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CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Mitchel L. Zoler/Frontline Medical News

Balanced crystalloids protect kidney better than saline

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – Treatment with balanced crystalloid intravenous fluids cut adverse renal events modestly but with statistical significance, compared with 0.9% saline in hospitalized patients in a pair of single-center randomized trials with more than 29,000 total patients.

Despite showing a number needed to treat with balanced crystalloids of roughly 100 to prevent one major renal event, compared with saline, the scope of intravenous fluid use makes even this relatively small improvement potentially important to tens of thousands of patients annually.

"It's a small but clinically important difference," Wesley H. Self, MD, said at the CHEST annual meeting.

"These fluids are used every day and in millions of patients annually in the United States and worldwide. There is no functional cost difference between them, and now we have the data to show that [balanced crystalloid fluids] produce a better patient outcome. It's reasonable to consider changing practice," based on the results, said Matthew W. Semler, MD, a pulmonologist at Vanderbilt University Medical Center in Nashville, Tenn., who led one of the two trials.

At Vanderbilt, where the two studies ran,

IN-HOSPITAL DEATHS REDUCED // *continued on page 4*

Nebulized glycopyrrolate improves lung function in COPD

BY DEBRA L. BECK
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – Glycopyrrolate, a novel nebulized long-acting muscarinic antagonist (LAMA) in development, was well-tolerated and significantly improved lung function and health status in COPD patients regardless of baseline lung function or age, according to a subgroup analysis of pooled results from two randomized trials.

There are currently no nebulized LAMAs approved for use in the U.S.

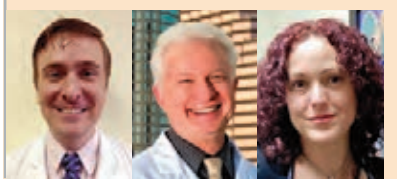
Jill Ohar, MD, FCCP, from Wake Forest University School of Medicine (Winston-Salem, N.C.), presented this secondary analysis of the GOLDEN-3 and GOLDEN-4 trials at the CHEST annual meeting. She and her colleagues evaluated the efficacy and safety of glycopyrrolate in patients with a forced expiratory volume (FEV_1) % predicted of less than 50 and an FEV_1 % predicted of greater than or equal to 50, in age ranges of less than 65 years, greater than or equal to 65 years and at least 75 years, as measured by trough FEV_1.

NEW FORM OF DRUG UPS FEV_1 // *continued on page 6*

INSIDE HIGHLIGHT

NEWS FROM CHEST

Critical Care Commentary:



***Clostridium difficile* in the ICU**

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In-hospital deaths reduced // *continued from page 1*

"we've changed our practice and are transitioning from primarily using saline to primarily balanced crystalloid," Dr. Semler said in a video interview available on www.mdedge.com/chestphysician. The main limitation to changing practice now because of the results is that the two trials both ran at a single center.

The findings Dr. Semler reported came from the Isotonic Solutions and Major Adverse Renal Events Trial (SMART). In this study, 7,860 intensive care unit (ICU) patients were randomized to be treated with a 0.9% saline intravenous fluid, while 7,942 ICU patients were randomized to be given a balanced crystalloid intravenous fluid, either lactated Ringer's or Plasma-Lyte A. The study's primary endpoint was the combined 30-day rate of in-hospital death, incident need for renal replacement therapy, or at least a doubling of the patient's baseline creatinine level, a marker of persistent renal dysfunction.

This outcome occurred in 14.3% of patients on balanced crystalloid fluid and 15.4% on saline, a 1.1% statistically significant ab-

solute difference. The endpoint components showed that patients treated with balanced crystalloid had 0.8% less in-hospital death and 0.4% less incident renal replacement therapy; both of these between-group differences were close to having statistical significance. The two treatment groups showed less difference in the rate of persistent renal dysfunction.

The second trial had an identical design but ran instead in the emergency department. The Saline Against Lactated Ringers or Plasmalyte in the Emergency Department (SALT-ED) trial randomized 6,708 to receive balanced crystalloid and 6,639 to receive saline. The combined primary renal endpoint was 0.9% less frequent with balanced crystalloid fluid, a statistically significant difference, Dr. Self, an emergency medicine physician at Vanderbilt, reported at the meeting. In this study the between-group differences for both incident renal replacement therapy and persistent renal dysfunction were statistically significant in favor of balanced crystalloid, but the between-group mortality difference was not significantly different.

The reason why balanced crystalloid fluid produced better renal outcomes than saline remains unclear. Both Dr. Semler and Dr. Self noted that the two balanced crystalloid fluids used in the study have chloride levels that closely match normal plasma levels, but the chloride concentration in 0.9% saline is about 50% higher than plasma. Some researchers have hypothesized, based on animal findings, that this difference may influence inflammation, blood pressure, acute kidney injury, and renal vasoconstriction.

The SMART and SALT-ED trials received no commercial funding. Dr. Semler had no disclosures. Dr. Self has been a consultant to Abbott Point of Care, BioTest, Cempra, Fering, Gilead, and Pfizer.

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VIEW ON THE NEWS

Fluid switch has big impact for small cost

The SMART and SALT-ED trials were awesome and beautifully planned. The researchers used a pragmatic design that is the wave of the future. The incremental benefit from balanced crystalloid fluids was small, about 1%, but it's a cheap solution. If you administer 7 L of fluid to a patient the incremental cost compared with 0.9% saline is about $45. Based on the number needed to treat that the studies found, this means it would cost less than $5,000 extra to prevent one major adverse kidney event. Nothing else in the ICU or ED compares with that. It's a phenomenal impact from a low-tech intervention.

Bennett P. deBoisblanc, MD, FCCP, is professor of medicine at Louisiana State University Health and director of Critical Care Services at the Medical Center of Louisiana in New Orleans. He had no disclosures. He made these comments from the floor during discussion of the two reports.

New form of drug ups FEV_1

// continued from page 1

"Glycopyrrolate works," reported Dr. Ohar. "It improves FEV_1 [at week 12], not only in the statistically significant manner but in a clinically significant manner, both at the 25-microgram and 50-microgram dose…And when you cut the data according to FEV_1, you again see a statistically significant improvement regardless [of whether] your FEV_1 at baseline was less than 50% of predicted versus greater than or equal to 50%."

DR. OHAR, FCCP

Similarly, both glycopyrrolate doses produced significant (*P* less than .05) and clinically meaningful lung function improvements vs. placebo in participants less than 65 years of age, at least 65 years, and greater than or equal to 75 years.

Glycopyrrolate use for 12 weeks led to greater improvements over placebo in St. George's Respiratory Questionnaire (SGRQ) total score, in patients in both lung function classes. There were a higher percentage of SGRQ responders in the treatment arms, compared with placebo arms.

The highest improvement in SGRQ (−6.287) was seen in the 47 patients that comprised the at-least-75 years of age subgroup receiving glycopyrrolate 25 mcg BID. "It's a small number of people, but I think it's [valuable] to see if the very aged act in any way differently than the entire greater than or equal to 65-year-old group," said Dr. Ohar.

Adverse event rates were similar for placebo and both glycopyrrolate doses, with no safety signals seen according to baseline lung function or age. Few cardiovascular events of special interest were seen.

"Looking at major adverse cardiovascular events, such as fatal MIs, other cardiovascular deaths, arrhythmias, etc., we see nothing that would suggest that the drug overall is associated with an undue number of these versus placebo," reported Dr. Ohar.

Glycopyrrolate use for 12 weeks led to greater improvements over placebo in St. George's Respiratory Questionnaire total score, in patients in both lung function classes. There were a higher percentage of SGRQ responders in the treatment arms, compared with placebo arms.

GOLDEN 3 and 4 were replicate, 12-week, phase 3, randomized, double-blind, placebo-controlled studies that evaluated glycopyrrolate solution administered by an investigational eFlow Close System (eFLOW CS) nebulizer in individuals with moderate-to-very severe COPD, including those with continued background use of a long-acting beta2-agonist (LABA), with or without an inhaled corticosteroid (ICS). In each of the trials, about 30% of patients were on LABA ICS, noted Dr. Ohar in her presentation. A total of 653 subjects were randomized in GOLDEN 3 and 641 in GOLDEN 4.

Its manufacturer, Sunovion Pharmaceuticals, resubmitted the product to the FDA in June 2017 in response to a Complete Response Letter received from the FDA in May 2017. The FDA is expected to act on the new submission on December 15, 2017. The novel agent is being considered for the long-term, maintenance treatment of airflow obstruction in people with COPD, including chronic bronchitis and/or emphysema.

Dr. Ohar reported that she serves on the advisory boards of several pharmaceutical companies. The other three authors are employees of Sunovion Pharmaceuticals Inc.

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: If approved, this would represent the first nebulized LAMA available in the U.S. – so in the small population of patients that is unable to utilize standard delivery devices, this would provide an option. It is unclear if this medication must be administered via the proprietary nebulizer that was used in the study – but if so, this would certainly add to the already extremely high cost of respiratory medications and further limit access for many patients.

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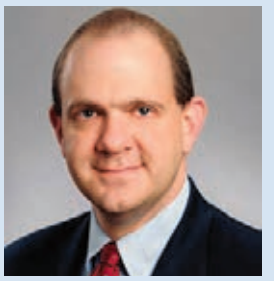
CHEST Physician is available at chestphysician.org.



David A. Schulman, MD, FCCP, is Medical Editor in Chief of CHEST Physician.

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Revised guidelines raise lung cancer screening age

BY MITCHEL L. ZOLER
Frontline Medical News

Photos Mitchel L. Zoler/Frontline Medical News

Dr. Peter J. Mazzone, FCCP

Dr. Gerard A. Silvestri, FCCP, and Dr. Renda Soylemez Wiener

EXPERT ANALYSIS FROM CHEST 2017 ▪ TORONTO – A proposed change to CHEST's lung cancer screening guideline calls for raising the upper age for screening recent cigarette smokers to 77 years of age from 74 years of age.

This proposal is part of draft guideline that was unveiled during the CHEST annual meeting but is still subject to tweaking by peer review until formal release in early 2018. The draft also offers expanded guidance on how to implement screening, containing three times as many recommendations as the current lung cancer screening guidelines (Chest. 2013 May; 143[5 Suppl]:e78S-e92S).

"We want screening to expand in a safe and effective way," said Peter J. Mazzone, MD, FCCP, chair of the expert panel that is preparing the revision for CHEST and a pulmonologist at the Cleveland Clinic. "We are less restrictive with these guidelines" than in the 2013 version.

Dr. Mazzone cited two major changes that will produce modest broadening of the criteria that determine which patients can appropriately get screening. The clearest change was the age range, which expanded from 55-74 years of age set in 2013 to reflect the age criterion for enrollment in the National Lung Screening Trial (New Engl J Med. 2011 Aug 4; 365[5]:395-409). The panel raised the upper age limit to 77 years of age to coincide with what Medicare covers, Dr. Mazzone explained, though it remains short of the 80-year old ceiling recommended by the U.S. Preventive Services Task Force.

The second, subtler change eased back on the outright ban that the 2013 guidelines placed on screening anyone who falls outside the target age range and smoking history (at least 30 pack years and either being a current smoker or having recently quit within the past 15 years) and who is without severe comorbidities.

The guidelines from 2013 said that screening people who fell outside these limits "should not be performed." In contrast, the new draft guideline simply said that people who fall outside of the age and smoking-history criteria but who are still considered high risk for lung cancer based on a risk-prediction calculator should not "routinely" undergo screening. Additionally, exceptions could be made for certain patients whose high risk appears to warrant screening, Dr. Mazzone and others from the expert panel noted.

The revision specified that a high-risk person outside of the core criteria might still be a reasonable candidate for screening if this person tallies at least a 1.51% risk of developing lung cancer during the next 6 years according to the $PLCO_{M2012}$ risk calculator (New Engl J Med. 2013 Feb 21; 368[8]:728-36).

"Some of the evidence allowed us to be a little more flexible," though not to the point of "opening screening widely" to people who fall outside the core target population; rather, clinicians get to have a little more discretion, said Dr. Mazzone, who directs the Cleveland Clinic's Lung Cancer Program. "We hope this will lead to more patients being screened in a high quality way," he said in an interview. The panel strove to "look beyond the National Lung Screening Trial and find other groups of patients who could benefit" from screening. "We say that other high-risk people should not, on the whole, be screened" but that clinicians could consider individuals as appropriate for screening on a case-by-case basis.

The revision "fills in the outline" for screening that was established in the 2013 guidelines, said Gerard A. Silvestri, MD, FCCP, a member of the revision panel, in a video interview, which is available at mdedge.com/chestphysician.

In addition to four evidence-based recommendations that help define who is and isn't an appropriate screening candidate, the revised guideline also included 11 mostly consensus-based "suggestions" about how screening programs should ideally operate.

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Rapid influenza test obviates empiric antivirals

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – A test that only requires a maximum 2-hour wait for results was highly accurate at detecting influenza and respiratory syncytial virus infection in lung transplant patients, according to research presented at the CHEST annual meeting on Oct. 30.

This rapid and highly accurate test for detecting three common respiratory viruses has dramatically cut the need for empiric treatments and the risk for causing nosocomial infections in lung transplant patients who develop severe upper respiratory infections, Macé M. Schuurmans, MD, FCCP, noted during the presentation.

This study involved 100 consecutive lung transplant patients who presented at Zurich University Hospital with signs of severe upper respiratory infection. The researchers ran the rapid and standard diagnostic tests for each patient and found that, relative to the standard test, the rapid test had positive and negative predictive values of 95%.

The number of empiric treatments with oseltamivir (Tamiflu) and ribavirin to treat a suspected influenza or respiratory syncytial virus infection (RSV) has "strongly diminished" by about two-thirds, noted Dr. Schuurmans, who is a pulmonologist at the hospital.

Until the rapid test became available, Dr. Schuurmans and his associates used a standard polymerase chain reaction test that takes 36-48 hours to yield a result. Using this test made treating patients empirically with oseltamivir and oral antibiotics for a couple of days a necessity, he said in a video interview available on www.mdedge.com/chestphysician. The older test also required isolating patients to avoid the potential spread of influenza or RSV in the hospital.

Mitchel L. Zoler/Frontline Medical News

Dr. Macé M. Schuurmans, FCCP

The rapid test, which became available for U.S. use in early 2017, covers influenza A and B and RSV in a single test with a single mouth-swab specimen.

"We now routinely use the rapid test and don't prescribe empiric antivirals or antibiotics as often," Dr. Schuurmans said. "There is much less drug cost and fewer potential adverse effects from empiric treatment." Specimens still also undergo conventional testing, however, because that can identify eight additional viruses that the rapid test doesn't cover.

Dr. Schuurmans acknowledged that further study needs to assess the cost-benefit of the rapid test to confirm that its added expense is offset by reduced expenses for empiric treatment and hospital isolation.

He had no disclosures. The study received no commercial support.

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Government uncertainty drives jump in ACA silver plan insurance premiums

BY GREGORY TWACHTMAN
Frontline Medical News

Silver plans on the Affordable Care Act insurance exchanges in 2018 will see an average premium increase of 34% nationwide, according to new research from Avalere Health.

"Plans are raising premiums in 2018 to account for market uncertainty and the federal government's failure to pay for cost-sharing reductions," Caroline Pearson, senior vice president at Avalere, said in a statement. "These premium increases may allow insurers to remain in the market and enrollees in all regions to have access to coverage."

Other drivers of this increase include lower than anticipated enrollment in the marketplace, limited insurer participation, insufficient action by the government to reimburse plans that cover higher-cost enrollees, and general volatility around the policies governing exchanges, according to the Avalere research.

The expected premium changes are highly variable by state. Iowa has the highest change in its silver plans, with an average premium increase of 69% for its silver plans, while at the other end of the spectrum, Alaska is actually seeing a 22% decrease.

"These rates may change prior to open enrollment depending on how states respond to the elimination of CSR [cost-sharing reduction] funding for the 2018 plan year," Avalere notes in its new analysis, adding that states may allow plans to refile for rate hikes now that CSR funding is likely dead. "In states where this occurs, it is expected that the newly updated rates will be substantially higher for the 2018 plan year."

There was a glimmer of hope that the CSR payments would resume after a compromise was reached in the Senate Health, Education, Labor & Pensions Committee by Chairman Lamar Alexander (R-Tenn.) and ranking member Patty Murray (D-Wash.) that would offer 2 years of funding along with flexibility in the waiver program to allow states to tweak Affordable Care Act requirements. However, Speaker Paul Ryan (R-Wis.) said the House would not be taking on any more health care action for the remainder of the year.

A spokeswoman from America's Health Insurance Plans said in an interview that, although the CSR payments are no more, premium tax credits still exist to help lower-income individuals obtain insurance coverage.

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VIEW ON THE NEWS

Mike Nelson, MD, FCCP, comments: One need not "google" too long to find that the United States performs quite poorly in overall health care when compared with other nations, despite spending more than any of the comparators...we're 37th this year. This information from Avalere Health portends a further drop in our ranking next year. The privilege of good health is a responsibility of the individual, but the right to affordable health care is a responsibility of the government. It is time for our legislators to stop playing partisan politics and start communicating to propose a workable and affordable solution.

Docs to receive better Medicare pay bump than proposed

BY GREGORY TWACHTMAN
Frontline Medical News

Physicians will see a 0.41% increase to their payments under the Medicare physician fee schedule in 2018, a slight increase from the proposed 0.31% uptick but still short of the 0.5% increase promised under the Medicare Access and CHIP Reauthorization Act (MACRA).

Officials at the Centers for Medicare & Medicaid Services were unable to find adequate funding in so-called misvalued codes to back the larger increase, as required by law, according to the final version of the 2018 physician fee schedule, released Nov. 2 and scheduled for publication in the Federal Register on Nov. 15.

The agency finalized a number of other provisions, including the rollback of reporting requirements for the recently completed Physician Quality Reporting System to better align those reporting requirements with the Merit-based Incentive Payment System requirements of the Quality Payment Program created by MACRA. Similar changes were made to the reporting requirements under the Medicare Electronic Health Record Incentive Program.

"We finalized these changes based on stakeholder feedback and to better align with the MIPS data submission requirements for the quality performance category," CMS said in a fact sheet detailing the provisions of the final rule.

CMS also is delaying the start of the appropriate use criteria (AUC) for imaging services, a program that would deny payments for imaging services unless the ordering physician consulted appropriate use criteria. The program will begin with an educational and operational testing year in 2020. Physicians will be required to start using AUCs and reporting this information on claims, but CMS will pay claims regardless of whether they correctly contain the required AUC data.

"This allows both clinicians and the agency to prepare for this new program," the agency said in the fact sheet. The CMS had proposed 2019 be the educational and operational testing year.

In response to comments submitted to the agency, CMS is changing its policy on billing codes for biosimilars administered under Medicare Part B.

"Effective January 1, 2018, newly approved biosimilar products with a common reference product will no longer be grouped in the same billing code," the agency said in the fact sheet. "By encouraging innovation and greater manufacturer participation in the marketplace, we believe that this policy change will result in the licensing of more biosimilar products, thus creating a stable and robust market, driving market competition, and decreasing uncertainty about access and payment."

The final rule implements proposed expansion of the Medicare Diabetes Prevention Program from a demonstration project to a nationwide program in 2018, however the implementation will be delayed for three months until April 1, 2018, rather than start at the beginning of the year. The program provides payments to physicians based on performance goals being met by patients, including meeting certain numbers of service and maintenance sessions with the program and achieving specific weight-loss goals.

CMS also finalized a number of new telemedicine payment codes.

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VIEW ON THE NEWS

Mike Nelson, MD, FCCP, comments: I always appreciate someone who has the time and willingness to read through, understand and succinctly summarize pertinent points of the Medicare Physician Fee Schedule (MPFS). The good news is that physicians will receive a pay increase and some of the increase in administrative burdens are being delayed. The bad news is that CMS admits that it is not yet ready to act upon some of the changes required by recent law. How do they expect clinicians, who have many fewer resources, to comply with these changes? There are defined comment periods to the MPFS each year and I would encourage all readers to comment. Like voting, it is one of the few ways to have one's voice heard.

More physicians excluded from MIPS

BY GREGORY TWACHTMAN
Frontline Medical News

More doctors will be exempt from participation in the Merit-Based Incentive Payment System in 2018, under a final rule issued by the Health & Human Service Department.

Health care providers will be excluded from MIPS if they have $90,000 or less in Medicare Part B billings, or if they see 200 or fewer Medicare patients next year. These reporting thresholds are higher than the ones from 2017, which were $30,000 or 100 patients, respectively. Providers participating in an advanced alternative payment model also will not be a part of the MIPS track. The "increase in the low-volume threshold is expected to exclude 540,000 clinicians who do not exceed that threshold," officials from the Centers for Medicare & Medicaid Services wrote in the final rule released Nov. 2.

Health care providers will be excluded from MIPS if they have $90,000 or less in Medicare Part B billings, or if they see 200 or fewer Medicare patients next year.

In comments when the rule was a draft, many organizations suggested that CMS allow clinicians who are ready to participate in MIPS to opt in even if they fall into the MIPS low-volume threshold category. While the agency did not codify this suggestion, officials noted that they intend to "revisit this policy in future rule making and are seeking comment on methods to implement this policy in a low-burden manner."

Medical societies were generally in favor of the new higher threshold, but it was met with resistance from associations representing group practices.

"The transition to value is challenging and CMS understandably wants to ease providers into value," Jerry Penso, MD, president and CEO of the American Medical Group Association, said in a statement. "But excluding providers isn't the same as learning how to deliver care in a value-based world. Taking accountability for the quality and cost of care requires years of experience. Despite CMS' intentions to ensure a smooth transition, AMGA is concerned that this rule actually hinders the prospects for value-based care."

CMS is providing a number of enhancements for small practices participating in MIPS.

Small practices (15 or fewer providers) will get five bonus points under MIPS and will continue to earn points for partial data reporting of quality measures. They also will be able to join virtual groups to help aggregate their reporting and improve

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abilities to access payment bonuses.

CMS also is slowly phasing in the cost performance category, which will account for 10% of a MIPS score and will include Medicare spending per beneficiary and total per capita cost measures. These measures are carried over from the Value Modifier program and will require no action from providers to calculate. CMS will measure the performance in this category.

Finally, the agency included a hardship exemption for those affected by major hurricanes in the Gulf Coast and Puerto Rico in 2017. Currently, those who lost access to their EHRs because of the hurricanes, other natural disasters, or public health emergencies can file a hardship exemption to have their Advancing Care Information (formerly the meaningful use program) score reweighted to reflect the issues. Applications must be filed by Dec. 31, 2017.

The final rule extends the reweighting policy to the other three categories (quality, cost, and improvement activities) through the 2018 performance year, with a deadline of Dec. 31, 2018, to file for a hardship exemption.

"Because our policies relating to reweighting the quality, cost, and improvement activities performance categories are not effective until next year, we are issuing an interim final rule for automatic extreme and

uncontrollable circumstances where clinicians can be exempt from these categories in the transition year without submitting a hardship exception application," CMS noted in the fact sheet. For 2017, that means clinicians in areas affected by the hurricanes who do not submit data will not receive any negative adjustment. Clinicians who do submit data will be scored as usual.

"The transition to value is challenging and CMS understandably wants to ease providers into value," said Jerry Penso, MD, president and CEO of the American Medical Group Association.

On the advanced APM track, under which physicians take on more risk in exchange for a potential for greater bonus payments, CMS said it is making it easier for clinicians to participate, including extending for an additional 2 years certain revenue and expenditure provisions that are used to determine nominal risk, changing the medical home models to slow the increase of the minimal amount of financial risk taken on, and making it easier for clinicians to earn bonus payments for APMs that begin or end mid-year.

The final rule was scheduled for publication in the Federal Register on Nov. 16.

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Caprini model is not a good predictor of PE

BY MARK S. LESNEY
Frontline Medical News

The Caprini score, commonly used to risk-stratify patients for the development of venous thromboembolism and to determine the optimal dose of prophylaxis, failed to predict the development of pulmonary embolism and hemodynamically significant PE in patients presenting with deep vein thrombosis (DVT), according to the results of a large, retrospective single-center study.

Recent surgery was not associated with the development of hemodynamically significant PE, but the presence of proximal DVT was, according to a report published

online in the Journal of Vascular Surgery: Venous and Lymphatic Disorders (2017. doi: 10.1016/j.jvsv.2017.08.015).

Nancy Huynh and her colleagues at the Yale University School of Medicine, New Haven, performed a retrospective review of 838 consecutive patients diagnosed with DVT between January 2013 and August 2014 in a single center. They used multivariable analysis to determine predictors of PE and hemodynamically significant PE.

Their results showed that patients who had undergone recent surgery were less likely to develop hemodynamically significant PE (13.3% vs. 27.2%; $P = .01$). In contrast, patients with proximal DVT were at higher risk for development of hemodynamically significant PE (80.7% vs. 64.2%; $P = .007$). They found no association between Caprini score and PE severity ($P = .17$) or the Caprini score and proximal DVT ($P = .89$).

"This study shows that the Caprini score does not correlate with the occurrence of PE or the severity of PE. On the other hand, a proximal location of DVT seems to have a high association with hemodynamically significant PE. Such patients may benefit from more aggressive anticoagulant therapy and work-up for PE," the researchers concluded.

The authors reported that they had no conflicts of interest.

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IGRA preferred test for latent TB diagnosis

BY DEBRA L. BECK
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – U.S.-based pulmonary and infectious disease specialists prefer interferon-gamma release assays (IGRA) over tuberculin skin tests (TST) for the diagnosis of latent TB infection, but may not fully understand how to use and interpret the test results, according to survey results presented at the CHEST annual meeting.

Adam G. Green, MD, conducted the research while he was a fellow in pulmonology/critical care at Montefiore Medical Center in New York. Dr. Green told attendees that about one-third of the world's population are infected with TB and about 15 million of those live in the United States. Two-thirds of U.S. cases are seen in foreign-born individuals and are clustered in four states—New, York, California, Florida, and Texas.

"Epidemiological models have indicated that in order to eliminate the threat of TB in the United States, it will require a strategy of targeting latent tuberculosis infection specifically among foreign-born individuals," he said during his presentation. "This highlights the need for us practitioners on the front line to have sound knowledge of identification, screening, and management of latent TB infection, especially given the multiple modalities for diagnosis."

Among 304 clinicians who responded to an invitation to an online questionnaire, 78% said they preferred to use IGRA over TST and 91% said they had a "good understanding" of how to use and interpret IGRA. However, when queried further on how to best use and interpret IGRAs according to current guidelines, their answers to 11 knowledge-based questions told a somewhat different story, said Dr. Green, who is an intensivist at Cooper University Health Care in Camden, N.J.

While 96% knew IGRAs are not helpful in monitoring response to TB treatment, 20% erroneously thought that a positive IGRA predicts latent TB infection reactivation in the future.

Most respondents correctly answered two "fundamental" questions on cross-reactivity of IGRAs with *Mycobacterium avium* complex and bacilli Calmette-Guérin (BCG) vaccination (84% and 96%, respectively). "While 80% sounds good, I think we're talking about ID and pulmonary docs at the best institutions across the United States, so I would have expected much higher," Dr. Green said.

Only one-third of respondents knew that the T-SPOT.TB test, an IGRA, had the highest sensitivity for identifying those with latent TB infection. And only about half were able to appropriately identify the need to initiate therapy for latent TB in a scenario in which the patient was at "high risk for latent tuberculosis with a positive tuberculin skin test and a negative interferon-gamma release assay."

Fellows comprised 42.5% of re-

Continued on following page

Outcomes better for patients with H1N1 vaccination

BY DEBRA L. BECK
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – Patients who received an influenza vaccination but still required hospitalization for H1N1 influenza had better outcomes, compared with unvaccinated patients, according to findings from a retrospective study.

In the hospital, vaccinated patients had significantly lower rates of acute kidney injury (6% vs. 35%; *P* = .038) and were more likely to be satisfactorily managed with noninvasive mechanical ventilation (41% vs. 6%; *P* = .004).


DR. CHANDAK

"Even though the vaccine is effective, it's not completely effective in preventing the illness," said Twinkle Chandak, MD, FCCP, a pulmonologist at the Berkshire Medical Center in Pittsfield, Mass., who presented the study at the CHEST annual meeting. The Centers for Disease Control and Prevention reported that 2015-2016 vaccination effectiveness was about 41%, she noted.

Dr. Chandak and her colleagues studied 72 cases of seasonal influenza requiring hospitalization from September 2015 to April 2016 at Berkshire Medical Center, a 300-bed teaching hospital in western Massachusetts. Based on rapid polymerase chain reaction testing, 51 of these patients were positive for H1N1, of which 38 had received a seasonal flu vaccine.

H1N1 patients who had received vaccination were significantly older (70.4 years vs. 59.6 years; *P* = .016) and were more often smokers (76% vs. 38%; *P* = .017), compared with patients who were unvaccinated.

The finding that the unvaccinated patients were younger and still had poorer outcomes "emphasizes the need for widespread vaccination," Dr. Chandak said.

There were several parameters that trended in favor of vaccination, but did not reach statistical significance due to the relatively small sample size, Dr. Chandak said. These included a trend toward more ICU admission in the unvaccinated, compared with vaccinated patients (21% and 12%, respectively; *P* = .699), a longer ICU stay (1.7 days and 0.2 days; *P* = .144), more multiorgan dysfunction syndrome (12% and 6%; *P* = .654), and more acute respiratory distress syndrome (6% and 0%; *P* = .547). Vasopressors were needed in a similar proportion of patients (12% of both groups).

During the 2009-2010 flu season, H1N1 was the cause of about 61 million cases of influenza in the United States, 274,000 hospitalizations, and 12,470 deaths, Dr. Chandak reported.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: "I never take the flu vaccine," my patient stated, following my suggestion that she be inoculated. "It makes me sick."

I reflected on the cases of influenza patients that I took care of the previous year in the ICU: the 50-year-old man with no comorbidities who died in respiratory failure; the 32-year-old pregnant woman who survived a 3-month hospitalization during which she was treated with ECMO and suffered irreversible kidney failure. "I take it every year," I told her.

While the influenza vaccine may not prevent all cases of influenza, those who develop influenza may have an attenuated illness. Data from Chandak and colleagues affirm improved outcomes in patients who receive the vaccine and still develop influenza.

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spondents and the remainder were attendings of varying levels of seniority. About half of respondents were pulmonologists and the other half infectious disease specialists. The majority (91%) were practicing or training in university hospitals.

One major limitation of the study, said Dr. Green, is the low response rate. "I would have liked 3,000 responses," he said, rather than just over 300.

To disseminate the questionnaire, he contacted pulmonary and infectious disease academic program directors and coordinators and asked them to forward the survey invitation to their full-time faculty and fellows. Dr. Green also acknowledged that his project missed those physicians not working in academic centers.

"I would like to think that the reason people didn't do as well as I had hoped is because of the conflicting literature out there and using not necessarily the guidelines but rather their current knowledge on what was most recently published," said Dr. Green. "But maybe there is a true misunderstanding."

The authors reported there were no product or funding disclosures relevant to this study.

Abnormal potassium level: A red flag in ACS

BY BRUCE JANCIN
Frontline Medical News

BARCELONA – A serum potassium level of at least 5.0 mmol/L or 3.5 mmol/L or less at admission for suspected acute coronary syndrome is a red flag for increased risk of in-hospital mortality and cardiac arrest, according to a Swedish study of nearly 33,000 consecutive patients.

That's true even if, as so often ultimately proves to be the case, the patient turns out not to have ACS, Jonas Faxén, MD, of the Karolinska Institute, Stockholm, reported at the annual congress of the European Society of Cardiology.

"This study highlights that, if you have a patient in the emergency department with a possible ACS and potassium imbalance, you should really be cautious," Dr. Faxén said.

He reported on 32,955 consecutive patients admitted to Stockholm County hospitals for suspected ACS during 2006-2011 and thereby enrolled in the SWEDEHEART (Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry.

Overall in-hospital mortality was 2.7%. In-hospital cardiac arrest occurred in 1.5% of patients. New-onset atrial fibrillation occurred in 2.4% of patients. These key outcomes were compared between the reference group – defined as patients with an admission serum potassium of 3.5 to less than 4.0 mmol/L – and patients with an admission serum potassium above or below those cutoffs.

In a multivariate logistic regression analysis adjusted for 24 potential confounders, including demographics, presentation characteristics, main diagnosis, comorbid conditions, medications on admission, and estimated glomerular filtration rate, patients with a serum potassium of 5.0 to less than 5.5 mmol/L were at 1.8-fold increased risk of in-hospital mortality. Those with a potassium of 5.5 mmol/L or greater were at 2.3-fold increased risk.

In contrast, a low rather than a high serum potassium was an independent risk factor for cardiac arrest. An admission potassium of 3.0 to less than 3.5 mmol/L carried a 1.8-fold increased risk of in-hospital cardiac arrest, while a potassium of less than 3.0 was associated with a 2.7-fold increased risk.


Bruce Jancin/Frontline Medical News

Dr. Jonas Faxén

A serum potassium below 3.0 mmol/L at admission also was associated with a 1.7-fold increased risk of new-onset atrial fibrillation.

Session cochair David W. Walker, MD, medical director of the East Sussex (England) Healthcare NHS Trust, observed, "When I was a junior doctor I was always taught that when patients came onto coronary care we had to get their potassium to 4.5-5.0 mmol/L. I think you might want to change that advice now."

The study was funded by the Swedish Heart and Lung Foundation and the Stockholm County Council.

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Cardiogenic shock boosts PAH readmissions 10-fold

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – Cardiogenic shock, acute kidney injury, and chronic obstructive pulmonary disease were the top drivers of 30-day rehospitalizations in U.S. patients after an index hospitalization for pulmonary artery hypertension, based on an analysis of U.S. national data from 2013.

An episode of cardiogenic shock boosted 30-day rehospitalizations nearly 10-fold in recently discharged pulmonary artery hypertension (PAH) patients. A history of chronic obstructive pulmonary disease (COPD) linked with a threefold higher rehospitalization rate, and acute kidney injury linked with a doubled number of 30-day rehospitalizations, Kshitij Chatterjee, MD, said at the CHEST annual meeting.

"We were surprised" that acute disorders – cardiogenic shock and acute kidney injury – played such a key role in triggering readmissions, said Dr. Chatterjee, a hospitalist at the University of Arkansas for Medical Sciences in Little Rock. He contrasted the impact of these acute disorders on PAH with the main drivers of rehospitalization for other diseases, such as COPD and pneumonia, that more often link with chronic comorbidities.

The powerful impact of cardiogenic shock in particular suggests that interventions that improve patient compliance with stabilizing treatments following an index PAH hospitalization might be effective at preventing a patient's quick return to the hospital. Contacting PAH patients a week after their index hospitalization discharge to make sure they are compliant with their diuretic regimen, for example, might help prevent a decompensation that then leads to cardiogenic shock and a return trip to the hospital, Dr. Chatterjee suggested.

Follow-up of PAH patients after an index hospitalization "is probably the single most important thing, because it can help with compliance," he said in an interview.

The rehospitalizations he studied could be for any cause. His analysis showed that the most common cause of rehospitalization was heart failure, which caused 23% of the rehospitalizations, followed by pulmonary hypertension that caused 20%, and acute kidney injury, responsible for 11% of the 30-day rehospitalizations.

Dr. Chatterjee's study used data collected during 2013 in the National Readmissions Database, run by the federal Agency for Healthcare Quality and Research. During that period, 776 patients entered a U.S. hospital with a primary diagnosis of PAH. During the 30 days following discharge, 114 (15%) returned to the hospital. During the second hospitalization 8% died, and the median length of stay for those who remained alive was 7 days.

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Two NOACS linked to increase in GI bleeding risk

BY AMY KARON
Frontline Medical News

Compared with conventional anticoagulants, both dabigatran and rivaroxaban conferred small but statistically significant increases in the risk of major gastrointestinal bleeding in a systematic review and meta-analysis of randomized trials reported in Clinical Gastroenterology and Hepatology. (doi: 10.1016/j.cgh.2017.04.031)

But other novel oral anticoagulants (NOACs) showed no such effect compared with warfarin, aspirin, or placebo, reported Corey S. Miller, MD, of McGill University, Montreal, and his associates. "The

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potentially increased risk of GI bleeding associated with dabigatran and rivaroxaban observed in some of our subgroup analyses merits further consideration," they wrote.

The NOACs (also known as non–vitamin K antagonist oral anticoagulants) help prevent stroke in patients with atrial fibrillation and prevent and treat venous thromboembolism. However, large AF trials have linked all except apixaban to an increased risk of major GI bleeding, compared with warfarin. Dabigatran currently is the only NOAC with an approved reversal agent, "making the question of GI bleeding risk even more consequential," the authors wrote.

They searched the MEDLINE, EMBASE, Cochrane, and ISI Web of Knowledge databases for reports of randomized trials of NOACs for approved indications published between 1980 and January 2016, which identified 43 trials of 166,289 patients. Most used warfarin as the comparator, but one study compared apixaban with aspirin and six studies compared apixaban, rivaroxaban, or dabigatran with placebo. Fifteen trials failed to specify bleeding sources and therefore could not be evaluated for the primary endpoint, the reviewers noted. In the remaining 28 trials, 1.5% of NOAC recipients developed major GI bleeding, compared with 1.3% of recipients of conventional anticoagulants (odds

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Intubation may increase cardiopulmonary risk

BY ANDREW D. BOWSER
Frontline Medical News

Prophylactic endotracheal intubation (PEI) prior to endoscopy for upper GI bleeding in critically ill adults may actually increase, rather than decrease, the risk of unplanned cardiopulmonary events, according to results of a retrospective cohort study.

The risk of patients developing pneumonia increased significantly, according to study author Umar Hayat, MD, Medicine Institute, Cleveland Clinic, and colleagues.

"The practice of PEI ... might be a factor that leads to this dreaded outcome [pneumonia] in patients presenting with upper GI bleeding, instead of preventing it," Dr. Hayat and colleagues wrote (Gastrointest Endosc. 2017;86:500-9. doi:10.1016/j.gie.2016.12.008).

The role of PEI in mitigating risk of cardiopulmonary adverse events remains controversial for patients presenting with upper GI bleeding, who can have mortality rates as high as 10% for nonvariceal bleeds and 20% for variceal causes, they said.

Data for 365 patients who had brisk upper GI bleeding were reviewed. The average patient age was 59 years and 64% were male; 144 (39.5%) underwent PEI prior to esophagogastroduodenoscopy (EGD).

The composite primary endpoint of the study, cardiopulmonary unplanned events, was defined as occurrence of pneumonia, pulmonary edema, acute respiratory distress syndrome, shock/hypotension, arrhythmia, myocardial infarction, or cardiac arrest within 48 hours of EGD. The final analysis included 200 intubated and nonintubated patients matched on a 1:1 basis using propensity score matching.

Post-EGD adverse outcomes were more common in patients who had undergone PEI prior to EGD (odds ratio, 3.8; 95% confidence interval, 1.4-10.2), published data show. The rate of unplanned cardiopulmonary events was 20% for intubated patients, compared with 6% for nonintubated patients ($P = .008$).

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ratio, 0.98; 95% confidence interval, 0.80-1.21). Five trials of dabigatran showed a 2% risk of major GI bleeding, compared with 1.4% with conventional anticoagulation, a slight but significant increase (OR, 1.27; 95% CI, 1.04-1.55). Eight trials of rivaroxaban showed a similar trend (bleeding risk, 1.7% vs. 1.3%; OR, 1.40; 95% CI, 1.15-1.70). In contrast, subgroup analyses of apixaban and edoxaban found no difference in risk of major GI bleeding versus conventional treatment.

One author received research grants and speaker honoraria from Boehringer Ingelheim Canada, Bayer Canada, Daiichi Sankyo, Bristol-Myers Squibb, and Pfizer Canada; another author disclosed serving as a consultant to Pendopharm, Boston Scientific, and Cook.

Lung injury risk higher with apheresis blood products

BY ROXANNE NELSON
Frontline Medical News

SAN DIEGO – The method of manufacturing can markedly influence the interaction of products containing red blood cells and lung cells, according to research presented at the annual meeting of the American Association of Blood Banks.

Compared with other RBC products, those derived from apheresis significantly increased pulmonary cell interleukin (IL)–6 and IL-8 production, and this was further exacerbated by cell stretching. Conversely, red cell–filtered products appeared to be the least likely to cause cell injury.

"Several studies have shown that red blood cell transfusion is associated with acute lung injury, and transfusion induces leakage in ICU patients," said lead study author Mathijs Wirtz, MD, of the Academic Medical Center, Amsterdam.

ICU patients who did not receive any transfusions had significantly lower leakage than those who were transfused. "There also seems to be a synergy between transfusion and mechanical ventilation," Dr. Wirtz said.

Studies have also shown that there are differences in the prevalence of transfusion-related acute lung injury when comparing Europe to the United States. Storage and manufacturing methods do differ between Europe and the United States, Dr. Wirtz noted. "This led to our hypothesis that lung injury inflicted by red blood cell transfusion is influenced by manufacturing methods."

In this study, Dr. Wirtz and his colleagues investigated the response of pulmonary cells to the different methods of manufacturing RBC products. Using type A or B blood obtained from eight donors, a variety of RBC products were manufactured for the study, including whole-blood filtered, red-cell filtered, apheresis derived, and whole-blood derived.

For measuring thrombin generation and analyzing extracellular vesicles (EV), supernatants were prepared after 4-5 days of storage for fresh and 41-42 days for stored. The researchers selected A549 type II alveolar cells to seed onto flexible membranes, which were then incubated with RBC supernatant also stretched 25% using a cell stretcher.

After 24 hours, the production of IL-8 and IL-6 was measured.

Both fresh and stored supernatants that were derived from apheresis significantly increased the production of IL-6 and IL-8 in pulmonary cells, compared with nonincubated controls and most of the other RBC products. The production of IL-6 and IL-8 was exacerbated by cell stretching.

Average IL-6 production in nonstretched cells was 91 pg/mL for fresh and 87 pg/mL for expired (*P* less than .05 vs. control and other RBC products). For stretched cells, it was 130 pg/mL and 150 pg/mL (*P* less than .05 vs. control). For controls, mean nonstretched and stretched production was 21 pg/mL and 85 pg/mL.

Mean IL-8 production in nonstretched cells was 2,100 pg/mL for fresh and 1,900 pg/mL for stored (*P* less than .05 vs. control and other RBC products). For stretched cells, the means were 4,100 pg/mL for fresh and 5,200 pg/mL for stored (*P* less than .05 vs. control).

The average nonstretched and stretched control IL-8 production was 1,200 pg/mL for fresh and 4,300 pg/mL for stored.

Products derived from apheresis also demonstrated a significantly higher ability to generate thrombin, compared with other RBC products, and a significantly increased number of RBC-derived EVs, compared with filtered red cell and whole blood–derived products (*P* less than .05).

Lifesaving future seen for electronic cigarettes

BY RICHARD FRANKI
Frontline Medical News

A switch from cigarettes to e-cigarettes has the potential to prevent almost 90,000 premature deaths in the United States in the year 2026, according to a study examining e-cigarette substitution scenarios.

The investigators' "optimistic scenario" – in which new smokers use e-cigarettes instead of cigarettes, smoking prevalence falls to 5% over a 10-year period, and e-cigarettes have a 5% excess risk over regular cigarettes – projects 380,832 premature deaths from smoking in the year 2026. Under a "status quo scenario," which projected current cigarette initiation and cessation rates and did not include e-cigarettes or other tobacco products, there would be 470,743 deaths, reported David T. Levy, PhD, and his associates (Tob Control. 2017 Oct 2. doi: 10.1136/tobaccocontrol-2017-053759).

Their "pessimistic scenario," which would involve more young people starting to use both e-cigarettes and tobacco, smoking prevalence falling to just 10% over a 10-year period, and e-cigarettes having a 40% excess risk over regular cigarettes, resulted in 456,297 premature deaths in 2026, only 14,446 fewer than the status quo scenario, said Dr. Levy of Georgetown University in Washington and his associates.

Further projections suggest that the optimistic scenario could result in almost 6.6 million fewer premature deaths and 86.7 million years of life gained by the year 2100, compared with the status quo scenario, while the pessimistic scenario would prevent 1.6 million deaths and add an extra 20.8 million years of life, they noted.

Since "a strategy of replacing cigarette by e-cigarette use can yield substantial gains, even with conservative assumptions about related risks … an endgame scenario for cigarettes might well be within reach, if new technologies for delivering nicotine with substantially less harm, but sufficient satisfaction, are harnessed with sufficient passion and political will to aggressively phase out tobacco cigarettes," Dr. Levy and his associates wrote.

The study was funded by grants from the National Institute on Drug Abuse and the National Cancer Institute. One investigator received a research grant from Pfizer and served as an advisory board member to Johnson & Johnson, which manufactures smoking cessation medications. No other conflicts of interest were declared.

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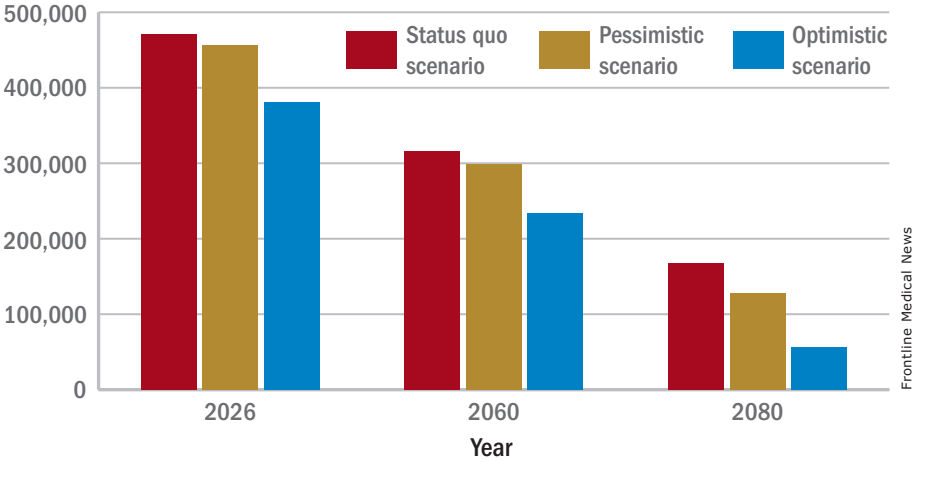
VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: This study seems to affirm the belief that e-cigarettes are a safer alternative to traditional cigarettes, and the thought "if patients are going to smoke, they are better than real cigarettes." While the available evidence mostly supports this, it must be recognized that there are significant assumptions being made regarding the relative safety of e-cigarettes – especially since there are no industry standards regarding their quality control or product contents. There exist significant conflicting data on both their safety and ability to serve as a cigarette alternative (for cessation or otherwise); and as with most things this complex, the truth probably is somewhere in the middle.

Premature deaths under e-cigarette substitution scenarios



Note: The scenarios were developed using data from the National Health Interview Survey and the American Cancer Society Cancer Prevention Studies.

Source: Tob Control. 2017 Oct 2. doi: 10.1136/tobaccocontrol-2017-053759

Remimazolam surpasses midazolam

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – An investigational sedative, remimazolam, that's similar to midazolam but with faster onset and offset, resulted in significantly better procedural success compared with midazolam in a multicenter, phase III trial with 431 patients.

The results also showed that remimazolam was as safe as midazolam (Versed), with a similar adverse event profile, said Gerard A. Silvestri, MD, FCCP, at the CHEST annual meeting.

Paion, the company developing remimazolam, plans to combine data from this bronchoscopy study with data collected from other procedural studies that included patients undergoing colonoscopy and upper gastrointestinal endoscopy, and seek U.S. Food and Drug Administration approval for the drug in 2018, according to a written statement.

The bronchoscopy trial enrolled patients at any of 15 U.S. centers with an American Society of Anesthesiologists (ASA) physical status classification of I-III and scheduled for diagnostic or therapeutic bronchoscopy. The enrolled patients averaged 62 years of age, and 38% were in ASA class III.

All patients received initial sedation treatment with fentanyl, followed by a three-to-one randomization to blinded remimazolam, blinded placebo that included midazolam rescue, or open-label midazolam. The study's primary efficacy endpoint was procedural success, defined as patients who underwent the complete procedure without need for an alternative sedative and without need for more than five doses

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VIEW ON THE NEWS

Eric Gartman, MD, FCCP. comments: This medication may represent a valuable addition to our options for moderate sedation during procedures – in that its main benefit seems to be in its onset of sedation. It will be important to assess this study's outcome data once published – especially with regard to the driver of the differences seen between groups in the composite primary outcome (i.e., successfully completing a procedure would be the important primary endpoint to most, and we should be interested to see if it was the dosing/time-based outcomes that drove the primary outcome differences between the groups). Further, if there are significant cost differences between these two medications, this will certainly limit their incorporation into practice unless there are significant differences in patient-centered outcomes.

Mitchel L. Zoler/Frontline Medical News

Dr. Gerard A. Silvestri

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of the patient's assigned medication within any 15-minute period during the procedure or need for more than three midazolam doses within any 12-minute period in the patients randomized to receive midazolam.

This primary endpoint occurred in 83% of 303 patients in the remimazolam arm, 5% of 59 patients in the placebo arm, and 34% of 69 patients in the midazolam arm, a statistically significant difference between the remimazolam patients and each of the comparator groups, reported Dr. Silvestri, a professor of medicine and a lung cancer pulmonologist at the Medical University of South Carolina in Charleston.

The results also demonstrated the faster onset and offset of remimazolam. Treatment achieved adequate sedation to start the procedure after a median of 5 minutes with remimazolam, a median of 15.5 minutes with midazolam, and a median of 17 minutes among patients in the placebo group. Once sedation finished, patients returned to being fully alert after a median of 6 minutes with

remimazolam, a median of 12 minutes with midazolam, and a median of 13.5 minutes for patients in the placebo arm.

"What's nice about remimazolam is that the adverse event profile is exactly the same as with placebo and midazolam, and you have a reversal agent," the same as what's used for midazolam, he said.

Midazolam is the current "workhorse" sedative, but "we can do better," commented Matthew B. Stanbrook, MD, FCCP, a pulmonologist at the University of Toronto. "There would be some benefit from a sedative with faster onset and offset," he said in an interview.

Dr. Silvestri suggested several additional studies he would like to see run on remimazolam to better understand its clinical performance and role. These include studying the drug in the elderly, patients with an ASA classification of IV, obese patients, and those on high narcotic doses. He also suggested comparing remimazolam directly with propofol, testing remimazolam as a stand-alone agent without fentanyl co-administration, and trying the drug during other pulmonary procedures such as pleural-catheter placement and other invasive procedures, and in ICU patients.

The trial was funded by Paion, the company developing remimazolam. Dr. Silvestri and Dr. Stanbrook had no relevant disclosures.

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Nebulized LABA safe for long-term use in COPD

BY DEBRA L. BECK
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – No long-term safety signals were seen in a randomized trial that tested the formoterol fumarate inhalation solution (Perforomist, Mylan) against placebo in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Safety was confirmed despite patients being permitted to remain on other background treatment for COPD, including inhaled corticosteroids and anticholinergics, in this study presented at the CHEST annual meeting. An additional benefit of the therapy was that it significantly improved lung function from

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baseline, according to some spirometry measures.

"These results are certainly reassuring from the safety perspective and confirm previously published shorter-term efficacy and safety studies with this medication," reported Nicola A. Hanania, MD, FCCP, from Baylor College of Medicine, Houston.

The Food and Drug Administration approved formoterol fumarate, a long-acting beta-2 agonist (LABA), as a nebulized maintenance treatment for bronchoconstriction in COPD. Because of a concern about long-term LABA safety in asthma patients, said Dr. Hanania, the FDA mandated this 1-year phase 4 study to evaluate the long-term safety of formoterol in patients with moderate to severe COPD.

Formoterol significantly improved trough forced expiratory volume in 1 second, compared with placebo at 3 and 6 months of treatment, Dr. Hanania noted.

This multicenter, double-blind, noninferiority study randomly assigned 1,071 patients with moderate

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to severe COPD (mean $FEV_{1,}$ 44.4% of predicted value, at least one exacerbation in the past 12 months) to receive either nebulized formoterol 20 mcg/2 mL twice daily or matching placebo for up to 12 months. Subjects were permitted to remain on stable COPD therapy, including inhaled corticosteroids and anticholinergics but excluding long-acting beta-agonists.

Formoterol was noninferior to placebo for the primary safety endpoint, defined as a first occurrence of respiratory-related death, COPD-related emergency department visit, or COPD-related hospitalization, with an estimated hazard ratio of 0.965.

"One thing we have to keep in mind is that formoterol is a full agonist, so there are dose-dependent adverse effects," said Nicola A. Hanania, MD.

Formoterol significantly improved trough forced expiratory volume in 1 second (FEV_1), compared with placebo at 3 and 6 months of treatment, with (least squares) mean estimated differences of 42 mL (P = .007) and 41 mL (P = .025), respectively, but not at 9 or 12 months. Forced vital capacity was significantly improved with formoterol over placebo at all study visits (3, 6, 9, and 12 months), but improvements from baseline in inspiratory capacity did not significantly differ from placebo.

Mean age of study patients was

Debra L. Beck/Frontline Medical News

Dr. Nicola Hanania

62.6 years and 48.5% were female. At baseline, about half of patients were still smokers, half were on inhaled corticosteroids, and about one-third were on concomitant long-acting muscarinic antagonists, mainly tiotropium, reported Dr. Hanania. The vast majority of patients had moderate or severe COPD, with less than 1% having very severe disease at baseline.

In response to a question on dosing, Dr. Hanania told attendees, "One thing we have to keep in mind is that formoterol is a full agonist, so there are dose-dependent adverse effects. So, even though you get better lung function as you go up on the dose, there's no free lunch and always the potential for adverse effects."

The safety data was previously presented at the American Thoracic Society meeting in May 2017 (Hanania N et al. Am J Respir Crit Care Med. 2017;195 A5473 [abstract]), while the lung function data are new, said Dr. Hanania.

Dr. Hanania reported being an adviser for several pharmaceutical companies, including Mylan. Four of the six authors of the study's abstract are employees of Mylan.

Tezacaftor-ivacaftor safe, effective in Phe508del CFTR

BY ANDREW D. BOWSER
Frontline Medical News

The combination of ivacaftor and the investigational agent tezacaftor is effective and has a favorable safety profile in patients with cystic fibrosis homozygous for the Phe508del CFTR mutation, according to results of a 24-week randomized, placebo-controlled clinical trial.

Patients receiving the tezacaftor-ivacaftor combination experienced a mean increase in their percentage of predicted forced expiratory volume in 1 second of 3.4 percentage points, compared with a mean decrease of 0.6 percentage points in the control group, at the end of the trial (*P* less than .001). The pulmonary exacerbation rate was 35% lower in the tezacaftor-ivacaftor treatment arm than in the placebo arm (*P* = .005), data show. These results were recently published in the New England Journal of Medicine (2017 Nov 3. doi: 10.1056/NEJMoa1709846).

Most adverse events were mild to moderate, and serious adverse events occurred less frequently in the tezacaftor-ivacaftor treatment arm, compared with the placebo arm, reported Jennifer L. Taylor-Cousar, MD, of National Jewish Health, Denver, and her coinvestigators.

Tezacaftor-ivacaftor's improved safety profile as compared with currently available therapy, "in addition to its effect on multiple efficacy end points, supports its use in a broad range of patients with [CF]," noted the investigators.

Ivacaftor was the first approved modulator of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, and tezacaftor is an investigational CFTR corrector. Tezacaftor demonstrated efficacy in a previous phase 2 trial that included patients either homozygous for the Phe508del mutation or heterozygous for the Phe508del and G551D mutations, Dr. Taylor-Cousar and her coauthors said in their report.

The combination of ivacaftor and another CFTR corrector, lumacaftor, is already available to treat cystic fibrosis patients who are homozygous for the Phe508del CFTR mutation. However, not all patients can receive lumacaftor-ivacaftor because of its respiratory side effects, and lumacaftor is associated with "prohibitive drug-drug interactions" due to considerable cytochrome P-450-3A induction, according to the study authors.

"The improved safety profile of combination therapy with tezacaftor-ivacaftor, as compared with currently available therapy, in addition to its effect on multiple efficacy end points, supports its use in a broad range of patients with cystic fibrosis," wrote Dr. Taylor-Cousar and her colleagues.

The phase 3 trial included 509 cystic fibrosis patients at least 12 years of age who were homozygous for the CFTR Phe508del mutation. The mean percentage of predicted forced expiratory volume in 1 second of the patients was 60.0, at baseline.

All patients were randomized to combination therapy with tezacaftor 100 mg once daily and ivacaftor 150 mg twice daily, or matched placebo. A total of 475 patients completed the 24-week trial. The incidence of serious adverse events was just 12.4% of tezacaftor-ivacaftor–treated patients, compared with 18.2% in the placebo arm, and no serious adverse events led to treatment discontinuation.

"The rate of respiratory adverse events was not higher in the tezacaftor-ivacaftor group than in the placebo group, which shows that the safety profile for tezacaftor-ivacaftor is better than that reported for lumacaftor-ivacaftor," Dr. Taylor-Cousar and her colleagues wrote.

Treatments that modulate CFTR are promising, according to the authors, because they treat the underlying cause of cystic fibrosis.

Vertex Pharmaceuticals supported the study. Dr. Taylor-Cousar reported personal fees from Vertex Pharmaceuticals outside of the submitted work. Full disclosures for all authors were published on the New England Journal of Medicine website.

TAVR wallops SAVR in cost-effectiveness

BY BRUCE JANCIN
Frontline Medical News

DENVER – A formal cost-effectiveness analysis indicates that transcatheter aortic valve replacement (TAVR) is substantially more cost effective than surgical valve replacement in patients at intermediate surgical risk similar to those enrolled in the landmark PARTNER 2 trial. The analysis demonstrated that over a 1- and 2-year follow-up period, as well as with projected lifetime follow-up, TAVR entails both lower long-term costs and greater quality-adjusted life expectancy, David J. Cohen, MD, reported at the Transcatheter Cardiovascular Therapeutics annual educational meeting.

"These findings, taken together with the clinical data we now have, suggest that TAVR should be the preferred strategy for such patients, based on both clinical and economic considerations," said Dr. Cohen, director of cardiovascular research at Saint Luke's Mid America Heart Institute in Kansas City, Mo.

His two-part, patient-level economic analysis examined data from nearly 2,000 participants in the PARTNER 2A randomized trial comparing TAVR, using the Sapien XT valve, with surgical aortic valve replacement (SAVR), as well as the experience with the current-generation Sapien 3 TAVR valve in 1,077 intermediate–surgical risk TAVR patients in the S3i registry. The analysis utilized Medicare claims data on the costs of the index hospitalization and follow-up care.

In PARTNER 2A, the average total cost of the index hospitalization for valve replacement was $61,433 with TAVR. That was just $2,888 more than the SAVR hospitalization, despite the far higher acquisition cost of the Sapien 3 valve, which was roughly $32,500, compared with $5,000 for the surgical valve. Most of this additional cost of the TAVR valve was counterbalanced by TAVR's 2-hour shorter procedural duration, the 6.4-day average length of stay, compared with 10.9 days for SAVR, and the fact that TAVR patients spent only 2.4 days in intensive care while SAVR patients averaged 4.6 days, Dr. Cohen explained at the meeting sponsored by the Cardiovascular Research Foundation.

During 24 months of postdischarge follow-up in the PARTNER 2A trial, SAVR patients racked up an average of $9,303 more in costs than TAVR patients. This was mainly because of their much higher rates of rehospitalization and time spent in skilled nursing facilities and rehabilitation centers, mainly during months 2-6 post discharge. The result was that 2-year total costs including the index hospitalization averaged $107,716 per TAVR patient and $114,132 per SAVR patient.

"One of the really remarkable findings of this study was what happened during follow-up," the cardiologist observed.

Extrapolating to projected remaining lifetime years, TAVR using the Sapien XT valve resulted in a cost savings of $7,949 per patient and a 0.15-year increase in quality-adjusted life expectancy compared with SAVR.

But since the time of PARTNER 2A, the Sapien XT valve has been replaced by the updated Sapien 3 valve. The analysis of the S3i registry showed that the economic dominance of TAVR over SAVR was even greater owing to improved valve technology and contemporary care patterns. For this analysis, because there has been no randomized trial of TAVR with the Sapien 3 valve versus SAVR, patients in the SAVR arm of PARTNER 2A served as the comparison group.

The cost of the index hospitalization was more than $4,000 less with TAVR in the S3i registry than with SAVR. The total cost of TAVR through 1 year of follow-up averaged $80,977, which was $15,511 less than the $96,489 for SAVR. The cost post discharge out to 1 year was more than $11,000 less per TAVR patient, driven by sharply lower rates of both cardiovascular and noncardiovascular hospitalizations as well as a greater than 50% reduction in days spent in rehab centers and skilled nursing facilities, compared with SAVR patients.

Projected over estimated remaining years of life, TAVR with the Sapien 3 valve yielded a cost savings of $9,692 per patient compared with SAVR, as well as a 0.27-year gain in quality-adjusted life-years.

Eighty-eight percent of patients in the S3i registry received their Sapien 3 valve via a transfemoral approach. When Dr. Cohen and his coinvestigators compared their costs and clinical outcomes to the subset of PARTNER 2A TAVR patients who got the Sapien XT valve transfemorally, the outcomes were "virtually identical," he said.

The PARTNER 2A trial, the S3i registry, and the cost-effectiveness analysis were funded by Edwards Lifesciences. Dr. Cohen reported receiving research funding from and serving as a consultant to Edwards Lifesciences and other device companies.

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VIEW ON THE NEWS

Hossein Almassi, MD, FCCP, comments: The catheter valve technology has dramatically changed the treatment of aortic valve stenosis. Initially approved for the prohibitive and high-risk patients, it has become a common practice for the intermediate risk, and soon to be followed in the low risk patients. The long-term durability of the TAVR valves, however, remains unknown and, therefore, its wide application to the low risk patients group with an expected longer life expectancy should await more data from large-scale studies.

Robotic-assisted pulmonary lobectomy removes large tumors

BY LUCAS FRANKI
Frontline Medical News

FROM CHEST 2017 ▪ Robotic-assisted pulmonary lobectomy is a safe and effective way to remove large tumors in patients with non–small cell lung cancer (NSCLC), according to the abstract of a study from the CHEST annual meeting by Nirav Patel, MD, FCCP, of the Tampa Bay Sleep Center, and colleagues.

The study covers a retrospective analysis of 345 NSCLC patients with tumors who underwent robotic-assisted pulmonary lobectomy performed by one surgeon from September 2010 through August 2016. The participants were grouped into the following three cohorts: patients with tumors less than 5 cm in diameter, patients with tumors from 5 to 7 cm, and patients with tumors larger than 7 cm. The researchers excluded patients with pulmonary metastases or benign lesions from the study.

The 1- and 3-year survival rates for patients with tumors less than 5 cm were 91% and 84%; they were 86% and 75% in patients with tumors from 5 to 7 cm, and 76% and 47% in patients with tumors larger than 7 cm, respectively. A tumor size larger than 7 cm was significantly associated with both worse 1-year and 3-year survival, compared with patients with a tumor less than 5 cm ($P = .004$).

Patients with smaller tumors were more likely to have simple lobectomy or lobectomy plus wedge, while patients with larger tumors were more likely to require lobectomy with chest wall resection. Increased tumor size was also associated with increased intraoperative estimated blood loss, skin-to-skin operative time, hospital length of stay, and overall conversion to open lobectomy.

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VIEW ON THE NEWS

Hossein Almassi, MD, FCCP, comments: Robotic thoracic surgery has gained wide acceptance mostly as a result of a more favorable perioperative hospital course and patient comfort. This report outlines the outcomes of robotic lobectomy performed by one experienced surgeon. As stated by the presenting author during the presentation, standard mediastinal lymph node dissection was part of the procedure. Patient survival was dependent on the tumor size, i.e., the stage of the tumor. With advances in technology, robotic thoracic surgery would potentially be the standard surgical approach in the near future for the treatment of most thoracic pathologies.

CHEST™ Physician
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Cold stored platelets control bleeding after surgery

BY ROXANNE NELSON
Frontline Medical News

SAN DIEGO – Cold stored leukoreduced apheresis platelets in platelet additive solution were effective for controlling bleeding in a small study of patients undergoing complex cardiothoracic surgery, according to findings presented at the annual meeting of the American Association of Blood Banks.

The volume of postoperative bleeding was significantly lower among patients who received cold stored platelets compared with those who received standard room temperature storage platelets. Thromboembolic events did not differ between the two groups, nor did measures of coagulation at varying time points. Platelet counts and blood usage were also similar in the two groups. The study was small, however, and further studies are needed to confirm the findings.

"These patients are undergoing major surgery and are at high risk in every aspect," said Torunn Oveland Apelseth, MD, PhD, of the Laboratory of Clinical Biochemistry, Haukeland (Norway) University Hospital. "They are at high risk for bleeding, at high risk for thromboembolic events and high blood usage, and there is a need for optimized blood components."

There has been debate over the use of cold stored platelets, she noted. While storage at 4° C shortens platelet circulation time, some research shows that cold stored platelets have better hemostatic function.

In this study, one patient cohort was transfused with leukoreduced apheresis platelets stored at 4° C in platelet additive solution for up to 7 days under constant agitation, while the other group received platelets stored at standard room temperature. The study endpoints were comparisons between the two groups of postoperative bleeding, total blood usage, and laboratory measures of coagulation and blood cell counts within the first postoperative day. Thromboembolic events in the 28 days after surgery were also evaluated.

The study evaluated 17 patients who received cold stored platelets and 22 who received room temperature storage platelets. Patient demographics for the two groups were similar – as were their international normalized ratios, activated partial thromboplastin times, and fibrinogen levels – before surgery, immedi-

VIEW ON THE NEWS

Hossein Almassi, MD, FCCP, comments: This is a small study on the impact of cold stored platelets transfusion in reducing the postoperative chest tube drainage in cardiac surgical patients. It did not affect the platelet count or blood usage.

ately after heparin reversal, and the morning following the procedure.

Platelet counts and hemoglobin levels also did not significantly differ between groups.

As measured by chest drain output after chest closure, patients who received cold stored platelets had a significantly lower median amount of bleeding in the postoperative period compared with patients given room temperature storage platelets: 576 mL vs. 838 mL. Average chest drain output after chest closure was 594 mL in those who did not receive any transfusions.

"These patients are undergoing major surgery and are at high risk in every aspect," said Torunn Oveland Apelseth, MD, PhD.

Thromboembolic events occurred in 3 patients (18%) who received cold stored platelets and 7 (31%) of those given room temperature storage platelets. The difference was not statistically significant. In addition, blood usage – platelets, red blood cells, and solvent/detergent-treated pooled plasma – was similar for the two cohorts.

"There were also no differences in the number of thromboembolic episodes or length of stay in ICU," said Dr. Apelseth, who recommended larger studies to explore the use of cold stored platelet transfusion in the critical care setting.

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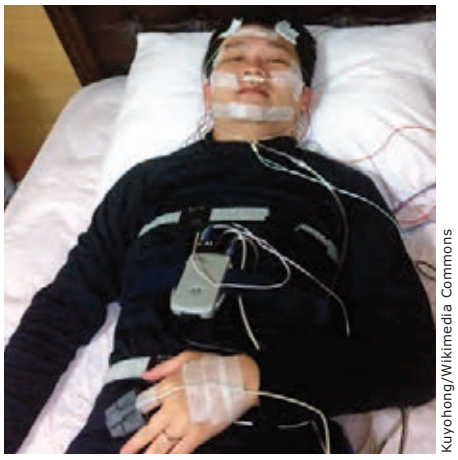
OSA home testing less costly than PSG

BY SHANNON AYMES
Frontline Medical News

Home respiratory polygraphy had similar efficacy with substantially lower per-patient cost, compared with traditional polysomnography for diagnosing obstructive sleep apnea, a study showed.

Obstructive sleep apnea (OSA) is a common chronic disease associated with higher risk of cardiovascular disease and traffic accidents and a lower quality of life. Although expensive and time intensive, the polysomnography (PSG) has been the preferred test for diagnosing OSA. Home respiratory polygraphy (HRP) uses portable devices that are less complex than polysomnography and has been shown to have similar effectiveness in diagnosing OSA, compared with PSG, in patients with a high clinical suspicion of OSA. However, there is limited evidence for the cost effectiveness of HRP, compared with PSG (Am J Respir Crit Care Med. 2017 Nov 1;196[9]:1181-90).



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Jaime Corral-Peñafiel, MD, of San Pedro de Alcántara Hospital, Cáceres, Spain, and his colleagues sought to compare the long-term effectiveness of HRP to PSG in patients with an intermediate or high suspicion for sleep apnea.

The investigators conducted a multicenter, randomized controlled, noninferiority trial and cost-effectiveness analysis comparing PSG with HRP. Inclusion criteria included snoring or observed sleep apnea, Epworth Sleepiness Scale (ESS) of 10 or higher, and no suspicion of alternative causes for daytime sleepiness. Patients with a suspicion for OSA were randomized to polysomnography or respiratory polygraphy protocols. Both arms received counseling on proper sleep hygiene; counseling on weight loss, if overweight; and auto-CPAP titration if continuous positive airway pressure (CPAP) was clinically indicated.

Assessment of CPAP compliance or dietary and sleep hygiene compliance was assessed at months 1 and 3. ESS, quality of life measures, well-being measures, 24-hour blood pressure monitoring, auto accidents, and cardiovascular events were assessed at baseline and at month 6.

CPAP treatment was indicated in 68% of the PSG arm, compared with 53% of the HRP arm. After

Continued on following page

Aspirin responsiveness improved in some with obstructive sleep apnea

BY KATIE WAGNER LENNON
Frontline Medical News

FROM CHEST 2017 ▪ Obstructive sleep apnea patients with endothelial dysfunction gained aspirin responsiveness after using continuous positive airway pressure (CPAP) therapy, according to the findings of a small study by Lirim Krveshi, DO, of Danbury (Conn.) Hospital, and colleagues.

"Endothelial dysfunction is an important phenomenon implicated in cardiovascular morbidity in obstructive sleep apnea (OSA) patients. While it has been demonstrated that CPAP improves endothelial function, our understanding of the pathophysiologic links between CPAP therapy and cardiovascular outcomes remain limited," wrote Dr. Krveshi and colleagues, in the study's abstract from the CHEST annual meeting.

The researchers examined 18 patients' endothelial function before and after using CPAP therapy for a median of 37 days, along with the relationship between endothelial function and aspirin responsiveness in these same patients. All study participants had been recently diagnosed with moderate to severe OSA and underwent modified peripheral artery tonometry and platelet aggregometry before and after beginning CPAP therapy. Most of the patients (14) demonstrated aspirin resistance at baseline.


DR. KRVESHI

Endothelial dysfunction was defined as having a reactive hyperemia index (RHI) of less than or equal to 1.67, while aspirin resistance was defined as having a reading of at least 550 aspirin reaction units (ARU).

At baseline, the average RHI of patients was 1.79 (standard deviation = 0.3), with 8 of the patients having had endothelial dysfunction. Following CPAP use, patients' RHI increased by an average of 1.94 (SD = 0.36), and endothelial dysfunction was present in just 5 of the study participants.

Following CPAP use, patients' RHI increased by an average of 1.94 (SD = 0.36), and endothelial dysfunction was present in just 5 of the study participants.

After using CPAP, those patients with endothelial dysfunction at baseline were responsive to aspirin, with their average ARU reading at 520 following therapy. In contrast, those patients with normal endothelial function at baseline remained resistant to aspirin following CPAP use, based on mean ARU values before and after therapy.

The researchers received funding from the Arthur Kotch Foundation.

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Continued from previous page

intention-to-treat analysis, there was no statistically significant difference between the two groups for ESS improvement (HRP mean, –4.2, vs. PSG mean, –4.9; $P = .14$). The groups demonstrated similar results for quality of life, blood pressure, polysomnographic assessment at 6 months, CPAP compliance, and rates of cardiovascular events and accidents at follow-up.

The cost-effective analysis demonstrated respiratory polygraphy was less expensive, saving more than 400 euros/patient. "Because the effectiveness (ESS and QALYs [quality-adjusted life-years]) was similar between arms, the HRP protocol is preferable due to its lower cost," the authors wrote.

In all, 430 patients were randomized to HRP or PSG and consisted mostly of men (70.5%) with a mean body mass index of 30.7 kg/m^2. The groups had similar rates of alcohol consumption and hypertension.

Limitations of the study included unblinded randomization to the participants and researchers and the possibility of variability in therapeutic decisions. However, the authors noted that intraobserver variability was minimized by using the Spanish Sleep Network guidelines and centralized assessment.

"[The] HRP management protocol is not inferior to PSG and presents substantially lower costs. Therefore, PSG is not necessary for most patients with suspicion of OSA. This finding could change established clinical practice, with a clear economic benefit," the authors concluded.

Home respiratory polygraphy continues to impress

This study adds strong evidence to support the use of home respiratory polygraphy for the diagnosis of obstructive sleep apnea in patients without major comorbidities such as severe chronic restrictive or obstructive lung disease, heart failure or unstable cardiovascular disease, major psychiatric diagnoses, and neuromuscular conditions, noted Ching Li Chai-Coetzer, MBBS, PhD, and R. Doug McEvoy, MBBS, MD, in an accompanying editorial (Am J Respir Crit Care Med. 2017 Nov 1;196[9]:1096-8). However, lower-cost methods to diagnose OSA would still not address unmet needs such as the cost of continuous positive airway pressure and scarcity of sleep physicians to assess patients with OSA, and still may be too expensive for underresourced populations, they said.

Dr. Chai-Coetzer and Dr. McEvoy are affiliated with the Adelaide Institute for Sleep Health at Flinders University and the Sleep Health Service, Southern Adelaide Local Health Network, both in South Australia.

The study was supported by Sociedad Española de Neumología, Air Liquide (Spain), Asociacion de Neumologos del Sur, and Sociedad Extremeña de Neumología. The investigators report no disclosures.

Dr. Chai-Coetzer reported grants from National Health and Medical Research Council of Australia and nonfinancial support from Biotech Pharmaceuticals. Dr. McEvoy reported grants and nonfinancial support from Philips Respironics, nonfinancial support from ResMed, and grants from Fisher & Paykel.

VIEW ON THE NEWS

Krishna Sundar, MD, FCCP, comments: Home sleep apnea testing technology has expanded tremendously in the last decade given the need for expedient diagnosis of obstructive sleep apnea. Despite the American Academy of Sleep Medicine's guidelines for using unattended portable monitoring in the diagnosis of obstructive sleep apnea (OSA) in adults with intermediate to high clinical probability of OSA (Collop et al. J Clin Sleep Med 2007) and widespread usage of a multitude of home sleep testing technologies, questions about its effectiveness in comparison to polysomnography (PSG) and overall cost-benefit benefit remain. This study establishes that home respiratory polygraphy (HRP) was non-inferior to PSG for diagnosis and subsequent OSA treatment using 6-month quality of life and sleepiness measures, but HRP achieved this at substantially lower costs. This was despite higher continuous positive airway pressure prescription rates in the PSG arm as compared to the HRP arm (68% vs. 53%) that was attributed to Apnea-Hypopnea Index underestimations from HRP. While a slightly higher improvement in deep sleep in the PSG arm was seen at 6 months, a number of other key measures such as 24-hour ambulatory blood pressures did not show a difference. Besides demonstration of comparable CPAP usages in the PSG and HRP arms (5.3 hr/d vs. 5.1 hr/d), this study highlights the increasing reliance on quality of life and blood pressure measures as relevant endpoints in cost analyses assessing OSA diagnosis and care-process outcomes.

PULMONARY PERSPECTIVES®

The rise and fall of treatment trials in group 3 pulmonary hypertension: Where do we go from here?

BY CHRISTOPHER KING, MD, FCCP

Treatment of fibrotic interstitial lung disease (ILD) is often dissatisfying to clinicians and patients. Despite significant advances in the field, particularly the validation of the efficacy of the antifibrotic drugs nintedanib (Richeldi L, et al. *N Engl J Med.* 2014;370[22]:2071) and pirfenidone (King TE Jr, et al. *N Engl J Med.* 2014;370[(22]:2083) in slowing the progression of idiopathic pulmonary fibrosis (IPF), we are still left with a paucity of therapeutic options to modulate the course of disease and improve functional outcomes. Given the difficulties in addressing the progression of parenchymal fibrosis, the pulmonary community has looked for alternative ways to approach treatment of ILD. One potential therapeutic inroad that has garnered substantial interest is the treatment of concurrent pulmonary hypertension (PH) or group 3 PH (Seeger W, et al. *J Am Coll Cardiol.* 2013;62 (25 Suppl):D109).

Group 3 PH – The rationale to treat

Group 3 PH has an indisputable association with adverse outcomes, including decreased functional status, increased need for supplemental oxygen, and decreased survival (King CS, Nathan SD. *Pulmonary Hypertension and Interstitial Lung Disease*. Ed 2. Ch 4.2017;67-84). In fact, PH is such a powerful predictor of survival in fibrotic ILD, the International Society of Heart and Lung Transplant (ISHLT) guidelines on candidate selection for lung transplantation cite development of PH as an indication for transplant listing (Weill D, et al. *J Heart Lung Transplant.* 2015;34:1). When one considers the strong association between group 3 PH and adverse outcomes, the numerous pulmonary vasodilator agents available to treat pulmonary arterial hypertension (PAH), and the success achieved in treating PAH, it is easy to see why group 3 PH is such a tempting therapeutic target.

Previous studies of pulmonary vasodilator therapy for group 3 PH

Over 20 studies assessing the effectiveness of pulmonary vasodilator therapy in ILD have been published (King CS, Nathan SD. *Pulmonary Hypertension and Interstitial Lung Disease*. Ed 2. Ch 4. 2017;67) The majority was small and unblinded with inherent limitations. To date, no randomized controlled trial (RCT) of therapy for group 3 PH has demonstrated efficacy. Several studies amongst the RCTs deserve highlighting. The most encouraging RCT of therapy for group 3 PH was STEP-IPF. This study compared sildenafil with placebo in 180 patients with advanced IPF. Though the study failed to demonstrate a difference in the primary endpoint of ≥ 20% increase in 6-minute walk test (6MWT) distance, it did show improvement in several secondary endpoints, including arterial oxygen saturation and quality of life measures (Zisman DA, et al. *N Engl J Med.* 2010;363[7]:620).

The BUILD-3 study compared bosentan with placebo in 617 patients with IPF. Enrolled patients were not required to have PH. While bosentan was well tolerated, it failed to improve the primary endpoint of time to disease progression or death or secondary endpoints regarding quality of life or dyspnea (King TE Jr, et al. *Am J Respir Crit Care Med. 2011*; 184[1]:92). A smaller study comparing bosentan with placebo in 60 patients with fibrotic ILD with right-sided heart catheterization (RHC) confirmed PH failed to demonstrate any difference in pulmonary vascular hemodynamics, functional status, or symptoms (Corte TJ, et al. *Am J Respir Crit Care Med.* 2014;190[2]:208). Studies of the newer endothelin receptor antagonists, macitentan (Raghu, et al. *Eur Respir J.* 2013;42[6]:1622) and ambrisentan (Raghu, et al. *Ann Int Med.* 2013;158[9]:641), were conducted and failed to demonstrate improvements in outcomes, as well. Overall, the results of the available RCTs of pulmonary vasodilator therapy in group 3 PH have been disappointing, failing to conclusively improve the primary outcome in any of the studies performed.

Hot off the presses – RISE-IIP

The latest letdown in group 3 PH is "Riociguat for the Treatment of Pulmonary Hypertension in Idiopathic Interstitial Pneumonia (RISE-IIP). The results of the study were recently presented at the European Respiratory Society meeting in Milan, Italy, by my colleague from Inova Fairfax Hospital (Falls Church, VA), Dr. Steven Nathan. Riociguat is a soluble guanylate cyclase stimulator approved for use in PAH and chronic thromboembolic pulmonary hypertension. The rationale for the study was that riociguat would improve pulmonary hemodynamics leading to improved functional status. Additionally, several preclinical models have demonstrated antifibrotic effects of the drug (Geschka S, et al. *PLoS One.* 2011;6:e21853). Justification for the study was also bolstered by promising results from a pilot study conducted in 22 patients with RHC-confirmed PH with a mean pulmonary artery pressure (mPAP) > 30 and fibrotic lung disease. In this study, patients treated with riociguat had improved pulmonary vascular resistance, cardiac output, and 6MWT distance.

To be included in RISE-IIP, patients were required to have an idiopathic interstitial pneumonia, PH confirmed by RHC with a mPAP ≥ 25 mm Hg, World Health Organization Functional Class 2-4 symptoms, and a forced vital capacity (FVC) ≥ 45% predicted. Pertinent exclusion criteria included significant left-sided heart disease and extent of emphysema greater than fibrosis on HRCT. Patients with connective tissue disease, chronic hypersensitivity pneumonitis, occupational lung disease, and sarcoidosis were ineligible to participate. The placebo-controlled portion of the study lasted 26 weeks then crossed into an open label extension trial.

Dr. King is with Inova Fairfax Hospital, Falls Church, Virginia.

The study enrolled 147 total patients, with 73 receiving riociguat and 74 in the placebo arm. There was no significant improvement in the primary outcome of change in 6MWT distance or the secondary combined endpoint assessing clinical worsening. The study was terminated early for safety due to an increased number of deaths and adverse events in the treatment group. During the blinded phase of the study, eight deaths (11%) occurred in the riociguat arm as compared with three deaths (4%) in the placebo arm. Seventy patients entered the open label extension phase of the trial, and 9 of these patients died. Eight of these deaths occurred in the patients previously receiving placebo who were switched to riociguat. The authors of the study found no conclusive potential etiology to explain the increased mortality seen.

RISE'ing from the ashes – Where do we go from here?

So, what should we take away from the negative results of the RISE-IIP trial? Some may argue that treatment of group 3 PH is a flawed premise and should be abandoned. Perhaps development of group 3 PH is an adaptive response to worsening fibrotic lung disease, and treatment of the PH is unlikely to alter outcomes and introduces the possibility of harm through worsening hypoxemia due to increased ventilation/perfusion mismatch with nonselective pulmonary vasodilation. I suspect the truth is somewhat more nuanced. I believe there is a select population with severe or "out-of-proportion" PH that may still benefit from vasodilator therapy. Trials targeting patients with a higher mPAP or low cardiac index could test this hypothesis but will be difficult to enroll. Another possibility is that our mechanism of drug delivery in prior trials has been suboptimal. Inhaled pulmonary vasodilator therapy should minimize the risk of worsening ventilation/perfusion mismatch. An RCT assessing the response to inhaled treprostinil in group 3 PH (NCT02630316) is currently enrolling at 96 centers across the United States. Until data support-

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CRITICAL CARE COMMENTARY

Clostridium difficile in the ICU: A "fluid" issue

BY ADAM PETTIGREW, MD; JOHN F. TONEY, MD; AND SANDRA GOMPF, MD

In critically ill patients admitted to the ICU, diarrhea (defined as three or more watery loose stools within 24 hours) is a common problem. The etiologies of diarrhea are many, with infectious and non-infectious causes encountered.

Clostridium difficile infection (CDI) is the most common infectious cause of diarrhea in the hospital, including the ICU. The Centers for Disease Control and Prevention estimates the number of overall CDI cases to number about a half-million per year, of which 1 in 5 patients will have a recurrence, and 1 in 11 people aged ≥65 years will die within a month of CDI diagnosis. Age is a poor prognostic risk; greater than 80% of *C difficile* deaths occur in people 65 and older.

The increased use of electronic sepsis screening tools and aggressive antibiotic treatment, often done through protocols, has recently been identified as paradoxically increasing CDI occurrence (Hiensch R et al. *Am J Infect Control.* 2017;45[10]:1091). However, similar rapid identification and management of CDI can result in improved patient outcomes.

Continued from previous page

ing positive effects from treating group 3 PH emerge, I would recommend against off-label treatment and encourage referral to clinical trials. Given the potential for harm, riociguat should be avoided in group 3 PH. If off-label therapy is being entertained in a patient with severe PH that is out of proportion to the extent of fibrotic lung disease, it should be initiated cautiously at a center experienced in treating PH. Finally, clinicians should refer appropriate candidates with ILD and group 3 PH for lung transplantation evaluation.

The great inventor Thomas Edison is credited with saying "I have not failed. I've just found 10,000 ways that won't work." While disappointing, negative studies are to be expected as we search for improved therapies for our patients. It's essential that we reflect upon these studies, so we can improve future trial design.

Issues with diagnosing CDI

Episodes of CDI can be rapid and severe, especially if due to hypertoxin producing–strains of *C difficile*, such as BI/NAP1/027, which produces significantly higher levels of Toxin A, Toxin B, and binary toxin CDT (Denève C, et al. *Int J*

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Antimicrob Agents. 2009;33:S24). Testing for CDI has been controversial; several methods have been employed to aid in the diagnosis of CDI. Currently, many institutions use either nucleic acid amplification tests (NAATs) for toxigenic *C difficile* or direct detection of the toxin produced by the bacteria. NAATs and past culture-based methods are more sensitive but less specific than toxin assays, whereas toxin assays are less sensitive but more specific than NAATs. However, detection of *C difficile* colonization due to high-sensitivity NAATs has caused a rise in the apparent rate of hospital-acquired CDI (Polage CR, et al. *JAMA Intern Med.* 2015;175[11]:4114).

To counter this, multi-step algorithmic approaches to CDI diagnosis have been recommended, including the use of glutamate dehydrogenase (GDH) antigen, toxin detection, and NAATs for toxin-producing *C difficile*. These multistep pathways attempt to minimize false-positive test results while affirming the presence or absence of true CDI (Fang F, et al. *J Clin Microbiol.* 2017; 55[3]:670).

However, controversy continues regarding which testing modalities are optimal, as some patients with positive toxin assays have asymptomatic colonization while some patients with negative toxin assays have CDI. The hope is that emerging, higher sensitivity toxin assays will decrease the number of CDI cases missed by negative toxin tests. Because *C difficile* toxins are labile at body temperature and susceptible to inactivation by digestive enzymes, stool samples must be expeditiously transported to the lab (time is of the essence), so as not to lose toxin or NAAT target detection. Repeat CDI testing for a "test for cure" is not recommended.

Management of CDI

The initial management of CDI has been discussed in many publications, including the current SHEA/IDSA Guidelines (Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31[5]:431).

Briefly, this involves stratifying CDI patients by clinical severity (mild, moderate, severe) and objective data (leukocytosis >15,000, septic shock, serum creatinine level > 1.5 times premorbid level) to guide initial antibiotic therapy. For mild/moderate first episode of CDI, oral or IV metronidazole is generally recommended; more severe disease is generally treated with oral vancomycin.

Complicated CDI in patients (hypotension/shock, ileus, toxic megacolon) requires aggressive management with both IV metronidazole and oral vancomycin (if ileus is present, consider vancomycin enemas). Additionally, fidaxomicin is available for oral CDI treatment and has been associated with decreased first-episode CDI recurrence.

The management of CDI recurrence commonly involves using oral vancomycin as a taper (or taper/pulse regimen) or using fidaxomicin. A recent publication (Sirbu et

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al. *Clin Infect Dis.* 2017;65[8]:1396) retrospectively compared vancomycin taper and pulse treatment strategies for 100 consecutive patients with CDI.

After taper, patents who received every other day (QOD) dosing had a cure rate of 61%, while those who received QOD dosing followed by every third day dosing achieved an 81% cure rate. A clinical trial comparing vancomycin standard therapy vs vancomycin taper with pulse vs fidaxomicin for first- and second-recurrence of CDI is underway.

Last year, the FDA approved bezlotoxumab, a monoclonal antibody that binds to *C difficile* toxin B. Bezlotoxumab treatment is indicated to reduce CDI recurrence in patients >18 years of age and is administered while CDI antibiotic therapy is ongoing.

When comparing 12-week efficacy using standard of care (SoC) CDI treatment vs SoC plus bezlotoxumab (SoC+Bmab), recurrence rates in SoC and SoC+Bmab were 27.6% vs1 7.4%, respectively, in one trial, and 25.7% vs 15.7% in another. While generally well-tolerated, bezlotoxumab is associated with increased risk for exacerbating heart failure. Data relating to the cost-effectiveness of bezlotoxumab are currently pending.

Fecal microbiota transplant (FMT)— duodenal or colonic instillation of donor fecal microbiota to "restore" normal flora— is an evolving CDI therapy with promising results but difficult administration. Although FMT has high published success rates, the FDA's policy of "enforcement discretion" permits practitioners to proceed with FMT only as an Investigational New Drug. This requires signed, informed consent to FMT as an investigational therapy with unknown long-term risks.

The FDA deemed these protections necessary as ongoing studies of the human microbiome have yet to define what constitutes "normal flora," and some investigators highlight the possibility of transmitting flora or gut factors associated with obesity, metabolic syndrome, or malignancy.

Experimental CDI preventive modalities include new antibiotics, monoclonal antibodies, probiotics, select other novel agents, and *C. difficile* vaccinations. These vaccines include recombinant fusion proteins and adjuvant toxoids, both of which have generally favorable tolerance profiles, as well as robust immune responses in clinical trial subjects. However, the efficacy of these vaccines at preventing clinical disease is still to be demonstrated.

Lastly, the ubiquitous use of proton pump inhibitors (PPI) in ICUs plays a role in promoting CDI incidence, severity, and recurrence. Accordingly, the pros and cons of PPI use must be weighed in each patient.

CDI prevention in the hospital environment

Hospital-acquired CDIs (HA-CDI) and nosocomial transmission clearly occur. A recent study of electronic health record data demonstrated that patients who passed through the hospital's emergency department CT scanner within 24 hours after a patient with *C difficile* were twice as likely to become infected (Murray SG, et al. *JAMA Internal Medicine.* published online October 23, 2017. doi:10.1001). Receipt of antibiotics by prior bed occupants was associated with increased risk for CDI in subsequent patients, implying that antibiotics can directly affect the risk for CDI in patients who do not themselves receive antibiotics. As such, aggressive environmental cleaning in conjunction with hospital antimicrobial stewardship efforts, such as appropriate use of antibiotics known to increase CDI occurrence, are required to minimize HA-CDI.

Contact precautions should be strictly enforced; wearing gloves and gowns is necessary for every encounter when treating patients with *C difficile*, even during short visits. Hand sanitizer does not kill *C difficile*, and although soap-and-water hand washing works better, it may be insufficient alone, reinforcing the importance of using gloves with all patient encounters.

The strain placed on ICUs by CDI has been increasing over the past several years. Physicians and hospitals are at risk for lower performance scores and reduced reimbursement due to CDI relapses. As such, burgeoning areas of debate and research include efforts to quickly and accurately diagnose CDI along with reducing recurrence rates. Yet, with all the capital investment, the most significant and cost-effective method to reduce CDI rates remains proper and frequent hand washing with soap and water. Prevention of disease remains the cornerstone to treatment.

NAMDRC Report

Pulmonary societies review legislative agenda

BY PHIL PORTE
Executive Director, NAMDRC

In mid-September, NAMDRC, along with the American Thoracic Society, the American Association for Respiratory Care, the COPD Foundation, the American Lung Association, and others met to discuss the components of a legislative agenda for the coming years. The primary purpose behind the meeting was the premise that IF the current Republican majority would shift in either the House or Senate after the 2018 election, the community should be prepared to move an already agreed upon legislative agenda. CHEST was involved in the preliminary discussions, as well as follow-up, but was not in attendance at the meeting due to a scheduling conflict. There was also tacit agreement that as these policies are fleshed out and crafted into specific legislative language, the community would re-evaluate the current political climate to determine the value of pushing an agreed upon agenda prior to the 2018 elections.

Various patient groups were also invited to participate, but scheduling conflicts precluded some societies from participating but signaled their desire to work with the broad pulmonary medicine community to pursue common goals.

Each society brought its legislative priorities to the table, and there was active discussion on issues ranging from funding for NIH/NHLBI, to CDC and its COPD Action Plan, to a range of Medicare-related issues.

NAMDRC brought three specific Medicare coverage and payment issues to the discussion: home mechanical ventilation, payment for high flow oxygen therapy, and site of service/Section 603 issues.

Home mechanical ventilation is admittedly a complex issue, but it is moving forward in at least two political directions. First, Senator Bill Cassidy (R-LA) and a physician by training, has signaled his desire

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to move this issue forward, either legislatively or giving CMS one last chance to move forward through the regulatory structure. He agrees that a payment system that inhibits access to appropriate bi-level mechanical ventilators and encourages access to more complex life-sustaining ventilators, regardless of documented medical need, is appropriate. While CMS does have the authority to act, it has chosen to ignore repeated requests for action over the past 4 years.

Ironically, the House Energy and Commerce Committee, which shares jurisdiction on the House of Representatives with the Ways and Means Committee on Medicare issues, has sent a request to the Congressional Budget Office to provide a cost estimate (a "score" in Washington vernacular) of likely savings from a legislative solution to this matter. In the current political climate, a legislative proposal that actually saves $$$ is politically attractive, and we are working both the regulatory and legislative pathway to seek a workable solution.

On the oxygen therapy issue, there is growing evidence that, for a small group of Medicare beneficiaries who need high flow oxygen therapy as their disease progresses (pulmonary fibrosis, end-stage COPD, etc), there are no oxygen systems readily available to meet that need outside the home. At home, numerous concentrators can meet that need, but outside the home, the ideal solution, liquid systems, is not readily available because of the payment system tied to competitive bidding. CMS payment data indicate that a very low percentage of oxygen users need more than 4 liters per minute, and current law would make a payment adjustment unique to certain patients a very difficult hurdle, particularly in the era of competitive bidding, a legislative change is the best solution facing the community. The challenge is to craft legislative language that addresses the need but would preclude abuse by suppliers who might jump at the chance for higher payment for liquid, well above current payment levels. And because liquid systems fit into a "delivery model" business plan, contrary to portable oxygen concentrators and transfill systems, the solution is not as easy as a payment bump to make provision of liquid systems more attractive.

Site of service regulations are hitting pulmonary rehabilitation particularly hard, and CMS concedes that the only solution is a legislative one. Under current policy, a pulmonary rehab program that is located off campus but needs to expand or move from its current location (losing a lease, for example), if the expanded program is NOT within 250 yards of the main hospital campus, the program is then reimbursed at the physician fee schedule rate, a rate cut of approximately 50%. Needless to say, hospitals are not pursuing that approach. Likewise, a hospital that chooses to open a NEW program is also constrained, needing to locate within 250 yards of the main campus or face the dramatic cut in payment.

As these issues evolve and the political climate perhaps opens unique opportunities, we can expect the broad pulmonary community to pursue these and other issues.

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BY RICHARD S. IRWIN, MD, MASTER FCCP
Editor in Chief, CHEST

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CHEST Foundation Champions

Champion…. You ARE A CHAMPION for your patients, and as a CHEST Foundation supporter, you are a Champion for Lung Health! These words are now staples in our foundation mission. To champion lung health through clinical research and community service grants, patient education, and community service, the impact your support can have is quite profound. You are a part of an elite group to be called "champions," and you should be celebrated for all the ways that you have championed lung health in 2017.

- YOU funded more than a half-million dollars in community service grants awarded to the next generation of CHEST leaders.
- YOU educated MILLIONS by supporting nationwide disease awareness campaigns for COPD, asthma, sarcoidosis, and lung cancer.
- YOU brought the Lung Health Experience to communities where over 1,000 people received COPD and asthma education, as well as spirometry screening.
- YOU created awareness in rare disease spaces and raised crucial support by partnering with family foundations, such as the Irv Family Foundation.
- The reach of these activities in 2017 has been astounding, and YOU, as a champion for lung health, have generated a great impact on the chest medicine community and the patients we serve.
- Now, the CHEST Foundation asks YOU to join us and support our efforts for 2018 by giving to the CHEST Foundation Annual Fund today. We ask you to help:
- Meet our fundraising goal of $700,000 for new clinical research and community service grants.
- Support NEW lung health disease awareness campaigns.
- Expand family foundation partnerships to create NEW patient resources.
- Provide NEW e-learning modules to aide patients and caregivers in managing health.

Your support today makes possible tomorrow's advances in lung health and chest medicine. YOU believe in patient outcomes and, for that commitment, we graciously thank you. YOU save lives by supporting clinical research, patient education, and community service.

Be THE Champion for Lung Health that patients and families count on, and make an impact today. YOU can be a champion and DONATE today through a new gift to the CHEST Foundation. We cannot meet our goals for the health professionals, patients, families, and caregivers we serve without you.

Thank you for your essential continued support!

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