, -0.087). Clinical cure at 14 to 21 days was observed in 108 of 126 (85.7%) in the intervention group and in 106 of 126 (84.1%) in the

control group in the intention-to-treat analysis (risk difference, 0.023; 97.5% confidence limit, -0.061).

### Comments

1. Outcome of the study is patient-oriented.
2. This study provides information to a question with uncertainty during a time when antibiotic stewardship is being recognized as crucial in light of the emergence of antibiotic resistance
3. Adherence to protocol and inclusion criteria reflects the fact that the study might be easily replicated in clinical practice
4. Children commonly exhibit a mixed pattern of disease (most of the cases viral) and it is likely that a proportion of patients may have been infected with non-bacterial illness to begin with.
5. The study should be replicated in different countries and settings.

### DURATION OF ANTIBIOTIC FOR UNCOMPLICATED RESPIRATORY TRACT INFECTIONS IN PRIMARY CARE

Llor C, Moragas A, Bayona C, et al. **Efficacy and safety of discontinuing antibiotic treatment for uncomplicated respiratory tract infections when deemed unnecessary. A multicentre, randomized clinical trial in primary care.** *Clin Microbiol Infect.* 2022;28(2):241-247. doi:10.1016/j.cmi.2021.07.035

### Summary

Clinical question: What are the benefits and harms of discontinuing unnecessary antibiotic therapy for uncomplicated respiratory tract infections (RTI) when antibiotics are considered no longer necessary? Methods and design: Multicentre, open-label, randomised controlled clinical trial in primary care centres from 2017 to 2020. Adults with RTIs – acute rhinosinusitis, sore throat, influenza, or acute bronchitis – who had previously taken any dose of antibiotic for less than 3 days. The patients were randomly assigned in a 1:1 ratio to discontinuing antibiotic therapy or the usual strategy of continuing antibiotic treatment. Primary outcome: duration of severe symptoms (using Likert scale). Results: A total of 463 patients were randomized, out of which 409 were considered valid for the analysis. The mean (SD) duration of severe symptoms was 3.0 (1.5) days for the patients assigned to discontinuation and

2.8 (1.3) days for those allocated to the control group (mean difference, 0.2 days [95%CI -0.1-0.4 days]). Moreover, patients assigned to antibiotic continuation presented a relative risk (RR) of adverse events of 1.47 (95% CI 0.80-2.71), but the need for further health care contact in the following 3 months was slightly lower (RR 0.61 [95% CI 0.28-1.37]).

### Comments

1. The RCT confirm the hypothesis that discontinuing antibiotic treatment for uncomplicated RTIs when clinicians consider it unnecessary is safe and notably reduces antibiotic consumption.
2. Adherence to protocol and inclusion criteria reflects the fact that the study might be easily replicated in clinical practice
3. The study was performed in Spain, one of the European countries with higher antibiotic consumption rate so it should be replicated in different national health care systems.
4. The prescriptions were considered unnecessary by the participating physician based on his/her personal evaluation.

### DURATION OF ANTIBIOTIC THERAPY FOR EXACERBATION OF BRONCHIECTASIS REQUIRING INTRAVENOUS ANTIBIOTICS

Bedi P, Carlidge MK, Zhang Y, et al. **Feasibility of shortening intravenous antibiotic therapy for bronchiectasis based on bacterial load: a proof-of-concept randomised controlled trial.** *Eur Respir J.* 2021;58(6):2004388. Published 2021 Dec 16. doi:10.1183/13993003.04388-2020

### Summary

Clinical question: Is it feasible, based on bacterial load, to shorten intravenous antibiotics during exacerbations? Methods and design: Patients requiring intravenous antibiotics for exacerbations were included. Participants were randomized into two groups: to receive antibiotics for 14 days (14-day group) or to have a shorter duration of treatment based on bacterial load (bacterial load-guided group [BLGG]). If the bacterial load was <106CFU·mL<sup>-1</sup> on day 7 or day 10 in the BLGG, antibiotics were stopped the following day. Primary outcome: clinical improvement by day 21

Results: A total of 47 participants were in the 14-day group and 43 were in the BLGG. 88% of participants in the BLGG were able to stop antibiotics by day 8 and potentially 81% of participants in the 14-day group could have stopped antibiotics at day 8. There was a nonsignificant trend for increased clinical improvement by day 21 in the 14-day group compared to the BLGG. However, overall group data showed the median time to next exacerbation was 27.5 days (12.5-60 days) in the 14-day group and 60 days (18-110 days) in the in BLGG ( $p=0.0034$ ).

### Comments

1. This trial attempted to tackle a relevant clinical question: reducing antibiotic usage for bronchiectasis exacerbation.
2. BLGG can be easily performed in patients with exacerbation of bronchiectasis requiring intravenous antibiotics (biomarker-guided therapy)
3. Further studies on the risk of future exacerbation should be performed
4. Shift in microbiome composition should be analyzed in further studies

### MICROBIOLOGY, RISK FACTORS AND TREATMENT OF ASPIRATION CAP

Marin-Corral J, Pascual-Guardia S, Amati F, et al. **Aspiration Risk Factors, Microbiology, and Empiric Antibiotics for Patients Hospitalized With Community-Acquired Pneumonia.** *Chest.* 2021;159(1):58-72. doi:10.1016/j.chest.2020.06.079

### Summary

Clinical question: What are the aspiration risk factors, microbiology patterns, and empiric anti-anaerobic use in patients hospitalized with CAP?

Study design and methods: Secondary analysis of GLIMP, an international, multicenter, point-prevalence study of adults hospitalized with CAP. Patients were stratified into three groups: (1) ACAP, (2) CAP/Aspiration risk factors (AspRF+) (CAP with AspRF), and (3) CAP/AspRF- (CAP without AspRF). Patients were further stratified in severe and non-severe CAP groups. Results: 2,606 patients with CAP were enrolled, of which 193 (7.4%) had ACAP. Risk factors independently associated with ACAP were male, bedridden, underweight, a nursing home resident, and having a

history of stroke, dementia, mental illness, and enteral tube feeding. Among non-ACAP patients, 1,709 (70.8%) had CAP/AspRF+ and 704 (29.2%) had CAP/AspRF-. Microbiology patterns including anaerobes were similar between CAP/AspRF-, CAP/AspRF+ and ACAP (0.0% vs 1.03% vs 1.64%). Patients with severe ACAP had higher rates of total gram-negative bacteria (64.3% vs 44.3% vs 33.3%,  $P = .021$ ) and lower rates of total gram-positive bacteria (7.1% vs 38.1% vs 50.0%,  $P < .001$ ) when compared with patients with severe CAP/AspRF+ and severe CAP/AspRF-, respectively. Most patients (>50% in all groups) independent of AspRFs or ACAP received specific or broad-spectrum anti-anaerobic coverage antibiotics.

### Comments

1. The study shows that anaerobes have a much lower incidence than previously thought in CAP.
2. The study supports the 2019 CAP guidelines in suggesting limiting anti anaerobic therapy to patients with empyema or lung abscess.
3. Overuse of broad-spectrum antibiotics with anti-anaerobic activity is a challenge for antimicrobial stewardship programs.

### OTHER ARTICLES OF INTEREST

Bielicki JA, Stöhr W, Barratt S, et al. **Effect of Amoxicillin Dose and Treatment Duration on the Need for Antibiotic Re-treatment in Children With Community-Acquired Pneumonia: The CAP-IT Randomized Clinical Trial** [published correction appears in *JAMA.* 2021 Dec 7;326(21):2208]. *JAMA.* 2021;326(17):1713-1724. doi:10.1001/jama.2021.17843

Voiriot G, Fartoukh M, Durand-Zaleski I, et al. **Combined use of a broad-panel respiratory multiplex PCR and procalcitonin to reduce duration of antibiotics exposure in patients with severe community-acquired pneumonia (MULTI-CAP): a multicentre, parallel-group, open-label, individual randomised trial conducted in French intensive care units.** *BMJ Open.* 2021;11(8):e048187. Published 2021 Aug 18. doi:10.1136/bmjopen-2020-048187

Vaughn VM, Gandhi TN, Hofer TP, et al. **A Statewide Collaborative Quality Initiative To Improve Antibiotic Duration And Outcomes Of Patients Hospitalized With Uncomplicated Community-Acquired Pneumonia** [published online ahead of print, 2021 Nov 13]. *Clin Infect Dis*. 2021;ciab950. doi:10.1093/cid/ciab950

Gilbert DN, Leggett JE, Wang L, et al. **Enhanced Detection of Community-Acquired Pneumonia Pathogens With the BioFire® Pneumonia FilmArray® Panel**. *Diagn Microbiol Infect Dis*. 2021;99(3):115246. doi:10.1016/j.diagmicrobio.2020.115246

Wittermans E, van de Garde EM, Voorn GP, et al. **Neutrophil count, lymphocyte count and neutrophil-to-lymphocyte ratio in relation to response to adjunctive dexamethasone treatment in community-acquired pneumonia**. *Eur J Intern Med*. 2022;96:102-108. doi:10.1016/j.ejim.2021.10.030

Aliberti S, Dela Cruz CS, Amati F, Sotgiu G, Restrepo MI. **Community-acquired pneumonia**. *Lancet*. 2021;398(10303):906-919. doi:10.1016/S0140-6736(21)00630-9

Schweitzer VA, van Heijl I, Boersma WG, et al. **Narrow-spectrum antibiotics for community-acquired pneumonia in Dutch adults (CAP-PACT): a cross-sectional, stepped-wedge, cluster-randomised, non-inferiority, antimicrobial stewardship intervention trial**. *Lancet Infect Dis*. 2022;22(2):274-283. doi:10.1016/S1473-3099(21)00255-3

Leo F, Bannehr M, Valenta S, et al. **Impact of a computerized physician order entry (CPOE)-based antibiotic stewardship intervention on the treatment duration for pneumonia and COPD exacerbations**. *Respir Med*. 2021;186:106546. doi:10.1016/j.rmed.2021.106546

High J, Enne VI, Barber JA, et al. **INHALE: the impact of using FilmArray Pneumonia Panel molecular diagnostics for hospital-acquired and ventilator-associated pneumonia on antimicrobial stewardship and patient outcomes in UK Critical Care-study protocol for a multicentre randomised controlled trial**. *Trials*. 2021;22(1):680. Published 2021 Oct 7. doi:10.1186/s13063-021-05618-6

Torres A, Cilloniz C, Niederman MS, et al. **Pneumonia**. *Nat Rev Dis Primers*. 2021;7(1):25. Published 2021 Apr 8. doi:10.1038/s41572-021-00259-0

## COPD

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### DEFINING ACUTE EXACERBATIONS OF COPD

Celli BR, Fabbri LM, Aaron SD, Agusti A, Brook R, Criner GJ, Franssen FME, Humbert M, Hurst JR, O'Donnell D, Pantoni L, Papi A, Rodriguez-Roisin R, Sethi S, Torres A, Vogelmeier CF, Wedzicha JA. **An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal.** *Am J Respir Crit Care Med* 2021; 204: 1251-1258.

#### Summary

Created by consensus of an international panel of COPD experts, the Rome proposal reviews the current definition and severity classification of acute exacerbations of COPD (ECOPDs) and suggests a revised definition to update existing ECOPD definitions, which have been essentially unchanged for 35 years. The authors argue that the existing definition is subjective (due to reliance on patient report and lack of measurable variables) and poorly specific in that ECOPD symptoms overlap with those of pneumonia, cardiac events, pulmonary embolism, etc. The proposed updated ECOPD definition is, "In a patient with COPD, an exacerbation is an event characterized by dyspnea and/or cough and sputum that worsen  $\leq$  14 days, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways." Severity is then defined as mild, moderate, or severe based on 1) dyspnea measured on 0-10 visual analog scale, 2) respiratory rate, 3) heart rate, 4) oxygen saturation, 5) serum CRP, and 6) arterial blood gas (ABG). The performance of the ABG is optional for suspected mild and moderate ECOPD; however, a "severe" ECOPD is defined by hypercapnia and acidosis.

#### Comments

1. The proposed updated ECOPD definition was made with consideration for not only clinical care but also COPD research and health services.

2. The proposed ECOPD severity classification is based on objective measurements rather than health care utilization, which is heterogeneous and depends on the availability of local resources and individual care patterns (e.g., presenting to the ED instead of primary care for a mild illness).
3. Of the many potential confounding morbidities, the panelists highlighted the need to consider heart failure, pneumonia, and pulmonary embolism as alternate or coexisting diagnoses to ECOPDs.
4. The manuscript is clear that the proposed updated ECOPD definition in the Rome proposal should be prospectively validated.

### COPD SCREENING AND DIAGNOSIS

Siddharthan T, Pollard SL, Quaderi SA, Rykiel NA, Wosu AC, Alupo P, Barber JA, Cardenas MK, Chandyo RK, Flores-Flores O, Kirenga B, Miranda JJ, Mohan S, Ricciardi F, Sharma AK, Das SK, Shrestha L, Soares MO, Checkley W, Hurst JR, Investigators GES. **Discriminative Accuracy of Chronic Obstructive Pulmonary Disease Screening Instruments in 3 Low- and Middle-Income Country Settings.** *JAMA* 2022; 327: 151-160.

#### Summary

Most COPD morbidity and mortality occurs in low- and middle-income countries (LMICs). The objective of the study was to compare the discriminative accuracy of three COPD screening instruments (two of which include peak expiratory flow [PEF]) using a reference standard COPD diagnosis - defined as post-bronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>) to forced vital capacity (FVC) ratio less than the Global Lung Function Initiative mixed ethnic population reference lower limit of normal - in a cross-sectional analysis of 10,709 adults in rural Uganda, semiurban Nepal, and urban Peru. The prevalence of COPD in these three countries was variable (7.4% in Uganda, 18.2% in Nepal, 2.7% in Peru) with 49.3% of individuals with COPD

having GOLD B-D disease and 16.4% having  $FEV_1 < 50\%$  predicted. Approximately 95% of COPD cases were previously undiagnosed. The screening tools were quickly administered (mean time 7.6 minutes) with 99.5% complete data capture. The area under the receiver operating characteristic curves (AUCs) of the 3 screening instruments ranged from 0.72 to 0.79 in the prediction of COPD. The authors argue that COPD screening instruments are feasible in LMICs; however, whether implementation is associated with improved clinical outcomes is not yet known.

### Comments

1. For two screening tools with a single threshold, sensitivity  $>90\%$  could be achieved, but resulted in many false positive COPD labels.
2. This study is limited by its cross-sectional nature, as the screening instruments may vary more widely in the prediction of incident COPD.
3. The heterogeneous prevalence of COPD in different LMICs will dictate whether COPD screening is reasonable or warranted on a country-by-country basis.
4. The study highlights the high rate of clinically significant undiagnosed COPD in LMICs and establishes the feasibility of screening tools as a proxy to spirometry in the diagnosis of COPD.

### PULMONARY EMBOLISM IDENTIFICATION IN COPD EXACERBATIONS

Jimenez D, Agusti A, Taberner E, Jara-Palomares L, Hernando A, Ruiz-Artacho P, Perez-Penate G, Rivas-Guerrero A, Rodriguez-Nieto MJ, Ballaz A, Aguero R, Jimenez S, Calle-Rubio M, Lopez-Reyes R, Marcos-Rodriguez P, Barrios D, Rodriguez C, Muriel A, Bertolotti L, Couturaud F, Huisman M, Lobo JL, Yusen RD, Bikdeli B, Monreal M, Otero R, Group ST. **Effect of a Pulmonary Embolism Diagnostic Strategy on Clinical Outcomes in Patients Hospitalized for COPD Exacerbation: A Randomized Clinical Trial.** *Jama* 2021; 326: 1277-1285.

### Summary

COPD patients hospitalized for acute exacerbation have been previously described to have a high prevalence of pulmonary embolism (PE). This study is a multicenter randomized trial of patients hospitalized for an acute exacerbation of COPD in Spain that compared an “active

strategy” for PE diagnosis using D-dimer testing and reflexive computed tomography pulmonary angiogram (CTPA) for PE diagnosis (n=370) to usual care (n=367) for a composite primary outcome of symptomatic venous thromboembolism (VTE), COPD readmission, or 90-day mortality. In the active strategy intervention group, of 181 patients with a positive D-dimer (and no clinical suspicion of PE) and in whom CTPA was performed, 16 patients (8.8%) were diagnosed with PE and were started on anticoagulation. In the usual care group, CTPA was performed in 5 patients with a clinical suspicion of PE and a PE was confirmed in 3 of these patients. At 90 days, the composite outcome had occurred in 110 (29.7%) of the active PE diagnosis strategy group compared to 107 (29.2%) of the usual care group (RR 1.02, 95% CI 0.82 to 1.28, P = 0.86). The active PE diagnostic strategy was not associated with improvement in the composite outcome compared to usual care.

### Comments

1. In the intervention group, pulmonary embolism was diagnosed in 19 (17 initially and 2 during 90-day follow up) or 5.1% of the 370 COPD patients hospitalized for an acute exacerbation.
2. In the usual care group, pulmonary embolism was diagnosed in 12 (3 initially and 9 during 90-day follow up) or 3.3% of the 367 COPD patients hospitalized for an acute exacerbation, similar to an ED study of PE in ECOPD, but far below the previously reported 22% prevalence of PE in COPD exacerbations of unclear etiology.
3. There were no differences in major bleeding or other serious adverse events in the intervention and usual care group.
4. Two important limitations of the study are an overestimation of PE frequency (estimated 10%) and an overestimation of the size of intervention effect (10% reduction in primary outcome) in performing power calculations for the study. Thus, a small effect of active PE diagnosis on health outcomes in COPD exacerbation may be present, but this study was underpowered to detect such an effect.

## COVID-19 RISK IN COPD

Aveyard P, Gao M, Lindson N, Hartmann-Boyce J, Watkinson P, Young D, Coupland CAC, Tan PS, Clift AK, Harrison D, Gould DW, Pavord ID, Hippisley-Cox J.

**Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study.** *Lancet Respir Med* 2021; 9: 909-923.

### Summary

This article utilized data from 1205 general practices and a total of ~8.26 million individuals over age 20 in England to study the association of chronic lung diseases (including COPD) and the use of inhaled corticosteroids (ICS) with the risk of severe COVID-19. The study reported 193,520 (2.3% of total) persons with COPD, of which 1,555 (0.8% of COPD) were hospitalized for COVID-19. Compared to persons without any respiratory diseases, in fully adjusted models considering age, sex, demographics, and non-respiratory illness, COPD was associated with an increased risk for hospitalization (HR 1.54, 95% CI 1.45-1.63) and death (HR 1.5, 95% CI 1.42-1.67). The modest increased risk for COVID-19 hospitalization and death in COPD patients in the fully adjusted model was higher than reported for asthma (HR 1.18 and 95% CI 1.13-1.24 in association with hospitalization; no increased risk of death), but similar to that of idiopathic pulmonary fibrosis (hospitalization: HR 1.59, 95% CI 1.30-1.95; death: HR 1.47, 95% CI 1.12-1.92). Regarding ICS use, 46.3% of individuals with COPD were using ICS regularly (at least 2 prescriptions in 150 days) and ICS use was associated with a small increased risk of COVID-19 hospitalization and death in fully adjusted models.

### Comments

1. The study was a retrospective analysis of the general population that allowed capture of comorbidities and exposures leading up to COVID-19 hospitalization.
2. Prior studies of respiratory disease associations with increased risk of severe COVID-19 may have been confounded by studying only hospitalized patients.
3. Women with COPD had higher relative hazard of death compared to men.
4. Estimates for risk of COVID-19 death associated with ICS use (compared to a long-acting beta agonist

and long-acting muscarinic use) in COPD patients is similar to what was reported in the OpenSAFELY cohort; however, it is difficult to remove confounding by indication and the ICS association with death may be due to ICS use being a marker for more severe COPD.

## EARLY ORIGINS OF COPD

Zhang J, Xu H, Qiao D, DeMeo DL, Silverman EK, O'Connor GT, Hobbs BD, Dupuis J, Cho MH, Moll M. **A Polygenic Risk Score and Age of Diagnosis of Chronic Obstructive Pulmonary Disease.** *Eur Respir J* 2022; in press (<https://doi.org/10.1183/13993003.01954-2021>).

### Summary

In over 15,900 participants from the COPDGene Study (non-Hispanic white [NHW] and African American [AA]) and Framingham Heart Study (FHS, European ancestry), a polygenic risk score (PRS) derived from genetic associations with spirometry - and previously associated with cross-sectional COPD risk - was tested for association with an earlier age of diagnosis of COPD. Age of COPD diagnosis was defined by either self-reported age of COPD diagnosis or age at initial COPD diagnosis as determined by spirometry (GOLD 2-4 moderate-to-severe airflow limitation) collected at a study visit. In time-to-event analyses, the PRS showed an age-dependent association with incident COPD with a larger effect on COPD risk at younger ages. The PRS (per standard deviation increase) was additionally associated with early-onset COPD (age of diagnosis < 50) in COPDGene NHW (OR 1.55, 95% CI 1.41-1.71), COPDGene AA (OR 1.23, 95% CI 1.05-1.43), and FHS (OR 2.47, 95% CI 2.12-2.88) participants. Further, the PRS was complementary to non-genetic early life risk factors for COPD including maternal smoking during pregnancy, active smoking during adolescence, childhood asthma, family history of COPD, and education history (as a surrogate for socio-economic status) in the prediction of early-onset COPD.

### Comments

1. The genome-wide association study of spirometry, from which this PRS was derived, reported that genetic risk loci for reduced lung function are enriched in regulatory regions in fetal lungs and have an overlapping association with height

suggesting these genetic variants may be important in lung growth and development.

2. The statistically significant, though smaller effect of the PRS in predicting early-onset COPD in COPDGene AA individuals is because the PRS was derived from a European ancestry genome-wide association study and highlights the need for expanded multi-ancestry genetic studies to improve specificity of genetic risk scores for non-European ancestry individuals.
3. The lung function polygenic risk score used in this manuscript has been previously associated with reduced lung growth and subsequent COPD in a longitudinal cohort of children with mild to moderate asthma.
4. This study adds to the mounting evidence that genetic risk to COPD is related to early life events including lung development and maximal attained lung capacity.
5. Knowledge of an individual's genetic risk to COPD, which is present at birth and fixed over a lifespan, may influence choices and behaviors related to modifiable COPD risk factors, such as cigarette smoking.

#### OTHER ARTICLES OF INTEREST

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## Asthma

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### INFANT BODY MASS INDEX TRAJECTORIES AND ASTHMA AND LUNG FUNCTION

Ali GB, Bui DS, Lodge CJ, Waidyatillake NT, Perret JL, Sun C, Walters EH, Abramson MJ, Lowe AJ, Dharmage SC.

**Infant body mass index trajectories and asthma and lung function** *J Allergy Clin Immunol*. 2021

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#### Summary

The impact of early rapid increase in body mass index (BMI) on asthma risk and subsequent lung function remains controversial. Anthropometric data on 620 infants from the Melbourne Atopy Cohort Study were collected up to 18 times in the first 24 months of the study. BMI trajectories were developed by using trajectory modeling. Associations between these trajectories and spirometry, fractional exhaled nitric oxide (FeNO), and current asthma status at 12 and/or 18 years of age were modeled by using multiple linear and logistic regression. A total of 5 BMI trajectories were identified. Compared with those children with the "average" trajectory, the children belonging to the "early-low and catch-up" and "persistently high" BMI trajectories were at higher risk of asthma at the age of 18 years (odds ratios = 2.2 [95% CI = 1.0-4.8] and 2.4 [95% CI = 1.1-5.3], respectively). These trajectories were also associated with a lower FEV1/FVC and a higher FeNO at age 18 years. Children belonging to the persistently low trajectory had lower FEV1 ( $\beta = -183.9$  mL) and FVC ( $\beta = -207.8$  mL) values at the age of 18 years. Maintenance of normal growth patterns may lead to improved adolescent respiratory health.

#### Comments

1. High BMI may induce a restrictive pattern leading to respiratory symptoms such as dyspnea, and in asthma, this contributes to poor asthma control.

2. The results of this study are in line with previous studies showing that obese patients with early onset of asthma have increased type-2 inflammation.
3. Measuring lung spirometry in children with BMI outside the average trajectory is important as it has already been shown that FEV1 in early adulthood is important in the genesis of COPD and this study suggests that underweight individuals have a restrictive pattern that could be due to undernutrition with reduced skeletal muscle or smaller lung size.
4. It is important to note that duration of exclusive breast-feeding was significantly shorter (<12 weeks) in participants belonging to the early-low and persistently high trajectories.
5. Western lifestyle is a potential modifiable risk factor for asthma and poor lung function.

### EUROPEAN RESPIRATORY SOCIETY GUIDELINES FOR THE DIAGNOSIS OF ASTHMA IN ADULTS

Louis R, Satia I, Ojanguren I, Schleich F, Bonini M, Tonia T, Rigau D, ten Brinke A, Buhl R, Loukides S, Kocks JWH, Boulet LP, Bourdin A, Coleman C, Needham K, Thomas M, Idzko M, Papi A, Porsbjerg C, Schuermans D, Soriano JB, Usmani OS. **European Respiratory Society Guidelines for the Diagnosis of Asthma in Adults**. *Eur Respir J*. 2022 Feb 15;2101585. doi: 10.1183/13993003.01585-2021. Online ahead of print.

#### Summary

Although asthma is affecting 5-10% of the population, the diagnosis of asthma remains a challenge. A task force (TF) was set up by the ERS to systematically review the literature on the diagnostic accuracy of tests used to diagnose asthma in adult patients and provide recommendation for clinical practice. The TF defined eight PICO questions that were assessed using GRADE approach, utilized the outcomes to develop an

evidenced-based diagnostic algorithm, with recommendations for a pragmatic guideline that took into account real-life patient experiences. The TF support the initial use of spirometry followed, if airway obstruction is present, by bronchodilator reversibility testing. If initial spirometry fails to show obstruction, further tests should be performed in the following order: FeNO, PEF variability or in secondary care, bronchial challenge. The authors present thresholds compatible with an asthma diagnosis for each test. The TF reinforce the priority to undertake spirometry and recognize the value of phenotyping. Measuring gas trapping by body plethysmography in patients with preserved FEV1/FVC ratio deserves further attention. The TF draw attention on the difficulty of making a correct diagnosis in patients receiving ICS or having comorbidities that may obscure the diagnosis.

### Comments

1. There is an urgent need for prospective studies in both primary and secondary care that would combine specific symptoms with spirometry indices expressed as LLN to make a diagnosis of asthma
2. In corticosteroid naïve patients, a cut-off of FeNO  $\leq$  0ppb is supportive of a diagnosis of asthma but a FeNO value  $<40$  ppb does not rule out asthma and similarly high FeNO levels themselves do not define asthma
3. The main advantage of this guideline is that it has been developed with input from patients, the European Lung Foundation, generalists and specialists in both primary and secondary care and respiratory nurse specialist.

### QUANTITATIVE CT METRICS ARE ASSOCIATED WITH LONGITUDINAL LUNG FUNCTION DECLINE AND FUTURE ASTHMA EXACERBATIONS: RESULTS FROM SARP-3

Krings JG, Goss CW, Lew D, Samant M, McGregor MC, Boomer J, Bacharier LB, Sheshadri A, Hall C, Brownell J, Schechtman KB, Peterson S, McEleney S, Mauger DT, Fahy JV, Fain SB, Denlinger LC, Israel E, Washko G, Hoffman E, Wenzel SE, Castro M. **Quantitative CT metrics are associated with longitudinal lung function decline and future asthma exacerbations: Results from SARP-3.** *J Allergy Clin Immunol.* 2021 Sep;148(3):752-762.

### Summary

The authors assessed whether quantitative computed tomography (qCT) metrics are associated with longitudinal decline in lung function and morbidity in asthma. They analyzed 205 qCT scans of adult patients with asthma and using multivariable regression models, they assessed the association of qCT measurements with the outcomes of future change in lung function, future exacerbation rate, and changes in validated measurements of morbidity. The median length of follow-up in this study was 4.3 years. The authors found that participants with more severe airway remodeling, more hyperinflation, and certain lung volume expansion gradation patterns on qCT were more likely to experience future lung function decline. Even after adjustment for covariates, including frequency of prior exacerbations and baseline eosinophil count, patients with more severe airway remodeling, more air trapping and less lung deformation were more likely to experience exacerbations. However, qCT metrics were generally not associated with clinically meaningful changes in asthma control or quality of life.

### Comments

1. Thoracic computed tomography allows a precise description of the anatomy of distal airways including remodeling but, due to the radiation exposure, it can't be performed repeatedly for treatment effects monitoring.
2. There is a need for future studies evaluating if alternative techniques such as forced oscillation technique, able to evaluate distal airway dysfunction, are also associated with future risk of exacerbations and lung function decline.
3. Novel biomarkers that can reliably predict which patients with asthma will experience an accelerated decline in lung function is an issue of utmost importance
4. We must be cautious on the interpretation of airway remodeling in this study (wall area %) as we don't have biopsies to confirm thickening of the basal membrane and because an increase in smooth muscle tone (in case of undertreatment or poor adherence) could also lead to increased wall area %.

## EXPERT CONSENSUS ON THE TAPERING OF ORAL CORTICOSTEROIDS FOR THE TREATMENT OF ASTHMA. A DELPHI STUDY

Suehs CM, Menzies-Gow A, Price D, Bleecker ER, Canonica GW, Gurnell M, Bourdin A. **Expert Consensus on the Tapering of Oral Corticosteroids for the Treatment of Asthma. A Delphi Study.** *Am J Respir Crit Care Med.* 2021;203(7):871-881.

### Summary

There is a need to minimize oral corticosteroid (OCS) use in patients with asthma to prevent their costly and burdensome adverse effects. A modified Delphi method was used to develop expert consensus statements relating to OCS use, tapering, adverse effects, adrenal insufficiency, and patient–physician shared decision-making. Initial statements proposed by experts were categorized, filtered for repetition, and presented back to experts over three ranking rounds to obtain consensus. 131 international experts participated and 296 statements were ranked. Numerous recommendations and guidance regarding appropriate OCS use were established. Experts agreed that OCS tapering should be attempted in all patients with asthma receiving maintenance OCS therapy, with personalization of tapering rhythm and speed. The importance of recognizing adverse effects was also established; however, a unified approach to the assessment of adrenal insufficiency was not reached. In this Delphi study, expert consensus statements were generated on OCS use, tapering, adverse-effect screening, and shared decision-making, which may be used to inform clinical practice. Areas of non-consensus also were identified, highlighting uncertainty among the experts around some aspects of OCS use in asthma, such as adrenal insufficiency, which underscores the need for further research in these domains.

### Comments

1. Depending on local reimbursement criteria, eligibility of patients with severe asthma for biologics sometimes require OCS tapering to allow identification of eosinophilic inflammation; whether an immediate withdrawal or a tapering is the best option remains to be evaluated.

2. It remains to be determined whether OCS tapering should be guided by biomarkers, especially in patients treated with biologics.
3. Future studies must be performed to identify predictors of failure to taper OCS, that could individualize the rhythm and speed of OCS tapering.

## RISANKIZUMAB IN SEVERE ASTHMA

Brightling CE, Nair P, Cousins DJ, Louis R, Singh D. **Risankizumab in Severe Asthma.** *NEJM* 2021 ;385 :1669-79.

### Summary

Interleukin-23 promotes Th17-cell proliferation, neutrophil recruitment and Th2 cytokine production. This phase 2a, multicenter, randomized, double-blind, placebo-controlled, 24-week trial assessed the efficacy and safety of risankizumab, an anti-interleukin-23p19 monoclonal antibody in adults with severe asthma. Eligible patients had at least 2 exacerbations or one severe exacerbation resulting in hospitalization or emergency visit. FEV1 was between 40 and 85% and the smoking history was less than 10 pack-years. A total of 105 patients received 90mg risankizumab subcutaneously once every 4 weeks while 109 were assigned to placebo group. The primary endpoint was the time to first asthma worsening (decrease in PEF, increase in rescue medication use, exacerbation or increase in ACQ5>0.75). The time to first asthma worsening was shorter with risankizumab than with placebo (40 days vs 86 days, p=0.03) and the annualized rate of asthma worsening was higher. Risankizumab did not affect sputum cell counts, but down-regulated genes involved in the activation of NK cells and cytotoxic T cells and the activation of the type 1 helper T and type 17 helper T transcription factors. These findings support the view that risankizumab exerted biologic effect on airway immunity, which may have contributed to the poor clinical outcome.

### Comments

1. Risankizumab provides an example that asthma can worsen with the use of biologics.
2. Risankizumab therapy downregulates innate airway immunity without any effect on the sputum cell counts.

3. The lack of benefit with risankizumab in asthma contrasts with the good clinical efficacy in psoriasis and Crohn's disease.
4. These findings challenge the current understanding of the detrimental role that Th17- and interleukin-23-mediated pathways play in the pathogenesis of severe asthma as IL-23 might be protective against loss of asthma control
5. Targeting the interleukin-23 and Th17 axis with risankizumab can reduce development of pathogenic Th17 cells; however, interleukin-23 has only a limited auxiliary role in amplifying type 2 responses.

### EFFICACY AND SAFETY OF ITEPEKIMAB IN PATIENTS WITH MODERATE-TO-SEVERE ASTHMA

Wechsler ME, Ruddy MDK, Pavord ID, Israel E, Rabe KF, Ford LB, Maspero JF, Abdulai RM, Hu CC, Martincova R, Jessel A, Nivens MC, Amin N, Weinreich DM, Yancopoulos GD, Goulaouic H. **Efficacy and Safety of Itepekimab in Patients with Moderate-to-Severe Asthma.** *NEJM* 2021; 385 :1656-1668.

#### Summary

Itepekimab is a human IgG4P monoclonal antibody against IL-33. In this phase 2 trial, they randomly assigned 296 moderate-to-severe asthmatics to receive 300mg subcutaneous itepekimab, itepekimab plus dupilumab (both at 300 mg), dupilumab (300 mg), or placebo every 2 weeks for 12 weeks. Eligibility criteria were pre-BD FEV1 value between 50 and 85% predicted and at least one severe asthma exacerbation. After randomization, LABA was discontinued at week 4, and inhaled glucocorticoids (ICS) were tapered over weeks 6 through 9. Primary endpoint was an event indicating a loss of asthma control defined as a reduction of at least 30% in the morning PEF or at least 6 additional use of rescue medication on 2 consecutive days, an increase by four of the most recent doses of ICS or an asthma exacerbation. Patient with a loss of asthma control returned to maintenance LABA+ICS and trial drug was discontinued. By 12 weeks, loss of asthma control occurred in 22% of itepekimab (OR vs placebo, 0.42), 27% of combination (OR:0.52), and 19% of dupilumab (OR: 0.33), as compared with 41% in placebo group. The combination of itepekimab and dupilumab was not superior to either treatment alone. The incidence of adverse events was similar in all four trial groups.

#### Comments

1. IL-33 initiates downstream signaling and activates cells of both the innate and adaptive immune systems resulting in type 2 and non-type 2 inflammation, and this is the first study showing the impact of targeting IL-33 in severe asthma.
2. The observation that dupilumab but not itepekimab showed an increase in post-BD FEV1 as compared with placebo at week 12, could be explained by the fact that Dupilumab inhibits more type 2 inflammation that is elicited by withdrawal from ICS and it suggests the greater impact of IL-13 on airway smooth muscle as compared to IL-33.
3. Improvement in ACQ5 (and AQLQ) observed in the itepekimab group was modest and similar to that provided by dupilumab, with 56% reaching minimal clinically important difference as compared to 38% in placebo group.
4. Overall combination of itepekimab and dupilumab did not bring superior effect than each compound used alone.
5. Most frequently encountered side effects were similar to those observed with anti-IL5 and anti-IL5(R) such as nasopharyngitis, rhinitis, nausea, and back pain

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## Sleep Medicine

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### SLEEP APNEA TREATMENT

Meyers D, Bierman A., Chang C., Berliner, E. **Draft Technology Assessment: Continuous Positive Airway Pressure Treatment for Obstructive Sleep Apnea by Agency for Healthcare Research and Quality (AHRQ).**

2021. Available from:

<https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/drafts-for-review/sleep-apnea-draftreport.pdf>

### Summary

Continuous positive airway pressure (CPAP) is the most common treatment for obstructive sleep apnea (OSA). The Agency for Healthcare Research and Quality (AHRQ) performed a systematic review and meta-analysis to assess the long-term effect of CPAP on clinical outcomes and the role of OSA severity as measured by the apnea-hypopnea index (AHI). They included 47 randomized clinical trials (RCT) and non-randomized comparative studies with changes in the AHI and  $\geq$  6-month follow-up of outcomes. The outcomes included: death, cardiovascular and cerebrovascular events, motor vehicle accidents, incident diabetes, depression, cognitive function, etc. In RCTs, they report low strength of evidence (SoE) that CPAP does not affect the risk of all-cause mortality (effect size, ES 0.87 95% confidence interval, CI 0.58 to 1.29), myocardial infarction (ES 1.06, 0.72 to 1.56), stroke (ES 0.86, 0.59 to 1.29), or composite cardiovascular outcomes. The authors report insufficient evidence regarding the effect of CPAP on angina, congestive heart failure, stroke, or atrial fibrillation. Similar findings were noted for incident diabetes and risk of motor vehicle accidents. The authors identified no studies that evaluated the AHI as a predictor of long-term outcomes. The variability of AHI definitions precluded valid cross-study evaluation.

The authors conclude: “The published evidence mostly does not support that CPAP prescription affects long-term, clinically important outcomes.”

### Comments

1. This report summarizes the evidence of the RCTs which do not show impact of CPAP on mortality and secondary prevention of cardiovascular and cerebrovascular disease.
2. The authors' conclusion does not reflect all of the available evidence regarding key clinically meaningful outcomes. The analysis did not include patient-centered outcomes including sleepiness and “hard” clinically important outcomes such as improvement in blood pressure.
3. Because sleepy individuals are most at risk of motor vehicle accidents and are thus excluded from RCTs, conclusions about CPAP's effect on this outcome cannot be drawn from secondary analyses of current RCTs.
4. Lack of predictive value of the changes in AHI highlights the need for a) novel physiologic markers of OSA consequences and b) consistent definitions and use of such markers in future RCTs
5. The findings reinforce the need to include individuals most at risk of adverse outcomes (e.g., sleepy individuals) in future RCTs

### SLEEP APNEA TREATMENT

Traaen GM, Aakerøy L, Hunt TE, Øverland B, Bendz C, Sande LØ, Aakhus S, Fagerland MW, Steinshamn S, Anfinson OG, Massey RJ, Broch K, Ueland T, Akre H, Loennechen JP, Gullestad L. **Effect of Continuous Positive Airway Pressure on Arrhythmia in Atrial Fibrillation and Sleep Apnea: A Randomized Controlled Trial.** *Am J Respir Crit Care Med.* 2021 Sep 1;204(5):573-582.

## Summary

OSA and atrial fibrillation commonly coexist, and their relationship is likely bidirectional. It is unknown if CPAP reduces the duration of atrial fibrillation in patients with OSA and AF. This RCT study randomized patients with paroxysmal AF (pAF) and OSA (AHI  $\geq$  15 events per hour) referred for catheter ablation to CPAP vs. usual care for five months. The RCT enrolled those with a body mass index of  $<$  40kg/m<sup>2</sup>, without excessive daytime sleepiness (Epworth sleepiness scale, ESS  $<$  15), and tolerant of CPAP for over one week (n = 109). The primary outcome was the mean time in pAF over the last three months of the intervention assessed by implanted loop recorder. Sixty-seven percent of participants used the treatment for  $\geq$  4 hours/night in the CPAP arm. The median AHI decreased from 23.1 to 2.3 events/hour. The mean time in pAF decreased from 5.6% to 4.1% in the CPAP arm (n = 55) and 5.0% to 4.3% in the usual care arm. The difference was not statistically significant. There were no significant changes in sleepiness (mean ESS 8.2 to 7.1) or sleep apnea-related quality of life (mean functional outcomes of sleep questionnaire scores 17.4 to 17.6, scale range 0 to 20).

## Comments

1. This study targets a key question in the field: Does the treatment of OSA with CPAP improve AF outcomes? The findings suggest that it may not.
2. CPAP therapy in this population is a challenge. Despite rigorous protocols of the investigators, only 68% could tolerate CPAP for 1 week, and of those, only 67% used it for  $\geq$  4 hours/night (regular use by only 46% of patients).
3. The findings are limited to patients with a very low burden of AF (5%). The study may be underpowered with prior reports of pAF burden of 18% in patients undergoing ablation. Similarly, five months may not be long enough to detect changes. It takes over six months for changes in left atrial size to be detected after other AF treatments (e.g., ablation).
4. Akin to implications from the AHRQ report, findings suggest that patients most likely to benefit from CPAP need to be targeted (e.g., sleepy individuals with quality of life affected by OSA).
5. The AHI may not be the best marker to assess risk of OSA and impact of CPAP.

## SLEEP APNEA RISK ASSESSMENT

Azarbarzin A, Sands SA, Younes M, Taranto-Montemurro L, Sofer T, Vena D, Alex RM, Kim SW, Gottlieb DJ, White DP, Redline S, Wellman A. **The Sleep Apnea-Specific Pulse-Rate Response Predicts Cardiovascular Morbidity and Mortality.** *Am J Respir Crit Care Med.* 2021 Jun 15;203(12):1546-1555.

## Summary

The AHI does not consistently predict cardiovascular disease (CVD) risk in patients with OSA. This study assessed whether a novel metric of OSA's physiological consequence, the average pulse-rate response to apneas and hypopneas (DHR), is a valuable marker. Investigators measured DHR from pulse oximetry. They tested the relationship between DHR and non-fatal and fatal CVD outcomes in two independent cohorts: MESA (Multi-Ethnic Study of Atherosclerosis) and the SHHS (Sleep Heart Health Study). In MESA, investigators observed a U-shaped relationship between DHR and subclinical CVD markers (coronary artery calcium, Framingham risk score). Both lowest ( $<$  6 beats/minute) and highest ( $>$  10 beats/minute) quartiles of DHR were at increased risk compared to mid-range DHR in cross-sectional analyses. In the SHHS with a mean follow-up of 10.7 years, the low and high DHR translated to a 26% and 29% increased overall mortality risk compared to the mid-range DHR group. Only the high DHR was associated with an increased risk of non-fatal CVD and overall CVD (60% and 68%, respectively). The findings were independent of AHI, time spent below 90% arterial oxygen saturation, and baseline CVD risk. Finally, the risk for all outcomes was greatest with high DHR in those with a high hypoxic burden.

## Comments

1. This study shows that the intensity of OSA's physiological consequences is not linearly related to the risk for CVD and death. This observation may explain CPAP therapy's "negative" trials to date that used a single AHI cut-off.
2. A relationship between high DHR and CVD outcomes in OSA is plausible. The high DHR may reflect either more severe respiratory events or an overly active autonomic system (or both).
3. Notably, a low DHR may also be a predictor of negative outcomes. This observation may be due to

an under-responsive cardiovascular system or established heart disease or diabetes. Supporting this, individuals with low DHR were older with a higher prevalence of CVD in this analysis.

4. Prospective validation and evaluation of response to CPAP are needed. If relationships are confirmed, DHR may be a valuable metric to select those most at risk of CVD for RCTs of CPAP therapy.

### IMPROVING METABOLIC OUTCOMES THROUGH SLEEP

Tasali E, Wroblewski K, Kahn E, Kilkus J, Schoeller DA. **Effect of Sleep Extension on Objectively Assessed Energy Intake Among Adults With Overweight in Real-life Settings: A Randomized Clinical Trial.** *JAMA Intern Med.* Published online February 07, 2022. doi:10.1001/jamainternmed.2021.8098

#### Summary

Short sleep duration is a risk factor for obesity. Can this risk be alleviated by extending sleep duration? In this single-center RCT, 80 young men and women (21 – 40 years) with body mass index of 25.0 – 29.9 kg/m<sup>2</sup> and habitual sleep duration of < 6.5 hours/night were randomized to sleep hygiene counseling (n = 40) or to a continuation of regular sleep. Those with OSA, insomnia, acute or chronic medical conditions were excluded. Sleep hygiene intervention was an individualized 60-minute session including techniques to improve environmental factors (e.g., noise, light) and sleep-wake schedules to accommodate sleep extension on day 0 and 15-minute counseling sessions on days 1 and 7. Investigators objectively measured sleep using actigraphy during the 2 week-run in period and during the 2 weeks of intervention. The primary outcome was a change in energy intake from baseline, measured as a sum of total energy use and change in body energy stores. Sleep duration increased in the intervention group by an average of 1.2 (95% CI 1.0, 1.4) hours/night compared to controls. Energy intake decreased by 270 (95% CI 147, 393) kCal/day. Energy expenditure did not change. The intervention group lost 0.5kg while the control group gained 0.4kg during the study.

#### Comments

1. The study suggests that preventing metabolic dysfunction by modifying sleep is possible. It corrects the societal misconception that more sleep

means gaining weight because less energy is exerted while sleeping.

2. Personalized sleep hygiene counseling includes common-sense recommendations for better sleep. In this study, 90 minutes of sleep hygiene intervention extended objectively measured sleep duration by a meaningful 1.2-hours per night—an important result.
3. Given that obesity plays a key role in outcomes of many respiratory disorders (e.g., asthma, pulmonary hypertension), a low burden sleep intervention may be a valuable tool to reduce meaningfully (~ 10%) the caloric intake.
4. Studies are needed to test the effects of sleep hygiene in those with comorbidities and those who are not sleep deprived.
5. Whether outcomes are sustained or diminish over time is not known.

### INSOMNIA IN OLDER ADULTS: TREATMENT

Irwin MR, Carrillo C, Sadeghi N, Bjurstrom MF, Breen EC, Olmstead R. **Prevention of Incident and Recurrent Major Depression in Older Adults With Insomnia: A Randomized Clinical Trial.** *JAMA Psychiatry.* 2022;79(1):33–41. doi:10.1001/jamapsychiatry.2021.3422

#### Summary

Older adults with insomnia are at a high risk of depression, affecting outcomes in many chronic respiratory conditions. Can treatment of insomnia in this population reduce the risk of developing depression? In this parallel-group, assessor-blinded RCT of 291 adults 60 years or older with insomnia, 156 individuals were randomized to 2 months of cognitive-behavioral therapy for insomnia (CBTi) in group sessions. The remainder received sleep education therapy (SET). The outcome was time to incident or recurrent major depressive disorder (diagnosed via structured clinical interview, DSM-5) over 3 years of follow-up. The average participant age was 70 years, sixty percent were women, and 82% were white. Fifty percent in the CBTi arm and 38% in the SET arm achieved insomnia remission at 2 months. This difference attenuated but remained significant at 3 years (26% vs. 19%). New depression occurred in 12% of the CBTi group compared to 26% in the SET group, with a 49% (95% CI 0.1 to 0.9) reduction in the likelihood of

depression. Findings persisted after adjustment for sex, education, comorbidities, and history of depression. The number needed to treat to prevent one case of depression was 7.1.

### Comments

1. Assessing for insomnia in our practice is essential. One in 4 participants from the control (SET) arm developed depression within 3 years in this study. Because depression increases the risk of exacerbations of respiratory disorders (e.g., COPD), heart failure, cognitive decline, and dementia alike, identifying insomnia as a potential therapeutic target is clinically relevant.
2. The study suggests that CBTi therapy for insomnia in an older adult is possible and efficacious. However, other interventions are needed. Only 26% remained insomnia free at 3 years (compared to 19% in the control arm).
3. Treating sleep problems can prevent depression in the elderly. Two months of CBTi in seven patients with insomnia can prevent one new case of depression.
4. Caution is warranted since the study participants were relatively healthy (e.g., non-obese, without severe chronic cardiac or respiratory conditions).
5. If findings are confirmed in effectiveness trials, CBTi in personal, phone, or digital form may offer a viable avenue to prevent depression in the elderly.

### OTHER ARTICLES OF INTEREST

#### Precision Sleep Medicine

Zinchuk AV, Chu JH, Liang J, Celik Y, Op de Beeck S, Redeker NS, Wellman A, Yaggi HK, Peker Y, Sands SA.

**Physiological Traits and Adherence to Sleep Apnea Therapy in Individuals with Coronary Artery Disease.** *Am J Respir Crit Care Med.* 2021 Sep 15;204(6):703-712. doi: 10.1164/rccm.202101-0055OC. PMID: 34156917; PMCID: PMC8521693.

Parekh A, Tolbert TM, Mooney AM, Ramos-Cejudo J, Osorio RS, Trembl M, Herkenrath SD, Randerath WJ, Ayappa I, Rapoport DM. **Endotyping Sleep Apnea One Breath at a Time: An Automated Approach for Separating Obstructive from Central Sleep-disordered Breathing.** *Am J Respir Crit Care Med.* 2021 Dec 15;204(12):1452-1462. doi: 10.1164/rccm.202011-4055OC. PMID: 34449303; PMCID: PMC8865720.

#### Insomnia

McCurry SM, Zhu W, Von Korff M, et al. **Effect of Telephone Cognitive Behavioral Therapy for Insomnia in Older Adults With Osteoarthritis Pain: A Randomized Clinical Trial.** *JAMA Intern Med.* 2021;181(4):530-538. doi:10.1001/jamainternmed.2020.9049

Yardley J, Kärppä M, Inoue Y, Pinner K, Perdomo C, Ishikawa K, Filippov G, Kubota N, Moline M. **Long-term effectiveness and safety of lemborexant in adults with insomnia disorder: results from a phase 3 randomized clinical trial.** *Sleep Med.* 2021 Apr;80:333-342. doi: 10.1016/j.sleep.2021.01.048. Epub 2021 Feb 1. PMID: 33636648.

#### Sleep and COVID

Morin CM, Bjorvatn B, Chung F, Holzinger B, Partinen M, Penzel T, Ivers H, Wing YK, Chan NY, Merikanto I, Mota-Rolim S, Macêdo T, De Gennaro L, Léger D, Dauvilliers Y, Plazzi G, Nadorff MR, Bolstad CJ, Sieminski M, Benedict C, Cedernaes J, Inoue Y, Han F, Espie CA. **Insomnia, anxiety, and depression during the COVID-19 pandemic: an international collaborative study.** *Sleep Med.* 2021 Nov;87:38-45. doi: 10.1016/j.sleep.2021.07.035. Epub 2021 Aug 4. PMID: 34508986; PMCID: PMC8425785.

Cheng P, Casement MD, Kalmbach DA, Castelan AC, Drake CL. **Digital cognitive behavioral therapy for insomnia promotes later health resilience during the coronavirus disease 19 (COVID-19) pandemic.** *Sleep.* 2021 Apr 9;44(4):zsa258. doi: 10.1093/sleep/zsa258. PMID: 33249492; PMCID: PMC7798633.

Gaspar LS, Hesse J, Yalçın M, Santos B, Carvalhas-Almeida C, Ferreira M, Moita J, Relógio A, Cavadas C, Álvaro AR. **Long-term continuous positive airway pressure treatment ameliorates biological clock disruptions in obstructive sleep apnea.** *EBioMedicine.* 2021 Mar;65:103248. doi: 10.1016/j.ebiom.2021.103248. Epub 2021 Feb 26. PMID: 33647771; PMCID: PMC7920825.

Meltzer LJ, Wahlstrom KL, Plog AE, Strand MJ. **Changing school start times: impact on sleep in primary and secondary school students.** *Sleep.* 2021 Jul 9;44(7):zsab048. doi: 10.1093/sleep/zsab048. PMID: 33855446; PMCID: PMC8271142.

## Health Disparities

Li X, Sotres-Alvarez D, Gallo LC, Ramos AR, Aviles-Santa L, Perreira KM, Isasi CR, Zee PC, Savin KL, Schneiderman N, Wassertheil-Smoller S, Sofer T, Daviglius M, Redline S. **Associations of Sleep-disordered Breathing and Insomnia with Incident Hypertension and Diabetes. The Hispanic Community Health Study/Study of Latinos.** *Am J Respir Crit Care Med.* 2021 Feb 1;203(3):356-365. doi: 10.1164/rccm.201912-2330OC. PMID: 32758008; PMCID: PMC7874314.

Corrigan J, Tsai WH, Ip-Buting A, Ng C, Ogah I, Peller P, Sharpe H, Laratta C, Pendharkar SR. **Treatment outcomes among rural and urban patients with obstructive sleep apnea: a prospective cohort study.** *J Clin Sleep Med.* 2021 Nov 29. doi: 10.5664/jcsm.9776. Epub ahead of print. PMID: 34823649.

## Sleep Apnea

Pascoe M, Wang L, Aylor J, et al. **Association of Hypoglossal Nerve Stimulation With Improvements in Long-term, Patient-Reported Outcomes and Comparison With Positive Airway Pressure for Patients With Obstructive Sleep Apnea.** *JAMA Otolaryngol Head Neck Surg.* 2022;148(1):61-69. doi:10.1001/jamaoto.2021.2245

Perger E, Taranto Montemurro L, Rosa D, Vicini S, Marconi M, Zanotti L, Meriggi P, Azarbarzin A, Sands SA, Wellman A, Lombardi C, Parati G. **Reboxetine Plus Oxybutynin for OSA Treatment: A 1-Week, Randomized, Placebo-Controlled, Double-Blind Crossover Trial.** *Chest.* 2022 Jan;161(1):237-247. doi: 10.1016/j.chest.2021.08.080. Epub 2021 Sep 20. PMID: 34543665.

## Hypersomnia

Bassetti CLA, Kallweit U, Vignatelli L, Plazzi G, Lecendreux M, Baldin E, Dolenc-Groselj L, Jennum P, Khatami R, Manconi M, Mayer G, Partinen M, Pollmächer T, Reading P, Santamaria J, Sonka K, Dauvilliers Y, Lammers GJ. **European guideline and expert statements on the management of narcolepsy in adults and children.** *J Sleep Res.* 2021 Dec;30(6):e13387. doi: 10.1111/jsr.13387. Epub 2021 Jun 25. PMID: 34173288.

Bogan RK, Thorpy MJ, Dauvilliers Y, Partinen M, Del Rio Villegas R, Foldvary-Schaefer N, Skowronski R, Tang L, Skobieranda F, Šonka K. **Efficacy and safety of calcium, magnesium, potassium, and sodium oxybates (lower-sodium oxybate [LXB]; JZP-258) in a placebo-controlled, double-blind, randomized withdrawal study in adults with narcolepsy with cataplexy.** *Sleep.* 2021 Mar 12;44(3):zsaa206. doi: 10.1093/sleep/zsaa206. Erratum in: *Sleep.* 2021 Jul 9;44(7): Erratum in: *Sleep.* 2021 Nov 12;44(11): PMID: 33184650; PMCID: PMC7953213.

## Neurocognition

Dunietz GL, Chervin RD, Burke JF, Conceicao AS, Braley TJ. **Obstructive sleep apnea treatment and dementia risk in older adults.** *Sleep.* 2021 Sep 13;44(9):zsab076. doi: 10.1093/sleep/zsab076. PMID: 33769542; PMCID: PMC8436135.

Beaudin AE, Raneri JK, Ayas NT, Skomro RP, Smith EE, Hanly PJ; Canadian Sleep and Circadian Network. **Contribution of hypercapnia to cognitive impairment in severe sleep-disordered breathing.** *J Clin Sleep Med.* 2022 Jan 1;18(1):245-254. doi: 10.5664/jcsm.9558. PMID: 34286691; PMCID: PMC8807902.

## Disparities in Pulmonary and Critical Care Disease

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### ASTHMA AND ALLERGY DISPARITIES

Martinez A, de la Rosa R, Mujahid M, Thakur N.

**Structural racism and its pathways to asthma and atopic dermatitis.** *Journal of Allergy and Clinical Immunology*. 2021 Nov 1;148(5):1112-20.

#### Summary

Martinez and colleagues discuss how structural racism is a root cause of asthma and atopic disease disparities and provide a conceptual framework that depicts the distal and proximal effects of structural racism on asthma and atopic disease outcomes. The authors highlight the role of several structural racism variables on asthma and atopic disease, including but not limited to, the role of residential segregation, social and economic position, environmental justice variables, interpersonal racism and discrimination, and mass incarceration on outcomes. The authors also hypothesize biological pathways (e.g., TH2, TH17, microbiome, epigenetics) that can explain the association between structural racism and asthma outcomes.

#### Comments

1. Residential segregation, socioeconomic position, and incarceration are examples of upstream pathways of structural racism.
2. Proximal pathways of structural racism include physical factors such as environmental hazards, built environmental, housing quality, occupational exposure.
3. Social environment factors such as wealth gap, financial strain, neighborhood violence, adverse childhood experiences are also examples of proximal structural racism pathways.
4. Upstream and proximal structural racism pathways affect the innate and adaptive immune response and the stress response to ultimately affect asthma outcomes and contribute to health disparities.

### COPD DISPARITIES

Baugh AD, Shiboski S, Hansel NN, Ortega V, Barjakteravic I, Barr RG, Bowler R, Comellas AP, Cooper CB, Couper D, Criner G. **Reconsidering the Utility of Race-Specific Lung Function Prediction Equations.** *American journal of respiratory and critical care medicine*. 2021 Dec 16(ja).

#### Summary

Baugh et. al., assessed whether race-specific lung function estimates contributed to racial disparities in COPD outcomes in Black adults. The authors used linear regression modeling to examine the relationship between spirometry parameters and COPD outcomes in patients with COPD and at risk for COPD using the SPIROMICS cohort (N=2,652). The lung function of Black patients differed based on equation used. Blacks had better lung function using a race-specific equation (FEV1 %predicted, 76.8% vs. 71.8%, p=0.02) and worse lung function when using Hankinson's Non-Hispanic White equation (FEV1 %predicted, 64.7% vs 71.8%, p<0.001) or the Global Lung Initiative's other race equation (FEV1%predicted, 70.0% vs 77.9%, p<0.001). Race-specific lung function prediction equations were inferior to universally applied alternatives.

#### Comments

1. FEV1 percent predicted varies based on equation used.
2. Universally applied equations are superior to race-specific equations in estimating the association between lung function and COPD outcomes.
3. The study analysis would be augmented if they incorporated ancestry in the analysis.

### CRITICAL CARE DISPARITIES

Ashana DC, Anesi GL, Liu VX, Escobar GJ, Chesley C, Eneanya ND, Weissman GE, Miller WD, Harhay MO, Halpern SD. **Equitably allocating resources during crises: racial differences in mortality prediction models.** *Am J Respir Crit Care Med*. 2021 Jul 15;204(2):178-86.

## Summary

Ashana et. al, tested the prognostic accuracy of the SOFA score and Laboratory-based Acute Physiology Score (LAPS2) among 113,158 Black and White patients admitted with sepsis or acute respiratory failure at 27 hospitals from 2013-2018. They calculated the discrimination and calibration for in-hospital mortality. Of the 113,158 included patients, 27,644 (24.4%) were Black. Compared to white patients, Black patients were younger (mean age 61.7 vs 67.7,  $p < 0.001$ ), more likely to be female, had higher SOFA scores (3.1 vs 2.9,  $p < 0.001$ ), lower LAPS2 (102.2 vs 103.1,  $p < 0.001$ ), and lower in-hospital mortality (7.5% vs 8.6%,  $p < 0.001$ ). Both the LAPS2 and SOFA underestimated in-hospital mortality for White patients and overestimated mortality for Black patients. In a simulation using categorical SOFA groups, 81.6% of Black patients were included in lower priority crisis standard of care categories and 9.4% of all Black patients were incorrectly excluded from high priority categories. Of note, the SOFA score that excluded creatinine reduced racial misclassification.

## Comments

1. Black patients had higher SOFA scores but lower mean LAPS2.
2. Black patients had lower unadjusted and adjusted in-hospital mortality.
3. SOFA had poor discrimination for in-hospital mortality that worsened when using crisis standards of care SOFA score categories.
4. LAPS2 had acceptable discrimination for in-hospital mortality but discrimination decreased when LAPS2 was categorized into fewer categories.

## LUNG CANCER DISPARITIES

Ritzwoller DP, Meza R, Carroll NM, Blum-Barnett E, Burnett-Hartman AN, Greenlee RT, Honda SA, Neslund-Dudas C, Rendle KA, Vachani A. **Evaluation of population-level changes associated with the 2021 US Preventive Services Task Force lung cancer screening recommendations in community-based health care systems.** *JAMA network open.* 2021 Oct 1;4(10):e2128176-.

## Summary

Ritzwoller et. al., compared the changes in sex, race and ethnicity, sociodemographic, and comorbidities of patients eligible for the 2013 and 2021 USPSTF Lung

Cancer Screening (LCS) program. They analyzed a historical cohort from 5 community-based health systems from 2010-2019. The cohort included 341,163 patients aged 50-80. There were 34,528 patients eligible for the 2013 LCS criteria. The 2021 LCS criteria expanded eligibility to 18,533 patients—a 53.5% increase. Over thirty percent of the newly eligible patients were 50-54 years (31.5%,  $N=5,833$ ). Compared to the 2013 cohort, the 2021 cohort was predominately women ( $N=9,631$ , 52%) and included a higher proportion of racial and ethnic minoritized patients. There was an over 60% increase in Asian/Native Hawaiian/Pacific Islander, Hispanic, and non-Hispanic Black patients compared to a 49.0% increase in non-Hispanic White patients. There was also a higher relative increase in women compared to men (61.2% vs 47.4%). The 2021 LCS criteria also identified more incidences of lung cancer (30%,  $N=379$ ).

## Comments

1. Almost a third of the expanded 2021 cohort was 50-54 years old.
2. The 2021 cohort included a higher proportion of females, racial and ethnic minoritized patients, low income patients, and healthier patients.
3. The 2021 guidelines identified more lung cancer diagnoses in racial and ethnic minoritized patients, females, and low SES groups.

## OTHER ARTICLES OF INTEREST

### Asthma Disparities

Jiang Y, Farrell AK, Tobin ET, Mair-Meijers HE, Wildman DE, Luca F, Slatcher RB, Zilioli S. **Socioeconomic status, financial stress, and glucocorticoid resistance among youth with asthma: Testing the moderation effects of maternal involvement and warmth.** *Brain, behavior, and immunity.* 2021 Aug 1;96:92-9.

Yan Q, Forno E, Herrera-Luis E, Pino-Yanes M, Qi C, Rios R, Han YY, Kim S, Oh S, Acosta-Pérez E, Zhang R. **A genome-wide association study of severe asthma exacerbations in Latino children and adolescents.** *European Respiratory Journal.* 2021 Apr 1;57(4).

Curry CW, Felt D, Kan K, Ruprecht M, Wang X, Phillips II G, Beach LB. **Asthma Remission Disparities Among US Youth by Sexual Identity and Race/Ethnicity, 2009-2017.** *J Allergy Clin Immunol Pract.* 2021 Sep 1;9(9):3396-406.

### COPD Disparities

Woo H, Brigham EP, Allbright K, Ejike C, Galiatsatos P, Jones MR, Oates GR, Krishnan JA, Cooper CB, Kanner RE, Bowler RP. **Racial segregation and respiratory outcomes among urban Black residents with and at risk of chronic obstructive pulmonary disease.** *American journal of respiratory and critical care medicine.* 2021 Sep 1;204(5):536-45.

### Lung Cancer Disparities

Pu CY, Lusk CM, Neslund-Dudas C, Gadgeel S, Soubani AO, Schwartz AG. **Comparison between the 2021 USPSTF lung cancer screening criteria and other lung cancer screening criteria for racial disparity in eligibility.** *JAMA oncology.* 2022 Jan 13

Núñez ER, Caverly TJ, Zhang S, Glickman ME, Qian SX, Boudreau JH, Slatore CG, Miller DR, Wiener RS. **Adherence to follow-up testing recommendations in US veterans screened for lung cancer, 2015-2019.** *JAMA Network Open.* 2021 Jul 1;4(7):e2116233-.

Pasquinelli MM, Tammemägi MC, Kovitz KL, Durham ML, Deliu Z, Guzman A, Rygalski K, Liu L, Koshy M, Finn P, Feldman LE. **Addressing sex disparities in lung cancer screening eligibility: USPSTF vs PLCOm2012 criteria.** *Chest.* 2022 Jan 1;161(1):248-56.

Charlot M, Stein JN, Damone E, Wood I, Forster M, Baker S, Emerson M, Samuel-Ryals C, Yongue C, Eng E, Manning M. **Effect of an antiracism intervention on racial disparities in time to lung cancer surgery.** *Journal of Clinical Oncology.* 2022 Feb;JCO-21.

Charlot M, Stein JN, Damone E, Wood I, Forster M, Baker S, Emerson M, Samuel-Ryals C, Yongue C, Eng E, Manning M. **Effect of an antiracism intervention on racial disparities in time to lung cancer surgery.** *Journal of Clinical Oncology.* 2022 Feb;JCO-21.

### Critical Care Disparities

Riviello ED, Dechen T, O'Donoghue AL, Cocchi MN, Hayes MM, Molina RL, Moraco NH, Mosenthal A, Rosenblatt M, Talmor N, Walsh DP. **Assessment of a crisis standards of care scoring system for resource prioritization and estimated excess mortality by race, ethnicity, and socially vulnerable area during a regional surge in COVID-19.** *JAMA network open.* 2022 Mar 1;5(3):e221744-.

### Thoracic Surgery Disparities

Lee AC, Madariaga ML, Liao C, Ferguson MK. **Gender bias in judging frailty and fitness for lung surgery.** *The Annals of thoracic surgery.* 2021 Dec 10.

### Other Disparities

Ramsey NB, Apter AJ, Israel E, Louisias M, Noroski LM, Nyenhuis SM, Ogbogu PU, Perry TT, Wang J, Davis CM. **Deconstructing the Way We Use Pulmonary Function Test Race-Based Adjustments.** *The Journal of Allergy and Clinical Immunology: In Practice.* 2022 Feb 17.

Gaffney AW, Himmelstein DU, Christiani DC, Woolhandler S. **Socioeconomic inequality in respiratory health in the US From 1959 to 2018.** *JAMA Internal Medicine.* 2021 Jul 1;181(7):968-76.

## General Critical Care

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### FLUID ADMINISTRATION IN THE ICU

Finfer S, Micallef S, Hammond N, Navarra L, Bellomo R, Billot L, Delaney A, Gallagher M, Gattas D, Li Q, Mackle D, Mysore J, Saxena M, Taylor C, Young P, Myburgh J; PLUS Study Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group; PLUS Study Investigators and Australian New Zealand Intensive Care Society Clinical Trials Group. **Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults.** *N Engl J Med.* 2022 Mar 3;386(9):815-826. doi: 10.1056/NEJMoa2114464. Epub 2022 Jan 18. PMID: 35041780.

#### Summary

Finfer and colleagues report the results of a double-blind, randomized, controlled trial, of critically ill adults who clinicians intended to give an i.v. fluid bolus and patient expected to stay in ICU  $\geq 48$  hrs (exclusion criteria: disqualifying fluid resuscitation, TBI, specific fluid requirements, pre-morbid life expectancy < 90 days), assigned to receive balanced multielectrolyte solution (BMES: Plasma-Lyte 148) or saline. A total of 5037 patients were recruited from 53 ICUs in Australia and New Zealand: 2433 patients to the BMES group and 2413 patients to the saline group. Prior to randomization, 56% and 23% of patients in the BMES and saline groups, respectively, received 500 mLs or more of unassigned study fluid. Subsequently, approximately 96% of patients received their assigned fluid for a median volume of trial fluid received was 3.9 L in the BMES group as compared to 3.7 L in the saline group.

530 deaths were reported in each group within 90 days (difference of -0.15 percentage points, 95% CI -3.60 to 3.30;  $P = 0.90$ ). With regards to secondary outcomes no differences were seen between groups in new renal-replacement therapy or serum creatinine level within 7 days of ICU stay or in days alive and free of mechanical ventilation/vasopressors, days alive out of ICU or out of

hospital. Finally, there were no meaningful differences in adverse and serious adverse events between groups.

#### Comments

1. No difference in outcome with adjustment for important baseline characteristics.
2. No heterogeneity in the effect of fluid assignment on 90-day mortality in any of predefined subgroups (severity of illness, presence of sepsis, kidney injury, age, sex, and ICU admission post-surgery).
3. Rigorous statistical analyses to account for possible crossover effects; no difference found in primary finding of no difference in within 90-day risk of death (inverse probability analysis).
4. Important trial to illustrate the impact of COVID-19 pandemic on non-COVID related research, forthright publication of modified statistical plan.

### PRE-HOSPITAL BLOOD PRODUCT ADMINISTRATION IN TRAUMATIC HEMORRHAGE

Crombie N, Doughty HA, Bishop JRB, Desai A, Dixon EF, Hancox JM, Herbert MJ, Leech C, Lewis SJ, Nash MR, Naumann DN, Slinn G, Smith H, Smith IM, Wale RK, Wilson A, Ives N, Perkins GD; RePHILL collaborative group. **Resuscitation with blood products in patients with trauma-related haemorrhagic shock receiving prehospital care (RePHILL): a multicentre, open-label, randomised, controlled, phase 3 trial.** *Lancet Haematol.* 2022 Apr;9(4):e250-261. doi: 10.1016/S2352-3026(22)00040-0. Epub ahead of print. PMID: 35271808.

#### Summary

Crombie and colleagues present results of a multicentre, phase 3, allocation concealed, open-label, parallel group, randomized controlled trial investigating whether packed red blood cells (PRBC) and lyophilised plasma (LyoPlas) was superior to saline at improving a composite outcome of episode mortality (death at any time between injury and discharge from the primary receiving facility) and failure to reach lactate clearance (<20% per hour in the first 2 hrs after randomisation).

Adults with traumatic injury and associated hypotension (defined as systolic blood pressure < 90 mm Hg or absence of palpable radial pulse) thought to be secondary to traumatic hemorrhage were recruited across four prehospital critical care services and their associated trauma networks in the UK. 432 participants were randomly assigned to PRBC-LyoPlas (n=209) and saline (n=223). Trial recruitment was stopped early due to disruptions related to the COVID-19 pandemic.

The composite outcome occurred in 128 (64%) of 199 participants receiving PRBC-LyoPlas as compared to 136 (65%) in the saline group (adjusted risk difference - 0.25%; 95% CI -9.0 to 9.0; p=0.996). Event rates for individual components of the primary outcome were not statistically significant between groups. Serious adverse events included acute respiratory distress in 6% of PRBC-LyoPlas patients and 2% of patients receiving saline. No treatment related deaths were reported.

### Comments

1. Prehospital routine administration of PRBCs and lyophilized plasma was not superior to saline for trauma related hemorrhagic shock in a civilian population.
2. Evidence did not support a differential treatment effect for those patients with delays in transportation/longer transportation times.
3. Adverse reactions were rare, suggesting that pre-hospital blood product administration was safe.
4. Study demonstrates that it is feasible to conduct large, pragmatic randomized trials in the out of hospital setting.

### MEDICAL MANAGEMENT AFTER RETURN OF SPONTANEOUS CIRCULATION IN ADULTS WITH OUT OF HOSPITAL CARDIAC ARREST (OHCA)

Dankiewicz J, Cronberg T, Lilja G, et al.; TTM2 Trial Investigators. Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest. *N Engl J Med*. 2021 Jun 17;384(24):2283-2294. doi: 10.1056/NEJMoa2100591. PMID: 34133859

### Summary

Dankiewicz and colleagues report the results of an open-label trial with blinded assessment of outcomes, randomly assigning 1900 adults with coma after an out-

of-hospital cardiac arrest of presumed cardiac or unknown cause to undergo targeted hypothermia at 33°C, followed by controlled rewarming, or targeted normothermia with early treatment of fever (body temperature,  $\geq 37.8^\circ\text{C}$ ). A total of 1850 patients were evaluated for the primary outcome of death from any cause at 6 months. At 6 months follow-up, 465 of 925 patients (50%) in the hypothermia group had died, as compared with 446 of 925 (48%) in the normothermia group (relative risk with hypothermia, 1.04; 95% CI 0.94 to 1.14; p=0.37). Of the 1747 patients in whom the functional outcome was assessed, 488 of 881 (55%) in the hypothermia group had moderately severe disability or worse (modified Rankin scale score  $\geq 4$ ), as compared with 479 of 866 (55%) in the normothermia group (relative risk with hypothermia, 1.00; 95% CI, 0.92 to 1.09). Outcomes were consistent in the prespecified subgroups. Arrhythmias were more common in the hypothermia group; no significant difference in any other adverse events was seen between groups.

### Comments

1. In patients with coma after out-of-hospital cardiac arrest, targeted hypothermia did not lead to a lower incidence of death by 6 months than targeted normothermia.
2. Cooling was not implemented pre-hospital; the TTM2 trial does not answer the question as to whether ultra-early cooling may be beneficial.
3. 20% of patients were co-enrolled in the TAME trial, 10% in each group, therefore mild hypercapnia could potentially be a confounder until the results of this trial are published.
4. This was a well conducted, rigorous clinical trial; its design was based on data achieved from multiple previous trials providing a robust sample size calculation and estimate of absolute risk reduction.

### INTUBATION TECHNIQUES TO IMPROVE FIRST PASS SUCCESS

Driver BE, Semler MW, Self WH, Ginde AA, Trent SA, Gandotra S, Smith LM, Page DB, Vonderhaar DJ, West JR, Joffe AM, Mitchell SH, Doerschug KC, Hughes CG, High K, Landsperger JS, Jackson KE, Howell MP, Robison SW, Gaillard JP, Whitson MR, Barnes CM, Latimer AJ, Koppurapu VS, Alvis BD, Russell DW, Gibbs KW, Wang L, Lindsell CJ, Janz DR, Rice TW, Prekker ME, Casey JD;

BOUGIE Investigators and the Pragmatic Critical Care Research Group. **Effect of Use of a Bougie vs Endotracheal Tube With Stylet on Successful Intubation on the First Attempt Among Critically Ill Patients Undergoing Tracheal Intubation: A Randomized Clinical Trial.** *JAMA.* 2021 Dec 28;326(24):2488-2497. doi: 10.1001/jama.2021.22002. PMID: 34879143; PMCID: PMC8655668.

### Summary

Driver and colleagues report the results of a multicenter, parallel-group, unblinded, pragmatic, randomized clinical trial performed at 15 sites (7 emergency departments and 8 ICUs) from 11 hospitals in the United States. The trial was approved with waiver of informed consent. Patients were eligible if they were undergoing tracheal intubation with the planned use of sedation and a nonhyperangulated (e.g., Macintosh or Miller) laryngoscope blade. Patients were randomized to intubation with use of bougie or use of endotracheal tube with a stylet. 1106 patients in total were randomized: 447 patients (80%) in the bougie group were successfully intubated on the first attempt as compared to 453 patients (83%) in the stylet group (absolute risk difference -2.6%; 95% CI, -7.3 to 2.2;  $p=0.27$ ). 11% ( $n=58$ ) in the bougie group and 8.8% ( $n=46$ ) patients experienced severe hypoxemia defined as oxygen saturation < 80% during the interval between induction and 2 minutes after tracheal intubation. The person performing the intubation was a resident 60% of the time, a fellow 34% of the time, and an attending physician only 2% of the time. Video laryngoscopy was used 75% of the time, with direct laryngoscopy being used in the other 25%. Sedation was administered in 98% of patients and a paralytic in 97%.

### Comments

1. Multicenter RCT showed no difference in first pass success when comparing the use of a bougie to a stylet; comfort with different devices between centres was variable.
2. There was a significantly lower rate of first pass success in the BOUGIE trial as compared to the BEAM trial (>95%) possibly due to site specific effects (multicentre vs single centre study; comfort with use of bougie for intubation).

3. Higher rates of use of video laryngoscopy as compared to other intubation RCTs (e.g. STYLETO trial).
4. Use of waived consent model, affords the opportunity to conduct a high-quality comparative effectiveness trial in a representative patient population.

### NUTRITION IN MECHANICALLY VENTILATED PEDIATRIC PATIENTS

Brown AM, et al and the NutriNet and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. **Bolus gastric feeds improve nutrition delivery to mechanically ventilated pediatric medical patients: Results of the COntinuous vs BOlus multicenter trial.** *JPEN JPparenter Enteral Nutr.* 2021 Dec 8. Doi: 10.1002/jpen.2305. Epub ahead of print. PMID: 34881440.

### Summary

Brown and colleagues report the results of a multicentre, prospective, randomized comparative effectiveness trial of bolus gastric feeding (BGF) vs continuous gastric feeding (CGF) with respect to timing and delivery of energy and protein in mechanically ventilated (MV) pediatric patients admitted to seven academic PICUs in the U.S. 158 MV children aged one month to 12 years intubated within 24 hrs of PICU admission with expected duration of ventilation of at least 48 hrs and who were eligible to begin enteral nutrition were enrolled. 147 patients were included in the analysis (BGF = 72, CGF = 75). Both groups had similar demographic characteristics overall however the children in the BGF group were slightly older as compared to the CGF group.

No difference was seen in the percentage of patients in each group who achieved goal feeds. Time to goal feeds was shorter in the BGF group with a median time to achieve goal feeds of 18 h as compared to 20 h in the CGF group ( $P = 0.0321$ ). Median percentage of target kilocalories (median kcal 0.78 vs 0.59;  $P \leq 0.0001$ ) and median percentage of protein delivered (median protein 0.77 vs 0.59;  $P \leq 0.0001$ ) was higher for BGF patients. No ventilator-associated infections were reported in either group.

## Comments

1. BGF led to shorter time to achieve goal nutrition as compared with CGF in MV pediatric patients, increasing the delivery of target energy and nutrition.
2. Rigorous implementation of procedures and protocols including convening site registered dietitians to standardize individual energy and protein goals; training of nursing staff on criteria to continue or pause feeds; and education of physicians in directing addition of prokinetics or constipation medications as needed.
3. Reported the results as per-protocol analysis however no difference in findings from intention to treat analysis.
4. Many possible physiological benefits to bolus feeding (e.g., stimulation in gut motility, circadian zeitgeber), further study into benefits on patient important outcomes needed.

## OTHER ARTICLES OF INTEREST

Hammond NE, Bellomo R, Gallagher M, Gattas D, Glass P, Mackle D, Micallef S, Myburgh J, Saxena M, Taylor C, Young P, Finfer S. **The Plasma-Lyte 148 versus Saline (PLUS) study protocol amendment.** *Crit Care Resusc.* 2019 Dec;21(4):284-86. PMID: 31778635.

Zampieri FG, Machado FR, Biondi RS, et al. **Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients: The BaSICS Randomized Clinical Trial.** *JAMA.* 2021;326(9):818-829. doi:10.1001/jama.2021.11684

Zampieri FG, Machado FR, Biondi RS, et al. **Effect of Slower vs Faster Intravenous Fluid Bolus Rates on Mortality in Critically Ill Patients: The BaSICS Randomized Clinical Trial.** *JAMA.* 2021;326(9):830-838. doi:10.1001/jama.2021.11444

Hammond NE, Zampieri FG, Tanna GLD, et al. **Balanced Crystalloids versus Saline in Critically Ill Adults – A Systematic Review with Meta-Analysis.** *NEJM Evidence.* Published January 18, 2022. DOI: 10.1056/EVIDoa2100010.

Lehr AR, Rached-d'Astous S, Parker M, et al. **Impact of balanced versus unbalanced fluid resuscitation on clinical outcomes in critically ill children: protocol for a systematic review and meta-analysis.** *Syst Rev.* 2019 Aug 5;8(1):195. doi: 10.1186/s13643-019-1109-2. PMID: 31383009; PMCID: PMC6683512.

Le May M, Osborne C, Russo J, So D, Chong AY, Dick A, Froeschl M, Glover C, Hibbert B, Marquis JF, De Roock S, Labinaz M, Bernick J, Marshall S, Maze R, Wells G. **Effect of Moderate vs Mild Therapeutic Hypothermia on Mortality and Neurologic Outcomes in Comatose Survivors of Out-of-Hospital Cardiac Arrest: The CAPITAL CHILL Randomized Clinical Trial.** *JAMA.* 2021 Oct 19;326(15):1494-1503. doi: 10.1001/jama.2021.15703. PMID: 34665203; PMCID: PMC8527358. jama.2021.20929.

Vallentin MF, Granfeldt A, Meilandt C, et al. **Effect of Intravenous or Intraosseous Calcium vs Saline on Return of Spontaneous Circulation in Adults With Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial.** *JAMA.* 2021 Dec 14;326(22):2268-2276. doi: 10.1001/jama.2021.20929.

Andersen LW, Isbye D, Kjærgaard J, et al. **Effect of Vasopressin and Methylprednisolone vs Placebo on Return of Spontaneous Circulation in Patients With In-Hospital Cardiac Arrest: A Randomized Clinical Trial.** *JAMA.* 2021 Oct 26;326(16):1586-1594. doi: 10.1001/jama.2021.16628. PMID: 34587236; PMCID: PMC8482303.

## Cystic Fibrosis

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### IMPACT OF COVID-19 ON CF CLINICAL CARE

Albon D, Van Citters AD, Ong T, Dieni O, Dowd C, Willis A, Ssabadosa KA, Scalia P, Reno K, Oates GR, Schechter MS.

**Telehealth use in cystic fibrosis during COVID-19:**

**Associated with race, ethnicity, and socioeconomic factors.** *J Cyst Fibros* 2021; 20S3: S49-S54

#### Summary

The COVID-19 pandemic has significantly impacted how care for people with cystic fibrosis (CF) is delivered. Telehealth has been shown to be an effective form of health care delivery in this patient population. It is anticipated that this mode of health care delivery will remain an important aspect of CF care with many clinics adopting a hybrid model in which patients can be seen either in person or remotely. Several studies have evaluated the implementation of telehealth in the CF clinics. Earlier studies have shown disparities in telehealth use based on socioeconomic status. Here, the authors analyzed surveys completed by people with CF, CF Care Programs, and the CF Foundation Patient Registry. 424 responses from people with CF and 286 program responses were included in the analysis. Differences were identified in telehealth use and care perceptions by ethnicity, race, and socioeconomic characteristics. Notably, racial/ethnic minorities were less likely to have had a telehealth visit ( $p=0.015$ ). This was most pronounced amongst the Hispanic/Latino population ( $p<.01$ ). Additionally, persons that reported financial difficulties found telehealth more difficult to use and were less likely to believe that their concerns were addressed during telehealth visits.

#### Comments

1. The COVID-19 pandemic rapidly introduced telehealth into the CF delivery of care model.
2. Telehealth is likely to continue to be an important aspect of CF care.

3. In order to provide equitable CF telehealth services, further studies are needed to better understand the barriers and promoters to use amongst a diverse population of people with CF.

### EXPANSION OF ELEXACAFTOR/TEZACAFTOR/IVACAFTOR TO INCLUDE CHILDREN AGED 6-11 YEARS

Zemanick ET, Taylor-Cousar JL, Davies J, Gibson RL, Mall MA, McKone EF, McNally P, Ramsey BW, Rayment JH, Rowe SM, Tullis E, Ahluwalia N, Chu C, Ho T, Moskowitz SM, Noel S, Tian S, Waltz D, Weinstock TG, Xuan F, Wainwright CE, McColley SA for the VX18-445-106 Study Group. **A Phase 3 Open-Label Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele.** *Am J Respir Crit Care Med* 2021; 203 (12): 1522-1532

#### Summary

Previously, elexacaftor/tezacaftor/ivacaftor was shown to be both safe and efficacious in people with CF 12 years of age and older with at least one F508del-CFTR allele. This study aimed to assess the safety, pharmacokinetics, and efficacy of elexacaftor/tezacaftor/ivacaftor in children aged 6 through 11 with F508del-F508del or F508del-minimal function genotypes. A total of 66 children completed this 24-week open-label phase 3 study and received either 50% of the adult daily dose (if they weighed < 30 kg) or full dose (if they weighed >30 kg). The primary endpoint was safety and tolerability. Furthermore, this study showed, through the 24 weeks, elexacaftor/tezacaftor/ivacaftor improved the percentage of predicted FEV1 (10.2 percentage points: 95% CI, 7.9-12.6), CFQR score (7.0 points: 95% CI, 4.7-9.2), lung clearance index (-1.71 units: 95% CI, -2.11 to -1.30), and sweat chloride (-60.9mmol/L: CI 95%, -63.7 to -58.2). Body mass index for age z-score was also increased over the treatment period.

### Comments

1. Continued positive studies support the safety and efficaciousness of triple modulator therapy in the younger population of people with CF.
2. This data strongly supports the use of triple modulator therapy in this young patient group.
3. As the downstream clinical consequences of CF often begin at early childhood, it is important to initiate treatment in this young patient group as early as possible.

### UPDATED GUIDANCE ON THE MANAGEMENT OF CHILDREN WITH INCONCLUSIVE DIAGNOSIS AFTER NEWBORN SCREENING

Barben J, Castellani C, Munck A, Davies JC, de Winter-de Groot KM, Gartner S, Kashirskaya N, Linnane B, Mayell SJ, McColley S, Ooi CY, Proesmans M, Ren CL, Salinas D, Sands D, Sermet-Gaudelus I, Sommerburg O, Southern KW, For the European CF Society Neonatal Screening Working Group (ECFS NSWG). **Updated guidance on the management of children with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID).** *J Cyst Fibros* 2021; 20: 810-819

### Summary

In recent decades, significant progress has been made in Newborn Screening (NBS) in CF. In the majority of cases, the pathway leading to CF diagnosis after a positive NBS result is clear. However, for those children with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID), the diagnostic and management pathway has continued to evolve. This update outlines both short and long-term management recommendations and highlights recent studies reporting clinical outcomes in infants with CRMS/CFSPID. The major change in the updated guidance is the recommendation to complete a detailed assessment of the child at 6 years of age including respiratory function, imaging, repeat sweat tests and further genetic investigations. This article serves as a complement to the recent case report identifying a false negative newborn screen and normal pancreatic function in a child born to a mother taking CFTR modulator therapy.

### Comments

1. We are continuing to rapidly increase our understanding of CF and CFTR-related disorders (CFTR-RD) in terms of both diagnosis and management.
2. Cystic fibrosis transmembrane conductance regulator (CFTR)-related metabolic syndrome/Cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID) is a global definition established within the past decade.
3. Diagnosing CF or CFTR-RD early enables CF health care teams to help families keep their child as healthy as possible for as long as possible.

### EXTRAPULMONARY COMPLICATIONS OF CF: INCIDENCE AND RISK FACTORS OF CANCER

Archangelidi O, Cullinan P, Simmonds NJ, Mentzakis E, Peckham D, Bilton D, Carr SB. **Incidence and risk factors of cancer in individuals with cystic fibrosis in the UK: a case-control study.** *J Cyst Fibros* 2021; S1569-1993(21) 01302-3

### Summary

As reported by the Cystic Fibrosis Foundation, the median predicted survival for people with CF is now 50 years of age. As diagnostics and clinical management of CF continue to improve, focus is now shifting towards emerging comorbidities and aging in this patient population. It is now recognized that people with CF are at increased risk for certain cancers as they age. This article reports the analysis of 12,886 registered patients in the United Kingdom CF population using a nested case-control study design to determine the associated risk factors of cancer in people with CF. The authors found that there is an increased risk of cancers, in particular cancers of the lower gastrointestinal tract. In univariable analysis, transplantation increased the odds of reporting any cancer by 2.46 times (95% CI: 1.3-4.6). CF related diabetes also increased the risk of reporting any cancer. Multivariable models showed that these associations remained. Importantly, the incidence of GI cancer was strongly related to CFRD status.

### Comments

1. Based on available data from the United States CF Foundation Patient Registry, the median age of onset of colorectal cancer in patients with CF is up

to 20-30 years younger as compared to the general public.

2. The current recommendation is to initiate colonoscopy screening at age 40 with re-screening every 5 years in people with CF.
3. Studies such as this support that earlier screening may be beneficial in this population.

## STANDARDIZING TREATMENT DURATION FOR PULMONARY EXACERBATIONS IN CF

Goss CH, Heltshe SL, West NE, Skalland M, Sanders DB, Jain R, Barto TL, Fogarty B, Marshall BC, Vandevanter DR, Flume PA; on behalf of the STOP2 Investigators. **A Randomized Clinical Trial Of Antimicrobial Duration for Cystic Fibrosis Pulmonary Exacerbation Treatment.** *Am J Respir Crit Care Med* 2021; 204 (11): 1295-1305

### Summary

Little evidence previously existed standardizing treatment duration for pulmonary exacerbations in CF. The STOP2 (Standardized Treatment of Pulmonary Exacerbations 2) study was a multicenter, randomized, controlled clinical trial in adults with CF in acute exacerbations. A total of 982 people were randomized. 277 participants met predefined early lung function and symptom improvement criteria and were randomized to 10 or 14 days of total treatment duration. The remaining 705 people received either 21 or 14 days of treatment. The primary outcome was change in the percent predicted FEV1 (ppFEV1) from treatment initiation to 2 weeks after cessation. Secondary outcomes included symptoms, weight, and adverse events. Mean ppFEV1 change was 12.8 and 13.4 for 10 and 14 days, respectively (-0.65 difference, 95% CI [-3.3 to 2.0]). Mean ppFEV1 change was 3.3 and 3.4 in the 21- and 14-day arms (-0.10 difference, 95% CI [-1.3 to 1.1]). This study showed that in people with CF with early treatment improvement, 10 days of intravenous antimicrobials was not inferior to 14 days. In individuals with less improvement in the initial week, 21 days was not superior to treatment for 14 days.

### Comments

1. Optimal duration of antibiotic treatment in CF pulmonary exacerbations has been a key knowledge gap in clinical management.

2. In adults with CF being treated for pulmonary exacerbations, extending beyond 14 days did not improve lung function.
3. In people with early treatment response, shortening intravenous antibiotic course to 10 days resulted in similar outcomes to 14 days.
4. This study should help to reduce practice variance and helps to define better practices.

## OTHER ARTICLES OF INTEREST

### CFTR Modulators

Barry PJ, Mall MA, Alvarez A, Colombo C, de Winter-de Groot KM, Fajac, Mcbennet KA, McKone EF, Ramsey BW, Sutharsan S, Taylor-Cousar, Tullis E, Ahluwalia N, Jun LS, Moskowitz SM, Prieto-Centurion V, Tian, S, Wlatz D, Xuan F, Zhang Y, Rowe SM, Polineni D for the VX18-445-104 Study Group. **Triple Therapy for Cystic Fibrosis Phe508del-Gating and -Residual Function Genotypes.** *N Engl J Med* 2021; 385 (9): 815-825

Flume PA, Biner RF, Downey DG, Brown C, Jain M, Fischer R, De Boeck K, Sawick GS, Chang P, Paz-Diaz H, Rubin JL, Yang Y, Hu X, Pasta DJ, Millar SJ, Campbell D, Wang X, Ahluwalia N, Owen CA, Wainwright CE; on behalf of the VX14-661-110 study group. **Long-term safety and efficacy of tezacaftor-ivacaftor in individuals with cystic fibrosis aged 12 years and older who are homozygous or heterozygous for Phe508del CFTR (EXTEND): an open-label extension study.** *Lancet Respir Med* 2021; 9: 733-46

Davies JC, Wainwright CE, Sawicki GS, Higgins MN, Campbell D, Harris C, Panorchan P, Haseltine E, Tian S, Rosenfeld M; on behalf of the ARRIVAL study group. **Ivacaftor in Infants Aged 4 to <12 months with Cystic Fibrosis and a Gatin Mutation.** *Am J Respir Crit Care Med* 2021; 203 (5): 585-593

Nichols DP, Donaldson SH, Frederick CA, Freedman SD, Gelfond D, Hoffman LR, Kelly A, Markeqicz MR, Pittman JE, Ratjen F, Rosenfeld M, Sagel SD, Schwarzenberg SJ, Singh PK, Solomon GM, Stalvey MS, Kirby S, VanDalfsen JM, Clancy JP, Rowe SM. **PROMISE: Working with the CF community to understand emerging clinical and research needs for those treated with highly effective CFTR modulator therapy.** *J Cyst Fibros* 2021; 20 (2); 205-212

Jain R, Kazmerski TM, Zuckerwise LC, West NE, Montemayor K, Aitken ML, Cheng E, Roe AH, Wilson A, Mann C, Ladores S, Sjoberg J, Proanski M, Taylor-Cousar JL. **Pregnancy in cystic fibrosis: Review of the literature and expert recommendations.** *J Cyst Fibros* 2021; S1569-1993(21)01338-2

### Diagnosis, Screening, Clinical Manifestations

Fortner CN, Seguin JM, Kay DM. **Normal pancreatic function and false-negative CF newborn screen in a child born to a mother taking CFTR modulator therapy during pregnancy.** *J Cyst Fibros* 2021; 20: 835-836

Shechter MS, Ostrenga JS, Fink AJ, Barker DH, Sawicki GS, Quittner AL. **Decreased survival in cystic fibrosis patients with a positive screen for depression.** *J Cyst Fibros* 2021; 20 (1): 120-126

### Therapeutics

Chan BK, Stanley G, Modak M, Koff JL, Turner PE.

**Bacteriophage therapy for infections in CF.** *Pediatric Pulmonology* 202; 56: S4-S9

Flume PA, Amelina E, Daines CL, Charlton B, Leadbetter J, Guasconi A, Aitken ML. **Efficacy and safety of inhaled dry-powder mannitol in adults with cystic fibrosis: An international, randomized controlled study.** *J Cyst Fibros* 2021; 20: 1003-1009

Dang Y, van Heusden C, Nickerson V, Chung F, Wang Y, Quinney NL, Gentsch M, Randell SH, Moulton HM, Kole R, NiiA, Juliano RL, Kreda SM. **Enhanced delivery of peptide-morpholino oligonucleotides with a small**

**molecule to correct splicing defects in the lung.** *Nuc Acids Res* 2021; 49 (11): 6100-6113

Mesinele J, Ruffin M, kemgang A, Guillot L, Boelle P, Corvol H. **Risk factors Pseudomonas aeruginosa airway infection and lung function decline in children with cystic fibrosis.** *J Cyst Fibros* 2021; 21: 45-51

Cogen JD, Onchiri FM, Hamblett NM, Gibson RL, Morgan WJ, Rosenfeld M. **Association of Intensity of Antipseudomonal Antibiotic Therapy With Risk of Treatment-Emergent Organisms in Children With Cystic Fibrosis and Newly Acquired Pseudomonas Aeruginosa.** *Clin Infect Dis.* 2021 Sep 15;73(6):987-993. doi: 10.1093/cid/ciab208. PMID: 33693586.

### Groundbreaking Research Advances

Cararro G, Langerman J, Sabri S, Lorenzana Z, Purkayastha A, Zhang G, Konda B, Aros CJ, Calvert BA, Szyaniak A, Wilson E, Mulligan M, Bhatt P, Lu J, Vijayaraj P, Yao C, Shia DW, Lund AJ, Israely E, Rickabaugh TM, Ernst J, Mense M, Randell SH, Vladar EK, Ryan AL, Plath K, Mahoney JE, Stripp BR, Gomperts BN. **Transcriptional analysis of cystic fibrosis airways at single-cell resolution reveals altered epithelial cell states and composition.** *Nat Med.* 2021; 27 (5): 806-814.

### Outcomes of COVID-19 and Impact on Care Delivery

Dowd C, Van Citters AD, Dieni O, Willis A, Powell L, Sabadosa KA. **Design and method for understanding the state of cystic fibrosis care amid the COVID-19 pandemic.** *J Cyst Fibros* 2021; 20S3: S3-S8

# Sepsis

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## TREATMENT OF SEPSIS

Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belle-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Hylander Møller M, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papatthanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. **Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021.** *Crit Care Med.* 2021 Nov 1;49(11):e1063-e1143. doi: 10.1097/CCM.0000000000005337. PMID: 34605781. also published in *Intensive Care Med* 2021 Nov;47(11):1181-1247. doi: 10.1007/s00134-021-06506-y. Epub 2021 Oct 2. PMID: 34599691;

## Summary

This is the 5th version of the Surviving Sepsis Campaign International Guidelines for the Management of Sepsis and Septic Shock. This extensive document was constructed based on a systematic review of the relevant literature using GRADE methodology and the objective is to provide guidance for early identification and appropriate management for adult patients with sepsis reflecting the best evidence available in six major domains. There are 93 statements, which address screening and initial resuscitation (n = 10), infection (n = 21), hemodynamics (n = 14), ventilation (n = 12), additional therapies (n = 16), and a whole new session on goals of care and long-term outcomes (n = 20). The new board is characterized by diversity with representatives of low-resource settings in each of the domains. There are new and important changes in

previous recommendations such as not to use qSOFA as the only screening tool, using capillary refill time as an alternative target to guide resuscitation, initiation of vasopressors peripherally if needed, use of balanced solutions over saline, use of high flow nasal oxygen over noninvasive ventilation and not to use vitamin C, as well as several new recommendations on safety discharge and long-term outcomes.

## Comments

1. The recommendation to use 30 ml/kg for the initial fluid resuscitation in patients with signs of hypoperfusion was maintained. However, the strength of recommendation was downgraded to weak due to the low quality of evidence, which is very important as weak recommendation in the GRADE system means that different choices are likely to be appropriate for different patients.
2. Based on a subgroup analysis of important recent randomized trials, there was a change in the previous recommendations on the choice of crystalloids from either saline or balanced solutions to a suggestion to use balanced solutions (weak recommendation), which might have impact in standards of care.
3. There is a new weak recommendation to start vasopressor peripherally if needed, aiming to reduce the time to pressors and duration of hypoperfusion. This is important as there is evidence that duration of hypotension is associated with worst outcomes and in resource limited settings, central lines are not easily available.
4. The recommended timing for antimicrobials is still immediately and within one hour of sepsis recognition in patients with shock or a high likelihood of sepsis but in those patients with possible sepsis but without shock, a limited rapid assessment of the likelihood of infection versus non-infection illness (up to 3 hours) is advisable to

reduce unnecessary antimicrobial exposure.

However, the safety and feasibility of this approach in resource-limited settings is not demonstrated.

5. The whole new session on long term outcomes has several recommendations including the need for written and verbal education about sepsis, the need for reconciling medications and the assessment and follow up for new and worsening physical, cognitive, and emotional problems experienced by sepsis survivors after hospital discharge, all of them being relevant not only for high income countries but mostly for low-resource settings where those strategies are badly needed.

### TREATMENT OF SEPSIS

Hammond NE, Zampieri FG, Di Tanna GL, Garside T, Adigbli D, Cavalcanti AB, Machado FR, Micallef S, Myburgh J, Ramanan M, Rice TW, Semler MW, Young PJ, Venkatesh B, Finfer S, Delaney A. **Balanced Crystalloids versus Saline in Critically Ill Adults — A Systematic Review with Meta-Analysis.** *NEJM Evid* 2022; 1 (2)  
DOI:<https://doi.org/10.1056/EVIDoa2100010>

#### Summary

In this systematic review and meta-analysis, Hammond and Zampieri et al aimed to compare the safety and efficacy of balanced crystalloid solutions and saline. They included only randomized clinical trials in critically ill patients. The primary outcome was 90-day mortality and among the secondary outcomes they reported the incidence of acute kidney injury (AKI), new treatment with renal replacement therapy (RRT), and ventilator-free and vasopressor-free days to day 28. The primary analysis was based on a random-effects model, however they also used Bayesian methods to describe probability terms. They reported data on 35,884 patients from 13 RCT, which includes the two last major trials, BASICS from Brazil and PLUS from ANZICS. The global population analysis showed that the estimated effect of using balanced crystalloids versus saline in critically ill adults ranges from a 9% relative reduction to a 1% relative increase in the risk of death, with a high probability that using balanced crystalloids reduces mortality. Regarding the sepsis subgroup, the authors found 5 trials, all of them considered as low risk of bias, reporting outcomes on patients with sepsis at baseline (n = 6754). The pooled estimate of the RR for mortality

for those assigned to receive balanced crystalloid solution compared with saline was 0.93 (95% CI, 0.86 to 1.01; I<sup>2</sup> = 22.3%). When one high-risk of-bias trial was also considered, the results were similar (RR, 0.93; 95% CI, 0.85 to 1.01; I<sup>2</sup> = 19.3%).

#### Comments

1. This meta-analysis contains new and original data as it is the first conducted after the completion of the two major RCTs with individual randomization, both very robust studies, the Brazilian BASICS study that included 10,500 patients and the ANZICS study PLUS, with 4,500 patients, thus providing greater precision on treatment effects and allowing a better hypothesis generation on the subgroups.
2. The statistical analysis was carefully performed using both frequentist and Bayesian analyses aiming to generate information to guide clinical practice.
3. The sepsis subgroup of patients is large, with almost 7,000 patients; however, the findings should still be seen as hypothesis generating when they point out a potential benefit of the use of balance solution, with an estimate of the effect consistent with a 14% relative reduction to a 1% relative increase in risk of death, meaning that further trials might be needed in this population.
4. There was no assessment of the secondary outcomes on the subgroup of septic patients, emphasizing the need for further trials to clarify potential benefit and harms.
5. There was no assessment of the previous use of the assigned fluids before randomization or the impact in chloride levels which also needs further clarification in future studies.

### TREATMENT OF SEPSIS

Sevransky JE, Rothman RE, Hager DN, Bernard GR, Brown SM, Buchman TG, Busse LW, Coopersmith CM, DeWilde C, Ely EW, Eyzaguirre LM, Fowler AA, Gaiieski DF, Gong MN, Hall A, Hinson JS, Hooper MH, Kelen GD, Khan A, Levine MA, Lewis RJ, Lindsell CJ, Marlin JS, McGlothlin A, Moore BL, Nugent KL, Nwosu S, Polito CC, Rice TW, Ricketts EP, Rudolph CC, Sanfilippo F, Viele K, Martin GS, Wright DW; VICTAS Investigators. **Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis: The VICTAS Randomized Clinical Trial.** *JAMA.* 2021 Feb 23;325(8):742-750. doi:

10.1001/jama.2020.24505. Erratum in: *JAMA*. 2021 Sep 21;326(11):1072. PMID: 33620405; PMCID: PMC7903252

### Summary

Since the first observational study suggesting improvement in sepsis outcomes with the use of Vitamin C, Thiamine, and Hydrocortisone in patients with septic shock, several small RCT and metanalysis have been published with inconsistent results. In this study, the authors randomized adult patients with sepsis-induced respiratory and/or cardiovascular dysfunction to receive either intravenous vitamin C (1.5 g), thiamine (100mg), and hydrocortisone (50mg) every 6 hours or placebo for 96 hours. The primary endpoint was ventilator- and vasopressor-free days in the first 30 days. They enrolled 501 participants in 43 sites, however the study was interrupted earlier than expected due to the lack of funding. There was no significant difference in the ventilator- and vasopressor-free days when patients from the intervention group (25 days [IQR, 0-29 days]) were compared with those on the placebo group (26 days [IQR, 0-28 days]), median difference of -1 day (95%CI, -4 to 2 days; P = .85) and no difference in mortality (intervention: 22% versus placebo: 24%). Although the authors concluded that the combined use of vitamin C, thiamine, and hydrocortisone did not increase ventilator- and vasopressor-free days among critically ill patients with sepsis as compared with placebo they recognized that the study was underpowered due to its early termination.

### Comments

1. The issue of using Vitamin C in septic shock seems still unresolved, as prior data suggested no benefit in terms of mortality according to the Surviving Sepsis Campaign guidelines (relative risk 0.9 [95% CI 0.69–1.18]). This additional underpowered study apparently would not change this previous point estimate.
2. The major issue in this study is the early interruption of the trial initially designed to include 2000 patients to detect a 1.5 increase in vasopressor and ventilator-free days but was terminated after the inclusion of only 501 patients, which not only resulted in an underpowered study but also is a violation of the implicit pact with the study participants who volunteered for the trial;

however it is still the largest trial published to date and the data clearly contributes to the collective knowledge on the intervention.

3. Quite unusually, a member of the Data Safety and Monitoring Board (DSMB) was also an author of the study which raised concerns and evoked an Editor's note in the *Journal of American Medical Association*, justifying the publication of the paper under these unusual circumstances by multiple reasons, including the fact that the study was terminated by the sponsor and not by the DSMB and the absence of commercial interest on the drugs of the intervention arm.
4. In the current study, only 39% of the patients were using vasopressor at enrolment and one issue in Vitamin C studies is the heterogeneity of the population, with some trials including only patients with septic shock (VITAMINS, ACT) and another also including patients with acute respiratory failure (CITRIS ALI), compromising our ability to detect an effect of the intervention.
5. In this study, the median time to receipt of intervention was 14.7 hours and there was no association between the time of intervention and treatment response; however, it is still unknown if earlier administration could be associated with best outcomes.

### SEPSIS PREVENTION

Rickard CM, Marsh NM, Larsen EN, McGrail MR, Graves N, Runnegar N, Webster J, Corley A, McMillan D, Gowardman JR, Long DA, Fraser JF, Gill FJ, Young J, Murgu M, Alexandrou E, Choudhury MA, Chan RJ, Gavin NC, Daud A, Palermo A, Regli A, Playford EG. **Effect of infusion set replacement intervals on catheter-related bloodstream infections (RSVP): a randomised, controlled, equivalence (central venous access device)-non-inferiority (peripheral arterial catheter) trial.** *Lancet*. 2021 Apr 17;397(10283):1447-1458. doi: 10.1016/S0140-6736(21)00351-2. PMID: 33865494

### Summary

Although guidelines suggest the replacement of infusion set every 4 days to prevent catheter-related bloodstream infection (CRBSI), the evidence to support this practice is weak. In this study, conducted in 10

Australian hospitals, the authors aimed to compare the effectiveness and costs of a 7-day versus 4-day replacement to prevent CRBSI in patients with central venous access devices and peripheral arterial catheters. The primary outcome was the incidence of CRBSI, which was adjudicated by physicians masked to allocation. They randomized 2944 patients to 7-day or 4-day infusion set replacement. For central venous access, on the 7-day group, 20 (1.78%) had CRBSI as compared with 16 (1.46%) in the 4-day group, (absolute risk difference 0.32%, 95% CI -0.73 to 1.37). They reported no adverse events. The authors concluded that the time for replacement can be safely extended to 7 days, which represents a reduction in costs and nurse workload.

### Comments

1. Prevention of catheter related bloodstream infection is a pivotal step in preventing nosocomial-acquired sepsis and its consequences as morbidity and mortality rates are high.
2. Previous literature did not provide clear evidence on the optimal timing for infusion set replacement, with several limitations and only two small studies assessed replacement beyond 4 days, thus this study provided for the first-time high-quality evidence to support decisions that can significantly reduce costs and workload in a subject that is part of clinical care worldwide.
3. Reducing costs and workload is even more important in resource limited settings, however, data generated in high income countries cannot be extrapolated to settings with higher incidence of CRBSI, which highlight the need to improve research capacity in these settings.
4. Although CRBSI treatment costs were not considered in the cost analysis (as there was no significant difference between the arms), the implicated savings is impacting as the adoption of a 7-day replacement is expected to save AU\$15 million every year only in Queensland where 26,500 central venous access and 33,700 peripheral arterial catheters are used yearly only by government hospitals, which translated to USA (3 million catheters) or UK (250,000 catheters) increases dramatically the potential savings, supporting actions to challenge traditional practices that might be wasting critical health resources.
5. Although this study has many strengths such as centralized randomization, the number of sites, the blinded assessment of the outcome, almost perfect follow-up, inclusion of multiple types of catheter and a heterogenous population and the fact that catheters did remain in place for 7-days, it also has some limitations such as the nonblinded nature of the intervention, the potentially underreporting of CLABSI as its pragmatic approach did not standardize blood cultures samplings, thus we need to be careful in extrapolating the evidence to blood, lipid, inotrope, chemotherapy, and cyclosporin infusions, or to low birth-weight neonates.

### EPIDEMIOLOGY OF SEPSIS

**Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis.** *Lancet*. 2022 Feb 12;399(10325):629-655. doi: 10.1016/S0140-6736(21)02724-0. Epub 2022 Jan 19. PMID: 35065702; PMCID: PMC8841637

### Summary

This study presents a comprehensive estimate of the burden of antimicrobial multidrug resistance (AMR) based on statistical models using 471 million individual records or isolates and 7585 study-location-years from systematic literature reviews, hospital systems, surveillance systems, and other sources. They estimated deaths and disability-adjusted life-years attributable to and associated with bacterial AMR for 23 pathogens and 88 pathogen–drug combinations. As the extent to which drug-resistant infections would be replaced by susceptible infections or by no infection is unknown, the authors constructed models using an alternative scenario in which all AMR infections were replaced by drug-susceptible infections to estimate the burden attributable to AMR. In addition, to estimate the burden associated with but not necessarily attributable to AMR they constructed models in which all MDR infections were considered as no infection. The authors reported an estimate of 1.27 million deaths directly attributable to resistance and 4.95 million deaths associated with bacterial AMR. The highest rate of deaths attributable to resistance occurred in sub-Saharan Africa (27.3 deaths per 100,000) with the lowest rate in Australasia, (6.5 deaths per 100,000). The most frequent infections were

lower respiratory and thorax infections, bloodstream infections, and intra-abdominal infections. The leading pathogens were *Escherichia coli* and *Staphylococcus aureus*, followed by *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.

### Comments

1. Sepsis is a final pathway to death for both community-acquired and healthcare-associated infections and AMR plays a major role in both scenarios, increasing morbidity and mortality.
2. This masterpiece study shows for the first time the high burden of AMR with millions of deaths every year, with only six pathogens accounting for 73.4% of all deaths attributable to bacterial AMR, highlighting the need to develop specific strategies to these deadly bacteria.
3. The highest burden is, as expected, in low-resource settings where the prevalence of infections is higher and prevention strategies, quality of care laboratory infrastructure to guide treatment, insufficient regulations, and inadequate access are drivers for resistance.
4. Understanding the burden of AMR is a key step to reduce sepsis AMR deaths by enhancing prevention strategies, improving current vaccination programs (*S pneumoniae* is one of the six leading pathogens) and future developments, reducing unnecessary exposure to antibiotics in no-human disease, improvement of stewardship programs, increasing access to current available antibiotics and the development of new ones all around the world as well as established adequate antimicrobial stewardship programs including research priorities and access to adequate antibiotics.
5. The understanding of AMR as a priority for global health among policy makers is fundamental mostly in resource-poor settings as there is still lack of high-quality data on infectious disease, pathogens, and microbiological laboratory data, which is important to base training and education programs, stewardship programs, preventive strategies and improving the laboratory capacity and the scientific understanding.

### SEPSIS EPIDEMIOLOGY - COVID

Karakike E, Giamarellos-Bourboulis EJ, Kyprianou M, Fleischmann-Struzek C, Pletz MW, Netea MG, Reinhart K, Kyriazopoulou E. **Coronavirus Disease 2019 as Cause of Viral Sepsis: A Systematic Review and Meta-Analysis.** *Crit Care Med.* 2021 Dec 1;49(12):2042-2057. doi: 10.1097/CCM.0000000000005195. PMID: 34259663; PMCID: PMC8594513

### Summary

Infection by SARS COV 2 is a heterogenous disease with some cases presenting with respiratory failure and multiple organ dysfunction syndrome. Thus, severe forms of coronavirus disease ultimately fulfilled sepsis criteria. However, the prevalence of COVID-related sepsis is still not well defined. Karakike et al aimed to review the literature searching for studies that reported on patients with confirmed COVID-19 who fulfilled sepsis-3 criteria or had infection-related organ dysfunctions. They used the Sepsis-3 definition, meaning any SOFA score greater than or equal to 2 at admission. To obtain the data, they used the exact number of patients reported with Sepsis-3, the median SOFA score or SOFA score extracted by reported organ failures. They aimed to report the prevalence as well as secondary outcomes such as the need for intensive care (ICU) admission and the prevalence of new onset of organ dysfunction in the ICU. Prevalence data was obtained from 56 studies in the ICU (38,058 adult patients) and 86 studies in the wards (179,119 adult patients) resulting in an estimated prevalence of 77.9% and 33.3%. Regardless of ICU or non-ICU admissions, the overall prevalence was 51.6. Acute respiratory distress syndrome was present in 87.5% and septic shock in 36.4% of the patients, being the two most common organ dysfunctions. They concluded that sepsis is frequent among patients with severe forms of COVID-19. This understanding might help planning management of these patients.

### Comments

1. The concept that severe COVID-19 is ultimately sepsis is important as there are common strategies to be explored such as prevention, early diagnosis and management, and the enhancement of

survivorship after hospital discharge with adequate follow-up and rehabilitation.

- The frequent use of supportive therapies highlights the relevance of multiple organ dysfunction and sepsis associated with virus infection, as 62.4% of the patients required invasive mechanical ventilation, 19.9% renal replacement therapy and 49.5 % vasopressors.
- The authors were not able to assess mortality in COVID sepsis versus COVID non-sepsis as the data was not available in the original studies, thus they used the ICU mortality and mortality among patients under mechanical ventilation as surrogates of sepsis-related mortality, reporting a mortality rate of 42.0% which probably also underestimates the true mortality rates, as supportive therapies such as non-invasive mechanical ventilation and high flow nasal oxygen are usual in this population.
- Another limitation is the reporting of sepsis in the original papers only as a complication of secondary bacterial infections which suggests that the medical community still underestimates the relevance of virus as a cause of sepsis.
- These results should be interpreted with caution as there are limitations due to the high heterogeneity of data, the usual issues with the absence of data on specific SOFA components and the difficulties to retrieve SOFA score, which might have underestimated the incidence of sepsis.

## OTHER ARTICLES OF INTEREST

### Balanced Solutions

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MSC, Manoel ALO, Silva-Junior JM, Duarte P, Soares RM, Miranda TA, de Lima LM, Gurgel RM, Paisani DM, Corrêa TD, Azevedo LCP, Kellum JA, Damiani LP, Brandão da Silva N, Cavalcanti AB; BaSICS investigators and the BRICNet members. **Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients: The BaSICS Randomized Clinical Trial.** *JAMA.* 2021 Aug 10;326(9):1-12.

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## Bronchiectasis

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### TREATMENT OF PSEUDOMONAS AERUGINOSA INFECTED BRONCHIECTASIS PATIENTS WITH TOBI PODHALER

Loebinger MR, Polverino E, Chalmers JD, Tiddens HAWM, Goossens H, Tunney M, Ringshausen FC, Hill AT, Pathan R, Angyalosi G, Blasi F, Elborn SJ, Haworth CS; iBEST-1 Trial Team. **Efficacy and safety of TOBI Podhaler in Pseudomonas aeruginosa-infected bronchiectasis patients: iBEST study.** *Eur Respir J.* 2021 Jan 5;57(1):2001451.

#### Summary

In this phase II, double-blind, randomized study, bronchiectasis patients infected with pseudomonas aeruginosa were randomized equally into 3 cohorts with escalating doses of tobramycin inhalation powder (TIP). Within each cohort, patients were further randomized to either receive it continuously, cyclically (alternating 28 days), or placebo for 16 weeks.

Overall, 107 patients were randomized to cohorts A (n=34), B (n=36) and C (n=37). All three TIP doses significantly reduced the P. aeruginosa sputum density from baseline to day 29 versus placebo in a dose-dependent manner ( $p \leq 0.0001$ , each). A smaller proportion of patients in the continuous-TIP (34.1%) and cyclical-TIP (35.7%) groups experienced pulmonary exacerbations versus placebo (47.6%) and also required fewer anti-pseudomonal antibiotics (38.6% on continuous TIP and 42.9% on cyclical TIP) versus placebo (57.1%) although not statistically significant. Pulmonary exacerbation of bronchiectasis was the most frequent (37.4%) adverse event. Overall, TIP was well tolerated, however, 23.4% of the patients discontinued the study drug due to adverse events.

#### Comments

1. Approved inhaled antibiotics for the treatment of bronchiectasis are sorely needed.
2. There is lack of evidence comparing continuous vs intermittent inhaled antibiotic administration in bronchiectasis.

3. This is the first study to evaluate the safety and efficacy of different doses and dosing regimens of TIP in patients with bronchiectasis and pulmonary P. aeruginosa infection.
4. The results demonstrated that all three doses of TIP (84 mg [three capsules] once daily, 140 mg [five capsules] once daily and 224 mg [four capsules] twice daily) significantly reduced the P. aeruginosa sputum density from baseline to day 29 compared with placebo.
5. The drug was well-tolerated with >90% compliance.

### BRONCHOSCOPIC AIRWAY CLEARANCE FOR ACUTE EXACERBATIONS OF BRONCHIECTASIS

Liu Y, Lu HW, Gu SY, Wang WW, Ge J, Jie ZJ, Jia JG, Gao ZT, Li J, Shi JY, Liang S, Cheng KB, Bai JW, Qu JM, Xu JF.

**Bronchoscopic airway clearance therapy for acute exacerbations of bronchiectasis.** *EBioMedicine.* 2021 Oct;72:103587. doi: 10.1016/j.ebiom.2021.103587. Epub 2021 Sep 16.

#### Summary

This is a randomized clinical trial exploring the efficacy of bronchoscopic airway clearance (B-ACT) as a treatment adjunct for acute exacerbations of bronchiectasis. 189 patients experiencing acute bronchiectasis exacerbation were randomized in a 3:1 ratio to the experimental arm and control arm respectively. The patients in the intervention arm received bronchoscopy with suctioning of secretions in addition to usual therapy while the patients in the control arm received only usual therapy. Usual therapy consisted of antibiotics chosen by the treating physician and other airway clearance measures. The patients were followed afterwards by telephone. The patients in the intervention arm showed a statistically significant improvement in the primary outcome, time to first exacerbation after the treatment.

## Comments

1. “Randomized controlled trials are required to evaluate the effects of airway clearance techniques in patients who are undergoing an exacerbation”. British Thoracic Society Guideline for bronchiectasis in adults. *Thorax*. 2019
2. This is the first randomized controlled trial that aims to explore the benefits and risks of B-ACT therapy in managing acute bronchiectasis exacerbations.
3. There was a statistically significant increase in the clinically meaningful primary outcome of time to first exacerbation after bronchoscopy as compared to usual therapy.
4. A limitation of this trial was inconsistent length of follow up after treatment.

## RELATING THE SPUTUM MICROBIOME WITH CLINICAL OUTCOMES IN BRONCHIECTASIS

Dicker AJ, Lonergan M, Keir HR, Smith AH, Pollock J, Finch S, Cassidy AJ, Huang JTJ, Chalmers JD. **The sputum microbiome and clinical outcomes in patients with bronchiectasis: a prospective observational study.** *Lancet Respir Med*. 2021 Aug;9(8):885-896.

### Summary

This was a longitudinal cohort study of patients with bronchiectasis from Eastern Scotland which aimed to investigate associations between sputum bacterial microbiome and severity of disease and long-term outcomes in bronchiectasis. Sputum was collected from 300 patients. 16S rRNA sequencing data were obtained on 281. Findings included the enrichment of pseudomonas in severe bronchiectasis. Haemophilus and streptococcus were not strongly associated with more severe disease. The loss of diversity of the microbiome was associated with lung function, symptoms, severity of disease, exacerbations and hospital admissions.

### Comments

1. This is the largest study of the bronchiectasis sputum microbiome to date.
2. Reduced microbiome diversity, particularly in the presence of Pseudomonas dominance, is associated with greater disease severity, increased frequency of exacerbations, increased severity of exacerbations, and an increased risk of all-cause mortality.

3. Further studies are needed to characterize different endotypes of bronchiectasis patients to allow the practice of “precision medicine.”

## A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED PILOT TRIAL TO ASSESS THE EFFICACY OF ROFLUMILAST IN BRONCHIECTASIS PATIENTS WITH FREQUENT EXACERBATIONS

Juthong S, Panyarath P. **Efficacy of Roflumilast in Bronchiectasis Patients with Frequent Exacerbations: A Double-Blinded, Randomized, Placebo-Controlled Pilot Clinical Trial.** *Tuberc Respir Dis (Seoul)*. 2022 Jan;85(1):67-73

### Summary

This was a double-blinded, randomized, placebo-controlled trial in which 34 patients who had 2 exacerbations or more in the previous 12 months were randomized to receive Roflumilast 500 µg or placebo and were followed for 24 weeks. Primary outcome was number of exacerbations in the 6 month period. There was no difference in exacerbation rates. The Roflumilast arm showed a trend towards improved FEV1 that was not statistically significant. There was a higher rate of adverse drug reactions in the Roflumilast arm. These included loss of appetite, fatigue, nausea, vomiting and diarrhea.

### Comments

1. Prior to this trial, the effectiveness of roflumilast to reduce bronchiectasis exacerbation has never been evaluated.
2. An agent which targets the underlying neutrophilic airway inflammation in bronchiectasis
3. In this small trial, Roflumilast, compared to placebo, did not result in improvement in exacerbation frequency.

## PSEUDOMONAS AERUGINOSA AND LUNG FUNCTION DECLINE IN PATIENTS WITH BRONCHIECTASIS

Martinez-García MA, Oscullo G, Posadas T, Zaldivar E, Villa C, Dobarganes Y, Girón R, Olveira C, Maíz L, García-Clemente M, Sibila O, Golpe R, Rodríguez J, Barreiro E, Rodríguez JL, Feced-Olmos L, Prados C, Muriel A, de la Rosa D; Spanish Registry of Bronchiectasis Group of SEPAR (RIBRON). **Pseudomonas aeruginosa and lung function decline in patients with bronchiectasis.** *Clin Microbiol Infect*. 2021 Mar;27(3):428-434.

**Summary**

This is an observational prospective study in which 849 bronchiectasis patients were followed from 1-4 years with annual lung function tests. Multiple variables were evaluated in these patients, including number of exacerbations, severity, microbiology, radiology and treatment. The main outcome studied was the forced expiratory volume in 1 second (FEV1). The annual rate of decline was found to be 31.6 ml/year but the decline was faster in older patients, those with pseudomonas aeruginosa chronic infection and higher number of previous exacerbations.

**Comments**

1. Eradication therapy to patients with new growth of pseudomonas is a grade D recommendation by the British thoracic guidelines.

2. This is the largest series by far specifically analyzing the decline in lung function in patients with bronchiectasis.
3. When controlled for baseline FEV1, the presence of chronic bronchial infection by *P. aeruginosa* (but not other potentially pathogenic microorganisms) only appeared as a risk factor of faster decline of lung function (higher than -70 mL/year).
4. None of the treatments analyzed long-term antibiotics (including inhaled antibiotics), macrolides, bronchodilators or respiratory physiotherapy) were associated with significant lung function changes.

# Long COVID and Post-Intensive Care Syndrome

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## SHORT-TERM PHYSICAL, MENTAL, AND COGNITIVE OUTCOMES FOLLOWING COVID-19 CRITICAL ILLNESS

Hodgson CL, Higgins AM, Bailey MJ, Mather AM, Beach L, Bellomo R, Bissett B, Boden IJ, Bradley S, Burrell A, Cooper DJ, Fulcher BJ, Haines KJ, Hodgson IT, Hopkins J, Jones AYM, Lane S, Lawrence D, van der Lee L, Liacos J, Linke NJ, Marques Gomes L, Nickels M, Ntoumenopoulos G, Myles PS, Patman S, Paton M, Pound G, Rai S, Rix A, Rollinson TC, Tipping CJ, Thomas P, Trapani T, Udy AA, Whitehead C, Anderson S, Serpa Neto A; COVID-Recovery Study Investigators and the ANZICS Clinical Trials Group. **Comparison of 6-Month Outcomes of COVID-19 vs Non-COVID-19 Survivors of Critical Illness.** *Am J Respir Crit Care Med.* 2022 Mar 8. doi: 10.1164/rccm.202110-2335OC. Epub ahead of print. PMID: 35258437

### Summary

In critically ill patients with COVID-19, few studies have reported the change in functional outcomes at 6-month compared to pre-illness levels or included a comparison cohort. This longitudinal cohort study was conducted at 26 ICUs in Australia. This study compared the 6-month outcomes of COVID-19 and non-COVID-19 adult, critically ill patients from two prospective observational studies, who received over 24 hours of mechanical ventilation. Demographic, clinical, and hospital outcomes were retrieved from electronic medical records. Patient-reported outcomes were measured by trained assessors via telephone and included: disability, health status, anxiety and depression, post-traumatic stress, cognitive function, and activities of daily living. For the primary outcome at 6-months: there was no difference in the incidence of death or new disability between patients with COVID-19 compared to non-COVID-19 acute respiratory failure (58/93 (62.4%) versus 99/150 (66%),  $p=0.58$ ). Similarly, the severity of disability, health related quality of life, psychological function and cognitive function at 6-months were similar between COVID-19 and non COVID-19 survivors. Both COVID-19 and non-COVID-19 patients

reported new disabilities in all domains of functioning, including physical function, psychological function, and cognitive function.

### Comments

1. This study importantly included a comparison between survivors of COVID-19, and non-COVID-19 acute respiratory failure, to better understand the impacts of COVID-19 on post-ICU disability.
2. A robust range of patient-reported outcome measures were selected, based on the recommended core outcome set for survivors of acute respiratory failure.
3. This study had a strong focus on the World Health Organization's International Classification of Functioning, Disability and Health that is useful to apply to COVID-19 to understand the impacts on health outcomes at an individual and population-level.
4. This study highlighted the importance of screening for new post-ICU impairments for all ICU survivors as survivors in this study reported new disability irrespective of diagnosis for COVID-19.
5. Measurement of baseline function is important to disentangle the impacts of critical illness on outcomes, however in this study it was measured at 6 months which is likely to introduce significant recall bias.

## MEDIUM-TERM PHYSICAL, MENTAL, AND COGNITIVE SYMPTOMS FOLLOWING COVID-19 CRITICAL ILLNESS

Heesakkers H, van der Hoeven JG, Corsten S, Janssen I, Ewalds E, Simons KS, Westerhof B, Rettig TCD, Jacobs C, van Santen S, Slooter AJC, van der Woude MCE, van den Boogaard M, Zegers M. **Clinical Outcomes Among Patients With 1-Year Survival Following Intensive Care Unit Treatment for COVID-19.** *JAMA.* 2022 Feb 8;327(6):559-565. doi: 10.1001/jama.2022.0040. PMID: 35072716; PMCID: PMC8787680.

## Summary

There are very few data describing the one-year outcomes post-COVID-19 critical illness. This exploratory multi-center cohort study, conducted in 11 Dutch hospitals, assessed the key domains of the Post-Intensive Care Framework by measuring the occurrence of physical, mental, cognitive symptoms at one-year in survivors of COVID-19 critical illness. These patient-reported outcomes were measured online or via paper using validated outcome measures for: frailty, fatigue, anxiety, depression, post-traumatic stress, cognition. Of the 452 eligible patients, 301 (66.8%) patients could be included. At 1 year after ICU treatment for COVID-19, physical symptoms were reported by 182 of 245 patients (74.3% [95% CI, 68.3% to 79.6%]), mental symptoms were reported by 64 of 244 patients (26.2% [95% CI, 20.8% to 32.2%]), and cognitive symptoms were reported by 39 of 241 patients (16.2% [95% CI, 11.8% to 21.5%]). In patients who survived 1 year following ICU treatment for COVID-19, physical, mental, or cognitive symptoms were frequently reported.

## Comments

1. This study leverages the Post-Intensive Care Syndrome framework by measuring the key domains (physical, mental, cognition), that avoids further splintering of the field.
2. Provides rare medium-term outcome data for COVID-19 patients out to 1 year.
3. While symptoms of PICS were frequently reported, this study lacks a comparator cohort so it is difficult to understand what is attributable to COVID-19 and what is attributable to the effects of critical illness.

## LONGITUDINAL PHYSICAL AND HEALTH-RELATED QUALITY OF LIFE FOLLOWING COVID-19 HOSPITALIZATION

Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, Hu P, Guo L, Liu M, Xu J, Zhang X, Qu Y, Fan Y, Li X, Li C, Yu T, Xia J, Wei M, Chen L, Li Y, Xiao F, Liu D, Wang J, Wang X, Cao B. **1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study.** *Lancet.* 2021 Aug 28;398(10302):747-758.

## Summary

In this large longitudinal cohort study from China, the primary aim was to compare the health impacts at 6 months and 1 year in hospitalized COVID-19 survivors.

The secondary aim was to investigate whether COVID-19 survivors returned to baseline health status 1 year after symptom onset compared with non-COVID-19 controls. A broad range of patient-reported, clinical, and performance-based outcomes were measured including: health related quality of life, physical examination, distance walked in six-minutes, laboratory tests, self-reported health care use and work status. Non-COVID-19 community-dwelling controls were matched for age, sex, and comorbidities. Overall, most patients had a good physical recovery at follow-up. The majority who were employed before COVID-19 had returned to their prior work. Some impairments lasted to 1 year in some patients including lung diffusion impairment, and radiographic abnormalities particularly in the small sub-cohort of patients who were critically ill. When compared to the control cohort, the health status in the COVID-19 cohort was lower.

## Comments

1. Baseline health status of the COVID-19 participants was unknown, and instead the baseline health status of the non-COVID-19 controls was used as an indication, which is likely to introduce bias.
2. Attrition was moderate, with only just over half of the cohort (58%) attending both follow-up visits and able to be included in the analyses.
3. The cumulative impact of comorbidities may be under appreciated in this study, as they appear to have been measured as isolated factors rather than potentially synergistic (i.e., in the case of multimorbidity).
4. No participants attended a professional rehabilitation program, which highlights potential regional differences in access to rehabilitation as standard care.
5. The comprehensive constellation of clinical, laboratory, patient-reported and patient-performance outcome measures, makes a unique contribution to the field.

## SHORT-TERM PSYCHOLOGICAL OUTCOMES OF FAMILY MEMBERS OF PATIENTS WITH COVID-19 CRITICAL ILLNESS

Azoulay E, Resche-Rigon M, Megarbane B, Reuter D, Labbé V, Cariou A, Géri G, Van der Meersch G, Kouatchet A, Guisset O, Bruneel F, Reignier J, Souppart V, Barbier F,

Argaud L, Quenot JP, Papazian L, Guidet B, Thiéry G, Klouche K, Lesieur O, Demoule A, Guitton C, Capellier G, Mourvillier B, Biard L, Pochard F, Kentish-Barnes N. **Association of COVID-19 Acute Respiratory Distress Syndrome With Symptoms of Posttraumatic Stress Disorder in Family Members After ICU Discharge.** *JAMA.* 2022 Feb 18. Mar 15;327(11):1042-1050. doi: 10.1001/jama.2022.2017. PMID: 35179564; PMCID: PMC8924722

### Summary

Little is known about the experience of COVID-19 on the mental health of family members' of critically ill patients. This prospective multicenter study was conducted in 23 ICUs in France. The primary aim was to determine the risk-adjusted association between hospitalization with COVID-19 ARDS and symptoms of PTSD in family members compared with hospitalization for ARDS of other causes. Well-validated outcome measures were used to capture post-traumatic stress disorder, depression, and anxiety symptoms as well as health-related quality of life. Interviews were completed by two clinical psychologists via telephone. Six hundred and two family members consented, with data collected on 517 (n = 303 in the COVID-19 group and n = 214 in the non-COVID-19 group). On average, family members in the COVID-19 group were less frequently allowed to visit the ICU (35% vs 88%), and more commonly received patient information by telephone call (84% vs 20%) compared with family members of non-COVID-19 ARDS patients. At 90-days post ICU discharge, PTSD symptoms were significantly more common in family members of patients with COVID-19 than in those with non-COVID-19 ARDS (35% [103/293] vs 19% [40/211]; difference, 16% [95% CI, 8% to 24%]; P < 0.001). Symptoms of anxiety were trending to significance in the COVID-19 vs the non-COVID-19 group (41% [121/294] vs 34% [70/207]; difference, 8% [95% CI, 0% to 16%]; P = 0.05). Symptoms of depression were also higher in the COVID-19 group (31% [91/291] vs 18% [37/209]; difference, 13% [95% CI, 6% to 21%]; P < 0.001).

### Comments

1. Family members of ICU survivors experience adverse mental health outcomes (Post-Intensive Care Syndrome Family (PICS-F) or Family Intensive Care Unit Syndrome (FICUS)) – this is a critical

knowledge gap due to the changed landscape of critical care delivery during the COVID-19 pandemic, including restricted or forbidden visitation, overlaid by other complex societal factors.

2. Rigorous outcome measurement instrument selection and administration via two psychologists, and supervised by a research nurse, reduced bias in this study.
3. This study builds on prior knowledge, finding the level of social support was associated with PTSD symptoms, which is particularly important during the pandemic when usual social support structures may have been significantly disrupted.
4. Understanding the positive psychological attributes of family members such as resilience may also be important to investigate.
5. There may have been sampling bias that may limit generalizability of the findings, as the participating sites were part of the unique FAMIREA study group – a multidisciplinary research network focused on understanding and improving the experience of family members of ICU patients.

### POST-HOSPITAL CARE DELIVERY FOLLOWING COVID-19

Valley TS, Schutz A, Peltan ID, Vranas KC, Mathews KS, Jolley SE, Palakshappa JA, Hough CL; National Heart, Lung, and Blood Institute Clinical Trials Network for the Prevention and Early Treatment of Acute Lung Injury (PETAL). **Organization of Outpatient Care After COVID-19 Hospitalization.** *Chest.* 2022 Jan 31. S0012-3692(22)00197-0. doi: 10.1016/j.chest.2022.01.034. Epub ahead of print. PMID: 35108571; PMCID: PMC8801392

### Summary

Post-ICU follow-up clinics and services for survivors of COVID-19 have growing clinical interest. Little is known about how these models of care are delivered in COVID-19 cohorts. This multi-site survey of hospitals participating in the National Heart, Lung, and Blood Institute Clinical Trials Network for the Prevention and Early Treatment of Acute Lung Injury (PETAL Network), sought to describe outpatient care delivery for post-acute COVID-19. There was a high response rate (92%) with 47 hospitals responding. Seventy-nine percent provided discharge information specific to COVID-19 – related to reasons to return to hospital or seek primary care. However, only 26% of hospitals provided

information related to potential symptoms or impairments of post-acute sequelae of COVID-19. Clinic visits (in-person or virtual) (43%) or telephone (38%) were the most common modes of contact. Seventy percent of hospitals had a post-discharge clinic specific to COVID-19 and most of these (73%) clinics were separate to their hospital's post-ICU clinic. Hospitals without post-acute COVID-19 clinics were more likely to be smaller, for-profit hospitals and in low-income ZIP codes, with a higher proportion of patients insured by Medicaid (than hospitals with clinics). The majority of hospitals with clinics required a referral for the patient to be seen, and patients underwent a range of pulmonary, physical, mental health, and cognitive assessment.

### Comments

1. By surveying the US PETAL network, this study provided a broad capture of diverse hospital settings (academic tertiary and community), although it is acknowledged that these were higher-resourced/urban centers, so the findings may lack generalizability.
2. This study could have been further strengthened by use of an EQUATOR-recommended reporting checklist for electronic surveys.
3. Importantly the paper captures current practice for post-acute COVID-19 and highlights areas for improvement – establishing effectiveness of clinics, what assessments should be undertaken, and how post-COVID-19 sequelae and management differs to other infections or Post-Intensive Care Syndrome.
4. Limited benefit for follow-up clinics in existing literature suggests careful consideration of implementing new services in the constrained health care setting during the pandemic is paramount
5. Conversely, implementation of these clinics offers additional opportunity to set up rigorous programs of evaluation

### RISK FACTORS FOR LONG COVID IN PEDIATRICS FOLLOWING COVID-19 HOSPITALIZATION

Osmanov IM, Spiridonova E, Bobkova P, Gamirova A, Shikhaleva A, Andreeva M, Blyuss O, El-Taravi Y, DunnGalvin A, Comberiat P, Peroni DG, Apfelbacher C,

Genuneit J, Mazankova L, Miroshina A, Chistyakova E, Samitova E, Borzakova S, Bondarenko E, Korsunskiy AA, Konova I, Hanson SW, Carson G, Sigfrid L, Scott JT, Greenhawt M, Whittaker EA, Garralda E, Swann OV, Buonsenso D, Nicholls DE, Simpson F, Jones C, Semple MG, Warner JO, Vos T, Olliaro P, Munblit D; and the Sechenov StopCOVID Research Team. **Risk factors for post-COVID-19 condition in previously hospitalised children using the ISARIC Global follow-up protocol: a prospective cohort study.** *Eur Respir J.* 2022 Feb 3;59(2):2101341. doi: 10.1183/13993003.01341-2021. PMID: 34210789; PMCID: PMC8576804

### Summary

The long-term outcomes of COVID-19 in children is poorly understood. This large prospective cohort study aimed to assess the incidence and associated risk factors for long-term COVID-19 outcomes in previously hospitalized children. Outcomes were collected via telephone interviews by trained assessors using the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) COVID-19 Health and Wellbeing Follow-up Survey for Children. Five hundred and eighteen children (61% of those eligible) were included. The median (interquartile range (IQR)) for age was 10.4 (3–15.2) years, and for follow-up since hospital discharge was 256 (223–271) days. At the time of follow-up, 24.3% of participants reported persistent symptoms – of which the most common symptoms were fatigue (10.7%), sleep disturbance (6.9%) and sensory problems (5.6%). Just over 8% of participants experienced co-occurrence of symptoms. Risk factors for persistent symptoms were: older age “6–11 years” (OR 2.74, 95% CI 1.37–5.75) and “12–18 years” (OR 2.68, 95% CI 1.41–5.4), and a history of allergic diseases (OR 1.67, 95% CI 1.04–2.67).

### Comments

1. This is one of the largest (>500 participants), prospective cohort studies in children and adolescents to date, which has investigated symptoms of Long Covid, in an otherwise limited field.
2. This cohort study lacks a comparator group, so it is difficult to ascertain the true incidence and prevalence of long-term symptoms related to COVID-19 hospitalization.

3. This was a single-site study which limits generalizability of these findings.
4. This study included an indicator of baseline health status pre COVID-19 that was assessed at interview using a 0–100 wellness scale (0 was the worst possible health and 100 was the best possible health), although may be subject to recall bias.
5. Further studies of Long Covid in pediatrics that includes a comparator cohort and longitudinal assessment is required.

## OTHER ARTICLES OF INTEREST

### Combined Physical, Mental Health, Cognitive Outcomes Post COVID-19 and PICS

Evans RA, McAuley H, Harrison EM, et al. **Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study** [published correction appears in *Lancet Respir Med*. 2022 Jan;10(1):e9]. *Lancet Respir Med*. 2021;9(11):1275-1287. doi:10.1016/S2213-2600(21)00383-0

Latronico N, Peli E, Calza S, Rodella F, Novelli MP, Cella A, Marshall J, Needham DM, Rasulo FA, Piva S; LOTO Investigators. **Physical, cognitive and mental health outcomes in 1-year survivors of COVID-19-associated ARDS**. *Thorax*. 2022 Mar;77(3):300-303.

Geense WW, Zegers M, Peters MAA, Ewalds E, Simons KS, Vermeulen H, van der Hoeven JG, van den Boogaard M. **New Physical, Mental, and Cognitive Problems 1 Year after ICU Admission: A Prospective Multicenter Study**. *Am J Respir Crit Care Med*. 2021 Jun 15;203(12):1512-1521.

### Physical Outcomes

Gérard M, Mahmutovic M, Malgras A, Michot N, Scheyer N, Jaussaud R, Nguyen-Thi PL, Quilliot D. **Long-Term Evolution of Malnutrition and Loss of Muscle Strength after COVID-19: A Major and Neglected Component of Long COVID-19**. *Nutrients*. 2021 Nov 6;13(11):3964.

### Psychological Outcomes

McGinty EE, Presskreischer R, Anderson KE, Han H, Barry CL. **Psychological Distress and COVID-19-Related Stressors Reported in a Longitudinal Cohort of US Adults in April and July 2020**. *JAMA*. 2020 Dec 22;324(24):2555-2557.

Parker C, Shalev D, Hsu I, Shenoy A, Cheung S, Nash S, Wiener I, Fedoronko D, Allen N, Shapiro PA. **Depression, Anxiety, and Acute Stress Disorder Among Patients Hospitalized With COVID-19: A Prospective Cohort Study**. *J Acad Consult Liaison Psychiatry*. 2021 Mar-Apr;62(2):211-219.

Perlis RH, Ognyanova K, Santillana M, Baum MA, Lazer D, Druckman J, Della Volpe J. **Association of Acute Symptoms of COVID-19 and Symptoms of Depression in Adults**. *JAMA Netw Open*. 2021 Mar 1;4(3):e213223.

### Cognitive and Neuropsychiatric Outcomes

Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, Rodrigues NB, Subramaniapillai M, Di Vincenzo JD, Cao B, Lin K, Mansur RB, Ho RC, Rosenblat JD, Miskowiak KW, Vinberg M, Maletic V, McIntyre RS. **Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis**. *Brain Behav Immun*. 2022 Mar;101:93-135.

Premraj L, Kannapadi NV, Briggs J, Seal SM, Battaglini D, Fanning J, Suen J, Robba C, Fraser J, Cho SM. **Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: A meta-analysis**. *J Neurol Sci*. 2022 Jan 29;434:120162.

Outcomes of Bereaved Caregivers of Critically Ill Adults Kentish-Barnes N, Cohen-Solal Z, Morin L, Souppart V, Pochard F, Azoulay E. **Lived Experiences of Family Members of Patients With Severe COVID-19 Who Died in Intensive Care Units in France**. *JAMA Netw Open*. 2021

Rehabilitation, Recovery, and Post-COVID-19 Care Ceravolo MG, Andrenelli E, Arienti C, Côté P, de Sire A, Iannicelli V, Lazzarini SG, Negrini F, Patrini M, Negrini S. **Rehabilitation and COVID-19: rapid living systematic review by Cochrane Rehabilitation Field - third edition. Update as of June 30th, 2021**. *Eur J Phys Rehabil Med*. 2021 Oct;57(5):850-857.

Parotto M, Myatra SN, Munblit D, Elhazmi A, Ranzani OT, Herridge MS. **Recovery after prolonged ICU treatment in patients with COVID-19**. *Lancet Respir Med*. 2021 Aug;9(8):812-814.

Parker AM, Brigham E, Connolly B, McPeake J, Agranovich AV, Kenes MT, Casey K, Reynolds C, Schmidt KFR, Kim SY, Kaplin A, Sevin CM, Brodsky MB, Turnbull AE. **Addressing the post-acute sequelae of SARS-CoV-2 infection: a multidisciplinary model of care.** *Lancet Respir Med.* 2021 Nov;9(11):1328-1341.

Outcomes after Mild COVID-19 in Health Care Workers  
Havervall S, Rosell A, Phillipson M, Mangsbo SM, Nilsson P, Hober S, Thålin C. **Symptoms and Functional Impairment Assessed 8 Months After Mild COVID-19 Among Health Care Workers.** *JAMA.* 2021 May 18;325(19):2015-2016.

### **Pediatric Outcomes Post COVID-19**

Racine N, McArthur BA, Cooke JE, Eirich R, Zhu J, Madigan S. **Global prevalence of depressive and anxiety symptoms in children and adolescents during COVID-19: a meta-analysis.** *JAMA Pediatr.* 2021.

Lindan CE, Mankad K, Ram D, et al. **Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study.** *Lancet Child Adolesc Health.* 2021;5(3):167-77.

Thallapureddy K, Thallapureddy K, Zerda E, Suresh N, Kamat D, Rajasekaran K, Moreira A. **Long-Term Complications of COVID-19 Infection in Adolescents and Children.** *Curr Pediatr Rep.* 2022 Feb 1:1-7. Epub ahead of print.

## Medical Education

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### DIVERSITY, EQUITY AND INCLUSION

Morris DB, Gruppuso PA, McGee HA, Murillo AL, Grover A, Adashi EY. **Diversity of the National Medical Student Body- Four Decades of Inequities.** *N Engl J Med* 2021; 384(17): 1661-1668. doi: 10.1056/NEJMsr2028487. PMID: 33913645

#### Summary

This study examined data on gender, race and ethnicity of U.S. medical school enrollees from 1978-2019. The data sets were provided by the Association of American Medical Colleges (AAMC) but excluded enrollees who were not U.S. citizens or permanent U.S. residents. Racial categories were selected to mirror those used by the U.S. Census Bureau. The percentages of enrollees in each category of gender and race or ethnic group were compared over time. The percentage of women enrollees increased from 24.4% in 1978 to 50.6% in 2019, with the biggest increase (12-fold) noted for Asian women. There was a marked decrease in White male enrollment from 61.2% to 25.7% in the same time period, offset by an increase in the percentage of Asian men from 2.1 % to 10.7%. In contrast, there were only modest increases in the percentages of Black women (3.6% to 4.4%) and an actual decrease in the percentage of Black men (3.1% to 2.9%). Compared to relative percentages in the U.S. Census, the medical school student body remains under-representative of men and women who identify as Black, Hispanic, American Indian/Alaskan Native, and Native Hawaiian/Other Pacific Islander, as well as White women.

#### Comments

1. This study further demonstrates the continued challenges in achieving a racially and ethnically diverse medical student body in U.S. medical schools, with notable downstream effects on the overall diversity of the physician workforce.
2. While U.S. medical schools have achieved gender parity amongst enrollees, the racial and ethnic

composition remains uneven compared to the U.S. Census, with persistent under-representation amongst Black, Hispanic, American Indian/Alaskan Natives and Native Hawaiian/Other Pacific Islander students.

3. The AAMC changed the methodology by which race was classified during the study period with changes allowing respondents to designate multiple races or ethnic groups rather than just one as was done prior to 2002, making interpretation of the trends amongst Hispanic enrollees (for whom more than 50% identified more than one race or ethnic group) more challenging to interpret.
4. Historically Black medical schools continue to play an important role in contributing to the diversity of the overall medical student body, accounting for 15% of Black male enrollees nationally.
5. The lack of significant improvement in the racial/ethnic diversity of the medical student body in the last 4 decades underscores the importance of a renewed focus on medical school admissions processes to promote recruitment of applicants from historically excluded groups by adopting holistic application review processes, addressing structural issues such as standardized testing, prerequisites, and advising, and investing in pipeline efforts.

### CLINICIAN WELL-BEING AND BURNOUT

Vance MC, Herberman HB, Ursano RJ, Zhao Z, Miller JT, Clarion MJD, West JC, Morganstein JC, Iqbal A, Sen S. **Exposure to Workplace Trauma and Posttraumatic Stress Disorder Among Intern Physicians.** *JAMA Network Open* 2021; 4(6): e2112837. doi:10.1001/jamanetworkopen.2021.12837. PMID: 34100937; PMCID: PMC8188264

#### Summary

This nationwide cohort study surveyed incoming interns across a variety of specialties at U.S. residency

programs nationwide in the 2018-2019 academic year. The primary outcome was prevalence of work-related trauma and prevalence of post-traumatic stress disorder (PTSD) among interns who experienced work-related trauma. Trauma exposure and PTSD symptoms were assessed using the Primary Care PTSD Screen for DSM-5. Surveys were distributed prior to starting internship and at 3-month intervals thereafter. Of the 1134 respondents, 58.6% were female and 61.6% were non-Hispanic White. The overall response rate was 26% (19% of surgical interns and 28% of non-surgical interns responded to the survey). In total, 56.4% of respondents reported work-related trauma exposure. Of the interns who reported work-related trauma, 19% screened positive for PTSD. Approximately 1 in 10 trainees screened positive for PTSD by the end of intern year. Trauma exposure ranged from 43.1% of anesthesiology trainees to 72.4% in emergency medicine. 56.6% of internal medicine trainees reported trauma exposure. Factors significantly associated with trauma exposure included specialty, early family environment, stressful life experiences at baseline or during internship and a current or lifetime history of depression. The highest rate of possible PTSD was seen amongst pediatrics interns (30%).

### Comments

1. This study demonstrates a concerning rate of trauma exposure and PTSD among a large nationwide sample of intern trainees in multiple specialties.
2. This study may underestimate the current prevalence of PTSD and trauma exposure amongst intern trainees as it was conducted prior to the COVID-19 pandemic.
3. PTSD rates among physicians in training were 3-fold higher than in the general population.
4. The low overall response rate of 26%, particularly among surgical interns as well as the absolute number of responses in any given specialty, may limit the generalizability of these findings across all specialty trainees.
5. While many of the factors significantly associated with work-related trauma exposure were considered non-work related static indicators, factors associated with PTSD were more likely to be work-related.

### CLINICAL TRAINING

Matta A, Adamson R, Hayes MM, Carmona H, Soffler MI, Benzaquen S, Gupta E. **Impact of the COVID-19 Pandemic on U.S. Pulmonary and Critical Care Medicine Fellowship Training.** *ATS Scholar* 2021; 2(4): 556-565. doi: 10.34197/ats-scholar.2021-0067OC. PMID: 35083462; PMCID: PMC8787736

### Summary

The authors conducted an anonymous 30-question web-based survey of Pulmonary and Critical Care Medicine (PCCM) program directors (PDs) nationally aimed at assessing the perceived impact of the COVID-19 pandemic on PCCM fellowship training at their respective institutions. A total of 69 of the 242 PDs surveyed (28.5%) completed the questionnaire, the majority of whom represented university-based programs throughout all regions of the United States. The areas most significantly impacted included PFT interpretation and ambulatory clinical experiences. The number of elective bronchoscopies performed by fellows was also negatively impacted, although the majority of trainees were still able to achieve the required number of bronchoscopies for graduation. In addition, there was a reported increase in the time PCCM trainees spent in the intensive care unit as well as an increase in the performance of a number of common intensive care unit (ICU) procedures such as central venous catheter insertion. Conversely, there was a perceived decrease in the number of intubations, tracheostomies and ICU bronchoscopies. There was also a reported increase in virtual conferences. Overall, PD perceptions of the COVID-19 pandemic on PCCM training were variable (34.4%) or negative (31.1%). Fewer perceived the pandemic as having positive (26.1%) or no impact (6.6%).

### Comments

1. This study indicates a potentially significant impact on ambulatory pulmonary fellowship training as a result of the COVID-19 pandemic.
2. The low survey response rate and lack of participation by PCCM trainees should be considered when drawing conclusions from this study.
3. The study findings provide insight for program leadership for potentially tailoring future

educational programming to meet the needs of the cohorts of trainees most directly impacted by the COVID-19 pandemic, with demonstrated need for potential enhancement of ambulatory, PFT and bronchoscopy training.

4. The study includes perceived changes in practice and educational patterns rather than documenting objective data such as changes in total numbers of procedures performed, outpatient encounters, etc.
5. The survey was distributed in November 2020 and therefore may not capture further impacts on PCCM training in subsequent COVID-19 surges, thereby potentially underestimating the pandemic's impact on clinical training.

### RECRUITMENT

Burk-Rafel J, Reinstein I, Feng J, Kim MB, Miller LH, Cocks PM, Marin M, Aphinyanaphongs Y. **Development and Validation of a Machine Learning-Based Decision Support Tool for Residency Applicant Screening and Review.** *Academic Medicine* 2021; 96(11S): S54-61. doi: 10.1097/ACM.0000000000004317. PMID: 34348383

### Summary

This study explored the use of a machine learning-based decision support tool (DST) for residency applicant screening and review for NYU Langone Internal Medicine (IM) applicants for the 2018-2020 application cycles. Electronic Residency Applicant Service (ERAS) data for 8243 applicants was downloaded and linked to invitation to interview by human reviewers. These data were used to generate an ML model using gradient boosting based on 61 applicant features (ex: demographics, medical school information, etc). Unstructured data such as letters of recommendation, personal statements, etc. were not included in the analysis. 1774 applicants (21.5%) were excluded for not meeting program requirements. An ML model to predict the probability of interview invitation was built using 80% of the applicants as training data. The model was then validated using the remaining 20% of applicants included in the study. For each applicant, the model produced a probability score for interview invite. The ML model areas under the receiver operating characteristic and precision recall curves were 0.95 and 0.76 respectively. The model had high performance

metrics for predicting interview offers, even in the absence of USMLE scores.

### Comments

1. The authors present a novel use of technology to potentially alleviate some of the administrative burden posed by reviewing large numbers of applicants to training programs; however, the amount of time and specific expertise necessary to build the model used in the study is not described.
2. The use of a machine-learning model to automate invitations to interview for training programs may propagate and automate bias rather than eliminate it.
3. The absence of incorporation of unstructured data such as letters of recommendation, personal statements and medical student performance evaluations may lead to lack of consideration of some of the unique characteristics of applicants that are valued in the holistic review process but missed in easily analyzable ERAS fields.
4. Interestingly, the model performance remained strong despite exclusion of USMLE scores, which have historically been used as an easily identifiable means to exclude applicants from further consideration.
5. The generalizability of this approach at other institutions or in other training programs outside of internal medicine is not yet known.

### ASSESSMENT

Heath JK, Wang T, Santhosh L, Denson J, Holmboe E, Yamazaki K, Clay AS, Carlos WG. **Longitudinal Milestone Assessment Extending Through Subspecialty Training: The Relationship Between ACGME Internal Medicine Residency Milestones and Subsequent Pulmonary and Critical Care Fellowship Milestones.** *Acad Med* 2021; 96(11): 1603-1608 doi: 10.1097/ACM.0000000000004165. PMID: 34010863

### Summary

This multicenter retrospective cohort analysis assessed the relationship between internal medicine (IM) residency and pulmonary and critical care medicine (PCCM) fellowship milestones. The study included all PCCM fellows enrolled in ACGME-accredited fellowship programs from 2017-2018 who had complete IM milestone ratings available from 2014-2017 (354 fellows;

65% male; representing 198 IM residencies and 143 PCCM fellowships). Focusing on interpersonal and communication skills (ICS) and professionalism, the authors assessed these milestones at each time point during IM residency to determine associations with receiving a corresponding low PCCM milestone rating (specifically  $\leq 2.5$ ) during the first fellowship year. ICS and professionalism domains were selected for their shared descriptions and behavioral anchors between IM and PCCM training. Approximately one-third of the PCCM trainees in this study were rated  $\leq 2.5$  during their first year of fellowship across the professionalism and ICS sub-competencies. IM trainees with low ratings in professionalism and ICS sub-competencies were more likely to have poor achievement on these domains in their first year of fellowship. Each ICS sub-competency and PROF03 was significantly associated with future lapses in fellowship.

### Comments

1. This study demonstrates an association between residency and fellowship milestone ratings in professionalism and ICS sub-competencies, potentially adding validity evidence to the utility of the ACGME milestone rating system.
2. Based on these findings, IM residency milestones may represent an opportunity for longitudinal assessment and the creation of individualized learning plans to target areas of potential deficiency for incoming fellows, although there is a potential for this data leading to negative biases with subsequent fellowship assessments.
3. The association of residency and fellowship milestone ratings in other domains besides professionalism and ICS is not known but warrants further exploration.
4. Ultimately, the study was underpowered to assess most of the sub-competency domains due to a high number of trainees with incomplete milestone data from residency training.
5. Future study of other subspecialties with more longitudinal milestone data is needed.

### OTHER ARTICLES OF INTEREST

#### Diversity Equity and Inclusion

Nguyen M, Mason HRC, O'Connor PG, Nunez-Smith M, McDade WA, Latimore D, Boatright D. **Association of Socioeconomic Status With Alpha Omega Alpha Honor Society Membership Among Medical Students.** *JAMA Network Open* 2021; 4(6): e2110730.

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## Recruitment

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## Assessment

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## Interventional Pulmonology

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### ROBOTIC BRONCHOSCOPY

Agrawal A, Ho E, Chaddha U, Demirkol B, Bhavani SV, Hogarth DK, Murgu S. **Factors Associated With Diagnostic Accuracy of Robotic Bronchoscopy With 12-Month Follow-up.** *Ann Thorac Surg.* 2022 Jan 17:S0003-4975(22)00042-X. doi: 10.1016/j.athoracsur.2021.12.041. Epub ahead of print. PMID: 35051388

#### Summary

This group reviewed consecutive cases of robotic bronchoscopy done at their institution over an 18-month period. Data was reviewed retrospectively, and all patients had at least 12-months of follow-up. The criteria used for diagnostic yield was conservative. Overall diagnostic accuracy was 77%, in line with other studies using robotic bronchoscopy. Localization, as defined by system imaging was 94%, however if defined by radial EBUS (rEBUS) imaging it was 82%. Of those with rEBUS views, 55% demonstrated eccentric views. Of those nodules not localized by rEBUS, most were subsolid or ground glass. Multivariate analysis revealed only larger nodules (>20mm) and presence of a rEBUS view was associated with higher yield. Notably, neither presence of a bronchus sign, nor the type of rEBUS view, were associated with higher yield, which may set robotic bronchoscopy apart from prior navigational platforms.

#### Comments

1. Though this study was designed to evaluate the factors that led to diagnostic accuracy of robotic bronchoscopy, several other important findings as they related to robotic bronchoscopy and nodule biopsy were elucidated.
2. Factors previously shown to influence yield in other navigational bronchoscopy platforms, such as bronchus sign, concentric rEBUS view, and location did not appear to effect yield in this study.
3. The only factors impacting yield were size and presence of any rEBUS view.

4. The fact that the type of rEBUS view did not effect yield suggests that robotic bronchoscopy may be able to overcome prior impediments associated with plastic catheters, namely tip stability and fine movements, which allow for accurate targeting
5. The inability to overcome a non rEBUS view still shows limitations of not having real-time image guidance for targeting nodules.

### ENDOBONCHIAL ULTRASOUND

Punjabi A, Al-Najjar H, Teng B, Borrill Z, Brown L, Nagarajan T, Gallagher J, Grundy S, Sundar R, Higgins C, Shackley D, Sinnott N, Balata H, Lyons J, Martin J, Brocklesby C, Crosbie P, Booton R, Evison M. **Performance monitoring of EBUS for the staging and diagnosis of lung cancer: auditing the Greater Manchester EBUS service against new national standards.** *BMJ Open Respir Res.* 2021 Jun;8(1):e000777. doi: 10.1136/bmjresp-2020-000777. PMID: 34172527; PMCID: PMC8237730.

#### Summary

This is the first study to publish performance measures relating to the quality metrics set by the British National Institute for Health and Care Excellence (NICE). The National EBUS service specification was instituted to drive quality EBUS services across the UK, with quality metrics in both diagnostic and staging EBUS settings. Five EBUS centers in the Greater Manchester Cancer Alliance reported their quality metrics in this study, and discussed how evaluation of these quality metrics against national benchmarks led to performance improvement measures. These metrics include time from referral to EBUS, tissue adequacy rates, cases needing repeat procedures, and sensitivity of N2/N3 disease. This study has significant impact in that it shows not only can EBUS quality metric reporting be instituted in day-to-day care, but also how this can result in quality improvement measures that drive higher quality patient care.

### Comments

1. Though more or less an observational trial, this was the first study to document the local outcomes of an EBUS-oriented quality metric initiative.
2. The quality metrics used by NICE not only includes bronchoscopic quality measures, but factors that integrate into the EBUS program, such as time from referral to procedure, pathology reporting timeliness, and successful molecular marker testing
3. This study lays the groundwork for EBUS quality metrics in the United States, where there are no current agreed upon quality metrics in clinical practice.

### PEDIATRIC BRONCHOSCOPY

Sharluyan A, Osona B, Frontera G, Brandstrup KB, Figuerola J, Sanz-Ruiz I, Salas A, Garrido B, Eva CG, Fernandez A, Peña-Zarza JA, Gil JA, Bover-Bauzá C, Sailer S. **High flow nasal cannula versus standard low flow nasal oxygen during flexible bronchoscopy in children: A randomized controlled trial.** *Pediatr Pulmonol.* 2021 Dec;56(12):4001-4010. doi: 10.1002/ppul.25655. Epub 2021 Sep 10. PMID: 34506689

#### Summary

This is a randomized clinical trial comparing high flow nasal cannula (HFNC) with low flow nasal cannula in the pediatric population undergoing bronchoscopy. Hypoxemia is the most frequent complication of pediatric flexible bronchoscopy procedures, and it may be substantial, especially when performed in infants or during BAL. Infants and children seem to be especially prone to hypoxemia compared to adults, likely relating to partial airway obstruction produced by the bronchoscope, and possibly suctioning of gas within a smaller airway resulting in regional atelectasis. This study group randomized 104 patients to either HFNC or NC, and then studied hypoxemic events in both groups (moderate, O<sub>2</sub> saturation between 90% and 94% for less than 60s; severe, <90% for more than 30s). Patients in the HFNC were significantly less likely to develop severe hypoxemia, with an absolute risk reduction of 0.27. These findings were especially prevalent in children undergoing BAL, with severe hypoxemia developing in 50% of the NC group vs 16% in the HFNC group. No difference in clinical sequelae (i.e. tachycardia, bradycardia, bag ventilation, or procedure interruption) were noted, however.

### Comments

1. This is the first prospective randomized clinical trial comparing HFNC with low flow NC in pediatric bronchoscopy
2. There was a significant reduction in hypoxemic events in the HFNC group compared with the low flow NC group.
3. Hypoxemia was strictly defined in this study, which had been a weakness of other HFNC studies in children.
4. Though hypoxemic events were decreased, there appeared to be no differences in resulting adverse outcomes, such as cardiovascular instability, need for bag ventilation, or interruption/abandonment of the procedure. However, the study may not have been powered to detect these differences.
5. Further studies will need to be done in larger populations to see if its use has clinical utility in preventing adverse outcomes, given the increase in cost of HFNC compared to low flow NC

### TRACHEAL STENOSIS

Kossyvaki V, Anagnostopoulos N, Kaltsakas G, Emmanouil P, Alsaïd A, Touman A, Tzavara C, Koulouris N, Stratakos G. **The Value of Dyspnea and Spirometry in Detecting Relapse of Benign Tracheal Stenosis.** *Respiration.* 2022;101(2):174-183. doi: 10.1159/000519216. Epub 2021 Oct 6. PMID: 34614495

#### Summary

This study group prospectively evaluated a cohort of 35 patients who were referred for benign tracheal stenosis. After bronchoscopic or surgical intervention, patients were followed at frequent intervals up to two years, with each evaluation including pulmonary function tests, recording of Medical Research Council (MRC) dyspnea scores, and bronchoscopic evaluation. Overall, 35 patients were studied, and follow-up visits were divided into types: relapse and non-relapse visits. A relapse was defined as a worsening of stenosis by >15% (measured by airway cross-sectional area) compared to the previous visit. The overall relapse rate was high (73% of patients undergoing endoscopic treatment, 36% of patients undergoing surgical treatment). Relapses were associated with significant reductions in PEF, FEF<sub>25%</sub>, and total peak flow, as well as increases in MRC scores. In the relapse group, the grade of stenosis

highly correlated with total peak flow (TPF), peak expiratory flow (PEF), FEF25%, and MRC (AUC ranging from 0.70 to 0.98). The optimal cutoff for PEF decrease in the relapse group was 11%, with a 93% sensitivity and 98% specificity, suggesting home PEF measurements could serve as an accurate screening tool that could possibly prevent unnecessary surveillance bronchoscopy.

### Comments

1. Though a handful of other studies have evaluated spirometric markers to detect relapse in benign idiopathic tracheal stenosis, this was the first study to evaluate spirometry and dyspnea score as predictors of relapse across all causes of tracheal stenosis, with the majority of patients in this cohort (>90%) having post-intubation/post-tracheostomy stenoses
2. Similar to other studies, PEF was shown to be a sensitive marker of re-stenosis in the mostly post-intubation, post-inflammatory cohort of benign tracheal stenosis.
3. A weakness of the trial was that no multivariate analysis was done to see if any combination of indices could be a better predictor of relapse.
4. Also not reported was the correlation of absolute MRC score with relapse rate and cross sectional area
5. Though promising, the use of PEF as a screening tool to predict relapse of stenosis, and/or whether it could obviate the need for routine surveillance bronchoscopy needs to be validated in larger trials before adopting widespread use.

### BRONCHOSCOPY IN COVID-19

Cumbo-Nacheli G, Colt H, Agrawal A, Cicensia J, Corbetta L, Goel AD, Goga A, Lee HJ, Murgu S, Pannu J, Senitko M, Tarantini F, Vujacich P, Williamson J, Yap E, Lentz RJ.

**Bronchoscopy in Patients With Known or Suspected COVID-19: Results From the Global Pandemic SARS-CoV-2 Bronchoscopy Database (GPS-BD).** *J Bronchology Interv Pulmonol.* 2022 Apr 1;29(2):146-154. doi: 10.1097/LBR.0000000000000805. PMID: 35318989.

### Summary

This study used an online survey tool to retrospectively query bronchoscopists about their experiences with patients with known or suspected COVID-10 over a six-

month period in 2020, from March to August. Data from 289 patients in 26 countries were collected and analyzed for trends and outcomes. One half (40%) of patients had proven COVID-19 infection at the time of bronchoscopy, and the majority of patients had a pre-existing comorbidity (82%) and/or organ failure (80%). Slightly over one-third of patients (37%) were intubated at the time of procedure. Bronchoscopy was performed with diagnostic intent in over half (57%), yielding management changes in 48%. The procedure was performed with therapeutic intent in 25%, mostly for secretion clearance. Complications attributed to bronchoscopy or significant clinical decline within 12 hours of the procedure occurred in 8%, with one death.

### Comments

1. This was an ambitious effort by a world-wide working group that helped define the utility of bronchoscopy early on in the COVID-19 pandemic.
2. Bronchoscopy in the setting of COVID-19 infection seems to have clinical benefit, with diagnosis and/or management change in almost half of the diagnostic cases.
3. Though our current understanding of COVID-19 management is more comprehensive than it was during the data collection period, this study gave important global insights to the use of bronchoscopy in this patient cohort, and helped define the role of bronchoscopy in this disease moving forward.
4. Though reasonable clinical benefits of bronchoscopy were suggested by the data, this must be balanced by the complication rate which is much higher than previously reported for non-COVID bronchoscopy.

### BRONCHOSCOPIC LUNG VOLUME REDUCTION

Hartman JE, Welling JBA, Klooster K, Carpaij OA, Augustijn SWS, Slebos DJ. **Survival in COPD patients treated with bronchoscopic lung volume reduction.** *Respir Med.* 2022 Mar 16;196:106825. doi: 10.1016/j.rmed.2022.106825. Epub ahead of print. PMID: 35325741.

### Summary

This study evaluated all patients with COPD who were referred to Groningen University Medical Center for evaluation for bronchoscopy lung volume reduction

(BLVR) from 2006 to 2019. During this time, data was collected, including pulmonary function testing, chest CT with quantitative analysis, SGRQ and CAT questionnaires, and all comorbidities were documented. A total of 1471 patients were included in the analysis, including 483 patients who were treated with BLVR (73% valves, 27% coils). Patients not treated with BLVR had more COPD exacerbations, better pulmonary function, lower PaO<sub>2</sub>, higher BMI, and less emphysema and air trapping measured on CT. However, patients treated with BLVR were more likely to have history of myocardial infarction, stroke, or percutaneous coronary intervention. The minimum follow-up duration was 633 days. The median survival time in patients receiving BLVR was 8.6 years compared to 6.9 years in the non-BLVR group ( $p < 0.001$ ). Factors that negatively influenced survival included older age, male gender, higher number of pack years, higher rate of COPD-related hospitalization, lower FEV<sub>1</sub> and DLCO, lower BMI, higher percentage of emphysema, and one or more cardiovascular comorbid conditions. When adjusted for these factors, not undergoing a BLVR treatment was an independent predictor of mortality (hazard ratio 2.01).

### Comments

1. This is the first study to report long term mortality outcomes in all patients treated with bronchoscopic lung volume reduction (BLVR).
2. This study differed from others with similar designs in that they included both BLVR responders and non-responders in their comparison to a non-BLVR group.
3. BLVR included patients treated with both coils and valves.
4. Though not a prospective randomized clinical trial, the likelihood one will ever get done is low, and this may be the best data set to draw upon now, and in the future.
5. Though tempting, using this data to compare BLVR survival with that from lung volume reduction surgery should be done with caution given very different study designs

### OTHER ARTICLES OF INTEREST

#### Bronchoscopic Treatment of Emphysema

Egenod T, Tricard J, Fumat R, Simonneau Y, Favard F, Guillot MS, Collot S, Dupuis M, Melloni B, Vergnenegre A,

Guibert N, Dusselier M. **Two-Stage Bronchoscopic Endobronchial Valve Treatment Can Lead to Progressive Lung Volume Reduction and May Decrease Pneumothorax Risk.** *Int J Chron Obstruct Pulmon Dis.* 2021 Jun 28;16:1957-1965. doi: 10.2147/COPD.S307829. PMID: 34234426; PMCID: PMC8254404.

Pison C, Shah PL, Slebos DJ, Ninane V, Janssens W, Perez T, Kessler R, Deslee G, Garner JL, Hartman JE, Degano B, Mayr A, Mayse M, Peterson AD, Valipour A. **Safety of denervation following targeted lung denervation therapy for COPD: AIRFLOW-1 3-year outcomes.** *Respir Res.* 2021 Feb 19;22(1):62. doi: 10.1186/s12931-021-01664-5. Erratum in: *Respir Res.* 2021 Mar 15;22(1):83. PMID: 33608007; PMCID: PMC7893728.

#### Bronchoscopy for COVID-19

Arenas-De Larriva M, Martín-DeLeon R, Urrutia Royo B, Fernández-Navamuel I, Gimenez Velandó A, Nuñez García L, Centeno Clemente C, Andreo García F, Rafecas Codern A, Fernández-Arias C, Pajares Ruiz V, Torrego Fernández A, Rajas O, Iturricastillo G, Garcia Lujan R, Comeche Casanova L, Sánchez-Font A, Aguilar-Colindres R, Larrosa-Barrero R, García García R, Cordovilla R, Núñez-Ares A, Briones-Gómez A, Cases Viedma E, Franco J, Cosano Povedano J, Rodríguez-Perálvarez ML, Cebrian Gallardo JJ, Nuñez Delgado M, Pavón-Masa M, Valdivia Salas MDM, Flandes J. **The role of bronchoscopy in patients with SARS-CoV-2 pneumonia.** *ERJ Open Res.* 2021 Jul 12;7(3):00165-2021. doi: 10.1183/23120541.00165-2021. PMID: 34258257; PMCID: PMC8183029.

#### EBUS

He RX, Hylton DA, Bédard ELR, Johnson S, Laing B, Valji A, Hanna WC, Turner SR. **Clinical Validation of the Canada Lymph Node Score for Endobronchial Ultrasound.** *Ann Thorac Surg.* 2022 Jan 11:S0003-4975(22)00020-0. doi: 10.1016/j.athoracsur.2021.11.071. Epub ahead of print. PMID: 35031289.

#### Cryobiopsy

Zhang J, Guo JR, Huang ZS, Fu WL, Wu XL, Wu N, Kuebler WM, Herth FJF, Fan Y. **Transbronchial mediastinal cryobiopsy in the diagnosis of mediastinal lesions: a randomised trial.** *Eur Respir J.* 2021 Dec 9;58(6):2100055. doi: 10.1183/13993003.00055-2021. PMID: 33958432.

Herth FJ, Mayer M, Thiboutot J, Kapp CM, Sun J, Zhang X, Herth J, Kontogianni K, Yarmus L. **Safety and Performance of Transbronchial Cryobiopsy for Parenchymal Lung Lesions.** *Chest.* 2021 Oct;160(4):1512-1519. doi: 10.1016/j.chest.2021.04.063. Epub 2021 May 7. PMID: 33971147.

### Bronchoscopy Anesthesia

Longhini F, Pelaia C, Garofalo E, Bruni A, Placida R, Iaquina C, Arrighi E, Perri G, Procopio G, Cancelliere A, Rovida S, Marrazzo G, Pelaia G, Navalesi P. **High-flow nasal cannula oxygen therapy for outpatients undergoing flexible bronchoscopy: a randomised controlled trial.** *Thorax.* 2022 Jan;77(1):58-64. doi: 10.1136/thoraxjnl-2021-217116. Epub 2021 Apr 29. PMID: 33927023.

### Bronchoscopy for Lung Nodule Diagnosis

Katsis J, Roller L, Aboudara M, Pannu J, Chen H, Johnson J, Lentz RJ, Rickman O, Maldonado F. **Diagnostic Yield of Digital Tomosynthesis-assisted Navigational Bronchoscopy for Indeterminate Lung Nodules.** *J Bronchology Interv Pulmonol.* 2021 Oct 1;28(4):255-261. doi: 10.1097/LBR.0000000000000766. PMID: 33734149.

Kalchiem-Dekel O, Connolly JG, Lin IH, Husta BC, Adusumilli PS, Beattie JA, Buonocore DJ, Dycoco J, Fuentes P, Jones DR, Lee RP, Park BJ, Rocco G, Chawla M, Bott MJ. **Shape-Sensing Robotic-Assisted Bronchoscopy in the Diagnosis of Pulmonary Parenchymal Lesions.** *Chest.* 2022 Feb;161(2):572-582. doi: 10.1016/j.chest.2021.07.2169. Epub 2021 Aug 9. PMID: 34384789; PMCID: PMC8941601.

### Transbronchial Microwave Ablation

Zeng C, Fu X, Yuan Z, Hu S, Wang X, Ping W, Cai Y, Wang J. **Application of electromagnetic navigation bronchoscopy-guided microwave ablation in multiple pulmonary nodules: a single-centre study.** *Eur J Cardiothorac Surg.* 2022 Feb 7;ezac071. doi: 10.1093/ejcts/ezac071. Epub ahead of print. PMID: 35136984.

Xie F, Chen J, Jiang Y, Sun J, Hogarth DK, Herth FJF. **Microwave ablation via a flexible catheter for the treatment of nonsurgical peripheral lung cancer: A pilot study.** *Thorac Cancer.* 2022 Apr;13(7):1014-1020. doi: 10.1111/1759-7714.14351. Epub 2022 Feb 14. PMID: 35166043; PMCID: PMC8977152

### Bronchoscopy in ILD

Nandy S, Raphaely RA, Muniappan A, Shih A, Roop BW, Sharma A, Keyes CM, Colby TV, Auchincloss HG, Gaissert HA, Lanuti M, Morse CR, Ott HC, Wain JC, Wright CD, Garcia-Moliner ML, Smith ML, VanderLaan PA, Bergei SR, Mino-Kenudson M, Horick NK, Liang LL, Davies DL, Szabari MV, Caravan P, Medoff BD, Tager AM, Suter MJ, Hariri LP. **Diagnostic Accuracy of Endobronchial Optical Coherence Tomography for the Microscopic Diagnosis of Usual Interstitial Pneumonia.** *Am J Respir Crit Care Med.* 2021 Nov 15;204(10):1164-1179. doi: 10.1164/rccm.202104-0847OC. PMID: 34375171; PMCID: PMC8759308.

### Pediatric Bronchoscopy

Ferraro VA, Baraldi E, Stabinger D, Zamunaro A, Zanconato S, Carraro S. **Pediatric flexible bronchoscopy: A single-center report.** *Pediatr Pulmonol.* 2021 Aug;56(8):2634-2641. doi: 10.1002/ppul.25458. Epub 2021 May 18. PMID: 33969642; PMCID: PMC8360175.

Wong MD, Thomas RJ, Powell J, Masters IB. **Flexible Bronchoscopy Diagnosis of Uncommon Congenital H-type Tracheoesophageal Fistula, Dual Fistulae, Bronchoesophageal Fistula, and Recurrence of Fistula in Children: A 20-year Experience.** *J Bronchology Interv Pulmonol.* 2022 Apr 1;29(2):99-108. doi: 10.1097/LBR.0000000000000793. PMID: 34282086.

### Therapeutic Bronchoscopy

Lee EYC, McWilliams AM, Salamonsen MR. **Therapeutic Rigid Bronchoscopy Intervention for Malignant Central Airway Obstruction Improves Performance Status to Allow Systemic Treatment.** *J Bronchology Interv Pulmonol.* 2022 Apr 1;29(2):93-98. doi: 10.1097/LBR.0000000000000808. PMID: 35318986.

## ARDS

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### ARDS PHENOTYPES

Sinha P, Delucchi KL, Chen Y. **Latent class analysis-derived subphenotypes are generalizable to observational cohorts of acute respiratory distress syndrome: A prospective study.** *Thorax* 2022; Jan;77(1):13-21. doi: 10.1136/thoraxjnl-2021-217158. Epub 2021 Jul 12. PMID: 34253679; PMCID: PMC8688287

### Summary

Building upon previous studies using latent class analysis (LCA) within previous ARDS clinical trial cohorts, this study delved into observational cohorts with greater heterogeneity than the narrow foci of these randomized controlled trials. LCA is a model-based approach that clusters subgroups within a larger heterogeneous population based on available data. In this approach, variables considered to help define these subgroups, or “classes”, included demographic data, ARDS risk factors, vasopressor use, and clinical labs/biomarkers (including IL-6, IL-8, sTNFR-1, protein C, and others). The authors used two existing and sizably different registries: the Validating Acute Lung Injury markers for Diagnosis (VALID) and Early Assessment of Renal and Lung Injury (EARLI) cohorts, both of which included invasive and non-invasive mechanically ventilated patients with ARDS. In both cohorts, a 2-class model was deemed to have the best fit and similar to previous studies, retaining a clear divergence between hyper- and hypoinflammatory subphenotypes (similar to past studies). These two classes also varied by comorbidities like alcohol abuse, liver disease, and neutropenia (hyperinflammatory) versus COPD (hypoinflammatory class). Trauma-associated ARDS, composing 28% of the VALID cohort’s patients, seemed to be a distinct class of patients, supporting the need for further exploration of the differences between ARDS triggers.

### Comments

1. Phenotyping ARDS patients, and continuing to reproduce these results in multiple cohorts—

including these two observational registries—brings the field substantially closer to both producing clinical management guidelines on treatment strategies best suited to each subphenotype AND informing future clinical trial design which stratifies analyses based on these groupings.

2. Due to the level of detail on comorbidities in these cohorts, as well as the inclusion of more patients with otherwise RCT-disqualifying conditions (e.g., end-stage liver disease), we have the guidance on how to better generalize these LCA subphenotypes to our general ARDS patient populations.
3. The direct clinical applications of this analysis still need to be operationalized into pragmatic assays for determining subphenotypes as the current discriminative biomarkers (i.e., IL-8, protein C) require time-intensive testing.
4. Combination of this testing with more readily identifiable data in the electronic health record may help us more quickly develop clinical applications (see below – Maddali et al, *Lancet Respir Med* 2022 and Duggal et al, *BMJ Open* 2022).
5. The relevance of these subphenotypes to downstream patient-centered outcomes is still unclear (see below – Hashem et al, *Thorax* 2021), but if they can help us identify who benefits from which specific therapies, we have the opportunity to clinically improve outcomes beyond just mortality.

### ARDS MANAGEMENT: PRESSURE TARGETS

Sarge T, Baedorf-Kassis E, Banner-Goodspeed V, et al. **Effect of esophageal pressure-guided positive end-expiratory pressure on survival from acute respiratory distress syndrome: A risk-based and mechanistic reanalysis of the EPVent-2 trial.** *Am J Respir Crit Care Med* 2021; 204(10): 1153-1163. doi: 10.1164/rccm.202009-3539OC. PMID: 34464237; PMCID: PMC8759303

## Summary

In this post-hoc analysis of the Esophageal Pressure-guided Ventilation 2 (EPVent-2) trial (which found no mortality/morbidity benefit with targeting esophageal pressure [Pes] vs. empirical high PEEP in patients with moderate to severe ARDS), the authors aimed to 1) investigate heterogeneity of treatment effect due to multiorgan dysfunction and 2) examine the contribution of targeting lung mechanics on outcomes. Defined as APACHE-II score, multiorgan dysfunction contributed significantly to the effect of Pes-guided PEEP on 60-day mortality—those with low APACHE scores did better with Pes-guiding PEEP titration, while those with high scores did worse. Similar findings were seen when looking at the trial's secondary outcomes of ventilator-free days and shock-free days. In the mechanistic study, the authors examined the effect of the absolute value of end-expiratory transpulmonary pressure (Pl) averaged through Day 3—a target which balances risks of atelectrauma from negative Pl and barotrauma from overly positive Pl—on 60-day mortality. Less than half of the trial patients had end-expiratory Pls within the postulated target range (-2 to 2cm H<sub>2</sub>O), and higher absolute values were associated with worse outcomes, including mortality and shock, even after adjusting for APACHE-II.

## Comments

1. This study captures the importance of accounting for patient differences in critical care trials and understanding that patients may respond differently to therapies, depending on their phenotype, comorbidities, and/or trigger for their respiratory failure (e.g., differential response to steroids, see below – Sinha et al, *AJRCCM* 2021).
2. The mechanistic aim's findings on the benefits of a neutral end-expiratory pleural pressure target provides more precise and useful guidance for esophageal manometry both in research and clinical practice.
3. The results also support that Pes-guided therapy to a Pl of 0-6 cm H<sub>2</sub>O in those with shock may have worsened hemodynamics and thereby worsened outcomes—other targets may be safer for this particular subgroup and warrant further investigation.

4. While this post hoc analysis is hypothesis generating, this study provides strong evidence to support the growing impetus to personalize ARDS management and to target more clinically meaningful targets (similar to Goligher et al, *AJRCCM* 2021 – see below), though we have a ways to go to implement pragmatic approaches to this individualized diagnostic and therapeutic approach.
5. The authors have a great explanation for why ARDS trials are so commonly negative, stopped for futility, and/or not as definitive in addressing the problem as originally planned—so much is dependent on patients' individual risks of death, disease-attributable risk (death driven by ARDS), mechanism-attributable risk (can we confidently say that the risk of death from ARDS is driven by the mechanism targeted by the trial), efficacy of intervention to modify this risk, and risk of “off-target effects” from the intervention

## ARDS MANAGEMENT: NON-INVASIVE VENTILATION

Perkins GD, Ji C, Connolly BA, et al. **Effect of noninvasive respiratory strategies on intubation or mortality among patients with acute hypoxemic respiratory failure and COVID-19: The RECOVERY-RS randomized clinical trial.** *JAMA* 2022; 327(6): 546-558. doi: 10.1001/jama.2022.0028. PMID: 35072713; PMCID: PMC8787685

## Summary

In this parallel-group, open-label, adaptive, randomized clinical trial, the investigators compared continuous positive airway pressure ventilation (CPAP) or high-flow nasal oxygen (HFNO) with usual oxygen therapy in hospitalized patients with acute hypoxemic respiratory failure secondary to COVID-19 infection. Patients were randomized to receive CPAP, HFNO, or oxygen therapy in a 1:1:1 basis or on a 1:1 basis if CPAP or HFNO was not available due to equipment resource constraints. The primary outcome was a composite of intubation or mortality within 30 days, with adjustment for treatment phase for COVID-19 waves and changes in standards of care (addition of dexamethasone and tocilizumab). There was a high crossover rate between arms (17% overall, with ~23% of the oxygen therapy group receiving either CPAP or HFNO). While the trial stopped early due to declining COVID-19 case numbers, patients randomized to CPAP had lower rates of the composite

outcome than the conventional oxygen therapy group (36.3% vs. 44.4%,  $p=0.03$ ), but this difference was driven by lower rates of intubation when CPAP was used, not a mortality benefit. No significant difference was seen between HFNO and oxygen therapy. Additionally, CPAP was associated with higher numbers of adverse events (as compared to HFNO or oxygen therapy).

### Comments

1. Though there was a high rate of crossover, the investigators employed inverse probability weighting to account for the bias introduced by the treatment change; this secondary analysis confirmed the primary findings.
2. The study terminated early, so may have been underpowered to see a difference in outcomes between HFNO and conventional oxygen therapy (as compared to Ospina-Tascon et al, *JAMA* 2021 – see below).
3. Interestingly, the trial was designed to only allow for CPAP, instead of an option for bi-level positive airway pressure ventilation (BIPAP), which limits the results' generalizability as BIPAP has been shown in other studies to be helpful in mitigating poor outcomes.
4. As fewer CPAP patients required admission to the ICU but mortality benefit was not found, we have to ask how does location of critical care delivery affect outcomes—would these patients have done better had all been able to be admitted to the ICU for higher level of monitoring and intubation earlier if needed?
5. Patients in the HFNC group had higher percentages of awake prone positioning, a treatment associated with improved outcomes in COVID-19, as compared to both the other two groups.

### ARDS MANAGEMENT: OXYGENATION

Schjørring OL, Klitgaard TL, Perner A, et al. **Lower or higher oxygenation targets for acute hypoxemic respiratory failure.** *N Engl J Med* 2021; 384(14): 1301-1311. doi: 10.1056/NEJMoa2032510. Epub 2021 Jan 20. PMID: 33471452

#### Summary

In this multicenter, stratified, parallel group clinical trial, the Handling Oxygen Targets in the ICU (HOT-ICU) investigators compared the effect of PaO<sub>2</sub> target of 60mm Hg vs. 90mm Hg for ICU patients with acute

hypoxemic respiratory failure on 90-day mortality. The cohort was primarily medical patients, requiring either invasive or non-invasive mechanical ventilation, with over half in each arm admitted with pneumonia. Sites adhered well to the protocol, with good separation between arms for the PaO<sub>2</sub> and SaO<sub>2</sub> measurements for all 90 days. No differences in 90-day mortality were seen between the two groups, nor was there a difference between the percentage of days alive without life support (ventilator-free days) or adverse events. However, the mortality of this cohort was double that estimated based on previous studies, attributed to the fact that this was a primarily medical ICU patient population and those with more severe hypoxemia.

### Comments

1. While many contend that targeting lower PaO<sub>2</sub> targets helps to get patients off ventilators faster (more aggressive weaning of the FiO<sub>2</sub>), this high quality study shows that it does not make as much as a difference as previously theorized.
2. As specific patient phenotypes or triggers of the acute hypoxemic respiratory failure may benefit from higher or lower targets, this study's similar rates of adverse events between the two target groups support the safety of pursuing more patient group-specific studies.
3. Protocol measurements were as rigorous as possible, with requirements of arterial blood gas measurements (PaO<sub>2</sub> and SaO<sub>2</sub>) and ongoing tracking of the corresponding peripheral saturations to the goal PaO<sub>2</sub> when a PaO<sub>2</sub> was not available.
4. Race/ethnicity was not included in this study—something that the authors highlight as a limitation; considering that peripheral measurements can be inaccurate and overestimate PaO<sub>2</sub> (see below — Wong et al, *JAMA Netw Open* 2021), we have to be careful targeting a lower PaO<sub>2</sub> using the surrogate of a peripheral measurement.

### ARDS MANAGEMENT: ECMO

Gannon WD, Stokes JW, Francois SA, et al. **Association between availability of ECMO and mortality in COVID-19 patients eligible for ECMO: A natural experiment.** *Am J Respir Crit Care Med* 2022. Published ahead of print Feb 25, 2022. <https://doi.org/10.1164/rccm.202110-2399LE>.

## Summary

Though a limited in scope, this study is a prospective analysis of all patients with acute hypoxemic respiratory failure secondary to COVID-19, referred for ECMO to a single health system over an eight-month time period. Using standardized criteria for severe ARDS (in line with EOLIA trial) and for exclusion criteria (no absolute contraindications and three or fewer relative contraindications for ECMO), patients' eligibility for ECMO was determined, followed by a separate determination if the resources were present for the patients to receive ECMO at that time within a receiving institution within the health system. The authors compared all-cause in-hospital mortality for those referred and accepted vs. denied due to lack of ECMO availability, adjusting for patients' clinical characteristics and the timing of consult (as resources changed over the course of the pandemic). Of the 240 referrals, only 90 (37.5%) were eligible for ECMO, but of these only 35 (38.9%) received ECMO in the health system. Death risk was substantially lower for those who received ECMO (adjusted hazard ratio 0.23, 95%CI 0.12-0.43), with results similar over time.

## Comments

1. While only a single health system study, the results support the benefit of ECMO, especially when using standard criteria for eligibility, inclusion, and exclusion (see below – Ramanathan et al, *Crit Care* 2021).
2. This study also demonstrates the significant impact of resource availability on patient outcomes during crisis—something experienced by many institutions during the pandemic—and supports the need for more national, unified approaches to emergency preparedness and shared resources during times of surge.
3. While some of the absolute and relative contraindications involve some subjective determinations (e.g., “chronic lung disease”, “presence of comorbidities”, “presence of acute kidney injury”), these contraindications' contribution to eligibility decisions were made by committee based on accepted guidelines, research, and clinical experience—a very real world limitation.
4. The patients who did not receive ECMO had more ventilator days before referral than those accepted

for ECMO, while the duration of pre-referral hospital length-of-day and timing of first eligibility for ECMO for both groups is not known/reported, all of which may be confounders to this analysis.

5. Overall, the small numbers in this study limit our ability to potentially generalize the ECMO benefit to our own patients, but making criteria for ECMO eligibility as transparent as possible is a way for referring physicians to start the process earlier in the patients' course.

## ARDS OUTCOMES

Turnbull AE, Ji H, Dinglas VD, Wu AW, et al.

**Understanding patients' perceived health after critical illness: Analysis of two prospective, longitudinal studies of ARDS survivors.** *Chest* 2022; 161(2): 407-417. doi: 10.1016/j.chest.2021.07.2177. Epub 2021 Aug 19. PMID: 34419426; PMCID: PMC8941599

## Summary

In this innovative, secondary analysis of the ARDSNet Long Term Outcomes Study (ALTOS) and the Improving Care of Acute Lung Injury Patients (ICAP) Study, Turnbull et al investigated how patients' perceived health quality (EQ-5D-VAS) differed from their actual health status (symptoms and self-reported function). This study used the patients' answers to validated instruments (EQ-5D-3L and SF-36v2) to create a prediction model for perceived health, and then compared the predicted score to the actual reported EQ-5D-VAS score which was also collected longitudinally in both cohorts (at 6 months and 12 months after ARDS). About half of the patients reported a perceived health quality that was statistically different than their actual health, and this difference changed over time. The authors found that the combined measures of physical, emotional, and social functional, as included in the validated instruments for long-term outcomes follow-up in ARDS, were somewhat predictive, but not fully determinative of perceived health. They raise the possibility of incomplete capture of health determinants by our current tools, the importance of measuring psychological resilience, potential influence of social comparison, and the possibility of a disconnect between expectations of ARDS survivorship at ARDS onset vs. longitudinally through recovery.

## Comments

1. Inpatient intensivists should incorporate more discussion of functional outcomes of ARDS survivorship with patients and their families, as patients start to recover in the ICU.
2. Post-ARDS outcomes are influenced by so much more than the patients' measurable comorbidities and functional status, emphasizing the psychosocial factors and importance of social support (which was not examined in this study).
3. In order to best care for our patients holistically, we must first undergo training about long-term outcomes, as the needs of this population are only growing with more survivors of COVID-19.
4. As we focus on ARDS survivorship and post-COVID-19 sequelae, we need to ask if our current instruments for measuring physical, emotional, functional, psychosocial, economic, etc. domains are sufficient for best identifying and managing the long-term care of these patients.
5. As these three instruments were not designed nor previously validated to be equated, the authors used a rigorous statistical approach to ensure that their model's prediction score was not biased toward negative or positive deviation from the true EQ-5D-VAS score.

## OTHER ARTICLES OF INTEREST

### ARDS Identification

Matthay MA, Thompson BT, Ware LB: **The Berlin definition of acute respiratory distress syndrome: should patients receiving high-flow nasal oxygen be included?** *Lancet Respir Med* 2021; 9(8): 933-936

Singhal L, Garg Y, Yang P, et al. **eARDS: A multi-center validation of an interpretable machine learning algorithm of early onset Acute Respiratory Distress Syndrome (ARDS) among critically ill adults with COVID-19.** *PLoS One* 2021; 16(9): e0257056.

### ARDS Phenotypes and Outcomes

Hashem MD, Hopkins RO, Colantuoni E, et al. **Six-month and 12-month patient outcomes based on inflammatory subphenotypes in sepsis-associated ARDS: Secondary analysis of SAILS-ALTOS trial.** *Thorax* 2022; 77(1): 22-30.

Maddali MV, Churpek M, Pham T, et al. **Validation and utility of ARDS subphenotypes identified by machine-learning models using clinical data: an observational, multicohort, retrospective analysis.** *Lancet Respir Med* 2022 Jan 10: S2213-2600(21)00461-6

Duggal A, Kast R, Van Ark E, et al. **Identification of acute respiratory distress syndrome subphenotypes de novo using routine clinical data: A retrospective analysis of ARDS clinical trials.** *BMJ Open* 2022; 12: e053297.

### Management of Hypoxemic Respiratory Failure

Qadir N, Bartz RR, Cooter ML, al. **Variation in early management practices in moderate-to-severe ARDS in the United States: The Severe ARDS: Generating Evidence Study.** *Chest* 2021; 160(4): 1304-1311.

Tatham KC, Ferguson ND, Zhou Q, et al. **Evolution of practice patterns in the management of acute respiratory distress syndrome: A secondary analysis of two successive randomized controlled trials.** *J Crit Care* 2021; 65: 274-281.

Wong A-KI, Charpignon M, Kim H, et al. **Analysis of discrepancies between pulse oximetry and arterial oxygen saturation measurements by race and ethnicity and association with organ dysfunction and mortality.** *JAMA Netw Open* 2021; 4(11): e2131674-e2131674.

Goligher EC, Costa ELV, Yarnell CJ, et al. **Effect of lowering Vt on mortality in acute respiratory distress syndrome varies with respiratory system elastance.** *Am J Respir Crit Care Med* 2021; 203(11): 1378-1385.

### ECMO

Ramanathan K, Shekar K, Ling RR, et al. **Extracorporeal membrane oxygenation for COVID-19: A systematic review and meta-analysis.** *Crit Care* 2021; 25(1): 211.

### Specific Treatment of COVID-19 Respiratory Failure

Grieco DL, Menga LS, Cesarano M, et al. **Effect of helmet noninvasive ventilation vs high-flow nasal oxygen on days free of respiratory support in patients with COVID-19 and moderate to severe hypoxemic respiratory failure: The HENIVOT randomized clinical trial.** *JAMA* 2021; 325(17): 1731-1743.

Ospina-Tascón GA, Calderón-Tapia LE, et al. **Effect of high-flow oxygen therapy vs conventional oxygen therapy on invasive mechanical ventilation and clinical recovery in patients with severe COVID-19: A randomized clinical trial.** *JAMA* 2021; 326(21): 2161-2171.

The COVID STEROID 2 Trial Group. **Effect of 12 mg vs 6 mg of dexamethasone on the number of days alive without life support in adults with COVID-19 and severe hypoxemia: The COVID STEROID 2 randomized trial.** *JAMA* 2021; 326(18): 1807-1817.

Sinha P, Furfaro D, Cummings MJ, et al. **Latent class analysis reveals COVID-19-related acute respiratory distress syndrome subgroups with differential responses to corticosteroids.** *Am J Respir Crit Care Med.* 2021; 204(11): 1274-1285