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# **CLINICAL**

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## SEPSIS AND SEPTIC SHOCK

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## MECHANISM

Francois B, Jeannet R, Daix T, Walton AH, Shotwell MS, Unsinger J, Monneret G, Rimmelé T, Blood T, Morre M, Gregoire A, Mayo GA, Blood J, Durum SK, Sherwood ER, Hotchkiss RS. **Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial.** *JCI Insight.* 2018; 3(5): e98960

## Summary

Prior work in sepsis suggests that a reduced number of circulating lymphocytes (i.e. lymphopenia) is associated with new opportunistic infections and greater mortality. However, it is unknown whether this is just an epiphenomenon of illness severity or represents a key mechanistic role. Multiple murine studies suggest that apoptosis-resistant lymphocytes improve sepsis survival after adoptive transfer, and that IL7 may be a key cytokine in lymphocyte proliferation and function. In this study, Françoise et al. conducted a prospective, multicenter, randomized, double-blind, placebo-controlled phase IIIb trial of CYT107, a recombinant IL7, in 27 patients with septic shock and severe lymphopenia of <900 lymphocytes/ $\mu$ l. The authors report that CYT107 was well-tolerated without inducing additional inflammation, sepsis-induced lymphopenia was reversed vs. placebo (3-4 fold increase in lymphocyte count), and that the proportion of circulating CD4+ and CD8+ T cells increased. CYT107 was administered via the intramuscular route for 2 different regimens, either a low frequency (once weekly) vs. high frequency (twice weekly). There were no increases in the frequency of clinically adjudicated secondary infections with CYT107 and no difference in mortality at 28 days.

## Comments

1. This trial is one of the first to test the “immune boosting” effects of a novel therapeutic rather than testing therapies that block inflammation and the host response.
2. The trial enrolled only 27 patients and was powered to detect differences biologic endpoints not patient centered outcomes.
3. This is the first trial to attempt to enhance adaptive immunity and reduce apoptotic cell death
4. Of those enrolled, the CD4+ T cell count was less than 200 cells/ $\mu$ l in more than 60% of patients, a criterion usually reserved for patient with HIV or AIDS.

5. These data suggest a transformational target for immunotherapy in sepsis, restoring adaptive immunity, and increasing the number of circulating CD4+ and CD8+ effector cells—worthy of larger randomized trial.

## CLINICAL TRIALS

Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, Billot L, Correa M, Glass P, Harward M, Joyce C, Li Q, McArthur C, Perner A, Rhodes A, Thompson K, Webb S, Myburgh J; ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group. **Adjunctive Glucocorticoid Therapy in Patients with Septic Shock.** *N Engl J Med.* 2018; 378(9): 797-808

## Summary

For the past half century, the role of corticosteroid therapy in septic shock has remained controversial. Multiple randomized trials, systematic reviews, and meta-analyses have not provided a definitive answer, and often note that prior trials were underpowered with a high risk of bias. This has resulted in significant practice variability, and concern about potential adverse effects. In this study, Venkatesh and colleagues report on the landmark Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial, an international, pragmatic, double-blind, parallel-group, randomized controlled trial that compared intravenous infusion of hydrocortisone (200 mg per day for 7 days) with matched placebo in 3800 patients with septic shock undergoing mechanical ventilation in an intensive care unit. They report similar baseline characteristics, time to initiation of study arm, and treatment adherence. They found no difference in the primary outcome of 90-day mortality between arms, as 511 of 1832 patients (27.9%) who had been assigned to receive hydrocortisone had died, and 526 of 1826 (28.8%) who had been assigned to receive placebo (odds ratio=0.95; 95%CI=0.82-1.10, p=0.50). No difference was present in any of the 6 pre-defined subgroups. The time to resolution of shock was shorter in the hydrocortisone group vs. placebo (median 3 vs. 4 days, hazard ratio=1.32, 95%CI=1.23-1.41, p<0.001). More adverse

events occurred in the hydrocortisone group vs. placebo, but these were not thought to impact patient outcomes.

### Comments

1. This is an incredibly well-conducted, placebo controlled trial, with one of the largest samples size in which to test the efficacy of corticosteroid therapy.
2. The patient population included septic shock with respiratory failure and was less ill with greater rate of surgical admissions compared the simultaneously published APROCCHSS trial (which found benefit for a combination of hydrocortisone and fludrocortisone vs. placebo among 1241 patients for 90-day mortality).
3. Despite the absence of benefit for 90-day mortality, the hydrocortisone arm improved shock resolution consistent with prior studies.
4. Different from prior trials, these authors administered corticosteroids as a continuous infusion and did not use a taper at the end of 7 days.
5. No treatment was guided by corticotropin testing or other surrogate measures of adrenal insufficiency.

Hernández G, Ospina-Tascón GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, Friedman G, Castro R, Alegría L, Teboul J, Cecconi M, Ferri G, Jibaja M, Pairumani R, Fernández P, Barahona D, Granda-Luna V, Biasi Cavalcanti A, Bakker J; for the ANDROMEDA-SHOCK Investigators and the Latin America Intensive Care Network (LIVEN). **Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial.** *JAMA*, 2019; 321(7):654-664.

### Summary

International clinical practice guidelines recommend that the resuscitation of patients with septic shock focus on the measurement of serum lactate or lactate clearance, thought to be surrogates for tissue hypoperfusion and adequacy of treatment. However, serum lactate can be elevated in other conditions, may not be elevated in all shock states, and lactate clearance may not be pragmatic to guide clinician decision making. An alternative approach is to monitor the bedside clinical examination using capillary refill time, but there is little empiric evaluation of this technique. In this study, Hernandez and colleagues report the results of a 2-arm clinical trial among 424 intensive care unit patients with early septic shock, randomized to an 8-hour resuscitation strategy that was guided by every 30 minute capillary refill time (CRT) vs. every 2-hour serum lactate measurement. All administration of fluids and vasopressors were recommended using a standard study protocol, and on average, the course of resuscitation was similar in both arms. The 28-day mortality rate was 43% in the lactate group compared to 35% in the CRT-guided group, corresponding to a hazard ratio of 0.75 (95%CI=0.55-1.01, p=0.06). The authors also report lower rates of organ dysfunction measured with Sequential Organ Failure Assessment (SOFA) at 72 hours in the CRT arm (p=0.045).

### Comments

1. The trial just missed a traditional cutoff for statistical significance and may have been underpowered to detect the pre-planned 15% absolute reduction in 28-day mortality.
2. CRT-guided therapy may be superior to lactate guided resuscitation but a larger confirmatory trial is required.
3. The study was not blinded and may be susceptible to bias.
4. Although the 2 arms tested may represent state-of-the-art care, the trial did not include a usual care arm or arm that combines the techniques.
5. A simple, standardized bedside clinical measurement of peripheral perfusion may be useful in the resuscitation of septic shock, and is particularly worthy of studying in resource-limited settings.

### NEW STRATEGIES FOR CARE

Komorowski M, Celi LA, Badawi O, Gordon AC, Faisal AA. **The Artificial Intelligence Clinician learns optimal treatment strategies for sepsis in intensive care.** *Nat Med*. 2018; 24(11): 1716-1720.

### Summary

Life-threatening organ dysfunction from sepsis is typically treated with vasopressors and intravenous (IV) fluids, yet the optimal combination is unknown. As a result, wide variability in clinicians' use of these treatments exists, perhaps contributing to unanticipated poor outcomes. Recently, clinical decision algorithms based upon reinforcement learning ("artificial intelligence (AI)") are proposed to improve patient outcomes in the intensive care unit. In this study, Komorowski et al. developed the "AI Clinician", a computational model developed from the Medical Information Mart for Intensive Care III (MIMIC-III) dataset. Among 17,083 patients with Sepsis-3, they used 48 variables to define 4-hour patient states, and then mapped the total IV fluid volume and maximum pressor dose administered to patients in each state in 25 combinations. After using a Markov decision process, the authors could determine the treatment patterns that optimized patient mortality using a series of rewards and penalties ("AI Clinician policy"). The authors then studied the eICU Research Institute Database, defined another cohort of sepsis patients (N=79,073), and identified vasopressor and fluid treatments that were consistent or discordant with that recommended by the optimal AI Clinician policy. They found that the clinicians' used a vasopressor close to that recommended by the AI policy in half of patients (56%) and only gave the recommended dose of IV fluids in one out of three patients (36%). The administration of more or less of either treatment was associated with worse mortality in a dose-dependent fashion.

### Comments

1. This retrospective evaluation is the first to model vasopressor and intravenous fluid treatment decisions for septic patients using reinforcement learning and artificial intelligence tools.
2. The validation of the AI policy against clinician actions in an external dataset is a significant strength.

3. No prospective evaluation was performed, and thus, the “real world” role of the AI Clinician is unknown.
  4. Multiple modeling and statistical assumptions could be varied in future evaluations, such as the handling of missing data or choice of states for which treatments were optimized (concurrent vs. future).
  5. It is hypothesis generating, and consistent with growing body of observational data, that the optimal resuscitation policy from the AI Clinician favored higher doses of vasopressors with less use of IV fluids compared to clinician choices.
3. This report included all patients in the New York State Clinical Sepsis database, not just those recognized in the emergency department.
  4. No data was available about the pre-policy period or from states in the nearby geographic area, which could provide context to the temporal trends.
  5. The study was not randomized, but rather a retrospective analysis of an existing cohort, and therefore we cannot make causal inferences about the relationship between sepsis bundle completion and patient outcomes.

## BUNDLED CARE

Levy MM, Gesten FC, Phillips GS, Terry KM, Seymour CW, Prescott HC, Friedrich M, Iwashyna TJ, Osborn T, Limeshow S. **Mortality Changes Associated with Mandated Public Reporting for Sepsis. The Results of the New York State Initiative.** *Am J Respir Crit Care Med.* 2018; 198(11): 1406-1412.

### Summary

Public reporting and performance measurement of health-care programs are intended to improve patient outcomes and reduce cost. In sepsis, there is limited experience and uncertainty surrounding these policy measures and their ability to drive clinician behavior. In 2013, New York State mandated bundled care for all patients with sepsis and septic shock, including a 3-hr bundle of blood cultures antibiotics, and serum lactate measurement, and a 6-hour bundle including a 30 ml/kg fluid bolus, administration of vasopressors, and re-measurement of serum lactate. In this study, Levy et al. reports on the rates of bundle initiation, completion, and risk-adjusted association with outcomes during the first 2 years after implementation. Among 91,557 patients, more than 8 of 10 had a sepsis protocol initiated, and the 3-hour bundle compliance increased from approximately 53 to 65% during the study period. Compliance with the 6-hour bundle was lower, increasing from 24 to 31%. Using an extensive set of risk-adjustment variables, the authors modeled the association between bundle compliance and in-hospital mortality, finding that over 2 years, the mortality rate decreased from 29 to 24% ( $p < 0.001$ ). Meanwhile, septic patients in whom the protocol was not initiated had a stable risk-adjusted mortality. Although not causal, these data suggest a strong relationship between increasing compliance with the state mandated sepsis bundles and improved risk-adjusted outcomes.

### Comments

1. This study evaluated a first-in-the-nation healthcare policy aimed at improving sepsis outcomes through statewide mandated protocols and public reporting.
2. Audits of case ascertainment and individual data elements suggested high accuracy for sepsis recognition.

## SEPSIS SUBCLASSES

Antcliffe DB, Burnham KL, Al-Beidh F, Santhakumaran S, Brett SJ, Hinds CJ, Ashby D, Knight JC, Gordon AC. **Transcriptomic Signatures in Sepsis and a Differential Response to Steroids: From the VANISH Randomized Trial.** *Am J Respir Crit Care Med.* 2018; Oct, EPUB ahead of Print

### Summary

Not all sepsis is the same. Recently, sepsis endotypes (e.g. subclasses with similar molecular profiles) were derived using genome wide gene expression profiling, identifying one type (SRS1) that is relatively immunosuppressed and one type (SRS2) that is relatively immunocompetent. Previously, these endotypes are reported to be prognostic but not found to be predictive of treatment response. In this study, Antcliffe et al. performed a secondary analysis of a double blind, factorial design randomized clinical trial of vasopressors and corticosteroids to determine if patients with SRS transcriptomic profiles had differential treatment responses. Among a 43% (N=176) subset of RCT patients with samples, the authors found that SRS types were distributed evenly. There was no significant interaction between SRS types and vasopressor treatment (Norepinephrine vs. Vasopressin,  $p=0.50$ ), but there was a significant interaction for corticosteroid therapy ( $p=0.02$ ). In other words, hydrocortisone treatment was only associated with increased mortality in those with the immunocompetent SRS2 phenotype (OR=7.9, 95%CI=1.6-39.9) but not SRS1. These data require validation but are a proof of concept that future trials should consider incorporation of sepsis subclasses in design and measurement of treatment effects.

### Comments

1. Sepsis endotypes are prognostic in other studies, but are not uniformly associated with treatment response.
2. These data are one of the first to report a treatment response linked to SRS transcriptomic profiles in sepsis.
3. More than half of patients in the VANISH trial did not have samples and were not included, which raises generalizability as a limitation.

4. SRS profiles were measured at septic shock onset prior to randomization but only among ICU patients.
5. It is possible that the average treatment effects reported in large neutral clinical trials of corticosteroid therapy may miss hidden heterogeneity by sepsis subclass.

## OTHER ARTICLES OF INTEREST

### Mechanistic Insight

Trinder M, Genga KR, Kong HJ, Blauw LL, Lo C, Li X, Cirstea M, Wang Y, Rensen PCN, Russell JA, Walley KR, Boyd JH, Brunham LR. **Cholesteryl Ester Transfer Protein Influences High-Density Lipoprotein Levels and Survival in Sepsis.** *Am J Respir Crit Care Med.* 2018 Oct 15. doi: 10.1164/rccm.201806-1157OC. [Epub ahead of print] PubMed PMID: 30321485.

Seeley JJ, Baker RG, Mohamed G, Bruns T, Hayden MS, Deshmukh SD, Freedberg DE, Ghosh S. **Induction of innate immune memory via microRNA targeting of chromatin remodelling factors.** *Nature.* 2018 Jul;559(7712):114-119. doi: 10.1038/s41586-018-0253-5. Epub 2018 Jun 27. PubMed PMID: 29950719; PubMed Central PMCID: PMC6044474.

Gustave CA, Gossez M, Demaret J, Rimmelé T, Lepape A, Malcus C, Poitevin-Later F, Jallades L, Textoris J, Monneret G, Venet F. **Septic Shock Shapes B Cell Response toward an Exhausted-like/Immunoregulatory Profile in Patients.** *J Immunol.* 2018 Apr 1;200(7):2418-2425. doi: 10.4049/jimmunol.1700929. Epub 2018 Feb 19. PubMed PMID: 29459404.

### Clinical Trials

Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, Cariou A, Forceville X, Schwebel C, Martin C, Timsit JF, Misset B, Ali Benali M, Colin G, Souweine B, Asehnoune K, Mercier E, Chimot L, Charpentier C, François B, Boulain T, Petitpas F, Constantin JM, Dhonneur G, Baudin F, Combes A, Bohé J, Loriferne JF, Amathieu R, Cook F, Slama M, Leroy O, Capellier G, Dargent A, Hissem T, Maxime V, Bellissant E; CRICS-TRIGGERSEP Network. **Hydrocortisone plus Fludrocortisone for Adults with Septic Shock.** *N Engl J Med.* 2018 Mar 1;378(9):809-818. doi: 10.1056/NEJMoa1705716. PubMed PMID: 29490185.

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**Randomized Clinical Trial.** *JAMA Netw Open.* 2018 Dec 7;1(8):e186076. doi: 10.1001/jamanetworkopen.2018.6076. PubMed PMID: 30646314; PubMed Central PMCID: PMC6324339.

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Dellinger RP, Bagshaw SM, Antonelli M, Foster DM, Klein DJ, Marshall JC, Palevsky PM, Weisberg LS, Schorr CA, Trzeciak S, Walker PM; EUPHRATES Trial Investigators. **Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level: The EUPHRATES Randomized Clinical Trial.** *JAMA.* 2018 Oct 9;320(14):1455-1463. doi: 10.1001/jama.2018.14618. PubMed PMID: 30304428; PubMed Central PMCID: PMC6233793.

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### Fluid Resuscitation

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#### Bundled Care and Guidelines

Evans IVR, Phillips GS, Alpern ER, Angus DC, Friedrich ME, Kisson N, Lemeshow S, Levy MM, Parker MM, Terry KM, Watson RS, Weiss SL, Zimmerman J, Seymour CW. **Association Between the New York Sepsis Care Mandate and In-Hospital Mortality for Pediatric Sepsis.** *JAMA.* 2018 Jul 24;320(4):358-367. doi: 10.1001/jama.2018.9071. PubMed PMID: 30043064.

Rhee C, Filbin MR, Massaro AF, Bulger AL, McEachern D, Tobin KA, Kitch BT, Thurlo-Walsh B, Kadar A, Koffman A, Pande A, Hamad Y, Warren DK, Jones TM, O'Brien C, Anderson DJ, Wang R, Klompas M; Centers for Disease Control and Prevention (CDC) Prevention Epicenters Program. **Compliance With the National SEP-1 Quality Measure and Association With Sepsis Outcomes: A Multicenter Retrospective Cohort Study.** *Crit Care Med.* 2018 Oct;46(10):1585-1591. doi: 10.1097/CCM.0000000000003261. PubMed PMID: 30015667; PubMed Central PMCID: PMC6138564.

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#### Epidemiology

Rhee C, Jones TM, Hamad Y, Pande A, Varon J, O'Brien C, Anderson DJ, Warren DK, Dantes RB, Epstein L, Klompas M; Centers for Disease Control and Prevention (CDC) Prevention Epicenters Program. **Prevalence, Underlying Causes, and Preventability of Sepsis-Associated Mortality in US Acute Care Hospitals.** *JAMA Netw Open.* 2019 Feb 1;2(2): e187571. doi: 10.1001/jamanetworkopen.2018.7571. PubMed PMID: 30768188.

Paoli CJ, Reynolds MA, Sinha M, Gitlin M, Crouser E. **Epidemiology and Costs of Sepsis in the United States-An Analysis Based on Timing of Diagnosis and Severity Level.** *Crit Care Med.* 2018 Dec;46(12):1889-1897. doi: 10.1097/CCM.0000000000003342. PubMed PMID: 30048332; PubMed Central PMCID: PMC6250243.

## HEALTH DISPARITIES

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## EARLY STAGE LUNG CANCER TREATMENT

Cykert S, Eng E, Walker P, Manning MA, Roberston LB, Arya R, Jones NS, Heron DE. **A system-based intervention to reduce Black-White disparities in the treatment of early stage lung cancer: A pragmatic trial at five cancer centers.** *Cancer Med.* Feb 2019. DOI: 10.1002/cam4.2005

## Summary

For the majority of patients, surgical lung resection is the guideline recommendation for cure of early stage, non-small cell lung cancer. Despite this recommendation, Black patients undergo surgery less often than similarly-matched White patients. This disparity goes beyond socioeconomic status, age, and co-morbid conditions. To address this disparity, authors worked with community partners to develop a multifaceted intervention that included real-time audit, race-specific accountability, and enhanced, patient-centered communication through the electronic medical record. Using a pragmatic trial design, authors prospectively enrolled 360 (32% Black) patients aged 18-85 years, diagnosed with Stage I or II lung cancer, and receiving care at one of 5 cancer centers. These patients were compared to a retrospective cohort (n=2841, 16% Black) of early stage lung cancer patients from the same centers. In this retrospective cohort group, 78% of White patients underwent surgical resection compared with 69% of the Black group. After intervention, 96% of all patients enrolled underwent surgical resection, closing the disparity gap and increasing treatment in both Black and White patients. By using a pragmatic study design, the study also demonstrates the feasibility of incorporating the intervention across several medical systems.

## Comments

1. This is one of few studies that have evaluated a multi-component intervention to address the Black-White treatment for non-small cell lung cancer.
2. Authors aim to close the Black-White treatment gap for non-small cell lung cancer with an innovative intervention design developed in conjunction with community partners.
3. The multi-faceted intervention not only closed the Black-White treatment gap, but also improved rates of surgical resection across all groups.
4. Limitations include using a retrospective cohort as a control group where secular trends may impact results; however, authors were able to determine that findings were above what would be expected for secular trend.

5. One major strength is the trials pragmatic design, demonstrating feasibility of intervention across multiple medical systems.

## SOCIOECONOMIC STATUS, IDIOPATHIC PULMONARY FIBROSIS, AND LUNG TRANSPLANT TREATMENT

Gaffney AW, Woolhandler S, Himmelstein D, McCormick D. Disparities in pulmonary fibrosis care in the United States: an analysis from the Nationwide Inpatient Sample. *BMC Health Services Research.* 2018; 18: 618

## Summary

Previous studies have demonstrated that individuals of low socioeconomic status (SES) undergo INTERVENTIONAL PULMONOLOGY less often compared with their higher SES counterparts. Using hospital admission data from the Nationwide Inpatient Sample (NWIS), authors examined whether socioeconomic status, defined by insurance status and zip-code level income, was associated with differences in INTERVENTIONAL PULMONOLOGY and mortality among hospitalized adults with idiopathic pulmonary fibrosis. Patients with no insurance or Medicaid insurance were younger, had fewer co-morbid conditions and were hospitalized with less severe disease compared with those with non-Medicaid insurance. Across all admissions with idiopathic pulmonary fibrosis as a primary or secondary diagnosis code, patients with no insurance or Medicaid insurance were significantly less likely to undergo lung transplant compared with patients with non-Medicaid (private or Medicare) insurance, even after adjusting for age, co-morbid conditions, and disease severity. Similarly, patients in the lower three quartiles of median ZIP code income were less likely to receive a transplant than those in the higher quartile. These findings remained true in a sensitivity analysis limited to patients less than 65 years of age. This study demonstrates the inequity in transplant access but needs to be interpreted with caution as results reflect hospital admissions and not individuals.

## Comments

1. Compared with patients with Medicare or private insurance, patients with no insurance or Medicaid insurance were less likely to undergo INTERVENTIONAL PULMONOLOGY for idiopathic pulmonary fibrosis.
2. Patients from the lowest three quartiles of ZIP-code level incomes were also less likely to receive lung transplant compared with those in the highest quartile.



3. One main limitation of the study is that the authors denominator was all admissions, where it is possible that one individual could contribute to more than one admission, potentially biasing results.

## ASTHMA ON THE NAVAJO NATION

Lowe AA, Bender B, Liu AH, Solomon T, Kobernick A, Morgan W, Gerald LB. **Environmental Concerns for Children with Asthma on the Navajo Nation.** *Ann Am Thorac Soc* 2018; 15(6):745-53.

### Summary

Asthma prevalence in American Indian/Alaskan Native children is higher than the national prevalence of asthma in the general U.S. pediatric population (13.0 vs. 8.6%). Moreover, asthma-related morbidity is also higher in this population compared with national averages. The Navajo reservation spans a significant geographic area over the southwestern U.S., crossing over six counties and three states. It is composed of 250,000 individuals with 44% of the population being children less than 19 years of age. The authors attempt to synthesize the research examining environmental risk factors for asthma in this high-risk group through a systematic review. Eight articles met inclusion criteria and four were specific to the Navajo population. 89% of Navajo families rely on biomass combustion as a primary source of heat, which has been demonstrated to be linked to respiratory tract infections and poor lung function in other populations. Only two studies have evaluated this relationship in Navajo children. Other risk factors include smoking and secondhand smoke exposure which are both higher in the Navajo population. Lastly, important outdoor exposure may include increased exposure to coal-fire sulfur emissions from residing in close proximity to coal-fired power plants, increased exposure to diesel exhaust and other traffic-related air pollutants from longer than average bus commutes to travel to and from school, and increased exposure to dust/sand as mobile sand dunes cover over 30% of the Navajo reservation. This study reviews important environmental contributors to asthma in children of the Navajo Nation.

### Comments

1. Biomass fuel for heating and cooking and personal tobacco smoke exposure are common in the Navajo Nation and likely an important contributor to respiratory health disparities, including asthma, in Navajo children.
2. Dust storms, dust from contaminate soil, and coal-fired power plants are potential risk factors for asthma that are unique to the Navajo Nation.
3. This systematic review demonstrates that there are a limited number of published studies that have examined risk factors for asthma in Navajo children.
4. Collaborative efforts with the Navajo Nation are necessary to address important environmental risk factors in order to reduce the burden of pediatric asthma.

## TUBERCULOSIS IN INDIGENOUS POPULATIONS

Dehghani K, Lan Z, Michelsen SW, Waites S, Benedetti A, Lejeune P, Torrie J, Robinson E, Vejvoda B, Mullah M, Redwood D, Cooper M, Fanning A, Yacoub W, Alvarez GG, Sørborg B, Long R, Menzies D. **Determinants of tuberculosis trends in six Indigenous populations of the USA, Canada, and Greenland from 1960 to 2014: a population-based study.** *Lancet Public Health.* 2018; 3: e133-42.

### Summary

Indigenous populations in the U.S., Canada, and Greenland are disproportionately burdened by tuberculosis (TB) compared with most other groups. Several population-based TB-control interventions (bacillus-Calmette-Guérin [BCG] vaccination of all infants, case finding, and treatment of latent TB infection) were implemented to address this disparity and to reduce TB-related mortality. Following implementation, TB notification rates rapidly declined between 1960 and 1980, when most population-wide efforts ended. It is unclear whether this decline was related to eradication efforts versus simultaneous improvements in socioeconomic status, nutrition, and housing quality, including crowding. Authors found that since 1980, TB notification rates continue to decline in Indigenous populations in Alberta, Alaska, and Eeyou Istchee; however, they demonstrated a rise in other areas including Nunavut, Nunavik, and Greenland. This ecological study demonstrates the effectiveness of large-scale, high-intensity population-targeted interventions, such as BCG vaccination and treatment of latent TB infection, at reducing TB notification rates in high burdened populations. In addition to differences in smoking, crowding in homes, and infant mortality-rates between populations, the removal of these population-wide eradication efforts likely contributed to the recrudescence of TB in some Indigenous populations.

### Comments

1. Population-wide tuberculosis efforts of BCG vaccination and treatment of latent TB infection led to rapid decline of TB notification rates across Indigenous populations in the USA, Canada, and Greenland.
2. Socio-environmental factors such as differences in smoking, overcrowded housing, and infant mortality across populations likely account, in part, for the recrudescence of TB in some Indigenous populations.
3. Strengths of the study include the number of socio-environmental indicators accounted for, the length of the time period covered, and the diversity of populations, spanning 3 countries, included.
4. Because of the ecological study design, the results presented are at the population level and do not confer individual-risk for TB in Indigenous populations.

## LUNG CANCER IN YOUNG WOMEN

Jemal A, Miller KD, Ma J, Siegel RL, Fedewa SA, Islami F, Devesa SS, Thun MJ. **Higher lung cancer incidence in young women than young men in the United States.** *NEJM*. 2018; 378:1999-2009.

### Summary

Historically, lung cancer incidence was always lower in women compared with men. As 80% of lung cancer deaths is attributed to cigarette smoking, this difference was thought to reflect the fact that women were historically less likely to smoke, initiated smoking at an older age, and smoked fewer cigarettes per day. Now, smoking behaviors between men and women have converged and are more similar. Using data from the North American Association of Central Cancer Registries (NAACCR) to identify lung cancer incidence from 1995 to 2014, the authors grouped lung cancer diagnosis by sex, race or ethnic category, five age groups (30-34, 35-39, 40-44, 45-49, and 50-54 years), and by four calendar periods (1995 to 1999, 2000 to 2004, 2005 to 2009, and 2010 to 2014). For the same groups (with the exception of Asian and Pacific Islanders), data from the National Health Interview Survey (NHIS) was used to determine the prevalence of current smoking and of former smoking, as well as the average number of cigarettes smoked per day. Examined by year of diagnosis, incidence decreased among both men and women, but the decline was greater in men. This resulted in a higher incidence rate ratio for women 30-34, 35-39, 40-44, and 45-49 years of age. When examined by race or ethnic group, the higher incidence rate ratio is isolated to Hispanic and non-Hispanic white women. Sex differences in smoking behaviors converge among individuals born during the 1960s and afterwards, but smoking prevalence remains higher in young black and Hispanic men compared with young black and Hispanic women. In addition, daily cigarette use among white men remains higher than white women. Among smokers, similar daily cigarette consumption is seen among black men and women. Sex differences in smoking behaviors do not explain the crossover from a higher incidence of lung cancer in men to a higher incidence in Hispanic and non-Hispanic white women. This is especially surprisingly as smoking prevalence in Hispanic women is lower than among Hispanic men and daily cigarette consumption is lower in white women compared to white men.

### Comments

1. The decline in lung cancer incidence has been steeper in men 30 to 54 years of age compared with women in the same age group.
2. Among non-Hispanic whites and Hispanics, lung cancer incidence rates are now higher in women compared with men despite similar smoking prevalence in men and women.

3. Differences in decline of different cancer types, specifically adenocarcinoma, may partially explain some of the findings in white women, this needs to be further examined in other race or ethnic groups.
4. Historically, Asian and Pacific Islander men smoked at significantly higher rates than women; however, the contribution of smoking-related behaviors on the observed convergence of lung cancer incidence between men and women was not evaluated due to lack of available data for this group.

## OTHER ARTICLES OF INTEREST

### Asthma

Liu Y, Pan J, Zhang H, Shi C, Li G, Peng G, Ma J, Zhou Y, Zhang L. **Short-term exposure to ambient pollution and asthma mortality.** *AJRCCM*. March 2019. DOI: 10.1164/rccm/201810-1823OC.

Sullivan PW, Ghushchyan V, Kavati A, Navaratnam P, Friedman HS, Ortiz B. **Health Disparities Among Children with Asthma in the United States by Place of Residence.** *J Allergy Clin Immunol Pract* 2019; 7:148-55.

Fitzpatrick AM, Gillespie SE, Mauger DT, Phillips BR, Bleecker ER, Israel E, Meyers DA, Moore WC, Sorkness RL, Wenzel SE, Bacharier LB, Castro M, Denlinger LC, Erzurum SC, Fahy JV, Gaston BM, Jarjour NN, Larkin A, Levy BD, Ly NP, Ortega VE, Peters SP, Phipatanakul W, Ramratnam S, Teague WG. **Racial disparities in asthma-related health care use in the National Heart, Lung, and Blood Institute's Severe Asthma Research Program.** *JACI*. 2019. DOI: 10.1016/j.jaci.2018.11.022.

### COPD

Croft JB, Wheaton AG, Liu Y, Xu F, Lu H, Matthews KA, Cunningham TJ, Wang Y, Holt JB. **Urban-rural county and state differences in chronic obstructive pulmonary disease- United States 2015.** *MMWR*. Feb 2018; 67(7).

### Lung Cancer

Wolf A, Alpert N, Tran BV, Liu B, Flores R, Taioli E. **Persistence of racial disparities in early-stage lung cancer treatment.** *J Thorac Cardiovasc Surg*. Dec 2018. DOI: 10.1016/j.jtcvs.2018.11.108.

Karant S, Rajan SS, Revere FL, Sharma G. **Factors affecting racial disparities in end-of-life care costs among lung cancer patients: a SEER-Medicare-based study.** *Am J Clin Oncol* 2019; 42:143-53.

Belot A, Fowler H, Njagi EN, Luque-Fernandez M-A, Maringe C, Magadi W, Exarchakou A, Quaresma M, Turculet A, Peake MD, Navani N, Rachet B. **Association between age, deprivation, and specific co-morbid conditions and the receipt of major surgery in patients with non-small cell lung cancer in England: A population-based study.** *Thorax* 2019; 74:51-59.

#### Critical Care

Chertoff J, Stevenson P, Hassan A. **Sepsis mortality in the U.S. Correctional System: an underappreciated disparity.** *Journal of Correctional Health Care.* 2018 24(4) 337-41.

#### Sleep Disparities

Genuardi MV, Althouse AD, Sarbaugh MS, Ogilvie RP, Patel SR. **Exploring the mechanisms of the racial disparity in drowsy driving.** *Sleep Health* 2018; 4:331-338. **Society for Heart and INTERVENTIONAL PULMONOLOGY.** *J Heart Lung Transplant.* 2017 Oct;36(10):1104-1113.

## COPD

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## TREATMENT OF COPD

Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, Dransfield MT, Halpin DMG, Han MK, Jones CE, Kilbride S, Lange P, Lomas DA, Martinez FJ, Singh D, Tabberer M, Wise RA, Pascoe SJ, Investigators I. **Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD.** *N Engl J Med.* 2018; 378: 1671-1680

## Summary

In this randomized trial involving 10,355 patients with COPD, 52 weeks of a once-daily combination of fluticasone furoate (an inhaled glucocorticoid), umeclidinium (a LAMA), and vilanterol (a LABA) [triple therapy] was compared with fluticasone furoate-vilanterol (ICS/LABA) and umeclidinium-vilanterol (LAMA/LABA). Each regimen was administered in a single Ellipta inhaler. The rate of moderate or severe exacerbations in the triple-therapy group was 0.91 per year, as compared with 1.07 per year in the ICS/LABA group (rate ratio with triple therapy, 0.85; 95% confidence interval [CI], 0.80 to 0.90; 15% difference;  $P < 0.001$ ) and 1.21 per year in the LAMA/LABA group (rate ratio with triple therapy, 0.75; 95% CI, 0.70 to 0.81; 25% difference;  $P < 0.001$ ). The annual rate of severe exacerbations resulting in hospitalization in the triple-therapy group was 0.13, as compared with 0.19 in the LAMA/LABA group (rate ratio, 0.66; 95% CI, 0.56 to 0.78; 34% difference;  $P < 0.001$ ). There was a higher incidence of pneumonia in the inhaled-glucocorticoid groups than in the LAMA/LABA group, and the risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with LAMA/LABA, as assessed in a time-to-first-event analysis (hazard ratio, 1.53; 95% CI, 1.22 to 1.92;  $P < 0.001$ ). Triple therapy resulted in a lower rate of moderate or severe COPD exacerbations than ICS/LABA or LAMA/LABA in this population. Triple therapy also resulted in a lower rate of hospitalization due to COPD than LAMA/LABA.

## Comments

1. Once-daily single-inhaler triple therapy (ICS/LABA/LAMA) resulted in a significantly lower rate of moderate or severe COPD exacerbations and better lung function and health-related quality of life than dual therapy with fluticasone furoate-vilanterol or the dual bronchodilator umeclidinium-vilanterol among patients with symptomatic COPD and a history of exacerbations.

2. The finding that ICS/LABA was superior to LAMA/LABA with respect to the rates of COPD exacerbations is in contrast to those of the FLAME trial.
3. The strengths of the IMPACT trial include the large number of patients enrolled and the comparison of triple therapy with dual therapies using the same molecules in the same delivery device.
4. Subjects in the IMPACT trial who were assigned to the LAMA-LABA group and had been previously receiving an ICS would have had to abruptly stop the ICS, thus it is unknown whether the abrupt discontinuation of ICS could have contributed to the finding of a lower rate of exacerbations in the ICS groups than in the LAMA-LABA group.

Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G, Guasconi A, Montagna I, Vezzoli S, Petruzzelli S, Scuri M, Roche N, Singh D. **Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial.** *Lancet* 2018; 391: 1076-1084.

## Summary

This study compared a single-inhaler triple combination of beclometasone dipropionate, formoterol fumarate, and glycopyrronium (BDP/FF/G) versus a single-inhaler dual bronchodilator combination of indacaterol plus glycopyrronium (IND/GLY) in terms of the rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment. This randomised, parallel-group, double-blind, double-dummy study was done at 187 sites across 17 countries. Eligible patients had symptomatic COPD, severe or very severe airflow limitation, at least one moderate or severe exacerbation in the previous year and were receiving inhaled maintenance medication. After a 2 week run-in period with one inhalation per day of IND/GLY, patients were randomly assigned (1:1), to receive 52 weeks of treatment with two inhalations of extrafine BDP/FF/G twice per day or one inhalation of IND/GLY per day. 1532 patients received BDP/FF/G ( $n=764$ ) or IND/GLY ( $n=768$ ). Moderate-to-severe exacerbation rates were 0.50 per patient per year (95% CI 0.45-0.57) for BDP/FF/G and 0.59 per patient per year (0.53-0.67) for IND/GLY, giving a rate ratio of 0.848 (0.723-0.995,  $p=0.043$ ) in favor of BDP/FF/G. In patients with symptomatic COPD, severe or very severe airflow limitation, and an exacerbation history despite maintenance therapy, extrafine BDP/FF/G significantly reduced the rate of moderate-to-severe exacerbations compared with IND/GLY, without increasing the risk of pneumonia.

## Comments

1. In patients with symptomatic COPD, an FEV1 of less than 50%, and an exacerbation history despite maintenance therapy, treatment with the extra-fine inhaled corticosteroid-containing triple therapy regimen of BDP/FF/G was more effective in reducing the rate of moderate-to-severe COPD exacerbations than the dual bronchodilator combination of IND/GLY.
2. The relative effect of BDP/FF/G versus IND/GLY on moderate-to-severe exacerbations was greater in patients with eosinophils greater than 2%; consistent with results from several published studies in which the effect of ICS (in combination with one or more bronchodilators) on exacerbations was more consistent in patients with higher blood eosinophil levels.
3. The relative effect of BDP/FF/G versus IND/GLY on moderate-to-severe exacerbations was also greater in patients with a clinical diagnosis of chronic bronchitis.

Chapman KR, Hurst JR, Frent SM, Larbig M, Fogel R, Guerin T, Banerji D, Patalano F, Goyal P, Pfister P, Kostikas K, Wedzicha JA. **Long-Term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease (SUNSET): A Randomized, Double-Blind, Triple-Dummy Clinical Trial.** *Am J Respir Crit Care Med.* 2018 Aug 1;198(3):329-339.

## Summary

This 26-week, randomized, double-blind, triple-dummy study assessed the direct change from long-term triple therapy to LAMA/LABA [indacaterol/glycopyrronium (110/50 µg once daily)] or continuation of triple therapy [ICS/LABA/LAMA (tiotropium [18 µg] once daily plus combination of salmeterol/fluticasone propionate [50/500 µg] twice daily)] in non-frequently exacerbating patients with moderate-to-severe COPD. Primary endpoint was noninferiority on change from baseline in trough FEV1. Moderate or severe exacerbations were predefined secondary endpoints. A total of 527 patients were randomized to LAMA/LABA and 526 to triple therapy. Inhaled corticosteroids withdrawal led to a reduction in trough FEV1 of -26 ml (95% confidence interval, -53 to 1 ml) with confidence limits exceeding the noninferiority margin of -50 ml. The annualized rate of moderate or severe COPD exacerbations did not differ between treatments (rate ratio, 1.08; 95% confidence interval, 0.83 to 1.40). Patients with  $\geq 300$  blood eosinophils/ $\mu\text{l}$  at baseline presented greater lung function loss and higher exacerbation risk. Adverse events were similar in the two groups. In patients with COPD without frequent exacerbations on long-term triple therapy, the direct de-escalation to LAMA/LABA led to a small decrease in lung function, with no difference in exacerbations. The higher exacerbation risk in patients with  $\geq 300$  blood eosinophils/ $\mu\text{l}$  suggests that these patients are likely to benefit from triple therapy.

## Comments

1. This study addresses a clinically relevant question as to whether patients with COPD with no more than one exacerbation in the previous year can have ICS safely withdrawn from long-term triple therapy.
2. ICS de-escalation led to a small but significant decrease in lung function of 26 ml in trough FEV1 with no difference in the rates or risk of COPD exacerbations between treatments.
3. Patients with high blood eosinophils ( $>300$  cells/ml) at baseline showed greater differences in lung function (mean decrease of 269 ml) and were at increased risk of exacerbations after ICS withdrawal confirming a post hoc observation in the WISDOM study.

Devereux G, Cotton S, Fielding S, McMeekin N, Barnes PJ, Briggs A, Burns G, Chaudhuri R, Chrystyn H, Davies L, De Soyza A, Gompertz S, Haughney J, Innes K, Kaniewska J, Lee A, Morice A, Norrie J, Sullivan A, Wilson A, Price D. **Effect of Theophylline as Adjunct to Inhaled Corticosteroids on Exacerbations in Patients With COPD: A Randomized Clinical Trial.** *JAMA* 2018; 320: 1548-1559.

## Summary

Preclinical investigations have demonstrated that low plasma concentrations (1-5 mg/L) of theophylline enhance anti-inflammatory effects of corticosteroids, thus the TWICS (theophylline with inhaled corticosteroids) trial was a pragmatic, double-blind, placebo-controlled, randomized clinical trial that enrolled patients with COPD in order to investigate the effectiveness of adding low-dose theophylline to inhaled corticosteroids in COPD. This study included 1578 participants in 121 UK primary and secondary care sites with COPD who had at least 2 exacerbations (treated with antibiotics, oral corticosteroids, or both) in the previous year and were using an inhaled corticosteroid. Participants were randomized to receive low-dose theophylline (200 mg once or twice per day) to provide plasma concentrations of 1 to 5 mg/L (determined by ideal body weight and smoking status) (n=791) or placebo (n=787). There were 1727 exacerbations in the theophylline group (mean, 2.24 [95% CI, 2.10-2.38] exacerbations per year) vs 1703 in the placebo group (mean, 2.23 [95% CI, 2.09-2.37] exacerbations per year); unadjusted mean difference, 0.01 (95% CI, -0.19 to 0.21) and adjusted incidence rate ratio, 0.99 (95% CI, 0.91-1.08). Among adults with COPD at high risk of exacerbation treated with inhaled corticosteroids, the addition of low-dose theophylline, compared with placebo, did not reduce the number COPD exacerbations over a 1-year period.

## Comments

1. This was a pragmatic clinical study design which attempted to replicate the use of low-dose theophylline in routine clinical practice with 121 geographically dispersed study centers, minimal inclusion criteria, infrequent study assessments, no changes to routine care, usual care settings, and use of participant-reported exacerbations.

2. The findings do not support the use of low-dose theophylline as adjunctive therapy to inhaled corticosteroids for the prevention of COPD exacerbations.
3. In secondary analysis, low-dose theophylline did reduce the number of severe COPD exacerbations requiring hospital admission but the most benefit being evident in a small (1%-2%) subgroup of patients frequently hospitalized with COPD.
4. There were no significant differences in non-COPD hospital admissions, episodes of pneumonia, FEV1, CAT score, mMRC dyspnea score, or mortality (COPD-related and overall) between the 2 groups
5. This study has several limitations, including more participants than anticipated (26%) ceased taking the study drug.

## OTHER ARTICLES OF INTEREST

### Treatment

Ferguson GT, Rabe KF, Martinez FJ, Fabbri LM, Wang C, Ichinose M, Bourne E, Ballal S, Darken P, DeAngelis K, Aurivillius M, Dorinsky P, Reisner C. **Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallelgroup, multicentre, phase 3 randomised controlled trial.** *Lancet Respir Med* 2018; 6: 747-758.

Walker PP, Pompilio PP, Zanaboni P, Bergmo TS, Prikk K, Malinovsky A, Montserrat JM, Middlemass J, Sonc S, Munaro G, Marusic D, Sepper R, Rosso R, Siriwardena AN, Janson C, Farre R, Calverley PMA, Dellaca RL. **Telemonitoring in Chronic Obstructive Pulmonary Disease (CHROMED). A Randomized Clinical Trial.** *Am J Respir Crit Care Med* 2018; 198: 620-628.

Martinez FJ, Rabe KF, Calverley PMA, Fabbri LM, Sethi S, Pizzichini E, McIvor A, Anzueto A, Alagappan VKT, Siddiqui S, Reisner C, Zetterstrand S, Roman J, Purkayastha D, Bagul N, Rennard SI. **Determinants of Response to Roflumilast in Severe Chronic Obstructive Pulmonary Disease. Pooled Analysis of Two Randomized Trials.** *Am J Respir Crit Care Med* 2018; 198: 1268-1278.

### Mechanism

Leitao Filho FS, Alotaibi NM, Ngan D, Tam S, Yang J, Hollander Z, Chen V, FitzGerald JM, Nislow C, Leung JM, Man SFP, Sin DD. **Sputum Microbiome is Associated with 1-Year Mortality Following COPD Hospitalizations.** *Am J Respir Crit Care Med*. 2018 Oct 30. doi: 10.1164/rccm.201806-1135OC. [Epub ahead of print] PubMed PMID: 30376356.

Vasilescu DM, Martinez FJ, Marchetti N, Galbán CJ, Hatt C, Meldrum CA, Dass C, Tanabe N, Reddy RM, Lagstein A, Ross BD, Labaki WW, Murray S, Xia M, Curtis JL, Hackett TL, Kazerooni EA, Criner GJ, Hogg JC, Han MK. **Non-Invasive Imaging Biomarker Identifies Small Airway Damage in Severe COPD.** *Am J Respir Crit Care Med*. 2019 Feb 22. doi: 10.1164/rccm.201811-2083OC. [Epub ahead of print] PubMed PMID: 30794432.

### Review

Labaki W, Lucas M, Kimmig LM, Mutlu GM, Han MK, Bhatt SP. **Update in Chronic Obstructive Pulmonary Disease 2018.** *Am J Respir Crit Care Med*. [Articles in press]

Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Criner GJ, Frith P, Halpin DMG, Han M, López Varela MV, Martinez F, Montes de Oca M, Papi A, Pavord ID, Roche N, Sin DD, Stockley R, Vestbo J, Wedzicha JA, Vogelmeier C. **Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD Science Committee Report 2019.** *Eur Respir J*. 2019 Mar 7. pii: 1900164. doi: 10.1183/13993003.00164-2019. [Epub ahead of print] Review.

## INTERVENTIONAL PULMONOLOGY

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## TREATMENT OF EMPHYSEMA

Criner GJ, Sue R, Wright S, Dransfield M, Rivas-Perez H, Wiese T, Scirba FC, Shah PL, Wahidi MM, de Oliveira G, Morrissey B, Cardoso PFG, Hays S, Majid A, Hsia, DW, Sung A, Jarad N, Kornaszewska M, Hazelrigg S, Krishna G, Armstrong B, Shargill NS, Slebos, DJ; for the LIBERATE Study Group. **A multicenter randomized controlled trial of Zephyr Endobronchial Valve treatment in heterogeneous emphysema (LIBERATE).** *Am J Respir Crit Care Med* 2018; 198:1151–1164.

## Summary

Previous studies have demonstrated that the treatment of severe emphysema with Endobronchial Valve (EBV) has not resulted in clinically meaningful changes compared to the standard of care (SOC). Post hoc analysis has identified that those patients with no collateral ventilation to the ipsilateral adjacent lobes and complete lobar occlusion with intact fissures responded best to the EBV therapy. In this multicenter, randomized, controlled trial, the effectiveness and safety of the Zephyr® EBV (pulmonx Redwood City CA) in the treatment of patients with heterogeneous emphysema and no collateral ventilation was evaluated. A total of 190 subjects were enrolled with a 2:1 randomization to either EBV with (SOC) (n=128) versus SOC alone (n=62). At 12 months, 47.7% of the EBV/SOC group and 16.8% SOC subjects had a change in FEV1 greater than or equal to 15% (P < 0.001). The EBV/SOC group also had significant changes in FEV1=0.106 L (P < 0.001), 6-minute-walk distance=+39.31 m (P = 0.002), and St. George's Respiratory Questionnaire=-7.05 points (P = 0.004); Pneumothorax was the most common serious adverse event in the treatment period (procedure to 45 days) occurring in 34/128 (26.6%) of EBV subjects.

## Comments

1. The LIBERATE trial demonstrated that patients with heterogeneous emphysema and no collateral ventilation had clinically significant benefits in quality of life, lung function, and exercise tolerance at 12 months when treated with the Zephyr® EBV.
2. Compared to the National Emphysema Treatment Trial (NETT) those patients that responded to the EBV therapy had a 20% wider range of lung function and exercise tolerance than those patients that responded in the NETT study.
3. The pneumothorax rate was similar to previous trials and did seem to have adverse effects on clinical outcomes.

4. Unlike the NETT trial where those patients that responded best to lung volumes reduction surgery where those with low exercise tolerance as determined by baseline six-minute walk test
5. In patients with severe emphysema that are not candidates for lung volume reduction surgery or INTERVENTIONAL PULMONOLOGY, EBV is a safe and practical treatment option.

## NAVIGATIONAL BRONCHOSCOPY

Folch EE, Pritchett M, Nead M, Bowling MR, Murgu SD, Krinsky WS, Murillo BA, LeMense GP, Minnich DJ, Bansal S, Ellis BQ, Mahajan AK, Gildea TR, Bechara RI, Szejman E, Flandes J, Rickman OB, Benzaquen S, Hogarth KD, Linden PA, Wahidi MM, Mattingley JS, Hood KL, Lin H, Wolvers JJ, Khandhar SJ; for the NAVIGATE Study Investigators. **Electromagnetic Navigation Bronchoscopy for Peripheral Pulmonary Lesions: One-Year Results of the Prospective, Multicenter NAVIGATE Study.** *Journal of Thoracic Oncology* 2018. Vol. 14 No. 3: 445-458

## Summary

The NAVIGATE trial is a prospective, multicenter, global, cohort study evaluating the safety and utility of electromagnetic navigational bronchoscopy [(ENB) superDimension™ navigation system] in the management of peripheral lung lesions. In the United States 1,215 consecutive subjects at 29 sites were enrolled and a 1-year interim analysis is reported. Among 1,157 subjects undergoing ENB guided biopsy: 94% (1092 of 1157) had navigation completed and tissue obtained, dye marking in 23, fiducial marker placement in 258, and lymph node sampling in 463 [96% with linear endobronchial ultrasound (EBUS)]. The majority (96%) of the subjects had at least 2 procedures performed during one anesthetic event (i.e. fiducial placement, mediastinal staging, and biopsy of the peripheral lesion). Follow-up was completed in 80% of subjects at 12 months. The tissue diagnostic yield was 73%, with a reported sensitivity (69%), specificity (100%), positive predictive value (100%), and negative predictive value (56%) for malignancy. ENB related Common Terminology Criteria for Adverse Events grade 2 or higher were 2.9 % pneumothorax (requiring chest tube placement and/or hospital admission) and 1.5 % for bronchopulmonary hemorrhage. Grade 4 respiratory failure was 0.7%. The median lesion size was 20.0 mm.

Radial endobronchial ultrasound and fluoroscopy was utilized in 91% and 57% of the cases respectively.

### Comments

1. The NAVIGATE trial is the largest prospective multicenter study evaluating the utility and safety of ENB.
2. This study concluded that ENB is a safe tool with a reasonable diagnostic yield to aid in the diagnosis of peripheral pulmonary nodules.
3. The one-year calculation of the diagnostic yield from NAVIGATE is consistent with the combined average of all the previous ENB studies.
4. The flexibility of ENB was highlighted in this study in that the majority of patients had more than one procedure performed during the same anesthetic event.
5. Given that both experienced and less experienced users were enrolled in the study, these data may represent the actual “real world” experience of the average ENB user.

## ENDBRONCHIAL ULTRASOUND-RADIAL

Tanner NT, Yarmus L, Chen A, Memoli JW, Mehta HJ, Pastis NJ, Lee H, Jantz MA, Nietert PJ, Silvestri GA. **Standard Bronchoscopy With Fluoroscopy vs Thin Bronchoscopy and Radial Endobronchial Ultrasound for Biopsy of Pulmonary Lesions. A Multicenter, Prospective, Randomized Trial.** *Chest.* 2018 Nov;154(5):1035-1043

### Summary

In this prospective, multicenter randomized trial, patients presenting for a bronchoscopic biopsy of peripheral pulmonary lesions were randomized to either standard bronchoscopy (SB) with fluoroscopic guidance (F) or thin bronchoscopy (TB) with fluoroscopic guidance. In the TB group adequate positioning for sampling was confirmed with radial endobronchial ultrasound (r-EBUS). If the (SB-F) biopsies were non-diagnostic as determined by immediate cytological evaluation, patients were crossed over to the (TB-rEBUS) group for sampling of the pulmonary lesions. All samples were standardized and collected utilizing cytologic brushings and forceps biopsy. A procedure was considered diagnostic if a malignancy or specific benign condition was identified based on the cytologic brushings or forceps biopsies. Most of the lesions were located in the upper lobes with a mean size of 30 mm and 69% had a bronchus sign. In the (TB-rEBUS) cohort a concentric ultrasound imaging was obtained in 57% of the patients. Bronchoscopy was diagnostic in 87/197 patients (44%). The (TB-rEBUS) group had a diagnostic yield of 49% (55/112) compared to 37% (32/85) in the (SB-F) cohort ( $p=0.11$ ). Forty-six patients were non-diagnostic in the (SB-F) group and crossed over to the (TB-rEBUS) cohort where 7/46 (15%) obtained a diagnosis.

### Comments

1. This study is unique among the bronchoscopic literature, in that it is designed as a randomized, prospective, multicenter trial.
2. Both standard bronchoscopy with fluoroscopic guidance and thin bronchoscopy with r-EBUS and fluoroscopic guidance provided a diagnosis less than 50% of the time for peripheral lung lesions.
3. The exclusion of 25 patients reduced the power to detect a difference in the diagnostic yield from the initial 85% to 81%, which may have had an adverse effect on the reported diagnostic yields.
4. The inability to add fine needle aspirations and bronchoalveolar lavage may have had a significant negative impact on the diagnostic yield as well.
5. It may be that we should focus on evaluating what are the best diagnostic pathways (i.e. what patients will benefit from the current available procedures) and the development of new technology that will lead us to the most efficient care in patients with peripheral pulmonary lesions.

## CONE BEAM COMPUTED TOMOGRAPHY

Pritchett MA, Schampaert S, deGroot JAH, Schirmer CC, van der Bom I. **Cone-Beam CT With Augmented Fluoroscopy Combined With Electromagnetic Navigation Bronchoscopy for Biopsy of Pulmonary Nodules.** *J Bronchol Intervent Pulmonol* 2018;25:274–282

### Summary

In this single center retrospective study, the utility of adding augmented fluoroscopy (AF) and cone beam computed tomography (CBCT) to electromagnetic navigational bronchoscopy (ENB) for the evaluation of peripheral pulmonary nodules (PPN) was assessed. In 75 consecutive patients being evaluated for a (PPN), CBCT data were acquired and a 3-dimensional segmentation of nodules was created. During the ENB procedure, these images were projected and fused with live fluoroscopy allowing real-time 3-dimensional guidance. Data was collected from 93 lesions with a median size of 16.0 mm and a diagnostic yield of 83%. There was no correlation with diagnostic yield and presence of a bronchus sign, lesion size, location, or visibility under standard fluoroscopy. Several various biopsy tools were utilized with no particular standardization: fine needle aspiration, biopsy forceps, bronchoalveolar lavage and needle cytology brush were all utilized at various times. Immediate cytologic evaluation was used in all cases. A pneumothorax occurred in 4% (3/75) of the patients.

### Comments

1. This is the largest study evaluating the combination of ENB and CBCT-AF for the evaluation of peripheral lung nodules.
2. The diagnostic yield in this study for ENB-CBCT-AF guided biopsy of peripheral lesions is higher than the average diag-



- nostic yield in the standard ENB bronchoscopic literature, but lower than the average diagnostic yield with the CT guided transthoracic needle aspiration (TTNA) approach.
- The complication rates for ENB-CBCT-AF are consistent with the standard ENB literature, but significantly less than the complication rates due to CT guided TTNA.
  - This study demonstrated that ENB-CBCT-AF biopsy of peripheral pulmonary lesions is safe and produces a high diagnostic yield.
  - Although intriguing, ENB-CBCT-AF guided biopsy may be only available to a few pulmonologist/surgeons that possess the skill and technology to utilize this diagnostic approach.

## ENDOBONCHIAL ULTRASOUND: CURVILINEAR

Webb TN, Flanagan E, Martin R, Parks C, Behara RI. **Effect of Routine Clopidogrel Use on Bleeding Complications After Endobronchial Ultrasound-guided Fine Needle Aspiration.** *J Bronchol Intervent Pulmonol* 2019; 26:10–14

### Summary

It is not uncommon that patients being treated with antiplatelet medications (clopidogrel and aspirin) require endobronchial ultrasound bronchoscopy (EBUS) guided fine needle aspiration (FNA) for the investigation of mediastinal and hilar lymphadenopathy. In some of these patients, stopping these medications can lead to a substantial danger of thrombotic complications. Webb et al. evaluated the risk of bleeding complication after an EBUS-guided FNA for abnormal mediastinal lymphadenopathy in patients that are unable to stop the antiplatelet medication. In this multicenter prospective trial, 40 patients being treated with clopidogrel and aspirin, unable to be withheld for the procedure, underwent EBUS guided FNA for investigation of mediastinal lymphadenopathy. An interventional pulmonologist performed all procedures and the first 3 samples were taken with a 22-gauge needle. If there was no significant bleeding (defined as the need for any intervention to obtain hemostasis), a 21-gauge needle was utilized for the next 3 sample collections. A total of 92 lymph nodes were sampled. There were no significant bleeding events reported at any of the cases or 24 hours after the procedure.

### Comments

- This study is the largest multicenter; prospective study evaluating the safety of EBUS guided FNA for mediastinal/hilar lymphadenopathy in patients on antiplatelet medication that are unable to be held for the procedure due to the high risk of a thrombotic complication.
- This trial was limited to interventional pulmonologists that have extensive experience in both EBUS-FNA and management of airway bleeding.
- Based on the results of this study, in patients that are unable to stop antiplatelet medication, EBUS-guided FNA for mediastinal/hilar lymph node sampling is safe with both 22- and 21-gauge needles.

- There may be a role for bridging these patients with short acting medications such as glycoprotein IIb/IIIa inhibitors. Hopefully, more investigation will be done to answer this question.
- These data certainly add to our understanding of the safety of EBUS-guided FNA in patients on antiplatelet medications, but we must take extreme caution when pursuing these biopsies.

## OTHER ARTICLES OF INTEREST

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Feller-Kopman DJ, Reddy CB, DeCamp MM, Diekemper RL, Gould MK, Henry T, Iyer NP, Lee YCG, Lewis SZ, Maskell NA, Rahman NM, Sterman DH, Wahidi MM, Balekian AA; on behalf of the American Thoracic Society, Society of Thoracic Surgeons, and Society of Thoracic Radiology. **Management of Malignant Pleural Effusions. An Official ATS/STS/STR Clinical Practice Guideline.** *Am J Resp Crit Care Med* 2018; 198:839-849

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Silvestri GA, Tanner NT, Kearney P, Vachani A, Massion PP, Porter A, Springmeyer SC, Fang KC, Midthum D, Mazzone P: for the PANOPTIC Trial Team. **Assessment of Plasma Proteomics Biomarkers's Ability to Distinguish Benign From Malignant Lung Nodules. Results of the PANOPTIC (Pulmonary Nodule Plasma Proteomic Classifier) Trial.** *CHEST* 2018; 154(3):491-500

Karthik Suresh, Voong KR, Shankar B, Forde PM, Ettinger DS, Marrone KA, Kelly RJ, Hann CL, Levy B, Feliciano JL, Brahmer JR, Feller-Kopman D, Lerner AD, Lee H, Yarmus L, D'Alesso F, Hales RK, Lin CT, Psoter KJ, Danoff SK, Naidoo J. **Pneumonitis in Non-Small Cell Lung Cancer Patients Receiving Immune Checkpoint Immunotherapy: Incidence and Risk Factors.** *Journal of Thoracic Oncology* Vol. 13 No. 12.1930-1939

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Wand O, Guber E, Guber A, Shochet GE, Israeli-Shani L, Shitrit D. **Inhaled Tranexamic Acid for Hemoptysis Treatment.** *CHEST* 2018. Volume 154, Issue 6, Pages 1379-1384

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Sato T, Yutaka Y, Ueda Y, Hamaji M, Motoyama H, Menju T, Aoyama A, Chen-Yoshikawa TF, Sonobe M, Date H. **Diagnostic Yield of Electromagnetic Navigational Bronchoscopy; Results of Initial 35 Cases in a Japanese Institute.** *J Thorac Dis* 2018;10(Suppl 14): S1615-S1619

Fernandes MGO, Santos V, Martins N, Sucena M, Pasos MM, Marques MM, Magalhaes AM, Bugalho A. **Endobronchial Ultrasound under Moderate Sedation versus General Anesthesia.** *J. Clin. Med.* 2018, 7(11), 421

Lee H, Lerner A, Coleman B, Semaan R, Mallow C, Arias S, Salwen B, Feller-Kopman D, Yarmus L. **Learning Electromagnetic Navigational Bronchoscopy and Percutaneous Transthoracic Needle Biopsy (LEAP): A Pilot Study.** *Journal of Bronchology and Interventional Pulmonology.* 2019. 26(1):55-61

Rojas-Solano JR, Ugalde-Gamboa Luis, Machuzak M. **Robotic Bronchoscopy for Diagnosis of Suspected Lung Cancer: A Feasibility Study.** *Journal of Bronchology & Interventional Pulmonology* 2018. 25(3):168-175

Sobieszcyk MJ, Yuan Z, Li W, Krimski W. **Biopsy of peripheral lung nodules utilizing cone beam computer tomography with and without trans bronchial access tool: a retrospective analysis.** *J Thorac Dis* 2018;10(10):5953-5959

Sanchez-Font A, Chalela R, Martin-Ontiyuelo C, Albero-Gonzalez R, Dalmases A, Longaron R, Alonso-Espinaco V, Curull V, Bellosillo B, Pijuan L. **Molecular Analysis of Peripheral Lung Adenocarcinoma in Brush Cytology Obtained by EBUS Plus Fluoroscopy-Guided Bronchoscopy.** *Cancer Cytopathol* 2018;126:860-871

Van Horn JE, Dahele M, Daniels JMA. **Bronchoscopic Manifestations of Airway Toxicity After Radiotherapy.** *Clinical Lung Cancer*, Vol. 19, No. 6, e875-8

## SARCOIDOSIS

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## PHENOTYPES OF SARCOIDOSIS

Schupp JC, Freitag-Wolf S, Bargagli E, Mihailović-Vučinić V, Rottoli P, Grubanovic A, Müller A, Jochens A, Tittmann L, Schnersch J, Olivieri C, Fischer A, Jovanovic D, Filipovic S, Videnovic-Ivanovic J, Bresser P, Jonkers R, O'Reilly K, Ho LP, Gaede KI, Zabel P, Dubaniewicz A, Marshall B, Kieszko R, Milanowski J, Günther A, Weihrich A, Petrek M, Kolek V, Keane MP, O'Beirne S, Donnelly S, Haraldsdottir SO, Jorundsdottir KB, Costabel U, Bonella F, Wallaert B, Grah C, Peroš-Golubičić T, Luisetti M, Kadija Z, Pabst S, Grohé C, Strausz J, Vašáková M, Sterclova M, Millar A, Homolka J, Slovákova A, Kendrick Y, Crawshaw A, Wuyts W, Spencer L, Pfeifer M, Valeyre D, Poletti V, Wirtz H, Prasse A, Schreiber S, Krawczak M, Müller-Quernheim J. **Phenotypes of organ involvement in sarcoidosis.** *Eur Respir J* 2018; 51(1): pii: 1700991

## Summary

The article describes the results of the baseline phenotype module of a European multicenter study to investigate the influence of genotype on disease phenotypes in sarcoidosis. The study cohort comprised 2163 Caucasian patients with sarcoidosis who were phenotyped at 31 centers according to a standardized protocol. The authors found that patients with acute onset were mainly female, young and of Scadding type I or II. Female patients showed a significantly higher frequency of eye and skin involvement and reported more often fatigue. Based on multidimensional correspondence analysis and subsequent cluster analysis, patients could be stratified into five distinct, yet undescribed, subgroups according to predominant organ involvement: 1) abdominal organ involvement, 2) ocular-cardiac-cutaneous-central nervous system disease involvement, 3) musculoskeletal-cutaneous involvement, 4) pulmonary and intrathoracic lymph node involvement, and 5) extrapulmonary involvement. The authors concluded that these new phenotypes can be used in clinical and biomedical studies to obtain homogenous and clearly defined sub-cohorts of sarcoidosis patients. The results will also be used for their future genotype-phenotype studies.

## Comments

1. The five new clinical phenotypes might be useful to recruit homogenous cohorts in future biomedical studies.
2. However, the phenotypes are probably only applicable in Caucasians and might not be useful in other ethnicities.

3. Unfortunately there was no data on types of skin involvement, so it was uncertain in which phenotype classical Löfgren syndrome is concealed.
4. Investigators were mainly pulmonologists, so an overrepresentation of pulmonary sarcoidosis is possible.
5. All study sites were tertiary referral centers, so an overrepresentation of patients with complicated, advanced sarcoidosis is likely.

## MORTALITY OF SARCOIDOSIS

Rossides M, Kullberg S, Askling J, Eklund A, Grunewald J, Arkema EV. Sarcoidosis mortality in Sweden: a population-based cohort study. *Eur Respir J* 2018; 51(2): pii:1701815.

## Summary

The article describes the results of a population-based cohort study into sarcoidosis mortality, taking into account disease heterogeneity. Individuals with incident sarcoidosis (n=8207) were identified from the Swedish National Patient Register using ICD codes (2003-2013). In a subset, cases receiving treatment  $\pm$  3 months from diagnosis were identified from the Prescribed Drug Register. Non-sarcoidosis comparators from the general population were matched to cases 10:1 on birth year, sex and county. Individuals were followed for all-cause death in the Cause of Death Register. Adjusted mortality rates, rate differences and hazard ratios (HRs) were estimated, stratifying by age, sex and treatment status. The mortality rate was 11.0 per 1000 person-years in sarcoidosis versus 6.7 in comparators (rate difference 2.7 per 1000 person-years). The HR for death was 1.61 (95% CI 1.47-1.76), with no large variation by age or sex. For cases not receiving treatment within the first 3 months, the HR was 1.13 (95% CI 0.94-1.35). For those receiving treatment HR was 2.34 (95% CI 1.99-2.75). Individuals with sarcoidosis are therefore at a higher risk of death compared to the general population; especially those whose disease needs treatment around diagnosis have a two-fold increased risk of death.

## Comments

1. Strength of this study is the use of high-quality registers with excellent coverage of the entire Swedish population.
2. The study shows that individuals with sarcoidosis who do not receive treatment at diagnosis have only a marginally increased risk of death.

- Individuals with sarcoidosis who need treatment around diagnosis have a two-fold increased risk of death and therefore represent a more vulnerable group.
- Unfortunately, due to the lack of clinical patient information the authors were not able to investigate mortality by disease phenotype or correlate their medication-based proxy for severity with other disease severity indices.
- Future studies are important to investigate mortality in sarcoidosis in well-defined patient subgroups with different disease phenotypes; early identification of those at increased risk might help improve their outcome.

## PULMONARY HYPERTENSION IN SARCOIDOSIS

Baughman RP, Shlobin OA, Wells AU, Alhamad EH, Culver DA, Barney J, Cordova FC, Carmona EM, Scholand MB, Wijsenbeek M, Ganesh S, Birring SS, Kouranos V, O'Hare L, Baran JM, Cal JG, Lower EE, Engel PJ, Nathan SD.

**Clinical features of sarcoidosis associated pulmonary hypertension: Results of a multi-national registry.** *Respir Med* 2018; 139: 72-78.

### Summary

This article describes the results of a multi-national registry of patients with sarcoidosis associated pulmonary hypertension (ReSAPH). A total of 176 patients with pulmonary artery wedge pressure (PAWP) of 15 mmHg or less and a mean pulmonary artery pressure (mPAP)  $\geq$  25 Hg were analyzed. Data collected included hemodynamics, forced vital capacity (FVC), diffusion capacity of carbon monoxide (DLCO), chest x-ray, and 6-min walk distance (6MWD). There was a significant correlation between DLCO percent predicted (% pred) and mPAP (Rho = -0.228,  $p = 0.0068$ ) and pulmonary vascular resistance (PVR) (Rho = -0.362,  $p < 0.0001$ ). PVR was significantly higher in stage 4 disease as in stage 0 or 1 disease ( $p < 0.05$  for both comparisons). About two-thirds of the SAPH patients came from the United States (U.S.). There was a significant difference in the rate of treatment between U.S. (67.5%) versus non-U.S. (86%) (Chi Square 11.26,  $p = 0.0008$ ) sites. The authors concluded that the clinical features of SAPH were similar across multiple centers in the U.S., Europe, and the Middle East. The severity of SAPH was related to reduced DLCO.

### Comments

- This multinational effort provides an interesting global perspective and insight into features of SAPH.
- The study was however not designed to determine the prevalence of SAPH within any individual clinic.
- Important was the absence of correlation between any of the spirometric values and severity of PH.
- The results suggest that presence of fibrosis is not essential for the development of SAPH and attests to the multi-factorial nature of its etiology.
- SAPH patients in the U.S. were less likely to receive treatment for their PH than their European counterparts.

## INFLIXIMAB BIOSIMILAR INFLECTRA® IN SARCOIDOSIS

Schimmelpennink MC, Vorselaars ADM, van Beek FT, Crommelin HA, Deneer VHM, Keijsers RGM, Veltkamp M. Efficacy and safety of infliximab biosimilar Inflectra® in severe sarcoidosis. *Respir Med* 2018; 138S :S7-S13.

### Summary

The article describes real-world data on the use of infliximab biosimilar Inflectra®, a monoclonal antibody against tumor necrosis factor alpha (TNF- $\alpha$ ) as third-line therapy in severe sarcoidosis. In this retrospective cohort study from the Netherlands, 29 patients treated with Inflectra®, were analyzed. Patients received Inflectra® intravenously monthly at a dose of 5 mg/kg. Trough levels were measured before every infusion. Before and after 6 months of induction therapy pulmonary function and disease activity were evaluated using Standardized Uptake Value (SUV) of the 18F-fluorodeoxyglucose by positron emission tomography (18F-FDG PET), soluble interleukin-2 receptor (sIL-2R), angiotensin converting enzyme (ACE) and health-related quality of life (HRQOL). In patients with pulmonary sarcoidosis as main treatment indication ( $n = 15$ ) the predicted FVC improved with 8.1%,  $p < 0.05$ . Furthermore, in the whole group HRQoL improved significantly ( $p < 0.001$ ), whereas SUVmax and sIL-2R significantly reduced ( $p < 0.001$  and  $p = 0.001$  respectively). Hospitalization due to infections occurred in four patients. None of the patients discontinued Inflectra® due to side effects. Furthermore, all patients had detectable trough levels indicating development of neutralizing antibodies.

### Comments

- Infliximab biosimilar Inflectra® appears to have similar efficacy and safety profile in the treatment of sarcoidosis compared to Remicade®.
- Inflectra® can therefore be considered a less expensive alternative for patients with refractory disease.
- Mean +8.1% change in FVC outweighs the improvement of 2.5% found by Baughman et al. in *AJRCCM* 2006;174(7):795-802.
- Although the study design has the possibility of recall bias, data presented is the only evidence available so far on the use of Inflectra® in sarcoidosis.
- Data are in line with results of NOR-SWITCH trial [Jorgensen et al. *Lancet* 2017;389(10086):2304-16].

## T-HELPER 17.1 CELLS IN SARCOIDOSIS

Broos CE, Koth LL, van Nimwegen M, In 't Veen JCCM, Paulissen SMJ, van Hamburg JP, Annema JT, Heller-Baan R, Kleinjan A, Hoogsteden HC, Wijsenbeek MS, Hendriks RW, van den Blink B, Kool M. **Increased T-helper 17.1 cells in sarcoidosis mediastinal lymph nodes.** *Eur Respir J* 2018; 51(3): pii:1701124.

### Summary

This article reports on the relatively new finding that T-helper (Th) 17.1 cells play a dominant role in the exaggerated interferon- $\gamma$  production in sarcoidosis lungs. In this study, the authors investigated 1) whether Th17.1 cells are increased in the lung-draining mediastinal lymph nodes (MLNs) of sarcoidosis patients and 2) whether frequencies of the Th17.1 cells at diagnosis correlate with disease progression. MLN cells from treatment-naïve pulmonary sarcoidosis patients (n=17) and healthy controls (n=22), and peripheral blood mononuclear cells (n=34) and bronchoalveolar lavage fluid (BALF) (n=36) from sarcoidosis patients were examined for CD4+ T-cell subset proportions using flow cytometry. Higher proportions of Th17.1 cells were detected in sarcoidosis MLNs than in control MLNs. Higher Th17.1 cell proportions were found in sarcoidosis BALF compared to MLNs and peripheral blood. Of potential clinical importance, BALF Th17.1 cell proportions were significantly higher in patients developing chronic disease than in patients undergoing resolution within 2 years of clinical follow-up.

### Comments

1. Data demonstrate that T-cells bearing a surface Th17.1 phenotype are excessively present in the sarcoidosis lung (bronchoalveolar lavage) and adjacent mediastinal lymph nodes.
2. The results suggest that Th17.1/Th1 ratio could serve as a novel prognostic indicator of disease course.
3. On the contrary, a recent study from Sweden has shown that Th17.1 cells are associated with disease remission (Kaiser et al. *Eur Respir J* 2016;48:484-94).
4. The observations provide reasons for investigating treatments targeting the Th17 pathway.
5. Whether expression of IL17 trumps interferon- $\gamma$  as a biomarker for disease activity in sarcoidosis will need further study.

## GENETICS OF SARCOIDOSIS

Besnard V, Calender A, Bouvry D, Pacheco Y, Chapelon-Abric C, Jeny F, Nunes H, Planès C, Valeyre D. G908R NOD2 variant in a family with sarcoidosis. *Respir Res* 2018; 19(1): 44.

### Summary

The article describes interesting genetic findings in a family with sarcoidosis. Sarcoidosis is a systemic disease characterized by the formation of immune granulomas in various organs, mainly the lungs and the lymphatic system. Exaggerated granulomatous reaction might be triggered in response to unidentified antigens in individuals with genetic susceptibility. The authors aimed to determine the genetic variants implicated in a familial case of sarcoidosis. They evaluated the clinical presentation and history, NOD2 profile, NF- $\kappa$ B and cytokine production in blood monocytes/macrophages in individuals from a family with late appearance of sarcoidosis. In their case of familial sarcoidosis with typical thoracic sarcoidosis they found carriage of the NOD2 2722G>C variant. This variant was associated

with the presence of three additional SNPs for the IL17RA, KALRN and EPHA2 genes, which discriminated patients expressing the disease from others. Despite a decrease in NF- $\kappa$ B activity, IL-8 and TNF-A mRNA levels were increased at baseline and in stimulated conditions.

### Comments

1. So far no convincing involvement of NOD2 mutations in sarcoidosis pathogenesis was evidenced.
2. This interesting case report however shows that the combination of polymorphisms in the NOD2, IL17RA, EPHA2 and KALRN genes might play a role.
3. The combination of polymorphisms in these genes could possibly contribute to a chronic pro-inflammatory status of macrophages.
4. Future functional studies are required to reveal the causal regulatory variation of the various loci and the immunogenetic basis related to sarcoidosis.

## MYCOBACTERIAL INFECTIONS

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## TREATMENT OF LATENT TB INFECTION

Menzies D, Adjobimey M, Ruslami R, Trajman A, Sow O, Kim H, Obeng Baah J, Marks GB, Long R, Hoepfner V, Elwood K, Al-Jahdali H, Gninafon M, Apriani L, Koesoemadinata RC, Kritski A, Rolla V, Bah B, Camara A, Boakye I, Cook VJ, Goldberg H, Valiquette C, Hornby K, Dion M-J, Li P-Z, Hill PC, Schwartzman K, Benedetti A. **Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults.** *N Engl J Med* 2018; 379:440-53.

## Summary

Although 4 months of daily rifampin (4R) has been a guideline recommended treatment for latent TB infection (LTBI), this regimen had not been studied in randomized trials. To evaluate the efficacy and safety of rifampin for the treatment of LTBI, investigators completed a phase 3 trial of 4 months of daily rifampin compared to 9 months of daily isoniazid for the prevention of TB disease. This randomized open-label trial enrolled adults from study sites in Canada, Brazil, West Africa, Asia, and Australia who were tuberculin skin test or interferon-gamma release assay (IGRA)-positive, and at increased risk for progression to TB disease. Participants were followed for 28 months after randomization to compare rates of TB, adverse events, and completion of treatment (defined as > 80% of doses). The study enrolled >6000 participants from 2009 to 2014 and included 614 participants previously enrolled in a phase 2 safety study. There were >6800 participants in the modified intention-to-treat analysis, and confirmed TB was diagnosed in 8 participants (4 in each arm). Rifampin was non-inferior to isoniazid for TB prevention. Completion rates in the rifampin arm were higher (79%) than the isoniazid arm (63%). The rate of grades 3-5 adverse events was lower in the rifampin arm, including drug-induced hepatitis.

## Comments

1. This study, together with an accompanying trial of 4R in children, demonstrates that rifampin is safer and more likely to be completed than isoniazid, with similar efficacy in preventing TB.
2. Two shorter rifamycin-based regimens, 4 months of rifampin or 3 months of weekly rifapentine/isoniazid, should be the preferred regimens for TB prevention as they are safer and more likely to be completed than isoniazid.

3. The superior safety profiles of rifamycin-based regimens should be grounds for expanding the screening and treatment of LTBI in the U.S., as this is key to TB elimination.
4. There has been resistance in high burden settings to the use of rifampin for TB prevention due to concerns of treating patients with unrecognized TB disease with a single agent, and it is unclear if there will be widespread uptake of 4R in these settings.

## TUBERCULOSIS VACCINE

Van Der Meeren O, Hatherill M, Nduba V, Wilkinson RJ, Muyoyeta M, Van Brakel E, Ayles HM, Henostroza G, Thienemann F, Scriba TJ, Diacon A, Blatner GL, Demoitie MA, Tameris M, Malahleha M, Innes JC, Hellstrom E, Martinson N, Singh T, Akite EJ, Khatoon Azam A, Bollaerts A, Ginsberg AM, Evans TG, Gillard P, Tait DR. **Phase 2b Controlled Trial of M72/AS01E Vaccine to Prevent Tuberculosis.** *N Engl J Med.* 2018;379(17):1621-34.

## Summary

An effective vaccine against TB is urgently needed. The M72/AS01E candidate vaccine (M72) contains the M72 recombinant fusion protein derived from 2 immunogenic *M. tuberculosis* antigens combined with the AS01 adjuvant system. This study reports the results of a primary analysis of a phase 2b trial of M72 efficacy in preventing TB disease that was funded by GSK and Aeras. This double-blind, randomized, placebo-controlled trial enrolled HIV-negative, IGRA-positive adults (18–50 years) from 3 countries, Kenya, Zambia, and South Africa, and randomized participants to 2 intravascular doses of M72 or placebo. 3283 participants were included in the per-protocol efficacy analysis, among whom the mean age was 29 years and 81% were enrolled in South Africa. A total of 32 cases of TB disease were diagnosed, 10 in the M72 arm and 22 in the placebo arm, over a mean follow-up time of 2.3 years. Overall M72 efficacy was 54% (95% CI=3-79%). Prespecified sub-group analyses suggested greater efficacy in participants < 25 years of age (84% efficacy compared to 10% in >25 years) and men (75% efficacy compared to 27% in women). The occurrence of serious adverse events was similar in both groups.

## Comments

1. Study results are highly promising if confirmed in future studies, and together with the study of BCG re-vaccination in individuals without LTBI, may offer complementary strategies for TB control.
2. Modeling studies suggest that a TB vaccine for adults with 40-60% efficacy could reduce TB cases in low- and middle-income countries by 24-57%.
3. There is uncertain efficacy of M72 vaccine in *M. tuberculosis* uninfected individuals and people living with HIV (regardless of LTBI status).
4. The authors attributed the observed gender-based differences in vaccine efficacy to gender imbalances across the age groups.
5. The observed differential efficacy by age and increasing vaccine efficacy with greater time from vaccination need further investigations.

## TREATMENT OF TB DISEASE

Imperial MZ, Nahid P, Phillips PPJ, Davies GR, Fielding K, Hanna D, Hermann D, Wallis RS, Johnson JL, Lienhardt C, Savic RM. **A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis.** *Nat Med* 2018; 24: 1708-15.

### Summary

Individualizing treatment of TB disease is desirable as the standard 6-month treatment of drug-susceptible TB (HRZE) may result in overtreatment of patients with mild disease and undertreatment of patients with severe TB. Three trials published in 2014 evaluated experimental 4-month fluoroquinolone-containing regimens for drug-susceptible pulmonary TB and showed that unfavorable outcomes were more common in the experimental groups compared to standard 6-month treatment. Using data from these trials, investigators performed an individual participant-level pooled analysis to identify characteristics associated with cure with a 4-month regimen and characteristics associated with unfavorable outcomes with both experimental and standard regimens. The study included 2001 participants who received fluoroquinolone-containing regimens and 1404 participants who received standard treatment. Treatment with the 4-month experimental regimens in participants with lower smear grades (<2+) or absence of radiographic cavities was non-inferior to the standard 6-month treatment; the smear findings were validated using results from a unique RCT. The strongest independent predictor of poor outcomes in both the experimental and standard treatment groups was medication non-adherence to >10% of prescribed doses (OR=5.8 for poor outcome). Additional independent predictors of poor outcomes included culture-positive sputum at treatment month 2, HIV-seropositivity, AFB-smear grade 3+ (compared to <2+), and low BMI.

## Comments

1. This study supports the need for trials to evaluate use of baseline characteristics to individualize length of treatment for drug-susceptible TB disease.
2. The strength of the associations between medication non-adherence and poor TB outcomes is novel and striking: as little as 10% non-adherence (i.e., a level of non-adherence that occurs when patients do not take their TB medications on weekends) was a strong predictor of poor outcomes.
3. It is unclear why men have an independent increased risk for poor TB outcomes and deserves further study.
4. Data was obtained from the Platform for Aggregation of Clinical TB Studies (TB-PACTS), demonstrating the importance of sharing de-identified trial data with the research community for secondary analyses.

## TREATMENT OF MULTIDRUG-RESISTANT TB

Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, Baghaei P, Bang D, Barry PM, Bastos ML, Behera D, Benedetti A, Bisson GP, Boeree MJ, Bonnet M, Brode SK, Brust JCM, Cai Y, Caumes E, Cegielski JP, Centis R, Chan PC, Chan ED, Chang KC, Charles M, Cirule A, Dalcolmo MP, D'Ambrosio L, de Vries G, Dheda K, Esmail A, Flood J, Fox GJ, Frechet-Jachym M, Fregona G, Gayoso R, Gegia M, Gler MT, Gu S, Guglielmetti L, Holtz TH, Hughes J, Isaakidis P, Jarlsberg L, Kempker RR, Keshavjee S, Khan FA, Kipiani M, Koenig SP, Koh WJ, Kritski A, Kuksa L, Kvasnovsky CL, Kwak N, Lan Z, Lange C, Laniado-Laborin R, Lee M, Leimane V, Leung CC, Leung EC, Li PZ, Lowenthal P, Maciel EL, Marks SM, Mase S, Mbuagbaw L, Migliori GB, Milanov V, Miller AC, Mitnick CD, Modongo C, Mohr E, Monedero I, Nahid P, Ndjeka N, O'Donnell MR, Padayatchi N, Palmero D, Pape JW, Podewils LJ, Reynolds I, Riekstina V, Robert J, Rodriguez M, Seaworth B, Seung KJ, Schnippel K, Shim TS, Singla R, Smith SE, Sotgiu G, Sukhbaatar G, Tabarsi P, Tiberi S, Trajman A, Trieu L, Udwardia ZF, van der Werf TS, Veziris N, Viiklepp P, Vilbrun SC, Walsh K, Westenhouse J, Yew WW, Yim JJ, Zetola NM, Zignol M, Menzies D. **Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis.** *Lancet* 2018;392(10150):821-34.

### Summary

In 2017, only 55% of patients treated for multidrug-resistant TB (MDR-TB) were cured. The investigators performed an individual patient data meta-analysis of treatment outcomes in patients with MDR-TB and associations with anti-TB drugs, number of drugs, and treatment duration. Analyses used propensity score-matched generalized mixed-effects models. Eligible studies reported end of treatment outcomes for >24 adults with pulmonary MDR-TB. Fifty studies that contributed 12,030 participants were included in the meta-analysis. 61% of participants had treatment success. Treatment success was favorably

associated with the use of bedaquiline, linezolid, levofloxacin, moxifloxacin, clofazimine, and carbapenems; the first 4 drugs listed were associated with reduced mortality. Amikacin was associated with greater success in treating susceptible isolates, whereas kanamycin and capreomycin were associated with worse outcomes regardless of susceptibility. Pyrazinamide, cycloserine, and terizidone were associated with modest benefit when treating susceptible isolates. Ethambutol, ethionamide, and PAS were not associated with improved outcomes regardless of susceptibility results. The use of at least 5 drugs in the initial phase and at least 4 drugs in the continuation phase was associated with decreased mortality. Outcomes were improved when the initial phase was continued for 5-7 months and total treatment length continued for 15-18 months, after sputum culture conversion.

### Comments

1. This study highlights the importance of bedaquiline, linezolid and later generation fluoroquinolones for treating MDR-TB, demonstrates a lack of equivalency among the injectables, and shows a lack of benefit of several commonly used drugs for the treatment of MDR-TB.
2. Although studies included in the meta-analysis are susceptible to confounding (i.e., observational studies, individualized treatments), the investigators attempted to address this concern through propensity score matching and sensitivity analyses that demonstrated robust findings.
3. These results have informed WHO MDR-TB guidelines to preferentially use Group A (levofloxacin/moxifloxacin, bedaquiline, linezolid) and Group B (clofazimine, cycloserine/terizidone) medications, and de-emphasize injectables based on poor effectiveness and/or drug-related toxicities.
4. These results underscore the importance of expanding global laboratory capacity to test first- and second-line drug susceptibility.
5. Ensuring access to Groups A and B medications is vital to addressing the drug-resistant TB epidemic.

### TB DIAGNOSIS

Dorman SE, Schumacher SG, Alland D, Nabeta P, Armstrong DT, King B, Hall SL, Chakravorty S, Cirillo DM, Tukvadze N, Bablishvili N, Stevens W, Scott L, Rodrigues C, Kazi MI, Joloba M, Nakiyingi L, Nicol MP, Ghebrekristos Y, Anyango I, Murithi W, Dietze R, Lyrio Peres R, Skrahina A, Auchynka V, Chopra KK, Hanif M, Liu X, Yuan X, Boehme CC, Ellner JJ, Denkinger CM. **Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study.** *Lancet Infect Dis* 2018; 18: 76-84.

### Summary

In 2010, WHO endorsed GeneXpert MTB/RIF (Xpert), a rapid, automated, nucleic acid amplification test, that can detect TB and rifampin resistance. Due to Xpert's decreased sensitivity in detecting paucibacillary TB, Xpert MTB/RIF Ultra (Ultra), a new cartridge that runs on the same Xpert device after a software upgrade, was developed with

improved sensitivity. Investigators performed a prospective study in 8 medium/high-TB burden countries to compare Ultra accuracy to Xpert for detection of TB and rifampin resistance. Individuals with pulmonary TB symptoms were recruited into a TB case detection group or MDR-TB high-risk group. Three sputum samples were collected over 2 days for testing with Xpert and Ultra (sample 1), and solid and liquid culture (samples 2 and 3, both media). 1753 participants were included in analyses (1439 case detection, 314 MDR-TB high risk group). 39% of participants were culture-positive for *M. tuberculosis*, of whom 31% had rifampin-resistant TB. Ultra was more sensitive for detecting TB overall (88%) and among smear-negative/culture-positive samples (63%), compared with Xpert (83% and 46%, respectively). Ultra was less specific for TB detection (96%) than Xpert (98%), particularly in participants with a prior history of TB (Ultra=93%, Xpert=98%). Both tests had similar accuracy for detecting rifampin resistance.

### Comments

1. Ultra is a more sensitive test for TB than Xpert with significant improvements in detecting AFB-smear negative disease.
2. Ultra is less specific than Xpert and as Ultra is rolled-out globally, these differences in accuracy may have important ramifications depending on TB prevalence
3. A new result category has been added to Ultra, "trace call", that corresponds to the lowest bacillary burden for *M. tuberculosis* detection, and WHO has issued recommendations on interpreting trace calls.
4. The impact of Ultra on patient outcomes needs to be studied, especially since Xpert has not been definitively shown to affect time to TB diagnosis, initiation of anti-TB treatment, or reduce mortality.

### TREATMENT OF PULMONARY MYCOBACTERIUM AVIUM COMPLEX

Griffith DE, Thomson R, Aksamit TR, Hasegawa N, Morimoto K, Addrizzo-Harris DJ, O'Donnell AE, Marras TK, Flume PA, Loebinger MR, Morgan L, Codecasa LR, Hill AT, Ruoss SJ, Yim JJ, Ringshausen FC, Field SK, Phillely JV, Wallace Jr. RJ, van Ingen J, Coulter C, Nezamis J, Winthrop KL. **Amikacin liposome inhalation suspension for treatment-refractory lung disease caused by Mycobacterium avium complex (CONVERT).** *Am J Respir Crit Care Med* 2018; 198:1559-1569.

### Summary

Nontuberculous mycobacterial (NTM) lung disease is more common than TB in the U.S. and is increasing in prevalence. Amikacin liposome inhalation suspension (ALIS), penetrates mycobacterial biofilms, and increases amikacin uptake by alveolar macrophages compared to non-liposomal amikacin preparations. A phase 3 industry-funded international study investigated ALIS efficacy when added to guideline-based therapy (GBT) compared to GBT alone. This was an interim analysis of an ongoing open-label, non-placebo-controlled study. Eligible participants were



MAC-positive while on GBT for at least 6 months and were currently receiving treatment or had stopped treatment <12 months prior to study enrollment. Patients with cystic fibrosis, immunodeficiency syndromes, or amikacin resistant isolates (MIC > 64 ug/mL) were excluded. The primary endpoint was culture conversion by month 6. The study included 336 participants (224 ALIS/GBT, 112 GBT), among whom 22% had macrolide-resistant isolates. Significantly more participants who were receiving ALIS achieved the primary endpoint (29%) compared to GBT alone (9%; adjusted OR=4.2, 95% CI=2.1-8.6). The most common adverse events were respiratory related and occurred more frequently in the ALIS arm (87%) compared to GBT-alone (50%), and 17% of ALIS-treated patients had adverse events that resulted in discontinuation of ALIS.

### Comments

1. This study found that patients treated with ALIS + GBT were more likely to achieve culture-conversion at month 6 compared to GBT-alone.
2. Adverse events were more common in the ALIS+GBT arm, although severe adverse events were similarly distributed between the 2 study arms.
3. There have been no studies comparing ALIS to nebulized (injectable) amikacin.
4. ALIS is the first FDA-approved medication for the treatment of MAC pulmonary disease.
5. Given culture conversion of 30% in the ALIS+GBT arm, novel treatments for MAC lung disease are needed.

## OTHER ARTICLES OF INTEREST

### TB Preventive Therapy

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Swindells S, Ramchandani R, Gupta A, Benson CA, Leon Cruz J, Mwelase N, Jean Juste MA, Lama JR, Valencia J, Omoz Oarhe A, Supparatpinyo K, Masheto G, Mohapi L, da Silva Escada RO, Mawlana S, Banda P, Severe P, Hakim J, Kanyama C, Langat D, Moran L, Andersen J, Fletcher CV, Nuermberger E, Chaisson RE, for the BRIEF TB/A5279 Study Team. **One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis.** *N Engl J Med* 2018; 379:454-463. *N Engl J Med* 2019; 380:1001-1011.

### Treatment of TB Disease

Colangeli R, Jedrey H, Kim S, Connell R, Ma S, Chippada Venkata UD, Chakravorty S, Gupta A, Sizemore EE, Diem L, Sherman DR, Okwera A, Dietze R, Boom WH, Johnson JL, Mac Kenzie WR, Alland D. **Bacterial Factors That Predict Relapse after Tuberculosis Therapy.** *N Engl J Med* 2018;379(9):823-33.

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men for rifampin-resistant tuberculosis. *N Engl J Med* 2019 Mar 13 [Epub ahead of print].

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#### TB Diagnosis in Low-Resource Settings

Gupta-Wright A, Corbett EL, van Oosterhout JJ, Wilson D, Grint D, Alufandika-Moyo M, Peters JA, Chiume L, Flach C, Lawn SD, Fielding K. **Rapid urine-based screening for tuberculosis in HIV-positive patients admitted to hospital in Africa (STAMP): a pragmatic, multicentre, parallel-group, double-blind, randomised controlled trial**. *Lancet*. 2018;392(10144):292-301. PMID:PMC6078909

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Yoon C, Semitala FC, Atuhumuza E, Katende J, Mwebe S, Asege L, Armstrong DT, Andama AO, Dowdy DW, Davis JL, Huang L, Kanya M, Cattamanchi A. **Point-of-care C-reactive protein-based tuberculosis screening for people living with HIV: a diagnostic accuracy study**. *Lancet Infect Dis*. 2017;17(12):1285-92. PMID:PMC5705273

#### TB Vaccines

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Gurunathan S, DiazGranados CA, Andersen P, Kromann I, Evans T, Ellis RD, Landry B, Hokey DA, Hopkins R, Ginsberg AM, Scriba TJ, Hatherill M. **Prevention of M. tuberculosis Infection with H4:IC31 Vaccine or BCG Revaccination**. *N Engl J Med*. 2018;379(2):138-49.

#### Other

Behr MA, Edelstein PH, Ramakrishnan L. **Revisiting the timetable of tuberculosis**. *BMJ*. 2018;362: k2738.

## ASTHMA

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## NEW THERAPEUTIC APPROACHES TO MILD ASTHMA

Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, Jorup C, Lamarca R, Siwek-Posluszna A, FitzGerald JM. **As-Needed Budesonide-Formoterol versus Maintenance Budesonide in Mild Asthma.** *N Engl J Med.* 2018;378(20):1877-87.

O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, Jorup C, Lamarca R, Ivanov S, Reddel HK. **Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma.** *N Engl J Med.* 2018;378(20):1865-76. Epub 2018/05/17. doi: 10.1056/NEJMoa1715274. PubMed PMID: 29768149.

## Summary

The treatment paradigm for the management of mild asthma has not changed in decades. Both the GINA and NAEPP guidelines recommend a stepwise approach to asthma therapy with the use of inhaled corticosteroids as maintenance therapy for patients with GINA step 2/3 disease. This pair of multicenter, randomized, double blind, placebo-controlled trials in patients with controlled step 2 or uncontrolled step 3 asthma were designed to determine whether all patients with mild persistent asthma require daily maintenance inhaled steroid (ICS) therapy or whether intermittent inhaled steroid/long acting beta agonist (ICS/LABA) therapy is an acceptable alternative. Furthermore, the authors were interested in shifting the treatment paradigm with regards to rescue bronchodilator therapy by introducing the concept of using ICS/LABA as relievers. These are important clinical questions given the increased recognition that up to 50% of patients with mild asthma have no evidence of underlying eosinophilic inflammation based on sputum differential cell counts and therefore are unlikely to benefit from inhaled corticosteroids. In this subgroup of patients administration of a bronchodilator would be immensely important in ameliorating asthma symptoms. In addition, the currently accepted approach of treating acute asthma symptoms with a bronchodilator without concomitant anti-inflammatory therapy should be considered as most acute symptoms likely result from both inflammation and bronchoconstriction.

## Comments

1. Daily maintenance therapy with budesonide resulted in better asthma symptom control and change in baseline FEV1 as compared to as needed ICS/LABA.
2. ICS/LABA was superior to as needed terbutaline but inferior to maintenance budesonide in achieving asthma control.
3. As needed ICS/LABA therapy was non-inferior to budesonide in reducing asthma exacerbations and time to first asthma exacerbation in both studies.
4. Importantly, as needed ICS/LABA and ICS were both superior to terbutaline in controlling asthma exacerbations indicating that the concept of using anti-inflammatory medications with relievers is crucial to reducing exacerbation risk in patients with asthma.
5. Not surprisingly, patients receiving as needed ICS/LABA therapy had a significant reduction in inhaled steroid exposure in comparison to the daily ICS group.
6. This study offers an alternative approach to patients with mild asthma particularly those that experience exacerbations but few asthma symptoms and no lung function impairment. We may be able to offer both bronchodilation with concomitant anti-inflammatory therapy for these patients while concurrently sparing them from unnecessary exposure to inhaled steroids at high doses.

## THRESHOLDS FOR TOXICITY WITH ORAL STEROID EXPOSURE MUCH LOWER THAN PREDICTED

Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Ling Zhi Jie J, Tran TN. **Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study.** *J Asthma Allergy.* 2018;11:193-204. Epub 2018/09/15. doi: 10.2147/JAA.S176026. PubMed PMID: 30214247; PMCID: PMC6121746.

## Summary

Exposure to oral corticosteroids(OCS) is very high in patients with asthma and other respiratory diseases. Even patients with mild disease receive OCS for treatment of acute exacerbations. Respiratory illnesses present the most common reason for OCS prescription and patients with severe asthma can receive multiple courses of OCS per year, some as many as 4-6 times per year. There is well-established data on OCS toxicity and it is well accepted that OCS causes multiple co-morbidities with long term exposure. However, little is known about the safety threshold for OCS and, therefore, clinicians are unable to make determinations about risk benefit ratio of therapy with OCS.

OCS sparing strategies are sorely needed and recommended below are two manuscripts that address OCS avoidance using high dose inhaled steroids. In addition, OCS exposure should be taken into serious consideration as an indication for initiating biologic therapy in patients with type II high asthma. Strategies for OCS sparing in T helper type II low asthma are still lacking at this time and represent an area of significant need.

### Comments

1. Adverse effects of OCS are noted at cumulative doses of 1.0 to <2.5grams which is equivalent to four lifetime courses of OCS.
2. OCS toxicity began to occur within a few years of initial exposure.
3. Clinicians should take OCS exposure into consideration when managing asthma and consider OCS sparing strategies early in the course of disease to avoid long term co-morbidities.

## BIOLOGICS FOR TYPE II ASTHMA EXPAND TO COVER NEW MECHANISMS

Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, Zhu H, Hamilton JD, Swanson BN, Khan A, Chao J, Staudinger H, Pirozzi G, Antoni C, Amin N, Ruddy M, Akinlade B, Graham NMH, Stahl N, Yancopoulos GD, Teper A. **Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma.** *N Engl J Med.* 2018;378(26):2475-85.

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### Summary

Targeted therapies for T helper type II asthma have been focused on IL-5 mediated eosinophilic inflammation and allergic asthma with elevated IgE and sensitization to allergens. Type II asthma also encompasses IL4/IL13-driven disease with increased fraction of exhaled nitric oxide (FeNO) and evidence of airways hyper responsiveness and mucous hypersecretion. IL13-mediated inflammation is critical in promoting goblet cell hyperplasia, mucous hypersecretion that results in airway remodeling as well as upregulation of inducible nitric oxide synthase (iNOS). Prior attempts to modulate IL-13-mediated inflammation with anti-IL13 antibodies failed to demonstrate improvements in asthma exacerbations and lung function. IL13 binds both the IL13 receptor and IL4-R alpha and thus can be modulated via antibodies that target this receptor. These phase 3 studies assessed the effect of dupilumab on

asthma demonstrated clinical efficacy and dupilumab was approved for an asthma indication by the FDA in November 2018. It remains unclear why singularly blocking IL13 mediated effects was not adequate in ameliorating asthma. Dupilumab is beneficial for type II asthma and works best in patients with elevated FeNO and eosinophils. The impact on eosinophils is not fully understood but is postulated to be the result of alterations in eotaxin-3 levels resulting in an inability of eosinophils to hone into tissues. The mechanistic bronchoscopy study with dupilumab will likely answer further questions about the impact of this therapy on eosinophilic infiltration into the airways of patients with asthma.

### Comments

1. Dupilumab demonstrates efficacy in patients with moderate to severe persistent asthma with T helper type II features (elevated eosinophils and FeNO) with a significant reduction in exacerbations and improvements in FEV1.
2. Dupilumab significantly decreased oral corticosteroid (OCS) dose in patients with OCS dependent asthma. It is approved in this population regardless of underlying eosinophil count.
3. There are transient elevations in eosinophils for approximately four months following initiation of dupixent and caution must be exercised in prescribing dupixent to patients with blood eosinophils >1500.
4. A marked and immediate reduction in FeNO occurs within two weeks of initiating dupixent therapy.
5. Serum IgE level decreased over the one year period of the study in patients treated with dupixent. This effect is likely related to modulation of B-cell switching that is mediated by IL4.

## OTHER ARTICLES OF INTEREST

### Prevention of Asthma Exacerbations Using High Dose Inhaled Steroids During Initial Loss of Asthma Control

Jackson DJ, Bacharier LB, Mauger DT, Boehmer S, Beigelman A, Chmiel JF, Fitzpatrick AM, Gaffin JM, Morgan WJ, Peters SP, Phipatanakul W, Sheehan WJ, Cabana MD, Holguin F, Martinez FD, Pongracic JA, Baxi SN, Benson M, Blake K, Covar R, Gentile DA, Israel E, Krishnan JA, Kumar HV, Lang JE, Lazarus SC, Lima JJ, Long D, Ly N, Marbin J, Moy JN, Myers RE, Olin JT, Raissy HH, Robison RG, Ross K, Sorkness CA, Lemanske RF, Jr., National Heart L, Blood Institute A. **Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations.** *N Engl J Med.* 2018;378(10):891-901.

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Impact of Clinical Characteristics and Asthma Phenotypes on

## Asthma Outcomes

Jevnikar Z, Ostling J, Ax E, Calven J, Thorn K, Israelsson E, Oberg L, Singhanian A, Lau LCK, Wilson SJ, Ward JA, Chauhan A, Sousa AR, De Meulder B, Loza MJ, Baribaud F, Sterk PJ, Chung KF, Sun K, Guo Y, Adcock IM, Payne D, Dahlen B, Chanez P, Shaw DE, Krug N, Hohlfeld JM, Sandstrom T, Djukanovic R, James A, Hinks TSC, Howarth PH, Vaarala O, van Geest M, Olsson H. **Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes study g. Epithelial IL-6 trans-signaling defines a new asthma phenotype with increased airway inflammation.** *J Allergy Clin Immunol.* 2019;143(2):577-90.

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## Imaging Modalities and Phenotypes Increase Understanding of Asthma

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## Impact of Targeted Therapy on Characteristics of Asthma Exacerbations

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## New Therapeutic Approaches to Asthma

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## ACUTE RESPIRATORY DISTRESS SYNDROME

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## ECMO FOR SEVERE ARDS

Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, Da Silva D, Zafrani L, Tirot P, Veber B, Maury E, Levy B, Cohen Y, Richard C, Kalfon P, Bouadma L, Mehdaoui H, Beduneau G, Lebreton G, Brochard L, Ferguson ND, Fan E, Slutsky AS, Brodie D, and Mercat A, for the EOLIA Trial Group, REVA, and ECMONet. **Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome.** *N Engl J Med.* 2018; 378:1965-75.

## Summary

Use of extracorporeal membrane oxygenation (ECMO) for patients with severe acute respiratory distress syndrome (ARDS) is increasing dramatically over the past 10 years, but the superiority of ECMO over conventional mechanical ventilation with low tidal volumes remains uncertain. Combes and colleagues addressed this question with “EOLIA,” an international randomized trial of 249 patients with severe ARDS, defined as a PaO<sub>2</sub>:FIO<sub>2</sub> ratio of less than 50 mmHg for more than 3 hours or less than 80 for more than 6 hours, or an arterial partial pressure of carbon dioxide of at least 60 mmHg with a pH less than 7.25 for at least 6 hours. The primary outcome of the trial was mortality at 60 days, which was 35% in the ECMO group and 46% in the control group (p=0.09). Notably, 35 patients (28%) in the control group received ECMO after meeting crossover criteria; 60 day mortality was 57% among crossovers. Despite an absolute mortality reduction of 11% in the intention to treat analysis, conclusion of the study was that “60-day mortality was not significantly different lower with ECMO than with a strategy of conventional mechanical ventilation that included ECMO as rescue therapy.”

## Comments

1. Mortality for very severe ARDS remains high, both with and without treatment with ECMO.
2. ECMO trials in ARDS may be challenging to perform and interpret, with high numbers of patients excluded for early receipt of ECMO, and a significant proportion receiving ECMO in the control group as “crossovers.”
3. Patients receiving ECMO for very severe ARDS are at increased risk for thrombocytopenia and bleeding compared with conventional mechanical ventilation.
4. The EOLIA trial found an absolute decrease in 60-day mortality of 11% in patients randomized to ECMO (35% versus 46%);

this was less than the expected mortality reduction of 20% and therefore the difference in mortality was concluded to be non-significant.

5. A post hoc Bayesian analysis of EOLIA (Goligher et al, JAMA 2018) and meta-analysis including EOLIA (Munshi et al, Lancet Respiratory Medicine 2019) both suggest that ECMO may be beneficial in reducing 60 day mortality in severe ARDS.

## ECCO2R FOR MODERATE ARDS

Combes A, Fanelli V, Pham T, Ranieri VM on behalf of the ESICM Trials Group and the SUPERNOVA Investigators. **Feasibility and safety of extracorporeal CO<sub>2</sub> removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study.** *Intensive Care Medicine* 2019 May;45(5):592-600

## Summary

The ARDS Network Investigators demonstrated that reducing tidal volume to 4-6 cc/kg predicted body weight and plateau pressure to below 30 cm H<sub>2</sub>O improves survival of patients with ARDS. Achievement of these targets may be limited in some patients by severe respiratory acidosis. It has been postulated that there may be additional benefit in achieving “ultra-protective ventilation” by reducing tidal volume to 3-4 cc/kg predicted body weight and plateau pressure to below 25 cm H<sub>2</sub>O, but recognized that such an approach may be poorly tolerated. Extracorporeal carbon dioxide removal (ECCO<sub>2</sub>R) offers an approach to minimize respiratory acidosis by clearing carbon dioxide outside of the lungs. Combes and colleagues enrolled 95 patients with moderate ARDS in a feasibility and safety study to determine (1) if ECCO<sub>2</sub>R would allow patients with ARDS to achieve ultra-protective ventilation, and (2) the safety of this approach. Patients with PaCO<sub>2</sub> > 60 mmHg were excluded from participation. By 24 hours, 82% of patients achieved ultra-protective ventilation. However, 39% of patients had adverse events, two of which were serious and attributed to ECCO<sub>2</sub>R. It appears that ECCO<sub>2</sub>R is feasible; a randomized trial is needed to assess potential benefit.

## Comments

1. The benefits of lung protective ventilation may be extended by targeting even lower tidal volumes and plateau pressures than

were tested in the ARDS Network ARMA trial—so called “ultra-protective ventilation.”

- Achievement of ultra-protective ventilation (tidal volume 3–4 cc/kg PBW, plateau pressure <25 cmH<sub>2</sub>O) may be limited by respiratory acidosis.
- Extracorporeal carbon dioxide removal (ECCO<sub>2</sub>R) can facilitate ultra-protective ventilation in patients with moderate ARDS by minimizing respiratory acidosis; 82% of patients in this feasibility study met ultra-protective targets using ECCO<sub>2</sub>R.
- ECCO<sub>2</sub>R is associated with high rates of adverse events, including pneumothorax, bleeding and coagulopathies.
- Additional investigations, including randomized clinical trials, are needed to determine if ultra-protective ventilation and ECCO<sub>2</sub>R improve outcomes for patients with ARDS.

### PEEP TITRATION IN MODERATE-SEVERE ARDS

Beitler JR, Sarge T, Banner-Goodspeed VM, Gong MN, Cook D, Novack V, Loring SH, Talmor D, for the EPVent2 Study Group. **Effect of Titrating Positive End-Expiratory Pressure (PEEP) With an Esophageal Pressure-Guided Strategy vs an Empirical High PEEP-FIO<sub>2</sub> Strategy on Death and Days Free From Mechanical Ventilation Among Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial.** *JAMA* 2019; 321(9) 846-857.

#### Summary

Titration of positive end-expiratory pressure (PEEP) to attempt to reduce atelectrauma may be hindered by inability to measure transpulmonary pressure (which requires measurement of pleural pressure) when relying on airway pressure alone. Pleural pressure can be estimated by measuring esophageal pressure. A single-center randomized trial demonstrated that a strategy of PEEP titration using esophageal pressure improved oxygenation, respiratory system compliance, and adjusted survival. Beitler and colleagues at 14 hospitals randomized 200 patients with moderate-severe ARDS (PaO<sub>2</sub>:FIO<sub>2</sub> < 200 mmHg) to a strategy of esophageal pressure-guided PEEP titration or a high PEEP:FIO<sub>2</sub> titration table (based on control group in OSCILLATE). The primary outcome was a ranked composite score that incorporated both death and days free of mechanical ventilation through day 28. Upon initiation of the study protocol, PEEP increased by a mean of 3 cmH<sub>2</sub>O in both groups, but the range of PEEP changes was much greater in the esophageal pressure-guided titration group (increased by up to 20 cmH<sub>2</sub>O and decreased by as much as 12 cm H<sub>2</sub>O). There was no difference in the primary end point between groups. Mortality at 28 days was around 31% in both groups, and there was no difference in ventilator free days. This study does not support routine use of esophageal pressure guided PEEP in ARDS.

#### Comments

- Ventilator induced lung injury has been shown to be dependent on transpulmonary pressure, which cannot be measured using

airway pressure alone but can be estimated using esophageal pressure.

- A previous single center randomized trial demonstrated benefit of a strategy of titrating PEEP using esophageal pressure when compared to a standard PEEP:FIO<sub>2</sub> table.
- EPVent-2 randomized 200 patients at 14 hospitals to either an esophageal pressure-guided PEEP strategy or a high PEEP:FIO<sub>2</sub> table-guided strategy.
- There was no difference in primary outcome (ranked composite of mortality and days free of mechanical ventilation at 28 days) between study groups, or in physiologic outcomes.
- There is likely no role for esophageal-pressure guided PEEP titration in routine management of patients with moderate-severe ARDS, especially if a high PEEP:FIO<sub>2</sub> table is used.

### LOW TIDAL VOLUME VENTILATION IN PATIENTS WITHOUT ARDS

Writing Group for the PReVENT Investigators. **Effect of a Low vs Intermediate Tidal Volume Strategy on Ventilator-Free Days in Intensive Care Unit Patients Without ARDS: A Randomized Clinical Trial.** *JAMA* 2018; 320(18): 1872-1880.

#### Summary

Low tidal volume ventilation improves survival in patients with ARDS, but the benefit of a lung protective strategy in patients without ARDS remains uncertain. At 6 hospitals in the Netherlands, the PReVENT investigators randomized patients expected to receive invasive ventilation for at least 24 hours to two ventilation strategies. Patients with ARDS were excluded, as were patients with significant hypoxemia (PaO<sub>2</sub>:FIO<sub>2</sub> ratio < 200 mmHg) and ARDS risk factors. Both strategies allowed both volume control and pressure support modes of ventilation. The lower tidal volume ventilation strategy targeted tidal volumes of 4 cc/kg PBW and allowed up to 6 cc/kg in the setting of severe dyspnea. The higher tidal volume ventilation strategy targeted tidal volumes of 10 cc/kg PBW and allowed down to 8 cc/kg in the setting of plateau pressure < 25 cm H<sub>2</sub>O. Patients who developed ARDS during the study were managed with conventional low tidal volume ventilation. The primary outcome measure was ventilator-free days and alive at day 28. There were 961 patients randomized, with median PaO<sub>2</sub>:FIO<sub>2</sub> ratio of 196 at baseline. Most patients in the lower tidal volume strategy were managed with pressure support ventilation within 24 hours of randomization, with a median tidal volume of 7.8 cc/kg PBW (interquartile range 6.3-9.5). There was no difference in ventilator free days, mortality, or development of ARDS between the strategies.

#### Comments

- The role of low tidal volume ventilation remains uncertain in patients with acute respiratory failure without ARDS, so the PReVENT study randomized patients without ARDS to two strategies that targeted lower (4 cc/kg PBW) and intermediate (10 cc/kg PBW) tidal volumes to address this knowledge gap.



2. Few patients in the lower tidal volume strategy achieved target tidal volume; most were managed with pressure support by day 1.
3. Separation of median tidal volumes between randomization arms decreased quickly, beginning at 4.2 cc/kg PBW on day 0, and decreasing to 2.7 cc/kg PBW on day 1 and 2 cc/kg PBW on day 2.
4. There was no difference in ventilator-free days, mortality or development of ARDS between randomization arms.
5. It remains unclear if there is a benefit to managing patients without ARDS with lower versus intermediate tidal volumes; a recent study by the NHLBI PETAL Network (Lanspa et al) suggests that the mortality benefit may be small and therefore an appropriately powered trial would need to be very large and likely unfeasible.

## RAPIDLY IMPROVING ARDS

Schenck EJ, Oromendia C, Torres LK, Berlin DA, Choi AMK, Siempos II. **Rapidly Improving ARDS in Therapeutic Randomized Controlled Trials.** *Chest* 2019; 155(3):474-482

### Summary

ARDS is recognized as a highly heterogeneous clinical syndrome. This heterogeneity is a challenge to clinical trials attempting to identify beneficial treatment. Indeed, the vast majority of trials—especially pharmacologic trials—have failed to demonstrate benefit. Identification of subgroups with increased risk of specific clinical outcomes (prognostic enrichment) or with increased likelihood of response to therapy (predictive enrichment) may be an important strategy to improving future trials. Similarly, identification of groups unlikely to benefit from a particular therapy may be similarly important. Schenck and colleagues propose that there is a phenotype of rapidly improving ARDS (defined as improving within 24 hours to either extubation or PaO<sub>2</sub>:FIO<sub>2</sub> ratio > 300) which is at low risk for adverse outcomes and unlikely to benefit from intervention. In a secondary analysis of 7 ARDS Network studies, 458 of 4,361 patients (10.5%) met criteria for rapidly improving ARDS (riARDS), and that the proportion of riARDS patients in ARDS Network trials increased over time. Schenck found that patients with riARDS had a significantly lower hospital mortality (10.2% compared with 26.3%) and could be identified by factors present at study enrollment. Future interventional studies of patients with ARDS might consider excluding patients with this rapidly improving phenotype.

### Comments

1. A significant proportion of patients enrolled in ARDS Network trials improve rapidly, achieving extubation or resolution of significant hypoxemia within 24 hours.
2. Patients with this “rapidly improving” phenotype have a markedly lower mortality than those without rapid improvement.
3. While there are a number of factors independently associated with riARDS (PaO<sub>2</sub>:FIO<sub>2</sub> ratio at screening, change in between

- screening and enrollment, number of vasopressors used, FIO<sub>2</sub>, and bilirubin), the model has a low positive predictive value.
4. Future clinical trials may attempt to exclude patients with riARDS, but may find challenges if enrollment window is short.

## OTHER ARTICLES OF INTEREST

Goligher EC, Tomlinson G, Hajage D, Wijeyesundera DN, Fan E, Juni P, Brodie D, Slutsky AS, Combes A. **Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome and Posterior Probability of Mortality Benefit in a Post Hoc Bayesian Analysis of a Randomized Clinical Trial.** *JAMA* 2018; 320(21): 2251-2259

Munshi L, Walkey A, Goligher E, Pham T, Uleryk EM, Fan E. **Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis.** *Lancet Respiratory Medicine* 2019; 7:163-72

Lanspa MJ, Gong MN, Schoenfeld DA, Lee KT, Grissom CK, Hou PC, Serpa-Neto A, Brown SM, Iwashyna TJ, Yealy DM, Hough CL, Brower RG, Calfee CS, Hyzy RC, Matthay MA, Miller RR 3rd, Steingrub JS, Thompson BT, Miller CD, Clemmer TP, Hendey GW, Huang DT, Mathews KS, Qadir N, Tidswell M; The National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network. **Prospective Assessment of the Feasibility of a Trial of Low-Tidal Volume Ventilation for Patients with Acute Respiratory Failure.** *Annals of the American Thoracic Society.* 2019 Mar;16(3):356-362

## GENERAL CRITICAL CARE

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## PHARMACOLOGIC MANAGEMENT OF DELIRIUM IN CRITICAL ILLNESS

Girard TD, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, Douglas IS, Malhotra A, Owens RL, Feinstein DJ, Khan B, Pisani MA, Hyzy RC, Schmidt GA, Schweickert WD, Hite RD, Bowton DL, Masica AL, Thompson JL, Chandrasekhar R, Pun BT, Strength C, Boehm LM, Jackson JC, Pandharipande PP, Brummel NE, Hughes CG, Patel MB, Stollings JL, Bernard GR, Dittus RS, Ely EW for the MIND-USA Investigators. **Haloperidol and ziprasidone for the treatment of delirium in critical illness.** *N Engl J Med* 2018; 379:2506-2516

## Summary

There is a high incidence of delirium in critically ill patients (as high as 30%) that is associated with enhanced morbidity and mortality. Prior literature has demonstrated conflicting findings as to whether antipsychotic medications prevent or treat delirium in ICU patients. Thus, it is unclear whether antipsychotic agents should play a role in prevention or treatment of ICU delirium. The Modifying the Impact of ICU-Associated Neurological Dysfunction-USA (MIND-USA) trial examined the effect of haloperidol (typical antipsychotic, n=192) vs. ziprasidone (atypical antipsychotic, n=190) vs. placebo, n=184) in critically ill subjects with acute respiratory failure or shock with confirmed delirium in a multicenter, double-blind, randomized trial across 16 U.S. hospitals. There was no difference between treatment groups for the primary outcome of days alive without delirium or coma, nor in secondary outcomes (including survival and length of ICU and hospital stay or decrease in sedation requirements), nor in safety end points (including frequency of extrapyramidal symptoms and corrected QT prolongation).

## Comments

1. This MIND-USA study demonstrated no benefit of typical or atypical antipsychotic medication in reducing the duration of delirium (primary outcome) nor in decreasing sedation requirements (secondary outcome).
2. Of note, the REDUCE trial, also published this year, demonstrated no mortality benefit of prophylactic haloperidol in critically ill patients at risk for delirium.
3. There was prior uncertainty as to the role of typical vs. atypical antipsychotic medications in management of ICU delirium, and the MIND-USA study was the first large trial to compare these classes of medications vs. placebo (although it is noted that

use of the antipsychotic quetiapine is likely more common than ziprasidone that was used in this study).

4. It remains uncertain whether there might be other agents that might prevent delirium that are currently under investigation.
5. The MIND-USA study had a high proportion of patients with hypoactive delirium (89%), so it remains unclear whether patients with hyperactive delirium might benefit in terms of control of agitation with antipsychotic medications.

## ADJUNCTIVE HYDROCORTISONE FOR SEPTIC SHOCK

Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, Cariou A, Forceville X, Schwebel C, Martin C, Timsit JF, Misset B, Ali Benali M, Colin G, Souweine B, Asehnoune K, Mercier E, Chimot L, Charpentier C, François B, Boulain T, Petitpas F, Constantin JM, Dhonneur G, Baudin F, Combes A, Bohé J, Loriferne JF, Amathieu R, Cook F, Slama M, Leroy O, Capellier G, Dargent A, Hissem T, Maxime V, Bellissant E; CRICS-TRIGGERSEP Network. **Hydrocortisone plus fludrocortisone for adults with septic shock.** *N Engl J Med* 2018; 378:809-818. (APROCCHSS)

## Summary

While high dose steroids were shown to be harmful in septic shock, numerous studies examining low-dose steroids (e.g. hydrocortisone 200 mg/day) in septic shock demonstrated conflicting results. Within the last year, two large randomized, blinded, multicenter controlled studies of low-dose steroids in septic shock also yielded conflicting results, but given differences in the trials, perhaps additional information can be gleaned. The Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial is reviewed by another speaker and randomized 3,800 patients with vasopressor-dependent septic shock and mechanical ventilation to a 7-day hydrocortisone infusion (200 mg/day) vs. placebo. The Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS, Activated Protein C was withdrawn from the market) trial examined 1,241 patients with vasopressor-dependent septic shock randomized to 7d of hydrocortisone (50 mg iv q6h) and fludrocortisone (50 mcg enterally/day) vs. placebo. APROCCHSS demonstrated improved 90-day mortality with hydrocortisone/fludrocortisone (43%) vs. placebo (49.1%, p=0.03) and had higher overall mortality than the ADRENAL trial which did not demonstrate a mortality benefit (hydrocortisone (27.9%) vs. placebo

(28.8%,  $p=0.5$ ). Both trials demonstrated improved shock resolution (secondary outcome), with low rates of serious adverse events other than hyperglycemia with bolus glucocorticoids.

### Comments

1. These two trials cumulatively examined the role of low-dose hydrocortisone in over 5,000 patients with septic shock and found a difference in the primary outcome (90-day mortality) between the trials, but similar benefits in the secondary outcome of resolution of shock in both studies.
2. Patients in the ADRENAL trial received a hydrocortisone infusion, rather than bolus doses of hydrocortisone, such that the time to a therapeutic drug level might take longer.
3. While the ADRENAL trial did not use adjunctive fludrocortisone, a prior study did not suggest different effects than with hydrocortisone alone.
4. Patients in the APROCCHSS were sicker than in the ADRENAL trial, as judged by a number of factors, including higher mortality.
5. While there is no clear answer as to the definitive role of low-dose steroids in septic shock, these new papers do not refute current guidelines suggesting low-dose hydrocortisone for septic patients with refractory shock without a contraindication to corticosteroids, and suggest that the benefit of steroids may outweigh the risk in sicker patients, in particular.

## FLUID RESUSCITATION IN CRITICAL ILLNESS

Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, Stollings JL, Kumar AB, Hughes CG, Hernandez A, Guillaumondegui OD, May AK, Weavind L, Casey JD, Siew ED, Shaw AD, Bernard GR, Rice TW for the SMART Investigators and the Pragmatic Critical Care Research Group. *Balanced crystalloids versus saline in critically ill adults*. *N Engl J Med* 2018; 378:829-839.

### Summary

The optimal solution for fluid resuscitation in critically ill patients has long been debated. Some studies have raised concern that intravenous saline may be associated with adverse events, including acute kidney injury and death. Additional studies suggested that use of balanced crystalloid solutions that more closely resemble the electrolyte composition of plasma might be associated with lower rates of renal injury and death, though results from the literature have been conflicting. This recent single-center study [Isotonic Solutions and Major Adverse Renal Events Trial (SMART)] used a pragmatic, cluster-randomized, multiple-crossover trial in five ICUs (including medical and nonmedical ICUs) in a single academic center to compare 0.9% saline vs. balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A based on the treating clinician's preference) in 15,802 adult subjects. The investigators demonstrated a 1.1% improvement with balanced crystalloids in the primary outcome of a major adverse kidney

event within 30 days (a composite outcome of death from any cause, new renal replacement therapy, or persistent renal dysfunction defined as an elevation of creatinine to greater than or equal to 200% of baseline).

### Comments

1. In this study, use of balanced crystalloids produced a lower rate of the composite outcome (death from any cause, new renal replacement therapy, or persistent renal dysfunction) compared with saline in ICU patients.
2. The effect size observed in this trial was modest, but if these findings apply to the large numbers of patients admitted to ICUs throughout the world yearly, the potential benefits could have broader impact.
3. Given relative hypotonicity of balanced crystalloids, clinicians treating patients with brain injury in this trial were given the option of administering 0.9% sodium chloride, so the findings of this study cannot be applied to the subgroup of ICU patients with traumatic brain injury.
4. The composite outcome was driven in large part by a reduction in persistent acute kidney injury at day 30 and supports the potential notion that the chloride load of 0.9% saline might have injurious renal effects.
5. These interesting results from a single center open-label study using a primary composite outcome have prompted some clinicians and studies to favor use of balanced crystalloids and will need to be interpreted by each clinician as it might apply to their individual patients.

## TIMING OF RENAL REPLACEMENT THERAPY IN CRITICAL ILLNESS

Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyère R, Lebert C, Bohé J, Badie J, Eraldi JP, Rigaud JP, Levy B, Siami S, Louis G, Bouadma L, Constantin JM, Mercier E, Klouche K, du Cheyron D, Piton G, Annane D, Jaber S, van der Linden T, Blasco G, Mira JP, Schwebel C, Chimot L, Guiot P, Nay MA, Meziani F, Helms J, Roger C, Louart B, Trusson R, Dargent A, Binquet C, Quenot JP; IDEAL-ICU Trial Investigators and the CRICS TRIGGERSEP Network. *Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis*. *N Engl J Med* 2018; 379:1431-1442.

### Summary

Acute kidney injury (AKI) frequently complicates septic shock and has high mortality. Without definitive indications for renal replacement therapy (RRT) (e.g., hyperkalemia, metabolic acidosis, volume overload), it remains unclear what the appropriate timing of initiation of RRT should be in septic shock. Two recent trials of early vs. delayed initiation of RRT produced conflicting results. This multicenter, open-label, controlled trial randomized 488 patients in 29 French ICUs with early septic shock (within 48h of vasopressors) and AKI (failure stage of the risk, injury, failure, loss, and end-stage kidney disease [RIFLE] classification defined by: creatinine 3X baseline or at least 4 mg/dl with rapid increase of at least 0.5 mg/dl; or urine output < 0.3

ml/kg for at least 24h; or anuria for at least 12h) without life-threatening AKI complications, to receive early RRT (within 12h of severe AKI) or delayed RRT (after 48h of persistent AKI if no emergent indication prior). Selection of the RRT mode was at the discretion of the clinician. The trial was stopped after the second interim analysis for futility. There was no observed difference in the primary outcome of death at 90 days (58% in early strategy vs. 54% in delayed strategy group,  $p=0.38$ ).

### Comments

1. There was no difference in 90-day mortality for early renal replacement therapy vs. delayed renal replacement therapy for patients with septic shock and severe AKI who had no immediate life-threatening complications attributable to AKI.
2. 17% of patients in the delayed strategy group developed criteria for emergency RRT (and required RRT prior to 48h), and the mortality was higher in this subgroup (though it cannot be determined whether this was a sicker subgroup of patients and/or whether earlier RRT would have altered the outcome).
3. In the delayed strategy group, 29% of patients did not receive RRT due to spontaneous recovery of renal function.
4. These results confirm the findings of the previously published Artificial Kidney Initiation in Kidney Injury (AKIKI) study in critically ill patients, as well as a subgroup analysis of that trial of patients with septic shock or ARDS.
5. Although there are variances in the definitions used for AKI and in utilization of modes of dialysis between studies and centers, this paper adds to the literature supporting no clear benefit for early initiation of RRT for AKI in septic shock if there aren't clear indications otherwise for a need for RRT.

## TRACHEAL INTUBATION OF CRITICALLY ILL ADULTS

Casey JD, Janz DR, Russell DW, Vonderhaar DJ, Joffe AM, Dischert KM, Brown RM, Zouk AN, Gulati S, Heideman BE, Lester MG, Toporek AH, Bentov I, Self WH, Rice TW, Semler MW, for the PreVent Investigators and the Pragmatic Critical Care Research Group. **Bag-mask Ventilation during Tracheal Intubation of Critically ill Adults.** *N Engl J Med* 2019; 380:811-821.

### Summary

Hypoxemia is a common ICU complication during intubation and has been associated with morbidity and mortality in critically ill patients. Rapid sequence intubation is intended to minimize hypoxemia by obtaining rapid onset of sedation and paralysis to limit the period of apnea prior to laryngoscopy. However, it has long been unclear whether use of positive pressure ventilation during the apneic phase after rapid sequence induction averts hypoxemia without increasing aspiration risk. This study is a multicenter, randomized trial examining 401 patients in 7 U.S. ICUs undergoing intubation to receive ventilation with bag-mask vs. no ventilation between induction and laryngoscopy. There was

a significantly lower oxygen saturation between induction and 2 minutes after tracheal intubation in the no-ventilation group (93%, IQR 81-99) vs. the bag-mask ventilation group (96%, IQR 87-99) (primary outcome,  $P=0.01$ ). Severe hypoxemia (oxygen saturation  $<80\%$ ) was observed more frequently in the no-ventilation group (22.8%) than in the bag-mask ventilation group (10.9%) (secondary outcome, RR 0.48; 95% CI 0.3 to 0.77). There was no significant difference between groups in operator-observed aspiration or incidence of a new opacity on chest radiography at 48 hours.

### Comments

1. This study demonstrated less hypoxia and no increased incidence of aspiration in critically ill patients receiving bag-mask ventilation compared to those receiving no intubation after induction and prior to laryngoscopy.
2. Management prior to induction was at the discretion of the clinician, and more patients in the bag-mask ventilation group received bag-mask ventilation than did the no-ventilation group prior to induction (39.7% vs. 10.9%; relative risk=3.65; 95% CI=2.37- 5.60).
3. Patients were excluded from the trial if the treating clinician felt that the patient had an indication for ventilation between induction and laryngoscopy (e.g., severe hypoxemia, severe acidemia) or had a contraindication for ventilation (e.g., increased aspiration risk from vomiting, hematemesis, hemoptysis).
4. This trial was performed solely in the ICU (with nearly 50% of patients having sepsis or septic shock and nearly 60% of patients having hypoxemic respiratory failure as the indications for intubation) and may not be applicable to patients in non-ICU settings.
5. While the benefit-risk ratio of bag-mask ventilation might not favor all-comers (e.g., healthy patients who can be fully pre-oxygenated and those at high risk for aspiration), bag-mask ventilation appears likely to benefit critically ill patients at high risk for rapid desaturation and who also are likely to be poorly tolerant of severe hypoxemia.

## GUIDING RESUSCITATION IN SEPTIC SHOCK

Hernández G, Ospina-Tascón GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, Friedman G, Castro R, Alegría L, Teboul JL, Cecconi M, Ferri G, Jibaja M, Pairumani R, Fernández P, Barahona D, Granda-Luna V, Cavalcanti AB, Bakker J; ANDROMEDA-SHOCK Investigators and the Latin America Intensive Care Network (LIVEN). **Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients with Septic Shock.** *JAMA* 2019; 321: 654-664.

### Summary

Guided fluid resuscitation in septic shock is challenging, and while there is not universal agreement on the best

method, monitoring lactate clearance is widely used. There are limitations in interpretability of lactate clearance, and lactate measurements may not be readily measurable at all sites. It has been proposed that persistent peripheral perfusion abnormalities after resuscitation, measured by capillary refill time (CRT), might correlate with organ dysfunction and mortality. It is unknown whether bedside CRT might be used to monitor resuscitation in septic shock. This study randomized 424 adults with early septic shock in 28 ICUs across 5 countries to determine whether peripheral perfusion-targeted resuscitation is more effective than lactate-guided resuscitation. The peripheral perfusion-targeted resuscitation group aimed to normalize CRT, and the lactate-guided resuscitation group aimed to normalize or decrease lactate levels more than 20% over 2 hour-periods during the 8-hour intervention. There was no significant difference in the primary outcome of 28-day mortality between the two groups (34.9% peripheral perfusion vs. 43.4% lactate group,  $P=0.06$ ). However, the peripheral perfusion group had less organ dysfunction at 72 hours than the lactate group (mean SOFA 5.6 vs. 6.6,  $P=0.045$ ), with no significant differences in the other secondary outcomes.

### Comments

1. Peripheral perfusion-targeted resuscitation did not result in statistically significant lower 28-day mortality than lactate-targeted resuscitation in early septic shock, although the study may have been underpowered to detect a meaningful difference.
2. CRT can have inter-rater variability that was not assessed in this study, although investigators at all sites were trained to use a standardized protocol (i.e., CRT was assessed by applying pressure with a glass microscope slide to the right index finger distal ventral surface for 10 seconds, then time for return to normal skin color was assessed with  $>3$  sec refill time registered as abnormal).
3. The peripheral perfusion and lactate-guided groups were managed with an identical protocolized approach to resuscitation that included assessment of fluid responsiveness, followed by a vasopressor challenge that tested higher mean arterial pressure targets in patients with chronic hypertension, followed by inodilator testing; and higher vasopressors or inodilators were maintained only if the patients were deemed responsive to them.
4. Patients in the peripheral perfusion group received 408ml less fluid in the first 8 hours than the lactate-guided group.
5. Although there was no statistical difference in 28-day mortality between the peripheral perfusion and lactate-guided resuscitation groups, the study raises the intriguing possibility that a bedside assessment of CRT, that could potentially be applied in resource-poor settings, could play a role in guiding resuscitation in septic shock.

## OTHER ARTICLES OF INTEREST

### Management of Distributive/Septic Shock

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Itenov TS, Johansen ME, Bestle M, Thormar K, Hein L, Gyldensted L, Lindhardt A, Christensen H, Estrup S, Pedersen HP, Harmon M, Soni UK, Perez-Protto S, Wesche N, Skram U, Petersen JA, Mohr T, Waldau T, Poulsen LM, Strange D, Juffermans NP, Sessler DI, Tønnesen E, Møller K, Kristensen DK, Cozzi-Lepri A, Lundgren JD, Jensen JU; Cooling and Surviving Septic Shock (CASS) Trial Collaboration. Induced hypothermia in patients with septic shock and respiratory failure (CASS): a randomized, controlled, open-label trial. *Lancet Respir Med* 2018; 6:183-192.

### Sodium Bicarbonate Therapy in the ICU

Jaber S, Paugam C, Futier E, Lefrant JY, Lasocki S, Lescot T, Pottecher J, Demoule A, Ferrandière M, Asehounne K, Dellamonica J, Velly L, Abback PS, de Jong A, Brunot V, Belafia F, Roquilly A, Chanques G, Muller L, Constantin JM, Bertet H, Klouche K, Molinari N, Jung B; BICAR-ICU Study Group. **Sodium Bicarbonate therapy for patients with severe metabolic acidemia in the intensive care unit (BICAR-ICU): a multicenter, open-label randomized controlled, phase 3 trial.** *Lancet* 2018; 392: 31-40.

### Delirium Management in Critically Ill Patients

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Evans IVR, Phillips GS, Alpern ER, Angus DC, Friedrich ME, Kissoon N, Lemeshow S, Levy MM, Parker MM, Terry KM, Watson RS, Weiss SL, Zimmerman J, Seymour CW. **Association Between the New York Sepsis Care Mandate and In-Hospital Mortality for Pediatric Sepsis.** *JAMA* 2018; 320: 358-367.

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### Sepsis Definitions and Assessments in Low-Resource Settings

Rudd KE, Seymour CW, Aluisio AR, Augustin ME, Bagenda DS, Beane A, Byiringiro JC, Chang CH, Colas LN, Day NPJ, De Silva AP, Dondorp AM, Dünser MW, Faiz MA, Grant DS, Haniffa R, Van Hao N, Kennedy JN, Levine AC, Limmathurotsakul D, Mohanty S, Nosten F, Papali A, Patterson AJ, Schieffelin JS, Shaffer JG, Thuy DB, Thwaites CL, Urayezya O, White NJ, West TE, Angus DC; Sepsis Assessment and Identification in Low Resource Settings (SAILORS) Collaboration. **Association of the Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) Score With Excess Hospital Mortality in Adults with Suspected Infection in Low- and Middle-Income Countries.** *JAMA* 2018; 319:2202-2211.

### Liberal vs. Conservative Oxygen Therapy in Critically Ill Adults

Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, Szczeklik W, Schünemann HJ, Neary JD, Alhazzani W. **Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis.** *Lancet* 2018; 391:1693-1705.

### Out of Hospital Cardiac Arrest

Perkins GD, Ji C, Deakin CD, Quinn T, Nolan JP, Scopinich C, Regan S, Long J, Slowther A, Pocock H, Black JJM,

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**ICU REHABILITATION**

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Winston-Salem, NC**SURGICAL ICU REHABILITATION**

Schaller SJ, Anstey M, Blobner M, et al. **Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial.** *Lancet.* 2016;388(10052):1377-1388.

**Summary**

Few studies have focused exclusively on the surgical ICU population. This international, multicenter RCT evaluated the effect of an early, multidisciplinary goal-directed ICU rehabilitation program versus usual care in 200 mechanically ventilated SICU patients. Inclusion criteria included previously functional adults admitted to the SICU and mechanically ventilated for at least 48 hours. The intervention consisted of a rehabilitation “facilitator” in each ICU that was focused on assigning, coordinating, and implementing a mobilization goal for the day with the clinical team. Most common conditions included abdominal surgeries (27%), trauma (26%) and vascular (17%). The primary outcome, the patients mean level of mobility (SICU Optimal Mobilization Score) during the ICU stay was higher in the intervention group (group difference of 0.7 SOMS units, 95% CI=0.4- 1.0,  $p<0.0001$ ). Secondary outcomes of ICU length of stay [mean of 3 days shorter (95% CI=-6- -1,  $p=0.005$ )] and functional mobility at hospital discharge were improved in the intervention group. Additional secondary outcomes such as discharge disposition to home (51% vs 21%,  $p=0.0007$ ) were increased in the intervention group. No differences were seen in muscle weakness, or quality of life at 3 months. Adverse events were more common in the intervention group (2.8 % vs 0.8%), though no serious adverse events such as falls or unplanned extubations were reported.

**Comments**

1. This ICU rehabilitation intervention was associated with a number of improved outcomes in this international multicenter RCT.
2. Previously functional surgical ICU patients may be an important group of patients to implement ICU rehabilitation therapies.
3. The intervention used a novel “facilitator tailored” multidisciplinary approach to determine and execute a daily mobility goal for each patient.
4. This data suggests that a focused, individualized daily personalization of ICU rehabilitation therapies may be a successful approach to improve outcomes.

**ICU REHABILITATION AND LONG-TERM QUALITY OF LIFE**

Wright SE, Thomas K, Watson G, et al. **Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): a multicentre, parallel-group, randomised controlled trial.** *Thorax.* 2018;73(3):213-221.

**Summary**

Optimal duration and intensity of daily ICU rehabilitation therapies are currently unknown. This multicenter RCT performed in mixed medical and surgical critically ill patients the United Kingdom aimed to evaluate the effect of increased duration of ICU rehabilitation (targeted goal of 90 minutes vs 30 minutes daily, 5 days per week) in 308 patients that had received at least 48 hours of invasive or non-invasive mechanical ventilation. While more ICU rehabilitation was delivered by the intervention, the target duration of 90 minutes per day in the intervention group was rare. The intervention group on average received 23 minutes of rehabilitation per day compared to 13 minutes per day in the control arm. Limitations to delivering the intervention were patient sedation and fatigue. The primary outcome of subjective physical function at 6 months, measured by the SF-36 PCS did not differ between the intervention and control groups.

**Comments**

1. This study demonstrates the complexity of delivering ICU rehabilitation interventions.
2. Participants had been in the ICU for approximately 5 days prior to randomization.
3. Only 41% of patients in the intervention and 34% of patients in the standard arm contributed to the primary outcome, and this missing data led to a study that was underpowered.
4. The focus on a primary outcome of long-term physical function is a novel and patient-centered approach, but is challenging due to late death and missing data.

**IN-BED CYCLING PLUS ELECTRICAL STIMULATION AND MUSCLE STRENGTH**

Fossat G, Baudin F, Courtes L, et al. **Effect of In-Bed Leg Cycling and Electrical Stimulation of the Quadriceps on Global Muscle Strength in Critically Ill Adults: A Randomized Clinical Trial.** *JAMA.* 2018;320(4):368-378.

**Summary**

Barriers to implementing ICU rehabilitation are common and novel approaches are needed. This French single cen-



ter RCT evaluated the effect of a combined in bed cycling ergometry plus neuromuscular electrical stimulation of the quadriceps muscle versus usual care in 314 medical-surgical ICU patients. Inclusion criteria included previously functional adults admitted to the ICU less than 72 hours prior to randomization. The intervention group received an in-bed cycling intervention with a 15-minute session, and quadriceps transcutaneous stimulation. Most common admission diagnoses were acute respiratory failure, sepsis, and acute exacerbation of chronic respiratory failure. The primary outcome of muscle strength at ICU discharge, using the Medical Research Council Sum Score, did not differ by treatment allocation [intervention 48 (IQR 29- 58) vs usual care 51 (IQR 37- 58)]. There were no detectable differences in in-hospital secondary outcomes or long-term questionnaire-based quality of life outcomes at 6 months.

### Comments

1. This study failed to show benefit of a combined cycling and neuromuscular electrical stimulation intervention in addition to baseline ICU rehabilitation on muscle strength at ICU discharge.
2. The cycling intervention was short in duration (15 minutes for five days per week) and active cycling was uncommon in the study.
3. This study started within 72 hours of ICU admission and used blinded physiotherapy assessors to capture the outcomes.
4. The “baseline” rehabilitation program in the usual care and intervention arms may be in excess of that delivered as usual care in many ICUs.
5. Edema can interfere with muscle transcutaneous stimulation and it is unclear how effective the transcutaneous stimulations on muscle contraction were in this study.

## IN BED CYCLING ATTENUATES MUSCLE PROTEOLYSIS IN EARLY SEPSIS

Hickmann CE, Castanares-Zapatero D, Deldicque L, et al. **Impact of Very Early Physical Therapy During Septic Shock on Skeletal Muscle: A Randomized Controlled Trial.** *Critical care medicine.* 2018;46(9):1436-1443

### Summary

A better understanding of the molecular aspects underlying ICU rehabilitation interventions is needed to move the field forward. This Belgian single center, small, mechanistic RCT evaluated the effect of an in bed cycling ergometer coupled with standard rehabilitation versus control in 21 patients with septic shock. Inclusion criteria included previously functional adults with septic shock. Patients could be enrolled up to 72 hours following ICU admission. The intervention group received two physiotherapy sessions daily for 1 hour per day, split between 30 minutes of in bed cycling and 30 minutes of progressive mobilization. The control group received standard physiotherapy 5 days per week. Muscle biopsies were performed on day 1 and day 7 for a total of 18 patients. The primary outcome was defined as the regulation of muscle protein degradation and synthesis pathways. Transcriptional activation of pro-

teolytic ubiquitin proteasome pathway genes (MAFbx and MuRF1) were non-significantly reduced by the intervention and similar trends were seen in selected autophagy markers. The intervention did not appear to augment muscle protein anabolic pathways. The secondary outcome of muscle fiber cross sectional area was preserved by the intervention (-25.8% +/- 21.6% in control vs 12.4% +/- 22.5% in intervention;  $p = 0.005$ ). Muscle strength did not differ between groups, but a significant number of patients were not able to participate in strength testing.

### Comments

1. This proof of concept mechanistic study suggests that an in-bed cycling intervention applied early to patients with septic shock preserves muscle mass by attenuating muscle proteolysis.
2. Differences in muscle strength or electrophysiologic assessment of neuromuscular injury did not differ, but assessments were limited by missing data.
3. Patients with septic shock, who have massive catabolism, may be an important disease state to focus ICU rehabilitation interventions.
4. This study suggests that an ICU cycling intervention occurring early in the course of septic shock may have the benefit of preserving muscle mass.

## GUIDELINES INCORPORATE ICU REHABILITATION

Devlin JW, Skrobik Y, Gelinas C, et al. **Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU.** *Critical care medicine.* 2018;46(9):e825-e873.

### Summary

In 2018, the Society of Critical Care Medicine updated the clinical practice guidelines for management of Pain Agitation and Delirium (from the 2013 guidelines). A multidisciplinary panel of experts and patients participated in the process and used the GRADE methodology to review the literature and develop recommendations. Due to the growing evidence of the links between Pain, Agitation and Delirium with ICU rehabilitation, the 2018 guidelines incorporated a separate category on recommendations of preventing immobility by implementing ICU rehabilitation. Importantly, the guidelines recommended performing ICU rehabilitation as a beneficial strategy to improve patient, family, and health system outcomes in critically ill adults (conditional recommendation, low quality evidence).

### Comments

1. The incorporation of ICU rehabilitation into clinical practice guidelines represents a major step that will likely increase implementation of this therapy.
2. The guidelines acknowledge the low quality of evidence supporting these guidelines, supporting the concept that further study on ICU rehabilitation is needed.

3. The ungraded guideline recommendations for starting and stopping criteria for ICU rehabilitation can be useful for developing local protocols.

## OTHER ARTICLES OF INTEREST

### In Bed Cycling Trial

Eggmann S, Verra ML, Luder G, Takala J, Jakob SM. **Effects of early, combined endurance and resistance training in mechanically ventilated, critically ill patients: A randomised controlled trial.** *PloS one.* 2018;13(11):e0207428.

### Feasibility Trials

Kho ME, Molloy AJ, Clarke FJ, Canadian Critical Care Trials Group, et al. **Multicentre pilot randomised clinical trial of early in-bed cycle ergometry with ventilated patients.** *BMJ Open Respiratory Research.* 2019;6:e000383.

McWilliams D, Jones C, Atkins G, et al. **Earlier and enhanced rehabilitation of mechanically ventilated patients in critical care: A feasibility randomised controlled trial.** *Journal of critical care.* 2018; 44:407-412.

Hodgson CL, Bailey M, Bellomo R, et al. **A Binational Multicenter Pilot Feasibility Randomized Controlled Trial of Early Goal-Directed Mobilization in the ICU.** *Critical care medicine.* 2016;44(6):1145-1152.

### The Patient Perspective

Corner EJ, Murray EJ, Brett SJ. **Qualitative, grounded theory exploration of patients' experience of early mobilisation, rehabilitation and recovery after critical illness.** *BMJ open.* 2019;9(2):e026348

### Point Prevalence of ICU Rehabilitation Practices in the U.S.

Jolley SE, Moss M, Needham DM, et al. **Point Prevalence Study of Mobilization Practices for Acute Respiratory Failure Patients in the United States.** *Critical care medicine.* 2017;45(2):205-215.

### Systematic Review

Tipping CJ, Harrold M, Holland A, Romero L, Nisbet T, Hodgson CL. **The effects of active mobilisation and rehabilitation in ICU on mortality and function: a systematic review.** *Intensive care medicine.* 2017;43(2):171-183

## ILD

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**DIAGNOSIS OF IDIOPATHIC PULMONARY FIBROSIS**

Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, Behr J, Cottin V, Danoff SK, Morell F, Flaherty KR, Wells A, Martinez FJ, Azuma A, Bice TJ, Bouros D, Brown KK, Collard HR, Duggal A, Galvin L, Inoue Y, Jenkins RG, Johkoh T, Kazerooni EA, Kitaichi M, Knight SL, Mansour G, Nicholson AG, Pipavath SNJ, Buendia-Roldan I, Selman M, Travis WD, Walsh S, Wilson KC, American Thoracic Society ERSJRS, Latin American Thoracic S. **Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline.** *Am J Respir Crit Care Med.* 2018;198(5):e44-e68.

**Summary**

Our understanding of interstitial lung diseases (ILD), including idiopathic pulmonary fibrosis (IPF), has substantially increased over the past few decades. As our understanding of these disease states evolve, the way in which we approach the diagnosis of ILD and IPF should be re-assessed in this context. As such, the 2011 joint guidelines for the diagnosis of IPF was recently updated by the same societies (ATS, ERS, JRS, ALAT) to incorporate new evidence and refine diagnostic criteria. Using similar methodology as in the past guidelines, they re-defined the imaging criteria to be in line with the Fleischner criteria (also published in 2018 and citation provided below) and provided an updated scanning protocol for high-resolution computed tomography (HRCT) imaging in ILD. Further, they assessed the evidence for 8 clinical questions as it relates to diagnostic modalities including the ascertainment of a complete history (e.g. medications and environmental exposures), serologic testing, bronchoscopy with bronchoalveolar lavage (BAL), surgical lung biopsy, transbronchial lung biopsy, cryobiopsy, multidisciplinary discussion and serum biomarkers.

**Comments**

1. There is an update to the radiologic criteria and now includes four HRCT categories: definite usual interstitial pneumonia (UIP), probable UIP, indeterminate for UIP, and alternative diagnosis.
2. Motherhood statements were made with regard to complete history and serologic testing in suspected cases of IPF in order to exclude potential causes of ILD.
3. Recommendations with regard to BAL cellular analysis, surgical lung biopsy, transbronchial lung biopsy, and cryobiopsy were made based on the type of pattern observed on HRCT.

4. A strong recommendation against the measurement of serum biomarkers (MMP-7, SPD, CCL-18, KL-6) was recommended.
5. A conditional recommendation was made for the use of multi-disciplinary discussion for decision-making in IPF.

**THE ROLE OF GENETICS IN INTERSTITIAL LUNG DISEASE**

Juge PA, Lee JS, Ebstein E, Furukawa H, Dobrinskikh E, Gazal S, Kannengiesser C, Ottaviani S, Oka S, Tohma S, Tsuchiya N, Rojas-Serrano J, Gonzalez-Perez MI, Mejia M, Buendia-Roldan I, Falfan-Valencia R, Ambrocio-Ortiz E, Manali E, Papis SA, Karageorgas T, Boumpas D, Antoniou K, van Moorsel CHM, van der Vis J, de Man YA, Grutters JC, Wang Y, Borie R, Wemeau-Stervinou L, Wallaert B, Flipo RM, Nunes H, Valeyre D, Saidenberg-Kermanac'h N, Boissier MC, Marchand-Adam S, Frazier A, Richette P, Allanore Y, Sibilia J, Dromer C, Richez C, Schaevebeke T, Liote H, Thabut G, Nathan N, Amselem S, Soubrier M, Cottin V, Clement A, Deane K, Walts AD, Fingerlin T, Fischer A, Ryu JH, Matteson EL, Niewold TB, Assayag D, Gross A, Wolters P, Schwarz MI, Holers M, Solomon JJ, Doyle T, Rosas IO, Blauwendraat C, Nalls MA, Debray MP, Boileau C, Crestani B, Schwartz DA, Dieude P. **MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease.** *N Engl J Med.* 2018;379(23):2209-19.

**Summary**

It has been observed that there are phenotypic similarities between rheumatoid arthritis associated interstitial lung disease (RA-ILD) and idiopathic pulmonary fibrosis (IPF). Given the clinical similarities, this study aimed to look at shared genetic risk between these two diseases, in particular the gain-of-function MUC5B promoter variant rs35705950. Using a discovery population and multi-ethnic replication sample, the authors tested the association of the MUC5B promoter variant in 620 patients with RA-ILD, 614 patients with RA without ILD, and 5448 unaffected controls. The authors report an association between the minor allele of the MUC5B promoter variant and RA-ILD, compared to controls (adjusted odds ratio 3.8, 95% CI 2.8-5.2,  $P=9.7 \times 10^{-17}$ ). The MUC5B promoter variant was associated with an increased risk of ILD among patients with RA, particularly among those with the usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (adjusted odds ratio 6.1, 95% CI 2.9-13.1,  $P=2.5 \times 10^{-6}$ ). There was no association between the

MUC5B promoter variant for RA without ILD compared to controls. Immunohistochemical staining of RA-ILD lung tissue demonstrates the localization of MUC5B protein in the metaplastic epithelia lining honeycomb cysts and the mucus in honeycomb cysts, similar to that observed in IPF.

#### Comments

1. The MUC5B promoter variant is associated with RA-ILD and driven by the UIP-phenotype.
2. The point estimates for the association of the MUC5B promoter variant with RA-ILD are similar to those observed with IPF.
3. These findings suggest that the MUC5B promoter variant may be a genetic risk factor for the UIP pattern in general.
4. Genetic risk factors for ILD, in particular RA-ILD and IPF, may allow us to identify at-risk populations.

### OXYGEN THERAPY IN INTERSTITIAL LUNG DISEASE

Visca D, Mori L, Tsiouri V, Fleming S, Firouzi A, Bonini M, Pavitt MJ, Alfieri V, Canu S, Bonifazi M, Boccabella C, De Lauretis A, Stock CJW, Saunders P, Montgomery A, Hogben C, Stockford A, Pittet M, Brown J, Chua F, George PM, Molyneaux PL, Margaritopoulos GA, Kokosi M, Kouranos V, Russell AM, Birring SS, Chetta A, Maher TM, Cullinan P, Hopkinson NS, Banya W, Whitty JA, Adamali H, Spencer LG, Farquhar M, Sestini P, Wells AU, Renzoni EA. Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial. *The Lancet Respiratory medicine*. 2018;6(10):759-70.

#### Summary

Oxygen desaturation is observed in many patients with interstitial lung disease (ILD) and contributes to the symptoms experienced by these patients. There is little data for use of supplemental oxygen in ILD and extrapolations have been made using the chronic obstructive pulmonary disease (COPD) literature. This extrapolation may be problematic given the more frequent and severe exercise-induced desaturation observed in ILD compared to COPD. Further, our 2011 treatment guidelines did not provide guidance on the use of supplemental oxygen therapy in patients with isolated exertional hypoxemia. This study aimed to assess the effects of ambulatory oxygen on health-related quality of life (HRQOL) in patients with ILD and exertional hypoxemia. They randomly assigned 84 patients to receive supplemental oxygen or no oxygen. They found that patients randomized to ambulatory oxygen therapy had significant improvements in HRQOL as measured by the King's Brief Interstitial Lung Disease questionnaire (K-BILD) compared to no oxygen. While certain subdomains of the K-BILD (i.e. breathlessness and activity and chest symptoms) were significantly improved between those randomized to oxygen vs. no oxygen, the psychological subdomain did

not reach statistical significance. This study suggests that supplemental oxygen therapy in ILD patients with isolated exertional hypoxemia is associated with improved HRQOL.

#### Comments

1. This was the first randomized controlled trial assessing the effects of ambulatory oxygen on HRQOL in ILD.
2. Ambulatory oxygen is associated with improved HRQOL in patients with ILD and exertional hypoxemia.
3. This was a limited duration (2 weeks followed by cross-over for 2 weeks) study so the long-term effects of supplemental oxygen therapy on HRQOL in ILD remains unknown.
4. Despite the improvement in HRQOL with use of supplemental oxygen, there remain physical and psychosocial barriers to the use of ambulatory oxygen.

### TREATMENT OF IDIOPATHIC PULMONARY FIBROSIS

Newton CA, Zhang D, Oldham JM, Kozlitina J, Ma SF, Martinez FJ, Raghu G, Noth I, Garcia CK. **Telomere Length and Use of Immunosuppressive Medications in Idiopathic Pulmonary Fibrosis.** *Am J Respir Crit Care Med*. 2018.

#### Summary

In 2012, the results of the IPFNet sponsored PANTHER-IPF [Evaluating the Effectiveness of Prednisone, Azathioprine and N-acetylcysteine (NAC) in Patients with IPF] were published and demonstrated that patients randomized to the combination of prednisone, azathioprine and NAC had increased mortality, hospitalization and treatment-related severe side effects compared to placebo. The reason for this difference in harm was unknown. In this study, the authors hypothesized that leukocyte telomere length (LTL) would be associated with differential risk of harm observed in this trial, based on data from the lung transplant literature. They measured LTL in the PANTHER-IPF cohort and two replication cohorts [one clinical trial (ACE-IPF, warfarin vs. placebo) and one observational cohort (University of Texas Southwestern)]. They found that the majority of patients in these cohorts had an LTL <10th percentile of normal. In PANTHER-IPF, exposure to prednisone, azathioprine and NAC was associated with harm in those with an LTL <10th percentile (HR 2.84, 95% CI 1.02-7.87), but not in those with an LTL ≥ 10th percentile (p=0.49). This interaction effect was also observed in the replication cohorts. This observation was not found in the NAC only arm or with warfarin.

#### Comments

1. There was an interaction between LTL and immunosuppression on outcome (death, transplant, FVC decline or hospitalization) in patients with IPF in two clinical trial cohorts and an observational cohort.

- LTL has been shown in prior studies to be a prognostic biomarker in patients with IPF.
- These data suggest that LTL could also have the potential to be a pharmacogenomic biomarker in patients with IPF.
- This is a post-hoc analysis of a clinical trial population not designed to assess for this interaction and requires further investigation.

## PREDICTING OUTCOMES IN IDIOPATHIC PULMONARY FIBROSIS

Jacob J, Bartholmai BJ, Rajagopalan S, van Moorsel CHM, van Es HW, van Beek FT, Struik MHL, Kokosi M, Egashira R, Brun AL, Nair A, Walsh SLF, Cross G, Barnett J, de Lauretis A, Judge EP, Desai S, Karwoski R, Ourselin S, Renzoni E, Maher TM, Altmann A, Wells AU. Predicting Outcomes in Idiopathic Pulmonary Fibrosis Using Automated Computed Tomographic Analysis. *Am J Respir Crit Care Med*. 2018;198(6):767-76.

### Summary

Idiopathic pulmonary fibrosis (IPF) is a progressive disease. Forced vital capacity (FVC) is the primary measure of outcome in IPF and has been correlated with survival. While there is a degree of measurement variation, a 10% FVC decline has been a surrogate marker of mortality. Cohort enrichment strategies in IPF clinical trials have been a focus in order to create more homogeneous study populations who are likely to experience increased clinical events. This study aimed to determine if computer analysis of computed tomographic (CT) imaging could be used to predict mortality. They compared this to other measures of mortality prediction and whether or not this modality could be used to enrich a clinical trial population. The computer scored CT variables using CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Rating) software, which included a vessel-related structure (VRS) score. Using a derivation (n=247) and validation (n=284) cohort, they found that the VRS score predicted survival and FVC decline at 12 months. These computer derived scores were also accentuated in less extensive disease. Using a VRS score of greater than 4.4%, they suggest this would reduce the sample size of an IPF clinical trial by 25%.

### Comments

- Automated computer scoring techniques may help inform prognosis in patients with IPF, particularly in those with less extensive disease at baseline.
- These computer algorithms may also help clinical trial efficiency by reducing a trial sample size by approximately 25%.
- The main limitation of this methodology is the requirement of noncontrast volumetric imaging acquired to generate appropriate reconstruction algorithms, as misclassification of radiologic features could occur depending on the technique used and the quality of the imaging.

## OTHER ARTICLES OF INTEREST

### Guideline Statements and Diagnostic Modalities in ILD

Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TV, Galvin JR, Goldin JG, Hansell DM, Inoue Y, Johkoh T, Nicholson AG, Knight SL, Raoof S, Richeldi L, Ryerson CJ, Ryu JH, Wells AU. **Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper.** *The Lancet Respiratory medicine*. 2018;6(2):138-53.

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Lederer DJ, Martinez FJ. **Idiopathic Pulmonary Fibrosis.** *N Engl J Med*. 2018;378(19):1811-23.

### Prognosis in ILD

Dotan Y, Vaidy A, Shapiro WB, Zhao H, Dass C, Toyoda Y, Marchetti N, Shenoy K, Cordova FC, Criner GJ, Mamary AJ. **Effect of Acute Exacerbation of Idiopathic Pulmonary Fibrosis on Lung Transplantation Outcome.** *Chest*. 2018;154(4):818-26.

Neighbors M, Cabanski CR, Ramalingam TR, Sheng XR, Tew GW, Gu C, Jia G, Peng K, Ray JM, Ley B, Wolters PJ, Collard HR, Arron JR. **Prognostic and predictive biomarkers for patients with idiopathic pulmonary fibrosis treated with pirfenidone: post-hoc assessment of the CAPACITY and ASCEND trials.** *The Lancet Respiratory medicine*. 2018;6(8):615-26.

Nolan CM, Maddocks M, Maher TM, Banya W, Patel S, Barker RE, Jones SE, George P, Cullinan P, Man WD. **Gait speed and prognosis in patients with idiopathic pulmonary fibrosis: a prospective cohort study.** *Eur Respir J*. 2018.

Jacob J, Hirani N, van Moorsel CHM, Rajagopalan S, Murchison JT, van Es HW, Bartholmai BJ, van Beek FT, Struik MHL, Stewart GA, Kokosi M, Egashira R, Brun AL, Cross G, Barnett J, Devaraj A, Margaritopoulos G, Karwoski R, Renzoni E, Maher TM, Wells AU. **Predicting outcomes in rheumatoid arthritis related interstitial lung disease.** *Eur Respir J*. 2019;53(1).

### The Role of Genetics in ILD

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Vogel J, Forrest WF, Collard HR, Wolters PJ, Kropski JA, Lancaster LH, Blackwell TS, Arron JR, Yaspan BL. **Analysis of protein-altering variants in telomerase genes and their association with MUC5B common variant status in patients with idiopathic pulmonary fibrosis: a candidate gene sequencing study.** *The Lancet Respiratory medicine.* 2018;6(8):603-14.

#### Symptom Targeted Treatment in ILD

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Kolb M, Raghu G, Wells AU, Behr J, Richeldi L, Schinzel B, Quaresma M, Stowasser S, Martinez FJ, Investigators I. **Nintedanib plus Sildenafil in Patients with Idiopathic Pulmonary Fibrosis.** *N Engl J Med.* 2018;379(18):1722-31.

#### Disease Targeted Treatment in IPF

Maher TM, van der Aar EM, Van de Steen O, Allamassey L, Desrivot J, Dupont S, Fagard L, Ford P, Fieuw A, Wuyts W. **Safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomised placebo-controlled trial.** *The Lancet Respiratory medicine.* 2018;6(8):627-35.

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Vancheri C, Kreuter M, Richeldi L, Ryerson CJ, Valeyre D, Grutters JC, Wiebe S, Stansen W, Quaresma M, Stowasser S, Wuyts WA, Investigators IT. **Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis. Results of the INJOURNEY Trial.** *Am J Respir Crit Care Med.* 2018;197(3):356-63.

Flaherty KR, Fell CD, Huggins JT, Nunes H, Sussman R, Valenzuela C, Petzinger U, Stauffer JL, Gilberg F, Bengus M, Wijsenbeek M. **Safety of nintedanib added to pirfenidone treatment for idiopathic pulmonary fibrosis.** *Eur Respir J.* 2018;52(2).

## TOBACCO DEPENDENCE

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## TREATMENT FOR TOBACCO DEPENDENCE

Anthenelli R, Benowitz NL, West R, St. Aubin L, McRae T, Lawrence D, Ascher J, Russ C, Krishen A, Evins AE. **Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomized, placebo-controlled clinical trial.** *Lancet* 2016. 387:2507.

## Summary

The EAGLES trial was a multi-center, double-blind, randomized placebo-controlled trial that examined the neuropsychiatric consequences of varenicline, bupropion, nicotine patch or placebo in two large cohorts of active smokers (N=8144) over 12 weeks with a further 12-week no treatment follow-up. The study involved 140 centers in 16 countries conducted between 2011-2015. One cohort (N=4074) had a history of psychiatric disorders; the other (N=3984) had no such history. The primary outcome was the incidence of a composite index of moderate and severe neuropsychiatric adverse events with an efficacy endpoint of biochemically-confirmed abstinence during weeks 9-12. In the non-psychiatric cohort, there were no differences in the incidence of neuropsychiatric events across the four treatment groups ranging from 1.3% among varenicline users to 2.5% among users of nicotine patch. The risk-difference of varenicline to placebo was -1.28 (5% CI=-2.40 - 0.15). In the psychiatric cohort, there were no differences among the treatment groups ranging from 4.9% in the placebo group to 6.7% in the bupropion group (6.5% in the varenicline group). The risk difference of varenicline to placebo was insignificant as were the comparison to placebo in the other treatment groups. Persons on varenicline, irrespective of psychiatric history, exhibited the highest abstinence rate compared with other groups.

## Comments

1. Persons with mental illness have extremely high prevalence of tobacco dependence, ranging from 40-60% depending on the underlying diagnosis.
2. This study provided the most persuasive data that there was no heightened risk of psychiatric decompensation with the use of varenicline, even in persons with mental illness and led to the lifting of the black box warning in December of 2016, a decision that generated some controversy.

3. The study was powered to detect a 4% or greater moderate or severe event incidence in each of the treatment groups, a threshold that was much higher than what has been observed for most drugs making the study underpowered especially using a novel composite endpoint.
4. Unresolved issues are whether the time frame for varenicline use should be flexible depending on the needs of the motivated smoker.
5. The study excluded persons with substance use disorders despite the fact that appreciable crossover effects exist among persons with tobacco dependence and other substance use disorders.

Hajek P, Phillips-Waller A, Przulj D, Pesola F, Smith KM, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L, Ross L, Goniewicz M, Wu Q, McRobbie HJ. **A Randomized Trial of E-Cigarettes versus Nicotine Replacement Therapy.** *NEJM* 2019 380(7): 629.

## Summary

Among the newer modified risk tobacco products, electronic cigarettes have generated the most interest and established a strong market imprint worldwide. Despite multiple claims, their utility as smoking cessation tools is unresolved. This pragmatic, unblinded, multicenter, randomized controlled trial was conducted in three National Health Service stop-smoking sites across the U.K. Smokers (N=886) who were neither pregnant nor breastfeeding with no clear quit date were recruited and randomized to either nicotine replacement therapies of their choice and combination or an e-cigarette starter pack with instructions to purchase further e-liquids of their choice for up to 3 months. Weekly counseling was also provided to all participants and was continued for 4 weeks after the quit date. Abstinence was queried at 26 and 52 weeks with biochemical confirmation at the latter if >50% reduction was reported. The sustained abstinence rate at 1 year was 18% among the e-cigarette users and 9.9% among the NRT users with a relative risk of abstinence of 1.83 (CI=1.30 - 2.58, 95%, p<0.001). Both e-cigarettes and NRT were considered less satisfying than cigarettes but e-cigarettes provided greater satisfaction than NRT. While only 9% of the abstinent NRT users were still using NRT at 1 year, more than 80% of the abstinent e-cigarette users were continuing to use these products.

## Comments

1. These findings, while ostensibly suggesting that e-cigarettes may have a role in the smoking cessation armamentarium, create a troubling “third way” in which combustible cigarette use is eliminated but ongoing nicotine dependence is enabled.
2. The smoking cessation rates in the NRT group at 26 weeks was much higher than reported in prior NRT trials making one question whether the cohort was representative of motivated smokers targeted in prior studies.
3. The open-label structure invites concerns about the confounding of quit attempts by perceived novelty or prior failed attempts with NRT (not ascertained).
4. The public health consequences of adult e-cigarette use are substantial given the epidemic of youth uptake with a strong footprint of products with extremely high nicotine content.
5. The trial data need to be weighed against the contemporaneous epidemic that has led to very high nicotine dependence among adolescents and teenagers.

## IMPLEMENTATION OF TOBACCO DEPENDENCE TREATMENT

Bernstein SL, Weiss J, Dewitt M, Tetrault JM, Hsiao AL, Dziura J, Sussman S, Miller T, Carpenter K, O'Connor P, Toll B. **A randomized trial of decision support for tobacco dependence treatment in an inpatient electronic medical record: clinical results.** *Implementation Science* 2019. 14(1):8.

### Summary

The initiation of tobacco dependence treatment in an inpatient setting takes advantage of what is generally considered a “teachable moment” since hospitals are smoke-free environments and the term of stay can be construed as a quit attempt. This single hospital system study randomized an EMR-embedded alert with a decision support tool and order set to 254 physicians who admitted patients self-designated as current smokers. The order set prescribed tobacco treatment medications, made a referral to a quitline, populated the problem list with “Tobacco Use Disorder,” and sent a secure message to the primary care physician about the study. The control arm received an alert but no decision support tool and order set. The patients were followed up at 1, 6, and 12 months with biochemical confirmation on all asserting abstinence at 12 months. The alert was fired for 10,339 patients (5391 with intervention physicians and 5548 with control physicians). Compared to control physicians, intervention physicians were more likely to order tobacco cessation medications, refer the patient to the quitline, populate the problem list with tobacco dependence designation, and message the primary care physician about the plan. A subgroup of 1044 enrollees were subjected to intensive follow-up for 1 year and showed 11.5% abstinence in the intervention arm and 11.7% abstinence in the control arm ( $p=0.94$ ) controlling for age, sex, race, ethnicity, and SES. There were no differences in abstinence at 1 month and 6 months.

## Comments

1. The current study created an automatic opt-out system that triggered a multicomponent intervention that did not require a tobacco treatment team and could be incorporated into a clinical workflow.
2. The lack of an effect on long-term abstinence is likely driven by the ease of availability of post-discharge medications and behavioral support.
3. Despite the recognition of hospitalization, especially for smoking related diseases, as a quit attempt and a “teachable moment,” the incorporation of inpatient tobacco dependence treatments have not resulted in long-term abstinence without discharge programs beyond quitlines.

## NEW SMOKING CESSATION TOOLS

Hatsukami DK, Luo X, Jensen JA, alAbsi M, Allen SS, Carmella SG, Chen M, Cinciripini PM, Denlinger-Apte R, Drobles DJ, Koopmeiners JS, Lane T, Le CT, Leischow S, Luo K, McClernon J, Murphy SE, Paiano V, Robinson JD, Severson H, Sipe C, Strasser AA, Strayer LG, Tang MK, Vandrey R, Hecht SS, Benowitz NL, Donny EC. **Effect of Immediate vs Gradual Reduction in Nicotine Content of Cigarettes on Biomarkers of Smoke Exposure.** *JAMA* 2018. 320(9):880.

### Summary

This study is a multicenter, double-blind, randomized, parallel-design trial of immediate vs. gradual reduction in nicotine content to very low levels over 22 weeks. Two weeks of baseline smoking was followed by 20 weeks of the intervention: immediate reduction to 0.4 mg of nicotine per gram of tobacco and gradual reduction from 15.5 mg to 0.4 mg per gram of tobacco with 5 monthly dose changes. The control group maintains conventional levels of nicotine in cigarettes, 15.5 mg per gram of tobacco. Smokers not ready to quit ( $N=1250$ ) at 10 U.S. sites were randomized to the three groups with 988 completing the study. During the study, behavioral counseling was offered to those who expressed an interest in quitting. The primary endpoint was between-group differences in 3 co-primary biomarkers of smoke exposure (exhaled CO, urine 3-HPMA and urine PheT) employing ROC measurements. Significant reductions in the triple toxicant readouts were observed in the immediate versus gradual reduction arms, specifically for CO (mean difference  $-4.06$  ppm,  $[-4.89 - -3.23, p<0.0055]$ ), 3-HPMA (ratio of geometric means 0.83,  $[0.77 - 0.88, p<0.0055]$ ), Phe-T (ratio of geometric means 0.88  $[0.83 - 0.93, p<0.0055]$ ). Significant reductions were also observed in the immediate versus control group for all three toxicant measures. No differences were observed in the gradual versus control group for CO, 3-HPMA or Phe-T.

### Comments

1. The incorporation of low nicotine cigarettes into a smoking cessation program, especially for highly dependent smokers, has generated a great deal of interest among the tobacco control community and the FDA.



2. Immediate nicotine reduction in cigarettes resulted in greater durable decreases in biomarkers of smoke exposure than gradual nicotine reduction.
3. Immediate reduction was associated with smoking fewer cigarettes per day, a greater reduction in dependence and more cigarette-free days but was also associated with greater early withdrawal symptoms, greater use of non-study cigarettes and higher drop-out rates.
4. Customized approaches to low nicotine strategy that incorporate the use of NRT, varenicline, or ENDS might mitigate the adverse consequences of the immediate approach.
5. The enrollment of smokers not ready to quit is an important choice and suggest that this is an intervention that does not have to be coupled to formal quit attempts or interest in quitting.

## TARGET IDENTIFICATION FOR TOBACCO DEPENDENCE

Brynildsen JK, Lee BG, Perron IJ, Jin S, Kim SF, Blendy JA. **Activation of AMPK by metformin improves withdrawal signs precipitated by nicotine withdrawal.** *PNAS* 2018. 115(16):4282.

### Summary

Despite the fact that tobacco dependence is the number one cause of preventable death in the United States and that 70% of active smokers want to quit, the armamentarium of agents to treat this disorder is anemic. Given the complexity of addiction and withdrawal, the lack of new targets that can be developed solely or in combination with established agents is surprising. In this study, the team builds on previous findings in murine models establishing 1) a role for the transcription factor CREB in nicotine triggered reward responses and 2) the identification of CREB targets for the elaboration of downstream pathways. In this study, AMPK which is a multi-protein complex with subunits regulated by CREB, is examined as a mediator of nicotine withdrawal. In a murine model of nicotine dependence induced by a two-week nicotine infusion, AMPK pathway activation was triggered in the hippocampus during infusion but receded upon withdrawal. Nicotine withdrawal in mice is punctuated by measurable anxiety behaviors. Mice treated with two activators of AMPK, including metformin, an FDA approved AMPK activator and diabetes treatment, showed none of these behaviors upon nicotine withdrawal. Finally, the loss of AMPK expression in the hippocampus resulted in enhanced anxiety symptoms upon withdrawal.

### Comments

1. This study demonstrates the elegant use of informative animal models, genetic profiling, gene targeting, and repurposed agents to identify novel targets for a complex behavior and may be a template for the development of new agents for nicotine dependence.
2. The development of rigorous models for nicotine dependence and withdrawal is needed to further refine the exploration of candidate agents.
3. High throughput and in vitro test systems will be critical to populating a pipeline for new agents.

## OTHER ARTICLES OF INTEREST

### Adoption of Tobacco Dependence Treatment

Benowitz NL, Pipe A, West R, Hays JT, Tonstad S, McRae T, Lawrence D, St Aubin L, Anthenelli RM. **Cardiovascular Safety of Varenicline, Bupropion, and Nicotine Patch in Smokers: A Randomized Clinical Trial.** *JAMA Intern Med.* 2018 May 1;178(5):622-631.

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Preloading Investigators. **Effects on abstinence of nicotine patch treatment before quitting smoking: parallel, two arm, pragmatic randomised trial.** *BMJ.* 2018 Jun 13;361:k2164.

Melzer AC, Clothier BA, Japuntich SJ, Noorbaloochi S, Hammett P, Burgess DJ, Joseph AM, Fu SS. **Comparative Effectiveness of Proactive Tobacco Treatment among Smokers with and without Chronic Lower Respiratory Disease.** *Ann Am Thorac Soc.* 2018 Mar;15(3):341-347.

Gilbody S, Peckham E, Bailey D, Arundel C, Heron P, Crosland S, Fairhurst C, Hewitt C, Li J, Parrott S, Bradshaw T, Horspool M, Hughes E, Hughes T, Ker S, Leahy M, McCloud T, Osborn D, Reilly J, Steare T, Ballantyne E, Bidwell P, Bonner S, Brennan D, Callen T, Carey A, Colbeck C, Coton D, Donaldson E, Evans K, Herlihy H, Khan W, Nyathi L, Nyamadzawo E, Oldknow H, Phiri P, Rathod S, Rea J, Romain-Hooper CB, Smith K, Stribling A, Vickers C. **Smoking cessation for people with severe mental illness (SCIMITAR+): a pragmatic randomised controlled trial.** *Lancet Psychiatry.* 2019 Apr 8.

Evins AE, Benowitz NL, West R, Russ C, McRae T, Lawrence D, Krishen A, St Aubin L, Maravic MC, Anthenelli RM. **Neuropsychiatric Safety and Efficacy of Varenicline, Bupropion, and Nicotine Patch in Smokers With Psychotic, Anxiety, and Mood Disorders in the EAGLES Trial.** *J Clin Psychopharmacol* 2019 39:108-116.

### New Approaches to Tobacco Dependence Treatment

Halpern SD, Harhay MO, Saulsgiver K, Brophy C, Troxel AB, Volpp KG. **A Pragmatic Trial of E-Cigarettes,**

**Incentives, and Drugs for Smoking Cessation.** *N Engl J Med.* 2018 Jun 14;378(24):2302-2310.

Ellerbeck EF, Nollen N, Hutcheson TD, Phadnis M, Fitzgerald SA, Vacek J, Sharpe MR, Salzman GA, Richter KP. **Effect of Long-term Nicotine Replacement Therapy vs Standard Smoking Cessation for Smokers With Chronic Lung Disease: A Randomized Clinical Trial.** *JAMA Netw Open.* 2018 Sep 7;1(5):e181843.

Shiffman S, Kurland BF, Scholl SM, Mao JM. Nondaily Smokers' Changes in Cigarette Consumption With Very Low-Nicotine-Content Cigarettes: A Randomized Double-blind Clinical Trial. *JAMA Psychiatry.* 2018 Oct 1;75(10):995-1002.

#### Health Consequences of Tobacco Products

Li D, Sundar IK, McIntosh S, Ossip DJ, Goniewicz ML, O'Connor RJ, Rahman I. **Association of smoking and electronic cigarette use with wheezing and related respiratory symptoms in adults: cross-sectional results from the Population Assessment of Tobacco and Health (PATH) study, wave 2.** *Tob Control.* 2019 Feb 13.

#### Use Patterns of Tobacco Products Among Youth

Anic GM, Sawdey MD, Jamal A, Trivers KF. **Frequency of Use Among Middle and High School Student Tobacco Product Users - United States, 2015-2017.** *MMWR Morb Mortal Wkly Rep.* 2018 Dec 14;67(49):1353-1357.

Pierce JP, Sargent JD, Portnoy DB, White M, Noble M, Kealey S, Borek N, Carusi C, Choi K, Green VR, Kaufman AR, Leas E, Lewis MJ, Margolis KA, Messer K, Shi Y, Silveira ML, Snyder K, Stanton CA, Tanski SE, Bansal-Travers M, Trinidad D, Hyland A. **Association Between Receptivity to Tobacco Advertising and Progression to Tobacco Use in Youth and Young Adults in the PATH Study.** *JAMA Pediatr.* 2018 May 1;172(5):444-451.

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#### Neurobiology of Nicotine Dependence

Walsh RM Jr, Roh SH, Gharpure A, Morales-Perez CL, Teng J, Hibbs RE. **Structural principles of distinct assemblies of the human  $\alpha 4\beta 2$  nicotinic receptor.** *Nature.* 2018 May;557(7704):261-265.

#### Smoking and Lung Cancer

Warren GW, Cartmell KB, Garrett-Mayer E, Salloum RG, Cummings KM. **Attributable Failure of First-line Cancer Treatment and Incremental Costs Associated With Smoking by Patients With Cancer.** *JAMA Netw Open.* 2019 Apr 5;2(4):e191703.

Zhang R, Lai L, Dong X, He J, You D, Chen C, Lin L, Zhu Y, Huang H, Shen S, Wei L, Chen X, Guo Y, Liu L, Su L, Shafer A, Moran S, Fleischer T, Bjaanaes MM, Karlsson A, Planck M, Staaf J, Helland Å, Esteller M, Wei Y, Chen F, Christiani DC. **SIPA1L3 methylation modifies the benefit of smoking cessation on lungadenocarcinoma survival: An epigenomic-smoking interaction analysis.** *Mol Oncol.* 2019 Mar 29.

#### Cannabis Use

Weinberger AH, Pacek LR, Wall MM, Gbedemah M, Lee J, Goodwin RD. **Cigarette smoking quit ratios among adults in the USA with cannabis use and cannabis use disorders, 2002-2016.** *Tob Control.* 2019 Apr 5.

## LUNG CANCER

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University College London  
London, United Kingdom**NIVOLUMAB PLUS IPILIMUMAB IN LUNG CANCER WITH A HIGH TUMOR MUTATIONAL BURDEN: CHECKMATE 227**

Hellmann MD, Ciuleanu TE, Pluzanski A et al. **Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden.** *N Engl J Med* 2018; 378(22):2093-2104

**Summary**

Through immune checkpoint blockade, several studies have demonstrated striking anti-tumour responses when monoclonal antibodies against co-inhibitory domains on immune cells are disengaged. Hellmann et al report their findings following completion of a phase III clinical trial where 550 patients with treatment naïve advanced NSCLC were randomized (1:1:1) to either a) nivolumab + ipilimumab b) nivolumab (240mg if PD-L1 greater/equal to 1% or 360mg + chemotherapy (CT) if less than 1% or c) CT. As per standard of care, maintenance pemetrexed was given to those following chemotherapy with non-squamous pathology. Crossover was not permitted. Using the Foundation Medicine 1 assay, tumour mutational burden (TMB) was calculated. In those with high TMB (identified as 10 or more mutations per megabase) combination immunotherapy demonstrated a longer 1-year progression free survival (PFS) compared with CT alone (42.6% vs. 13.2%, HR=0.58, p<0.001) and median PFS was longer (7.2m vs. 5.5m, HR=0.58, p<0.001). In addition, overall response rate (ORR - 45.3% vs. 26.9%) and duration of response [DoR Not reached NR (95% CI=12.8 to NR) vs. 5.4m (4.2-6.9)] were also higher in this group.

**Comments**

1. TMB is a useful predictive biomarker of response, although there was no correlation with PD-L1 expression.
2. The success rate of obtaining TMB was only 58%, although the authors believe this can be improved in clinical practice if testing is performed earlier in the treatment pathway.
3. The PFS KM curves begin to plateau at time of analysis, suggesting a longer duration of response in subsequent analyses.
4. Immunotherapy given up to 2 years; is this enough?
5. Toxicity of doublet immunotherapy is less than CT but more than anti-PD1 monotherapy.

**NEOADJUVANT PD-1 BLOCKADE IN RESECTABLE LUNG CANCER**

Forde PM, Chaft JE, Smith KN et al. **Neoadjuvant PD-1 Blockade in Resectable Lung Cancer.** *N Engl J Med* 2018; 378(21):1976-1986

**Summary**

Surgical management of NSCLC is infrequently coupled with systemic treatment. Adjuvant chemotherapy provides modest outcomes in a select few. In a pilot study, patients with stage I-IIIa NSCLC were recruited to receive two pre-operative doses of nivolumab (3mg/kg) prior to resection of their tumour. Following the removal of 21 tumours, 20 of which were completely removed, 9 out of 20 underwent a major pathological response (45%) meaning 10% or less of the tumour at pathological review was viable. Response could be predicted based on tumour mutational burden. Those with the highest (TMB) correlated with a major pathological response compared to those with lower levels. Evidence of T cell priming was also shown in an individual case where specific T cell clones against anti-tumour neo-antigens expanded in the circulation following anti-PD1 therapy. Also see the NADIM study (recommended text), an unrelated phase II single arm study utilizing nivolumab with CT both pre- and post surgery up to 1 year. Early data has suggested a complete response rate of 62% in 13 cases, although this requires further maturation.

**Comments**

1. Pathological responses have been seen in less cases (approximately 20%) who received neoadjuvant CT, which correlated with survival.
2. Maturation of this study is necessary in order to observe a survival benefit, but results are encouraging.
3. Pathological response did not correlate with radiological response but it did with TMB.
4. Priming of anti-tumour T cells could help target cancer cells elsewhere (micrometastases).
5. No delays to surgery occurred.

**OVERALL SURVIVAL WITH DURVALUMAB AFTER CHEMORADIOTHERAPY IN STAGE III NSCLC (PACIFIC)**

Antonia SJ, Villegas A, Daniel D et al. **Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC.** *N Engl J Med* 2018; 379(24):2342-2350

**Summary**

The rationale of combining radiation therapy with immune checkpoint inhibition is best exemplified by the multinational phase III PACIFIC clinical trial. 713 patients were recruited with unresectable stage III NSCLC, to receive 2 cycles of platinum based chemotherapy concurrently with definitive doses of radiation therapy followed by either the anti-PD-L1 monoclonal antibody durvalumab (10mg/kg) (n=473) or placebo (n=236) up to 12 months. At 24 months

follow up overall survival (OS) was reported at 66.3% vs. 55.6% ( $p=0.005$ ) in favour of durvalumab. Median OS was not reached in the immunotherapy arm [(95% CI=34.7-NR) vs. 28.7m (95% CI=22.9-NR), HR=0.68,  $p=0.0025$ ]. Median PFS was 17.2m vs. 5.6m (HR=0.51) in favour of durvalumab. Grade 3 or more toxicity was marginally higher in the immunotherapy arm (30.5% vs. 26.1%).

#### Comments

1. This is a practice changing study.
2. Median OS has still not been reached in the immunotherapy arm as the survival arm begins to plateau.
3. All pre-specified subgroups derived benefit.
4. New sites of disease were less frequent in the durvalumab arm, most common being lung.
5. Median time to death / distant metastases was longer in the durvalumab arm (28.3m v 16.2m, HR 0.53).

### PEMBROLIZUMAB PLUS CHEMOTHERAPY IN METASTATIC NON-SMALL-CELL LUNG CANCER, KEYNOTE 189

Gandhi L, Rodriguez-Abreu D, Gadgeel S et al. **Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer.** *N Engl J Med* 2018; 378(22): 2078-2092

#### Summary

In treatment-naïve patients with advanced (stage IIIB/IV) non-squamous NSCLC, no known sensitizing EGFR/ALK alterations have been shown to benefit from combination immune checkpoint blockade and chemotherapy. This multinational, randomized clinical study recruited 616 patients to 4 cycles of pemetrexed + platinum followed by either pembrolizumab (200mg, every 3 weeks) or placebo and maintenance pemetrexed. Crossover was permitted to the immunotherapy arm in the those who progressed. 12 month survival was superior in the pembrolizumab arm; 69.2% vs. 49.4% (HR=0.49,  $p<0.001$ ). Grade 3 or greater adverse events were similar in both arms; 67.2% v 65.8% respectively. Benefit was seen in all levels of PD-L1 expression, with the greatest survival seen at 50% or more expression.

#### Comments

1. This is a change of practice study combining anti-PD1 therapy with chemotherapy.
2. A trial comparing frontline pembrolizumab monotherapy with combination is needed.
3. Survival curves begin to plateau at time of analysis.
4. Grade 3 of greater toxicity profile similar between the groups.
5. Intracranial response not measured as patients excluded with cerebral metastases.

### BRIGATINIB VERSUS CRIZOTINIB IN ALK-POSITIVE NON

### SMALL CELL LUNG CANCER, ALTA-1L

Camidge DR, Kim HR, Ahn MJ et al. **Brigatinib versus crizotinib in ALK-positive non small cell lung cancer.** *N Engl J Med* 2018; 379(21): 2027-2039

#### Summary

Targeted therapy against the fusion product of the EML4-ALK translocation has revolutionized treatment and prognosis in this small group of lung cancer patients. Further generations of ALK inhibitors, proven beneficial in crizotinib resistant disease, are demonstrating superior survival advantages in the frontline setting such as in this phase III clinical trial comparing the next generation ALK inhibitor, brigatinib, with crizotinib in patients with NSCLC (stage IIIB/IV) harbouring translocations in ALK. 275 patients with ALK translocated disease were randomized (1:1) to either brigatinib (180mg od) or crizotinib (250mg bd). Crossover into the brigatinib arm was permitted at progression. At the first interim analysis, 12 month progression-free survival (PFS) was superior in the brigatinib arm (67% vs. 43%, HR=0.49,  $P<0.001$ ). Benefits were also seen in overall response rate (71% vs. 60%) including intracranial response (78% vs. 29%).

#### Comments

1. Patient characteristics consistent with previous studies.
2. 27% of patients received chemotherapy prior to study participation, however all were ALK targeted TKI naïve.
3. HR of 0.20 in patients with baseline brain metastases.
4. 12 month duration of response superior in brigatinib arm (75 v 41%).
5. 29% of the total cohort had brain metastases.

### FIRST-LINE ATEZOLIZUMAB PLUS CHEMOTHERAPY IN EXTENSIVE-STAGE SMALL-CELL LUNG CANCER

Horn L, Mansfield AS, Szczesna A et al. **First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer.** *N Engl J Med* 2018; 379(23):2220-2229

#### Summary

Standard of care in SCLC constitutes chemotherapy offering excellent initial response rates but inevitable progression of the disease in many. Anti PD-L1 therapy has been tested across several tumour types with success. This randomized phase III study recruited patients to receive etoposide and carboplatin with either placebo (n=202) or atezolizumab (n=201) until disease progression or intolerable toxicity. Median overall survival was reported to be 12.3m vs. 10.3m in favour of atezolizumab (HR=0.70,  $p=0.007$ ). PFS was also superior (5.2m vs. 4.3m, HR=0.77,  $p=0.02$ ). Similar toxicity profile

between the two groups.

#### Comments

1. No difference in survival was observed between patients with treated brain metastases and not, although numbers assessed were low.
2. Older patients (>65) performed better.
3. Tumour mutational burden was not predictive of response.

#### OTHER ARTICLES OF INTEREST

Lopes G et al. **Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS)  $\geq$  1%: Open-label, phase 3, KEYNOTE-042 Study.** *Journal of Clinical Oncology* 2018 36:18\_suppl, LBA4-LBA4

Borghaei H et al. **24-Month Overall Survival from KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin with or without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous Non-Small Cell Lung Cancer.** *J Thorac Oncol* 2019; 14(1):124-129

Papadimitrakopoulou V. A et al. **IMpower132: PFS and Safety Results with 1L Atezolizumab + Carboplatin/ Cisplatin + Pemetrexed in Stage IV Non-Squamous NSCLC.** Presented at: International Association for the Study of Lung Cancer's (IASLC) 2018 World Conference on Lung Cancer (WCLC); 2018 Sept 23-26; Toronto, Ont, Canada. Abstract #OA05.07

Socinski MA et al. **Atezolizumab for the first line treatment of metastatic non-squamous NSCLC.** *N Engl J Med* 2018, 378(24):2288-2301

Cappuzzo et al. **IMpower130: Progression-free survival (PFS) and safety analysis from a randomised phase III study of carboplatin + nab-paclitaxel (CnP) with or without atezolizumab (atezo) as first-line (1L) therapy in advanced non-squamous NSCLC.** Presented at: ESMO congress; 2018 Oct 22; Munich, Germany Abstract # LBA 53

Paz-Ares L et al. **Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer.** *N Engl J Med* 2018; 379(21):2040-2051

Rizvi et al. **Durvalumab with or without tremelimumab vs platinum based chemotherapy as first-line treatment for metastatic non-small cell lung cancer: MYSTIC.** Presented at: ESMO Immuno-Oncology Congress, 2018 Dec 13; Geneva, Switzerland, Abstract LBA6

Nakamura A et al. **Phase III study comparing gefitinib monotherapy (G) to combination therapy with gefitinib, carboplatin, and pemetrexed (GCP) for untreated patients (pts) with advanced non-small cell lung cancer (NSCLC) with EGFR mutations (NEJ009).** Presented at: ASCO Annual Meeting; 2018 Jun 1-5; Chicago, IL

Horn et al. **Ensartinib (X-396) in ALK-Positive Non-Small Cell Lung Cancer: Results from a First-in-Human Phase I/II, Multicenter Study.** *Clin Cancer Res* 2018; 24(12):2771-2779

Novello S et al. **Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study.** *Ann Oncol* 2018; 29(6):1409-1416

Provencio-Pulla et al. **Neoadjuvant chemo/immunotherapy for the treatment of stages IIIA resectable non-small cell lung cancer (NSCLC): A phase II multicenter exploratory study.** *NADIM study-SLCG*, 10.1200/JCO.2018.36.15\_suppl.8521

## PALLIATIVE MEDICINE

Rebecca Aslakson, MD, PhD, FAAHPM, FCCM

\*May Hua, MD, MSc will present this talk in place of Rebecca Aslakson

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## FAMILY SUPPORT IN THE ICU

White DB, Angus DC, Shields AM, Buddadhumaruk P, Pidro P, Paner C, Chaitin E, Chang CCH, Pike F, Weissfeld L, Kahn JM, Darby JM, Kowinsky A, Martin S, Arnold RM. **A randomized trial of a family-support intervention in Intensive Care Units.** *NEJM* 2018; 378 (25): 2365-2375.

## Summary

Data suggest frequent suboptimal communication between ICU clinicians and surrogate decision makers (SDMs) and significant SDM psychological distress. Evidence-based approaches to ameliorate family distress and facilitate surrogate decision making are scarce. Implementing an intervention grounded in modern decision theory and designed to address SDM affective and cognitive challenges, the PARTNER trial used a multi-center, stepped-wedge, cluster-randomized-by-ICU study design to compare a multi-component family support intervention delivered by the ICU team with usual care. The primary outcome was SDM psychological symptoms 6 months after patient hospital discharge. In the intervention arm, extensively-trained ICU nurses provided daily, protocolized check-ins with families; arranged interdisciplinary family meetings (IDFMs) within 48 hours of ICU admission and every 5 days after; and prepared family before and after each IDFM. With good intervention fidelity and blinding of outcome assessors, 1420 severely-ill ICU patients were enrolled with no significant differences detected between study arms in the primary outcome. The intervention was associated with increased ICU mortality (1.43,  $p=0.001$ ) but not 6-month mortality (OR=1.18,  $p=0.17$ ). Secondary outcomes of Quality of Communication and Patient Centeredness scores improved in the intervention arm. Among decedents, the intervention was associated with shorter mean ICU length-of-stay (4.4 vs. 6.8 days).

## Comments

1. The PARTNER trial leveraged existing ICU nurses, rather than adding new clinicians or facilitators.
2. The PARTNER intervention was associated with shorter ICU and hospital length-of-stay (6.7 vs. 7.4 days,  $P=0.045$  and 10.4 vs 13.5 days,  $P<0.001$ , respectively), with the decrease mediated by the shortened ICU LOS among decedents.
3. These findings are consistent with the results of two other recent trials that did not find family psychological outcomes associated with either presence of a communication facilitator (Curtis JR et al, *Am J Resp Crit Care Med* 2016) or delivery of

proactive prognostic communication from a palliative care specialist (Carsons et al, *JAMA* 2016).

4. In-hospital mortality was higher in the intervention arm (OR=1.43 [1.10-1.87],  $P=0.001$ ) but 6 month mortality was unchanged between study arms (OR=1.18 [0.93-1.5],  $P=0.17$ ).
5. Across study arms, only 1-2.6% of patients were living independently at 6 months following hospital discharge.

## CBT FOR PREVENTION OF PTSD

Wade DM, Mouncey PR, Richards-Belle A, Wulff J, Harrison DA, Sadique Z, Grieve RD, Emerson LM, Mason AJ, Aaronovitch D, Als N, Brewin CR, Harvey SE, Howell DCJ, Hudson N, Mythen MG, Smyth D, Weinman J, Welch J, Whitman C, and Rowan KM. Effect of a nurse-led preventive psychological intervention on symptoms of posttraumatic stress disorder among critically ill patients: a randomized clinical trial. *JAMA* 2019; 321(7):665-75.

## Summary

Previous research supports a high incidence of post-traumatic stress disorder (PTSD) among ICU survivors and that cognitive behavioral therapy (CBT) approaches have been effective in mitigating stress and PTSD symptoms in other populations. The team developed and tested effectiveness of a nurse-led, complex psychological intervention (POPPI) for critically ill patients that involved (1) promotion of a therapeutic environment surrounding the patient (optimize sleep, reduce noise, improve patient orientation, increase family involvement) and (2) provision of up to three one-to-one, 30-minute CBT stress support sessions for ICU patients scoring poorly on the Intensive care Psychological Assessment Tool and which were delivered by highly-trained ICU nurses. The primary outcome was mean patient-reported PTSD symptom severity with pre-specified secondary outcomes of days alive and free from sedation to day 30, ICU length-of-stay, mood symptoms, and health-related quality of life. In a parallel-group, cluster-randomized-by-ICU clinical trial conducted in 24 ICUs in the United Kingdom, 1458 patients were enrolled from Sept 2015 to Jan 2016. With 79.3% follow-up at six months, the results supported no significant differences between treatment arms in primary or secondary outcomes. Post hoc analysis suggested potential dose-related effect with reduction in anxiety (STAI-6) among patients who received all 3 CBT sessions.

## Comments

1. ICU nurses were trained to deploy a complex psychological support intervention rooted in Cognitive Behavioral Therapy for ICU patients with stress symptoms.
2. In a large, multi-site, cluster-randomized, intention-to-treat, randomized trial, the intervention of the promotion of a therapeutic environment around the patient and deployment of nurse-delivered Cognitive Behavioral Therapy for stressed ICU patients did not improve PTSD symptoms, days alive from sedation, ICU length-of-stay, mood symptoms, and/or health-related quality of life.
3. Among stressed patients in the ICU in the study, 63.7% received 3 CBT sessions, 16.6% received 2 sessions, 10.6% received 1 session, and 9.0% received 0 sessions.
4. Explanation for the negative study results could include: innate treatment ineffectiveness, incomplete training of ICU nurses in the CBT techniques, insufficient treatment dose, suboptimal timing of treatment and/or choice of a population unlikely/unable to optimally benefit from the treatment.

## SITE OF DEATH

Teno JM, Gozalo P, Trivedi AN, Bunker J, Lima J, Ogarek J, Mor V. **Site of death, place of care, and health care transitions among US Medicare beneficiaries, 2000-2015.** *JAMA* 2018; 320(3):264-71.

### Summary

For nearly two decades, JM Teno and collaborators have used Medicare enrollment and claims data and nursing home assessment data from the Centers for Medicare & Medicaid Services (CMS) Minimum Data Set to track site of death, place of care, and health care trajectory among Medicare U.S. decedents; previous reports were published in 2003 and 2013. This publication updates the dataset to include data points of 2000, 2005, 2009, 2011, and 2015. Results were summarized across 1,361,879 decedents with Medicare fee-for-service (MFS) from 2000-2015 and 871,845 decedents with Medicare Advantage (MA) from 2011-2015. Among MFS decedents, mean age at death increased from 81.9 in 2000 to 83.5 in 2015 and MA decedents had a mean age at death of 82.0 in 2011 and 82.1 in 2015. Among MFS decedents from 2000 to 2015, hospice services at time of death increased from 21.6% to 50.4%, but ICU use during the last 30 days-of-life increased from 24.3% to 29.1% in 2011 and stayed stable at 29.0% in 2015. Among MFS decedents, patients with health care transitions during the last 3 days-of-life increased from 10.3% in 2000 to 14.2% in 2009 but then subsided to 11.2% in 2011 and 10.8% in 2015.

### Comments

1. From 2000 to 2015, fewer MFS decedents died in an acute care hospital (32.6% to 19.8%) and more utilized hospice services at time of death (21.6% to 50.4%).
2. Though hospice use from 2000-2015 among MFS decedents increased, the rate of ICU use during the last month of life also increased from 2000-2009 (24.3% to 29.2%) and stayed stable from 2009 to 2015 (29.2% to 29.0%).

3. Though the MA dataset (2011-2015) was smaller than the MFS dataset (2000-2015), findings were similar between the datasets for the available and concurrent time periods although MA decedents were less likely to die in a nursing home, more likely to die at home or in a community setting, and less likely to be hospitalized during the last 30 and 90 days-of-life (9.3% reduction of hospitalization in last 30 days-of-life between MA and MFS groups in 2015).
4. In 2015, among MFS decedents with a late hospice referral (< 3 days before death), 42.9% were admitted directly from a hospitalization involving an ICU stay.

## UNDERTREATMENT OF ICU DYSPNEA

Gentzler ER, Derry H, Ouyang DJ, Lief L, Berlin DA, Xu CJ, Maciejewski PK, Prigerson HG. **Underdetection and undertreatment of dyspnea in critically ill patients.** *Am J Resp Crit Care Med.* 2018 Nov 28. Epub ahead of print.

### Summary

The prevalence and management of ICU-related dyspnea and pain are unclear. At a single, urban, academic center from June 2016-April 2018, this team completed an observational study evaluating dyspnea and pain prevalence and management among 138 hospitalized patients who were admitted to the MICU, fluent in English, and able to consent or having a caregiver proxy for consent. In total, 144 of 207 eligible patients (69.6%) were enrolled with 101 caregivers and 46 of 50 (92%) ICU nurses enrolled. Within a half-hour of each other, the patient, caregiver, and nurse were daily asked to rate the patient's dyspnea and pain on a 0-10 Numeric Rating Scale (NRS) for each symptom. Data on nurse medication administration for the following 12 hours were abstracted from the medical record. An NRS of  $\geq 4$  for either symptom was considered to be "significant." Among patients, 47% and 41% reported significant dyspnea and pain, respectively. In contrast, 61% and 46% of caregivers and 34% and 22% of nurses reported patients having significant dyspnea and pain, respectively. As compared to patients with non-significant nurse-rated pain, patients with significant nurse-rated pain were 2.7 times more likely to get opioids. Patients with significant nurse-rated dyspnea were not more likely to get opioids (OR=0.72, [0.35, 1.46]). Caregiver ratings of dyspnea correlated better with patient ratings (kappa=0.19,  $p<0.001$ ) as compared to nurse-patient ratings correlation (kappa=0.19,  $p=0.39$ ).

### Comments

1. In this single site, observational study, a high proportion (47%) of MICU patients had significant self-rated dyspnea and as compared to nurse ratings, caregiver ratings of patient dyspnea were more accurate (kappa=0.19,  $p<0.001$  versus kappa=0.19,  $p=0.39$ ).
2. In total, 89 of the 138 study patients (65%) were receiving mechanical ventilation (by tracheostomy or endotracheal tube) at the time of the study with 19% of these patients able to rate their own symptoms.
3. Detection of dyspnea did not increase patient likelihood of receiving opioids (OR=0.72 [0.35,1.46]) nor administration of

benzodiazepines, inhaled bronchodilators, ventilator adjustments, supplemental oxygen, or respiratory device changes.

- Nurses were more likely to report difficulty in managing patient dyspnea as compared to managing patient pain (76% vs. 61%,  $p = 0.01$ ).

## END OF LIFE SPENDING

Einav L, Finkelstein A, Mullainathan S, Obermeyer Z. **Predictive modeling of U.S. health care spending in late life.** *Science* 2018 Jun 29; 360(6396): 1462-65.

### Summary

While end of life care spending is often denigrated as “wasteful,” the actual situation is more nuanced. Measuring prospective (“ex ante”) spending provides a different picture than retrospective (“ex post”, the typical approach) spending. Using a methodologically rigorous, machine-learning algorithm to generate prospective predicted mortality for a random sample of 6 million 2008 Medicare enrollees, this team analyzed yearly Medicare spending as compared to either predicted (“ex ante”) or actual (“ex-post”) mortality. Using an “ex-post” approach, 5% of Medicare decedents accounted for 21% of Medicare spending. Yet, even with methodologically-rigorous modeling, prognostic predictability of death was poor; in the authors’ words, “there is no sizable mass of people for whom death is certain (or even near certain).” 90% of actual decedents were prospectively estimated to have a <50% mortality. Individuals with high (>46% likelihood) predicted one-year mortality accounted for <5% of spending. Rather, most spending was by individuals with low predicted mortality who became sick and being “sick,” this group had a higher mortality. Even when using an “oracle” prediction model informed by actual patient outcomes and with an AUC of 0.96, individuals with a “high” predicted mortality of >47% still only accounted for 5% of total spending.

### Comments

- While end of life care is often denigrated as “wasteful,” the actual situation is far more complex and nuanced.
- The majority of Medicare spending is on patients who become sick and then these sick patients have a higher mortality.
- When viewed prospectively, being “sick” is a confounder that explains most of the high costs attributed to decedents.
- High costs attributed to decedents are exacerbated by a framing effect where the defined time-point of “death” accounts for spending in the twelve months prior and thus is more likely to account for a time of intense, and costly, patient sickness.
- Better predictive models are unlikely to meaningfully inform end of life care-associated spending as even with an abnormally prescient “oracle” prediction model, prospective predictability of actual patient death did not yield a sufficiently high predicted mortality which could account for a majority of Medicare spending.

## OTHER ARTICLES OF INTEREST

### Family Support in the ICU

Azoulay E, Forel JM, Vinatier I, et al. **Questions to improve family-staff communication in the ICU: a randomized controlled trial.** *Intensive Care Med* 2018; 44:1879-1887.

McIlroy PA, King RS, Garrouste-Orgeas M, Tabah A, Ramanan M. **The effect of ICU diaries on psychological outcomes and quality of life of survivors of critical illness and their relatives: a systematic review and meta-analysis.** *Crit Care Med* 2019; 47(2):273-279.

Kleinpell R, Heyland DK, Lipman J, Sprung CL, Levy M, Mer M, Koh Y, Davidson J, Taha A, Curtis JR, **Council on the World Federation of Societies of Intensive and Critical Care Medicine. Patient and family engagement in the ICU: Report from the task force of the World Federation of Societies of Intensive and Critical Care Medicine.** *J Crit Care* 2018; 48:251-256.

Wendlandt B, Ceppe A, Choudhry S, Nelson JE, Cox CE, Hanson LC, Danis M, Tulsy JA, Carson SS. **Risk factors for post-traumatic stress disorder symptoms in surrogate decision-makers of patients with chronic critical illness.** *Ann Am Thorac Soc* 2018; 15(12):1451-1458.

### Palliative Care: Both Primary and Specialist

Barkley JE, McCall A, Maslow AL, Skudlarska BA, Chen X. **Timing of palliative care consultation and the impact on thirty-day readmissions and inpatient mortality.** *Journal Palliat Med* 2018, epub ahead of press.

Cox CE, Hough CL, Carson SS, White DB, Kahn JM, Olsen MK, Jones DM, Somers TJ, Kelleher SA, Porter LS. **Effects of a telephone- and web-based coping skills training program compared with an education program for survivors of critical illness and their family members. A randomized clinical trial.** *Am J Respir Crit Care Med* 2018; 197(1):66-78.

Hoerger M, Greer JA, Jackson VA, Park ER, Pirl WF, El-Jawahri A, Gallagher ER, Hagan T, Jacobsen J, Perry LM, Temel JS. **Defining the elements of early palliative care that are associated with patient-reported outcomes and the delivery of end-of-life care.** *J Clin Oncol* 2018; 36(11): 1096-1102.

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ered by a self-directed mobile app and by telephone compared with an education programme for survivors of critical illness: a pilot randomized clinical trial. *Thorax* 2019; 75(1):33-42.

#### End of Life, Decision-Making, and Goal-Concordant Care

Cox CE, White DB, Hough CL, Jones DM, Kahn JM, Olsen MK, Lewis CL, Hanson LC, Carson SS. **Effects of a personalized web-based decision aid for surrogate decision makers of patients with prolonged mechanical ventilation: a randomized clinical trial.** *Ann Intern Med* 2019 Jan 29, epub ahead of print.

Gershon AS, Maclagan LC, Luo J, To T, Kendzerska T, Stanbrook MB, Bourbeau J, Etches J, Aaron SD. **End-of-life strategies among patients with advanced chronic obstructive pulmonary disease.** *AJRCCM* 2018; 198(11):1389-1396.

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Sanders JJ, Curtis JR, Tulsy JA. **Achieving goal-concordant care: a conceptual model and approach to measuring serious illness communication and its impact.** *J Palliat Med* 2018; 21 (S2): S17-S27.

Kerckhoffs MC, Kant M, van Delden JJM, Hooft L, Kesecioglu J, van Dijk D. **Selecting and evaluating decision-making strategies in the intensive care unit: a systematic review.** *J Crit Care* 2019; 51:39-45.

#### Patient Stress and Symptom Support

Khandelwal N, Hough CL, Downey L, Engelberg RA, Carson SS, White DB, Kahn KM, Jones DM, Key MD, Reagan W, Porter LS, Curtis JR, Cox CE. Prevalence, risk factors, and outcomes of financial stress in survivors of critical illness. *Crit Care Med* 2018; 46(6):e530-e539.

Wilson ME, Majzoub AM, Dobbler CC, Curtis JR, Nayfeh T, Thorsteinsdottir B, Barwise AK, Tilburt JC, Gajic O, Montori VM, Murad MH. **Noninvasive ventilation in patients with do-not-intubate and comfort-measures-only orders: a systematic review and meta-analysis.** *Crit Care Med* 2018; 46(8): 1209-1216.

#### ICU Utilization

Burnham JP, Chi S, Ma J, Dans MC, Kollef MH. **Reduction in antimicrobial use among medical intensive care patients during a randomized crossover trial of palliative care consultation.** *Infect Control Hosp Epidemiol* 2019; Mar 6 epub ahead of print.

Ramos JGR, Ranzani OT, Perondi B, Dias RD, Jones D, Carvalho CRR, Velasco IT, Forte DN. **A decision-aid tool for ICU admission triage is associated with a reduction in potentially inappropriate intensive care unit admissions.** *J Crit Care* 2019; 51:77-83.

#### 4th Edition Clinical Practice Guidelines for Quality Palliative Care

National Consensus Project for Quality Palliative Care. Clinical Practice Guidelines for Quality Palliative Care, 4th edition. Richmond, VA: **National Coalition for Hospice and Palliative Care**; 2018. <https://www.national-coalition-hpc.org/ncp>.

Ahluwalia SC, Chen C, Raaen L, Motala A, Walling AM, Chamberlin M, O'Hanlon C, Larkin J, Lorenz K, Akinniranye O, Hempel S. **A systematic review in support of the National Consensus Project Clinical Practice Guidelines for Quality Palliative Care, Fourth Edition.** *J Pain Sympt Manage* 2019; 56(6): 831-870.

#### PCOR Research

Feemster LC, Saft HL, Bartlett SJ et al. **Patient-centered outcomes research in pulmonary, critical care, and sleep medicine. An official American Thoracic Society Workshop Report.** *Ann Am Thorac Soc* 2018; 15(9):1005-1015.

## UPDATE ON PULMONARY VASCULAR DISEASES

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## CLINICAL CLASSIFICATION OF PULMONARY HYPERTENSION

Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis M, Krowka M, Williams PG, Souza R. **Haemodynamic definitions and updated clinical classification of pulmonary hypertension.** *European Respiratory Journal* 2018.

### Summary

Since the 1st World Symposium on Pulmonary Hypertension (WSPH), pulmonary hypertension (PH) has been defined as mean pulmonary arterial pressure (mPAP)  $\geq 25$  mmHg at rest. Recent data from normal subjects has shown that normal mPAP is  $14.0 \pm 3.3$  mmHg, and two standard deviations above this mean value would suggest  $mPAP \geq 20$  mmHg as above the upper limit of normal. At the 6th WSPH, the definition of PH was changed to acknowledge that  $mPAP \geq 20$  mmHg should serve as the new cut-off. Since mPAP can be affected by cardiac output and fluid balance, it was proposed that pulmonary arterial hypertension (PAH) should be further defined as  $mPAP \geq 20$  mmHg, a pulmonary artery wedge pressure of  $\leq 15$  mmHg and a pulmonary vascular resistance of  $\geq 3$  Woods Units. Regarding clinical classification, the main changes were the inclusion in group 1 of a subgroup “pulmonary arterial hypertension (PAH) long-term responders to calcium channel blockers”, due to the specific prognostic and management of these patients, and a subgroup “PAH with overt features of venous/capillaries (pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis) involvement”, due to evidence suggesting a continuum between arterial, capillary and vein involvement in PAH. Finally, review of the data on use of exercise hemodynamics revealed too many uncertainties to allow the reintroduction of a definition of exercise PH.

### Comments

1. The new definition of PH is  $mPAP \geq 20$  mmHg.
2. The new definition of PAH is  $mPAP \geq 20$  mmHg,  $PAWP \leq 15$  mmHg and  $PVR \geq 3$ WU.
3. A clinically meaningful definition of exercise PH remains to be determined.
4. Thyroid disorders are no longer included in the clinical classification of PH.

## RISK STRATIFICATION AND TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

Galiè N, Channick RN, Frantz RP, Grünig E, Jing ZC, Moiseeva O, Preston IR, Pulido T, Safdar Z, Tamura Y, McLaughlin VV. **Risk stratification and medical therapy of pulmonary arterial hypertension.** *Eur Respir J.* 2019 Jan 24;53(1).

### Summary

For most patients with PAH, early combination therapy has become the standard of care, but the decisions on adjusting existing or adding new medications has become a subject of intense research. The current treatment strategy is based on the severity of the newly diagnosed PAH patient as assessed by a multiparametric risk stratification approach. Different risk stratification tools (REVEAL, French Registry, COMPERA, SPAHR) have become available that integrate clinical, exercise, right ventricular function and hemodynamic parameters to define a low-, intermediate- or high-risk status according to the expected 1-year mortality. This stratification drives the new treatment algorithm for PAH which recommends initial oral combination therapy with an endothelin receptor antagonists and a phosphodiesterase-5 inhibitor for low- or intermediate-risk patients. Patients at high risk should be started on upfront combination therapy and an IV prostacyclin. Patients who achieve low risk status within 3-6 months should be maintained on therapy and followed closely; for patients who remain at intermediate risk, escalation to prostacyclin (i.e. triple therapy) is recommended. Finally, for those patients who fail to improve their risk status on triple therapy, early referral to lung transplantation should be contemplated.

### Comments

1. Patients should be risk stratified at initial and follow up appointments using a risk assessment tool.
2. Patients at low- and intermediate- risk should be started on upfront combination therapy.
3. Initial monotherapy should be considered for patients with very mild disease or who are stable on one agent.
4. Patients with a positive acute vasoreactivity test should be treated with high doses of calcium channel blockers.
5. High risk patients should be treated with triple therapy that includes an IV prostacyclin.

## GENETICS OF PULMONARY ARTERIAL HYPERTENSION

Morrell NW, Aldred MA, Chung WK, Elliott CG, Nichols WC, Soubrier F, Trembath RC, Loyd JE. **Genetics and genomics of pulmonary arterial hypertension.** *Eur Respir J.* 2018 Jan 24;53(1).

### Summary

Based on existing knowledge, around 25–30% of patients diagnosed with idiopathic PAH have an underlying Mendelian genetic cause for their condition. Mutations in *BMPR2* remain the most common cause of hereditary (70–80% of families) and idiopathic (10–20%) PAH. In the last year, whole-genome sequencing of large families and patient cohorts have led to the discovery of new genes associated with PAH (*TBX4*, *ATP13A3*, *GDF2*, *SOX17*, *AQP1*) and *PVOD* (*EIF2AK4*). The role of common genetic variation contributing to the etiology or clinical course of PAH is less well defined and only one GWAS study has been done which detected a locus on *CBLN2* with an OR of 1.97. Regarding disease penetrance, studies looking at epigenetic modifiers such as microRNAs, DNA methylation and histone markers have provided evidence of a sophisticated network of gene regulation in the pulmonary vasculature. The document also addresses genetic testing in PAH patients and recommend that this should be offered to *PVOD/PCH* and selected (hereditary, idiopathic and drug-induced) PAH patients. Genetic education and counselling should be performed prior to genetic testing for PAH to address the complex issues of incomplete penetrance, surveillance, reproductive questions and psychosocial issues.

### Comments

1. *BMPR2* mutations remain the most common cause of hereditary PAH.
2. Prevalence and penetrance of newly discovered gene mutations remains to be determined.
3. *PVOD/PCH* patients should be screened for mutations in *EIF2AK4*.
4. Genetic testing should be considered in patients with family history of PAH and *PVOD/PCH*.

## CHRONIC THROMBOEMBOLIC PULMONARY VASCULAR DISEASE

Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, Ogo T, Tapson VF, Ghofrani HA, Jenkins DP. **Chronic thromboembolic pulmonary hypertension.** *Eur Respir J.* 2018.

### Summary

Chronic thromboembolic disease (CTED) is a new entity characterized by similar symptoms and perfusion defects as chronic thromboembolic pulmonary hypertension (CTEPH) but without PH at rest. At present, there is no evidence that CTED evolves to CTEPH. Cardiopulmonary

exercise tests and echocardiographic evaluations are recommended to exclude patients with other causes for dyspnea (e.g. obesity, deconditioning). Selected patients with CTED may benefit from pulmonary endarterectomy (PEA), but major perioperative complications can occur in 40% of patients. Regarding CTEPH, the new treatment guidelines still recommend anticoagulation and PEA as the treatment of choice. For those deemed inoperable, the recommendation is to use medical therapy (Riociguat) and consider balloon angioplasty (BPA). The place of PH-targeted medical therapy and BPA relative to surgery is dependent on the anatomical distribution of disease and is not fully defined. Using medical therapy as a “bridge to PEA” is more controversial, and is felt to delay timely surgical referral and, therefore, definitive treatment. Patients with symptomatic PH following PEA should receive medical therapy and be considered for BPA or repeat PEA if indicated. Combining endarterectomy with BPA either as a hybrid or stepwise approach is being studied at select centers of excellence.

### Comments

1. CTED is a new clinical entity in which PH is absent but perfusion defects are present.
2. PEA remains the treatment of choice for CTEPH.
3. BPA should be considered in selected cases of inoperable CTEPH.
4. The role for medical therapy as a bridge to PEA remains to be established.

## DRUG AND TOXIN-INDUCED PULMONARY HYPERTENSION

Zamanian RT, Hedlin H, Greuenwald P, Wilson DM, Segal JI, Jordan M, Kudelko K, Liu J, Hsi A, Rupp A, Sweatt AJ, Tuder R, Berry GJ, Rabinovitch M, Doyle RL, de Jesus Perez V\*, Kawut SM\*. **Features and Outcomes of Methamphetamine-associated Pulmonary Arterial Hypertension.** *Am J Respir Crit Care Med.* 2018 Mar 15;197(6):788–800.

### Summary

The classification of PAH associated with drugs and toxins was revised to include drugs with Definite (i.e. data based on outbreaks, epidemiological case–control studies or large multicenter series) and Possible (i.e. multiple case series or cases with drugs with similar mechanisms of action) association. Methamphetamine is now considered a definite cause of PAH (METH-PAH) based on a large series of 90 cases seen at Stanford University over 10 years. Compared to IPAH, METH-PAH patients are less likely to be female, have more severe hemodynamic compromise at diagnosis and worse outcomes. Given reports of PAH associated with drugs routinely used in clinical practice (e.g. tyrosine kinase inhibitors, antiretrovirals, interferons), it is imperative that pharmacovigilance efforts be undertaken to take action and avoid future PAH epidemics.

**Comments**

1. Methamphetamine is a definite cause of PAH
2. A history of drug and toxin exposure should be part of the evaluation of PAH patients.
3. Dasatinib is a definite cause of PAH and should be avoided in patients with risk factors for PH.
4. Pharmacovigilance should play a major role in public health initiatives to prevent outbreaks of drug induced PAH.

**PEDIATRIC PULMONARY VASCULAR DISEASES**

Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S, Ivy DD, Berger RMF. **Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management.** *Eur Respir J.* 2019 Jan 24;53(1).

**Summary**

The Pediatric Task Force of the 6th WSPH chose to follow the new proposed adult definition of PH for pediatric patients.

Based on available genetic data, mutations in TBX4 and ACVRL1 appear enriched in pediatric hereditary and idiopathic PAH. Regarding genetic testing, it was recommended that this should be performed in expert centers with a genetic counselling group. Classification of pediatric PAH was also reviewed to stress differences in etiologies compared to adults. Patients with single ventricle physiology were recognized as an emerging phenotype and was included in group 5 of the clinical classification. Furthermore, separate designations were given to congenital/acquired cardiovascular conditions leading to post-capillary PH (group 2.4), developmental lung disorders (group 3.5), other pulmonary artery obstructions (group 4.2) and complex CHD (group 5.4). Regarding therapy, a trial of endothelin receptor antagonists and PDE5 inhibitors alone or in combination (if patient is considered high risk) is advisable, with further consideration for addition of inhaled or intravenous prostacyclin depending on clinical risk. Finally, the task force acknowledge possible role for palliative therapy with atrial septostomy or Potts shunt but acknowledged that further studies are required to determine how these interventions should be prioritized.

**Comments**

1. Pediatric PAH is defined as mPAP $\geq$ 20mmHg, PAWP $\leq$ 15mmHg and PVR $\geq$ 3WU.
2. Mutations in TBX4 and ACVRL1 are enriched in pediatric hereditary and idiopathic PAH.
3. Clinical classification of pediatric PH includes etiologies different from those of adults.
4. Therapy should be driven on risk stratification and regular clinic assessment.
5. Atrial septostomy and Potts shunt can be considered in selected cases.

**OTHER ARTICLES OF INTEREST**

Mercurio V, Mukherjee M, Tedford RJ, Zamanian RT, Khair RM, Sato T, Minai OA, Torres F, Girgis RE, Chin K, Damico R, Kolb TM, Mathai SC, Hassoun PM. **Improvement in Right Ventricular Strain with Ambrisentan and Tadalafil Upfront Therapy in Scleroderma-associated Pulmonary Arterial Hypertension.** *Am J Respir Crit Care Med.* 2018 Feb 1;197(3):388-391.

Budas GR, Boehm M, Kojonazarov B, Viswanathan G, Tian X, Veeroju S, Novoyatleva T, Grimminger F, Hinojosa-Kirschenbaum F, Ghofrani HA, Weissmann N, Seeger W, Liles JT, Schermuly RT. **ASK1 Inhibition Halts Disease Progression in Preclinical Models of Pulmonary Arterial Hypertension.** *Am J Respir Crit Care Med.* 2018 Feb 1;197(3):373-385.

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Callejo M, Mondejar-Parreño G, Barreira B, Izquierdo-Garcia JL, Morales-Cano D, Esquivel-Ruiz S, Moreno L, Cogolludo Á, Duarte J, Perez-Vizcaino F. **Pulmonary Arterial Hypertension Affects the Rat Gut Microbiome.** *ci Rep.* 2018 Jun 26;8(1):9681.

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Provencher S, Archer SL, Ramirez FD, Hibbert B, Paulin R, Boucherat O, Lacasse Y, Bonnet S. **Standards and Methodological Rigor in Pulmonary Arterial Hypertension Preclinical and Translational Research.** *Circ Res.* 2018 Mar 30;122(7):1021-1032.

## MEDICAL EDUCATION

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## DUTY HOURS

Silber JH, Bellini LM, Shea JA, Desai SV, Dinges DF, Basner M, Even-Shoshan O, Hill AS, Hochman LL, Katz JT, Ross RN, Shade DM, Small DS, Sternberg AL, Tonascia J, Volpp KG, Asch DA. **Patient Safety Outcomes under Flexible and Standard Resident Duty-Hour Rules.** *N Engl J of Med* 2019; 380: 905-14.

## Summary

This cluster randomized noninferiority trial is the primary outcome and patient safety reporting arm of the iCOMPARE (Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education) 2015-2016 investigation of flexible versus standard duty hours for internal medicine (IM) residents. 31 IM residency programs were randomized to standard duty hour restrictions and compared on mortality and safety outcomes to 32 residency programs allowed to use more flexible duty hours (most notably removing the 16-hour restriction on shift length). Program directors (PDs) in the flexible duty-hour arm were given latitude, but not required, to remove limits on shift length and mandatory time between shifts. Difference-in-difference analysis evaluated the primary outcome of unadjusted 30-day mortality change from pretrial year to trial year for both groups. Secondary safety outcomes were also evaluated. The change in 30-day mortality for patients in the flexible programs (12.5 % in trial year vs. 12.6% in pre-trial year) was noninferior to that in the standard programs (12.2% in trial year vs. 12.7% in pre-trial year). The test for noninferiority was significant ( $p=0.03$ ) essentially concluding that giving PDs the opportunity to use flexible duty hours did not harm patients. Most secondary outcomes were also noninferior.

## Comments

1. The results of this noninferiority study suggest that giving program directors discretion to make schedules without continuous duty hour limits did not harm patients or lead to worse outcomes.
2. 30-day mortality and several other patient safety outcomes were not adversely affected, including unadjusted 7-day readmissions, Medicare payments, and AHRQ patient safety indicators (Agency for Healthcare Research and Quality); whilst 30 day readmissions missed the noninferiority threshold, this may be due to the generous and conservative standard afforded a 1% threshold margin in the context of a 61% baseline of prolonged stay in the standard groups.

3. Program directors were permitted but not required to use extended shifts, and the PDs did not use all the latitude offered to them as standard duty hours were maintained for at least some rotations at each institution.
4. This study did not evaluate what happens when trainees work extended shifts.
5. Consideration should be made to re-examine well-intended duty hour shift regulations enabled in 2011.

## ASSESSMENT VALIDATION: MILESTONES

Hauer KE, Vandergrift J, Lipner RS, Holmboe ES, Hood S, McDonald FS. National Internal Medicine Milestone Ratings: Validity Evidence From Longitudinal Three-Year Follow-up. *Acad Med.* 2018 Aug; 93(8): 1189-1204.

## Summary

This retrospective cohort study assessed 35,217 PGY1-PGY3 residents in US IM categorical residency programs in academic years (AY) 2013, 2014, and 2015 in order to further validate milestones via 3 approaches: determination if “not assessable” items decreased over time, reporting of mean longitudinal milestone ratings for individual IM residents over their 3 years of training, and evaluation of the correlation of medical knowledge (MK) milestones in each PGY with certification exam scores to determine predictive validity of milestones to certification exam scores. The results showed a significant trend toward a decreased percentage of residents with any “not assessable” ratings from AY2013 to AY2015 with drops from 22.5% to 16.6% in PGY1s, 12.3% to 8.1% in PGY2s, and 5.1% to 2.6% in PGY3s. PGY1s starting in AY2013 showed an increase in milestones average from PGY1 average of around 3 (range 2.73-3.19) to around 3.5 in PGY2 (range 3.27-3.66) to around 4 in PGY3 (range 4.00-4.22), which was significant ( $p$  trend < 0.001). Both MK1 and MK2 milestones correlated to the 2016 certification exam scores in all 3 PGYs and for each increase of 0.5 units in MK ratings the difference in exam scores for PGY3s was about 19.

## Comments

1. Prior work confirmed validation of the milestones as post graduate year (PGY) increased and correlated end-of-training medical knowledge milestones with certification exam scores, but also revealed that some competencies were “not assessable” and this study addresses prior gaps in knowledge.

2. Together these 3 approaches support the argument that milestones are a valid method to rate resident performance in the overall context of competency based medical education.
3. The milestones can influence curriculum development as items “not assessable” dropped over time suggesting that programs can alter the curriculum and clinical assignments to enable increased milestone visualization.
4. This study extends prior certification exam score correlation from final end-of-training assessment and allows the opportunity for early intervention in those residents with low medical knowledge scores as early as PGY1; lower MK scores can trigger remediation early in training.
5. Only one measure of performance was correlated in this study to milestones (certification exam score performance) so further correlation with additional measures of performance are still needed.

## EDUCATION ENHANCED PROCEDURE OUTCOMES

Barsuk JH, Cohen ER, Williams MV, Scher J, Jones SF, Feinglass J, McGaghie WC, O’Hara K, Wayne DB. **Simulation-based Mastery Learning for Thoracentesis Skills Improves Patient Outcomes: A Randomized Trial.** *Acad Med.* 2018; 93: 729-735.

### Summary

Physicians-in-training often perform thoracenteses in academic medical centers and complications are more common in less-experienced physicians with iatrogenic pneumothorax (IP) complicating the procedure up to 19% of the time. Two parallel investigations at a single academic medical center from December 2012 to May 2016 were performed. First, a randomized trial compared thoracentesis complication rates amongst second- and third-year internal medicine (IM) residents assigned to the intervention arm where they received thoracentesis simulation-based mastery learning (SBML) education versus traditional training where no simulation training was given. An observational study was also performed and compared the SBML resident group above to thoracenteses performed by traditionally-trained residents, pulmonary, or interventional radiology. 917 thoracenteses were performed on 709 patients noting ultrasound use for each. SBML residents had insignificant differences in clinically meaningful IP, hemothorax, and re-expansion pulmonary edema (REPE) compared with traditionally-trained residents. However, SBML residents had a trend towards lower combined clinically meaningful complications compared with traditionally trained residents (0% vs 7.9%;  $p=0.06$ ) and SBML had significantly lower clinically meaningful IPs compared with combined traditionally-trained residents, pulmonary, and IR referrals ( $p=0.02$ ). When comparing SBML-trained residents with all the other groups, the SBML residents performed thoracentesis with lower combined clinically meaningful complications ( $p=0.008$ ).

### Comments

1. Second- and third-year IM residents who completed the SBML intervention performed procedures with a trend toward lower rates of combined clinically meaningful complications compared with traditionally trained residents and had significantly lower rates of clinically meaningful IP and combined clinically meaningful complications compared to a collective group of traditionally-trained residents and pulmonary and IR physicians.
2. This investigation differed from prior studies because these authors only evaluated the impact of education
3. Significant procedure complications were rare (for example 60 or 6.5% of procedures resulted in IP, of which only 7 or 11.6% were clinically meaningful) so no multivariate analysis could be used to control comparisons of performer group for potentially significant patient risk factors.
4. This was a single center study so applicability may be limited.
5. SBML appears to be a compelling way to teach high stakes procedures and adds to the growing body of evidence that shows medical education can be a powerful quality improvement tool.

## INTERVENTIONS TO PREVENT AND REDUCE PHYSICIAN BURNOUT

West CP, Dyrbye LN, Erwin PJ, Shanafelt TD. **Interventions to prevent and reduce physician burnout: a systematic review and meta-analysis.** *Lancet.* 2016; 388: 2272-81.

### Summary

Physician burnout has reached widespread levels and threatens patient care, professionalism, healthcare provider safety, and healthcare systems. This oft-cited systematic review and meta-analysis identified multiple interventions that could prevent and reduce physician burnout. The authors required studies to provide physician-specific burnout data using validated burnout measures from commonly accepted sources of evidence. Studies including medical students and non-physician health-care providers were excluded. Outcomes evaluated included changes in overall burnout, emotional exhaustion, and depersonalization. 15 randomized control trials (RCTs) and 37 cohort studies met eligibility criteria. From these studies, multiple interventions proved effective, including both structural and organizational interventions, in addition to individual-focused strategies. Organizational or structural interventions that showed improvement included clinical work process modifications and reductions in work length or duration, U.S. duty hour requirements, and practice delivery changes. Individual-focused interventions showing benefits included communications training, self-care training, mindfulness based approaches, small group curricula, stress management, and interventions that included increased support group initiatives including belonging interventions. Some studies included funding to cover physician to join these interventions during the workday. This investigation supports the notion that BOTH individual-focused and structural or organizational strategies can result in meaningful reductions in physician burnout.

## Comments

1. Validated and meaningful interventions to reduce physician burnout exist.
2. It appears that physician burnout could be best reduced when multifaceted interventions are applied from the individual as well as organizational perspectives.
3. Further research is needed to determine how best to combine or amalgamate individual and organizational changes together.
4. Further research is needed to identify which interventions are most effective for which populations.
5. As medical educators we are poised and situated in a position to help implement these strategies.

## ASSESSMENT AND FEEDBACK

Watling CJ, Ginsburg S. **Assessment, feedback and the alchemy of learning.** *Med Educ.* 2019; 53: 76-85.

### Summary

This literature review and forward-thinking proposal for future assessment and feedback consideration asks the reader to imagine a medical education world that concomitantly uses feedback and evaluation to assess learner performance while simultaneously asking it to deliver coaching to improve learning. Numerous landmark articles pertaining to evaluation, assessment, and feedback are cited and reviewed which further strengthen the claims and “asks” within. The lines between assessment and feedback are blurred in medical education often so an attempt is made to reconcile the tensions and difficulties faced when trying to amalgamate feedback and the “judging” of performance with coaching for improvement. Multiple concerns of feedback are reviewed and explored as feedback delivered with formative intent is often perceived by learners as summative. Learners are also afraid to fail when they feel their performance is being judged. Saving face is important to learners and more observations can lead to more opportunities to “lose face.” Learners would need to feel “safe to fail” to further explore the boundaries of their knowledge. With all this mentioned, the authors ask us to consider an alchemistic world where robust assessment of learner competence is combined with coaching in low stakes enterprises to enhance learner development.

### Comments

1. The evaluation of performance is critical to assessment but in of itself is not the only driver or absolute entity of assessment.
2. Assessment should also generate meaningful feedback to help guide learning and lead to learner improvement.
3. Multiple tensions exist to combine assessment of learner competence and coaching for learner development.
4. Learner perceptions that they must perform well can hinder learning and limit the boundaries, so making room in our curricula for low stakes or “zero-stakes” moments such as that which can be found in medical simulation experiences, could support more effective learning.
5. As medical educators we should consider a world of alchemistic assessment where assessment and feedback are blended to promote a culture of improvement rather than that of just performance.

## OTHER ARTICLES OF INTEREST

### Assessment and Evaluation

Holt KD, Miller RS, Vasiliadis J, Byrne LM, Cable C, Grosso L, Bellini LM, McDonald FS. **Relationships Between the ACGME Resident and Faculty Surveys and Program Pass Rates on the ABIM Internal Medicine Certification Examination.** *Acad Med.* 2018 Aug; 93(8): 1205-1211.

Kinnear B, Warm EJ, Hauer KE. **Twelve tips to maximize the value of a clinical competency committee in post-graduate medical education.** *Med Teach.* 2018 Nov; 40(11): 1110-1115.

Schumacher DJ, King B, Barnes MM, Elliott SP, Gibbs K, McGreevy JF, Del Rey JG, Sharma T, Michelson C, Schwartz A; Members of the APPD LEARN CCC Study Group. **Influence of Clinical Competency Committee Review Process on Summative Resident Assessment Decisions.** *J Grad Med Educ.* 2018 Aug; 10(4): 429-437.

### Burnout

O'Connor AB, Halvorsen AJ, Cmar JM, Finn KM, Fletcher KE, Kearns L, McDonald FS, Swenson SL, Wahi-Gururaj S, West CP, Willett LL. **Internal Medicine Residency Program Director Burnout and Program Director Turnover: Results of a National Survey.** *Am J Med.* 2019 Feb; 132(2): 252-261.

### Competency Based Curricula

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