

American Thoracic Society International Conference

# CLINICAL YEAR IN REVIEW



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**May 19 - May 24**  
**Washington, DC**  
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Daniel Brodie, MD

Columbia University Medical Center/New York-Presbyterian Hospital  
Department of Medicine  
New York, NY**POSTEXTUBATION HIGH-FLOW NASAL CANNULA TO PREVENT REINTUBATION**

Hernandez G, Vaquero C, Gonzalez P, Subira C, Frutos-Vivar F, Rialp G, Laborda C, Colinas L, Cuenca R, Fernandez R. **Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: a randomized clinical trial.** *JAMA* 2016; 315(13): 1354-1361.

**Summary**

Hypoxemia after planned extubation is common and reintubation may be required in some patients. Noninvasive ventilation appears to decrease the risk of reintubation in patients who are at high risk for this outcome. High-flow nasal cannula (HFNC) reduced reintubation after cardiac surgery and in a general critical care population. Whether HFNC reduces the rate of reintubation in a low-risk population is unknown. This multicenter, randomized, controlled trial in seven intensive care units in Spain, enrolled 527 adults who fulfilled criteria for planned extubation and were at low risk for reintubation, as predefined by the investigators. Low risk criteria included: age below 65 years, adequate secretion management, and absence of heart failure or moderate-to-severe COPD. Patients who had passed a spontaneous breathing trial after receiving invasive mechanical ventilation for more than 12 hours were randomized to HFNC or conventional oxygen therapy administered immediately after extubation, and for 24 hours thereafter. Major exclusion criteria included do-not-resuscitate orders as well as accidental and self-extubations. The primary outcome, reintubation within 72 hours, was less common in the HFNC group [4.9% vs. 12.2% in the conventional group; absolute difference, 7.2% (95%CI, 2.5% to 12.2%);  $P = .004$ ]. The number of patients needed to treat to prevent one reintubation with HFNC was 14 (95%CI, 8 to 40). The secondary outcome of postextubation respiratory failure was less common in the HFNC group (8.3% vs 14.4%;  $P = .03$ ). Time to reintubation was not different between the groups. All patients tolerated the HFNC and no adverse events were reported.

**Comments**

1. This study demonstrates a clear advantage in using HFNC as compared with conventional oxygen therapy to reduce the risk of reintubation at 72 hours in these low-risk patients after planned extubation.
2. The unusual focus on low-risk patients suggests that even this population, with its already low rate of reintubation, may benefit by driving the reintubation rate down further.
3. Patients with hypercapnia during their spontaneous breathing trial were excluded because, as the authors note, most of their clinicians preferred to use preventive

noninvasive ventilation rather than HFNC or conventional oxygen therapy at the time the trial was designed.

4. A notable limitation is that the clinicians were not blinded to the study group, although the risk of bias was partially mitigated by excluding the investigators from clinical decision-making and predefining criteria for reintubation

**POSTOPERATIVE NONINVASIVE VENTILATION TO PREVENT REINTUBATION**

Jaber S, Lescot T, Futler E, Paugam-Burtz C, Seguin P, Ferrandiere M, Lasocki S, Mimoz O, Hengy B, Sannini A, Pottecher J, Abback P-S, Riu B, Balafia F, Constantin J-M, Masseret E, Beaussier M, Verzilli D, De Jong A, Chanques G, Brochard L, Molinari N: for the NIVAS Study Group. **Effect of noninvasive ventilation on tracheal reintubation among patients with hypoxemic respiratory failure following abdominal surgery: a randomized clinical trial.** *JAMA* 2016; 315(13): 1345-1353.

**Summary**

Post-operative respiratory failure requiring invasive mechanical ventilation (IMV) increases morbidity and mortality. Avoiding IMV may improve outcomes. This multicenter, stratified, randomized, parallel-group clinical trial compared standard oxygen therapy with noninvasive ventilation (NIV) in 293 patients in 20 intensive care units in France. The study included patients who experienced post-operative acute hypoxemic respiratory failure within seven days of abdominal surgery. The primary outcome was tracheal intubation for any cause within seven days following randomization. Parameters for initially setting NIV were standardized. Predefined criteria were used for reintubation. The use of high-flow nasal cannula (HFNC) was not permitted in either group. Reintubation occurred in 33.1% in the NIV group as compared with 45.5% in the standard oxygen therapy group (absolute difference, -12.4%; 95%CI, -23.5% to -1.3%;  $P = .03$ ). NIV was also associated with more invasive ventilator-free days and fewer health care-associated infections (most prominently: a lower rate of intensive care unit-acquired pneumonia). There was a trend toward improved 90-day mortality in the NIV group. There were no significant differences in serious adverse events between the groups.

**Comments**

1. This well-designed, multicenter, randomized controlled trial supports the use of NIV via face mask, in patients with acute hypoxemic respiratory failure after abdominal surgery.
2. The study groups were well balanced after randomization with the exception of a larger percentage of patients with chronic obstructive pulmonary disease (COPD) in the

- NIV group (19.6% vs. 12.6%), which may have biased the results in favor of NIV given what we know about the potential benefits of NIV in COPD patients.
3. Another limitation of this study is the lack of blinding, which was addressed by having predefined criteria for reintubation, yet bias could still have been present.
  4. The main mechanism of benefit in this study is likely the avoidance of invasive mechanical ventilation and the consequent decrease in health care-associated infections, which were led by a decrease in intensive care unit-acquired pneumonia in the NIV group.
  5. The study involved no comparison with HFNC oxygen therapy, and so the relative merits of NIV as compared with HFNC in this population remain unknown.

### POSTEXTUBATION HIGH-FLOW NASAL CANNULA VS NONINVASIVE VENTILATION TO PREVENT REINTUBATION

Hernandez G, Vaquero C, Colinas L, Cuenca R, Gonzalez P, Canabal A, Sanchez S, Rodriguez ML, Villascargas A, Fernandez R. **Effect of postextubation high-flow nasal cannula vs noninvasive ventilation on reintubation and postextubation respiratory failure in high-risk patients: a randomized clinical trial.** *JAMA* 2016; 316(15): 1565-1574.

#### Summary

Earlier in 2016, this same group from Spain published a randomized controlled trial (also in *JAMA*), which demonstrated that the use of high-flow nasal cannula (HFNC) oxygen in postextubation patients at low risk for reintubation reduces the risk of reintubation compared with conventional oxygen therapy. The present study ran concurrently and addressed the issue of postextubation patients at high risk of reintubation. Noninvasive ventilation (NIV) has shown benefit in this setting compared with oxygen therapy. In this multicenter, randomized, noninferiority study, they compared HFNC with NIV, administered immediately after extubation, and for 24 hours thereafter. The authors hypothesized that HFNC is noninferior to NIV for preventing reintubation in high-risk patients. 604 adults with at least one predefined risk factor suggesting they would be high risk for reintubation, who had passed a spontaneous breathing trial after receiving invasive mechanical ventilation for more than 12 hours, were randomized. Major exclusion criteria included do-not-resuscitate orders as well as accidental and self-extubations. Titration of HFNC and NIV were both protocolized and the investigators used predefined criteria for reintubation. The primary outcomes were reintubation, occurring in 22.8% in the HFNC group compared with 19.1% in the NIV group (absolute difference, -3.7%; 95%CI, -9.1% to  $\infty$ ); and postextubation respiratory failure occurring in 26.9% with HFNC and 39.8% with NIV (risk difference, 12.9%; 95%CI, 6.6% to  $\infty$ ), which reached the noninferiority threshold. Median post-randomization intensive care unit length of stay was lower in the HFNC group. Importantly, adverse events requiring withdrawal of therapy were not observed in patients in the HFNC group, as compared with a rate of 42.9% in the NIV group ( $P < .001$ ).

#### Comments

1. HFNC was not inferior to NIV in preventing reintubation and postextubation respiratory failure in patients at high risk of reintubation.
2. The finding of noninferiority is important because there may be advantages to HFNC compared with NIV, as evidenced by the disparity in adverse events requiring withdrawal of therapy; with greater comfort and lower cost, this study could provide the rationale for preferentially selecting HFNC in many of these patients.
3. As with many other studies of NIV and HFNC, the clinicians were not blinded to the study group, although (as with the prior study by this group) the risk of bias was partially mitigated by excluding the investigators from clinical decision-making and predefining criteria for reintubation.

### HELMET NONINVASIVE VENTILATION IN ARDS

Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. **Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: a randomized controlled trial.** *JAMA* 2016; 315(22): 2435-2441.

#### Summary

Noninvasive ventilation (NIV) delivered via face mask (FM) has been shown to improve outcomes in selected patients with acute respiratory failure, especially in the setting of chronic obstructive pulmonary disease and cardiogenic pulmonary edema. However, NIV has produced mixed results in acute hypoxemic respiratory failure and the acute respiratory distress syndrome (ARDS). Nonetheless, a recent large observational study suggests that it is being used in as many as 15% of ARDS patients. Failure of NIV in this setting could be due, in part, to the FM interface itself, especially its inability to reliably or comfortably provide high levels of positive end-expiratory pressure (PEEP) due to air leak. The authors hypothesized that a helmet interface, a transparent hood covering the entire head and sealed at the neck, could overcome this limitation and decrease the need for endotracheal intubation (ETI). This unblinded, single center, randomized, controlled trial of 83 patients with ARDS according to the Berlin criteria, randomized patients after eight hours of NIV via FM, to continued FM NIV or switching to the helmet interface. Titration of ventilatory parameters, predefined criteria for ETI, weaning parameters and prespecified adverse events were standardized across both groups. The primary outcome was the proportion of patients requiring ETI, which favored the helmet interface, occurring in 61.5% in the FM group and 18.2% in the helmet group (absolute difference, -43.3%; 95% CI, -62.4% to -24.3%;  $P < .001$ ). The helmet group also had significantly higher ventilator-free days, lower intensive care unit length of stay and lower hospital and 90-day mortality. No significant differences in adverse event rates were noted.

#### Comments

1. This well-performed randomized, controlled trial of helmet NIV vs. FM NIV showed a remarkable and statistically significant difference in the need for ETI

favoring the helmet interface, and an equally striking difference in meaningful secondary endpoints, including 90-day mortality.

2. Physiologic differences seen between the groups, including median sustained PEEP and respiratory rate after transition to the helmet interface, may provide biologic plausibility to the results of the study.
3. Despite all this, the results must be interpreted with considerable caution given that this is a single center, unblinded study of an inadequately understood technology, applied to patients with ARDS in the absence of agreed upon criteria for NIV in this setting, and the study was stopped early for both efficacy and safety (likely resulting in overestimation of the effect size).
4. Further study to provide external validity and generalizability is needed before the helmet interface could be considered standard practice; comparisons with high flow nasal cannula in this setting might also be informative.
5. The article was controversial at the time of publication in JAMA given its limitations, accounting for its designation in the journal (appropriately) as a "Preliminary Communication".

## UNDERSTANDING THE TOOLS WE USE FOR ARDS

Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld GD, Thompson BT, Wrigge H, Slutsky AS, Pesenti A; for the LUNG SAFE Investigators and the ESICM Trials Group. **Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries.** *JAMA* 2016; 315(8): 788-800.

### Summary

Limited information exists about patients with the acute respiratory distress syndrome (ARDS) within the context of routine clinical practice around the world. This study, the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE), is a multicenter, international, prospective cohort study. The study was conducted during two periods, each consisting of four consecutive weeks in the winter of 2014 within the northern and southern hemispheres respectively, using a large convenience sample from 459 intensive care units (ICUs) in 50 countries across 5 continents. All patients undergoing invasive mechanical ventilation or noninvasive ventilation in those ICUs during the four-week periods were enrolled. The primary outcome was the ICU incidence of ARDS as defined by the Berlin criteria. Secondary outcomes included clinician recognition of ARDS, ventilator management, use of adjunctive interventions and outcomes from ARDS. Of 29,144 patients admitted to the participating ICUs during the study period, 3,022 (10.4%) met criteria for ARDS. Overall clinician recognition of ARDS ranged from 51.3% in mild to 78.5% in severe ARDS. However, clinician recognition of ARDS at the time criteria were met was only 34.0%, highlighting routine delays in diagnosis. Among those receiving invasive mechanical ventilation, the period prevalence of mild ARDS was 30.0%; moderate ARDS,

46.6%; and severe ARDS, 23.4%. Prone positioning was used in only 16.3% of patients with severe ARDS. Clinician recognition of ARDS was associated with the use of higher levels of positive end-expiratory pressure, more frequent prone positioning and use of neuromuscular blockade. Hospital mortality was 34.9% for those with mild, 40.3% for those with moderate, and 46.1% for those with severe ARDS.

### Comments

1. This is the first major epidemiologic study of ARDS patients using the Berlin criteria, and it appears to unmask widespread under-recognition and under-treatment.
2. The study may have overestimated the incidence of ARDS, most notably because of the gathering of data only during winter months, and likewise it may have overestimated the degree of under-recognition of ARDS by not distinguishing clinician failure to diagnose from clinician judgment of an alternate explanation for hypoxemia.
3. The frequent failure of clinicians to recognize ARDS would tend to suppress the use of appropriate therapies; remarkably, fewer than two thirds of patients with ARDS in this study received a tidal volume of 8 ml/kg or less of predicted body weight.
4. Bearing in mind all the caveats of a convenience sample, the LUNG SAFE study is a gold mine of information about ARDS and how it may (or may not) be recognized and managed in the real world.
5. The sheer size and geographic range of this well-conducted study make it a powerful generator of hypotheses about the epidemiology, recognition, implementation of evidence-based practices, and outcomes of patients with ARDS.

## OTHER ARTICLES OF INTEREST

### NONINVASIVE VENTILATION

Carteaux G, Millan-Guilarte T, De Prost N, Razazi K, Abid S, Thille AW, Schortgen F, Brochard L, Brun-Buisson C, Mekontso Dessap A. **Failure of noninvasive ventilation for de novo acute hypoxemic respiratory failure: role of tidal volume.** *Crit Care Med* 2016; 44: 282-290.

Thille AW, Boissier F, Ben-Ghezala H, Razazi K, Mekontso-Dessap A, Brun-Buisson C, Brochard L. **Easily identified at-risk patients for extubation failure may benefit from noninvasive ventilation: a prospective before-after study.** *Critical Care* 2016; 20: 48.

Bellani G, Laffey JG, Pham T, Madotto F, Fan E, Brochard L, Esteban A, Gattinoni L, Bumbasirevic V, Piquilloud L, van Haren F, Larsson A, McAuley DF, Bauer PR, Arabi YM, Ranieri M, Antonelli M, Rubenfeld GD, Thompson BT, Wrigge H, Slutsky AS, Pesenti A; On behalf of the LUNG SAFE Investigators and the ESICM Trials Group. **Non-invasive ventilation of patients with ARDS: Insights from the LUNG SAFE Study.** *Am J Respir Crit Care Med* 2016; in press

### HIGH-FLOW NASAL CANNULA

Mauri T, Turrini C, Eronia N, Grasselli G, Volta CA, Bellani G, Pesenti A. **Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure.** *Am J Respir Crit Care Med* 2016; in press.

Semler MW, Janz DR, Lentz RJ, Matthews DT, Norman BC, Assad TR, Keriwala RD, Ferrell BA, Noto MJ, McKown AC, Kocurek EG, Warren MA, Huerta LE, Rice TW; for the FELLOW Investigators and the Pragmatic Critical Care Research Group. **Randomized trial of apneic oxygenation during endotracheal intubation of the critically ill.** *Am J Respir Crit Care Med* 2016; 193: 273-280.

#### HIGH-FREQUENCY OSCILLATORY VENTILATION IN PEDIATRICS

Bateman ST, Borasino S, Asaro LA, Cheifetz RM, Diane S, Wypij D, Curley MAQ; for the RESTORE Study Investigators. **Early high-frequency oscillatory ventilation in pediatric acute respiratory failure: a propensity score analysis.** *Am J Respir Crit Care Med* 2016; 193: 495-503.

#### NEW TOOLS FOR TRACHEOSTOMY

Gobatto ALN, Besen BAMP, Tierno PFGMM, Mendes PV, Cadamuro F, Joelsons D, Melro L, Carmona MJC, Santori G, Pelosi P, Park M, Malbouisson LMS. **Ultrasound-guided percutaneous dilational tracheostomy versus bronchoscopy-guided percutaneous dilational tracheostomy in critically ill patients (TRACHUS): a randomized noninferiority controlled trial.** *Intensive Care Medicine* 2016; 42: 342-351.

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**RENAL REPLACEMENT THERAPY INITIATION**

Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, Boyer A, Chevrel G, Lerolle N, Carpentier D, deProst N, Lautrette A, Bretnol A, Mayaux J, Nseir S, Megarbane B, Thirion M, Forel J-M, Maizel J, Yonis H, Markowicz P, Thiery G, Tubach F, Ricard J-D, Dreyfuss D. AKIKI Study Group. **Initiation strategies for renal-replacement therapy in the intensive care unit.** *N Engl J Med* 2016; 375:122-33. DOI: 10.1056/NEJM oa16030175

**Summary**

The optimal timing of initiation for renal replacement therapy (RRT) among patients with acute kidney injury (AKI) remains controversial with conflicting results related to mortality and other benefits associated with early versus later RRT initiation. This study provides new insights into this important clinical question through a multi-center, randomized trial conducted in 31 intensive care units over a 28 month time period. The trial included 620 patients with Kidney Disease: Improving Global Outcomes (KDIGO) stage 3 who required mechanical ventilation, vasopressors, or both but did not have indications for immediate RRT (e.g. hyperkalemia). The early-strategy group began RRT within 6 hours of KDIGO stage 3. The late-strategy group was followed expectantly and RRT initiated based on pre-specified laboratory derangements, pulmonary edema, or oliguria/anuria > 72 hours after randomization. There were no differences between groups with respect to the primary outcome of overall survival at day 60 which was 48.5% in the early group and 49.7% in the late-strategy group. Among those in the late-strategy group, 49% never received RRT and among those who did, the time between randomization and RRT initiation was 50 hours. The early strategy group had slower recovery of renal function and higher rates of catheter-related blood stream infections.

**Comments**

1. This clinical trial that does not support routine, early initiation of RRT among patients with acute kidney injury who do not have urgent indications for RRT initiation such as metabolic derangements or pulmonary edema.
2. The finding that almost one-half of subjects in the late-strategy group avoided RRT and experienced earlier renal recovery has substantial ramifications for patient resource utilization.
3. The higher incidence of CLBSI among the early-strategy group has important patient-safety implications given the significant impact CLBSI has on patient morbidity and mortality.
4. A majority of patients (85%) in both groups were receiving vasopressor support at the time of study enrollment, yet the mode of RRT was intermittent hemodialysis in 50% of subjects which may limit generalizability to ICUs in which

continuous RRT is the conventional practice among patients with shock.

5. This study supports the use of careful clinical observation and expectant management regarding RRT initiation among ICU patients suffering from acute kidney injury

Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, Boanta A, Gerß J, Meersch M. **Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial.** *JAMA* 2016; 315(20):2190-2199. DOI:10.1001/jama.2016.5828

**Summary**

This second study on timing of initiation of RRT among ICU patients with AKI is a randomized, single-center study conducted over a 23 month period. The trial included 231 adult patients with KDIGO stage 2 despite optimal resuscitation who also had a plasma neutrophil gelatinase-associated lipocalin > 150ng/ml with one or more of the following: severe sepsis, use of vasopressors, refractory fluid overload, or progression of non-renal organ system failures. Early RRT was initiated within 8 hours of stage 2 AKI. Delayed RRT was initiated within 12 hours of stage 3 AKI or if a metabolic indication for RRT developed. Both groups were treated with identical RRT protocols and all patients received continuous RRT. The primary outcome of overall 90 day mortality was significantly improved in the early initiation group at 39.3% versus in the delayed group at 54.7%. Several secondary outcomes were also improved in the early initiation group versus the delayed group including: renal function recovery by day 90 (53.6% versus 38.7%); less duration of RRT (9 days versus 25 days); and shorter hospital length of stay (51 days versus 82 days). Among those in the delayed group, 90.7% ultimately received RRT.

**Comments**

1. This single center randomized trial supports early initiation of RRT among ICU patients with AKI on the basis of 90 day overall mortality and several clinically important outcomes including renal recovery.
2. An important factor limiting generalizability is the enrollment criteria of a plasma neutrophil gelatinase-associated lipocalin > 150ng/ml (an indicator of severity of AKI) which is not used in routine clinical practice.
3. All patients received the same RRT protocol with continuous RRT and thus whether similar outcomes would be replicated with intermittent RRT is unknown.
4. The actual therapeutic differences between the early and late initiation groups were small with 90.7% of patients in the delayed group ultimately receiving RRT on average within 24 hours of the early initiation group.



5. Despite modest therapeutic differences between the early and delayed groups, substantial improvements in primary and secondary outcomes were observed that should be interpreted with caution given the risk of overestimating effect sizes in single center studies.

## TREATMENT OF AGITATED ICU DELIRIUM

Reade MC, Eastwood GM, Bellomo R, Bailey M, Bersten A, Cheung B, Davies A, Delaney A, Ghosh A, van Haren F, Harley N, Knight D, McGuinness S, Mulder J, O'Donoghue S, Simpson N, Young P; DahLIA Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. **Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: A randomized clinical trial.** *JAMA* 2016; 315(14):1460-1468. DOI: 10.1001/jama.2016.2707

### Summary

Agitated delirium is a significant problem for ICU patients receiving mechanical ventilation and may impede ventilator liberation. The DahLIA Investigators enrolled 74 intubated, mechanically ventilated patients in a prospective, double-blind, placebo-controlled, parallel-group randomized, multi-center clinical trial. Patient's treating physicians had to perceive the degree of agitation as being sufficiently severe so as to make lessening sedation and extubation unsafe. Additional requirements included physical and/or pharmacologic sedation and quantification of agitated delirium via CAM-ICU and MAAS scores. Patients in the dexmedetomidine group were started at dose of 0.5 µg/kg/h and titration was based on physician ordered sedation goals. After 48 hours of study drug, treating physicians could prescribe open-label dexmedetomidine. The dexmedetomidine group showed significant improvement in the primary outcome of reduced ventilator-free hours in the 7 days post-randomization (median, 144.8 hours vs 127.5 hours). Several secondary outcomes were also improved including: reduced time to extubation (median, 21.9 hours vs 44.3 hours) and accelerated resolution of delirium (median, 23.3 hours vs 40.0 hours). There were no significant differences in adverse events between treatment and placebo groups.

### Comments

1. This study supports the use of dexmedetomidine, a sedative α<sub>2</sub>-agonist, as a treatment for agitated delirium in the specific and clinically important subset of patients who are perceived to fail liberation from mechanical ventilation due to their delirium.
2. This study contrasts with other studies of dexmedetomidine in which it has been evaluated as a sedative for mechanically ventilated patients and builds on secondary findings from these studies which suggested dexmedetomidine may have efficacy in treating delirium.
3. The mechanism(s) by which dexmedetomidine achieves improvement in delirium may include both primary therapeutic effect and/or as a sparing agent for alternative sedatives and analgesics.
4. The study screened 21,500 ICU admissions of intubated patients in order to randomize 74 subjects

so generalizability is a concern and the very specific clinical scenario studied (i.e. agitated delirium precluding extubation) should be considered when applying these findings to clinical practice.

5. Due to slower than expected enrollment, the study was stopped prior to the planned target of 96 patients raising a concern for an exaggerated effect size. Simulations were conducted to ascertain the risk of false positive results which was found to be < 7%.

## ICU QUALITY IMPROVEMENT

Writing Group for the CHECKLIST-ICU Investigators and the Brazilian Research in Intensive Care Network (BRICNet). **Effect of a quality improvement intervention with daily round checklists, goal setting, and clinician prompting on mortality of critically ill patients: A randomized clinical trial.** *JAMA*. 2016;315(14):1480-1490. DOI:10.1001/jama.2016.3463

### Summary

ICU quality improvement (QI) is an important issue and a variety of approaches have demonstrated improved outcomes, often tied to a specific initiative. In this study, the BRICNet investigators undertook the goal of implementing and evaluating a multi-faceted ICU QI intervention throughout Brazil. The study enrolled 118 ICUs into a two phase study. Phase 1 was an observational period during which clinical outcomes, care process measures, and perceived ICU work climate were measured. Phase 2 was a cluster randomized trial in which half the ICUs received the multi-faceted intervention (daily checklist review by the ICU team, goal setting during multidisciplinary rounds, and follow-up clinician prompting for 11 care processes). During each phase, participating ICUs enrolled 40-60 consecutive patients with an ICU stay > 48 hours. In phase 2, 3327 patients were enrolled in intervention ICUs and 3434 in usual care ICUs. The study did not meet the primary outcome of reduced in-hospital mortality nor did it improve secondary clinical outcomes of reduced ICU mortality, CLBSI, VAP, or UTI. However, a number of care process measures did improve in the intervention ICUs versus control ICUs including adherence to tidal volumes ≤ 8cc/kg predicted body weight (67.5% versus 58.9%); moderate sedation levels (40.5% versus 35.0%); and reduced urinary catheter use (62.8% versus 74.8%). Perceptions of team work climate and safety climate also improved in intervention ICUs.

### Comments

1. Although the QI intervention did not improve in-hospital mortality or secondary clinical outcomes, several processes of care measures did improve as did indicators of ICU safety environment which have been previously associated in other investigations with improved patient outcomes.
2. Many QI reports apply multi-faceted strategies targeting the area of interest and utilizing before/after designs and a notable strength of this study is the cluster randomized design with an observational run-in period.

3. The importance of organizational culture, including safety climate and multidisciplinary care, are believed to be important determinants to patient outcomes yet challenging to empirically alter. It is notable that the intervention was able to modify two domains of safety climate.
4. The clinical domains included in the QI checklist were broad, touching on numerous ICU patient safety initiatives currently at the forefront and ranging from ventilator and sedation management, DVT prophylaxis, and nutrition to all major device related infections. This may have represented too many separate initiatives for participating ICUs to address concurrently.
5. Another potential explanation for lack of clinical improvement may be the relatively short duration of the intervention which was less than five months and future research should extend intervention activities over a longer period of time to ascertain if process of care improvements will translate into substantive clinical improvements.

## ICU PHYSICAL THERAPY

Moss M, Nordon-Craft A, Malone D, Van Pelt D, Frankel SK, Warner ML, Kriekels W, McNulty M, Fairclough DL, Schenkman M. **A randomized trial of an intensive physical therapy program for patients with acute respiratory failure.** *Am J Respir Crit Care Med.* 2016;193(10):1101-1110. DOI: 10.1164/rccm.201505-1039OC

### Summary

Multiple studies have demonstrated ICU-acquired weakness is common and imposes substantial morbidity and mortality among ICU survivors which has inspired various ICU physical therapy (PT) programs. This study sought to determine whether an intensive PT program for patients with acute respiratory failure could improve long-term physical functional performance compared to standard PT care. This randomized trial enrolled 120 patients from five ICUs over approximately five years. Patients had to have received mechanical ventilation for  $\geq$  four days and were randomized at the time of awakening. Each site had a dedicated PT team for the intervention versus standard care groups. The intensive PT group received active treatment for 28 days from enrollment including in-home/outpatient treatment. The standard care group did not receive outpatient PT but received attention control with telephone follow-up. The primary outcome was a validated and structured assessment of functional status one month after study enrollment. Secondary outcomes included ICU- and hospital-free days, discharge to home, and all-cause mortality. The intensive PT group received a substantially higher dose than the standard group by all implementation measures; however, there was no difference in either primary or secondary outcomes between groups.

### Comments

1. This study utilized a novel, patient-centered outcome via the short form of the Continuous Scale Physical Functional Performance Test (CS-PFP-10) which reflects the ability to conduct typical activities of living such

as sweeping or carrying groceries. The CS-PFP-10 quantifies physical performance based on time, weight, and distance and thus reflects a combination of strength, balance, and endurance that is predictive of the ability to live independently.

2. This was a rigorous study that achieved early and meaningful differentiation regarding PT dose between the intensive and standard PT groups but unfortunately did not achieve significant differences with regards to patient outcomes up to six months after study enrollment.
3. Patients received their first PT sessions on average eight days after initiation of mechanical ventilation at which point most patients will have experienced substantial loss in muscle mass. Additional research is needed to learn whether earlier PT might mitigate loss of strength and portend improved patient outcomes.
4. Patients with ventilator dependent respiratory failure are a heterogeneous group who may derive differential benefits from various doses of PT, thus, in addition to timing, further research into up-titrating the dose of PT based on patient response may add important new insights.
5. While earlier studies of ICU PT have found positive impact on patient and resource use measures, recent clinical trials are calling these benefits into question although given the favorable patient safety profile risk appears low

## INTUBATION DURING CARDIOPULMONARY RESUSCITATION

Andersen LW, Granfeldt A, Callaway CW, Bradley SM, Soar J, Nolan JP, Kurth T, Donnino MW; American Heart Association's Get With The Guidelines-Resuscitation Investigators. **Association between tracheal intubation during adult in-hospital cardiac arrest and survival.** *JAMA.* 2017. DOI: 10.1001/jama2016.20165. [Epub ahead of print]

### Summary

This retrospective, observational study utilized data from the Get With the Guidelines-Resuscitation (GWTG-R) repository to examine the impact of timing of endotracheal intubation during cardiopulmonary resuscitation on patient survival and neurologic outcomes. Data were collected between 2000 through 2014 from 108,079 patients at 668 hospitals. Most patients (66.3%) were intubated within 15 minutes of cardiac arrest. Due to the large sample size and detailed measures available in the GWTG-R database, sophisticated analytic techniques could be applied to create a case-control study based on the minute of intubation relative to the onset of cardiac arrest in which intubated patients were matched to control patients that hadn't yet been intubated by that same specific minute. For each outcome studied, intubated patients did worse including lower survival (16.3% vs 19.4%), lower likelihood of ROSC (57.8% vs 59.3%), and lower rate of good neurological outcome (10.6% vs 13.6%). Multiple sub-groups were examined including shockable versus non-shockable rhythms and primary respiratory etiology as cause for cardiac arrest and among no sub-group did endotracheal intubation improve outcomes. For most sub-groups all outcomes were worse among patients intubated within 15 minutes.

## Comments

1. This study is congruent with other observational reports of both in-hospital and out-of-hospital cardiac arrest demonstrating that endotracheal intubation is associated with worse patient outcomes although a unique feature of this report is the highly specific time of intubation relative to the cardiac arrest that enabled a more detailed assessment.
2. While aggregated patient outcomes were worse, the subgroups with shockable rhythms and those in the “medical cardiac” illness group demonstrated especially poor outcomes associated with intubation within 15 minutes of cardiac arrest.
3. Despite the availability of robust data, the possibility of residual confounding due to unmeasured variables such as illness severity or clinician expertise remains a risk and so these findings should not be interpreted as causal.
4. The lack of randomized trials regarding the role of endotracheal intubation in the context of in-hospital cardiac arrest means that current resuscitation practices are derived from clinical tradition as opposed to high quality evidence and thus large observational data sources represent important tools to provide empiric insight.
5. In 2010 the mantra in cardiopulmonary resuscitation (CPR) was changed from ‘ABC’ (Airway, Breathing, Circulation) to ‘CAB’ (Circulation, Airway, Breathing) with the goal of minimizing potential interruptions to CPR, a paradigm shift these data would appear to support.

## OTHER ARTICLES OF INTEREST

### RCT'S OF PREVENTIVE INTERVENTIONS

Kor DJ, Carter RE, Park PK, Festic E, Banner-Goodspeed VM, Hinds R, Talmor D, Gajic O, Ware LB, Gong MN. **Effect of Aspirin on Development of ARDS in At-Risk Patients Presenting to the Emergency Department: The LIPS-A Randomized Clinical Trial.** *JAMA.* 2016;315(22):2406-14. DOI: 10.1001/jama.2016.6330;

Timsit JF, Azoulay E, Schwebel C, Charles PE, Cornet M, Souweine B, Klouche K, Jaber S, et.al. **Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, Candida Colonization, and Multiple Organ Failure: The EMPIRICUS Randomized Clinical Trial.** *JAMA.* 2016;316(15):1555-64. DOI: 10.1001/jama.2016.14655;

Gordon AC, Perkins GD, Singer M, McAuley DF, Orme RM, Santhakumaran S, Mason AJ, Cross M, Al-Beidh F, Best-Lane J, Brealey D, Nutt CL, McNamee JJ, Reschreiter H, Breen A, Liu KD, Ashby D. **Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis.** *N Engl J Med.* 2016;375(17):1638-48. DOI: 10.1056/NEJMoa1609409;

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Gordon AC, Mason AJ, Thirunavukkarasu N, Perkins GD, Cecconi M, Cepkova M, Pogson DG, Aya HD, Anjum A, Frazier GJ, Santhakumaran S, Ashby D, Brett SJ. **Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic**

**Shock: The VANISH Randomized Clinical Trial.** *JAMA.* 2016;316(5):509-18. DOI: 10.1001/jama.2016.10485

### PATIENT-FAMILY CENTERED CARE

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Cameron JI, Chu LM, Matte A, Tomlinson G, Chan L, Thomas C, Friedrich JO, Mehta S, et.al. **One-Year Outcomes in Caregivers of Critically Ill Patients.** *N Engl J Med.* 2016;374(19):1831-41. DOI: 10.1056/NEJMoa1511160.

### RESUSCITATION

Prandoni P, Lensing AW, Prins MH, Ciammaichella M, Perlati M, Mumoli N, Bucherini E, Visona A, Bova C, Imberti D, Campostrini S, Barbar S. **Prevalence of Pulmonary Embolism among Patients Hospitalized for Syncope.** *N Engl J Med.* 2016;375(16):1524-31. DOI: 10.1056/NEJMoa1602172;

Chan PS, Berg RA, Tang Y, Curtis LH, Spertus JA. **Association Between Therapeutic Hypothermia and Survival After In-Hospital Cardiac Arrest.** *JAMA.* 2016;316(13):1375-82. DOI: 10.1001/jama.2016.14380

### VENTILATOR MANAGEMENT

Panwar R, Hardie M, Bellomo R, Barrot L, Eastwood GM, Young PJ, Capellier G, Harrigan PW, Bailey M. **Conservative versus Liberal Oxygenation Targets for Mechanically Ventilated Patients. A Pilot Multicenter Randomized Controlled Trial.** *Am J Respir Crit Care Med.* 2016;193(1):43-51. DOI: 10.1164/rccm.201505-1019OC;

Girardis M, Busani S, Damiani E, Donati A, Rinaldi R, Marudi A, Morelli A, Antonelli M, Singer M. **Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: The oxygen-icu randomized clinical trial.** *JAMA.* 2016;316(15):1583-9. DOI: 10.1001/jama.2016.11993.

### PEDIATRIC CRITICAL CARE

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Gupta P, Rettiganti M, Rice TB, Wetzel RC. **Impact of 24/7 In-Hospital Intensivist Coverage on Outcomes in Pediatric Intensive Care. A Multicenter Study.** *Am J Respir Crit Care Med.* 2016;194(12):1506-13. DOI: 10.1164/rccm.201512-2456OC.

### ICU CLINICIAN BURNOUT

Moss M, Good VS, Gozal D, Kleinpell R, Sessler CN. **An Official Critical Care Societies Collaborative Statement: Burnout Syndrome in Critical Care Health Care Professionals: A Call for Action.** *Am J Respir Crit Care Med.* 2016; 194(1): 106-113. DOI: 10.1164/rccm.201604-0708ST

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## CRANIECTOMY FOR HEAD TRAUMA

Hutchinson PJ, Kolias AG, Timofeev IS, et al. **Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension.** *N Engl J Med* 2016;375:1119-1130.

### Summary

408 patients with traumatic brain injury and refractory intracranial hypertension were randomized to receive either a decompressive craniectomy or medical management. The primary outcome measure was the Glasgow Outcome Scale – Extended. At six months, 27% of the decompressed group had died, compared with 40% of the medical group. Patients in the surgical arm had less time with elevated ICP but more complications. Moderate disability and good recovery rates in the surgical arm were not different from those in the medical arm

### Comments

1. The majority of the craniotomies were bifrontal procedures, already shown to be deleterious in the DECRA trial (Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med* 2011;364: 1493-502).
2. The outcomes of the patients undergoing lateral hemicraniectomy, the preferred procedure in North America, have not been reported separately.
3. Since patients undergoing the bifrontal procedure may have worse outcomes, we await data about these lateral surgery patients.
4. ICU length of stay was 15 days in the surgical group and 21 days in the medical group.
5. 19% of the surgical arm received barbiturates for ICP control, compared to 87% of the medical arm.

## WITH INTRAVENOUS RT-PA TREATMENT FOR ACUTE STROKE, FASTER YIELDS BETTER OUTCOMES BUT MAY NOT BE SAFER

Whiteley WN, Emberson J, Lees KR, et al. **Risk of intracerebral haemorrhage with alteplase after acute ischaemic stroke: a secondary analysis of an individual patient data meta-analysis.** *Lancet Neurol* 2016;15:925-933.

### Summary

Data from 6756 participants in nine randomized trials of rt-PA for acute ischemic stroke vs placebo were analyzed on a per-patient basis. Symptomatic intracranial hemorrhage occurred in 6.8% of active treatment patients, compared

with 1.3% of controls (OR 5.55); fatal hemorrhage occurred in 2.7% vs 0.4% (OR 7.14). Symptomatic hemorrhage was defined in two different ways (parenchymal hemorrhage 2, as in the NINDS trials, and using the SITS-MOST definition, which is more commonly employed in European trials). The higher risk was independent of treatment delay (up to 4.5 hours) or patient age, but did increase with increasing stroke severity. Despite this, there was benefit based on the modified Rankin scale of functional outcome in all groups.

### Comments

1. Prior analyses lacked the power to examine this number of variables to estimate the effects of each on patient outcomes.
2. Although the efficacy of rt-PA decreases with time up to 4.5 hours, the benefit of treatment is still measureable out to this time point.
3. Age less than or greater than 80 years did not affect the risk of hemorrhage after rt-PA.
4. Even in patients with the most severe strokes (NIHSS > 22), the benefit of rt-PA exceeded the risk.
5. These trials preceded the advent of endovascular thrombectomy; whether intravenous rt-PA should precede attempts to remove large vessel thrombi remains under investigation.

## ENDOVASCULAR THROMBECTOMY IN STROKE DUE TO LARGE VESSEL OCCLUSION HAS A PROFOUNDLY BENEFICIAL EFFECT

Goyal M, Menon BK, van Zwam WH, et al. **Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials.** *Lancet* 2016; 387:1723-1731.

### Summary

A patient-level meta-analysis of data from five randomized trials of endovascular thrombectomy for acute ischemic stroke due to large vessel occlusion studied 1287 patients. The primary outcome was reduction in disability on the modified Rankin scale. In addition to the whole population, the authors studied subgroups including the site of occlusion (internal carotid, first or second branch of the middle cerebral), age, sex, baseline stroke severity, use of rt-PA, baseline ASPECT score (a measure of tissue damage in the CT scan on presentation), and time from stroke onset to randomization. Overall, thrombectomy led to a significant reduction in disability (OR 2.49); the number needed to treat or reduce disability by at least one mRS point was 2.6.

### Comments

1. Patients older than 80 years had at least as great a benefit as younger patients (OR 3.68).
2. Patients treated more than 300 minutes from stroke onset still benefitted (OR 2.43); most stopped enrolling at six hours.
3. Patients not eligible for intravenous rt-PA still benefitted (OR 2.43).
4. Intracranial bleeding was not significantly different between the treated patients and the controls.
5. Mortality was slightly better, but not significantly so, in the thrombectomy group (15.3% vs 18.9%).

### REMOVAL OF INTRAVENTRICULAR CLOT IN ICH PATIENTS WITH VENTRICULAR BLEEDING DID NOT IMPROVE OUTCOMES ... YET

Hanley DF, Lane K, McBee N et al. **Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial.** *Lancet* 2017;389:603-611.

### Summary

500 acute intracerebral hemorrhage patients (with hemorrhage volume < 30 mL) in whom an external ventricular drain had been placed for clinical reasons were randomized to receive either repeated doses of rt-PA (1 mg/dose) or saline, after repeated CT scans showed that the hemorrhage size was stable. All personnel were masked regarding the drug being administered. The primary outcome measure was the mRS at 180 days, performed by evaluators masked to the treatment assignment. There was no significant difference in outcome between the groups. There was lower mortality at 180 days in the treated group (hazard ratio 0.6), but at the cost of more patients with severe disability (RR 1.99). There was no difference in bleeding rates between the two groups.

### Comments

1. Getting into this study was difficult; 10,538 ICU patients were evaluated to randomize 500.
2. There is a signal suggesting that IVH volume (calculated by computer) of 20 mL or greater might benefit ... stay tuned.
3. However, in general, there is no apparent benefit in trying to clear blood from the ventricular system with rt-PA, despite great enthusiasm for doing so.
4. Investigators often guessed wrong regarding whether an individual patient was receiving rt-PA or saline; saline might have been effective, although the rate of clearance is similar to other observational studies without intervention.
5. There are new devices that can remove clot, but they are unproven at this point.

### AUTOIMMUNE ENCEPHALITIS IS THE MOST COMMONLY PROVEN ETIOLOGY OF REFRACTORY AND SUPER-REFRACTORY STATUS EPILEPTICUS

Gaspard N, Foreman BP, Alvarez V, et al. **New-onset refractory status epilepticus: Etiology, clinical features, and outcome.** *Neurology* 2015;85:1604-1613..

### Summary

This is a retrospective review of 130 cases of new-onset refractory status epilepticus (NORSE). 19% of the patients had an autoimmune encephalitis, and 18% had a paraneoplastic disorder. 22% of patients died, 12% had a good outcome (mRS 0-1), 26% fair (mRS 2-3), and 39% poor (mRS 4-5). Uncontrolled SE was the cause of death in 27% of the patients in whom an etiology was found, but 59% of the cases in which no etiology was determined. Withdrawal of support was the proximate cause of death in 12 patients..

### Comments

1. Of the autoimmune encephalitides, anti-NMDA receptor encephalitis was the most common.
2. Only 8% of patients were eventually shown to have an infectious cause of their syndrome.
3. In 52% of patients, no etiology was determined.
4. 38% of patients had no abnormalities on MRI.
5. CSF was abnormal in 73%; 52% had a pleocytosis, but rarely above 15 WBCs; protein was only modestly elevated.

### BRAIN-INJURED PATIENTS WHO CAN COUGH CAN BE EXTUBATED DESPITE A LOW GLASGOW COMA SCALE SCORE

McCredie VA, Ferguson ND, Pinto RL et al. **Airway Management Strategies for Brain-injured Patients Meeting Standard Criteria to Consider Extubation. A Prospective Cohort Study.** *Ann Am Thorac Soc* 2017;14:85-93

### Summary

The authors prospectively identified 192 adult brain-injured patients receiving mechanical ventilation. 79% were extubated, and 21% underwent tracheostomy directly. Extubation failure was no more common in patients who were extubated more than 24 hours after intubation than those extubated earlier. Lower GCS often lead to a delay in extubation when it was otherwise being considered, but higher GCS scores were not associated with more successful extubations..

### Comments

1. Diminished consciousness is frequently cited as a reason to delay extubation in patients who have adequate oxygenation and ventilation.

2. Earlier studies have suggested that, in the presence of an adequate cough, such patients can be safely extubated rather than requiring a tracheostomy.
3. In this study, the presence of a cough was the strongest predictor of extubation success.
4. Although the presence of a gag reflex increased the likelihood of successful extubation, the cough was a much stronger predictor.
5. Increasing age and more positive fluid balance decreased the likelihood of success..

## OTHER ARTICLES OF INTEREST

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de Oliveira Manoel AL, Goffi A, Marotta TR, et al. **The critical care management of poor-grade subarachnoid haemorrhage.** *Crit Care*. 2016 Jan 23;20:21.

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Gordon AC, Mason AJ, Thirunavukkarasu N, Perkins GD, Cecconi M, Cepkova M, Pogson DG, Aya HD, Anjum A, Frazier GJ, Santhakumaran S, Ashby D, Brett SJ. **Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial.** *JAMA*. 2016;316(5):509-18. DOI: 10.1001/jama.2016.10485

Hanley DF, Thompson RE, Muschelli J, et al. **Safety and efficacy of minimally invasive surgery plus alteplase in intracerebral haemorrhage evacuation (MISTIE): a randomised, controlled, open-label, phase 2 trial.** *Lancet Neurol*. 2016 Nov;15(12):1228-1237.

Hocker SE, Wijdicks EF. **Neurologic complications of sepsis.** *Continuum (Minneapolis)*. 2014 Jun;20(3 Neurology of Systemic Disease):598-613.

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**cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: an ancillary study to a randomised controlled trial.** *Lancet Respir Med*. 2016 Mar;4(3):203-12.

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Raman J, Ballal A, Hota B, et al. **Reconstructive valve surgery within 10 days of stroke in endocarditis.** *Asian Cardiovasc Thorac Ann*. 2016 Jul;24(6):523-9

Oude Lansink-Hartgring A, Hessels L, Weigel J, et al. **Long-term changes in dysnatremia incidence in the ICU: a shift from hyponatremia to hypernatremia.** *Ann Intensive Care*. 2016 Dec;6(1):22.

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**COMORBIDITY OF SDB AND ASTHMA**

Wang Y, Liu K, Hu K, Yang J, Li Z, Nie M, Dong Y, Huang H, Chen J. **Impact of obstructive sleep apnea on severe asthma exacerbations.** *Sleep Med.* 2016;26:1-5

**Summary**

Asthma and obstructive sleep apnea (OSA) commonly co-aggregate. There are several explanations for this, including the occurrence of common risk factors (obesity) for each condition, as well as causal associations. This prospective study evaluated the incidence of asthma exacerbations among 146 patients with asthma followed for one year. It also compared the prevalence of OSA in the asthma group with 157 matched controls without asthma. OSA was found in 19.2% of the asthma patients and 9.6% of the controls (RR: 2.25; 1.15-4.40;  $p=0.016$ ). A 14-fold increase in asthma exacerbations was reported in those with OSA compared to those without OSA. Frequency of asthma exacerbations was correlated with level of AHI and overnight hypoxemia. These findings were interpreted as evidence for OSA as a risk factor for asthma and asthma exacerbations. Mechanisms may relate to a pro-inflammatory state secondary to OSA-related hypoxia and oxidative stress, elevations in leptin levels with immune-modulation, or OSA-related alterations in parasympathetic-sympathetic balance.

**Comments**

1. The criteria (threshold) for diagnosing OSA were not clear, although most appeared to have mild to moderate sleep apnea.
2. Although a high 14-fold increase in risk of asthma exacerbations was observed, the confidence intervals surrounding this estimate was large.
3. BMI was higher among the OSA group and its role in asthma exacerbation unclear.
4. The overall higher prevalence of OSA among asthmatics vs controls, and increased asthma exacerbations suggests value in considering each alternative condition when caring for asthmatic or OSA patients

**TREATMENT OF SLEEP APNEA ON CARDIOVASCULAR OUTCOMES**

McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, Mediano O, Chen R, Drager LF, Liu Z, Chen G, Du B, McArdle N, Mukherjee S, Tripathi M, Billot L, Li Q, Lorenzi-Filho G, Barbe F, Redline S, Wang J, Arima H, Neal B, White DP, Grunstein RR, Zhong N, Anderson CS. **CPAP**

**for prevention of cardiovascular events in obstructive sleep apnea.** *N Engl J Med.* 2016;375:919-931

**Summary**

The SAVE trial – The Sleep Apnea Cardiovascular Endpoints trial is a large international randomized controlled trial evaluating the role of CPAP for secondary prevention of cardiovascular disease. The study randomized 2,717 patients with moderate to severe OSA (oxygen desaturation  $>12$ ) and existing CVD, ages 45 to 75 years old, to CPAP or usual care. The primary endpoint was a composite of myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or transient ischemic attack. Participants were following for a mean of 3.7 years. Despite support, patients used CPAP for an average of only 3.3 hours per night during the duration of the intervention. No significant differences between the CPAP and control group were observed in the composite endpoint or individual cardiovascular endpoint in primary analyses. However, secondary analyses showed decreased sleepiness, anxiety, depression scores, reduced missed work days, and improved quality of life. A subanalysis that focused on patients adherent to CPAP (with a propensity matched control group) showed a lower risk of stroke (hazard ratio: 0.56; 95% CI 0.32, 1.0).

**Comments**

1. Patients with severe sleepiness (Epworth Sleepiness Scale  $>15$ ) were excluded from the trial; thus, results cannot be generalized to this high risk group.
2. Modest CPAP adherence result in a suboptimal intervention.
3. Despite low CPAP adherence, significant improvements were seen in multiple patient reported outcomes.
4. The results suggest that with adequate CPAP, cerebrovascular disease, in particular, may benefit from CPAP.

**TREATMENT OF CENTRAL SLEEP APNEA: NEUROSTIMULATION**

Costanzo MR, Ponikowski P, Javaheri S, Augostini R, Goldberg L, Holcomb R, Kao A, Khayat RN, Oldenburg O, Stellbrink C, Abraham WT. **Transvenous neurostimulation for central sleep apnoea: A randomised controlled trial.** *Lancet.* 2016;388:974-982

**Summary**

The results from the SERVE-HF trial, which found that adaptive servo-ventilation used in patients with central sleep apnea and heart failure with reduced ejection fraction

(EF<45%) was associated with increased cardiovascular mortality, left a void in treatment options for this patient population. Phrenic nerve stimulation is a promising therapy but long term data are lacking. A prospective multicenter randomized trial evaluated the impact of a transvenous phrenic nerve stimulator (leading to diaphragmatic simulation) on change in the AHI after 6 months of treatment. 151 patients with predominant central sleep apnea (AHI >20; >50% central events) were randomized to the neurostimulator or to no treatment (device implantation with no stimulation). The sample was heterogeneous, with heart failure present in 64%, diabetes in 30% and prior stroke in 8%. At 6 months, the AHI was reduced to >50% of baseline value in 51% of the treated group and 11% of the control group ( $p<0.0001$ ). However, mean follow up AHI remained elevated even with treatment (25.4). Sleepiness and global quality of life improved more in the treatment group compared to the control group. At 12 months, 8% of the treatment group has a serious adverse event associated with the procedure/treatment.

### Comments

1. The study showed that transvenous neurostimulation of the phrenic nerve results in significant reductions in the AHI, particularly central events, in a heterogeneous population with predominant central sleep apnea.
2. Although the AHI did not “normalize,” the intervention resulted in improved oxygen saturation, sleepiness, arousal index, and global health score.
3. The magnitude of improvement in AHI was similar to what has been reported for CPAP in the CANPAP trial.
4. Additional research is needed to determine if clinical endpoints are impacted by this treatment

### TREATMENT OF OBSTRUCTIVE SLEEP APNEA IN PATIENTS WITH CORONARY ARTERY DISEASE: CPAP

Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunstrom E. **Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with non-sleepy obstructive sleep apnea: The RICCADSA randomized controlled trial.** *Am J Respir Crit Care Med.* 2016; 194(5):613-20.

### Summary

The RICCADSA (Randomized Intervention with CPAP in CAD and OSA) is a single site, prospective randomized controlled trial that examined the impact of CPAP (vs no CPAP) in patients with moderate OSA (AHI>15) and without sleepiness (Epworth Sleepiness Scale score < 10) who had a recent coronary artery revascularization procedure. The primary endpoint was a composite cardiovascular endpoint (repeat revascularization, myocardial infarction, or cardiovascular mortality). A total of 244 patients were randomized to one of the treatment arms, and followed for a median of 57 months. The incidence of the composite

endpoint was 18.1% in the CPAP group and 22.1% in the control group, resulting in a non-significant hazard ratio of 0.80; 0.10-0.86). Almost 50% of those prescribed CPAP returned it after 2 years use. Those who continued to use CPAP for more than 4 hours per night had a significant reduction in cardiovascular events compared to those who were not adherent to CPAP.

### Comments

1. CPAP adherence is low among non-sleepy patients with coronary artery disease.
2. The study suggested a high rate of moderate sleep apnea in patients with coronary artery disease.

### PREGNANCY AND SLEEP APNEA

Facco FL, Parker CB, Reddy UM, Silver RM, Koch MA, Louis JM, Basner RC, Chung JH, Nhan-Chang CL, Pien GW, Redline S, Grobman WA, Wing DA, Simhan HN, Haas DM, Mercer BM, Parry S, Mobley D, Hunter S, Saade GR, Schubert FP, Zee PC. **Association between sleep-disordered breathing and hypertensive disorders of pregnancy and gestational diabetes mellitus.** *Obstetrics and gynecology.* 2017;129:31-41

### Summary

The nuMoM2b (Nulliparous Pregnancy Outcomes Study: Monitoring Mothers To Be) is a multicenter prospective cohort study of nulliparous women studied in early and late pregnancy with in-home sleep apnea testing. This study aimed to determine whether sleep apnea was associated with an increase incidence of hypertensive disorders or pregnancy and gestational diabetes. In total, 3,705 women were studied. Sleep disordered breathing (SDB), defined as an AHI >5, was present in 3.6% of women in early pregnancy and in 8.3% of women in late pregnancy. After adjusting for age, BMI and chronic hypertension, SDB was associated with an almost 2-fold increased prevalence of preeclampsia and 3.5-fold increased prevalence of diabetes. Higher levels of AHI categories were associated with increased odds for gestational diabetes and hypertensive disorders of pregnancy.

### Comments

1. The prevalence of SDB increases from early to late pregnancy.
2. Independent of age and BMI, SDB is associated with an increased risk of hypertensive disorders of pregnancy and gestational diabetes.
3. The extent to which results could be confounded by visceral obesity, sedentary activity, insufficient sleep and race was not fully evaluated.
4. Prevalence of hypertensive disorders and gestational diabetes increases with increasing severity of SDB.



## HEART FAILURE AND SLEEP APNEA

Javaheri S, Blackwell T, Ancoli-Israel S, Ensrud KE, Stone KL, Redline S. **Sleep-disordered breathing and incident heart failure in older men.** *Am J Respir Crit Care Med.* 2016;193:561-5681

### Summary

A prospective cohort study of 2,865 men (mean age 76 years) followed for a mean of 7.3 years was conducted to determine whether sleep disordered breathing (SDB) at baseline was associated with an increased risk of developing incident or decompensated heart failure. SDB was measured using full in-home polysomnography (Type 2 device). Heart failure was adjudicated. Analyses separated the influences from predominant central from obstructive sleep apnea. 11% of the sample had an elevated central apnea index (>5) or Cheyne Stokes Respiration (CAI/CSR). 45% had an obstructive apnea index > 15, consistent with moderate SDB. After adjusting for multiple potential confounders, including baseline heart failure, CSA and CSR were each associated with a significantly increased incidence of incident heart failure (Odds ratios: 1.55 to 2.29). These results remained significant after adjusting for sleep fragmentation, hypoxemia and obstructive apnea. The Obstructive Apnea Hypopnea Index was not associated with incident heart failure after adjusting for confounders..

### Comments

1. Both Cheyne Stokes Respiration (defined as present or absent: > 10 minutes) and Central Apnea Index (>5) were significantly associated with incident heart failure, even after adjusting for confounders.
2. Cheynes Stokes Respiration was more strongly associated with incident heart failure than the Central Apnea Index, and this association persisted after adjusting for sleep fragmentation and hypoxemia.
3. The relationship between incident heart failure and Obstructive Sleep Apnea was confounded by age and obesity.
4. It is possible that increased sympathetic nervous activity, associated with CSR/CSA, contributes to adverse cardiac function.
5. A study weakness was the lack of cardiac imaging data and inability to fully tease apart the causal associations..

## OTHER ARTICLES OF INTEREST

Liu L, Cao Q, Guo Z, Dai Q. **Continuous positive airway pressure in patients with obstructive sleep apnea and resistant hypertension: A meta-analysis of randomized controlled trials.** *J Clin Hypertens (Greenwich).* 2016;18:153-15.

Campos-Rodriguez F, Queipo-Corona C, Carmona-Bernal C, Jurado-Gamez B, Cordero-Guevara J, Reyes-Nunez N, Troncoso-Acevedo F, Abad-Fernandez A, Teran-Santos J, Caballero-Rodriguez J, Martin-Romero M, Encabo-Motino A, Sacristan-Bou L, Navarro-Esteva J, Somoza-Gonzalez M, Masa JF, Sanchez-

Quiroga MA, Jara-Chinarro B, Orosa-Bertol B, Martinez-Garcia MA. **Continuous positive airway pressure improves quality of life in women with obstructive sleep apnea. A randomized controlled trial.** *Am J Respir Crit Care Med.* 2016;194:1286-1294.

Bakker JP, Wang R, Weng J, Aloia MS, Toth C, Morrical MG, Gleason KJ, Rueschman M, Dorsey C, Patel SR, Ware JH, Mittleman MA, Redline S. **Motivational enhancement for increasing adherence to cpap: A randomized controlled trial.** *Chest.* 2016;150:337-345.

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## EARLY DIAGNOSIS OF INTERSTITIAL LUNG DISEASE

Araki T, Putman RK, Hatabu H, Gao W, Dupuis J, Latourelle JC, Nishino M, Zazueta OE, Kurugol S, Ross JC, San Jose Estepar R, Schwartz DA, Rosas IO, Washko GR, O'Connor GT, Hunninghake GM. **Development and Progression of Interstitial Lung Abnormalities in the Framingham Heart Study.** *Am J Respir Crit Care Med.* 2016; 194: 1514-1522.

### Summary

In this pivotal study from the Framingham Heart Study population, the prevalence, progression and prognostic utility of subclinical interstitial lung abnormalities (ILA) is evaluated. ILA have been associated with decreased pulmonary function tests and reduced exercise capacity, but the natural history of their progression is well understood. In this study, 1867 subjects with 2 sequential chest computed tomography (CT) scans (mean difference 6.4yrs), were independently scored by three blinded reviewers for the presence of ILA, the radiological pattern, and the change between the two CT scans. This study demonstrates that 8% of the participants had ILA, with the majority (83%) having a subpleural reticular pattern. In addition, 6% had developed or had progressive ILA during the follow up period. Subjects with progression were more likely to be older, have a greater smoking exposure, and more likely to have increasing copies of the MUC5B promoter polymorphism. Those with ILA progression had greater physiological decline and increased mortality than those without ILA. This increased mortality has been confirmed separately by the same investigators in four separate cohorts. These findings suggest that there may be important clinical implications for early, subclinical interstitial lung abnormalities.

### Comments

1. Over a six year follow up period, the development and progression of ILA are commonly observed (in 6%) in the general population.
2. There are demographic and genetic risk factors for progression of ILA including older age, increased tobacco smoke exposure, and the MUC5B promoter genotype
3. ILA progression is associated with accelerated clinical decline and increased risk of death during follow up.
4. There may be important clinical consequences for subjects with subclinical ILA.
5. Consideration as to the risks and benefits for screening for early diagnosis of interstitial lung disease must be evaluated in further studies.

## DIAGNOSIS OF INTERSTITIAL LUNG DISEASE (MULTIDISCIPLINARY TEAM MEETING)

Walsh SL, Wells AU, Desai SR, Poletti V, Piciucchi S, Dubini A, Nunes H, Valeyre D, Brillet PY, Kambouchner M, et.al. **Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study.** *Lancet Respir Med* 2016; 4: 557-565.

### Summary

In this multicenter evaluation of 70 patients presenting to the interstitial lung disease (ILD) unit at the Royal Brompton Hospital, London, the agreement between multidisciplinary team meetings (MDTM) in seven countries for the diagnosis of ILD was assessed. Clinicians, radiologists and pathologists (if biopsy was performed) at each site independently assessed each case, and selected up to five differential diagnoses each with its diagnostic confidence (%). This process was repeated by each site at their MDTM. The overall agreement for first-choice ILD diagnosis between MDTM was only moderate (Kappa 0.50), although the agreement for a first-choice diagnosis of idiopathic pulmonary fibrosis (IPF) or connective tissue disease-related ILD was good (weighted Kappa 0.71; 0.73 respectively). The distinction between IPF and other ILD diagnoses at each MDTM was supported by a non-significant difference in mortality during follow-up. These findings have high clinical relevance, given the recommendation for ILD diagnosis at MDTM in the current guidelines. While it is reassuring that the inter-MDTM agreement for the diagnosis of IPF and CTD-ILD is good, it is somewhat disconcerting that the gold-standard for other ILD diagnoses is variable across centers. This study highlights the importance of standardizing MDTM and ILD diagnosis globally.

### Comments

1. There is only moderate diagnostic agreement overall for the first-choice ILD diagnosis between MDTM.
2. Diagnostic agreement between MDTM is good for IPF and CTD-ILD.
3. The diagnostic agreement for hypersensitivity pneumonitis was low.
4. This pivotal study highlights the need for standardization of the approach to ILD diagnosis at MDTM globally.
5. In particular, this study lends support for the need for more specific diagnostic criteria for the diagnosis of hypersensitivity pneumonitis.

## TRIGGERS OF PROGRESSION OF INTERSTITIAL LUNG DISEASE

Kreuter M, Wuyts W, Renzoni E, Koschel D, Maher TM, Kolb M, Weycker D, Spagnolo P, Kirchgaessler KU, Herth FJ, Costabel U. **Antacid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis.** *Lancet Respir Med* 2016; 4: 381-389.

### Summary

In this large post-hoc analysis of patients from the placebo group from the three phase III pirfenidone studies (CAPACITY 004, CAPACITY 006, and ASCEND), the effect of antacid therapy at baseline was evaluated against IPF disease progression. Gastro-oesophageal reflux disease has a relatively high prevalence in patients with IPF, and to date, its relationship with the pathogenesis of the disease remains unclear. Several retrospective studies have suggested a survival benefit for patients treated with antacid therapy, or indeed surgical fundoplication. In this study, the effect of antacid therapy use (either histamine H<sub>2</sub>-receptor antagonists or proton-pump inhibitors; n=291, 47%) vs no antacid therapy (n=333, 53%) was evaluated against the primary endpoint, disease progression at one year. Interestingly, there was no significant difference demonstrated in disease progression between the two groups (p=0.484), nor for all-cause or IPF related mortality. Adverse events were also similar between the two groups, except for infection and pulmonary infection which were, in fact, higher in patients with advanced IPF using antacid therapy versus those not using antacid therapy. These findings are particularly pertinent to consider in view of the conditional 2015 ATS/ERS guideline recommendation in favor of antacid therapy for asymptomatic gastro-oesophageal reflux in IPF patients.

### Comments

1. In contrast with the findings of previous studies, these findings do not support any beneficial effect of antacid therapy in patients with IPF.
2. Patients with advanced IPF who received antacid therapy had a significantly higher incidence of overall and pulmonary infections than those not receiving antacid therapy.
3. Long-term controlled studies are urgently needed to further evaluate the effect of antacid therapy in patients with IPF, particularly advanced disease.

## IPF BIOMARKERS

White ES, Xia M, Murray S, Dyal R, Flaherty CM, Flaherty KR, Moore BB, Cheng L, Doyle TJ, Villalba J, Dellaripa PF, Rosas IO, Kurtis JD, Martinez FJ. **Plasma Surfactant Protein-D, Matrix Metalloproteinase-7, and Osteopontin Index Distinguishes Idiopathic Pulmonary Fibrosis from Other Idiopathic Interstitial Pneumonias.** *Am J Respir Crit Care Med* 2016; 194: 1242-1251.

### Summary

In this landmark, biomarker study, a panel of 35 extracellular matrix (ECM)-related and lung specific proteins were evaluated for their utility to distinguish IPF from alternative interstitial lung diseases (a-ILD). A derivation cohort of 86 IPF patients was analyzed to determine the optimal biomarker panel, before this was applied to a separate validation cohort. The pre-specified panel of biomarker analytes was analyzed via five multiplexed assays simultaneously (FibroPlex version 2). The three best performing candidate biomarkers were consistently metalloproteinase 7 (MMP-7), surfactant protein D (SPD) and osteopontin. A multivariable model incorporating these biomarkers was constructed to best distinguish IPF from a-ILD. The combination of these biomarkers led to an adjusted area under the curve for IPF diagnosis of 0.766 with 82.6% of IPF patients having at least one biomarker above the threshold level. A one-point elevation in the biomarker index score led to a 1.9x higher likelihood of an IPF diagnosis (p=0.005). These findings were confirmed in the validation cohort. Interestingly, the biomarker profile did not distinguish IPF from Rheumatoid Arthritis associated ILD.

### Comments

1. Plasma levels of SP-D, MMP-7, and osteopontin may be useful (alone and in combination) to distinguish IPF from alternative ILD.
2. There was no utility for this plasma biomarker panel to distinguish IPF from Rheumatoid Arthritis associated ILD.
3. These findings have potential clinical implication for ILD patients with an uncertain diagnosis, who are unable or unwilling to undergo surgical lung biopsy.
4. Further studies, including this biomarker panel together with traditional clinical markers predictive of an IPF diagnosis are necessary.

## ACUTE EXACERBATION OF IDIOPATHIC PULMONARY FIBROSIS

Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, Lee JS, Maher TM, Wells AU, Antoniou KM, et al. **Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report.** *Am J Respir Crit Care Med* 2016; 194: 265-275.

### Summary

This international working group provides a comprehensive update on acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF). Key changes proposed by this working group included the removal of the term "idiopathic" from the definition of AE-IPF in recognition that there is little clinical or biological data supporting the distinction between idiopathic and non-idiopathic exacerbations. The revised definition of AE-IPF proposed is "an acute, clinically significant respiratory deterioration characterized by evidence of new, widespread alveolar abnormality." A second important change in the diagnostic criteria was the

change from the more specific time period of 30 days, to “typically less than one month” to allow more flexibility in the diagnosis of AE-IPF. A third change included the exclusion of cardiac failure or fluid overload as the cause of the respiratory deterioration. While there are many unanswered questions with regard to the etiology, pathobiology and management of AE-IPF, this working group provides a conceptual framework for respiratory deterioration in IPF, allowing these questions to be systematically approached in future research studies.

### Comments

1. The revised definition of AE-IPF is “an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality.”
2. The time-frame for AE-IPF has been redefined as acute worsening or development of dyspnea typically less than one month duration.
3. The term idiopathic has been removed from the AE-IPF definition, in recognition that there is little to distinguish idiopathic from non-idiopathic exacerbations.
4. The deterioration of AE-IPF must not be fully explained by cardiac failure or fluid overload.
5. While this working group provides a clear framework to consider AE-IPF, there are many unanswered questions which urgently need assessment in future clinical trials.

### TREATMENT OF INTERSTITIAL LUNG DISEASE

Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, Goldin J, Arriola E, Volkman ER, Kafaja S, et.al, Scleroderma Lung Study III. **Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial.** *Lancet Respir Med* 2016; 4: 708-719.

### Summary

This multicenter double-blind parallel group randomized controlled trial from 14 centers across the U.S.A evaluated the use of mycophenolate mofetil compared to oral cyclophosphamide in patients with scleroderma-related interstitial lung disease of moderate severity (forced vital capacity, FVC 45-80%). 142 patients were randomized to receive mycophenolate mofetil (n=69; target dose 1500mg twice daily) for 24 months, or oral cyclophosphamide (n=72; target dose 2mg/kg/day) for 12 months followed by placebo for 12 months. The primary endpoint, change in FVC as a percentage of the predicted value (FVC%) over the course of 24 months, was assessed in a modified intention-to-treat analysis. Of the 126 patients included in the final analysis, the adjusted FVC% improved from baseline to 24 months by 2.19% in the mycophenolate mofetil group and 2.88% in the cyclophosphamide group, with no difference in the course of the FVC% between the two treatment groups. Fewer patients receiving mycophenolate mofetil had significant side effects, withdrew from the study

drug, or died (7% vs 15%) compared to those receiving cyclophosphamide. Improvements in skin scores and dyspnea scores with both therapies suggest an overall systemic benefit for both medications.

### Comments

1. Treatment of scleroderma-related interstitial lung disease with either mycophenolate mofetil for 2 years or cyclophosphamide for 1 year leads to small but significant improvements in FVC %.
2. There was no additional efficacy of mycophenolate mofetil over oral cyclophosphamide for the treatment of scleroderma-related interstitial lung disease.
3. Mycophenolate mofetil was associated with less toxicity and was better tolerated, with fewer withdrawals than oral cyclophosphamide
4. These findings support the increasing clinical use of both mycophenolate mofetil and oral cyclophosphamide for patients with scleroderma-related interstitial lung disease.

### OTHER ARTICLES OF INTEREST

#### DIAGNOSING INTERSTITIAL LUNG DISEASE

Jacob J, Bartholmai BJ, Rajagopalan S, Kokosi M, Nair A, Karwoski R, Walsh SL, Wells AU, Hansell DM. **Mortality prediction in idiopathic pulmonary fibrosis: evaluation of computer-based CT analysis with conventional severity measures.** *Eur Respir J* 2017; 49.

Tomassetti S, Wells AU, Costabel U, Cavazza A, Colby TV, Rossi G, Sverzellati N, Carloni A, Carretta E, Buccioli M, Tantalocco P, Ravaglia C, Gurioli C, Dubini A, Piciucchi S, Ryu JH, Poletti V. **Bronchoscopic Lung Cryobiopsy Increases Diagnostic Confidence in the Multidisciplinary Diagnosis of Idiopathic Pulmonary Fibrosis.** *Am J Respir Crit Care Med* 2016; 193: 745-752.

#### PROGRESSION OF INTERSTITIAL LUNG DISEASE

Ley B, Bradford WZ, Vittinghoff E, Weycker D, du Bois RM, Collard HR. **Predictors of Mortality Poorly Predict Common Measures of Disease Progression in Idiopathic Pulmonary Fibrosis.** *Am J Respir Crit Care Med* 2016; 194: 711-718.

Russell AM, Adamali H, Molyneaux PL, Lukey PT, Marshall RP, Renzoni EA, Wells AU, Maher TM. **Daily Home Spirometry: An Effective Tool for Detecting Progression in Idiopathic Pulmonary Fibrosis.** *Am J Respir Crit Care Med* 2016; 194: 989-997.

#### PATHOBIOLOGY AND GENETICS OF INTERSTITIAL LUNG DISEASE

Molyneaux PL, Willis Owen SA, Cox MJ, James P, Cowman S, Loebinger M, Blanchard A, Edwards LM, Stock C, Daccord C, Renzoni EA, Wells AU, Moffatt MF, Cookson WO, Maher TM. **Host-Microbial Interactions in Idiopathic Pulmonary Fibrosis.** *Am J Respir Crit Care Med* 2017.

Fingerlin TE, Zhang W, Yang IV, Ainsworth HC, Russell PH, Blumhagen RZ, Schwarz MI, Brown KK, Steele MP, Loyd JE, et.al. **Genome-wide imputation study identifies novel HLA**

**locus for pulmonary fibrosis and potential role for auto-immunity in fibrotic idiopathic interstitial pneumonia.** *BMC Genet* 2016; 17: 74.

Newton CA, Batra K, Torrealba J, Kozlitina J, Glazer CS, Aravena C, Meyer K, Raghu G, Collard HR, Garcia CK. **Telomere-related lung fibrosis is diagnostically heterogeneous but uniformly progressive.** *Eur Respir J* 2016; 48: 1710-1720.

Petrovski S, Todd JL, Durheim MT, Wang Q, Chien JW, Kelly FL, Frankel C, Mebane CM, Ren Z, Bridgers J, Urban TJ, Malone CD, Finlen Copeland A, Brinkley C, Allen AS, O'Riordan T, McHutchison JG, Palmer SM, Goldstein DB. **An Exome Sequencing Study to Assess the Role of Rare Genetic Variation in Pulmonary Fibrosis.** *Am J Respir Crit Care Med* 2017.

#### TREATMENT OF INTERSTITIAL LUNG DISEASE

Khanna D, Albera C, Fischer A, Khalidi N, Raghu G, Chung L, Chen D, Schiopu E, Tagliaferri M, Seibold JR, Gorina E. **An Open-label, Phase II Study of the Safety and Tolerability of Pirfenidone in Patients with Scleroderma-associated Interstitial Lung Disease: the LOTUSS Trial.** *J Rheumatol* 2016; 43: 1672-1679.

Kreuter M, Wijsenbeek MS, Vasakova M, Spagnolo P, Kolb M, Costabel U, Weycker D, Kirchgaessler KU, Maher TM. **Unfavourable effects of medically indicated oral anticoagulants on survival in idiopathic pulmonary fibrosis: methodological concerns.** *Eur Respir J* 2016; 48: 1524-1526.

Behr J, Bendstrup E, Crestani B, Gunther A, Olschewski H, Skold CM, Wells A, Wuyts W, Koschel D, Kreuter M, Wallaert B, Lin CY, Beck J, Albera C. **Safety and tolerability of acetylcysteine and pirfenidone combination therapy in idiopathic pulmonary fibrosis: a randomised, double-blind, placebo-controlled, phase 2 trial.** *Lancet Respir Med* 2016; 4: 445-453.

Nathan SD, Albera C, Bradford WZ, Costabel U, Glaspole I, Glassberg MK, Kardatzke DR, Daigl M, Kirchgaessler KU, Lancaster LH, Lederer DJ, Pereira CA, Swigris JJ, Valeyre D, Noble PW. **Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis.** *Lancet Respir Med* 2017; 5: 33-41.

Raghu G, Wells AU, Nicholson AG, Richeldi L, Flaherty KR, Le Maulf F, Stowasser S, Schlenker-Herceg R, Hansell DM. **Effect of Nintedanib in Subgroups of Idiopathic Pulmonary Fibrosis by Diagnostic Criteria.** *Am J Respir Crit Care Med* 2017; 195: 78-85.

#### INTERSTITIAL LUNG DISEASE SYMPTOMS

Swigris JJ, Esser D, Wilson H, Conoscenti CS, Schmidt H, Stansen W, Leidy NK, Brown KK. **Psychometric properties of the St George's Respiratory Questionnaire in patients with idiopathic pulmonary fibrosis.** *Eur Respir J* 2017; 49.

Milne KM, Kwan JM, Guler S, Winstone TA, Le A, Khalil N, Camp PG, Wilcox PG, Ryerson CJ. **Frailty is common and strongly associated with dyspnoea severity in fibrotic interstitial lung disease.** *Respirology* 2016 Nov 9. doi: 10.1111/resp.12944

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University of Michigan  
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Ann Arbor, MI**SCREENING FOR COPD**

Siu AL, Bibbins-Domingo K, Grossman DC, Davidson KW, Epling JW, Garcia FA, Gillman M, Kemper AR, Krist AH, Kurth AE, Landefeld CS, Mangione CM, Harper DM, Phillips WR, Phipps MG, Pignone MP. **Screening for Chronic Obstructive Pulmonary Disease: US Preventive Services Task Force Recommendation Statement.** *JAMA* 2016;315:1372-7.

**Summary**

Estimates suggest a significant number of individuals with COPD are undiagnosed, but the best way to identify these individuals has not been completely clear. In its 2016 update, the U.S. Preventive Services Task Force (USPSTF) maintained its 2008 recommendation against screening asymptomatic adults for COPD including the use of prescreening questionnaires and spirometry. The task force based their recommendation on lack of adequate evidence that screening asymptomatic persons alters the course of disease or improves health outcomes. Asymptomatic individuals are defined as individuals who do not recognize or report respiratory symptoms, but the report states this does not apply to at-risk persons who present to clinicians with symptoms such as chronic cough, sputum production, dyspnea or wheeze or to individuals with a family history of alpha-1 antitrypsin deficiency. The report also emphasizes that all adults who use tobacco should be counseled to quit. The report also notes that future trials are needed to better assess the effects of screening and treatment of at-risk individuals in primary care on long-term health outcomes.

**Comments**

1. While this recommendation is based on the best available evidence, it is worth noting the key word “asymptomatic.” Many individuals at increased risk for COPD self-restrict activity to minimize symptoms.
2. The recommendation is based on lack of evidence, not negative evidence. USPSTF actually found no studies that directly assessed the effects of screening for COPD in asymptomatic adults on morbidity, mortality, or health-related quality of life. The USPSTF also found no studies that examined the effectiveness of screening on relevant immunization rates.
3. The recommendation assumes that medical treatments for COPD reduce symptoms and exacerbations but do not alter natural history or reduce mortality.
4. The USPSTF also found no studies to provide evidence to estimate the short- or long-term harms of these screening tests.

5. The Global Initiative for Chronic Obstructive Lung Disease recommends case-finding in symptomatic patients but does not recommend screening in asymptomatic populations.

**SYMPTOMATIC SMOKERS WITH PRESERVED SPIROMETRY**

Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, Gouskova NA, Hansel NN, Hoffman EA,anner RE, Kleerup E, Lazarus SC, Martinez FJ, Paine R, Rennard S, Tashkin DP, Han MK for the SPIROMICS Research Group. **Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function.** *N Engl J Med* 2016;374:1811-21.

**Summary**

A diagnosis of COPD is currently based on the presence of airflow obstruction as defined by a post-bronchodilator forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio of less than 0.70 assessed with spirometry. However, it is recognized that some smokers who do not meet this definition for airflow obstruction still experience significant respiratory symptoms. Woodruff and colleagues performed an analysis of the SPIROMICS cohort and demonstrated that among current or former smokers with preserved pulmonary function, those who were symptomatic, as defined by a COPD Assessment Test (CAT) score  $\geq 10$ , had a higher rate of respiratory exacerbations (0.27 vs. 0.08 events per year,  $p < 0.001$ ), a shorter 6-minute walk distance and greater airway wall thickening on chest CT as compared to unobstructed smokers who were asymptomatic. In fact, exacerbation frequency and airway wall thickening approached the level of abnormality seen in symptomatic GOLD 1 and 2 individuals. However, the “symptomatic smokers with preserved spirometry” had a paucity of emphysema as compared to GOLD 1 and 2 individuals. Many of these symptomatic smokers were already being treated by their own physicians with bronchodilators (42%) and inhaled corticosteroids (23%).

**Comments**

1. This study highlights the need to think about the broader effects of smoking related morbidity beyond COPD alone.
2. It remains uncertain at this point whether these patients represent a transitional pre-COPD phase or a separate clinical entity.

3. Additional analyses were performed to adjust for history of asthma and current smoking and the results remained essentially the same.
4. The authors also demonstrated that CAT score was a better predictor for future exacerbations than post-bronchodilator FEV1.
5. The fact that a significant proportion of individuals studied were already being treated with bronchodilators underscores the need to establish a therapeutic evidence basis for this patient population.

## SUPPLEMENTAL OXYGEN IN COPD

Long-Term Oxygen Treatment Trial Research Group. **A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation.** *N Engl J Med.* 2016;375(17):1617-1627.

### Summary

The use of supplemental oxygen for patients with mild-to-moderate hypoxemia in COPD is widespread, but up until recently the evidence basis for this was provided primarily by two trials conducted in patients with severe resting hypoxemia. The Long-Term Oxygen Treatment Trial was originally designed to determine whether supplemental oxygen in COPD patients with moderate resting desaturation (oxyhemoglobin saturation of 89-93%) delays time to death, after seven months and the randomization of only 34 patients, the trial was redesigned to also include patients with moderate exercise-induced desaturation (SpO<sub>2</sub> 80% for  $\geq 5$  minutes and  $< 90\%$  for  $\geq 10$  minutes during 6-minute walk test) and to incorporate time to first hospitalization for any cause into a composite primary outcome. Ultimately 738 patients were randomized to receive long-term supplemental oxygen (24-hour oxygen for those with resting desaturation and during exercise and sleep for those with exercise desaturation) versus no long-term supplemental oxygen. In time-to-event analysis, no difference between supplemental and no-supplemental oxygen groups in time to death or first hospitalization was found (hazard ratio 0.94; 95% CI 0.79-1.12;  $p=0.52$ ). No difference in rates of hospitalization, COPD exacerbations, quality of life, lung function or 6-minute walk distance was detected.

### Comments

1. Patients in the supplemental-oxygen group who had a COPD exacerbation 1-2 months before enrollment, those greater than 71 years at enrollment and those with lower quality of life at enrollment did experience longer time to death or first hospitalization although these effects did not remain significant when adjusted for multiple comparisons.
2. Lack of evidence for benefit should not be confused with a lack of clinical effectiveness in some patients. A trial of oxygen therapy may still be warranted in selected patients with moderate exertional hypoxemia and intractable breathlessness despite appropriate evidence-based treatment otherwise.

3. The LOTT was an unblinded study which may have confounded the results.
4. Mean oxygen use was 15.1 hours per day in the 24-hour group and 11.3 hours per day in the sleep-exercise group. The possibility that longer exposures to oxygen might have given different results cannot be excluded.
5. At this time, there has been no change in Medicare reimbursement guidelines for supplemental oxygen in patients with COPD.

## DUAL BRONCHODILATORS AND COPD EXACERBATIONS

Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, Thach C, Fogel R, Patalano F, Vogelmeier CF for the FLAME Investigators. **Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD.** *N Engl J Med* 2016;374:2222-34.]

### Summary

While there are an increasing number of LABA/LAMA (long acting beta agonist / long acting muscarinic antagonist) combination inhalers available on the market for COPD, their role in the treatment of COPD and in particular their effectiveness in the prevention of exacerbations as compared to ICS/LABA (inhaled corticosteroid / LABA) therapy has been less clear. The FLAME trial was a 3,362 person, 52-week study comparing the efficacy of a LABA/LAMA (indacaterol/glycopyrronium) with an ICS/LABA (fluticasone propionate / salmeterol) in decreasing the annual rate of COPD exacerbations. This study found an 11% lower rate of exacerbations in the indacaterol/glycopyrronium treated group as compared to the salmeterol/fluticasone group (rate ratio 0.89,  $p=0.0003$ ). Those treated with indacaterol/glycopyrronium also had a longer time to first exacerbation (71 days vs. 51 days;  $p<0.001$ ) and a lower annual rate of moderate or severe exacerbations (rate ratio 0.83,  $p<0.001$ ). The exacerbations remained lower in the indacaterol-glycopyrronium treated arm regardless of the baseline blood eosinophil count. The incidence of pneumonia was also lower in the indacaterol/glycopyrronium treated subjects, 3.2% vs. 4.8%,  $p=0.02$ .

### Comments

1. Data from FLAME helped to inform the updated GOLD 2017 statement that recommends LABA/LAMA as first choice therapy for GOLD patients.
2. Among individuals with greater than or equal to 2% blood eosinophils, the rate of moderate or severe exacerbations was still significantly lower in the indacaterol/glycopyrronium treated group than the salmeterol/fluticasone group, rate ratio 0.85,  $p=0.01$ . Additional analyses examining other eosinophil cutoffs demonstrated similar results.
3. These data should be interpreted in the context of the WISDOM study (Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management) trial where post hoc analyses demonstrated that withdrawal of

- inhaled glucocorticoids did increase the rate of moderate and severe exacerbations among individuals with a blood eosinophil count of 4% or higher or an absolute eosinophil count of at least 300 cells per microliter.
- The definition for a moderate exacerbation requiring treatment with systemic corticosteroids or antibiotics or both and severe requiring hospitalization is consistent with other studies. However, it should be noted that an electronic diary, completed by the patient twice daily, was also used to assess symptoms and if diary data suggested worsening of symptoms, the diary triggered an alarm for the patient to contact the site. It is possible use of the electronic diary influenced the rate and types of exacerbations reported.
  - More data are still need on longer term outcomes comparing LABA/LAMA to ICS/LABA and on whether there are subgroups of patients who might experience greater benefit from treatment with one treatment regimen over the other.

## ICS/LABA AND CARDIOVASCULAR MORTALITY IN COPD

Vestbo J, Anderson. JA, Brook RD, Calverley PM, Celli BR, Crim C, Martinez F, Yates J, Newby DE for the SUMMIT Investigators. **Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial.** *Lancet* 2016;387:1817-26

### Summary

While studies to date suggest good efficacy of inhaled therapies in COPD for symptom improvement and exacerbation reduction, no study to date has demonstrated an impact of therapy on mortality. SUMMIT was a double-blind, randomized clinical trial performed at 1,368 centers in 43 countries of 16,590 patients to compare fluticasone furoate/vilanterol to fluticasone furoate alone, vilanterol alone and placebo with respect to all-cause mortality. Inclusion criteria included FEV1% predicted between 50-70%, mMRC score of two or greater and either history of or increased risk for cardiovascular disease. No difference was seen in all-cause mortality in any of the treatment arms as compared to placebo. However, in pre-specified secondary analyses, rate of FEV1 decline was reduced by ICS/LABA therapy by 8 ml per year. All active treatment arms reduced the rate of exacerbations. No differences in risk of pneumonia or cardiovascular events were reported in any of the treatment groups.

### Comments

- The SUMMIT study design was informed by results of the TORCH trial where post-hoc analyses suggested a reduction in cardiovascular mortality with ICS/LABA therapy.
- The reductions in FEV1 decline are nearly identical to that seen in post-hoc subgroup analysis of GOLD 2 patients in the UPLIFT study comparing tiotropium to placebo.

- No data on baseline blood eosinophils were collected as part of this trial.
- While maximum length of follow-up was four years, many patients underwent significantly shorter follow-up as this was an event-driven study where follow-up continued until at least 1000 deaths occurred.
- Concomitant use of a long-acting muscarinic antagonist at baseline was not allowed.

## EFFICACY OF ICS/LABA IN A “REAL WORLD” SETTING

Vestbo J, Leather D, Diar Bakerly N, New J, Gibson JM, McCorkindale S, Collier S, Crawford J, Frith L, Harvey C, Svedsater H, Woodcock A for the Salford Lung Study Investigators. **Effectiveness of Fluticasone Furoate-Vilanterol for COPD in Clinical Practice.** *N Engl J Med* 2016; 375:1253-1260.

### Summary

Treatment studies in COPD have been criticized for strict inclusion criteria that may not relate to “real world” COPD patient populations. The Salford Lung Study was a randomized, open label study conducted to compare once-daily fluticasone furoate-vilanterol to usual care in an unrestricted COPD patient population recruited from clinics in Salford and South Manchester, England. This community is unique in that it is served primarily by a single hospital and a single electronic health record connecting primary and secondary care. The goal of the trial was to simulate a clinical practice environment where trial conduction and monitoring was incorporated into routine care delivery. In this study of 2,799 patients, the rate of moderate or severe exacerbations was lowered with fluticasone furoate-vilanterol as compared to usual care by 8.4% over a one-year period. No significant difference was seen in the annual rate of COPD-related contacts to primary or secondary care. No difference in time to first moderate or severe exacerbation was seen between treatment groups. No excess serious adverse events of pneumonia were seen in the fluticasone treated group.

### Comments

- As a significant proportion of patients in the usual care arm were also on ICS-LABA inhalers, the reduction in exacerbation frequency seen in the treatment arm may be due to the once-daily frequency of the medication which may have improved adherence.
- It is also possible that outcomes were influenced by bias introduced by the unblinded nature of the trial.
- Diagnosis of COPD was based on physician reported diagnosis and not spirometry.
- In the fluticasone furoate/vilanterol arm of the study, 22% of the patients switched back to their prior treatment vs. 11% in the usual care group making the results more difficult to interpret.



## OTHER ARTICLES OF INTEREST

## EPIDEMIOLOGY

Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. **The Presence of Chronic Mucus Hypersecretion across Adult Life in Relation to Chronic Obstructive Pulmonary Disease Development.** *Am J Respir Crit Care Med* 2016;193(6):662-72.

## DIAGNOSIS

Jordan RE, Peymane A, Sitch A, Enocson A, Blissett D, Jowett S, Marsh J, Riley RD, Miller MR, Cooper BG, Turner AM, Jolly K, Ayres JG, Haroon S, Stockley R, Greenfield S, Siebert S, Daley AJ, Cheng KK, Fitzmaurice D. **Targeted case finding for chronic obstructive pulmonary disease versus routine practice in primary care (Target COPD): a cluster-randomised controlled trial.** *Lancet Respir Med*. 2016;4(9):720-730.

Martinez FJ, Mannino D, Leidy NK, Malley KG, Bacci ED, Barr RG, Bowler RP, Han MK, Houfek JF, Make B, Meldrum CA, Rennard S, Thomashow B, Walsh J, Yawn BP; High-Risk-COPD Screening Study Group. **A New Approach for Identifying Patients with Undiagnosed COPD.** *Am J Respir Crit Care Med* 2016 [epub ahead of print].

## TREATMENT

Sciurba FC, Criner GJ, Strange C, Shah PL, Michaud G, Connolly TA, Deslée G, Tillis WP, Delage A, Marquette CH, Krishna G, Kalhan R, Ferguson JS, Jantz M, Maldonado F, McKenna R, Majid A, Rai N, Gay S, Dransfield MT, Angel L, Maxfield R, Herth FJ, Wahidi MM, Mehta A, Slebos DJ; RENEW Study Research Group. **Effect of Endobronchial Coils vs. Usual Care on Exercise Tolerance in patients with Severe Emphysema: The RENEW Randomized Clinical Trial.** *JAMA* 2016;315(20):2178-89.

Lindson-Hawley N, Banting M, West R, Michie S, DPhil BS, Aveyard P. **Gradual versus Abrupt Smoking Cessation.** *Annals of Internal Medicine*. 2016;164:585-592.

Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. **Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials.** *Lancet Respir Med*. 2015;3(6):435-42.

Martinez FJ, Rabe KF, Sethi S, Pizzichin E, McIvor A, Anzueto A, Alagappan VK, Siddiqui S, Rekeda L, Miller CJ, Zetterstrand S, Reisner C, Rennard SI. **Effect of Roblumilast and Inhaled Corticosteroid/Long-Acting Beta2-Agonist on COPD exacerbations (RE(2)SPOND). A randomized Clinical Trial.** *Am J Respir Crit Care Med* 2016;194(5):559-64.

Pavord I, Lettis S, Anzueto A, Barnes N. **Blood Eosinophil count and pneumonia risk in patients with chronic obstructive pulmonary disease: a patient-level meta-analysis.** *Lancet Respir Med*. 2016;4(9):681-683.

Singh D, Papi A, Corradi M, Pavlišová I, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, Vestbo J. **Single inhaler triple therapy versus inhaled corticosteroid plus long-acting Beta2-agonist therapy for COPD (TRILOGY): a double-blind, parallel group, randomized controlled trial.** *The Lancet*. 2016;388.

## MECHANISM

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Beran D, Zar HJ, Perrin C, Menezes AM, Burney P; Forum of International Respiratory Societies working group collaboration. **Burden of asthma and COPD and access to essential medicines in low-income and middle-income countries.** *Lancet Respir Med*. 2015;3(2):159-70.

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## NEW UNDERSTANDING OF PAH MECHANISMS

Rhodes CJ, Ghataorhe P, Wharton J, Rue-Albrecht KC, Hadinnapola C, Watson G, Bleda M, Haimel M, Coghlan G, Corris PA, Howard LS, Kiely DG, Peacock AJ, Pepke-Zaba J, Toshner MR, Wort SJ, Gibbs JS, Lawrie A, Gräf S, Morrell NW, Wilkins MR. **Plasma Metabolomics Implicates Modified Transfer RNAs and Altered Bioenergetics in the Outcomes of Pulmonary Arterial Hypertension.** *Circulation*, 2016; 135:460-475

### Summary

Although insulin resistance and lipid metabolism are known to be altered in pulmonary arterial hypertension (PAH), the full breadth of metabolic abnormalities have not previously been described and given the well-described relationship linking mitochondrial metabolism and PAH, this would be highly informative on pathways amenable to intervention. In this manuscript, Rhodes and colleagues compared over 1300 metabolites in the plasma of 116 PAH patients and controls (disease and healthy) using a non-targeted mass spectrometry-based platform. They found 53 metabolites distinguished idiopathic and heritable PAH patients from controls and 62 that were prognostic of survival in PAH. A pathway-based analysis identified energy metabolism and stress response pathways are perturbed in PAH. Correction of several metabolites correlated with a good clinical response. Interestingly, patients with a clinical response to calcium channel blockers had metabolite profiles similar to healthy controls, suggesting a different disease etiology in this cohort.

### Comments

1. Metabolite profiles in plasma can distinguish PAH from healthy and disease controls.
2. Metabolite profiles and their change over time may be useful in predicting outcomes and response to therapy in PAH.
3. This study highlighted stress responses as a key feature of altered metabolism in PAH.
4. Patients with PAH who are successfully treated with calcium channel blockers may have a different disease etiology from the great majority of PAH patients who do not respond to these medications.

## NEW PAH THERAPIES

Kawut SM, Archer-Chicko CL, CeMichele A, Fritz JS, KKlinger JR, Ky B, Palevsky HI, Palmisciano AJ, Patel M, Pinder D, Probert KH, Smith KA, Stanczyk F, Tracy R, Vaidya A, Whittenhall ME, Ventetuolo CE. **Anastrozole**

**in pulmonary arterial hypertension: A randomized, double-blind, placebo-controlled trial.** *Am J Respir Crit Care Med* 2017;195:360-8

### Summary

It has long been recognized that women are at higher risk for PAH than men, even in the context of heritable PAH. There has been tremendous growth in the past decade in understanding how estrogen and its metabolites may promote PAH and animal models have even suggested that anti-estrogen therapies may be beneficial for PAH but also may be a detriment to right ventricular function. Thus far, however, there have been no trials of anti-estrogen therapy in humans with PAH. In this important pilot study, Kawut and colleagues treated 18 patients with PAH with 3 months of placebo or anastrozole, which prevents the conversion of androgens to estrogen in peripheral tissues. Importantly, the authors included only men and post-menopausal women in their study. The co-primary endpoint was change in plasma estradiol levels and change in TAPSE as a marker of right ventricular function in a safety assessment. First, anastrozole appeared to be safe and well tolerated in this cohort of patients and did not reduce right ventricular function as measured by TAPSE. Anastrozole did reduce plasma estradiol levels. Second, there was a statistically significant increase in six minute walk distance in the cohort treated with anastrozole compared with placebo. This study is an important translation of many lines of basic science studies on the role of estrogen in PAH to beginning to treat human disease. Further study of anastrozole in larger numbers of patients will be required before it can be confidently prescribed as a treatment for PAH, however.

### Comments

1. Female sex is the strongest predictor for development of PAH.
2. Estrogens appear to play a role in development of PAH in rodent models.
3. Anastrozole appears to increase six minute walk distance more than placebo in this pilot study
4. Anastrozole appears safe and well tolerated.
5. A large-scale multicenter trial of anastrozole in PAH is warranted.

## CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, Bresser P, Torbiciki A, Mellemkjaer S, Lewczuk J, Simkova I, Barbera JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Jais X, Ambroz D, Treacy C, Morsolini, Jenkins D, Lindner J, Darteville P, Mayer E, Simonneau G. **Long-term outcomes of patients with chronic thromboembolic pulmonary hypertension: Results from an international prospective registry.** *Circulation* 2016;133:859-71.

### Summary

Chronic thromboembolic pulmonary hypertension is recognized as a not uncommon cause of pulmonary hypertension that, importantly, can be cured or significantly improved in most patients with pulmonary thromboendarterectomy. The procedure is only recommended after confirmation of chronic thromboembolic disease using radiology procedures such as pulmonary angiography and should only be carried out at expert centers with experience in evaluation and management of this complex condition. Off label PAH-directed therapies have been used in patients with chronic thromboembolic pulmonary hypertension including PDE5 inhibitors, endothelin receptors and prostaglandins and riociguat has recently been FDA-approved for patients with post-pulmonary thromboendarterectomy pulmonary hypertension and inoperable disease. This recent publication from the largest registry of chronic thromboembolic pulmonary hypertension evaluated long-term predictors of survival in this disease, both in operated and medically-managed patients. The key findings of this important work are that in the 679 newly diagnosed patients enrolled in this study, 60% percent were considered to have operable disease and underwent pulmonary thromboendarterectomy. Of the not operated cohort, 61% were treated with medical therapy using standard PAH treatments. 12% of patients who were treated surgically were NYHA functional class IV, highlighting that this is not a contraindication to surgery. However, in both operated and not-operated patients, the strongest predictor of mortality was being NYHA functional class IV. In this registry, survival was improved at all time points up to three years in the operated cohort vs. the not-operated group (3 year survival 89% vs. 70%). The use of bridging PAH therapy was associated with higher mortality after pulmonary thromboendarterectomy though this may track closely with patients with more severe disease, (e.g. NYHA functional class IV). Overall, this manuscript strongly supports operative management of chronic thromboembolic pulmonary hypertension when appropriate and highlights important risk factors for death (e.g. advanced disease) in both operated and not-operated patients.

### Comments

1. Survival is improved in patients with CTEPH treated with pulmonary thromboendarterectomy compared with not operated patients.
2. The strongest predictor of mortality in both operated and not operated groups is NYHA functional class IV status.
3. Approximately 20-25% of patients in both cohorts had no identified prior acute venous thromboembolism event.
4. Bridging PAH therapy to surgical procedure was associated with higher mortality at two years.

## MECHANISMS OF RIGHT VENTRICULAR FAILURE IN PH

Brittain EL, Talati M, Fessel JP, Zhu H, Penner N, Calcutt MW, West JD, Funke M, Lewis GD, Gerszten RE, Hamid R, Pugh ME, Austin ED, Newman JH, Hemnes AR. **Fatty acid metabolic defects and right ventricular lipotoxicity in human pulmonary arterial hypertension.** *Circulation* 2016;133:136-44.

### Summary

Recent work has highlighted the role of metabolic disease in PAH, suggesting that insulin resistance and lipid dysregulation are common in patients with pulmonary arterial hypertension. The right ventricle is the most important predictor of mortality in PAH and is a highly metabolically active tissue, making it likely to be affected by metabolic disease. While animal and human studies have shown high rates of glucose oxidation in the PAH right ventricle, the role of fat metabolism in the RV has been little studied, despite the knowledge that fatty acid oxidation is the major source of ATP in the normal right ventricle. In this manuscript, Brittain and colleagues used blood samples from PAH and control patients to demonstrate increased free fatty acids circulating in PAH and used a metabolomics approach to demonstrate that acylcarnitines, key transporters of fat into the mitochondria are elevated in PAH plasma compared to controls. In the myocardium, there was increased triglyceride in autopsy PAH RV compared to controls. They then went on to measure lipid deposition in vivo in controls and PAH patients using magnetic resonance spectroscopy and found 7 fold higher lipid content in the PAH myocardium compared to controls. In rodent models, they were able to demonstrate a failure of RV myocardium to augment fatty acid oxidation when supplied with palmitate. Taken together, these data support the hypothesis that lipid metabolism is abnormal in PAH and may contribute to RV dysfunction through lipotoxicity. As there are metabolic interventions, such as metformin, that may address this pathobiology, the translation of these data to new right ventricle-directed therapies in PAH shows high potential.

### Comments

1. PAH patients have high levels of insulin resistance and circulating fatty acids.

2. Acylcarnitines, which transport fat into mitochondria, are altered in PAH patients' blood and in their hearts.
3. Living patients with PAH have markedly increased right ventricular lipid content compared to controls.
4. Mitochondrial fatty acid oxidation is impaired in the PAH right ventricle.
5. Metabolic interventions in human patients need to be tested to determine if they improve right ventricular function and outcomes in PAH.

## CHALLENGING DEFINITION OF PULMONARY HYPERTENSION

Maron BA, Hess E, Maddox TM, Optowsky AR, Tedford RJ, Lahm T, Joynt KE, Kass DJ, Stephens T, Stainislawski MA, Swenson ER, Goldstein RH, Leopold JA, Zamanian RT, Elwing JM, Plomondon ME, Grunwald GK, Baron AE, Rumsfeld JS, Choudhary G. **Association of borderline pulmonary hypertension with mortality and hospitalization in a large patient cohort: insights from the veterans affairs clinical assessment, reporting and tracking program.** *Circulation* 2016;133:1240-1248.

### Summary

In the original WHO categorization of pulmonary hypertension, a mean pulmonary arterial pressure of  $\geq 25$  mmHg was chosen as a cutoff for pulmonary hypertension. Though this number was admittedly arbitrarily selected, it was based on the expertise of the participants. This cutoff has persisted since 1973. Recent World Symposia on Pulmonary Hypertension have maintained this cutoff, and defined patients with mean pulmonary arterial pressure between 20-24 mmHg as "borderline." Recent work by Maron et al has challenged this dogma. In this analysis of nearly 22,000 veterans with right heart catheterization data, they found increased mortality in patients with pulmonary arterial pressures beginning at 19 mmHg and rising continuously thereafter. They examined demographic characteristics of the cohort with mean pressure of 19-24 compared with patients whose mean pressure was below 19 mmHg or 25 mmHg or higher. They found that patients with this intermediate phenotype were more likely to be older and African American and to have higher prevalence of metabolic disease, such as obesity, diabetes, systemic hypertension and left heart failure. While the association of mortality with mean pulmonary artery pressure is strong, there is no data demonstrating that therapy in this population would improve survival or that patients with this intermediate phenotype ultimately go on to meet the current definition of pulmonary hypertension.

### Comments

1. In this VA cohort, mean pulmonary artery pressure of 19 mmHg or greater, previously not defined as abnormal, is associated with increased mortality.
2. Patients with a mean pressure of 19-24 mmHg were more likely to be older and African American than patients whose mean pressure was less than 19 mmHg.

3. It is unknown if patients with this intermediate phenotype progress to meet criteria for pulmonary hypertension (mean pulmonary arterial pressure of  $\geq 25$  mmHg) or if these patients would benefit from pulmonary – vascular specific therapies.

## NEW PULMONARY HYPERTENSION PHENOTYPES

Opitz CF, Hoeper MM, Gibbs JSR, Kaemmerer H, et al. **Pre-capillary, combined and post-capillary pulmonary hypertension: A pathophysiological continuum.** *J Am Coll Cardiol* 2016;68:368-78

### Summary

The phenotype of patients with mixed Group 1 and Group 2 has recently been recognized, but little is known about how these patients are different or similar to traditional pulmonary hypertension phenotypes, specifically pulmonary arterial hypertension and group 2, pulmonary venous hypertension. In this manuscript, the authors used registry data to compare clinical phenotypes and outcomes in traditional idiopathic PAH (IPAH), patients with atypical PAH, defined by 3 or more risk factors for left heart disease, and those with Group 2 PH treated with PAH-directed therapy. They found that patients with atypical PAH were older and more obese, but had similar hemodynamics including mean pulmonary arterial pressure and cardiac index. Treatment effects, measured by change in exercise capacity, functional class and natriuretic peptides, were present in all groups at 12 months, but the effects were most pronounced in typical IPAH, least in the Group 2 PH and intermediated in the atypical PAH group. These data suggest that what the authors call "atypical PAH" likely is a distinct phenotype both diagnostically and prognostically.

### Comments

1. A substantial portion of patients do not meet traditional guidelines for specific diagnosis of pulmonary hypertension with features of both Group 1 and Group 2 pulmonary hypertension.
2. Patients with atypical PAH phenotype have more obesity and comorbidities but similar hemodynamics.
3. Patients with idiopathic PAH appear to derive the most benefit from PAH-directed therapies.
4. Patients with heart failure with preserved ejection fraction benefit the least from PAH-directed therapies.

## OTHER ARTICLES OF INTEREST

### BASIC SCIENCE IN PH

Sa S, Gu M, Chappell J, Shao NY et al. **iPSC model of pulmonary arterial hypertension reveals novel gene expression and patient specificity.** *Am J Respir and Crit Care Med.* 2016

Yan L, Chen X, Talati M, Nunley BW, Gladson S, Blackwell T, Cogan J, Austin E, Wheeler F, Loyd J, West J, Hamid R. **Bone Marrow-derived Cells Contribute to the Pathogenesis of Pulmonary**

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#### INSIGHTS IN RIGHT VENTRICULAR FAILURE AND THERAPY

Talati MH, Brittain EL, Fessel JP, Penner N, Atkinson J, Funke M, Grueter C, Jerome WG, Freeman M, Newman JH, West J, Hemnes AR. **Mechanisms of Lipid Accumulation in the Bone Morphogenetic Protein Receptor Type 2 Mutant Right Ventricle.** *Am J Respir Crit Care Med.* 2016 Sep 15;194(6):719-28.

West JD, Voss BM, Pavliv L, de Caestecker M, Hemnes AR, Carrier EJ. **Antagonism of the thromboxane-prostanoid receptor is cardioprotective against right ventricular pressure overload.** *Pulm Circ.* 2016 Jun;6(2):211-23.

Frumpp AL, Goss KN, Vayl A, Albrecht M, Fisher A, Tursunova R, Fierst J, Whitson J, Cucci AR, Brown MB, Lahm T. **Estradiol improves right ventricular function in rats with severe angioproliferative pulmonary hypertension: effects of endogenous and exogenous sex hormones.** *Am J Physiol Lung Cell Mol Physiol.* 2015 May 1;308(9):L873-90.

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#### CLINICAL ASSESSMENT AND CARE OF PATIENTS WITH PH

Montani D, Girerd B, Jaïs X, Levy M, Amar D, Savale L, Dorfmueller P, Seferian A, Lau EM, Eyries M, Le Pavec J, Parent F, Bonnet D, Soubrier F, Fadel E, Sitbon O, Simonneau G, Humbert M. **Clinical phenotypes and outcomes of heritable and sporadic pulmonary veno-occlusive disease: a population-based study.** *Lancet Respir Med.* 2017 Feb;5(2):125-134.

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Assad TR, Hemnes AR, Larkin EK, Glazer AM, Xu M, Wells QS, Farber-Eger EH, Sheng Q, Shyr Y, Harrell FE, Newman JH, Brittain EL. **Clinical and Biological Insights Into Combined Post- and Pre-Capillary Pulmonary Hypertension.** *J Am Coll Cardiol.* 2016 Dec 13;68(23):2525-2536.

#### CTEPH

Brenot P, Garcia Alonso C, Gerardin B, Bourkaib R, Jais X, Simonneau G, Fadel E. **TCT-89 Balloon pulmonary angioplasty for chronic thromboembolic hypertension: report of a two-year experience in a surgical center.** *J Am Coll Cardiol.* 2016 Nov 1;68(18S):B36.

Simonneau G, D'Armini AM, Ghofrani HA, Grimminger F, Jansa P, Kim NH, Mayer E, Pulido T, Wang C, Colorado P, Fritsch A, Meier C, Nikkho S, Hoeper MM. **Predictors of long-term outcomes in patients treated with riociguat for chronic thromboembolic pulmonary hypertension: data from the CHEST-2 open-label, randomised, long-term extension trial.** *Lancet Respir Med.* 2016 May;4(5):372-80.

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Stein MM, Hrusch CL, Gozdz J, Igartua C, Pivniouk V, Murray SE, Ledford JG, Marques dos Santos M, Anderson RL, Metwali N, Neilson JW, Maier RM, Gilbert JA, Holbreich M, Thorne PS, Martinez FD, von Mutius E, Vercelli D, Ober C, Sperling AI. **Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children.** *N Engl J Med.* 2016 Aug 4;375(5):411-21. doi: 10.1056/NEJMoa1508749. PMID: 27518660

**Summary**

Two isolated populations with similar lifestyles but major differences in asthma prevalence were studied (Hutterites and Amish). The populations are genetically similar but the prevalence of asthma and allergic sensitization was 4-6 times lower in Amish children compared to Hutterite children of a similar age. In addition, there are major differences in farming practices with the Amish practicing traditional methods (single family farms with livestock) while the Hutterites have large industrialized communal farms. The authors observed that median endotoxin levels were significantly higher in Amish house dust with differences in microbial composition. More importantly, in a mouse model of allergic asthma, the intranasal instillation of the house dust from the Amish was found to significantly inhibit airway hyperreactivity and eosinophilia (compared to the Hutterites). The protective effects of the Amish house dust were not observed in mice deficient in molecules important in innate immune signaling (MyD88 and Trif). The authors postulate that the Amish home environment is protective of developing asthma by 'shaping the innate immune response.'

**Comments**

1. This work is an important extension of previous findings that children raised on traditional dairy farms have a low frequency of asthma suggesting a protective effect of contact with farm animals and high microbial exposures.
2. The two isolated populations (Amish and Hutterites) do not differ genetically ruling out genetic differences as the cause for the observed differences in asthma prevalence.
3. Although their lifestyle in respect to multiple risk factors for asthma and allergic diseases are similar in many ways, there are important differences in their farming practices with the Amish children having increased exposure to farm animals.

4. Key to this study was the testing of the effects of the Amish house dust in a murine model of asthma demonstrating the role of innate immunity which may in the future lead to prevention of disease instead of treatment after asthma develops.

Peters MC, McGrath KW, Hawkins GA, Hastie AT, Levy BD, Israel E, Phillips BR, Mauger DT, Comhair SA, Erzurum SC, Johansson MW, Jarjour NN, Coverstone AM, Castro M, Holguin F, Wenzel SE, Woodruff, PG, Bleecker ER, Fahy JV for the National Heart Lung and Blood Institute Severe Asthma Research Program. **Plasma interleukin-6 concentrations, metabolic dysfunction and asthma severity: a cross-sectional analysis of two cohorts.** *Lancet Respir Med* 2016; 4:574-84. PMID: 27283230 PMCID: PMC5007068

**Summary**

Most of the emphasis in understanding the pathogenesis of asthma has emphasized eosinophilic (type 2) inflammatory mechanisms. Targeting these inflammatory mechanisms has been the goal of most of the current biologic therapies in asthma. The importance of this paper by Peters and co-workers is that it emphasizes the potential role of non T2 mechanisms in more severe asthma. The authors extended previous observations on the potential role of the IL6 pathway in more severe asthma sub-phenotypes (Hawkins, et.al, JACI 2012; 130:510-515) to more general asthma populations (636 asthma patients from two populations: UCSF and SARP replicate samples and 93 normal controls). These cohorts had data related to metabolic disorders (hypertension, diabetes, obesity, as well as asthma severity and Type 2 inflammation). IL6 related outcomes were assessed in blood, sputum, and quantitative gene expression was performed to determine relationships between IL6, metabolic health, and asthma severity. Based on an upper 95th cortile value established in the normal controls, elevated IL6 levels were found in 14% of UCSF and 26% of SARP subjects, a more severe asthma cohort. Plasma IL6 levels were not associated with sputum IL6 protein or transcript levels in blood, or type 2 inflammation but were correlated with C-reactive protein and neutrophils. The high IL6 asthmatics had higher BMI, higher prevalence of metabolic disorders, lower lung function and more frequent asthma exacerbations. Seventy five % of high IL6 patients were obese, 63% of obese subjects were IL6 low. Non-obese IL6 high asthmatics had more frequent exacerbations. Thus, systemic IL6 inflammation

and metabolic dysfunction were found in an asthma subset and in a small subset of non-obese asthma.

### Comments

1. Study demonstrates the importance of non-Type 2 inflammation in severe asthma.
2. Findings support the potential value of evaluating anti-IL6 pathway therapy in a small subset of non-Th2 asthmatics which could further inform on mechanisms underlying severe asthma.
3. There is a question of whether IL6 causes severe asthma or is additive to other pathophysiologic mechanisms in asthma.
4. It is possible that these IL6 findings may reflect complex interactions with IL6R and other IL6 pathway proteins, some of which are under genetic control.

### ASTHMA PHENOTYPES

Lefaudeaux D, De Meulder B, Loza MJ, Pepper N, Rowe A, Baribaud F, Bansal AT, Lutter R, Sousa AR, Corfield J, Pandis I, Bakke PS, Caruso M, Chanez P, Dahlén SE, Fleming LJ, Fowler SJ, Horvath I, Krug N, Montuschi P, Sanak M, Sandstrom T, Shaw DE, Singer F, Sterk PJ, Roberts G, Adcock IM, Djukanovic R, Auffray C, Chung KF; U-BIOPRED Study Group. **U-BIOPRED clinical adult asthma clusters linked to a subset of sputum omics.** *J Allergy Clin Immunol.* 2016 Oct 20. pii: S0091-6749(16)31185-doi:10.1016/j.jaci.2016.08.048. [Epub ahead of print] PMID:27773852

### Summary

It is well known that asthma is a heterogeneous disease and multiple investigators have previously performed analyses to define subgroups of subjects with differing clinical phenotypes and/or differing endotypes. In this manuscript, the authors analyze a very well characterized cohort of adults with asthma. They divided the cohort into a training and validation set and should reproducibly of their clusters in the two data sets. They defined four clusters with differing phenotypes; T1) well controlled moderate to severe asthma, T2) late onset with a history of smoking and chronic airflow obstruction, T3) similar to cluster T2 but nonsmokers and T4) mainly obese females with uncontrolled asthma despite relatively normal lung function. In addition, the authors observed significant differences in both sputum proteomics and transcriptomics between the clusters further defining disease heterogeneity. The more severe clusters (T2, T3, T4) compared to cluster T1 had higher sputum eosinophils with no differences in sputum neutrophils, exhaled nitric oxide or serum IgE levels. In summary, four stable and reproducible clusters with different phenotypes and endotypes were observed further defining the underlying basis for asthma heterogeneity.

### Comments

1. Further understanding of asthma heterogeneity is important in understanding the variable response to asthma therapies and the development of severe disease.
2. Major prior studies of asthma which have not included subjects with a significant prior or current history of smoking would not have observed cluster T2 which may be confounded with ACOS or COPD.
3. Characterizing the phenotypic derived clusters by sputum cell counts (eosinophils and neutrophils) as well as the common biomarkers of exhaled nitric oxide and serum IgE levels is an important next step in defining asthma heterogeneity.

### BIOLOGIC THERAPY OF SEVERE ASTHMA

Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleecker ER, Brightling CE, Pavord ID. **Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies.** *Lancet Respir Med.* 2016 Jul;4(7):549-56. doi: 10.1016/S2213-2600(16)30031-5. Epub 2016 May 10. PMID: 27177493

### Summary

This paper reports on two Phase 3b studies on the efficacy of lebrikizumab, an IL13 inhibitor, in patients with moderate to severe asthma. IL13 is a Type 2 inflammatory cytokine that could contribute to several pathophysiologic characteristics observed in asthma including, mucous production, smooth muscle hyperplasia, fibrous, bronchial hyper-responsiveness, IgE synthesis and eosinophilic airway inflammation. An earlier phase 2 study with this drug showed efficacy improving lung function better in a biomarker high group (periostin or FeNO) (Corren *ital.* *N Engl J Med* 2011; 365: 1088-1098). Periostin is an IL13 induced matricellular protein secreted in bronchial epithelial cells and detected in serum. More than 2100 patients with moderate to severe asthma were studied in two identical trials (Lavolta I and II). Inclusion criteria were treatment with moderate to high dose ICS, one additional controller, a FEV1 between 40-80% with a bronchodilator response and an ACQ-5 greater than 1.5. There were no requirements for a prior exacerbation or specified biomarkers. The study failed to provide consistent results for the primary exacerbation endpoint nor did it show the expected improvements in FEV1 or ACQ-5. Results were stratified by high periostin or high eosinophil levels did not consistently identify benefit from this anti IL13.

### Comments

1. The subjects were recruited without specified prior exacerbations and the overall exacerbation rates were low so perhaps a therapeutic signal was lost using this study design strategy.

2. There is the possibility that IL13 blockade alone is not sufficient to reduce asthma exacerbations and only effects lung function.
3. The chosen biomarker may not be predicative and others, perhaps FeNO should be evaluated.
4. Asthma is heterogeneous and the correct subpopulation responsive to IL13 inhibition may not have been identified.
5. An important question to address is whether there are severe asthma subpopulations or endotypes that may be more responsible to IL5 versus IL13/4 inhibition (or do they target the same subjects).
6. Further investigation of predictive biomarkers is necessary

Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, Pirozzi G, Sutherland ER, Evans RR, Joish VN, Eckert L, Graham NM, Stahl N, Yancopoulos GD, Louis-Tisserand M, Teper A. **Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting  $\beta_2$  agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial.** *Lancet*. 2016 Jul 2;388(10039):31-44. doi: 10.1016/S0140-6736(16)30307-5. Epub 2016 Apr 27. PMID:27130691

### Summary

This phase 2b study evaluates dupilumab, a fully humanized anti IL4Ra monoclonal antibody that blocks both IL4 and IL13 signaling in moderate to severe uncontrolled asthma. Patients were recruited that were treated with moderate to high dose ICS, a second controller and despite this therapy remained poorly controlled (ACQ greater than 1.5). They were also required to have at one asthma exacerbation or hospitalization requiring therapy with systemic corticosteroids in the past year. 769 patients were randomized. The largest improvement in lung function and exacerbations were observed with every two week therapy. Therapy with this IL4Ra antagonist reduced severe asthma exacerbations (70%) in the overall population and marginally better in the high blood eosinophil subgroup. Improvement in FEV1 was observed in the overall group and the high eosinophil group showed somewhat better improvement than the low eosinophil group. Overall IL4/13Ra with dupilumab improved pulmonary function and reduced severe exacerbations in moderate to severe uncontrolled asthma patients irrespective of baseline eosinophil count.

### Comments

1. Overall, very promising clinical results were observed for IL4/13 inhibition therapy in severe asthma.
2. This raises the question of whether IL4Ra blockade that effects both IL13 and IL4 signaling is necessary in comparison to IL13 blockade alone (Hanania 2016).
3. Another potential question is that patients in this study may have been less severe since they are not required to have experienced at least one severe asthma exacerbation in the past year.
4. It is difficult to directly compare the results with anti IL5 therapy since the population in this trial may have been somewhat less severe than those included in the IL5 registration trials.



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## LATENT TUBERCULOSIS INFECTION

Mancuso JD, Diffenderfer JM, Ghassemieh BJ, Horne DJ, Kao TC. **The prevalence of latent tuberculosis infection in the United States.** *Am J Respir Crit Care Med* 2016;194:501-509.

### Summary

Individuals with latent TB infection (LTBI) represent a reservoir from which active cases of disease arise continuing the spread of *M. tuberculosis*. In the United States (U.S.), targeted testing and treatment of LTBI is a major focus of TB control. In order to estimate the prevalence of LTBI in the U.S., investigators used TST and interferon-gamma release assay data from the National Health and Nutrition Examination Survey (NHANES). The patient population included 6,083 people aged  $\geq 6$  years who had a TST and QuantiFERON-TB Gold In-Tube test (QFT-GIT). The estimated prevalence of LTBI in 2011-2012 was 4.4% as measured by TST and 4.8% by QFT-GIT that corresponds to 12,398,000 and 13,628,000 individuals, respectively. Prevalence declined slightly compared to the 2000 survey among the U.S.-born but remained constant among foreign-born. Higher risk groups included the foreign-born, close contacts to active TB cases and certain racial/ethnic groups. Asian individuals had the highest prevalence of LTBI (25% had a positive TST and 18% had a positive QFT-GIT). Use of the QFT-GIT resulted in higher prevalence of LTBI in U.S.-born and lower prevalence in foreign-born persons likely due to BCG vaccination in the latter. Foreign-born persons represent an increasingly larger proportion of the pool of LTBI (73%).

### Comments

1. The prevalence of LTBI has remained stable between 2000 and 2012 although the number of those infected has increased by 1.2 million to 12.4 million.
2. The prevalence of LTBI was 4.4% by TST and 4.8% by QFT-GIT.
3. QFT-GIT resulted in a higher prevalence estimate in the U.S.-born but lower estimate in the foreign-born.
4. Other high-risk groups included contacts to active cases, older individuals (cohort) and certain racial and ethnic groups.
5. Incarcerated and homeless individuals are not included in NHANES and BCG vaccination, duration of residence outside the U.S., and geographic region of origin among those born outside the U.S. were not available.

## SCREENING AND TREATMENT OF LATENT TB INFECTION

US Preventive Services Task Force. **Screening or latent tuberculosis infection in adults. US Preventive Services Task Force Recommendation Statement.** *JAMA* 2016;316(9):962-969.

### Summary

The USPSTF makes recommendations about the effectiveness of specific preventive services for patients without obvious related signs or symptoms of disease. Its recommendations are based on the evidence of benefits and harms of the service and as assessment of the balance. Costs are not considered. After reviewing the evidence on screening for LTBI in asymptomatic adults seen in primary care, the USPSTF made the following recommendation: The USPSTF recommends screening for LTBI in populations at increased risk (B recommendation). The evidence report included 72 studies with 51,711 patients. No study evaluated the benefits and harms of screening compared with no screening. Populations at increased risk for LTBI include persons who were born in, or are former residents of countries with increased tuberculosis prevalence and persons who live in, or have lived in high-risk congregate settings (e.g., homeless, correctional facilities). Screening tests include the Mantoux tuberculin skin test and interferon-gamma release assays which are moderately sensitive and highly specific for the detection of LTBI. Treatment should follow CDC guidelines. Isoniazid had higher rates of hepatotoxicity than placebo or rifampin.

### Comments

1. The USPSTF recommendation is a significant step in the right direction toward elimination of TB in the U.S. but targeted testing is a critical but insufficient step in TB prevention.
2. In order to eliminate TB, the U.S. will have to move much of the screening for LTBI and treatment of LTBI into the private sector.
3. The recommendation addressed two specific high-risk groups but did not address persons with HIV infection or contacts to infectious TB cases as the latter is likely to be seen in public health settings.
4. The Patient Protection and Affordable Care Act requires private health plans to cover services recommended with either an A or B recommendation at no cost to the consumer.
5. In order for this recommendation to be successful, there must be linkage to accessible and affordable treatment.

## TREATMENT AND PREVENTION OF TB/HIV

Hosseinipour MC, Bisson GP, Miyahara S, et al. **Empirical tuberculosis therapy versus isoniazid in adult outpatients with advanced HIV initiating antiretroviral therapy (REMEMBER): a multicountry open-label randomized controlled trial.** *Lancet* 2016;387:1198-1209.

### Summary

Mortality within the first 6 months after initiating antiretroviral therapy is often due to tuberculosis (TB) in resource-limited settings. Differentiation of subclinical TB from latent TB or active disease can be difficult in these settings. In order to evaluate whether empirical TB treatment would reduce early mortality compared with isoniazid (INH) preventive therapy, investigators conducted a multi-country open-label randomized controlled trial. HIV infected patients with CD4 counts of < 50 cells/microL from ten countries were randomized to antiretroviral therapy (ART) and empirical TB treatment or ART and INH treatment. 850 patients were enrolled between 2011 and 2014. The median CD4 count was 18 cells/microL. At 24 weeks, 22 (5%) participants from each group died or were of unknown status. However, there was an increase in incident TB and HIV disease progression in the empirical group. Grade 3 or 4 signs and symptoms occurred in 50 (12%) in the empirical group versus 46 (11%) in the INH group. INH preventive therapy was well tolerated and associated with lower mortality than in previous studies.

### Comments

1. Uptake of WHO guidelines recommending INH treatment of HIV infected patients with advanced disease has been low in part due to the concern for identifying active TB disease and the possibility of generating drug resistance.
2. This study showed no difference in survival between the empirically treated group and the INH preventive treatment group although in the former there was a higher rate of TB and AIDS progression.
3. There was no difference in adverse symptoms, signs, or laboratory values between groups.
4. INH could be safely given to HIV infected individuals with advanced HIV disease.
5. In settings where routine symptom screening is done in outpatients presenting for ART therapy, there is no benefit to empirical TB therapy compared with WHO recommended INH preventive therapy.

## NONTUBERCULOUS MYCOBACTERIA AND CYSTIC FIBROSIS

Bryant JM, Grogono DM, Rodriguez-Rincon D, et al. **Emergence and spread of a human-transmissible multidrug-resistant nontuberculous mycobacteria.** *Science* 2016;354:751-758.

### Summary

Patients with cystic fibrosis (CF) are at high risk of developing lung infection due to *Mycobacterium abscessus*. NTM are typically acquired from the environment and transmission from person to person has been considered highly unusual. In order to evaluate the possibility of transmission of *M. abscessus* group between CF patients, investigators performed whole genome sequencing of 1080 isolates from 517 patients collected from sites in the United Kingdom, United States, Republic of Ireland, Denmark, Sweden, Netherlands and Australia. Multiple clades of near-identical isolates were identified suggesting transmission of circulating clones. Most patients were infected with "clustered" isolates. Using Bayesian analysis, the investigators estimated that the most recent common ancestor infecting patients arose around 1978. Through a series of experiments, the investigators were able to show examples of potential person to person transmission and that the clones were better able to survive within macrophages, cause more virulent infections in mice, and were associated with worse treatment outcomes in humans.

### Comments

1. *M. abscessus* infections are increasing in CF patients and create significant morbidity.
2. This study was able to identify genetically highly similar strains of *M. abscessus* and *M. massiliense* in countries consistent with person to person transmission.
3. The isolates showed increased virulence/pathogenicity in macrophages and mice.
4. Treatment outcomes were worse but the details of treatment were not provided.

## TREATMENT OF PULMONARY MYCOBACTERIUM AVIUM COMPLEX

Olivier KN, Griffith DE, Eagle G, et al. **Randomized trial of liposomal amikacin for inhalation of nontuberculous mycobacterial lung disease.** *Am J Respir Crit Care Med* 2016;Oct 17. [Epub ahead of print].

### Summary

Pulmonary infections due to nontuberculous mycobacteria (NTM) are on the rise but there are no drugs that are approved for treatment. A phase 2 study investigated efficacy and safety of liposomal amikacin for inhalation (LAI) in treatment of refractory pulmonary NTM disease. Patients were randomly assigned to LAI (590 mg) or placebo administered once daily for 84 days with the option of an additional 84 days of open label use. The primary endpoint was change from baseline to day 84 on a semi-quantitative growth scale with other endpoints including sputum conversion, 6-minute walk distance, and adverse events. The modified intent-to-treat population included 89 patients (44 LAI, 45 placebo). The primary endpoint was not achieved ( $p=0.072$ ) however, a greater proportion of the LAI

group demonstrated  $\geq 1$  negative sputum culture (32% vs 9%,  $p=0.006$ ) and demonstrated improvement in 6-minute walk test (+20.6 vs -25.0 meters,  $p=0.017$ ). No patient who an MIC of greater than 64  $\mu\text{g/ml}$  or a molecularly determined amikacin mutation achieved culture conversion. Serious adverse events occurred in 18.2% of those receiving LAI vs 8.9% on placebo. Seven (15.9%) patients in the LAI group and none in the placebo group discontinued study drug for treatment-emergent adverse events.

### Comments

1. The study showed significant activity of LAI over placebo in patients with refractory pulmonary MAC as measured by secondary endpoints.
2. The study showed both a mycobacteriologic improvement (culture conversion at 84 days) that was sustained as well as improvement in 6-minute walk.
3. Adverse effects were more common with LAI than placebo and LAI was discontinued more frequently than placebo.
4. Additional study of LAI with other NTM and in CF patients is warranted.

## HEAT-COOLER UNIT-RELATED DISSEMINATED MYCOBACTERIUM CHIMAERA

Chand M, Lamagni T, Kranzer K, et al. **Insidious risk of severe *Mycobacterium chimaera* infection in cardiac surgery patients.** *Clin Infect Dis* 2017;64:335-342.

### Summary

Invasive *M. chimaera* infections related to heater-cooler units (HCU) used during cardiopulmonary bypass surgery have been reported from several countries with the initial reports coming from Switzerland. Whole genome sequencing has demonstrated remarkable similarity between HCU and patient isolates. This study evaluated the risk of invasive *M. chimaera* infection in the U.K. through a multipronged investigative approach using national laboratory and hospital admission data, cohort study, microbiological and aerobiological investigations of HCU, and whole genome sequencing of clinical and environmental isolates. Eighteen probable cases of cardiopulmonary bypass-associated infection were identified; all had undergone valve replacement in 11 hospitals between 2007 and 2015, a median of 19 months prior to onset (3 months to 5 years). Risk increased after 2010 from  $< 0.2$  to 1.65 per 10,000 person-years in 2013. Endocarditis was the most common presentation ( $n=11$ ). Nine patients had died. The investigators demonstrated that aerosol was released through holes in the HCU tanks. *M. chimaera* and other pathogens were isolated from water and air samples. Whole genome sequencing demonstrated highly similar strains.

### Comments

1. Disseminated *M. chimaera* infections have been reported from multiple countries including the U.S. and Canada.

2. This study found areas on the HCU that could result in leakage and aerosolization of infected water.
3. Whole genome sequencing was able to match HCU isolates with patient isolates with high degree of certainty.
4. Overall mortality was high as reported in other studies.

## OTHER ARTICLES OF INTEREST

### LATENT TUBERCULOSIS INFECTION

Miramontes R, Hill AN, Yelk WRS, Lambert LA, Navin TR, Castro KG, LoBue PA. **Tuberculosis infection in the United States: prevalence estimates from the National Health and Nutrition Examination Survey, 2011-2012.** *PLoS One* 2015;10:e0140881.

Ghassemieh GJ, Attia EF, Koelle DM, Mancuso JD, Narita M, Horne DJ. **Latent tuberculosis infection test agreement in the National Health and Nutrition Examination Survey.** *Am J Respir Crit Care Med* 2016;194:493-500.

### SCREENING AND TREATMENT OF LATENT TB INFECTION

Kahwati LC, Feltner C, Halpern M, et al. **Primary Care Screening and Treatment for Latent Tuberculosis Infection in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force.** *JAMA*. 2016 Sep 6;316(9):970-83.

Reves R, Daley CL. **Screening for latent tuberculosis infection: A key step toward achieving tuberculosis elimination in the United States.** *JAMA Intern Med*. 2016 Oct 1;176(10):1439-1440

### NONTUBERCULOUS MYCOBACTERIA AND CYSTIC FIBROSIS

Bryant JM, Grogono DM, Greaves D, et al. **Whole-genome sequencing to identify transmission of *Mycobacterium abscessus* between patients with cystic fibrosis: a retrospective cohort study.** *Lancet*. 2013 May 4;381(9877):1551-60.

Aitken ML, Limaye A, Pottinger P, et al. **Respiratory outbreak of *Mycobacterium abscessus* subspecies *massiliense* in a lung transplant and cystic fibrosis center.** *Am J Respir Crit Care Med*. 2012 Jan 15;185(2):231-2.

### TREATMENT OF PULMONARY MYCOBACTERIUM AVIUM COMPLEX

Olivier KN, Shaw PA, Glaser TS, et al. **Inhaled amikacin for treatment of refractory pulmonary nontuberculous mycobacterial disease.** *Ann Am Thorac Soc*. 2014 Jan;11(1):30-5.

### HEAT-COOLER UNIT-RELATED DISSEMINATED MYCOBACTERIUM CHIMAERA

Sax H, Bloemberg G, Hasse B, et al. **Prolonged outbreak of *Mycobacterium chimaera* infection after open-chest heart surgery.** *Clin Infect Dis*. 2015 Jul 1;61(1):67-75.

Kohler P, Kuster SP, Bloemberg G, et al. **Healthcare-associated prosthetic heart valve, aortic vascular graft, and disseminated *Mycobacterium chimaera* infections subsequent to open heart surgery.** *Eur Heart J*. 2015 Oct 21;36(40):2745-53.

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**ASTHMA**

Durack J, Lynch SV, Nariya S, Bhakta NR, Beigelman A, Castro M, Dyer AM, Israel E, Kraft M, Martin RJ, Mauger DT, Rosenberg SR, Sharp-King T, White SR, Woodruff PG, Avila PC, Denlinger LC, Holquin F, Lazarus SC, Lugogo N, Moore WC, Peters SP, Que L, Smith LJ, Sorkness CA, Wechsler ME, Wenzel SE, Boushey HA, Huang YJ; National Heart, Lung and Blood Institute's "AsthmaNet". **Features of the bronchial bacterial microbiome associated with atopy, asthma, and responsiveness to inhaled corticosteroid treatment.** *J Allergy Clin Immunol.* 2016 Nov 10. pii: S0091-6749(16)31283-0.

**Summary**

Asthma is clinically heterogeneous and microbial factors have long been postulated to play a role in asthma. Prior studies found significant associations between features of more severe asthma and patterns of bronchial microbiota composition. However, the influence of inhaled corticosteroid use and background atopy on such findings has been unclear. In a multi-center investigation by the NHLBI AsthmaNet, investigators studied the bronchial bacterial microbiome in three groups: atopic mild asthma patients not on inhaled steroid therapy, atopic (aeroallergen-sensitized) subjects without asthma, and non-atopic healthy individuals. Asthmatic subjects were then randomized to inhaled fluticasone or placebo inhaler treatment for six weeks, after which the microbiome was re-examined. Bacterial microbiota were analyzed using 16S rRNA gene sequencing, and the functional potential of the bacterial community determined using inferred metagenomic analysis. Significant differences in the bronchial bacterial microbiome were observed between the groups, including discrete differences associated with asthma or with atopy alone. Predicted bacterial functions associated with asthma included increased representation of pathways for amino acid, short-chain fatty acid, and xenobiotic metabolism. Type 2-"high" asthma subjects harbored significantly less bronchial bacterial burden than type 2-"low" subjects. Fluticasone treatment led to changes in bacterial community composition, and non-responsiveness to fluticasone was associated with differences in baseline community composition.

**Comments**

1. Steroid-naïve mild asthma is itself associated with alterations in the bronchial bacterial microbiome.

2. The amount of type 2 airway inflammation present is linked to differences in bronchial bacterial content.
3. Controlling for allergic status is an important consideration for studies of the respiratory microbiome.
4. Analysis of fluticasone effects on the bronchial microbiome was limited by a relatively small number of subjects with adequate paired brush samples for comparison.
5. The presence of non-bacterial microbiota (i.e. fungi, viruses) was not assessed due to technical limitations.

**COPD**

Wang Z, Bafadhel M, Haldar K, Spivak A, Mayhew D, Miller BE, Tal-Singer R, Johnston SL, Ramsheh MY, Barer MR, Brightling CE, Brown JR. **Lung microbiome dynamics in COPD exacerbations.** *Eur Respir J.* 2016 Apr;47(4):1082-92.

**Summary**

Bacterial or viral infections are implicated in 70-80% of acute COPD exacerbations. Little is known about the role of broader changes in the airway microbiome in COPD exacerbations. This study applied 16S rRNA gene sequencing methods to characterize bacterial community changes in sputum collected from 87 subjects during clinical stability, at exacerbation, and post-treatment. Exacerbation phenotypes were classified using previously defined microbiological and clinical criteria (bacterial, viral, eosinophilic, and pauci-inflammatory phenotypes). Overall, exacerbation samples demonstrated reduced alpha-diversity with non-significant increases in the relative abundance of Proteobacteria members (3-5% change in *Haemophilus* and *Moraxella* spp.) and a decrease in Firmicutes (*Streptococcus*). Segregating events by exacerbation phenotype demonstrated significant differences in bacterial community composition between bacterial and eosinophilic exacerbations, with the above differences seen mainly in the bacterial phenotype. Consistent with prior reports, treatment with antibiotics versus oral corticosteroids alone was found to have contrasting effects on sputum bacterial composition, with steroid treatment resulting in Proteobacteria enrichment. Analysis for relationships between sputum inflammatory mediators and the bacterial community identified negative correlations between CXCL8/IL-8, alpha-diversity and the relative abundance of several taxa representing *Haemophilus*, *Moraxella* and *Streptococcus* members..

### Comments

1. Results of this culture-independent analysis of the COPD sputum microbiome confirm a bacterial exacerbation phenotype as previously defined by sputum culture results.
2. Eosinophilic exacerbations were not associated with evident changes in the sputum bacterial community but bacterial interactions are possible given observations in the other combined phenotypes.
3. This larger study confirms previous reports that treatment with oral corticosteroids alone leads to airway enrichment in Proteobacteria, the long-term consequences of which are unknown.
4. No healthy or non-exacerbating COPD control groups were studied, so the specificity of the bacterial community dynamics observed to acute exacerbations is unclear.

### MICROASPIRATION AND THE LUNG MICROBIOME

Segal LN, Clemente JC, Tsay JC, Koralov SB, Keller BC, Wu BG, Li Y, Shen N, Ghedin E, Morris A, Diaz P, Huang L, Wikoff WR, Ubeda C, Artacho A, Rom WN, Sterman DH, Collman RG, Blaser MJ, Weiden MD. **Enrichment of the lung microbiome with oral taxa is associated with lung inflammation of a Th17 phenotype.** *Nat Microbiol.* 2016 Apr 4;1:16031.

### Summary

Microaspiration is common even in healthy individuals, and gastroesophageal reflux can complicate lung diseases including cystic fibrosis, asthma, and pulmonary fibrosis. A prior small investigation found that bronchoalveolar lavage fluid enriched in predominantly supraglottic bacteria, i.e. oral-related anaerobes like Prevotella and Veillonella, was associated with increased numbers of BAL lymphocytes and neutrophils. In this study characteristics of this BAL microbiome phenotype, termed "pneumotype-SPT," were further dissected using a multi-omic translational approach. Acellular BAL samples from 49 healthy subjects derived from three cohorts were analyzed. Subjects were mostly male (64%), had normal lung function and reported no respiratory symptoms. 63% had a current or former history of smoking. Unsupervised hierarchical cluster analysis of 16S rRNA gene sequence data demonstrated two distinct bacterial community profiles, as seen before. Pneumotype-SPT was associated with a significantly different functional profile by several assessments including predicted metagenomic content, metabolite correlations and elevation in Th17-related BAL cytokines. Similarity of the BAL microbiome to upper airway samples also correlated with a higher percentage of IL17+CD4+ BAL cells, and alveolar macrophages from pneumotype-SPT subjects displayed blunted TLR4 responses. The study concludes that lungs enriched in pneumotype-SPT-associated bacteria display a pro-inflammatory phenotype characterized by Th17-related immune responses.

### Comments

1. This larger study of acellular BAL from asymptomatic subjects from three different cohorts extends the previously reported association between lung prevalence of certain oral-related bacteria and lung inflammation.
2. The health versus disease consequences of these relationships are unclear since the majority of subjects had an at-risk smoking history.
3. The species of Prevotella and Veillonella linked to the observed lung responses are not known but would be of interest to further investigate and understand their functions.
4. While microbiota-metabolite correlations suggest direct links within a compartment, it can be difficult to resolve local vs. distant generation of metabolites detected in the lung and their quantification.

### LUNG TRANSPLANTATION

Bernasconi E, Pattaroni C, Koutsokera A, Pison C, Kessler R, Benden C, Soccal PM, Magnan A, Aubert JD, Marsland BJ, Nicod LP; SysCLAD Consortium. **Airway Microbiota Determines Innate Cell Inflammatory or Tissue Remodeling Profiles in Lung Transplantation.** *Am J Respir Crit Care Med.* 2016 Nov 15;194(10):1252-1263

### Summary

Chronic lung allograft dysfunction is a significant barrier to long-term survival after transplant, and control of inflammation and tissue remodeling are important underlying processes. The influence of lung microbiota and bacterial community dynamics on these processes in the first year post-transplant was assessed using BALs collected from 112 patients, coupled with host gene expression studies and in vitro studies of bacterial effects on monocyte-derived macrophages. Bacterial profiles were determined by 16S rRNA-based methods, and BAL cellular RNA was used to assess expression of innate immune cell functions linked to inflammatory, intermediate (immunoregulatory) or remodeling profiles. Lung microbiota were characterized by three dysbiotic patterns defined by dominance of Bacteroidetes, Firmicutes, or Proteobacteria, and a non-dysbiotic group with a balanced composition. These microbiota characteristics were associated with distinct gene expression profiles; Proteobacteria or Firmicutes-related dysbiosis was more prevalent in samples with pro-inflammatory profiles, whereas Bacteroidetes-related dysbiosis was more prevalent in samples with a remodeling profile. These relationships were further examined using four bacterial species representative of the microbiota groups in single and co-culture studies of their effects on human monocytic cell line-derived macrophages (THP-DM). The co-culture studies demonstrated attenuating effects of "non-dysbiotic" bacterial species on the inflammation elicited by species from the Firmicutes/Proteobacteria phyla.

### Comments

1. The study findings highlight the likely importance of lung microbiota interactions in shaping innate immune responses in the transplanted lung microenvironment.
2. In a subset of paired samples, temporal shifts in innate immune response profiles were observed as well as transitions from one bacterial community pattern to another, suggesting dynamic interactions between the two features longitudinally.
3. The collection timeframe of the samples analyzed did not allow for insights into associations with chronic rejection.
4. The effects of antimicrobial therapies on the microbiota patterns could not be evaluated due to large clinical variation.
5. Primary immune cells from the transplanted lung were not used for the exposure experiments and would be of interest to assess similarity of responses to the microbiota.

### IDIOPATHIC PULMONARY FIBROSIS

Huang Y, Ma SF, Espindola MS, Vij R, Oldham JM, Huffnagle GB, Erb-Downward JR, Flaherty KR, Moore BB, White ES, Zhou T, Li J, Lussier YA, Han MK, Kamniski N, Garcia JG, Hogaboam CM, Martinez FJ, Noth I; COMET Investigators. **Microbes associate with host innate immune response in idiopathic pulmonary fibrosis.** *Am J Respir Crit Care Med.* 2017 Feb 3, in press.

#### Summary

Prior studies have identified relationships between polymorphisms in host defense genes and IPF risk or survival. This study applied a systems biology approach to examine relationships between BAL bacterial microbiota and transcriptional patterns in peripheral blood mononuclear cells. 68 IPF patients from the COMET study had paired specimens available for 16S rRNA gene sequencing analysis of BAL and microarray analysis of PBMC gene expression. In addition, a subset of patients had samples used to study lung fibroblast responsiveness to TLR9 stimulation (CpG-ODN) and circulating leukocyte phenotypes. Interaction networks were constructed based on the collective results and clinical outcomes. Higher bacterial species richness was associated with down-regulation of innate immune response pathways (NOD, TLR, and RIG-I-like receptor pathways) that in turn were associated with worse progression-free survival. Several bacterial taxa demonstrated positive correlations with various immune pathways, including NOD-like receptor signaling (*Streptococcus*), TLR expression/TLR signaling (*Staphylococcus* and *Prevotella*) and TOLLIP expression (*Pseudomonas*). Additional associations were identified between specific bacterial genus members and fibroblast responsiveness to CpG-ODN and phenotypes of circulating T-cells.

### Comments

1. These results provide function-oriented evidence in support of bacterial-host interactions in the pathogenesis of IPF and survival outcomes.
2. The associations involving several bacterial OTUs highlight that a collection of bacterial-host interactions may be important in IPF progression, although causal direction cannot be determined.
3. It is unclear if similar associations exist between the identified microbiota members and innate immune responses in IPF lung cells (e.g. alveolar macrophages).
4. Whether specific lung microbiota modulate existing host defense alterations in IPF and functionally contribute to disease progression is uncertain.

### NON-CYSTIC FIBROSIS BRONCHIECTASIS

Taylor SL, Woodman RJ, Chen AC, Burr LD, Gordon DL, McGuckin MA, Wesselingh S, Rogers GB. **FUT2 genotype influences lung function, exacerbation frequency and airway microbiota in non-CF bronchiectasis.** *Thorax.* 2016 Aug 8. pii:thoraxjnl-2016-208775.

#### Summary

Non-CF bronchiectasis patients suffer significant morbidity from complications of chronic airway infection including exacerbations. Bacterial colonization patterns commonly include culture isolation of *Haemophilus influenzae* and *Pseudomonas aeruginosa*. It is unclear if the broader composition of airway microbiota influences exacerbations in non-CF bronchiectasis and further, whether microbiota patterns are associated with host-specific mucosal factors that shape susceptibility to infections such as variability in mucosal glycan expression. Loss-of-function mutations in the FUT2 gene result in an inability to express glycans on mucosal surfaces; such individuals are known as “non-secretors” whereas “secretors” carry at least one functional copy. Here, sputum collected at baseline from subjects in the BLESS trial was analyzed using 16S rRNA gene pyrosequencing and fungal and virus-specific Q-PCR. Paired FUT2 genotype (23 “non-secretors”, 48 heterozygote and 22 homozygote “secretors”) and sputum bacterial community data were determined in 93 patients. Sputum profiles were dominated by either *P. aeruginosa* (n=25), *H. influenzae* (n=33), or other species (n=35). Non-secretors demonstrated significantly lower prevalence of *P. aeruginosa*-dominated airway infections, higher lung function and fewer exacerbations during the trial, compared to secretor genotypes. The prevalence of non-dominant bacterial taxa or the presence of tested fungi (*C. albicans* and *A. fumigatus*) and viruses, however, did not differ between non-secretors and secretors.

**Comments**

1. Stratification of non-CF bronchiectasis patients by FUT2 genotype may have prognostic value in identifying patients at increased risk for exacerbation and disease progression.
2. Sputum microbiota relationships to FUT2 genotype were limited to associations with *P. aeruginosa* dominance, leaving unclear what microbiota interactions underlie exacerbations and outcomes in non-Pseudomonas-dominated, non-secretor patients.
3. The study was likely underpowered technically to discriminate relationships between less abundant members of the microbiota and secretor status.

Shenoy MK, Iwai S, Lin DL, Worodria W, Ayakaka I, Byanyima P, Kaswabuli S, Fong S, Stone S, Chang E, Davis JL, Faruqi AA, Segal MR, Huang L, Lynch SV. **Immune Response and Mortality Risk Relate to Distinct Lung Microbiomes in Patients with HIV and Pneumonia.** *Am J Respir Crit Care Med.* 2017 Jan 1;195(1):104-114.

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**OTHER ARTICLES OF INTEREST**

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Dickson RP, Singer BH, Newstead MW, Falkowski NR, Erb-Downward JR, Standiford TJ, Huffnagle GB. **Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome.** *Nat Microbiol.* 2016 Jul 18;1(10):16113.

Korten I, Mika M, Klenja S, Kieninger E, Mack I, Barbani MT, Gorgievski M, Frey U, Hilty M, Latzin P. **Interactions of Respiratory Viruses and the Nasal Microbiota during the First Year of Life in Healthy Infants.** *mSphere.* 2016 Nov 23;1(6).

Molyneaux PL, Willis Owen SA, Cox MJ, James P, Cowman S, Loebinger M, Blanchard A, Edwards LM, Stock C, Daccord C, Renzoni EA, Wells AU, Moffatt MF, Cookson WO, Maher TM. **Host-Microbial Interactions in Idiopathic Pulmonary Fibrosis.** *Am J Respir Crit Care Med.* 2017 Jan 13.

Prevaes SM, de Winter-de Groot KM, Janssens HM, de Steenhuijsen Piters WA, Tramper-Stranders GA, Wyllie AL, Hasrat R, Tiddens HA, van Westreenen M, van der Ent CK, Sanders EA, Bogaert D. **Development of the Nasopharyngeal Microbiota in Infants with Cystic Fibrosis.** *Am J Respir Crit Care Med.* 2016 Mar 1;193(5):504-15.

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University of Dundee  
Scottish Centre for Respiratory Research  
Dundee, United Kingdom**PATIENT CHARACTERISTICS IN THE UNITED STATES**

Aksamit TR, O'Donnell AE, Barker A, Olivier KN, Winthrop KL, Daniels ML, Johnson M, Eden E, Griffith D, Knowles M, Metersky M, Salathe M, Thomashow B, Tino G, Turino G, Carretta B, Daley CL. **Adult bronchiectasis patients: a first look at the United States Bronchiectasis Research Registry.** *Chest* 2016; Nov 23. pii: S0012-3692(16)62354-1. doi: 10.1016/j.chest.2016.10.055.

**Summary**

Bronchiectasis is a heterogeneous disorder caused by a wide range of different underlying diseases and with diverse patient characteristics. As an "orphan" disease, its characteristics and natural history have not been well documented. There are limited data regarding bronchiectasis from the United States. Multicenter registries such as the United States Bronchiectasis Research Registry and the European EMBARC registry provide the opportunity to better characterize the disease.

This article presents the first data from the U.S. registry, describing data on 1826 patients recruited from 2008 to 2014. Patients were predominantly female and never smokers with moderate lung function impairment. A key finding of this study was that 63% of patients had a history of isolation of non-tuberculous Mycobacteria. Other aetiologies and comorbidities included pneumonia in nearly 70%, COPD in 20% and rheumatological diseases in 8%. The first data on treatment of bronchiectasis in the U.S. is presented with the most frequent treatments being inhaled bronchodilators (61%), corticosteroids (39%) and suppressive antibiotics (39%).

**Comments**

1. The high frequency of NTM disease in the U.S. contrasts with European data, and suggests that investigation for NTM should be mandatory for bronchiectasis patients presenting in the United States.
2. This study shows a high burden of disease, with a mean of 3 exacerbations in the past 2 years and a high burden of symptoms
3. 1/3 of patients have *Pseudomonas aeruginosa* infection at baseline in the registry- a population we know has more severe disease and a worse outcome.
4. There are no licensed therapies for bronchiectasis, and all treatments described in this registry are off label. The most frequently used drugs, such as bronchodilators and inhaled steroids, have no supporting trial evidence.

5. The Registry along with other longitudinal international studies will provide the opportunity to understand outcomes and the impact of different patient characteristics and therapies, while also supporting randomized trials.

**A LINK BETWEEN BRONCHIECTASIS AND CARDIOVASCULAR DISEASE**

Navaratnam V, Millett ER, Hurst JR, Thomas SL, Smeeth L, Hubbard RB, Brown J, Quint JK. **Bronchiectasis and the risk of cardiovascular disease: a population-based study.** *Thorax*. 2017 Feb;72(2):161-166. doi: 10.1136/thoraxjnl-2015-208188.

**Summary**

We have learned from other respiratory diseases, particularly COPD, that much of the mortality is attributable to comorbidities rather than directly due to respiratory failure. Bronchiectasis is a systemic inflammatory disorder, and is closely associated with comorbidities that have been linked to increased cardiovascular complications. A link between bronchiectasis and cardiovascular disease, has, however, not been clearly established.

Navaratnam and colleagues used a large electronic database with 10,942 patients with a recorded diagnosis of bronchiectasis to establish a link between bronchiectasis and cardiovascular events. After a median of 5.6 years follow-up, comparing patients with bronchiectasis to controls without bronchiectasis, first cardiovascular events occurred more frequently in bronchiectasis patients (hazard ratio 1.42 95% CI 1.25-1.60,  $p < 0.001$ ). Stroke rates were also 69% higher in bronchiectasis patients vs controls. The same effects were observed after excluding co-existing COPD and those with a history of smoking.

The authors conclude that bronchiectasis likely increases the risk of cardiovascular disease and stroke. This has important implications for wholistic care of these patients where management of comorbidities may have an important impact on outcome

**Comments**

1. Routine datasets give an entirely different view of bronchiectasis compared to registries or cohorts from specialist centers, with higher rates of COPD and asthma associated disease and a higher rate of smokers



2. The increased rates of cardiovascular disease and stroke observed in this study are clinically important. The mechanism is unclear and should be further investigated with possibilities including systemic inflammation or the effect of exacerbations.
3. Limitations of routine datasets include a lack of CT validation of the bronchiectasis diagnosis and limited collection of confounders, so conclusions should be treated with caution.
4. There are currently no data on prevention of cardiac events in patients with bronchiectasis.
5. Bronchiectasis is a heterogeneous disorder and this dataset does not contain sufficient phenotypic detail to identify the patient groups at highest risk.

## COMORBIDITIES AND OUTCOMES

McDonnell MJ, Aliberti S, Goeminne PC, Restrepo MI, Finch S, Pesci A, Dupont LJ, Fardon TC, Wilson R, Loebinger MR, Skrbic D, Obradovic D, De Soyza A, Ward C, Laffey JG, Rutherford RM, Chalmers JD. **Comorbidities and the risk of mortality in patients with bronchiectasis: an international multicentre cohort study.** *Lancet Respir Med.* 2016 Dec;4(12):969-979. doi: 10.1016/S2213-2600(16)30320-4.

### Summary

The majority of bronchiectasis patients are elderly and therefore frequently have comorbidities. Approximately 50% of patients have an underlying disorder predisposing to bronchiectasis, such as rheumatological disease, inflammatory bowel disease, ciliary disorders and allergic bronchopulmonary aspergillosis. The impact of these comorbidities and aetiologies on clinical presentation and outcomes of bronchiectasis have not been defined. This European cohort study of 986 patients used multivariable analysis to identify risk factors for mortality over 5 years. The study identified that comorbidities were common, with a median of 4 comorbidities per patient, and showed that multiple comorbidities including haematological malignancy, COPD, inflammatory bowel disease, connective tissue diseases and asthma were associated with higher mortality. A model based on these characteristics was more accurate at predicting mortality than disease severity scores. The study concludes that patients with specific aetiologies and comorbidities such as those above should be followed-up more carefully and the treatable comorbidities should be identified and managed to improve outcomes.

### Comments

1. A number of comorbidities and aetiologies are associated with worse outcomes in bronchiectasis, including mortality and severe exacerbations.
2. Scoring systems such as the bronchiectasis severity index and the aetiology and comorbidity index can

predict disease outcomes with a high degree of accuracy, and have been independently validated.

3. An association was demonstrated between comorbidities and exacerbations, while patients with *Pseudomonas aeruginosa* infection also had more frequent comorbidities, suggesting a link between comorbidities and lung disease.
4. Prediction models have predominantly only been tested in Europe, and require further validation in other health care systems including the United States

## BRONCHIECTASIS IN COPD

Diaz AA, Young TP, Maselli DJ, Martinez CH, Gill R, Nardelli P, Wang W, Kinney GL, Hokanson JE, Washko GR, San Jose Estepar R. **Quantitative CT measures of bronchiectasis in smokers.** *Chest.* 2016 Nov 24. pii: S0012-3692(16)62460-1. doi: 10.1016/j.chest.2016.11.024. [Epub ahead of print]

### Summary

Bronchiectasis is increasingly reported in patients with COPD. Some have suggested that bronchiectasis may influence outcomes or may be a “phenotype” of COPD. This manuscript has important implications for our understanding of bronchiectasis in COPD. Using data from the COPD Gene study, Diaz and colleagues sought to use quantitative CT to objectively measure airway and vascular size and associated features in 21 smokers with a radiological diagnosis of bronchiectasis (including 17 with COPD) and 21 never smoking controls.

In health, the bronchus should be smaller than the adjacent vessel at every level on CT. Therefore a bronchial:arterial ratio (BA ratio) >1 indicates “dilatation” and may be reported as bronchiectasis. This study, however, reports that subjects with bronchiectasis had increased BA ratios primarily driven by reductions in the vessel diameter. Subjects with “bronchiectasis” did not have major increases in bronchial diameter compared to healthy subjects at the same level, but had smaller blood vessels giving the “artificial” appearance of bronchiectasis. Wall thickness was associated with sputum production, the defining symptom of clinical bronchiectasis, and inversely related to FEV1, but BA ratio was not. Oxygen saturations were correlated to bronchial artery diameters leading the authors to speculate that reduced vessel size may indicate hypoxic vasoconstriction.

These findings are intriguing, as we see more and more patients with bronchiectasis COPD overlap. This is a small study and it is important to point out that larger studies will be needed. Nevertheless, the situation is clearly not as simple as some have suggested with bronchiectasis as an infection driven “phenotype” of COPD.

## Comments

1. Radiological bronchiectasis is not always due to bronchial dilatation, but may also reflect pulmonary vascular disease.
2. As radiological bronchiectasis does not necessarily reflect "clinical bronchiectasis" its role in guiding treatment is likely to be limited.
3. Consider airway infection, pulmonary vascular disease and NTM infection in patients with COPD and bronchiectasis, but also be aware that bronchiectasis may reflect an incidental finding with no clinical significance.
4. Bronchial wall thickness may be a useful radiological indicator of active inflammation.
5. These data should be interpreted with caution given the small sample size.

## RISING DISEASE PREVALENCE IN THE U.K.

Quint JK, Millett ER, Joshi M, Navaratnam V, Thomas SL, Hurst JR, Smeeth L, Brown JS. **Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study.** *Eur Respir J.* 2016 Jan;47(1):186-93. doi: 10.1183/13993003.01033-2015.

## Summary

Bronchiectasis was previously thought to be a rare or orphan disease. Accurate assessment of prevalence of bronchiectasis helps to understand disease burden as well as characterize the patients. Using routine health care data from the U.K., Quint and colleagues describe the prevalence of the disease from 2004 to 2013. They observed an increase of approximately 40% in the prevalence over that nearly 10 year period, rising to a prevalence of 485 per 100,000 in men and 566 per 100,000 in female at the end of the study period.

Interestingly, 30% of patients were current smokers, which is at odds with rates reported in the U.S. bronchiectasis registry and European cohorts. 42% of patients had a prior history of asthma while 36% had a prior history of COPD. No other aetiologies account for more than 10% of bronchiectasis cases.

This dataset did not allow exploration of why the prevalence was increasing so rapidly.

## Comments

1. Bronchiectasis prevalence is increasing rapidly, particularly in individuals with a past history of asthma and COPD.
2. Possible reasons for the increasing prevalence include increasing use of CT, increased disease awareness or the aging population, as bronchial/arterial ratio increases with age.
3. Mortality rates in this population for bronchiectasis patients were more than twice the mortality rate in

the general population, independent of age and other confounders.

4. Similar data have been reported from Germany and the U.S., suggesting a global increase in bronchiectasis impact.

## OTHER ARTICLES OF INTEREST

Diaz AA, Young TP, Maselli DJ, Martinez CH, Maclean ES, Yen A, Dass C, Simpson SA, Lynch DA, Kinney GL, Hokanson JE, Washko GR, San José Estépar R. **Bronchoarterial ratio in never-smokers adults: Implications for bronchial dilation definition.** *Respirology.* 2017 Jan;22(1):108-113. doi: 10.1111/resp.12875.

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Chalmers JD, McDonnell MJ, Rutherford R, Davidson J, Finch S, Crichton M, Dupont L, Hill AT, Fardon TC, De Soyza A, Aliberti S, Goeminne P. **The generalizability of bronchiectasis randomized controlled trials: A multicentre cohort study.** *Respir Med.* 2016 Mar;112:51-8. doi: 10.1016/j.rmed.2016.01.016.

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## ANTIBODY-MEDIATED REJECTION

Levine DJ, Glanville AR, Aboyou C, Belperio J, Benden C, Berry GJ, Hachem R, Hayes D Jr, Neil D, Reinsmoen NL, Snyder LD, Sweet S, Tyan D, Verleden G, Westall G, Yusef RD, Zamora M, Zeevi A. **Antibody-mediated rejection of the lung: A consensus report of the International Society for Heart and Lung Transplantation.** *J Heart Lung Transplant* 2016;35:397-406.

### Summary

Antibody-mediated rejection (AMR) has been defined in other transplanted organs but there has not been a standardized definition in lung transplants. A working group of the International Society of Heart and Lung Transplantation (ISHLT) developed a working definition to facilitate further research and improve clinical identification of this syndrome, though many gaps in knowledge currently exist. Evidence of allograft dysfunction is a prerequisite for “clinical AMR” and is broadly defined as alterations in pulmonary physiology, gas exchange, radiologic features or functional performance. The level of certainty in AMR diagnosis depends on the number of diagnostic criteria present. Definite AMR includes 3/3 of the following factors while probable AMR includes 2/3 of: (1) circulating donor-specific anti-HLA antibodies (DSA), (2) histopathologic changes consistent with AMR; and (3) C4d staining of interstitial alveolar capillaries in a linear pattern as evidence of complement fixation. Other causes of graft dysfunction such as infection should generally be excluded, but probable AMR may be diagnosed with concurrent causes of graft dysfunction if other diagnostic criteria are present. The report also includes definitions for “subclinical AMR” where allograft dysfunction is not present.

### Comments

1. Similar to prior ISHLT consensus definitions of primary graft dysfunction and bronchiolitis obliterans syndrome, this is an empiric definition which will be useful in facilitating further dialogue and discovery and will likely be revised over time as knowledge gaps are addressed.
2. The optimal approach to treating clinical AMR (or the more contentious “subclinical AMR” where graft function is preserved) is unclear and the consensus report did not include treatment recommendations.
3. The report and accompanying supplementary material highlight many areas for further research including immunologic testing for DSA and non-HLA antibodies, standardization of the pathology of AMR, and refining clinical aspects of AMR diagnosis and treatment.

## ACCESS TO TRANSPLANTATION

Sell JL, Bacchetta M, Goldfarb SB, Park H, Heffernan PV, Robbins HA, Shah L, Raza K, D'Ovidio F, Sonett JR, Arcasoy SM, Lederer DJ. **Short stature and access to lung transplantation in the United States. A cohort study.** *Am J Respir Crit Care Med* 2016;193:681-8.

### Summary

Lung transplant centers frequently attempt to match donor lungs to recipients based on height or total lung capacity. The authors hypothesized that this may disadvantage transplant candidates of below-average height. This retrospective cohort study included 13,346 adults listed for lung transplantation in the United States between 2005 and 2011. Associations between recipient height and outcomes on the waiting list and post-transplant were evaluated using multivariable competing risk survival models. Compared with candidates of average height (170-176.5 cm), candidates in the lowest height quartile (<162 cm) had a 34% lower rate of transplantation, a 62% higher rate of death or removal from the waiting list due to clinical deterioration, and a 42% higher rate of respiratory failure on the waiting list. Women comprised 93% of individuals in the lowest height quartile. Height was not associated with survival after transplantation.

### Comments

1. Shorter individuals are subjected to a disparity in access to transplantation; this disparity particularly affects women who may also be disadvantaged by allosensitization.
2. One potential solution is reappraisal of accepted surgical practices to increase transplantation of “oversized” organs, or “downsizing” of donor lungs through lobar transplantation or non-anatomic volume reduction.
3. The authors also advocate for earlier transplant referral of short individuals, and inclusion of candidate height in the lung allocation algorithm.
4. This work adds to other recent literature demonstrating geographic and social (insurance status, socioeconomic status) barriers to transplantation; recognition of these disparities may prompt earlier referral for lung transplantation and guide advocacy efforts to promote a more equitable health care system.

## CHRONIC LUNG ALLOGRAFT DYSFUNCTION PHENOTYPES

DerHovanesian A, Todd JL, Zhang A, Li N, Mayalall A, Finlen Copeland CA, Shino M, Pavlisko EN, Wallace DW, Gregson A, Ross DJ, Saggat R, Lynch JP, Belperio J, Snyder LD, Palmer SM, Weigt SS. **Validation and refinement of chronic lung allograft dysfunction phenotypes in bilateral and single lung recipients.** *Ann Am Thorac Soc* 2016;13:637-635

### Summary

It is now well-recognized that chronic lung allograft dysfunction can present with a restrictive phenotype (termed restrictive allograft syndrome, or restrictive CLAD) which carries a worse prognosis than the more common obstructive phenotype of bronchiolitis obliterans syndrome. This restrictive phenotype has been defined by loss of total lung capacity in bilateral lung transplant recipients. This two-center retrospective cohort study examined the predictive validity of an alternate definition of forced vital capacity (FVC) loss in single and bilateral lung transplant recipients, and examined the additional utility of pleural or parenchymal fibrosis on chest computed tomography (CT). 389 recipients with CLAD were included in the study. CLAD was defined by >20% FEV1 loss and sub-classified by presence or absence of concomitant >20% FVC loss. Subjects with FVC loss had a higher mortality risk, and this applied to both bilateral (HR=2.75, 95% CI 2.02-3.73) and single (HR=1.80, 95% CI 1.09-2.98) lung transplant recipients. In subjects without FVC loss, CT fibrosis was also associated with a higher mortality risk in both single and bilateral recipients.

### Comments

1. Validation of the proposed FVC loss definition of restrictive CLAD phenotype in single lung transplant recipients is important, as it was unclear whether native lung FVC loss could limit the prognostic utility of PFT changes in this setting.
2. Pleural or parenchymal fibrotic changes on CT may be especially useful in single lung transplant recipients, since it is easier to identify whether changes have occurred in the native or the transplanted lung.
3. One important caveat is that FVC loss may not be indicative of restriction if the FVC is being reduced by air trapping; lung volumes were not measured in this study and so could not be used to validate this definition of restrictive physiology.
4. It is possible that combinations of imaging and pulmonary function measurements will have the highest predictive value; see additional references for alternate approaches to CLAD phenotyping.
5. Irrespective of measurement method used, otherwise unexplained loss of graft function in a restrictive pattern is an ominous development which is largely untreatable and should prompt consideration of re-transplantation, although this may also be associated with inferior outcomes.

## LONG-TERM COMPLICATIONS

Mansh M, Binstock M, Williams K, Hafeez F, Kim J, Glidden D, Boettger R, Hays S, Kukreja J, Golden J, Asgari MM, Chin-Hong P, Singer JP, Arron ST. **Voriconazole exposure and risk of cutaneous squamous cell carcinoma, Aspergillus colonization, invasive aspergillosis and death in lung transplant recipients.** *Am J Transplant* 2016;16:262-70.

### Summary

Some lung transplant programs use voriconazole for prophylaxis of Aspergillus infections in lung transplant recipients; however it is not known whether the benefits of this practice outweigh the risks. This single-center retrospective cohort study included 455 lung recipients transplanted between 1991-2012 in San Francisco. 84.5% of subjects were exposed to voriconazole. Multivariate survival models were used to examine associations between voriconazole exposure and outcomes including diagnosis of cutaneous squamous cell carcinoma (SCC), Aspergillus colonization, invasive aspergillosis and all-cause mortality. There were several changes in immunosuppressive protocols and approach to prophylaxis and treatment of Aspergillus infections during this period; however, the authors attempted to adjust for these changes. During the study period, 19% of subjects developed at least one SCC, 26% developed Aspergillus colonization, and 17% developed invasive aspergillosis. Voriconazole exposure was associated with an increased risk of SCC (HR 1.73, 95% CI 1.04-2.88) and this effect was dose-dependent. Voriconazole exposure was associated with a lower risk of Aspergillus colonization, but not of invasive aspergillosis. Voriconazole exposure was associated with reduced all-cause mortality among subjects who developed Aspergillus colonization (HR=0.34, 95% CI 0.13-0.91) but not among those who did not develop colonization. Other antifungal agents including inhaled amphotericin B and posaconazole were not associated with an increased risk of SCC.

### Comments

1. There were several important limitations to this work including the observational design, high prevalence of voriconazole exposure, and inability to account for known confounders including smoking, skin type, sun exposure, and intensity of immunosuppression.
2. Nevertheless, this study demonstrates that a "one-size-fits-all" approach to prophylaxis may be inappropriate and confer increased risks of SCC without reducing infection or mortality risk.
3. This study suggests that targeted prophylaxis of individuals who are colonized with Aspergillus may be beneficial, but this should be studied in the context of a randomized trial.
4. It is possible that other biomarkers such as BAL galactomannan may help further refine the approach to

targeted prophylaxis and limit antifungal therapy to those with a favorable risk-benefit ratio.

5. Sun protection counselling and regular skin surveillance are also very important in the management of all lung transplant recipients, but especially those at higher risk by virtue of prior skin cancer history, fair skin type, age, male sex, residence in a region of high sun exposure and exposure to photosensitizing medications.

## INNOVATIVE CLINICAL CARE MODELS

DeVito Dabbs A, Song MK, Myers BA, Li R, Hawkins RP, Pilewski JM, Bermudez CA, Aubrecht J, Begey A, Connolly M, Alrawashdeh M, Dew MA. **A randomized controlled trial of a mobile health intervention to promote self-management after lung transplantation.** *Am J Transplant* 2016;16:2172-80.

### Summary

Given the high frequency of adverse outcomes after lung transplantation, patients are encouraged to take an active role in monitoring their health, hoping this will promote medication adherence and earlier identification of treatable complications. This single-center randomized controlled trial assigned 201 first-time lung recipients at hospital discharge to either usual care (including recording of health indicators in paper logs) or a mobile health (mHealth) intervention which consisted of a smartphone programmed to allow recording of health indicators (e.g. lung function, vital signs), viewing of trends in indicators over time, and automated feedback to contact the coordinator if indicators fell outside normal parameters. Smartphone data were not automatically shared with the transplant team. Outcomes were assessed up to 12 months post-transplant. The mHealth group demonstrated more self-monitoring, better adherence, and more frequent reporting of abnormal results than the standard care group. However, there was no difference in re-hospitalization rates or mortality between the two groups. In a follow-up report of 182 survivors of the 12-month trial (see additional references) with a median follow up of 5.7 years post-transplant, there was no difference in BOS rates between the intervention and control groups. In the entire cohort irrespective of treatment assignment, self-monitoring and reporting of abnormal results to the health care team in the first 12 months were associated with lower subsequent risks of death and BOS.

### Comments

1. Of note, both groups showed a decline in self-management behaviors over time, which perhaps contributed to the lack of difference noted in health outcomes between the two groups.
2. Limitations to generalizability include the relatively old patient cohort (either mainly or exclusively in their 50s and 60s with a high prevalence of COPD), whereas nonadherence may be more prevalent among younger

patients; the provision of smartphones and the use of older technology.

3. The follow up analysis did show that early self-management behaviors and reporting of abnormal health indicators were subsequently associated with better outcomes.
4. It is possible that technologies which embed self-management into patients' own smartphones and/or automatically report poor self-management or abnormal results to transplant teams will provide earlier opportunities for intervention and improve outcomes, but this article illustrates that mobile technologies cannot be automatically assumed to be effective.

## SAFETY OF ANTIFIBROTIC MEDICATIONS

Delanote I, Wuyts W, Yserbyt J, Verbeken EK, Verleden GM, Vos R. **Safety and efficacy of bridging to lung transplantation with antifibrotic drugs in idiopathic pulmonary fibrosis: a case series.** *BMC Pulm Med* 2016;16:156.

### Summary

With the long-awaited advent of effective therapies to delay progression of idiopathic pulmonary fibrosis, transplant programs have lacked information about whether these drugs are safe to continue in patients on the waiting list for transplantation. This single-center case series of 9 patients is the largest reported experience to date. The series include patients who received lung transplants while taking nintedanib or pirfenidone. They were compared with a small group of 6 contemporaneously transplanted control patients who did not receive antifibrotics. Moderate declines in lung function on the waiting list were observed in both treated and control patients. Significant weight loss occurred in treated patients. There were no obvious indications of increased perioperative or post-transplant risks of antifibrotics with respect to bleeding, wound healing, anastomotic complications, primary graft dysfunction, early CLAD or survival after a median 19.8 month follow up.

### Comments

1. While no patients died on the waiting list while taking antifibrotic drugs, the authors did not report how many patients had to discontinue these drugs after listing for side effects such as weight loss, GI intolerance or hepatitis.
2. Several patients were enrolled in randomized clinical trials post-transplant, which may have had effects on observed outcomes.
3. While more experience is needed to draw firm conclusions about the safety of these drugs, these preliminary data provide some reassurance.
4. While the same group has previously published a case report on treatment of restrictive allograft syndrome with pirfenidone, it is not clear whether these drugs have any benefit in the post-transplant setting.

## OTHER ARTICLES OF INTEREST

## DONOR-SPECIFIC ANTIBODIES

Tikkanen JM, Singer LG, Kim SJ, Li Y, Binnie M, Chaparro C, Chow CW, Martinu T, Azad S, Keshavjee S, Tinckam K. De Novo DQ. **Donor-Specific Antibodies Are Associated with Chronic Lung Allograft Dysfunction after Lung Transplantation.** *Am J Respir Crit Care Med* 2016;194(5):596-606.

Wallace WD, Li N, Andersen CB, Arrossi AV, Askar M, Berry GJ, DeNicola MM, Neil DA, Pavlisko EN, Reed EF, Remmelink M, Weigt SS, Weynand B, Zhang JQ, Budev MM, Farver CF. **Banff study of pathologic changes in lung allograft biopsy specimens with donor-specific antibodies.** *J Heart Lung Transplant* 2016; 35:40-8.

## ACCESS TO TRANSPLANTATION

Ramos KJ, Quon BS, Psoter KJ, Lease ED, Mayer-Hamblett N, Aitken ML, Goss CH. **Predictors of non-referral of patients with cystic fibrosis for lung transplant evaluation in the United States.** *J Cyst Fibros* 2016;15(2):196-203

Egan TM, Edwards LB. **Effect of the lung allocation score on lung transplantation in the United States.** *J Heart Lung Transplant* 2016;35:433-9.

Tsuang WM; Chan KM; Skeans MA; Pyke J; Hertz MI; Israni AJ; Robbins-Callahan L; Visner G; Wang X; Wozniak TC; Valapour M. **Broader geographic sharing of pediatric donor lungs improves pediatric access to transplant.** *Am J Transplant* 2016;16:930-7.

## CHRONIC LUNG ALLOGRAFT DYSFUNCTION PHENOTYPES AND PROGNOSIS

Saito T, Horie M, Sato M, Nakajima D, Shoushtarizadeh H, Binnie M, Azad S, Hwang DM, Machuca TN, Waddell TK, Singer LG, Cypel M, Liu M, Paul NS, Keshavjee S. **Low-dose computed tomography volumetry for subtyping chronic lung allograft dysfunction.** *J Heart Lung Transplant* 2016;35:59-66.

Suhling H, Dettmer S, Greer M, Fuehner T, Avsar M, Haverich A, Welte T, Gottlieb J. **Phenotyping chronic lung allograft dysfunction using body plethysmography and computed tomography.** *Am J Transplant* 2016;16:3163-3170.

Belloli EA, Degtiar I, Wang X, Yanik GA, Stuckey LJ, Verleden SE, Kazerooni EA, Ross BD, Murray S, Galban CJ, Lama VN. **Parametric response mapping as an imaging biomarker in lung transplant recipients.** *Am J Respir Crit Care Med* 2016 Oct 25. [Epub ahead of print].

Verleden SE, Ruttens D, Vandermeulen E, Bellon H, Dubbeldam A, De Wever W, Dupont L, Van Raemdonck DE, Vanaudenaerde BM, Verleden GM, Benden C, Vos R. **Predictors of survival in restrictive chronic lung allograft dysfunction after lung transplantation.** *J Heart Lung Transplant* 2016; 35:1078-84.

## CHRONIC LUNG ALLOGRAFT DYSFUNCTION PREVENTION

Ruttens D, Verleden SE, Vandermeulen E, Bellon H, Vanaudenaerde BM, Somers J, Schoonis A, Schaevers V, Van Raemdonck DE, Neyrinck A, Dupont LJ, Yserbyt J, Verleden GM, Vos R. **Prophylactic azithromycin therapy after lung transplantation: Post hoc analysis of a randomized controlled trial.** *Am J Transplant* 2016;16:254-61.

Strueber M, Warnecke G, Fuge J, Simon AR, Zhang R, Welte T, Haverich A, Gottlieb J. **Everolimus vs. mycophenolate mofetil de novo after lung transplantation: a prospective, randomized open-label trial.** *Am J Transplant* 2016;16:3171-3180.

Gottlieb J; Zamora MR; Hodges T; Musk AW; Sommerwerk U; Dilling D; Arcasoy S; DeVincenzo J; Karsten V; Shah S; Bettencourt BR; Cehelsky J; Nochur S; Gollob J; Vaishnav A; Simon AR; Glanville AR. **ALN-RSV01 for prevention of bronchiolitis obliterans syndrome after respiratory syncytial virus infection in lung transplant recipients.** *J Heart Lung Transplant* 2016;35:213-21.

## INNOVATIVE CLINICAL CARE MODELS

Rosenberger EM, DeVito Dabbs AJ, DiMartini AF, Landsittel DP, Pilewski JM, Dew MA. **Long-term follow up of a randomized controlled trial evaluating a mobile health intervention for self-management in lung transplant recipients.** *Am J Transplant* 2016 Sep 24 (Epub ahead of print).

## EX-VIVO LUNG PERFUSION

Yeung JC, Krueger T, Yasufuku K, de Perrot M, Pierre AF, Waddell TK, Singer LG, Keshavjee S, Cypel M. **Outcomes after transplantation of lungs preserved for more than 12 h: a retrospective study.** *Lancet Respir Med*; 2016 Nov 17 (Epub ahead of print).

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## LUNG CANCER SCREENING

Katki HA, Kovalchik SA, Berg CD et al. **Development and Validation of Risk Models to Select Ever-Smokers for CT Lung Cancer Screening.** *JAMA Intern Med.* 2017; 177:399-406.

### Summary

While a straightforward definition of “high risk” is necessary for the practical purposes of clinical trials such as the NLST, in clinical practice, we know that lung cancer risk estimation includes factors beyond age and smoking. Risk-based strategies argue that screening recommendations should accommodate “equal management of people at equal risk.” Risk assessment of the NLST population identifies subgroups with varying risks, with the majority of benefit (decreased lung cancer deaths) occurring in the highest risk groups, and relatively little benefit realized in the lowest risk groups. Katki and colleagues developed models for lung cancer incidence and death in ever-smokers from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) control group, using the assumption that the NLST mortality reduction of 20.4% would be applicable to ever-smokers independent of exposure level. These were validated in the chest radiography arms of the PLCO and NLST; the death model was additionally validated in the National Health Interview Survey population. They conclude that screening 9 million ever-smokers ages 50-80 identified by modeling as at highest 5-year risk of lung cancer (>1.9%) would result in a 20% relative increase in CT-preventable deaths compared to screening the 9 million Americans eligible by USPSTF recommendations.

### Comments

1. Screening the 9 million Americans eligible by USPSTF recommendations was projected to result in the prevention of 46,488 (95%CI, 43,924-49,053) lung cancer deaths over 5 years, vs. screening 9 million ever-smokers aged 50-80 identified as at highest 5-year risk of lung cancer (> 1.9%) by the risk models, which was projected to prevent 55,717 (95%CI, 53,033-58,400) lung cancer deaths over 5 years ( $P < .001$ ).
2. Compared with USPSTF recommendations, the risk model-based strategy was projected to have greater estimated screening effectiveness [Number Needed to Screen to prevent one lung cancer death: 194 (95%CI, 187-201) vs 162 (95%CI, 157-166);  $P < .001$ ], and greater estimated screening efficiency [fewer false-positive screening examinations per prevented death: 133 (95%CI, 128-137) vs. 116 (95%CI, 113-119);  $P < .001$ ].

3. The results suggest that application of risk-based strategies would preferentially replace the low-risk, low-benefit USPSTF-eligible population with a readily identifiable high-risk, high-benefit USPSTF-ineligible population.
4. At present, the Centers for Medicare and Medicaid Services will only support lung cancer screening for individuals who meet the USPSTF lung cancer screening recommendation criteria.
5. Whether lung cancer risk predictive models should be used in determining who should be screened deserves further study.

## LUNG CANCER SCREENING: IMPLEMENTATION

Kinsinger LS, Anderson C, Kim J, Larson M, Chan SH, King HA, Rice KL, Slatore CG, Tanner NT, Pittman K, Monte RJ, McNeil RB, Grubber JM, Kelley MJ, Provenzale, Datta SK, Sperber NS, Barnes L, Abbott DH, Sims KJ, Whitley RL, Wu RR, Jackson GL. **Implementation of Lung Cancer Screening in the Veterans Health Administration.** *JAMA Intern Med.* 2017; 177:399-406.

### Summary

Implementation of high quality lung cancer screening is challenging, as demonstrated by this Veterans Health Administration (VHA) clinical demonstration project. Among a total primary care population of 93,033 individuals at 8 VHA hospitals, 4246 met USPSTF screening criteria. Accurate smoking history information was difficult to obtain from the electronic health record, and only 2106 (57.7%) patients agreed to be screened. Clinical care coordination (scheduling, patient education, shared decision making, communicating results, follow up, etc.) required a full-time coordinator at each site. Multiple revisions of protocols, electronic tools, and educational materials were necessary. Using the Fleischner Society pulmonary nodule guidelines, 59.7% of screened patients had positive findings; 66.5% of nodules were < 6 mm in diameter. A wide range of nodular findings among the 8 sites was noted (30.7% to 85%), raising the possibilities of geographic differences or substantial variation in radiologist reporting. 40% of patients had other incidental, non-nodule findings. The rate of lung cancer on the prevalence scan was 1.4%.

This observational study should not be interpreted as arguing against lung cancer screening. It does point out that implementation of screening is a complex process, and ideally should be undertaken by a committed team using standardized approaches and algorithms.

## Comments

1. High quality lung cancer screening requires a multidisciplinary effort to rigorously structure selection of patients, radiology reporting, identification of lung nodules, standardized lung nodule management, and data collection and reporting.
2. The American College of Radiology recommends radiology reporting for LDCT lung cancer screening studies be done with Lung-RADS, which provides structured algorithms for nodule reporting and management, and aims to minimize false positive findings.
3. The policy statement from the American Thoracic Society and the American College of Chest Physicians articulates the components necessary to develop and implement high quality lung cancer screening; these are recapitulated in the memo from the Centers for Medicare and Medicaid Services outlining the requirements for authorization and reimbursement of lung cancer screening.
4. Nearly half of patients in this demonstration project who met USPSTF criteria elected not to undergo lung cancer screening; the reasons for this should be further investigated.

## PULMONARY NODULES

MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, Mehta AC, Ohno Y, Powell CA, Prokop M, Rubin GD, Schaefer-Prokop CM, Travis WD, Van Schil PE, and Bankier AA. **Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017.** *Radiology* 2017. <http://pubs.rsna.org/doi/abs/10.1148/radiol.2017161659> (ahead of print).

### Summary

Pulmonary nodules are exceedingly common incidental findings on CT imaging. An estimated 1.5 million individuals in the US will have a pulmonary nodule identified by CT scanning annually, of which only a small, albeit notable, minority will be diagnosed with lung cancer. The 2017 Fleischner Society Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images replaces the previous 2005 and 2013 guidelines for incidental solid and subsolid nodules. This standardization of approach is intended to reduce unnecessary follow-up examinations for findings unlikely to be significant or harmful to patients, without proscribing clinical care that should be informed by individual patient characteristics.

It is important to recognize that these guidelines refer specifically to pulmonary nodules identified incidentally on CT imaging. This is in distinction to patients who undergo low-dose chest CT for lung cancer screening, who comprise a different population with distinct lung cancer risk, and for whom a separate specific guideline for interpretation of findings should be used.

The new guidelines include multiple substantive changes in recommendations for both solid and subsolid nodules, only a few of which are outlined below. Given the prevalence

of incidental pulmonary nodules, a thorough review of the entire guidelines is strongly encouraged.

## Comments

1. The guidelines recommend that all chest CT scans be reconstructed and archived with contiguous thin sections (<1.5 mm) to enable accurate measurement, and that the definition of the diameter of a nodule should be the average of long- and short-axis diameters measured on the CT image with the largest nodule dimensions.
2. The threshold size for solid nodules warranting routine follow up has been increased from 4 mm to 6 mm; solid nodules < 5mm do not require routine follow-up unless there is specific concern for higher risk because of nodule morphology or location.
3. The threshold size for subsolid (pure ground glass or part-solid) nodules has been changed to 6 mm; selected subsolid nodules with diameter less than but close to 6 mm in size with concerning morphology or other patient risk factors may merit follow up, with consideration for longer intervals between imaging (2- and 4-years).
4. For subsolid nodules, pure ground glass nodules > 6 mm in diameter that demonstrate stability at 6-12 months should have longer interval imaging follow up (2-year) for 5 years; part-solid nodules > 6 mm with a solid component < 6 mm that demonstrate stability at 3-6 months should have annual follow up for 5 years.
5. These guidelines are not intended for use in the following groups of patients: 1) persons undergoing CT scanning for the purpose of lung cancer screening; 2) patients with known primary cancers at risk for metastases; 3) children and adults younger than 35 years; 4) immunocompromised patients at risk for infection.

Kakinuma R, Noguchi M, Ashizawa K, Kuriyama K, Maeshima AM, Koizumi N, Kondo T, Matsuguma H, Nitta N, Ohmatsu H, Okami J, Suehisa H, Yamaji T, Kodama K, Mori K, Yamada K, Matsuno Y, Murayam S, Murata K. **Natural History of Pulmonary Subsolid Nodules: A Prospective Multicenter Study.** *J Thorac Oncol* 2016; 11(7):1012-1028.

### Summary

Subsolid pulmonary nodules present several challenges: they lack a standardized radiographic nomenclature, their natural history is poorly understood, and they have a high likelihood of being pre-malignant or malignant lesions, but often display less aggressive biologic behavior.

Kakinuma and colleagues describe the natural history of subsolid pulmonary nodules in this prospective study of 975 patients with 1229 subsolid nodules. They propose three practical definitions: pure ground glass nodules (PGGN); heterogeneous ground glass nodules (HGGN); solid component detected only on lung windows and not on mediastinal windows; part-solid nodules: solid component detected on both lung and mediastinal windows. Mean nodule diameter at enrollment was 7.8 + 3.4 mm. Over a mean follow up of 4.3 years, 1.2% of PGGNs developed into HGGNs, and 5.4% into part-solid nodules; median time for the latter was 3.8 + 2 years.



19.8% of HGGNs developed into part-solid nodules; median time to development was 2.1 + 2.3 years. 35 of 977 PGGNs and 7 of 78 HGGNs were resected; all were atypical adenomatous hyperplasia, adenocarcinoma in situ (AIS), or minimally invasive adenocarcinoma (MIA). 49 of 174 part-solid nodules were resected; 12 were invasive adenocarcinomas. All tumors were Stage 1 (78 Stage IA; 2 Stage IB).

### Comments

1. On the basis of a receiver operating characteristic analysis for differentiating AIS and MIA from invasive adenocarcinoma, the cutoff value of the maximal diameter of a solid component was 3.3 mm (sensitivity 61%, specificity 91%).
2. The minimum periods for the development of part-solid nodules with a solid component 3.3 mm or larger in maximal diameter were 1.8 years for nodules that began as PGGNs, and 2.5 years for nodules that began as HGGNs.
3. The thoracic community should establish standardized criteria for radiographic description of subsolid nodules, including standardization of the CT slice thickness used to evaluate these nodules.
4. Observation of subsolid nodules appears to be an appropriate initial strategy, with the intervals between imaging informed by the presence or absence of a solid component on lung and/or mediastinal windows, and the development or lack thereof of a solid component during follow up.
5. The variation between medical guideline recommendations for duration of follow up for part-solid nodules (ACCP: surveillance CT for at least 3 years for pure ground glass nodule, and 3-5 years for part-solid nodules; Fleischner Society: surveillance CT for at least 5 years for pure ground glass lesions and nodules with solid component  $\leq 5$  mm; NCCN: annual low-dose CT scanning until the patient is no longer eligible for definitive treatment) reflects the need for further study in this area.

## LUNG CANCER STAGING

Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. **The Eighth Edition Lung Cancer Stage Classification.** *Chest* 2017; 151(1):193-203.

### Summary

The purpose of stage classification for malignancy is to provide a common language that consistently describes the anatomic extent of disease. The staging nomenclature facilitates reliable communication about tumor stage, provides prognostic information, and identifies homogeneous populations for clinical trials. It is important to recognize that stage classification does not include tumor molecular information, should not be used as a treatment algorithm, and cannot be used to define an individual patient's prognosis, which will be influenced by many factors other than anatomic extent of disease. Periodic revisions of the staging classifications for cancers are necessary, to update outcomes in more current patient

populations that reflect advances in staging technologies and cancer treatment.

The International Association for the Study of Lung Cancer (IASLC) amassed a global database to inform the new staging classification, including 94,708 patients from 16 countries diagnosed from 1999–2010. Recommendations for revisions of the Tumor (T), Node (N), and Metastasis (M) descriptors, and stage groupings (TNM) were based on differences in outcomes. This review of the new Eighth Edition summarizes the efforts of several groups for IASLC, identifies key changes in the staging classification, and clarifies the subgroup of patients with multiple pulmonary sites of lung cancer.

### Comments

1. The new Eighth Edition of the stage classification for lung cancer was implemented globally in January, 2017, except in the United States, where the anticipated date of implementation is January, 2018.
2. While stage is often used to define groups for whom specific treatments are recommended, treatment for a given patient must be individualized, influenced by an array of factors, including age, histologic subtype, treatment rendered, the presence of comorbidities and/or competing causes of death, patient access to care and the quality of the care delivered, etc.
3. Key changes in the staging classification: the T descriptor has undergone several revisions, including new definitions for T1 – T4 based on size and centrality; the N descriptor remains largely unchanged, except that the anatomic midline was shifted to the left paratracheal border and the extent of the subcarinal station was expanded; the M descriptor now differentiates oligometastatic disease (M1b) from disease with multiple distant metastases (M1c).
4. The assignment of TNM groups into different stages was determined by clinical outcomes.
5. Staging for patients with multiple pulmonary sites of lung cancer was more rigorously defined in four categories: 1) Second primary lung cancer; 2) Primary lung cancer with one or more separate, related tumor nodules; 3) Multiple ground glass or lepidic nodules; 4) "Pneumonic-type" lung cancer.

## LUNG CANCER TREATMENT

Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR. **Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer.** *N Engl J Med* 2016; 375:1823-1833.

### Summary

The programmed death-1 (PD-1) pathway is being intensely investigated as a therapeutic target for non-small cell lung cancer (NSCLC). Activated B and T cells express PD-1, an immune checkpoint inhibitor that normally down-regulates excessive immune responses. PD-L1, one of two ligands

identified for PD-1, is highly expressed by approximately one-fourth of NSCLCs. Blocking tumor immune checkpoint inhibition with anti-PD-1 antibodies presumably restores the ability of the immune system to recognize and respond to tumor neoantigens, which are abundant in tumors such as smoking-associated lung cancers that typically harbor large sequential mutational burden.

This randomized multi-center study demonstrated that therapy with pembrolizumab, a humanized anti-PD-1 monoclonal antibody, was superior to platinum-based combination chemotherapy as first-line treatment for advanced NSCLC. The study population was limited to NSCLC patients with high PD-L1 tumor proportion score (PD-L1 expression on >50% of tumor cells); patients with sensitizing EGFR mutations or ALK translocations were excluded. Treatment with pembrolizumab compared to standard cytotoxic chemotherapy resulted in significantly longer progression-free survival [HR for disease progression or death, 0.50 (95%CI, 0.37-0.68);  $P<0.001$ ], improved overall survival [HR for death, 0.60 (95%CI, 0.41-0.89);  $P=0.005$ ], and fewer serious treatment side effects (rate of grade 3-5 adverse events: 26.6% vs. 53.3%).

### Comments

1. This is the first randomized trial to demonstrate superiority of immunotherapy compared to cytotoxic chemotherapy as first-line therapy for advanced NSCLC with high PD-L1 tumor expression.
2. Longer progression-free survival and overall survival with anti-PD1 therapy were observed in both non-squamous and squamous histologies, and is particularly notable for the latter, considering the relative lack of treatment options for this group.
3. Prior studies have demonstrated that PD-L1 is useful as a biomarker, as a significantly increased response rate to pembrolizumab is observed in patients with PD-L1 expression on at least 50% of tumor cells.
4. The efficacy of pembrolizumab in patients with low tumor proportion score is unknown, but nivolumab, another checkpoint inhibitor, has been demonstrated to be of benefit as second-line therapy in non-biomarker enriched populations of patients with advanced NSCLC.
5. First-line treatment of advanced NSCLC can now be approached more strategically, with the decision to initiate therapy targeted to EGFR sensitizing mutations, ALK translocations or ROS1 rearrangements, immunotherapy, or platinum-based chemotherapy based on a deeper and more personalized understanding of the biology of an individual patient's tumor.

### LUNG CANCER QUALITY OF LIFE

Wright AA, Keating NL, Ayanian JZ, Chrischilles EA, Kahn KL, Ritchie CS, Weeks JC, Earle CC Landrum MB. **Family Perspectives on Aggressive Cancer Care Near the End of Life.** *JAMA* 2016; 315:284-292.

### Summary

Despite important treatment advances, many lung cancer patients will still die from their disease. Most terminally ill patients are consistent in their goals to have relief from pain and to die at home. Thirty years ago, 70% of cancer deaths in the U.S. occurred in acute care hospitals. For lung cancer, this rate is now 20%, likely reflecting an appreciation that less aggressive care and enhanced services addressing end of life needs and goals contribute to improved quality of life near death.

This study investigated quality of life and attainment of patient end of life goals as perceived by family members of 1146 patients with advanced lung or colorectal cancer. Medicare claims data were used to assess care rendered in the 6 months preceding death. Next-of-kin or patient-identified family member/close friend were interviewed after the patient's death regarding their perceptions of patient goal-congruent care, including preferred site of death, and their assessment of quality of care. 51.3% reported excellent end of life care. Among multiple variables measured, ICU admission within 30 days of death, < 3 days of hospice care, and death occurring in the hospital were associated with a lower likelihood that patients received preference-congruent care and larger differences in family member-reported quality of care.

### Comments

1. Improving the quality of the end of life for the over 150,000 people in the U.S. and the hundreds of thousands of people in the world who will die from lung cancer in 2017 is an important and necessary goal.
2. Care for patients with advanced-stage lung cancer should be congruent with their preferences, and should include counseling to understand those preferences and goals.
3. The study suggests that earlier hospice enrollment, avoidance of ICU admissions, and allowing death to occur at the patient's preferred site may improve the quality of end of life care.
4. The National Quality Form (NQF) and the American Society of Clinical Oncology have endorsed indicators of overly aggressive end of life care, including repeated hospitalizations, emergency department visits, admission to an ICU within the last month of life, patient receipt of chemotherapy within 2 weeks prior to death, and late or absent hospice referrals.

### OTHER ARTICLES OF INTEREST

#### LUNG CANCER SCREENING

Fucito LM, Czabafy S, Hendricks PS, Kotsen C, Richardson D, Toll BA, Association for the Treatment of Tobacco Use and Dependence/Society for Research on Nicotine and Tobacco Synergy Committee. **Pairing smoking-cessation services with lung cancer screening: A clinical guideline from the Association for the Treatment of Tobacco Use and Dependence and the Society for Research on Nicotine and Tobacco.** *Cancer* 2016; 122:1150-1159.

Gould MK. **Who Should Be Screened for Lung Cancer? And Who Gets to Decide?** *JAMA* 2016; 315:2279-2281.

Tammemagi MC. **Applications of risk prediction models to lung cancer screening: a review.** *J Thorac Imaging* 2015; 30:88-100.

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Wille MM, Dirksen A, Ashraf H, Saghir Z, Bach KS, Brodersen J, Clementsen PF, Hansen H, Larsen KR, Mortensen J, Rasmussen JF, Seersholm N, Skov BG, Thomsen LH, Tonnesen P, Pedersen JH. **Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-Risk Profiling.** *Am J Respir Crit Care Med* 2016; 193:542-551

#### PULMONARY NODULES

Sawada S, Yamashita N, Sugimoto R, Ueno T, Yamashita M. **Long-term Outcomes of Patients with Ground-Glass Opacities Detected Using CT Scanning.** *Chest* 2017; 151:308-315.

Detterbeck FC. **Achieving Clarity About Lung Cancer and Opacities.** *Chest* 2017; 151:252-254.

#### LUNG CANCER STAGING

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#### LUNG CANCER TREATMENT

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#### LUNG CANCER QUALITY OF LIFE

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Simon L.F. Walsh, MD, MRCP

King's College Hospital Foundation Trust  
Department of Radiology  
London, United Kingdom**COMPUTER-AIDED EVALUATION OF HRCT FOR PROGNOSIS IN IPF**

Jacob J, Bartholmai BJ, Rajagopalan S, Kokosi M, Nair A, Karwoski R, et al. **Mortality prediction in IPF: evaluation of automated computer tomographic analysis with conventional severity measures.** *Eur Respir J.* 2016.

**Summary**

In this study of 283 IPF patients, Jacob et al. compared CALIPER-derived measures of disease severity with semiquantitative visual CT evaluation and pulmonary function. A noteworthy feature of this study was the measurement of pulmonary vascular volume (PVV), a novel CT variable that captures the volumes of the pulmonary arteries and veins as a percentage of the total lung volume. On multivariate analysis, the only CT-derived variables, which were independently predictive of mortality, were honeycombing (HR 1.21,  $p=0.0004$ , 95%CI 1.09-1.34) and PVV (HR 1.39,  $p<0.0001$ , 95%CI 1.25-1.54) as assessed by CALIPER. The only physiological variable retained in the analysis was the composite physiological index (CPI) (HR 1.05,  $p<0.0001$ , 95%CI 1.02-1.07). These findings were extended to create two 3-stage categorical scores; one based on CALIPER-derived honeycombing, PVV and the CPI (CALIPER-CPI score) and one based on CALIPER-derived honeycombing and the PVV (CALIPER-only score). Both of these CALIPER-derived composite scores demonstrated improved mortality prediction and goodness of fit when compared to the categorical GAP staging system.

**Comments**

1. For prognostication, CALIPER outperforms semiquantitative visual CT evaluation.
2. CALIPER-derived CT pattern scores may be used in staging systems, which provide stronger mortality signal when compared to the categorical GAP staging system.
3. Pulmonary vascular volume, a novel CT variable is a significant independent predictor of mortality in IPF.

**COMPUTER-AIDED EVALUATION OF HRCT FOR PROGNOSIS IN CONNECTIVE TISSUE DISEASE-RELATED INTERSTITIAL LUNG DISEASE**

Jacob J, Bartholmai BJ, Rajagopalan S, Brun AL, Egashira R, Karwoski R, et al. **Evaluation of computer-based computer tomography stratification against outcome models in connective tissue disease-related interstitial lung disease: a patient outcome study.** *BMC Med.* 2016;14(1):190.

**Summary**

This study evaluated the utility of CALIPER as a prognostic tool in a cohort of 203 patients with all-comers connective tissue disease-related interstitial lung disease (CTD-ILD). A strength of this study was that by testing CALIPER in a mixed population of patients with different CTDs, the investigators overcome difficulties applying their data to different CTD subgroups or patients with overlapping CTD features. Using CALIPER-derived CT variables, the authors stratified the cohort into three outcome groups each with distinct morphological characteristics (as measured by CALIPER) and function profiles (as measured by lung function). The authors improved mortality prediction by substituting FVC and DLco in the GAP staging model (HR 1.74  $p<0.0001$  95%CI 1.45-2.08) with this CALIPER-generated patient stratification (HR 2.00,  $p<0.0001$  95%CI 1.63-2.45). Combining the GAP staging system and patient stratification augmented prognostication further. A second key finding was that similar to IPF; pulmonary vascular volume was the most powerful independent predictor of mortality in all-comers CTD-ILD (HR 1.57,  $p<0.0001$  95%CI 1.35-1.82).

**Comments**

1. Computer-aided analysis of ILD combined with lung function can be used to stratify patients with CTD-ILD into prognostically distinct groups regardless of their underlying CTD diagnosis.
2. As in IPF, pulmonary vascular volume, a novel CT variable is a significant independent predictor of mortality in connective tissue disease-related ILD.

**CLINICAL AND RADIOGRAPHIC PREDICTORS OF HISTOPATHOLOGIC UIP**

Brownell R, Moua T, Henry TS, Elicker BM, White D, Vittinghoff E, et al. **The use of pretest probability increases the value of high-resolution CT in diagnosing usual interstitial pneumonia.** *Thorax.* 2017.

**Summary**

This study examined the test characteristics of non-definite UIP patterns on HRCT for UIP on lung biopsy using all patients evaluated at the University of California at San Francisco ILD from September 2002 to July 2015. Only patients with a prospectively scored lung biopsy were included. Patients with definite UIP on HRCT, a connective tissue disease or cystic lung disease were excluded. Patients with a possible UIP pattern on HRCT showed a specificity of 91.2% (95% CI 87.2% to 94.3%), a positive

predictive value (PPV) of 62.5% (95% CI 49.5% to 74.3%) and likelihood ratio (LR+) of 4.01 (95% CI 2.54 to 6.33) for definite/probable UIP on surgical biopsy. A combination of possible UIP on HRCT, male gender, age  $\geq 60$  years, and increasing severity of traction bronchiectasis increased the PPV to 95% but reduced sensitivity to 16.8%. Age (stratified into 50-59,  $\geq 60$ ), male gender and possible UIP with a traction bronchiectasis score of  $\geq 4$  were identified as predictors of UIP on surgical lung biopsy and combined to create a "UIP-score." This score demonstrated high discriminative performance for identifying histopathologic UIP on surgical lung biopsy (C statistic 0.74, 95% CI 0.69 to 0.78). The combination of "inconsistent with UIP" on HRCT and candidate predictors did not provide adequate predictive power to "rule in" histopathologic UIP (maximum PPV achieved was 38%). The UIP-score demonstrated similar predictive power for histopathologic UIP in a validation cohort made up of fibrotic lung disease patients from the Mayo Clinic, Rochester.

#### Comments

1. Age is a significant clinical predictor of IPF.
2. When the HRCT pattern is that of "possible UIP," the presence of traction bronchiectasis predicts histopathologic UIP.
3. A prediction model can be generated using age, gender, HRCT pattern and the presence of traction bronchiectasis, which demonstrates high discriminative performance for identifying histopathologic UIP on surgical lung biopsy.
4. These findings together corroborate those of Fell et al. (AJRCCM 2010;181:832) and support recent subgroup analysis from the Impulsis trials (Raghu G et al. AJRCCM 2017;195:78-85).].

### CLINICAL AND RADIOGRAPHIC PREDICTORS OF A CLINICAL DIAGNOSIS OF IPF

Salisbury ML, Xia M, Murray S, Bartholmai BJ, Kazerooni EA, Meldrum CA, et al. **Predictors of idiopathic pulmonary fibrosis in absence of radiologic honeycombing: A cross sectional analysis in ILD patients undergoing lung tissue sampling.** *Respir Med.* 2016;118:88-95

#### Summary

This study evaluated 200 patients enrolled in the Lung Tissue Research Consortium with a diagnosis of fibrotic lung disease. All patients underwent surgical lung biopsy, and those with a diagnosis of a connective tissue disease were excluded. Candidate variables including age, gender, smoking status, forced vital capacity and HRCT features were combined to form a diagnostic model for predicting a clinical diagnosis of IPF. In this study, a model-based probability of IPF was 80% or greater in patients of 60 years or more, and with reticular patterns occupying more than one-third of their total lung volume on HRCT. The specificity for IPF in patients meeting or exceeding these

criteria was 96% (95% CI 91-100%), and use of this model resulted in 16% of lung biopsies being avoided.

#### Comments

1. Age is a significant clinical predictor of IPF.
2. In the absence of honeycombing, the combination of reticular patterns (greater than one third the total lung volume) and age (60 years or more) may predict a clinical diagnosis of IPF with a probability of 80%.
3. The use of this predictive model resulted in 16% of surgical lung biopsies being avoided in patients with suspected IPF.

### INTERSTITIAL LUNG ABNORMALITIES

Araki T, Putman RK, Hatabu H, Gao W, Dupuis J, Latourelle JC, et al. **Development and Progression of Interstitial Lung Abnormalities in the Framingham Heart Study.** *Am J Respir Crit Care Med.* 2016;194(12):1514-22.

#### Summary

Several recent analyses of antifibrotic therapy in IPF have demonstrated identical treatment effects above and below FVC thresholds of 70% and 80%. These findings have stimulated interest in identifying subclinical IPF for the purpose of early intervention. Recent studies of subclinical "interstitial lung abnormalities" (ILA) provide a basis for IPF screening, but until now, these studies have been confined to lung cancer screening data. Araki et al. investigated prevalence and patterns of progression of ILA's in a general population of patients derived from the Framingham Heart Study (FHS). Out of 1867 patients, 118 (6%) had ILA's, which progressed (12). Increasing age and increasing copies of the MUC5B promoter polymorphism were associated with ILA progression. ILA progression was associated with a greater FVC decline compared to participants without ILA (20 ml; SE, 66 ml;  $P = 0.0005$ ) and with participants without progression (25 ml; SE, 611 ml;  $P = 0.03$ ). ILA progression was also associated with increased risk of death when compared to those without ILA's (median follow-up time four years, HR 3.9; 95% confidence interval, 1.3-10.9;  $p=0.01$ ).

#### Comments

1. These results support the growing body of evidence indicating that ILA's are clinically significant and that their identification may play a role in early IPF diagnosis.
2. ILA prevalence (which is an order of magnitude higher than IPF prevalence) is an important issue that needs to be studied further.
3. Since ILA's can be characterized morphologically, future studies will need to selectively evaluate ILA patterns that are most likely to represent early IPF (e.g. subpleural reticular ILAs) rather than study ILA's as a single entity.

## OTHER ARTICLES OF INTEREST

Egashira R, Jacob J, Kokosi MA, Brun AL, Rice A, Nicholson AG, Wells AU, Hansell DM. **Diffuse Pulmonary Ossification in Fibrosing Interstitial Lung Diseases: Prevalence and Associations.** *Radiology* 2017, Feb 9. DOI: <http://dx.doi.org/10.1148/radiol.2017152419>

Raghu G, Wells AU, Nicholson AG, Richeldi L, Flaherty KR, Le Maulf F, et al. **Effect of Nintedanib in Subgroups of Idiopathic Pulmonary Fibrosis by Diagnostic Criteria.** *Am J Respir Crit Care Med*. 2017;195:78-85.

Salisbury ML, Lynch DA, van Beek EJR, Kazerooni EA, Guo J, Xia M, Murray S, Anstrom KJ, Yow E, Martinez FJ, Hoffman EA, Flaherty KR. IPFnet Investigators. **Idiopathic Pulmonary Fibrosis: Adaptive Multiple Features Method Fibrosis Association with Outcomes.** *Am J Respir Crit Care Med* 2016; Oct 21, DOI: <http://dx.doi.org/10.1164/rccm.201607-1385OC>

Walsh SL, Wells AU, Desai SR, Poletti V, Piciocchi S, et.al. **Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case cohort study.** *Lancet Respir Med*. 2016;4:557-65

Walsh SLF, Calandriello L, Sverzellati N, Wells AU, Hansell DM, Consort UIP. **Interobserver agreement for the ATS/ERS/JRS/ALAT criteria for a UIP pattern on CT.** *Thorax* 2016;71:45-51.

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**IMPACT OF THE AFFORDABLE CARE ACT**

Sommers BD, Blendon RJ, Orav EJ, Epstein AM. **Changes in utilization and health among low-income adults after Medicaid expansion or expanded private insurance.** *JAMA Internal Medicine* 2016, 176: 1501-1509

**Summary**

More than 30 states expanded Medicaid under the Affordable Care Act (ACA). Although the ACA resulted in increased health care coverage for millions, its impact on utilization and health remain less clear. To address this, the investigators evaluated survey data from November 2013 through December 2015 of U.S. citizens ages 19 to 64 years with incomes below 138% of the federal poverty level in Kentucky, Arkansas, and Texas (totaling 8676 subjects). The investigators found no differences in sex, income, or marital status. As expected, by 2015, they found that expansion was associated with reduced uninsured rate compared to non-expansion. Interestingly, expansion was associated with increases in access to primary care, fewer skipped medication due to cost; reductions in out-of-pocket spending, likelihood of emergency department visits; and increased outpatient visits. Screening for diabetes, glucose testing, and regular care for chronic conditions also increased. Quality of care ratings improved as did the share of adults reporting excellent health. Comparisons between Arkansas versus Kentucky showed increased private coverage in Arkansas, with increased Medicaid in Kentucky. However, other than higher diabetic glucose testing rates in Kentucky, no other differences were identified when comparing type of expansion.

**Comment**

1. The authors conclude that Kentucky's Medicaid program and Arkansas's private option were associated with significant increases in outpatient utilization, preventive care, and improved health care quality; reductions in emergency department use; and improved self-reported health.
2. Although dependent on self-reported outcomes, this manuscript is one of the few manuscripts examining the impact of the ACA on health utilization and related outcomes.
3. The comparison of a state with Medicaid expansion (Kentucky) to a private option (Arkansas) and to a state with no expansion (Texas) represents a strength.
4. Of interest, the investigators found improvements in receipt of checkups, care for chronic conditions, and

quality of care even in areas with primary care shortages, suggesting that insurance expansion has had an impact even in areas with relative shortages perhaps through the use of "safety net providers."

5. A subgroup analysis suggested that racial/ethnic minorities may be differentially affected by alternative expansion approaches.
6. The study has limitations including the use of random-digit dialing telephone survey, which may introduce bias, and that annual family income was used to define the study sample, which does not necessarily measure ACA-related eligibility. Of course, no clear causal interpretations can be made.

**IMPACT OF GENETIC DIAGNOSIS ON HEALTH DISPARITIES**

Manrai AK, Funke BH, Rehm HL, Olesen MS, Maron BA, Szolovits P, Margulies DM, Loscalzo J, Kohane IS. **Genetic misdiagnoses and the potential for health disparities.** *NEJM*, 2016, 375: 655-665.

**Summary**

Today, access to genetic testing has improved chances of early diagnosis of complex disorders. One example is hypertrophic cardiomyopathy. Using sequencing results, clinicians can assess the risk of hypertrophic cardiomyopathy in patients' relatives and diagnose the condition in patients with ambiguous presentations. However, the impact of such approach on health disparities is unclear. To address this, the authors used a publicly available exome database and identified variants that had previously been considered causal in hypertrophic cardiomyopathy and that are overexpressed in the general population. Importantly, they studied these variants in diverse populations and found that patients of African American or unspecified ancestry received positive results with variants misclassified as pathogenic. Later, all of these variants were re-categorized as benign. It turns out that the variants that were most common in the general population were significantly more common among black Americans than among white Americans. Furthermore, the authors showed that simulations revealed that the inclusion of even small numbers of black Americans in control cohorts would have probably prevented such misclassifications.

**Comments**

1. The authors conclude that there is a need for sequencing the genomes of diverse populations, both in asymptomatic

controls and the tested patient population, to avoid misdiagnoses.

2. The use of ancestry-matched controls to interpret any identified variants is recommended.
3. Further studies in additional populations of different ancestry backgrounds are expected to result in reclassifications of certain variants.
4. This study shows that disparities may result from errors related neither to access to care nor to proposed physiological differences.
5. In addition to black Americans, studies should be conducted using genomic data from Native Americans, Asian Americans, and other populations.

## DISPARITIES IN LEADING CAUSES OF DEATH

Chang MH, Moonesinghe R, Athar HM, Truman BI. **Trends in disparity by sex and race/ethnicity for the leading causes of death in the United States-1999-2010.** *J Public Health Manag Pract.* 2016, 22 (Supp 1): S13-S24.

### Summary

There are data suggesting significant trends in disparities related to the leading causes of death within United States demographic subgroups, but these data seem limited and outdated. To address this, the authors used cause of death and population estimates from the National Vital Statistics System to calculate age-adjusted death rates for the 10 leading causes of death during 1999-2010. They found that of the 10 leading causes of death, age-adjusted death rates by sex and race/ethnicity declined during the period of study for 6 causes, but increased for 4 causes. Interestingly, sex and racial/ethnic disparities between groups persistent for each year and cause of death. The decreasing trend was greatest for cerebrovascular disease and the increasing trend was greatest for Alzheimer's disease. For each sex and year, the disparity in death rates between Asian/Pacific Islanders and other groups varies by cause of death. In 2010, the Asian/Pacific Islander - non-Hispanic black disparity was largest for heart disease, malignant neoplasms, cerebrovascular disorders, and nephritis. The Asian/Pacific - Alaska Native disparity was largest for unintentional injury, diabetes mellitus, influenza, and pneumonia, and suicide. The Asian/Pacific Islander - non-Hispanic white disparity was largest for chronic lower respiratory diseases and Alzheimer disease.

### Comments

1. Age-adjusted death rates have improved for some leading causes of death, but have decreased for others.
2. Disparities in age-adjusted death rates vary according to cause of death and race/ethnic ancestry.
3. The authors conclude that these findings can be used to improve policies and practices and to evaluate progress in eliminating disparities and their social determinants in vulnerable populations.

## DISPARITIES IN LUNG CANCER INCIDENCE

Tabatabai MA, Kengwoung-Keumo J-J, Oates GR, Guemmegne JT, Akinlawon A, Ekadi G, Fouad MN, Singh KP. **Racial and gender disparities in incidence of lung and bronchus cancer in the United States: A longitudinal analysis.** *PLOS one.* 2016, 1-19, DOI:10.1371/journal.pone.0162949. (September)

### Summary

It is well known that certain populations in the United States carry a disproportionate burden of cancer. These investigators used work models to analyze lung and bronchus cancer age-adjusted incidence rates by race, gender, and prevalence of smoking in 38 states and the District of Columbia, and across geographic regions from 1999 to 2012. They found that in this period of time, age-adjusted incidence rates in lung cancer decreased in all states and regions. However, Whites continue to have lower age-adjusted incidence rates for lung cancer than Blacks in all states and in five of the eight geographic regions. Interestingly, disparities in incidence rates between Black and White men were found to be significantly larger than those found between Black and White women. Even more interesting are the data generated by modeling which predict that the gender gap in the incidence rates for Whites would disappear by mid-2018, and for Blacks by 2026, but the racial gap will remain. The investigators also found a downward trend in the prevalence of daily smoking in both genders, although males have a higher rate than females. The highest and lowest prevalence of daily smoking were found in the Mid-South and New England, respectively. As expected, a significant correlation was found between lung cancer incidence rates and smoking prevalence.

### Comments

1. The authors conclude that although age-adjusted incidence rates in lung cancer have decreased throughout the United States, racial and gender disparities remain.
2. Tobacco exposure continues to represent the most important cause of lung cancer. Considering the data presented, efforts directed at curtailing the impact of tobacco should continue.
3. In addition to the longitudinal data, the study includes the use of longitudinal linear mixed-effects model that describes the dynamics of lung cancer incidence rates by race, gender, and smoking prevalence. This model should be quite valuable in predicting future impact of lung cancer in various United States regions.

## DISPARITIES IN ACUTE RESPIRATORY FAILURE

Bime C, Poongkunram C, Borgstrom M, Natt B, Desai H, Parthasarathy S, Garcia JG. **Racial differences in mortality from severe acute respiratory failure in the United States, 2008-2012.** *Ann Am Thorac Soc.* 2016, 13: 2184-2189.



### Summary

Racial disparities in acute critical illnesses such as sepsis and acute respiratory failure are increasingly recognized. To investigate this further, the authors used a large, representative United States nationwide database to examine the hypothesis that black and Hispanic patients with severe acute respiratory failure have higher mortality rates when compared with non-Hispanic whites. The analysis revealed that, after adjusting for sex, age, race, disease severity, type of hospital, and median household income for patient ZIP code, blacks had a greater odds ratio of in-hospital death when compared with non-Hispanic whites, and Hispanics had a greater odds ratio of in-hospital death when compared to non-Hispanic whites. Similar trends were found for Asian and Pacific Islanders and Native Americans when compared with non-Hispanic whites.

### Comments

1. The authors conclude that Blacks, Hispanics, and other racial minorities in the United States exhibit significantly higher in-hospital sepsis-related respiratory failure associated mortality when compared with non-Hispanic whites.
2. The analysis was retrospective, but took advantage of data from the Agency for Healthcare Research and Quality, Nationwide Inpatient Sample, Healthcare Cost, and Utilization Project. Hospitalizations with acute respiratory failure were identified using a combination of International Classification of Diseases, Ninth Revision codes.
3. Factors responsible for these disparities are unclear.

### GENETICS IN COPD

Busch R, Qiu W, Lasky-Su J, Morrow J, Criner G, DeMeo D. **Differential DNA methylation marks and gene comethylation of COPD in African Americans with COPD exacerbations.** *Respir Res*, 2016, 17:143. DOI 10.1186/s12931-016-0459-8

### Summary

Chronic obstructive pulmonary disease (COPD) carries significant morbidity in mortality and is the third-leading cause of death worldwide. The authors hypothesized that COPD-associated DNA methylation marks in African Americans might contribute to disease pathogenesis and, importantly, that their identification would help improve understanding of racial disparities in this condition. To test this, they assessed DNA methylation from whole blood samples in 362 African American smokers obtained from the PA-SCOPE cohort. They found five differentially methylated CpG probes significantly associated with COPD among African Americans. The top ranked gene association was MAML1, which appears to affect NOTCH-dependent angiogenesis in murine lung. Network modeling

yielded co-methylation modules associated with COPD with enrichment for gene sets related to inflammatory pathways known to be relevant in COPD. Other genes were related to lung development processes.

### Comments

1. The authors identified a total of 12 differentially methylated CpG sites associated with COPD that mapped to biologically plausible genes.
2. The genes identified might be contributing to racial differences in COPD susceptibility and severity.
3. While much data have been generated identifying racial disparities in respiratory disorders, this work unveils potential targets for intervention.
4. Further research will be needed to understand the biological consequences of such findings and, importantly, to identify meaningful approaches for therapy based on these findings.

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The Center for Health Research and Dept of Pulmonary/Critical Care  
Portland, OR**FAMILY MEETING RANDOMIZED CLINICAL ICU TRIAL**

Carson SS, Cox CE, Wallenstein S, Hanson LC, Danis M, Tulskey JA, Chai E, Nelson JE. **Effect of palliative care-led meetings for families of patients with chronic critical illness: A randomized clinical trial.** *JAMA* 2016 Jul 5;316(1):51-62

**Summary**

Family caregivers of patients with chronic critical illness are an important and logical target for improving the ICU experience, especially if it improves psychological distress. In this multicenter randomized clinical trial supporting surrogate decision makers of patients with chronic critical illness, the study assessed whether augmenting the usual support of surrogates with at least two structured conversations delivered by palliative care-trained consultants would decrease family psychological distress at 3 months, improve perceptions of communication quality, or decrease end of life treatment intensity. The trial enrolled 365 surrogate decision-makers of adult patients requiring at least 7 days of mechanical ventilation. The intervention group received team-based specialty care that focused on providing emotional support, communicating validated prognostic information about 1-year survival, and discussing the patient's values and preferences. The study identified no difference between study groups for the primary outcome measure of surrogates' symptoms of depression and anxiety 3 months after the patient's hospitalization (Hospital Anxiety and Depression Scale mean scores of 12.2 in the intervention group and 11.4 in the control group) nor differences in surrogates' perceptions of the quality of communication and end of life treatment intensity. They did observe increased surrogates' posttraumatic stress symptoms at 3-month follow-up in the intervention group.

**Comments**

1. The authors conclude that among families of patients with chronic critical illness, the use of palliative care-led informational and emotional support meetings compared with usual care did not reduce anxiety or depression symptoms and may have increased post-traumatic stress disorder symptoms.
2. The study was both rigorous and pragmatic in that the intervention was designed to be scalable and promote widespread adoption into practice, building on over two decades of work in this area.
3. The study did not assess expectations or accuracy of surrogates' perceptions of prognosis and thus may not

have fulfilled a change in the theoretical underpinnings that improving surrogates' prognostic expectations would improve the decision-making experience or persistent psychological sequela.

4. Although mortality in each group was similarly approaching 40% at one month, it is unclear if efforts to normalize and present the options of comfort-focused care may have changed the effect.
5. The study falls in line with many others that demonstrate how difficult it is to improve complex decision-making for the critically ill and does not support routine palliative care-led discussion of goals of care for all families of patients with chronic critical illness.

**PROGNOSTIC DISCORDANCE IN THE CRITICALLY ILL**

White DB, Ernecoff N, Buddadhumaruk P, Hong S, Weissfeld L, Curtis JR, Luce JM, Lo B. **Prevalence of and factors related to discordance about prognosis between physicians and surrogate decision makers of critically ill patients.** *JAMA* 2016 May 17;315(19):2086-94.

**Summary**

Surrogates are called to participate in shared-decision-making for incapacitated critically ill patients and as such should have decisional capacity that includes fully understanding the care choices, the likely outcomes, and the alternatives to appreciate and discourse with the care team on behalf of their loved ones. This mixed-methods study assessed comprehension of medical information and misperceptions about prognosis by individuals making decisions by exploring factors related to physician-surrogate discordance – defined as a difference between a physician's and a surrogate's prognostic estimates of at least 20%. Using quantitative surveys and qualitative interviews across multiple types of ICUs in a U.S. medical center, the authors documented discordance in over half of 229 surrogates and 99 physicians involved in the care of 174 critically ill patients. Discordant reasons for optimism identified included loved-one's need to maintain hope, beliefs that the patient had unique strengths unknown to the physician, and religious convictions. Uncertainty in prognosis was demonstrated, as nearly 60% survived and surrogate estimates were more pessimistic than those of physicians in 20%. The study demonstrates concrete aspects involved in the challenges of end of life decision-making in the ICU and provides targets for improved empathic communication in the face of undeniable uncertainty.

### Comments

1. Surrogates tend to be overly optimistic about prognosis, which may lead to persisting burdensome interventions with limited benefit and delay more palliative care focused therapy.
2. In 24 of the 122 discordant cases (20%), estimates of surrogates were more pessimistic than those of physicians – surrogates attributed this to intrinsic optimism by physicians or a lack of full knowledge of the patient's status.
3. ICU family discussions are emotional interactions that include the struggle to cope with uncomfortable prognostic information and complicated family roles as surrogate decision-makers.
4. The study highlights the need for ICU practitioners to be empathic active listeners when providing information and engaging families in understanding possible outcomes.

### VANTAGE POINTS TO ASSESS QUALITY OF PALLIATIVE CARE IN THE ICU

Mularski RA, Hansen L, Rosenkranz SJ, Leo MC, Nagy P, Asch SM. **Medical record quality assessments of palliative care for ICU patients: Do they match nurses' and families' perspectives?** *Ann Am Thorac Soc* 2016 May; 13(5):690-698

### Summary

In ongoing efforts to understand and improve palliative care provision in the intensive care unit, valid and broad measurements of the quality of care delivered is needed. In the next in a series to develop endorsed palliative care indicator statements initiated by the Robert Wood Johnson Foundation End-of-Life Peer Workgroup, these investigators fully operationalized and tested a comprehensive quality evaluation measure set using a rigorous multidisciplinary Delphi process focused on optimizing the validity and feasibility of chart review-derived metrics. Fourteen process measures assessed the quality of care delivered across the established domains of palliative care for the ICU. Additionally, data was triangulated from two other perspectives: family satisfaction reports and nurse ratings from those providing care in the ICU. From 150 patient evaluations with an average ICU length of stay of 7.5 days, the study demonstrated that ICU patients received 53% of recommended palliative care. Family satisfaction ratings were high and not correlated to measured quality delivered. Nurses rated the quality of care higher than medical record review and similarly had poor correlation with chart based process measures. The authors suggest that each measurement vantage may provide relevant evaluations of quality to guide improvement and innovation work.

### Comments

1. Deficits were identified across seven domains of technical quality that were not correlated with either nurse or family ratings.
2. Different perspectives may supplement technical quality of care as measured through chart-based metrics.
3. The full operationalized measure set is freely available in the public domain at Annals ATS webpage [http://www.atsjournals.org/doi/suppl/10.1513/AnnalsATS.201508-501OC/suppl\\_file/mularski\\_data\\_supplement.pdf](http://www.atsjournals.org/doi/suppl/10.1513/AnnalsATS.201508-501OC/suppl_file/mularski_data_supplement.pdf)

### PALLIATIVE CARE IMPROVES OUTCOMES

Kavalieratos D, Corbelli J, Zhang D, Dionne-Odom JN, Ernecoff NC, Hanmer J, Hoydich ZP, Ikejiani DZ, Klein-Fedyshin M, Zimmermann C, Morton SC, Arnold RM, Heller L, Schenker Y. **Association between palliative care and patient and caregiver outcomes: A systematic review and meta-analysis.** *JAMA*. 2016 Nov 22;316(20):2104-2114

### Summary

It has been over a decade since the AHRQ Evidence-based Practice Program conducted the last comprehensive evaluation of palliative care and provided the field with a massive systematic review and meta-analysis. This current effort sought to determine the association of palliative care with quality of life (QOL), symptom burden, survival, and other outcomes for people with life-limiting illness and for their caregivers by evaluating and synthesizing randomized clinical trials reported through July 2016. Narrative synthesis and random-effects meta-analysis was conducted to translate estimates of QOL to comparable units expressed by the Functional Assessment of Chronic Illness Therapy-palliative care scale (FACIT-Pal) instrument [range, 0-184 (worst-best); minimal clinically important difference 9 points] and symptom burden expressed by the Edmonton Symptom Assessment Scale (ESAS) [range, 0-90 (best-worst); MCID 5.7 points]. Forty-three RCTs provided data on 12,731 patients and 2,479 caregivers. Palliative care was associated with statistically and clinically significant improvements in patient QOL at the 1- to 3-month follow-up (SMD 0.46) with FACIT-Pal improvement of 11 points and ESAS improvement of -10 points. There was no association between palliative care and survival. Palliative care was associated consistently with improvements in advance care planning, patient and caregiver satisfaction, and lower health care utilization.

### Comments

1. In this meta-analysis, palliative care interventions were associated with improvements in patient QOL and symptom burden.
2. Findings for caregiver outcomes were inconsistent and many associations were no longer significant when limited to trials at low risk of bias.

3. An accompanying editorial notes that negative studies included in the analysis suggests caution that protocolized care delivered by specialists may not be effective without regard to what makes palliative care meaningful to many patients, families, and clinicians: frequent and longitudinal follow-up, close involvement with the primary clinical team, and a focus on relief of physical and psychosocial distress.
4. Investigators designing RCTs in the future would be wise to carefully examine the nuances of the trials and methods summarized in this comprehensive review.

## PALLIATIVE CARE IN COPD

Rush B, Hertz P, Bond A, McDermid RC, Celi L. **Use of palliative care in patients with end-stage COPD and receiving home oxygen: National trends and barriers to care in the United States.** *Chest.* 2017;151(1):41-46

### Summary

In an effort to investigate the use of palliative care in patients with end-stage COPD and exacerbations, the investigators used a large U.S. database (Nationwide Inpatient Sample inclusive 2006-2012) to conduct a retrospective nationwide cohort analysis on adult COPD patients receiving home oxygen and admitted to hospital for an exacerbation. Identifying over 55 million hospitalizations with 181,689 patients with COPD/home oxygen/hospital exacerbation, the study found only 3,145 patients (1.7%) also had palliative care contact. There was a 4.5-fold relative increase in palliative referrals from 2006 (0.45%) to 2012 (2.56%). Patients receiving consultations were older, had longer hospitalizations, were more often white, had comorbid cancer diagnoses, and more frequent use of invasive or non-invasive ventilation use, amongst other factors. Socioeconomic status and hospital type also associated with palliative care referral. Having a Do Not Resuscitate status also increased the odds of having associated palliative care consultation. During the same time, comparable rates for palliative care in metastatic cancer were over 4 times higher. Although the authors demonstrated an increase in palliative care for COPD patients over the study period, specialist palliative care occurred in only a minority of patients with end-stage COPD admitted to hospital with an exacerbation.

### Comments

1. Despite that advanced care planning and referral to palliative care for individuals with advanced COPD is a longstanding guideline recommendation, studies have demonstrated low uptake in this population.
2. Despite encouraging trends in national hospice rates for end of life care and availability and use of palliative care for patients with chronic persistent disease, significant care gaps exist in lung diseases.

3. The present study with nearly 95% complete national sampling across the U.S. starkly documents the deficit in provision of palliative care for COPD patients with hospitalized exacerbations, the strongest predictor for near-term future mortality.
4. The study identifies a number of barriers that should be taken up by subsequent investigation and policy work.

## COPD AND ILD IN THE ICU

Brown CE, Engelberg RA, Nielsen EL, Curtis JR. **Palliative care for patients dying in the intensive care unit with chronic lung disease compared with metastatic cancer.** *Ann Am Thorac Soc.* 2016 May;13(5):684-9

### Summary

The investigators explored differences in receipt of elements of palliative care among patients with interstitial lung disease (ILD) and chronic obstructive pulmonary disease (COPD) who died in ICU, compared with patients with cancer. Combining data from 15 Seattle-area hospitals from the Integrating Palliative and Critical Care study between 2003 and 2008, extensive medical record abstraction was used to identify eight elements of palliative care delivery. Multivariable logistic and linear regression was used to compare differences in receipt of elements of palliative care and length of stay. The study found patients with isolated diagnoses of COPD ( $n = 592$ ), ILD ( $n = 79$ ), or metastatic cancer ( $n = 158$ ). Compared with patients with cancer, patients with COPD were more likely to receive cardiopulmonary resuscitation before death and patients with ILD were less likely to have documentation of pain assessment in the last day of life. Patients with ILD and COPD were less likely to have a do-not-resuscitate order in place at the time of death and less likely to have documentation of discussions about prognosis than patients with cancer. Patients with COPD had longer hospital lengths of stay, and patients with COPD and ILD had longer ICU lengths of stay.

### Comments

1. Palliative care provision has been shown to be higher in patients with cancer compared to patients with chronic lung diseases, despite high morbidity and mortality.
2. The majority of deaths in intensive care units (ICUs) follow decisions to withhold or withdraw life-sustaining treatments, suggesting that palliative care is critically important in this setting.
3. Among patients who die in the ICU, patients with ILD and COPD receive fewer elements of palliative care and have longer lengths of stay.
4. Like the nationwide study and prior smaller explorations, these findings identify areas for improvement in caring for patients with chronic lung diseases.

## OTHER ARTICLES OF INTEREST

## LUNG DISEASE

Liang Z, Hoffman LA, Nouraie M, Kass DJ, Donahoe MP, Gibson KF, Saul MI, Lindell KO. **Referral to palliative care infrequent in patients with idiopathic pulmonary fibrosis admitted to an intensive care unit.** *J Palliat Med.* 2017 Feb;20(2):134-140.

## ICU CARE

Chang DW, Acosta D, Shapiro MF. **Priority levels in medical intensive care at an academic public hospital.** *JAMA Intern Med.* 2017;177(2):280-28.

Swinton M, Giacomini M, Toledo F, Rose T, Hand-Breckenridge T, Boyle A, Woods A, Clarke F, Shears M, Sheppard R, Cook D. **Experiences and expressions of spirituality at the end of life in the intensive care unit.** *Am J Respir Crit Care Med.* 2017 Jan 15;195(2):198-204.

Teno JM, Gozalo P, Khandelwal N, Curtis JR, Meltzer D, Engelberg R, Mor V. **Association of increasing use of mechanical ventilation among nursing home residents with advanced dementia and intensive care unit beds.** *JAMA Intern Med.* 2016 Dec 1;176(12):1809-1816.

Cox CE, Curtis JR. **Using technology to create a more humanistic approach to integrating palliative care into the intensive care unit.** *Am J Respir Crit Care Med* 2016;193:242-250.

Zalenski RJ, Jones SS, Courage C, Waselewsky DR, Kostaroff AS, Kaufman D, Beemath A, Brofman J, Castillo JW, Krayem H, Marinelli A, Milner B, Palleschi MT, Tareen M, Testani S, Soubani A, Walch J, Wheeler J, Wilborn S, Granovsky H, Welch RD. **Impact of palliative care screening and consultation in the ICU: A multihospital quality improvement project.** *J Pain Symptom Manage.* 2017 Jan;53(1):5-12.e3.

## PRACTICE AND UTILIZATION

Aldridge MD, Epstein AJ, Brody AA, Lee EJ, Cherlin E, Bradley EH. **The impact of reported hospice preferred practices on hospital utilization at the end of life.** *Med Care.* 2016 Jul;54(7):657-63.

Grudzen CR, Richardson LD, Johnson PN, Hu M, Wang B, Ortiz JM, Kistler EA, Chen A, Morrison RS. **Emergency department-initiated palliative care in advanced cancer: A randomized clinical trial.** *JAMA Oncol.* 2016 Jan 14. doi: 10.1001/jamaoncol.2015.5252.

Horton JR, Morrison RS, Capezuti E, Hill J, Lee EJ, Kelley AS. **Impact of inpatient palliative care on treatment intensity for patients with serious illness.** *J Palliat Med.* 2016 Sep;19(9):936-42

## GUIDELINE STATEMENTS

Davidson JE, Aslakson RA, Long AC, Puntillo KA, Kross EK, Hart J, Cox CE, Wunsch H, Wickline MA, Nunnally ME, et.al. **Guidelines for Family-Centered Care in the Neonatal, Pediatric, and Adult ICU.** *Crit Care Med.* 2017 Jan;45(1):103-128.

Kon AA, Davidson JE, Morrison W, Danis M, White DB. **Shared Decision-Making in Intensive Care Units. Executive Summary of the American College of Critical Care Medicine and**

**American Thoracic Society Policy Statement.** *Am J Respir Crit Care Med.* 2016 Jun 15;193(12):1334-6.

## ONGOING / FUTURE WORK

Courtright KR, Madden V, Gabler NB, Cooney E, Small DS, Troxel A, Casarett D, Ersek M, Cassel JB, Nicholas LH, Escobar G, Hill SH, O'Brien D, Vogel M, Halpern SD. **Rationale and design of the randomized evaluation of default access to palliative services (REDAPS) trial.** *Ann Am Thorac Soc.* 2016 Sep;13(9):1629-39.

Cox CE, Wysham NG, Kamal AH, Jones DM, Cass B, Tobin M, White DB, Kahn JM, Hough CL, Carson SS. **Usability testing of an electronic patient-reported outcome system for survivors of critical illness.** 2016 Jul; 25(4): 340-349.



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