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Courtesy Dr. Peter Weina

Two trials involving ciprofloxacin had two “very different outcomes,” noted Peter J. Weina, PhD, MD, at an FDA advisory committee meeting.

FDA panel does not back inhaled ciprofloxacin

BY IAN LACY
Frontline Medical News

HYATTSVILLE, MD. – A Food and Drug Administration advisory panel voted against recommending Linhaliq, ciprofloxacin dispersion for inhalation (cipro DI), to treat adult non-cystic fibrosis bronchiectasis (NCFBE) patients who have chronic lung infections with *Pseudomonas aeruginosa*.

At a meeting last month, the FDA's Antimicrobial Drugs Advisory Committee members voted 12-3 against recommending the drug, with 1 member abstaining. Data discrepancies between two phase

3 clinical trials, ORBIT-3 and ORBIT-4, were deciding factors for many of the members who voted against cipro DI.

“Two trials that have two very different outcomes – and no matter how we try and explain what the difference was, there was something really missing there,” said advisory committee member Peter J. Weina, PhD, MD, chief of the department of research programs at Walter Reed National Military Medical Center, Bethesda, Md.

NCFBE is often treated with antibacterial drugs, which temporarily reduce inflammation and bacterial load. One of the most common

CIPROFLOXACIN WINS FEW VOTES // *continued on page 6*

LABA/ICS combos' boxed warning axed

BY KATIE WAGNER LENNON
Frontline Medical News

The Food and Drug Administration has eliminated the boxed warning for risk of asthma-related death from the labels of products containing both an inhaled corticosteroid (ICS) and a long-acting beta-agonist (LABA), the agency announced.

In 2011, the FDA required companies manufacturing fixed-dose LABA-ICS combination products to conduct 26-week clinical safety trials to evaluate the risks of serious adverse asthma-related events in patients treated with these drugs. Specifically, the companies had to compare the risks of taking a LABA in combination with an ICS with the risks of taking an ICS alone.

The removal of the boxed warning follows the FDA's review of these trials, which found that treating asthma with LABAs in combination with ICS did not result in patients experiencing significantly more serious asthma-related side effects and asthma-related deaths, compared with those being treated with an ICS alone, according to the FDA announcement. “Results of subgroup analyses for gender, adolescents 12-18 years, and African Americans are consistent

CHANGES TO LABA/ICS LABELS // *continued on page 4*

INSIDE HIGHLIGHT



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with the primary endpoint results,” the statement added.

“These trials showed that LABAs, when used with ICS, did not significantly increase the risk of asthma-related hospitalizations, the need to insert a breathing tube known as intubation, or asthma-related deaths,

compared to ICS alone,” the FDA said in the statement.

The trials also demonstrated that using the combination reduced asthma exacerbations, compared with using ICS alone, and that most of the exacerbations “were those that required at least 3 days of systemic

corticosteroids” – information that is being added to the product labels, according to the FDA.

The products that will no longer carry this boxed warning in their labels include AstraZeneca’s budesonide/formoterol fumarate dihydrate (Symbicort) and

GlaxoSmithKline’s fluticasone furoate/vilanterol (Breo Ellipta) and fluticasone propionate/salmeterol (Advair Diskus and Advair HFA).

The FDA also approved updates to the Warnings and Precautions section of labeling for the ICS/LABA class, which now includes a description of

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VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: Although these data have been available for some time, this action officially and definitely puts this issue to rest. This update by the FDA is unlikely to cause large changes in clinical practice since LABA/ICS combinations have been thought safe for some time but will serve to reassure the occasional patient who previously was reticent to use these medications after reading the package insert.



the four trials. Information on the efficacy of the drugs, found in the trials, has been added to the Clinical Studies section of the labels as well.

In a related safety announcement, the FDA stated the following: “Using LABAs alone to treat asthma without an ICS to treat

lung inflammation is associated with an increased risk of asthma-related death. Therefore, the Boxed Warning stating this will remain in the labels of all single-ingredient LABA medicines, which are approved to treat asthma, chronic obstructive pulmonary disease (COPD), and wheezing caused by exercise. The labels of medicines that contain both an ICS and LABA also retain a Warning and Precaution related to the increased risk of asthma-related death when LABAs are used without an ICS to treat asthma.”

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FDA approves starting dose of roflumilast

BY KATIE WAGNER LENNON

Frontline Medical News

The Food and Drug Administration has approved the use of a 250-mcg dose of roflumilast for patients with chronic obstructive pulmonary disease (COPD) for 4 weeks, followed by the use of 500-mcg therapeutic doses, according to a statement from the drug's marketer, AstraZeneca.

The larger doses of roflumilast (Daliresp) are currently indicated for reducing the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations, according to the statement. The selective phosphodiesterase-4 inhibitor, roflumilast, was approved for this use in 500-mcg doses in 2011. The new smaller doses of the drug are being offered to help reduce the rate of treatment discontinuation with use of the higher therapeutic dosing. The 250-mcg doses of roflumilast are not to be used as treatment for COPD.

The FDA confirmed its approval for the use of 250-mcg doses of roflumilast as described by the drug's marketer, in Section 2 of the FDA prescribing label.

The approval of use of the 250-mcg doses was based on data from the OPTIMIZE study, according to the statement.

In eight controlled clinical trials, the most common adverse effects were diarrhea, weight loss, nausea, headache, back pain, influenza, insomnia, dizziness, and decreased appetite.

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SOURCE: AstraZeneca press release, Jan 24, 2018.

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colonizing bacteria in NCFBE infections is *P. aeruginosa*, which is often associated with increased risk of death and hospital admission.

Prior studies involving inhaled bacterial drugs such as gentamicin and colistin to treat NCFBE have yielded mixed results, and none has been approved for that indication by the FDA.

The FDA granted cipro DI orphan drug status in June 2011 and fast-track approval in August 2014. Cipro DI's developer, Aradigm, conducted two phase 3 clinical trials to support inhaled ciprofloxacin for the NCFBE indication.

The two phase 3 clinical trials, ORBIT-3 and ORBIT-4, were nearly identical in design. Patients in both were randomized 2:1 to receive cipro DI or placebo once daily for six cycles of 56 days each.

The efficacy results of the ORBIT-3 and ORBIT-4 trials were mixed.

In ORBIT-3, there was very little difference between the treatment and placebo arms, with a median difference of 78 days for the primary endpoint of time to first pulmonary exacerbation (PE) (hazard ratio, 0.99; $P = .974$). ORBIT-3 also showed no difference between treatment and placebo in the frequency of PEs by week 48 of the study (incidence ratio, 0.852).

In contrast, a marginal treatment effect was observed in ORBIT-4, with a median time difference to first PE of 72 days between the placebo and treatment arms (HR, 0.71; $P = .032$). ORBIT-4 also demonstrated an ability to reduce the number of PEs (incidence ratio,

0.631) by approximately 36.9% by week 48.

Adverse events were the most common reason leading to patient discontinuation in both studies, accounting for 13.1% and 5.3% in the treatment arms of ORBIT-3 and ORBIT-4, respectively.

Despite some of the positive findings in ORBIT-4, FDA presenter LaRee Tracy, PhD, of the FDA's office of biostatistics voiced concerns about the trial data – specifically, the failure to reach the primary endpoint in ORBIT-3. “If I were to be a [statistically speaking] ‘strict’ person, I wouldn’t be looking at the frequency of the [secondary]

“If I were to be a [statistically speaking] ‘strict’ person, I wouldn’t be looking at the frequency of the [secondary] endpoints, because the primary [endpoint] failed,” Dr. Tracy noted.

endpoints, because the primary [endpoint] failed,” Dr. Tracy noted. She also voiced concerns about a re-analysis Aradigm conducted after the trial data were unblinded, stating that the changes made to the original analysis plan “lend a lot of concerns for me.”

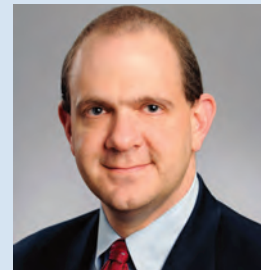
Both ORBIT-3 and ORBIT-4 presented uncertainties related to the long-term use of cipro DI. The durability of efficacy and safety findings did not extend beyond a year, leaving some committee members wondering about the development of antibiotic resistance in cipro DI-treated patients. In addition, members were concerned that long-term use of cipro DI could limit the utility of systemic fluoroquinolones to treat severe bacterial and pneumonia infections in NCFBE patients.

The FDA usually follows the recommendations of its advisory panels, which are not binding.

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VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: My patients with bronchiectasis pose daily management problems. Symptoms of chronic cough with sputum production respond variably to inhaled bronchodilators. I reserve short-course oral antibiotics and glucocorticoids for exacerbations of disease, which seems to be effective. Some patients respond well to chest percussive and cough-assist devices. Select patients seem to respond well to chronic oral macrolides. Inhaled antibiotics intuitively appear attractive, and I have had patients with gram-negative colonization of the airways who I think respond to this treatment. However, I am forced to admit that good outcome data for these treatments are not available. Further research is needed.



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Most influenza-related deaths occur after discharge

BY ELI ZIMMERMAN

Frontline Medical News

SAN DIEGO – More than half of hospitalized, influenza-related deaths occurred within 30 days of discharge, according to a study presented at an annual scientific meeting on infectious diseases.

As physicians and pharmaceutical companies attempt to measure the burden of seasonal influenza, discharged patients are currently not considered as much as they should be, according to investigators.

Among 968 deceased patients studied, 444 (46%) died in hospital,

than those who died during their influenza-related hospitalizations,” said Mr. McGowan, who added that patients aged 85 years and older made up more than half of those who died after discharge.

Patients who died in hospital were significantly more likely to have influenza listed as a cause of death. Overall, influenza-related and non-influenza-related respiratory issues were the two most common causes of

death listed on death certificates of patients who died during hospitalization or within 14 days of discharge, while cardiovascular or other symptoms were listed for those who died between 15 and 30 days after discharge.

“Those who were admitted from the nursing home were almost exclusively discharged to either hospice care or back to a nursing home,” Mr. McGowan said.

while 524 (54%) died within 30 days of discharge.

Investigators conducted a retrospective study of 15,562 patients hospitalized for influenza-related cases between 2014 and 2015, as recorded in Influenza-Associated Hospitalizations Surveillance (FluSurv-NET), a database of the Centers for Disease Control and Prevention.

The majority of the studied patients were women (55%) and the majority were white.

Those who died were more likely to have been admitted to the hospital immediately after influenza onset, with 26% of those who died after discharge and 22% of those who died in hospital having been admitted the same day. In contrast, 13% of those who lived past 30 days were admitted immediately after onset.

A total of 46% of those who died after hospitalization had a length of stay longer than 1 week, compared to 15% of those who lived.

Among patients who died after discharge, 356 (68%) died within 2 weeks of discharge, with the highest number of deaths occurring within the first few days, according to presenter Craig McGowan of the influenza division of the CDC.

Age also seemed to be a possible mortality predictor, according to Mr. McGowan and his fellow investigators. “Those who died were more likely to be elderly, and those who died after discharge were even more likely to be 85 [years or older]

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Admission and discharge locations among patients who did not die were almost 80% from a private residence to a private residence, while observations of those who died revealed a different pattern. “Those individuals who died after discharge were almost evenly split between admission from a nursing home or a private residence,” Mr. McGowan said. “Those

who were admitted from the nursing home were almost exclusively discharged to either hospice care or back to a nursing home.”

Mr. McGowan noted rehospitalization to be a significant factor among those who died, with 34% of deaths occurring back in the hospital after initial discharge.

Influenza testing of studied pa-

tients was given at clinicians’ discretion, which may make the sample not generalizable to the overall influenza population, and the investigators included only bivariate associations, which means there were likely confounding effects that could not be accounted for.

Mr. McGowan and his fellow investigators plan to expand their

research by determining underlying causes of death in these patients, to create more accurate estimates of influenza-associated mortality.

Mr. McGowan reported no relevant financial disclosures.

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SOURCE: McGowan C et al. ID Week 2017, Abstract 951.

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Hyperbaric oxygen may cut CO deaths

BY ANDREW D. BOWSER

Frontline Medical News

FROM THE JOURNAL *CHEST*® ■ In patients with carbon monoxide poisoning, hyperbaric oxygen therapy

was associated with a lower rate of mortality, according to results of a recent retrospective study.

The mortality reduction was particularly evident among patients under 20 years of age and in patients

with acute respiratory failure, authors of the study said in a report published in *Chest* (2017 Nov. doi: 10.1016/j.chest.2017.03.049).

“The results provide important references for decision making in

the treatment of carbon monoxide poisoning,” Chien-Cheng Huang, MD, department of emergency medicine, Chi-Mei Medical Center, Tainan, Taiwan, and colleagues wrote in their report.

While hyperbaric oxygen has been suggested for severe carbon monoxide poisoning, 100% normobaric oxygen is considered standard treatment, according to Dr. Huang and colleagues.

“There has been no consensus about whether hyperbaric oxygen therapy is better than 100% normobaric oxygen alone, or the number of sessions of hyperbaric oxygen therapy that are necessary regarding mortality and morbidity,” they wrote.

In a Taiwanese nationwide poisoning database, Dr. Huang and colleagues identified 25,737 patients diagnosed with carbon monoxide poisoning between 1999 and 2012. Of those patients, 7,278 had hyperbaric oxygen therapy.

After researchers adjusted for variables including age, sex, and underlying comorbidities, the mortality rate was lower in patients who underwent hyperbaric oxygen therapy, compared with those who did not (adjusted hazard ratio, 0.74; 95% confidence interval, 0.67-0.81), data show.

The reduction in mortality was especially notable in patients younger than age 20 years (adjusted HR, 0.45; 95% CI, 0.26-0.80), according to the researchers.

A similarly greater magnitude of mortality benefit also was found for patients who had acute respiratory failure, “which supports acute respiratory failure being an indication for hyperbaric oxygen therapy,” investigators wrote. “Further studies are warranted to clarify this issue.”

The number of hyperbaric oxygen therapy sessions appeared to make a difference in mortality. Patients who received two or more sessions had a lower rate of mortality than did those who had only one session, according to the report.

Predictors of mortality, described in more detail in the published report, included older age, diabetes, alcoholism, and suicide attempts, among other factors.

“In addition to considering hyperbaric oxygen therapy for reducing mortality, control of other concomitant mortality predictors is necessary,” the authors concluded.

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Inpatient antiviral treatment reduces ICU admissions among influenza patients

BY ELI ZIMMERMAN

Frontline Medical News

SAN DIEGO – Administering inpatient antiviral influenza treatment may reduce admissions to the ICU among adults hospitalized with flu, according to a study presented at ID Week 2017, an infectious diseases meeting.

While interventions did not directly affect flu-related deaths, lower ICU admission rates could reduce morbidity and ease the financial burden felt during influenza season.

Investigators retrospectively studied 4,679 influenza patients admitted to Canadian Immunization Research Network Serious Outcomes Surveillance (SOS) Network hospitals during 2011-2014. Of the 54% of patients given inpatient antiviral treatment, the risk of being admitted to the ICU was reduced by 90% (odds ratio, 0.10; 95% confidence interval, 0.08-0.13; P less than .001).

Antiviral treatment was not protective against death outcomes in patients with either influenza A or influenza B (odds ratio, 0.9; 95% confidence interval, 0.7-1.2; P = .454).

The median age of patients was 70 years, with a majority older than 75 years (41%); most presented with one or more comorbidities (89%) and had influenza A (72%).

Researchers found that, of the 4,679 patients studied, a total of 798 (16%) were admitted to the ICU, 511 (11%) required mechanical ventilation, and the average length of hospital stay was 11 days.

Of those, 444 (9%) died within 30 days of discharge.

Researchers also found that only 38% of those studied had received the current seasonal vaccine upon admittance. These numbers may be skewed from the general population, because unvaccinated patients are more likely to be hospitalized.

Along with the results of antivirals on hospitalized patients, researchers wanted to uncover how the

Even when administered 4.28 days after symptom onset, antiviral treatments in patients were associated with significant reductions in ICU admissions and the need for mechanical ventilation.

effectiveness of inpatient vaccine administration would vary based on treatment timing, said presenter Zach Shaffelburg of the Canadian Center for Vaccinology, Dalhousie University, Halifax, N.S.

Even when administered 4.28 days after symptom onset, antiviral treatments in patients were associated with significant reductions in ICU admissions and the need for mechanical ventilation.

The investigators concluded that antivirals show a strong association with positive effects on serious, influenza-related outcomes in hospitalized patients and, while therapy remained effective with later treatment start, patients would benefit the most from initiation as soon as possible.

Currently, the U.S. Centers for Disease Control and Prevention and the Canadian Immunization Research Network (CIRN) have guidelines instructing best practice for inpatient antiviral treatment; however, the number of hospitalized patients given treatment has declined in Canada since 2009, according to Mr. Shaffelburg.

The reason more patients were not receiving inpatient antiviral treatment may be related to studies of different populations that failed to show significant impact, Mr. Shaffelburg suggested during a question and answer session following the presentation: “I think a lot of that comes from outpatient studies that involve patients who are younger and quite healthy [who received] antivirals, and it showed a very minimal impact,” Mr. Shaffelburg said. “So a lot of people saw that study and thought, ‘What’s that point of giving it if it’s not going to make an impact?’”

Mr. Shaffelburg and his colleagues are planning to continue their study of inpatient antiviral treatment, focusing more on the effectiveness of treatment in relation to time administered after onset.

Mr. Shaffelburg reported having no disclosures. The study was funded by the CIRN SOS network, Canadian Institutes for Health Research, and a partnership with GlaxoSmithKline Biologicals. Some of the investigators were GSK employees or received grant funding from the company.

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SOURCE: Shaffelburg Z et al. IDWeek 2017, Abstract 890.

Continued from previous page

ed based on their results.

Accidental deaths from carbon monoxide poisoning also are a major issue in the United States, where each year, there are an estimated 1,000-2,000 cases, according to the authors. Additionally, accidental carbon monoxide poisoning has “increased greatly in the past 10 years,” they said in the report.

Other studies have shown that, compared with normobaric oxygen, hyperbaric oxygen therapy did not reduce neurologic complications, the authors noted. Even so, that fact “does not suggest that hyperbaric oxygen therapy is not beneficial regarding mortality,” they wrote. “In fact, it is possible that reducing mortality may increase morbidities such as neurologic sequelae.”

Dr. Huang and coauthors reported no conflicts of interest related to the study, which was supported by Chi-Mei Medical Center in Taiwan.

VIEW ON THE NEWS

Data compelling, but “distant” from ideal

Use of hyperbaric oxygen therapy to treat carbon monoxide poisoning has been “controversial since its inception” since early promoters “tended to place hyperbaric treatment ahead of strong supporting data,” wrote Clayton T. Cowl, MD, FCCP, in an editorial regarding the study by Dr. Huang and colleagues.

By contrast, the current study by Dr. Huang and colleagues includes data for more than 7,000 patients receiving hyperbaric oxygen therapy over a 13-year time span, compared with those who did not receive it. They found that mortality rates were significantly improved among patients who received hyperbaric oxygen therapy, “even after adjusting for multiple variables,” Dr. Cowl remarked.

These data are compelling

because they come from what is believed to be the first large-scale study that specifically examines mortality as an endpoint in an entire nation, as opposed to smaller cohorts in single centers or even multiple institutions, he said in his editorial.

“Have we reached the point of clearly establishing that delivery of pure oxygen in a high-pressure environment is more effective in treating patients who have carbon monoxide poisoning than is normobaric supplemental oxygen alone? Probably not,” Dr. Cowl wrote.

“The retrospective database study by Huang et al, despite its large size and interesting findings, remains distant from the ideal of a large blinded multi-center randomized controlled trial using a standardized protocol to

compare normobaric supplemental oxygenation with hyperbaric oxygen therapy delivery for this cohort,” he explained. “However, its size, scale, and findings add credibility to the mounting data supporting HBOT [hyperbaric oxygen treatment] for this indication.”

Dr. Cowl is with the division of preventive, occupational, and aerospace medicine and the division of pulmonary and critical care medicine, Mayo Clinic. His comments came from an editorial in the *Journal of Chest®* (doi: 10.1016/j.chest.2017.07.022). He declared no financial or nonfinancial disclosures related to the editorial.



First month of LABA/LAMA ups cardiovascular risk

BY M. ALEXANDER OTTO

Frontline Medical News

New use of inhaled long-acting beta₂-agonists (LABAs) or long-acting antimuscarinic antagonists (LAMAs) was associated with a 1.5-fold increased cardiovascular risk within 30 days of initiation in patients with chronic obstructive pulmonary disease, irrespective of prior cardiovascular disease status and history of exacerbations, according to a review of more than 280,000 COPD patients in Taiwan.

The relationship between cardiovascular disease (CVD) and LABAs and LAMAs in chronic obstructive pulmonary disease has long been debated. The new study addressed some limitations of previous studies, which had found conflicting results ranging from no increased risk to up to a 4.5-fold increased risk of cardiovascular events when the medications were used for COPD.

Previous randomized trials haven't raised much concern, but they included prior users who may have developed tolerance to the heart effects and excluded patients with baseline CVD. "We caution physicians to closely monitor new users of LABAs or LAMAs for cardiovascular symptoms." Health care professionals should be vigilant for any cardiovascular symptoms during the first 30 days of inhalation therapy, said investigators led by Meng-Ting Wang, PhD, of the National Defense Medical Center, Taipei, Taiwan.

"We suspect that there may exist a subgroup of patients with COPD who are particularly at risk of CVD with initial exposure to LABAs or LAMAs. ... We suggest that the use of inhaled long-acting bronchodilators in COPD

needs to be carefully assessed, and a thorough cardiovascular physical examination, especially heart rate measurement and electrocardiograms, needs to be performed" before prescribing LABAs and LAMAs, they wrote in JAMA Internal Medicine.

The team identified 284,220 COPD patients in the Taiwan National Health Insurance Research Database during 2007-2011 who were new to the medications. During a mean follow-up of 2 years, 37,719 developed severe CVD requiring hospitalization or emergency care.

The team compared their CVD subjects with controls who did not have a heart event and found that new LABA and LAMA use in COPD was associated with a 1.50-fold (95% confidence interval, 1.35-1.67; *P* less than .001) and a 1.52-fold (95% CI, 1.28-1.80; *P* less than .001) increased cardiovascular risk within 30 days of initiation, respectively.

The LABA- and LAMA-associated CVD risk remained significant, regardless of patients' CVD history and COPD exacerbations. Analyses of individual CVD outcomes revealed increased risks of coronary artery disease and heart failure with LABA and LAMA treatment and an increased risk for cardiac arrhythmias with LAMA therapy.

The cardiovascular risks peaked at around the 30th day of treatment, waned from 31 to 60 days of treatment, and fell below the baseline risk from 71 to 240 days.

"Given that CVD is highly prevalent among patients with COPD, clinicians should also pay attention to the management of CVD risk factors throughout the duration of LABA or LAMA therapy. ... If needed, a preventive therapy for CVD should be con-

sidered during the initial treatment of inhaled long-acting bronchodilators," the investigators said.

LABAs and LAMAs are believed to cause sympathetic overactivation by activating sympathetic beta₂ adrenergic receptors and suppressing parasympathetic muscarinic-3 receptors, which could contribute to the CVD risk. Also, LABA and LAMA use in COPD has been observed to increase inflammatory cytokine levels.

The subjects were 40 years or old-

er; the mean age was 71.4 years and 68.9% of the participants were men.

The work was supported by Taiwan's Ministry of Science and Technology. The investigators had no disclosures.

Eli Zimmerman contributed to this report.

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SOURCE: Wang MT et al. JAMA Intern Med. 2018 Jan 2. doi: 10.1001/jamainternmed.2017.7720.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: Long-acting beta-agonists (LABA) and long-acting muscarinic antagonists (LAMA) are agents commonly used to treat patients with chronic obstructive pulmonary disease (COPD). These inhaled medications have been generally considered to be safe and have a favorable side-effect profile. Although there have been some speculative data that suggest that these agents may be associated with increased cardiovascular risk, prospective, controlled studies have generally suggested that the cardiovascular risk is not increased with the use of these medicines.

A recent article in JAMA suggests that patients with COPD who have been initiated on LAMA and LABA agents may have an increased risk of cardiovascular events in the weeks following initiation. Using a large insurance database, investigators from Taiwan found that patients with new prescriptions

for these drugs have increased cardiovascular events. These researchers further suggest that previous studies may have overlooked this phenomenon, as longitudinal studies would have studied cardiovascular risk among patients with established use patterns of LAMA and LABA agents, instead of just patients initiated upon therapy. They suggest that the longitudinal populations may therefore be censored and excluded patients who had effects shortly after commencing the medications.

One strength of this study is the size of the database, which is robust, and the novel treatment that this study uses to address the research question. Weaknesses include the study's necessarily retrospective design, and the fact that the population is from a single geographic area. Further research will be needed to understand whether or not the initiation of LABA and LAMA medications in COPD patients is associated with increased cardiovascular risk.

Influenza: All that and MI, too

BY RICHARD FRANKI

Frontline Medical News

Myocardial infarction admissions were six times more likely to occur in the week after a positive test for influenza than in the year before or the 51 weeks after the infection, according to analysis of a Canadian cohort that links laboratories with administrative databases.

The investigators used this cohort data to define definitions of "risk interval" – the first 7 days after flu detection – and a combined "control interval" – 52 weeks before the flu detection and 51 weeks after the end of the risk interval.

Among the total of 364 hospital admissions for MI in patients with confirmed influenza, 20

occurred during the defined 1-week risk interval (20 admissions/week) and 344 occurred during the control interval (3.3 admissions/week), giving an incidence ratio (IR) of 6.05, Jeffrey C. Kwong, MD, of the University of Toronto and his associates reported in the New England Journal of Medicine.

There was little difference between days 1 and 3 after flu confirmation (IR, 6.3) and days 4-7 (IR, 5.8), but risk dropped off quickly after that, with IRs of 0.6 at days 8-14 and 0.75 at days 15-28. Risk was increased for older adults, those with influenza B infection, and those who had their first MI, the investigators said.

MI incidence also was elevated after infection with noninfluenza respiratory viruses, although

to a lesser extent than with influenza, which suggests that "influenza is illustrative of the role that acute respiratory infections have in precipitating acute myocardial infarction," Dr. Kwong and his associates wrote.

The study was supported by the Canadian Institutes of Health Research, by Public Health Ontario, and by the Institute for Clinical Evaluative Sciences. Dr. Kwong reported grants from Canadian Institutes of Health Research during the conduct of the study, as well as grants from Canadian Institutes of Health Research and University of Toronto.

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SOURCE: Kwong JC et al. N Engl J Med. 2018. 378(4):345-53. doi: 10.1056/NEJMoa1702090.

Pay for performance not improving Medicare results

BY GREGORY TWACHTMAN

Frontline Medical News

Hospital pay-for-performance programs are not leading to significant improvements in clinical process scores or 30-day mortality rates for Medicare beneficiaries, according to an analysis of Medicare claims data.

"No evidence that hospitals [that were] operating under pay for performance programs for more than a decade had better process scores or lower mortality than other hospitals was found," Igna Bonfrer, PhD, of Erasmus University, Rotterdam, the Netherlands, and colleagues wrote in a study published Jan. 4, 2018, in *BMJ*.

"These findings suggest that, even among hospitals that volunteered to participate in pay for performance programs, having additional time is not likely to turn pay for performance programs into a success in the future," the investigators noted.

Researchers looked at Medicare claims data from nearly 1.4 million patients aged 65 years and older across 1,189 hospitals. That total included 214 hospitals that were early adopters of pay for perfor-

mance programs, including the Hospital Quality Incentive Demonstration (HQID) and the current Hospital Value-Based Purchasing (HVBP) program, and 975 hospitals that adopted the programs at a later date. The study authors examined clinical process scores and 30-day mortality rates from 2003 to 2013.

Hospitals that were early adopters of a pay for performance program typically started from a higher baseline process measure score (91.5), compared with late adopters (89.9).

However, improvements among the early adopters "were smaller during the HQID period, although early adopters continued to perform at a slightly higher level than the late adopters during the pre-HVBP period," the researchers explained. "Over the HVBP period, early and late adopters no longer differed in their clinical process scores."

Indeed, a ceiling was ultimately reached, with early and late adopters approaching the same level (98.5 vs. 98.2).

For the 30-day mortality rates, both groups "started from a similar baseline (14.9% and 14.8% for the early and late adopters in the fourth

quarter of 2003) and ended at the same rate of 9.9% for both groups in the fourth quarter of 2013," Dr. Bonfrer and colleagues wrote.

The researchers suggested that the programs did not yield better results because of small financial incentives, coupled with program complexities that made it "difficult for hospitals to meaningfully engage in the program." They also suggested that having to wait until year end to receive any financial incentives could have limited the impact.

"We found that hospitals that have been under financial incentives for more than a decade have not been able to reduce patient mortality more than late adopters, which had only been under financial incentives for less than 3 years," the researchers concluded. "Given its cost, policy-makers in the [United States] should consider one of two things: revise the current program or potentially end it."

The changes suggested include increasing financial incentives and focusing on process measures that matter most to patients (mortality, patient experience, and functional status), rather than the current

VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP,

comments: The most objective assessment of a process often comes from an independent review by an uninvolved party. This study using "Big Data" calls into question the hypothesis that the carrot may work more effectively than the stick, at least in the realm of hospital care. Sometimes the only way to know if something will work is to try it, but then make appropriate adjustments should the plan fail ... a colloquial way to describe scientific method. It will be interesting to see if CMS responds to this information with an adjustment in policy.

measure set that is larger and more difficult to track.

The researchers did not report any financial conflicts of interest.

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SOURCE: Dr. Igna Bonfrer et al. *BMJ* 2018;360:j5622.

CMS launches advanced alternative payment model

BY GREGORY TWACHTMAN

Frontline Medical News

The Centers for Medicare & Medicaid Services is launching a new voluntary bundled payment demonstration project that for the first time will qualify as an advanced alternative payment model under the Quality Payment Program.

The Bundled Payments for Care Improvement Advanced (BPCI Advanced) "builds on the ear-

lier success of bundled payment models and is an important step in the move away from fee-for-service and towards paying for value," CMS Administrator Seema Verma said in a statement. "Under this model, providers will have an incentive to deliver high-quality care."

Medicare-certified acute care hospitals and physician group practices are eligible to take part in the BPCI Advanced, according to Medicare documentation. They will be categorized either as "conveners" – entities that bring together multiple parties for the purpose of coordinating care, as well as apportioning financial risks – or as "nonconveners" – those who bear financial risk for themselves only.

Both categories of participants may enter into agreements with individual physicians and non-physician providers to furnish care under the bundled payment model.

The program will provide a single retrospective payment and one risk track, with a 90-day clinical episode duration. It will cover 29 inpatient episodes and three outpatient clinical episodes. Payment will be tied to performance on quality measures.

The 29 inpatient clinical episodes cover a range of conditions, including liver disorders (excluding malignancy, cirrhosis, and alcoholic hepatitis); various cardiac conditions; chronic obstructive pulmonary disease, bronchitis, and asthma; spinal fusion; joint replacements; femur, hip, or pelvis fractures; gastrointestinal hemorrhage or

obstruction; renal failure; sepsis; simple pneumonia and respiratory infections; stroke; and urinary tract infections.

The three outpatient clinical episodes include percutaneous coronary intervention, cardiac defibrillator implantation, and back and neck surgery except spinal fusion.

Seven quality measures will be tracked as part of the payment. For all clinical episodes, measurement of all-cause hospital readmissions and advance care plan will be required.

The other five will be applied to the payment when appropriate, as follows:

- Perioperative care: selection of prophylactic antibiotic: first- or second-generation cephalosporin.
- Hospital-level risk-standardized complication rate following elective primary total hip arthroplasty and/or total knee arthroplasty.
- Hospital 30-day, all-cause, risk-standardized mortality rate following coronary artery bypass graft surgery.
- Excess days in acute care after hospitalization for acute myocardial infarction.
- AHRQ patient safety indicators.

CMS had an open-door forum on Jan. 30 for those who were interested in participating in BPCI Advanced.

Applications for participation will be accepted through March 12.

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VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: While this may not be a panacea for all of the ills of our expensive but broken health-care system, it is heartening to see CMS at least propose new models of health-care delivery. The move away from a fee-for-service model was inevitable for government-funded health care given the ever-increasing costs coupled with the dismal rankings when compared with other nations. The United States spends more than any other nation but is 37th in the WHO health-care performance ratings ... ouch. Unfortunately, as long as health-care remains a political football, change for the better may be miserably slow.

Budesonide fails to cut deaths in preemies

BY JIM KLING

Frontline Medical News

The administration of inhaled budesonide to extremely preterm infants did not increase the risk of neurodevelopmental disability but did increase mortality, in a study by Dirk Bassler, MD, of the University of Zürich and his associates.

An older study led by Dr. Bassler and published in the New England Journal of Medicine (2015;373:1497-506) showed that inhaled budesonide significantly reduced the incidence of bronchopulmonary dysplasia, which has been linked to higher mortality and chronic respiratory and cardiovascular impairment.

Systemic glucocorticoids have been linked to greater risk of neurodevelopmental disability, but only a few studies have examined the effect of inhaled glucocorticoids, such as budesonide, in preterm infants. These studies, including the earlier one by Dr. Bassler and his colleagues, were either small, covered a short period of time, or involved late administration of the drug.

In the two studies by Dr. Bassler and his colleagues, 863 preterm infants between 23 weeks' and just

under 28 weeks' gestation who required any form of positive-pressure respiratory support were randomized to receive inhaled budesonide (two puffs, 200 mcg per puff) or placebo every 12 hours. They began within 24 hours of birth and continued for the first 14 days of life. Following that, patients received one puff ev-

"There was no significant difference between the groups in adverse long-term outcomes in our study. However, the fact that fewer infants died in the placebo group than in the budesonide group complicates the interpretation of the treatment of budesonide."

ery 12 hours until they no longer required supplemental oxygen and positive-pressure support, or reached a postmenstrual age of 32 weeks.

The treatment resulted in a significant reduction in bronchopulmonary dysplasia at a postmenstrual age of 36 weeks (28.2% in the budesonide group vs. 37.4%; $P = .01$), in the older study.

In the new study, which was also published in the New England Journal of Medicine, Dr. Bassler and his associates found higher mortality (19.9% vs. 14.5%; relative risk, 1.37; 95% confidence interval, 1.01-1.86; $P = .04$) in the group of patients who had received inhaled budesonide. Additionally, at a corrected age of 18-22 months, surviving infants who received inhaled budesonide had a similar risk of neurodevelopmental disability as those patients who took the placebo.

Broadly speaking, 48.1% of infants who received budesonide had a neurodevelopmental disability, compared with 51.4% of infants who received placebo (RR adjusted for gestational age, 0.93; 95% CI, 0.80-1.09; $P = .40$). The two groups also had no statistically significant differences in their frequencies of cerebral palsy, blindness, hearing loss, or cognitive delay.

"There was no significant difference between the groups in adverse long-term outcomes in our study. However, the fact that fewer infants died in the placebo group than in the budesonide group complicates the interpretation of the treatment of budesonide," the researchers wrote.

Supported by a grant from the European Union and by Chiesi Farma-

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This is an important

study regarding bronchopulmonary dysplasia prevention. The study suggests starting budesonide within 24



hours of life resulted in a lower rate of bronchopulmonary dysplasia than placebo but fewer infants died in the placebo group. A bigger question for me is "what is the evidence for starting inhaled steroids prior to neonatal intensive care unit discharge?" Pediatric pulmonologists would like to know if it decreases subsequent respiratory-related ER visits and readmissions.

ceutici. Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

SOURCE: N Engl J Med. 2018;378:148-57.

Young e-cigarette users graduating to the real thing

BY RICHARD FRANKI

Frontline Medical News

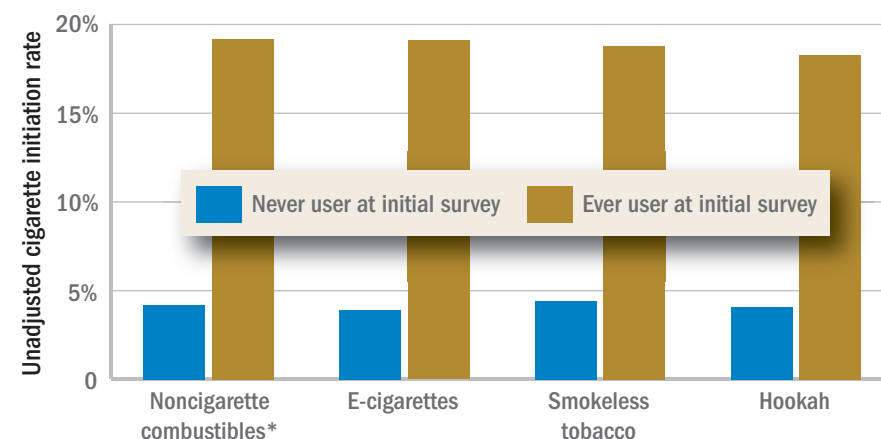
Children who use noncigarette forms of tobacco are significantly more likely to try cigarettes in the future, according to survey data from more than 10,000 young people aged 12-17 years.

An initial survey (wave 1) was conducted as part of the nationally representative Population Assessment of Tobacco and Health (PATH) study, with a follow-up (wave 2) administered to participants a year later. The analysis by Shannon L. Watkins, PhD, of the University of California, San Francisco, and her associates was based on data for 10,384 respondents who reported never smoking a cigarette in wave 1 and whose later cigarette use, which occurred in less than 5% overall, was reported in wave 2.

Among those who said that they had ever used an e-cigarette – the most popular of the noncigarette

RESULTS OF FOLLOW-UP SURVEY

Young people who tried cigarettes in the year after initial survey



*bidis, cigarillos, filtered cigars, kreteks, pipes, and traditional cigars

Note: Based on data for 10,384 Population Assessment of Tobacco and Health respondents.

Source: JAMA Pediatr. 2018 Jan 2. doi: 10.1001/jamapediatrics.2017.4173

forms in wave 1 – 19.1% reported that they had tried a cigarette in the subsequent 12 months, compared with 3.9% who had never used an e-cigarette in wave 1. The results

were similar (see graph) for the other forms of noncigarette tobacco: noncigarette combustibles (bidis, cigarillos, filtered cigars, kreteks, pipes, and traditional cigars),

hookah (tobacco waterpipe), and smokeless tobacco (chewing tobacco, dissolvable tobacco, moist snuff, and snus).

Those who used multiple noncigarette products were more likely than users of a single product to initiate cigarette use by wave 2. With never use of any tobacco as the reference, one model used by the investigators put the odds ratios of cigarette ever use at 4.98 for e-cigarettes only, 3.57 for combustibles only, and 8.57 for use of multiple products.

This study was supported by grants from the National Cancer Institute, Food and Drug Administration Center for Tobacco Products, National Institute on Drug Abuse, and National Center for Advancing Translational Sciences. No conflicts of interest were reported.

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SOURCE: Watkins S et al. JAMA Pediatr. 2018 Jan 2. doi: 10.1001/jamapediatrics.2017.4173.

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HPV vaccine cuts juvenile respiratory papillomatosis numbers

BY BIANCA NOGRADY

Frontline Medical News

Introduction of a national human papillomavirus vaccination program in Australia has been associated with declines in the incidence of juvenile-onset recurrent respiratory papillomatosis, according to a nationwide study.

Juvenile-onset recurrent respiratory papillomatosis (JORRP) is a rare condition characterized by recurring growths in the larynx that often can require multiple operations to remove. The disease typically emerges around age 3-4 years and most cases are thought to be caused by human papillomavirus (HPV) subtypes 6 and 11, which are acquired from the mother during birth.

In this prospective study using data from the Australian Paediatric Surveillance Unit, researchers examined the incidence of juvenile-onset recurrent respiratory papillomatosis from October 2011 to December 2015, set against the background of the introduction of Australia's national HPV vaccination program between 2007 and 2009 (J Infect Dis. 2017 Nov 9. doi: 10.1093/infdis/jix498).

Overall, just 15 cases were reported during the course of the study; 7 in the first year, 3 in the second year, 2 each in the third and fourth years, and 1 case in the last year. The annual rates declined from 0.16 per 100,000 children aged 0-14 years in 2012 to 0.02 per 100,000 in 2016.

Of the cases identified, none of the mothers had been vaccinated against HPV before pregnancy and 20% had a history of genital warts. Seven cases were genotyped: Four were HPV-6 and three were HPV-11. Of the 15 cases, 13 were born vaginally.

"Our data strongly suggest that the previously documented impact of quadrivalent HPV vaccination in dramatically reducing the prevalence of HPV-6 and HPV-11 genital infection in the Australian population is translating to a reduction in the risk of transmission to infants intrapartum and subsequent development in some of these children of JORRP," wrote Daniel Novakovic, MD, of the University of Sydney Medical School, and his coinvestigators.

The authors noted that their initial estimate of infection rates was lower than that seen in other

studies, such as the 0.5 per 100,000 rate seen in private health insurance data, and the 1.0 per 100,000 seen with Medicaid data in the United States.

Given that the study period started nearly 5 years after the vaccination program began, they suggested that this lower prevalence may reflect the early impact of the vaccine, particularly given that the prevalence of genital warts had already dramatically declined by that point.

However they also stressed that their study relied on clinicians actively reporting cases, and that given surveillance only began after the introduction of the vaccination program, no data were available on the incidence before that point.

The study was supported by a research grant from Merck and by the Australian Paediatric Surveillance Unit, which is supported by the Australian Government Department of Health. Three authors declared research funding from Merck/Seqirus for HPV studies. Two authors declared funding, speaking fees, and other support from a range of pharmaceutical companies.

Scrubbing homes of allergens may tame asthma, costs

BY DOUGLAS BIRCH, KAISER HEALTH NEWS

After years of studying the causes of asthma, a pediatrician turned public health sleuth thinks there's a way to substantially reduce its impact.

But the approach faces a big hurdle: getting someone to pay for it, said Elizabeth C. Matsui, MD, a professor at Johns Hopkins University in Baltimore.

Dr. Matsui, who suffered from asthma as a child, has spent much of her career studying the link between poor housing and asthma in low-income neighborhoods. In particular, she's looked at the effects of mouse allergens, typically found in high concentrations in urban homes.

Dr. Matsui cited a 2004 study in the New England Journal of Medicine that described measures to reduce home allergen levels and concluded that they were linked to reductions in asthma symptoms.

That research "was highly successful and impactful," but the approach wasn't widely adopted. "So here we have this trial that was published more than 10 years ago that shows [indoor allergen control] works," said Dr. Matsui, who did not participate in the study. "But the families who need it most can't afford to do these things, don't have control oftentimes over their home environment, and insurance or other payers

don't cover these things."

Dr. Matsui has proposed new incentives for hospitals to provide home intervention, including Medicaid waivers. But, she said, scientists can't use research money for these programs. "Delivery of community health care programs would require a different type of funding."

As a result, doctors and scientists doubted if a plan to control home allergens would scale up, and insurers questioned whether benefits to their bottom line would justify the added cost.

"We have this enormous public health problem in that there are housing conditions that directly affect allergen exposure in this population of kids," Dr. Matsui said. "We have dedicated individuals and groups who are trying to solve the problem. But we don't have a system that is able to solve the problem."

A 2017 study by Dr. Matsui, published in JAMA, suggests that even without intensive professional cleaning services, families that receive some training can substantially reduce home allergens on their own.

That finding suggests health agencies should routinely offer to educate asthma-affected families in home allergen control. "There's potentially a large benefit," Dr. Matsui said.

In a separate study, Dr. Matsui's group is following 200 Baltimore children to see if those in homes scrubbed of allergens need fewer treatments

with rescue inhalers. If they do, that could give health insurers an incentive to pay for the approach.

There's another incentive: Clearing the air in a child's home may be critical in cases where medications alone don't work. "We continue to see a lot of kids that, despite being on medication, don't have well-controlled asthma," Dr. Matsui said.

Asthma drugs can also have serious side effects, she said, especially at higher doses, and may suppress symptoms without halting lung damage.

Dr. Matsui's work on asthma began while working as a pediatrician at Baltimore's Franklin Square Hospital in 1998. As part of her job, she spent a half-day each week in a school health clinic in a low-income area.

Dr. Matsui was struck by the number of kids she saw with severe asthma, she said, and set up a home health visit program to help them. But she wasn't certain the program was working, so she consulted with experts at Hopkins.

In 2004, she earned a master's from the Johns Hopkins School of Public Health. Today, she is one of the nation's leading asthma researchers.

Dr. Matsui said her career was shaped by her own struggle with childhood asthma. "I think that that probably played a role, consciously or unconsciously," she said.

KHN's coverage of health disparities

in east Baltimore is supported by The Annie E. Casey Foundation. Kaiser Health News is a nonprofit news service covering health issues. It is an editorially independent program of the Kaiser Family Foundation that is not affiliated with Kaiser Permanente.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: Environment is certainly

a factor in asthma control. We are lucky enough to have a network in our county that will take pediatric asthma cases to help with asthma education. The nurse will even accompany the child and parent to their outpatient visits to help advocate for help with their asthma management and go into the home to see if there is a cockroach problem or a dusty environment, for example. They will also help families learn how to better organize the child's bedroom so there is less dust! Some Medicaid HMOs will pay for this care management plan but not all of the insurances in our area.



Macrolide use cuts failure risk in pediatric CAP

BY ELI ZIMMERMAN

Frontline Medical News

SAN DIEGO – Macrolide use showed lower treatment failure rates than did amoxicillin or beta-lactam treatment for pediatric community acquired pneumonia (CAP) patients, according to a study presented at an annual scientific meeting on infectious diseases.

While guidelines recommend amoxicillin as the first-line therapy against CAP, investigators have noticed an increase in macrolide prescriptions to pediatric outpatients, despite reported shortcomings in its use against atypical pneumonia.

“Macrolides are probably prescribed out of proportion to the presence of atypical pneumonia in that practice setting,” said Lori Handy, MD, of Children’s Hospital of Philadelphia.

“We also know that, depending on the study, up to 40% of *Streptococcus pneumoniae* is resistant to macrolides, meaning there are children out there who may have *S. pneumoniae* who are receiving therapy not targeted at their disease pathogen,” she said, during her presentation at the scientific meeting.

To examine the possible impact of an increase

in macrolide prescriptions, the investigators conducted a retrospective cohort study of 10,470 CAP pediatric patients across 31 primary care practices in the Children’s Hospital of Philadelphia network who were diagnosed between January 2009 and December 2013.

The studied cohort was split into three groups based on treatment options: amoxicillin monotherapy (4,252, 40.6%), macrolide monotherapy (4,459, 42.6%), and broad-spectrum beta-lactams (1,759, 16.8%).

Patient age ranged from 3 months to 18 years, the majority were white, with a roughly equal number of each sex. Of the children studied, 634 (6.1%) experienced treatment failure, defined as a change in antibiotics, an emergency department visit for related symptoms, or hospitalization for pneumonia, all of which had to occur more than 24 hours after a pediatric visit, according to Dr. Handy.

Of the children who failed treatment, 341 (54%) were in the amoxicillin group, 145 (23%) were in the macrolide group, and 147 (23%) were in the broad-spectrum group.

Patients younger than age 5 years who received macrolide therapy were half as likely to experience treatment failure compared with those given

amoxicillin (odds ratio, 0.52; 95% confidence interval, 0.34-0.78).

“What this translates to in practice is that about 32 children would need to be treated with macrolides to prevent one failure in the amoxicillin group,” said Dr. Handy.

Patients 5 years and older showed even lower odds of treatment failure, at approximately one-third the rate of amoxicillin-treated patients (OR .31 [95% CI, 0.23-0.92]).

Dr. Handy stated that the retrospective nature of the study and the possibility of changes in the epidemiology of CAP occurring since 2013 should be considered when evaluating the findings.

In addition, she pointed out, CAP is a clinical diagnosis, and there is generally no microbiological data associated with it in order to determine the etiology of the infection.

Dr. Handy and her colleagues reported having no relevant financial disclosures.

The event was the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society.

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Lung recovery high after ECMO in asthma

BY DEBRA L. BECK

Frontline Medical News

AT CHEST 2017 ■ TORONTO – Extracorporeal membrane oxygenation (ECMO) is associated with lung recovery rates as high as 90% in pediatric patients with near-fatal asthma, but complication risks were high and the cannulation technique employed made a significant difference to outcomes, according to a study presented at the CHEST annual meeting.

“ECMO for near-fatal asthma is a potentially life-saving intervention, however, clinicians should be aware of the potentially severe complications, particularly with venoarterial cannulation in this population,” said Rebecca Kohlberg-Davis, MD, a pediatric resident at Connecticut Children’s Medical Center, Hartford.

ECMO is being used in the setting of near-fatal pediatric asthma, but there are limited data on outcomes in this population. Dr. Kohlberg-Davis and her colleagues conducted a retrospective analysis of all children with asthma treated with ECMO using the Extracorporeal Life Support Organization registry.

During 1988-2016, 371 children with status asthmaticus underwent ECMO cannulation using one of two methods; 65% were treated with



Dr. Rebecca Kohlberg-Davis, a pediatric resident at Connecticut Children’s Medical Center

ECMO using venovenous (VV) cannulation and 33% were treated using venoarterial (VA) cannulation. Both VV and VA require insertion of a cannula to take deoxygenated blood from a central vein or the right atrium. VA ECMO returns the oxygenated blood, under pressure, to the arterial side of the circulation (typically to the aorta), supporting cardiac output, while VV ECMO returns oxygenated blood back to a large vein and does not support circulation.

The median patient age was 7.5 years and 56% were male. The median ECMO run duration was 123 hours.

Overall, lung recovery was seen

in 83% of patients, and 77% were discharged from the hospital. Of the children who received VV cannulation, 90% experienced lung recovery, while VA cannulation was associated with a 69% rate of lung recovery and significantly more complications. Among those who experienced lung recovery, those who received VV cannulation had a 3.6-fold higher likelihood of survival ($P = .006$), Dr. Kohlberg-Davis reported.

At presentation, 88% of patients had hypercarbic respiratory failure and were more likely to receive VV cannulation ($P = .003$); 34% had hypoxemic respiratory failure and 27% had mixed respiratory failure and were more likely to receive VA cannulation. Those with hypoxemic respiratory failure had a significantly lower likelihood of lung recovery (odds ratio, 4.9; P less than .0001), she said.

Eighty percent of runs had one or more complications and 20% had three or more. Of that 80%, most involved cardiovascular complications (53%), while 36% were hemorrhagic and 35% mechanical. The most common cardiovascular complications were the need for inotropic support (39%) and hypertension requiring vasodilators (18%). The most common hemorrhagic complications were bleeding at the cannula

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments:

This is a large study looking at the use of extracorporeal membrane oxygenation (ECMO) patients dying of status asthmaticus. It is interesting that the pCO_2 seemed to predict the type of ECMO used and outcomes. Of course, an ounce of prevention (i.e., appropriate asthma management) is the most important thing to say about any pediatric intensive care unit asthma study! Having said all of this, we have known that venovenous ECMO is preferred for a long time.

(23%) and surgical site (8%), while mechanical complications were mostly clots (19%) and cannulation problems (12%).

Children who received VA cannulation had a significantly higher rate of neurologic complications, compared with those who received VV cannulation (22% vs. 5%).

The authors reported having nothing to disclose.

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Varenicline reduces heavy drinking in male smokers

BY MADHU RAJARAMAN

Frontline Medical News

The smoking cessation aid varenicline tartrate is effective for reducing heavy drinking in men with alcohol use disorder and comorbid cigarette smoking, according to findings published Dec. 20, 2017. The drug also increased smoking abstinence in participants overall, reported Stephanie S. O'Malley, PhD, of the department of psychiatry at Yale University, New Haven, Conn., and her coauthors.

In a phase 2, randomized, double-blind study of 131 patients, varenicline treatment resulted in a significant decrease in the percentage of heavy drinking days (PHDD) at 9-16 weeks in men, compared with placebo ($P = .09$). Additionally, 29% of men taking varenicline had no heavy drinking days (NHDD) during the trial period. NHDD was defined as never drinking four or more drinks per day for women or five or more drinks per day for men, Dr. O'Malley and her colleagues wrote in JAMA Psychiatry.

Women had a smaller decrease in PHDD ($P = .15$), and 5% had NHDD, compared with 25% of the women on placebo.

The trial was conducted between September 2012 and August 2015 at research facilities affiliated with Columbia University in New York and with Yale. The study group was made up

of 92 men and 39 women aged 18-70 years who met DSM-IV-TR criteria for alcohol dependence. Most of the respondents (52.7%) identified themselves as black. They reported heavy drinking at least twice per week for the preceding 90 days, having seven or fewer consecutive days of alcohol abstinence, and smoking at least twice per week, the investigators reported.

Among participants receiving varenicline, 13% achieved prolonged smoking abstinence at 13-16 weeks, the authors reported, whereas none of the participants on placebo quit smoking ($P = .003$).

The sex differences in the trial may be attributed to differences in baseline characteristics, such as greater alcohol dependence and lower nicotine dependence, Dr. O'Malley and her colleagues said.

Additionally, women were more likely to reduce or discontinue varenicline dose. "From a methodological perspective, we permitted dose reductions to minimize adherence problems because lower varenicline doses are effective for smoking cessation," they said.

"Individuals treated for alcoholism are more likely to die of smoking than from alcohol-related causes," they wrote, and "most smokers do not receive smoking-cessation assistance, yet heavy-drinking smokers see these behaviors as highly associated."

Continued on following page

VIEW ON THE NEWS

Study paves way for further research on substance use

Despite its limitations, this study provides an important contribution to the body of addiction research, wrote A. Eden Evins, MD, MPH, in an accompanying editorial.

"Outcome measures that take into account multiple addictions are largely unexplored," Dr. Evins said.

In addition to demonstrating its tolerability in patients with substance use disorders, the study makes "a creative contribution toward improved treatment trials for those who use multiple addictive substances by including an exploratory mixed outcome of no heavy drinking days and no tobacco use," she wrote.

Future research should further explore sex differences, as well as proactive treatment strategies for smokers who are not ready to quit but are willing to try medications to improve their chances of quitting, Dr. Evins concluded.

Dr. Evins is affiliated with the Center for Addiction Medicine at the department of psychiatry at Massachusetts General Hospital and with Harvard Medical School, both in Boston. She disclosed financial relationships with Forum Pharmaceuticals, Pfizer, and Brain Solutions.



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Tracheobronchial tree size changes may predict IPF outcomes

BY HEIDI SPLETE

Frontline Medical News

FROM CHEST 2017 ■ Changes in tracheobronchial tree size may serve as a practical and noninvasive method for predicting disease severity in patients diagnosed with idiopathic pulmonary fibrosis, according to data from 150 adults.

To determine the potential predictive value of tracheobronchial tree changes on mortality, Ankush Ratwani, MD, of Georgetown University, Washington, and colleagues reviewed data from adults with IPF seen at a single center between March 2012 and December 2016. The findings were presented at the CHEST annual meeting.

The researchers measured the tracheal diameters of the patients and used the GAP index, an established system for predicting mortality in IPF patients, to determine a relationship. Overall, they found a significant correlation between GAP index scores and increasing tracheobronchial tree size across eight measurements of different levels along the tracheobronchial tree “with an increase in GAP index stage for every level of increase in tracheal measurements (P less than .005),” they noted.

Measurements included the anterior-posterior diameter at the subglottic level, aortic arch, carina, right main stem bronchus, and left main stem bronchus, as well as transverse diameter assessment at the subglottis, aortic arch, and carina. The average anterior-posterior tracheal diameters were 21.77 mm for the subglottis, 21.84 mm for the aortic arch, 20.47 mm for the carina, 15.19 for the right main stem bronchus, and 14.21 mm for the left main stem bronchus.

No correlation appeared between

tracheal size and lung volume, which suggests that enlargement of the trachea is likely caused by other factors beyond fibrosis, and next steps for research should determine whether tracheal size is an independent predictor of mortality in IPF patients, the investigators noted.

“With the field of treatment and management changing for IPF over the last few years, it has becoming increasingly important to prognose these patients in order to find where they fit in the spectrum for treatment or lung transplant,” Dr. Ratwani said in an interview. “Additionally, there needs to be a noninvasive measure to show disease progression, such as with using CT scans, and correlate with other prognostic indicators to hopefully create a regression formula that encompasses multiple parameters,” he explained.

“The results were surprising in that there was a correlation of a radiographic measure that has not been looked at previously with a validated measure of prognostication in IPF (GAP Index),” Dr. Ratwani said.

Although the findings do not imply more than a correlation, the results serve as “a good start to validate the theory that as the distal airways enlarge (traction bronchiectasis) in later stages of IPF, so may the proximal airways, which may be used to easily measure disease progression and guide the conversation for transplant or treatment,” Dr. Ratwani noted. His next steps for research include studying transplant-free survival in correlation with tracheal size, as well as serial changes between CT scans with correlations of lung volumes and survival.

Dr. Ratwani and his coauthors reported having no disclosures.

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Continued from previous page

Lastly, the trial was limited by the small sample size of women.

“Future studies should evaluate the effectiveness and safety of varenicline in women and men separately in larger samples to establish whether the observed effects are of clinical significance,” the authors concluded.

The study was funded by grants from the National Institutes of Health and from Connecticut’s Department

of Mental Health and Addiction Services. Pfizer, the manufacturer of varenicline under the name Chantix, provided varenicline and placebo pills.

The authors disclosed relationships with several companies, including Pfizer.

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SOURCE: O’Malley SS et al. JAMA Psychiatry. 2017 Dec 20. doi: 10.1001/jamapsychiatry.2017.3544.

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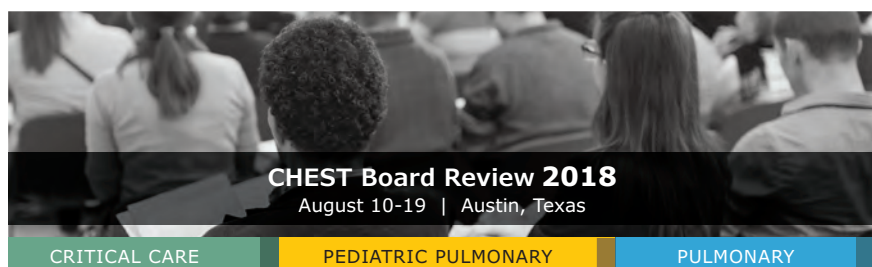
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Cancer screening needed earlier, more frequently in CF

BY MICHELE G. SULLIVAN

Frontline Medical News

Adults with cystic fibrosis (CF) should undergo screening colonoscopy for colorectal cancer every 5 years beginning at age 40 years, unless they have had a solid organ transplant – in which case, screening should begin at age 30 years. For both groups, screening intervals should be shortened to 3 years if any adenomatous polyps are recovered.

The new screening recommendation is 1 of 10 set forth by the Cystic Fibrosis Foundation, in conjunction with the American Gastroenterological Association. The document reflects the significantly increased risk of colorectal cancer among adults with the chronic lung disorder, Denis Hadjiliadis, MD, and his colleagues wrote in the February issue of *Gastroenterology*. CF patients face up to a 10-fold risk of colorectal cancer, compared with the general population; the risk approaches a 30-fold increase among CF patients who have undergone a lung transplant.

In addition to making recommendations on screening intervals and protocols, the document asks clinicians to reframe their thinking of CF as a respiratory-only disease.

“Physicians should recognize that CF is a colon cancer syndrome,” wrote Dr. Hadjiliadis, direc-

tor of the Adult Cystic Fibrosis Program at the University of Pennsylvania, Philadelphia, and his coauthors.

The increased colorectal cancer risk has become increasingly evident as CF patients live longer, Dr. Hadjiliadis and the panel wrote.

“The current median predicted survival is 41 years, and persons born in 2015 have an estimated average life expectancy of 45 years. The increasing longevity of adults with CF puts them at risk for other diseases, such as gastrointestinal cancer.”

In addition to the normal age-related risk, however, CF patients seem to have an elevated risk profile unique to the disease. The underlying causes have not been fully elucidated but may have to do with mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), which are responsible for the excess thickened mucosal secretions that characterize CF. CFTR also is a tumor-suppressor gene in the intestinal tract of mice, and is important in gastrointestinal epithelial homeostasis. “Absence of CFTR is associated with dysregulation of the immune response, intestinal stem cells, and growth signaling regulators,” the authors noted.

In response to this observed increased risk of colorectal cancers among CF patients, the Cystic Fibrosis Foundation convened an 18-member task force to review the extant literature and compile colorectal cancer screening recommendations for CF patients who show no signs of such malignancies. The team reviewed 1,159 articles and based its findings on the 50 most relevant. The papers comprised observational studies, case-control studies, and case reports; there are no randomized clinical trials of screening for this population.

The American Gastroenterological Association reviewed and approved all of the recommendations:

- Screening decisions should be a collaborative process between the CF patient and clinician,

taking into account comorbidities, safety, and quality of life. This should include a discussion of expected lifespan; patients with limited lifespan won't benefit from screening for a slow-growing cancer. Patients should also consider that the colonoscopy prep for CF patients is somewhat more complex than for non-CF patients. “Given these complexities, the task force agreed that individuals with CF and their providers should ... carefully assess the risks and benefits of CRC screening and its impact on the health and quality of life for the adult with CF.”

- The decision team should include an endoscopist. An endoscopist with CF training is preferred, but the panel noted these specialists are rare.
- Colonoscopy is the preferred method of screening for CF patients, since it can both detect and remove polyps. “This is one of the main reasons why colonoscopy is the screening procedure of choice for other high-risk groups,” the panel noted.
- There is insufficient evidence to recommend alternative screening methods in CF patients, including CT scanning, colonography, stool-based tests, or flexible sigmoidoscopy.
- In CF patients without signs of CRC, screening should commence at age 40 years and be repeated every 5 years as long as the results are negative.
- Any CF patient who has had adenomatous polyps on a screening colonoscopy should have a repeat colonoscopy within 3 years, unless clinical findings support more frequent screening.
- For any adult CF patient older than age 30 years who has undergone a solid organ transplant, screening colonoscopy should commence within 2 years of transplantation. “Although the absolute risk of CRC in individuals with CF is extremely low for patients younger than 30 years, the risk ... greatly increases after lung transplantation,” to 25-30 times the age-ad-

Continued on page 29

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: According to the Cystic Fibrosis Foundation Patient Registry, more than 30,000 people are living with cystic fibrosis (CF) in the United States. More than half of the CF population is over 18 years of age! It is extremely important to talk to patients about preventative medicine which was not a topic of conversation CF healthcare providers were adding to their management plan in the past.

Flu season takes another turn for the worse

BY RICHARD FRANKI

Frontline Medical News

By one measure at least – the proportion of outpatient visits for influenza-like illness (ILI) – this flu season is now the worst in almost a decade, according to data from the Centers for Disease Control and Prevention.

For the week ending Jan. 13, visits for ILI rose to 6.3% of outpatient visits nationwide – the highest figure reported since the 2009-2010 season, which hit an early peak of 7.7% in October of 2009. The slight pause that occurred in the first week of January as the rate rose only from 5.7% to 5.8% now looks more like the earlier

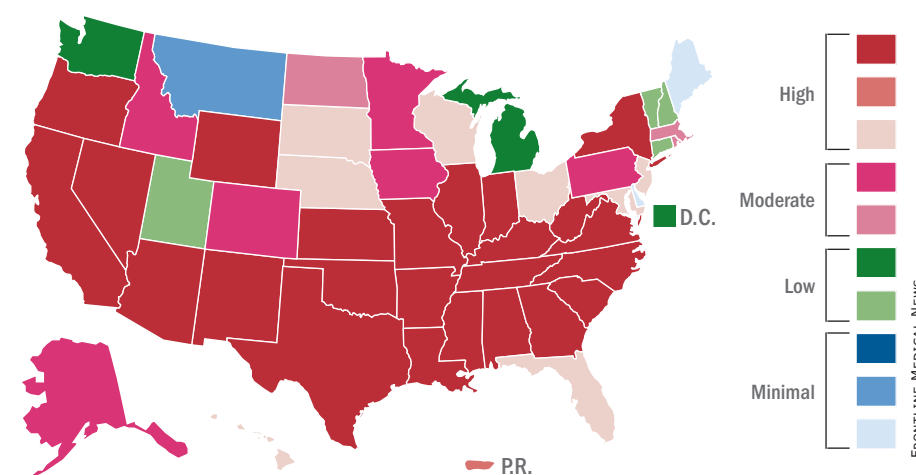
trend from December, when the level of outpatient visits more than doubled over a 3-week period, data from the CDC FluView website show.

“The geographic spread of influenza in Puerto Rico and 49 states was reported as widespread” for the week ending Jan. 13, and 24 states had the highest level of ILI activity on the CDC's 1-10 scale, the CDC influenza division reported Jan 19.

There were 10 flu-related pediatric deaths reported during the week, with two occurring in the week ending Jan. 13. A total of 30 deaths in children have been associated with influenza so far for the 2017-2018 season, the CDC said.

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Influenza-like illness activity level, week ending Jan. 13, 2018



Note: Based on data from the U.S. Outpatient Influenza-like Illness Surveillance Network.

Source: Centers for Disease Control and Prevention

Shorter walk test predicts survival in IPF

BY HEIDI SPLETE

Frontline Medical News

FROM CHEST 2017 ■ The 1-minute walk test is as effective as the 6-minute walk test at predicting transplant-free survival in patients with idiopathic pulmonary fibrosis (IPF), based on data from 179 adults. The findings were presented at the CHEST annual meeting.

The 6-minute test is often used to evaluate functional capacity in IPF patients, but is not always practical in a busy clinic setting, according to Flavia S. Nunes, MD, of Inova Fairfax Hospital in Falls Church, Va., and colleagues.

“Among the clinical and physiologic predictors associated with survival in IPF, the 6MWT [6-minute walking test] has been increasingly used over the past 5 years as a secondary endpoint in the efficacy analyses of potential therapies for IPF. Validation of shorter time of walking might make the test more feasible to be applied in routine clinical care,” Dr. Nunes said in an interview.

To determine the predictive value of the first minute of the 6-minute test, the researchers reviewed data from 142 men and 37 women at a tertiary referral center between May 2010 and February 2017. The average age of the patients was 68 years, the average body mass index was 28.3 kg/m², and 27% used oxygen supplementation during the walk test.

Overall, the mean distance for the 6-minute

test was 372 m, and the average distance for the 1-minute test was 65 m. Study participants who achieved a 6-minute walk distance greater than 372 m were defined as high walkers, and those with a 6-minute walk distance less than 372 m were defined as low walkers. A strong correlation appeared between the 6-minute distance and 1-minute distance in terms of predicting survival, and 1-year transplant-free survival was significantly better in high walkers than in low walkers (27 months vs. 22 months; $P = .015$).

Dr. Nunes said she was not surprised by the results, in part because previous research has shown a strong correlation among 2-minute, 6-minute, and 12-minute walking tests.

Although more research is needed to validate the findings, the results suggest that the 1-minute test might be a practical substitute for the 6-minute test by providing similar prognostic information more quickly and easily than the 6-minute test, the researchers said.

“It is important for clinicians to know that the time chosen to assess exercise tolerance by walking tests might not be critical,” said Dr. Nunes. “Shorter walks are not only less time consuming, and easier for both patients and clinicians, but are also reproducible and discriminatory of survival.”

“We need to validate the test performance characteristics and prognostic value of distance walked in a 1MWT compared to the standard 6MWT in an independent cohort of patients with IPF,”



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Dr. Nunes noted. “Additionally, the evaluation of alternate instruction, for example changing the wording from ‘walk as far’ to ‘walk as fast’ might facilitate a better effort, and a greater distance with improved reproducibility. Other novel parameters and modifications to the 6MWT or 1MWT might further improve the utility of these tests in the management of IPF and other patients,” she added.

The researchers had no financial conflicts to disclose.

Continued from page 24

- justed baseline, the panel wrote. “Increased posttransplantation survival means that many transplant patients will enter older age groups where there is an increased risk of cancer.” Screening should be performed after recovery and within 2 years, unless there was a negative colonoscopy in the 5 years before transplant.
- Thereafter, patients who have had a solid organ transplant should undergo colonoscopy every 5 years, based on their life expectancy. “In cases where the expected survival time is limited (less than 10 years), screening should not be performed. For adults appropriately selected, lung transplantation usually increases survival probability. Therefore, a lung transplantation candidate with a short life expectancy is likely to become a screening candidate before and after transplantation at the appropriate ages described here, because the potential survival increases to approximately 10 years.”
 - Colonoscopy should be repeated every 3 years on CF patients with transplants with a history of adenomatous polyps. This interval may be as short as 1 year for

patients with high-risk, large, or multiple polyps.

- CF patients should undergo more intense bowel prep for colonoscopy, with three to four washes of a minimum of 1 liter of purgative per wash; the last wash should occur 4-6 hours before the procedure. Split-prep regimens (several smaller-volume washes) are better than a single larger-volume wash. The panel suggested a sample CF-specific regimen available from the Minnesota Cystic Fibrosis Center.

The new document reflects expert consensus on the currently available data, the panel said. As more data emerge, the recommendations might change.

“It is possible that different subpopulations will need more or less frequent schedules for rescreening and surveillance. Our recommendations are making an effort to balance the risk of missing advanced colorectal cancer and minimizing the burden and risk of too frequent examinations.”

None of the panel members had any financial disclosures.

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SOURCE: Hadjiliadis D et al. Gastroenterology. 2017 Dec 28. doi.org/10.1053/j.gastro.2017.12.012.

Comparing arterial ratios may aid IPF risk assessment

BY HEIDI SPLETE

Frontline Medical News

FROM CHEST 2017 ■ An arterial ratio can help identify idiopathic pulmonary fibrosis (IPF) patients with a poor prognosis, suggests the findings of registry data from 50 adults. Such patients might benefit from pharmacotherapy or transplants, the researchers noted.

The ratio of the main pulmonary artery diameter (PA) to the ascending aorta diameter (A) as seen on a chest CT correlates with pulmonary artery pressure, M. Faisal Siddiqui, MD, a pulmonologist in New York, and his colleagues wrote in an abstract from the agenda of the CHEST annual meeting. To determine whether higher PA:A ratios were associated with more biomarker abnormalities, the researchers reviewed 122 CT scans from 50 adults with IPF.

Overall, 48% of the patients had a PA:A ratio of at least 1, according to Dr. Siddiqui and his coauthors. These patients had significantly

higher fibrosis scores ($P = .0006$), GAP index scores ($P = .0144$), brain natriuretic peptide scores ($P = .0046$), and pulmonary arterial systolic pressure ($P = .0063$) compared with patients who had PA:A ratios of less than 1, according to the Kruskal-Wallis test. This test also showed no significant differences on measures of coronary artery calcium, aortic valve calcifications, mitral valve calcifications, bronchial wall thickening, emphysema, and spirometry data between the two patient groups, based on PA:A ratios.

Use of the Pearson correlation revealed a positive relationship between PA:A ratios greater than 1 and coronary artery calcium scores, fibrosis scores, and pulmonary arterial systolic pressure, but a negative relationship between a high PA:A ratio and both diffusing capacity and forced vital capacity.

These findings were limited by a small study population. Dr. Siddiqui and his coauthors had no financial conflicts to disclose.

HRS: Consider ablation for asymptomatic atrial fib

BY MITCHEL L. ZOLER

Frontline Medical News

ORLANDO – When the Heart Rhythm Society and several collaborating groups published in October 2017 the first revised consensus statement on atrial fibrillation ablation in 5 years, the document included a novel and perhaps unexpected suggestion: Ablation for asymptomatic atrial fibrillation “may be considered.”

This was “the first time” any group of experts suggested an indication potentially existed for ablating asymptomatic atrial fibrillation (AF), Hugh Calkins, MD, said at the annual International AF Symposium.

“You might say ‘are you out of your mind recommending ablation for asymptomatic AF?’” conceded

who are passionate about ablation know about it.

“Our goal was not to send a message that this isn’t for everyone. It’s for very select patients and for very select operators after a very careful

discussion” of the risks and potential benefits from performing the procedure on a truly asymptomatic patient.

The ideal candidate for this approach would be a relatively young

patient, say someone in their 50s, who is identified as having AF incidentally, such as someone with an irregular pulse that’s found during a routine examination that leads to an ECG and definitive identification



MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

Dr. Hugh Calkins, noted that the statement was a “soft” recommendation.

Dr. Calkins, professor of medicine and director of the arrhythmia service at Johns Hopkins Medicine in Baltimore. But Dr. Calkins quickly added that this was a “soft” recommendation by being in the “may be considered” category, and he also noted that it received broad support from about 90% of the members of the statement’s 60-member writing group (Heart Rhythm. 2017 Oct;14[10]:e445-e494).

In addition, he personally believed that an amber light for this strategy made a lot of sense.

“I have done it. I think that catheter ablation has gotten to the point in terms of safety and efficacy that this is reasonable,” Dr. Calkins said in an interview.

He also acknowledged that this recommendation is sort of buried in the text of the consensus statement and does not appear in any summary diagram “because the reviewers wanted us to hide it. Only those

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of AF despite the patient's complete denial of having symptoms.

The next step, Dr. Calkins suggested, would be to treat the patient with an antiarrhythmic drug, such as amiodarone or flecainide, and with cardioversion and see whether this stops the AF and makes the patient feel better. If the patient reports improvement, it suggests the

The pros for immediate ablation are that, when left unablated, the patient will face a substantially increased lifetime risk for stroke, dementia, and new-onset heart failure.

AF really is symptomatic and management could then proceed as with any case of symptomatic AF. But if

the patient perceives no change and the AF then recurs in a persistent presentation despite drug treatment,

the cardiologist could then discuss with the patient the pros and cons of an ablative procedure.

The pros for immediate ablation are that, when left unablated, the patient will face a substantially increased lifetime risk for stroke, dementia, and new-onset heart failure, and after 2-3 years of continued

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persistent AF the left atrium would remodel and become much less likely to respond to ablation with little prospect for the patient ever returning to a normal sinus rhythm. “It’s either a rhythm control strategy now, or we’ll leave you in AF for the rest of your life,” Dr. Calkins explained. “If I were 50 years old and

had asymptomatic AF, there’s no way I’d want to have AF for the rest of my life.” The risks from ablation are that the procedure has about a 68% success rate and about a 1% rate of complications.

“A patient with asymptomatic paroxysmal AF doesn’t have much to lose by waiting and seeing whether symptoms develop, but for the pa-

tient with persistent AF there is a penalty for allowing continuous AF, because after 2-3 years you won’t be able to successfully ablate it. In the past, we left patients with asymptomatic AF that way for the rest of their life, but now we know that, if patients remain in AF over time, they will lose the option to have it ablated, and their risk of stroke, dementia,

and heart failure will increase.”

Dr. Calkins has been a consultant or adviser to or received honoraria from Abbott, AtriCure, Boehringer Ingelheim, Boston Scientific, iRhythm, Medtronic, Pfizer, St. Jude, and Toray. He has also received research funding from Boston Scientific and Medtronic.

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Conflicting results for thrombolysis treatment

BY ANDREW D. BOWSER

Frontline Medical News

In patients with acute proximal deep vein thrombosis who were undergoing anticoagulation, add-

ing pharmacomechanical catheter-directed thrombolysis did not reduce risk of the postthrombotic syndrome, according to results of a phase 3, randomized, controlled trial.

Moreover, addition of pharmacom-

echanical thrombolysis increased risk of major bleeding risk, investigators wrote in a report published in the New England Journal of Medicine (2017;377:2240-52).

The trial results contrast with recent

reports from another randomized trial, known as CAVENT, which suggested that pharmacomechanical thrombolysis might help reduce incidence of postthrombotic syndrome (Lancet Haematol. 2016;3[2]:e64-71).

“Our trial, for uncertain reasons, did not confirm these findings,” wrote Suresh Vedantham, MD, of Washington University, St. Louis, and his coauthors.

Postthrombotic syndrome is associated with chronic limb swelling and pain and can lead to leg ulcers, impaired quality of life, and major disability. About half of patients with proximal deep vein thrombosis (DVT) will develop the postthrombotic syndrome within 2 years, despite use of anticoagulation therapy, Dr. Vedantham and his colleagues noted.

Pharmacomechanical thrombolysis is the catheter-directed delivery of a fibrinolytic agent into the thrombus, along with aspiration or maceration of the thrombus. The goal of the treatment is to reduce the burden of thrombus, which in turn might reduce risk of the postthrombotic syndrome.

However, in their randomized trial known as ATTRACT, rates of postthrombotic syndrome between 6 and 24 months after intervention were 47% in the pharmacomechanical thrombolysis group and 48% in the control group (risk ratio, 0.96; 95% confidence interval, 0.82-1.11; $P = .56$). Control group patients received no procedural intervention.

Major bleeds within 10 days of the intervention were 1.7% and 0.3% for the pharmacomechanical thrombolysis and control groups ($P = .049$).

Dr. Vedantham and his coauthors suggested that perhaps the number of patients enrolled (692 in ATTRACT, versus 209 in CAVENT) or the greater use of mechanical therapies in ATTRACT versus longer recombinant tissue plasminogen activator infusions in CAVENT accounts for the differences.

The study was supported by multiple sources, including the National Heart, Lung and Blood Institute, Boston Scientific, Covidien (now Medtronic), Genentech, and others. Dr. Vedantham reported receiving grant support from Cook Medical and Volcano. Some of the other authors reported financial ties to Abbott Vascular, Boston Scientific, Medtronic, and other pharmaceutical and device companies.

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SOURCE: Vedantham S et al. N Engl J Med. 2017;377:2240-52.

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DAPT duration: How low can you go?

BY BRUCE JANCIN

Frontline Medical News

DENVER – Six months of dual-antiplatelet therapy proved equivalent in terms of safety, efficacy, and bleeding risk to the guideline-recommended standard 12 months in ST-elevation MI patients after primary percutaneous coronary intervention (PCI) with a second-generation drug-eluting stent in the randomized DAPT-STEMI trial.

“This trial, for the first time, showed that in the modern DES [drug-eluting stent] era, event-free STEMI patients do not benefit from a prolonged DAPT [dual-antiplatelet therapy] beyond 6 months, as currently recommended, and sets the stage for further dedicated research in this important topic,” Elvin Kedhi, MD, PhD, declared in presenting the DAPT-STEMI results at the Transcatheter Cardiovascular Therapeutics annual educational meeting.

DAPT-STEMI was a prospective randomized international study that enrolled 1,100 STEMI patients who underwent primary PCI with the second-generation Resolute Integrity zotarolimus-eluting stent and were placed on 6 months of DAPT. After that truncated period of DAPT, patients who had not had an ischemic or bleeding event or other reason for ineligibility during the initial 6 months were then randomized to continue DAPT for another 6 months in accord with current guidelines or were switched to single-antiplatelet therapy (SAPT) with aspirin.

Among the 861 completers, the composite primary outcome of death, MI, revascularization, stroke, and major bleeding during months 6-24 occurred in 4.8% of the SAPT group, a 27% relative risk reduction com-

pared with the 6.6% rate in the DAPT group. Thus, 6 months of DAPT met the prespecified endpoint of noninferiority compared with the standard 12 months of DAPT, reported Dr. Kedhi, head of interventional cardiology and clinical research and innovation at the Isala Heart Center in Zwolle, The Netherlands.

The secondary composite endpoint of death, MI, stroke, stent thrombosis, or TIMI major bleeding occurred in 3.2% of the SAPT group and 4.3% of



DR. KEDHI



DR. KEREIAKES

the DAPT group, for a 25% relative risk reduction.

All individual components of the composite endpoints occurred at the same or lower rate in the SAPT group compared with the DAPT arm, he noted at the meeting, which was sponsored by the Cardiovascular Research Foundation.

At a press conference where Dr. Kedhi presented the DAPT-STEMI results, discussant Dean J. Kereiakes, MD, explained why he didn't find the study results surprising.

“The second- and third-generation stents are better. They're safer. And in STEMI, where you may have multicentric disease and an acute systemic inflammatory process, the other treatments that we're giving – statins, ACE inhibitors, etc. – are also preventing ischemic events,” said Dr. Kereiakes, medical director of the Christ Hos-

pital Heart and Vascular Center in Cincinnati.

Press conference moderator Gary S. Mintz, MD, put the DAPT-STEMI findings in perspective: “The need for DAPT has decreased along with all the stent-related complications. There's always been a greater focus on DAPT for preventing events and a relatively lesser focus on the adverse consequences of DAPT. And anybody who's a clinician who takes care of patients knows that drug-related bleeding after stent implantation is not a trivial occurrence,” observed Dr. Mintz, chief medical officer at the Cardiovascular Research Foundation in Washington.

DAPT-STEMI isn't the final word on DAPT duration

At a late-breaking clinical trials session, comoderator Eric D. Peterson, MD, noted that, in earlier megatrials such as PEGASUS, DAPT, and PLATO, there were signals that extending DAPT beyond 12 months might be even more beneficial than the guideline-recommended 12 months.

“It seems somewhat counterintuitive that now you have better results with less. Any speculation as to why?” asked Dr. Peterson, executive director of the Duke Clinical Research Institute and professor of medicine at Duke University in Durham, N.C.

“It's true that DAPT reduces the general risk of thromboembolic events, but it does so at a relative risk reduction rate of about 20%, while it augments the bleeding risk by over 200%. And ask yourself, what is the benefit of this 6 months of extra DAPT on the lifelong process of atherosclerosis? It's almost invisible,” Dr. Kedhi explained.

Although Dmitriy N. Feldman, MD, of Cornell University in New York,

noted that DAPT-STEMI was statistically underpowered to be definitive, he found the results encouraging.

“It's very reassuring that the stent thrombosis rates are quite low: 0.7% and 0.9%. ... This is a very select group – patients had to tolerate the first 6 months of DAPT without MACE events or bleeding. But it is reassuring that in patients who are able to do well at 6 months, this is an option,” the interventional cardiologist said.

Session moderator Gregg W. Stone, MD, called DAPT-STEMI “hypothesis generating” in light of its limited size and statistical power.

“At least it raises the concept of shorter-duration DAPT, whereas I'd say before today it was not a concept. We were always talking about prolonging DAPT in the highest-thrombotic risk STEMI patients, and now we can at least think about shortening it, whether for all patients or for higher-bleeding-risk patients,” observed Dr. Stone, a professor of medicine at Columbia University in New York.

As a matter of fact, DAPT durations even briefer than 6 months are under active investigation. Dr. Kedhi is co-principal investigator in the Onyx ONE clinical trial, a new prospective, 85-center, randomized, single-blind trial of a mere 1 month of DAPT in 2,000 high-bleeding-risk coronary artery disease patients undergoing PCI with the Resolute Onyx DES or the BioFreedom drug-coated stent.

The DAPT-STEMI trial was funded by Maasstad Cardiovascular Research. Dr. Kedhi reported receiving consultant fees and/or institutional grants from Medtronic, Abbott Vascular, Meril. OrbusNeich, Boston Scientific, AstraZeneca, and Pfizer.

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SOURCE: Kedhi E. TCT 2017.

PCI outcomes not better at top-ranked hospitals

BY ANDREW D. BOWSER

Frontline Medical News

Outcomes after percutaneous coronary intervention (PCI) are not superior when performed in U.S. hospitals ranked as “best” in a prominent national rating system as compared with nonranked hospitals, according to results of a recent retrospective analysis.

Rates of in-hospital mortality, acute kidney injury, and bleeding were similar for hospitals in the 2015 U.S. News & World Report's “Best Hospitals” rankings and nonranked hospitals, Devraj Sukul, MD, reported at the American Heart Association Scientific Sessions.

“These findings should reassure patients that safe and appropriate PCI is being performed across the country,” said Dr. Sukul of the division of cardiovascular medicine, University of Michigan, Ann Arbor.

The findings were based on a retrospective analysis of PCIs documented in the National Cardiovascular Data Registry CathPCI Registry.

Dr. Sukul and his colleagues limited their analysis to hospitals that both participated in that registry and performed at least 400 PCIs during July 2014–June 2015. That narrowed it down to 654 hospitals, including 44 out of the 50 hospitals ranked by U.S. News & World Report in 2015.

A total of 509,153 PCIs were performed over the 1-year study period, including 55,550 (10.9%) performed at the top-ranked hospitals.

After adjustment for patient risk, there was no difference in post-PCI in-hospital mortality between top-ranked and nonranked hospitals investigators reported (adjusted odds ratio, 0.96; $P = .64$).

There were also no differences in acute kidney injury (aOR, 1.10; $P = .1$) or bleeding (aOR, 1.15; $P = .052$) for top-ranked vs. nonranked hospitals, according to investigators.

In addition, top-ranked hospitals had a “slightly lower proportion” of appropriate PCI, Dr. Sukul reported.

Continued on following page

Transcatheter valve-in-ring a winner in mitral disease

BY BRUCE JANCIN

Frontline Medical News

DENVER – Transseptal mitral valve implantation of an off-the-shelf, commercially available transcatheter aortic valve replacement (TAVR) in high-surgical-risk patients with a failing surgically implanted mitral ring prosthesis has become a reasonable treatment strategy in light of the interim findings of the ground-breaking MITRAL trial, Mayra E. Guerrero, MD, said at the Transcatheter Cardiovascular Therapeutics annual educational meeting.

Her presentation of the preliminary results of the MITRAL (Mitral Implantation of Transcatheter Valves) trial showed this valve-in-ring (ViR) treatment strategy using the Sapien 3 valve was associated with low 30-day morbidity and mortality rates and impressive symptomatic improvement.

In contrast, another arm of the MITRAL trial showed that placement of the Sapien 3 TAVR valve in high-surgical-risk patients with severe mitral stenosis caused by mitral annular calcification (MAC) of their native valve is a treatment strategy that's not yet ready for prime time, she added at the meeting, which was sponsored by the Cardiovascular Research Foundation.

The ViR arm of the observational multicenter prospective MITRAL trial included 30 patients with extremely high surgical risk and either severe mitral stenosis as defined by a mitral valve area of 1.5 cm² or less or moderate mitral stenosis plus severe mitral

regurgitation. Access for transcatheter mitral valve replacement (TMVR) was transseptal in 100% of patients.

The technical success rate at exit from the catheterization lab was 70%. The procedural success rate at 30 days was 62%.

Six patients required a second valve. This was mainly because of malpo-



DR. GUERRERO

sitioning of the first valve with resultant mitral regurgitation; however, this problem became a nonissue as operator experience grew. All six affected patients were alive at 30

days, and four of

the six were New York Heart Association (NYHA) functional class I or II.

In-hospital and 30-day mortality rates were low. There was one cardiovascular death and one noncardiac death in hospital, with no additional deaths through 30 days. No cases of stroke, acute MI, or valve embolization or thrombosis occurred. The mean mitral valve area at 30 days was 2.1 cm², although three patients still had a mitral valve area of less than 1.5 cm². Three patients experienced acute renal failure requiring hemodialysis. Seventy-five percent of patients had no or only trace mitral regurgitation by echocardiography; the rest had mild regurgitation.

At baseline more than 60% of the patients were NYHA class III, 10%

were class IV, and the rest were class II; at 30 days, more than 30% were NYHA class I, 40% were class II, and the rest were class III.

Heart valve design changes, such as a longer inner skirt, might further improve the technical success rate for ViR, according to Dr. Guerrero, an interventional cardiologist at North-Shore University HealthSystem in Evanston, Ill.

Picking the right ring

Studies have shown one-third of recipients of a surgical mitral ring or valve repeat interventions within 10 years, so she made a plea to surgeons: "If we are going to be treating patients with valve-in-ring TMVR, that means when surgeons do a repair they should pick a ring that is amenable to a ViR procedure. So don't use flexible incomplete bands or very rigid rings because those are really difficult to treat later on. We should pick a ring thinking of the future. That ring is going to fail at some point, and when it fails it's going to make our lives much easier if we'd picked the right ring."

MAC TMVR needs more work

In the MAC arm of the MITRAL trial, 96 patients were screened so the researchers could find 30 candidates for TMVR. The 61 rejections were for high risk of left ventricular outflow tract obstruction (LVOTO), embolization, or both.

The technical success rate at exit from the cath lab in the MAC patients was 73%, with a 30-day procedural

success rate of 46% and a 19% 30-day mortality. Three patients developed severe LVOTO with hemodynamic compromise.

One transseptal and one transapical TMVR were complicated by LVOTO, both treated by bailout alcohol septal ablation. This led Dr. Guerrero and her co investigators to the concept of preemptive alcohol septal ablation, which they used in seven patients deemed at high risk for LVOTO an average of 6 weeks prior to transseptal TMVR as a successful risk reduction strategy.

Survival climbing with operator experience

"In the early days of the TMVR MAC registry, the 30-day mortality rate was 37%. It came down to 22% in the middle third of the registry, then about 18% in the final third. Now we've got it down in MITRAL to 16.7%, but when you separate the rate in the transseptal versus the transatrial patients, it's 13% versus 20%. The difference is not statistically significant, but it's promising, and I think we are making great progress," Dr. Guerrero said.

The MITRAL trial was partially supported by Edwards Lifesciences. Dr. Guerrero reported receiving a research grant from that company and serving as a consultant to Tendyne Holdings/Abbott and on a speakers bureau for Abiomed.

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SOURCE: Guerrero M. TCT 2017.

Continued from previous page

Appropriate PCIs – defined as those performed according to evidence-based indications – have been increasingly emphasized over the past decade.

Though rates of appropriate PCI were relatively high in both groups, the odds of having an appropriate PCI were nevertheless significantly higher at nonranked hospitals (89.2% for ranked and 92.8% for nonranked hospitals; *P* less than .001).

Although some recent reports suggest hospital-level appropriateness may not necessarily correlate with clinical outcomes, Dr. Sukul remarked, "we believe that PCI appropriateness is an important indicator of quality, serving as a measure of physician decision making when faced with treating the vast array of coronary artery disease presentations."

Dr. Sukul is supported by a National Institutes of Health postdoctoral research training grant.

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SOURCE: Sukul D. AHA Scientific Sessions 2017.

VIEW ON THE NEWS

Local hospitals do PCI well

It should be welcome news to the public that outcomes of PCI conducted at top-ranked hospitals were not superior to those of procedures performed at nonranked hospitals.

This study addresses what is often the foremost question of a patient and their family in their hometown: Is my local hospital doing a good job? To the extent measured by the variables in this study, it is reassuring that the answer appears to be "Yes."

It is hard to argue that health care should be immune from rankings in an era where consumers have access to ratings for just about every product and service available.

However, the public may be confused regarding the multiple national hospital ranking systems that are available today, particularly since these rating systems do not consistently identify hospitals as top performers.

Each rating system uses different data sources, has its own rating methodology, defines different measures of performance, and has a different focus. Many have argued that transparency will improve health care but, for the public, this is getting to the point of "too much information."

Gregory J. Dehmer, MD, of the Department of Medicine (Cardiology Division) Texas A&M University, and Baylor Scott & White Health, Temple, made the comments above in an accompanying editorial (JACC Cardiovasc Interv. 2017 Nov 1. doi: 10.1016/j.jcin.2017.11.001). He reported no financial relationships relevant to the topic.

Pulmonary Perspectives®

Postoperative pulmonary complications of cardiac surgery

BY CHRISTOPHER NOEL, MD

Cardiac surgery patients are sicker today than in previous decades due to an aging population and a rising complexity in medical care. There is an increasing reliance on noncardiac surgeons to care for these patients. The optimal postoperative providers and structure of the ICU where patients are cared for remain unclear, but

Table 1

Pulmonary Complications Following Cardiac Surgery

Atelectasis
Pneumonia
Pleural effusion
Pulmonary edema
Phrenic nerve injury
Pneumothorax
Prolonged mechanical ventilation

what is irrefutable is patients' increased postoperative morbidity. Pulmonary complications are a leading cause of morbidity in these patients, occurring in up to one-fifth of cases (Szelowski LA, et al. *Curr Probl Surg*. 2015;52[1]:531). Common pulmonary complications of cardiac surgery are listed in Table 1. Those complications, captured by The Society of Thoracic Surgeons (STS) Cardiac Surgery Database, include receiving ventilation longer than 24 hours, pneumonia, pulmonary embolism, and pleural effusion requiring drainage (The Society of Thoracic Surgeons. STS National Database. <https://www.sts.org/registries-research-center/sts-national-database>. Accessed January 9, 2018).

It should come as no surprise that cardiac surgery can have pronounced effects on lung function. The anesthetic agents, chest wall alteration, and direct lung manipulation can all affect pulmonary parameters. Functional residual capacity (FRC) can decrease by up to 20% with anesthesia (Szelowski LA, et al. *Curr Probl Surg*. 2015;52[1]:531), and the thoracic manipulation and alteration of rib cage mechanics with a classic median sternotomy approach can lead to decreases in forced vital capacity (FVC) and expiratory volume in the first sec-



Dr. Noel is a Critical Care Fellow, Cooper Medical School of Rowan University, Camden, New Jersey.

ond of forced expiration (FEV₁) that can last for months after surgery. Use of the cardiopulmonary bypass circuit can also lead to bronchoconstriction. These changes in pulmonary function are less pronounced in alternative surgical approaches, such as partial sternotomies (Weissman C. *Seminars in Cardiothoracic and Vascular Anesthesia: Pulmonary Complications After Cardiac Surgery*. Glen Head, NY: Westminster Publications; 2004).

The most frequent pulmonary consequence of cardiac surgery is atelectasis, seen on postoperative chest radiographs in approximately 50% to

Continued on following page



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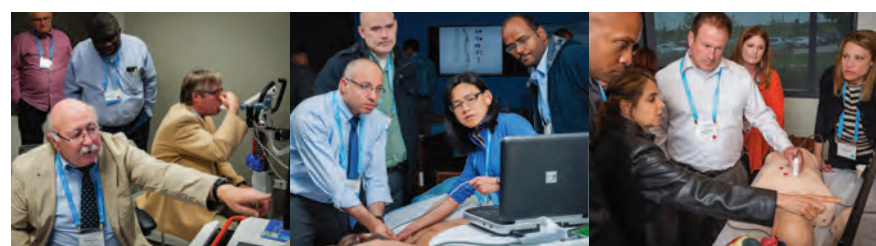
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President's Report

As I sit here and write this article, it is hard to fathom that a quarter of my year as the President of CHEST has passed by. Thanks again for this incredibly humbling opportunity to serve as your President.

I hope many who read this were able to get to Toronto and experience CHEST 2017. Special thanks to our Program Chair, Peter Mazzone, and to his Co-Chair Diane Lougheed from the Canadian Thoracic Society; the Scientific Program Committee; our excellent and committed CHEST 2017 faculty, who give their valuable time to ensure we are delivering the best clinical education possible; and our incredibly talented CHEST staff for all their work to make this meeting a reality.

What a great opportunity to learn and stay up to date while exposed to such meaningful content from so many outstanding clinical educators in so many traditional and innovative ways. For those who were able to be there, I hope you were able to experience the value of learning in a highly interactive setting while

taking the opportunity to build and nurture old and new friendships and relationships.

As we move forward, there is so much going on:



**JOHN STUDDARD,
MD, FCCP**

1. The Editor in Chief Search Task Force, under the leadership of Dr. David Gutterman and Nicki Augustyn, is hard at work with their diverse and talented colleagues on this critically important task.

2. The Scientific Program Committee, under Dr. David Schulman's direction, is hard at work building October's CHEST 2018 in San Antonio. It is so exciting to watch this group plan and create, in new and innovative ways, the content for this meeting to be held October 6-10.

3. By the publication date of this article, your Board of Regents most likely will have put the finishing touches, under the leadership of Jenny Nemkovich, our Chief of Staff, on our next 5-year strategic plan.

4. The Board of Regents is also moving forward with a uni-

form, business-like process and approach in delivering international education offerings and meeting opportunities. Special thanks to Bob Musacchio, our COO and the SVP of Strategy and Innovation, Sue Reimbold, wearing her hat of Market Growth; and Chad Jackson, VP of Innovation and Development, for their direction in this area.

5. Thanks to the Diversity/Inclusion Task Force for their continued work to ensure that the principles of diversity of thought and inclusion permeate all of our conversations and work on the volunteer and professional sides of CHEST.

6. Thanks also to our Training and Transitions Committee and their leadership, Drs. Gabe Bosslet and Matt Miles, and the support of Dr. Richard Irwin and our CHEST® journal for the introduction of the CHEST Teaching, Education, and Career Hub in the journal, which made its debut in January.

7. Also, emphasizing the critical importance of relationships, thanks to our colleagues and partners with so many sister societies with whom we are working closely

to help advance the practice of chest medicine. I am confident that we are building better relationships built on common goals, transparency, communication, and trust than we have in many years.

8. Last, and certainly not least, one of the jobs of President I am most looking forward to is serving on the Board of Trustees of the CHEST Foundation as an ex officio member. Having served on this Board for about 10 years, I am so glad to be joining my CF family once again. What an amazing group of volunteers, leaders, and staff serving CHEST and our patients in such amazing ways.

These are but a few of so many things that are transpiring at CHEST. People have asked me if it is intimidating to take on this responsibility. With the support of such diversely talented leaders in our Presidential line; an incredibly mature and engaged BOR; and a CEO, senior leadership, and diverse and talented staff that we have at CHEST, all characterized by incredible intellect and energy, it is pretty easy to be just another member of a great team.

Thanks again for your unwavering support of CHEST and our mission.

Continued from previous page

90% of patients (Szelowski LA, et al. *Curr Probl Surg.* 2015;52[1]:531). Induction, apnea during cardiopulmonary bypass, manual compression of the lungs for surgical exposure, internal mammary harvesting, and pleurotomy can lead to atelectasis in the intraoperative setting while weak cough, poor inspiratory efforts, interstitial edema, and immobility further contribute postoperatively (Weissman 2004). While frequently seen, clinically significant pulmonary consequences from this radiographic finding alone are rare (Weissman 2004).

Pleural effusions are seen on immediate postoperative chest radiographs in the majority of patients. Additionally, 10% to 40% of patients develop pleural effusions 2 to 3 weeks after surgery secondary to postpericardiotomy syndrome. While some effusions require drainage and further intervention (eg, hemothorax), most effusions require no specific treatment and resolve over time (Weissman 2004).

The prevalence of pneumonia following cardiac surgery varies based on differences in study populations and diagnostic criteria, but it remains an important source of morbidity and mortality. In one series, postoperative pneumonia occurred in 3.1% of patients, with higher rates observed in patients who were older, had worse left ventricular ejection fraction, had COPD, experienced longer bypass times, and received more red blood

cell transfusions in the operating room (Allou N, et al. *Crit Care Med.* 2014;42[5]:1150). A meta-analysis found that an average of 6.37% of patients developed ventilator-associated pneumonia (VAP), and this rose to 35.2% in those receiving ventilation for greater than 48 hours. Those who developed VAP had an odds ratio of dying of 15.18 (95% CI 5.81-39.68) compared with those who did not (He S, et al. *J Thorac Cardiovasc Surg.* 2014;148[6]:3148).

A small proportion of patients go on to develop ARDS. While relatively uncommon, ARDS carries a high mortality rate. Many possible etiologies for ARDS in cardiac surgery patients have been proposed, including an inflammatory response related to the cardiopulmonary bypass circuit, reperfusion injury secondary to reduced pulmonary blood flow during bypass, protamine administration, transfusion, hypothermia, and lack of ventilation during bypass (Weissman 2004); (Stephens RS, et al. *Ann Thorac Surg.* 2013;95[3]:1122). Type of surgery may also play a role, as patients who undergo aortic surgery are at an even greater risk (Stephens 2013). As with other cases of ARDS, treatment is supportive: low tidal volume ventilation and careful management of fluid balance, as well as paralysis, prone positioning, and consideration for extracorporeal membrane oxygenation (ECMO), as appropriate (Stephens 2013).

Therapies to prevent postoperative pulmonary

complications have included early extubation, aggressive pain control, deep breathing, physical therapy, early mobilization, and noninvasive ventilation in the form of CPAP and intermittent positive pressure breathing. A meta-analysis of 18 trials looking at the use of various forms of prophylactic postoperative physiotherapy did not show a difference in any measured clinical outcome (Pasquina P, Walder B. *Br Med J.* 2003;327[7428]:1379).

However, the heterogeneity, short follow-up, and low quality of included studies made it difficult to draw meaningful conclusions on the benefit or lack thereof for these therapies. More recent studies have shown promise for chest physiotherapy started several weeks prior to elective coronary bypass graft surgery and extended CPAP via nasal CPAP mask immediately following extubation (Hulzebos EH. *JAMA.* 2006;296[15]:1851), (Stephens 2013).

Ongoing areas for improvement include further clarification and standardization of best practices for postcardiac surgery patients, including blood product transfusion, optimal tidal volumes for surgical and postsurgical ventilation, timing of extubation, and the use of preventive therapies in the pre- and postsurgical periods. As providers who care for these patients, understanding how we can improve their postoperative pulmonary recovery will allow us to enhance our patient's experience.

How Will You Champion Lung Health in 2018?

Our CHEST Foundation grantees are doing amazing research and community service projects that are paving the way for change and improvements in chest medicine. How will you help champion lung health?

“This award carries great importance to me as a young clinician who is in the early phase of my career. I’m driven by my passion for researching this disease (PAH). This award helps establish me as a strong clinical researcher – where I see my career heading. It also helps us identify those clues that can lead to changing how this disease state is treated. Everything starts with an idea.”



DR. SAHAY

Sandeep Sahay, MD, FCCP

Houston Methodist Hospital – Houston, Texas
CHEST Foundation Research Grant in Pulmonary Arterial Hypertension

Title: *Alterations of Estrogen Metabolism in the Development of Portopulmonary Hypertension*

“This grant has allowed me to do this project, period. Having support from the CHEST Foundation automatically gives me credibility at my new institution. As I would meet with people to discuss my project, they would see that a big organization is supporting me, and that is the outside validation to show that this must be a useful project. The grant really helps me hit the ground running, and plants the seed to help us do a larger project in the future.”



DR. HARRIS

Drew Harris, MD

Yale University – New Haven, Connecticut
CHEST Foundation Research Grant in Asthma

Title: *Utilizing Medical-Legal Partnership to Promote Asthma Health Equity*



“I recently completed my MD, and because of this grant, I am able to do a completely independent research study. I’ve also been recently short-listed for a clinical lecturer post at my

“As I would meet with people to discuss my project, they would see that a big organization is supporting me, and that is the outside validation to show that this must be a useful project. The grant really helps me hit the ground running, and plants the seed to help us do a larger project...” said Drew Harris, MD.

university...which positions me to be the lead for quantitative imaging should I receive the post. This grant added gravitas to my project, and, without it, I don’t think I would have had as big of a boost.”

Diana Crossley, MBChB

University Hospital Birmingham – Birmingham, England
CHEST Foundation and the Alpha-1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency
Title: *Functional Magnetic Resonance Lung Imaging Using Inhaled Hyperpolarised 129Xenon: A Pilot Study of the Clinical Utility in Alpha One Antitrypsin Deficiency (AATD).*



DR. SILVERMAN

“Because of this grant, we are able to be effective teachers to Haitian pediatricians, so they can more effectively intervene and save childrens’ lives. We are able to translate these critical care materials into French and provide the best opportunity for learning to our colleagues there.”

Adam Silverman, MD

Connecticut Children’s Medical Center – Hartford, Connecticut

CHEST Foundation Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP

Title: *Haitian Pediatric Critical Care Collaborative Training Course*

The CHEST Foundation is accepting grant applications now until March 31 in the following areas:

- CHEST Foundation Research Grant in Lung Cancer – \$50,000 - \$100,000 2-year grant*
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- CHEST Foundation and the Alpha-1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency – \$25,000 1-year grant
- CHEST Foundation Research Grant in Pulmonary Fibrosis – \$50,000 1-year grant
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- CHEST Foundation Research Grant in Women’s Lung Health – \$10,000 1-year grant
- CHEST Foundation Research Grant in Cystic Fibrosis – \$15,000 – \$30,000 1-year grant
- CHEST Foundation Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP – \$2,500- \$15,000 1-year grant

*Amount contingent on funding.

Go to chestfoundation.org/grants to apply now.

Meet Our CHEST President-Designate

Stephanie M. Levine, MD, FCCP, is an expert in lung transplantation, pulmonary and critical care issues in pregnancy and women’s lung health, and eosinophilic lung disorders. She is a Professor of Medicine in the Division of Pulmonary Diseases and Critical Care Medicine at the University of Texas Health Science Center in San Antonio, Texas; the Program Director of the Pulmonary and Critical Care Fellowship at the University of Texas Health Science Center; and the Director of the Medical Intensive

Care Unit and Bronchoscopy Laboratory at the University Hospital. She also is a staff physician at the Audie Murphy Veteran Administration Hospital. Dr. Levine has authored or co-authored over 270 manuscripts, chapters, reviews, editorials, and abstracts, primarily in her major field of interest, lung transplantation. She has been Editor of both Critical Care SEEK and Pulmonary SEEK. In 2009, she received the CHEST Presidential Citation Award; in 2010, the CHEST Distinguished Service Award; and in

2017, the Master Clinician Educator Award. Dr. Levine has been active in CHEST international activities with CHEST World Congress meetings, the 2017 Basel Joint CHEST/SPG Congress in collaboration with the Swiss Lung Association, and with the pulmonary/critical care subspecialty training programs being developed in China. She was President and Chair of the CHEST Foundation from 2010-2014 and is currently on the CHEST Board of Regents. Dr. Levine’s presidential term will begin in October 2019.



DR. LEVINE

Critical Care Commentary

On Diagnosing Sepsis

BY STEVEN Q. SIMPSON, MD, FCCP

Two years ago, a panel appointed by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, referred to as a consensus conference, proposed a new definition for sepsis and new diagnostic criteria for sepsis and septic shock, known as Sepsis-3 (Singer M, et al. *JAMA*. 2016;315[8]:801). The panel proposed that sepsis be defined as life-threatening organ dysfunction due to a dysregulated host response to infection. Upon reflection, one could see that what we had called definitions of sepsis, severe sepsis, and septic shock for over 2 decades actually represented diagnostic criteria more than concise definitions. In that regard, a concise definition is a useful addition in the tool kit for training all health-care professionals to recognize sepsis and to treat it early and aggressively.

However, the diagnostic criteria leave something to be desired, in terms of both practicality and sensitivity for detecting patients whose infection has made them seriously ill. Those who participate in quality improvement efforts in their own hospitals will recognize that to promote change and to achieve a goal of better, higher quality care, it is important to remove obstacles in the system and to structure it so that doing the right thing is easier than not doing it. For sepsis, the first step in the process, recognizing that sepsis is present, has always been complex enough that it has been the bane of the enterprise. As many as two-thirds of patients with sepsis presenting to the ED with severe sepsis never receive that diagnosis while in the hospital. (Deis AS, et al. *Chest*. 2018;153[1]:39). As any sepsis core measure coordinator can attest, diagnostic criteria that are readily visible on retrospective examination are often unnoticed or misinterpreted in real time.

The crux of this issue is that the very entity of sepsis is not a definite thing but a not-quite-focused idea. Much is known of pathophysiologic features that seem to be important, but there is no one unifying pathologic condition. Contrast that with another critical illness, myocardial infarction. The very name states the unifying pathology. Our predecessors were able to work backward from an understanding that acute blockage of a small artery led to ischemia and infarction, in order to identify methods to detect it while it is happening—measuring enzymes and evaluating an ECG. For sepsis, we don't even understand why patients are sick or why they die. There is a complex interaction of inflammation, microcirculatory thrombosis, mitochondrial dysfunction, immune suppression, but there is no one combination of those things that is yet understood in a way that lends itself to diagnostic testing. The best we can say is that the patient

reacted to their infection in a way that was detrimental to their own body's functioning. Rather than recognizing a few symptoms and sending a confirmatory test, with sepsis, we must tote up the signs and symptoms in the domains of recognizing infection and recognizing organ dysfunction, then determine whether they are present in sufficient amounts; it is an exercise that requires mental discipline.

If the diagnostic criteria we use, whether Sepsis-1, 2, or 3, are all gross descriptions of complex internal interactions that are not specific, then the syndrome that any of these criteria identifies is also not specific for anything particular. It falls to the medical community, as a whole, to determine exactly what it is that we desire a given syndrome to be indicative of. The Sepsis-3 authors

decided that the appropriate syndrome should predict death or prolonged ICU stay. They used several large data sets to develop and validate infection-associated variables that would have good predictive ability for that outcome, and they compared what they found with sepsis by the Sepsis-1 definition, infection plus SIRS (Seymour C, et al. *JAMA*. 2016;315[8]:762). Infection + SIRS is a strawman in this com-

parison, because they tested its predictive ability for the outcome against that of the Sequential Organ Failure Assessment (SOFA) and the Logistic Organ Dysfunction Score (LODS). These two scoring systems were developed as severity of injury scales and validated as mortality predictors; the higher the score, the likelier mortality, whereas SIRS clearly contains no information about organ dysfunction. The comparator of interest for this outcome is actually severe sepsis, infection plus SIRS plus organ dysfunction.

Although the criteria the Sepsis-3 investigators used for defining patients with suspected infection were novel and reasonable, we lack additional important information about the patients they studied. They did not report the spectrum of treatments for sepsis in their cohort, whether early or late, adequate or inadequate, so it is impossible to determine whether the criteria address patients who are undertreated, patients who are treated late, patients who will die regardless of adequate therapy, or some combination. In other words, there is no way to tell whether patients who were recognized early in their course via Sepsis-1 criteria and treated aggressively and effectively may have avoided shock, ICU admission, and death. It is, of course, the business of physicians and nurses to help patients avoid exactly those things. Multiple studies have now demonstrated that SIRS criteria are more sensitive than SOFA-based screens, specifically qSOFA, for identifying infection with organ dysfunction, and that qSOFA is more specific for mortality (Serafim, et al. *Chest*. 2017; <http://dx.doi.org/10.1016/j.chest.2017.12.015>).



Dr. Simpson is Professor, Interim Director; Division of Pulmonary and Critical Care Medicine, University of Kansas, Kansas City, Kansas.

In contrast, the Sepsis-1 authors proposed infection plus SIRS as a sensitive screening tool that could warn of the possibility of an associated organ dysfunction (Sprung, et al. *Crit Care Med*. 2017;45[9]:1564). Previous to the Sepsis-1 conference, Bone and colleagues had defined the sepsis syndrome, which incorporated both SIRS and organ dysfunction (Bone, et al. *Crit Care Med*. 1989;17[5]:389). It was the collective insight of the Sepsis-1 participants to recognize that SIRS induced by infection could be a harbinger of organ failure. The Sepsis-3 authors believe that SIRS is a “normal and adaptive” part of infection and that it is “not useful” in the diagnosis of sepsis. That analysis neglects a couple of important things about SIRS. First, numerous studies demonstrate that infection with SIRS is associated with a mortality rate of 7% to 9%, which is by no means trivial (Rangel-Frausto MS, et al. *JAMA*. 1995;273[2]:117). Second, the components of SIRS have been recognized as representative of serious illness for millennia; the assertion that the Sepsis-1 definitions are not evidence-based is mistaken and discounts the collective experience of the medical profession.

Finally, SIRS is criticized on the basis of being nonspecific. “If I climb a flight of stairs, I get SIRS.” This is clearly a true statement. In fact, one could propose that the name could more accurately be Systemic Stress Response Syndrome, though “scissors” is certainly less catchy than “sirs” when one says it aloud. However, the critique neglects an important concept, encapsulated in Bayes' Theorem. The value of any positive test result is largely dependent on the prevalence of the disease being tested for in the population being tested. It is unlikely that the prevalence of sepsis is very high among patients whose SIRS is induced by climbing a flight of stairs. On the other hand, tachycardia and tachypnea in a patient who is indulging in no activity while lying on a bed feeling miserable should prompt a search for both the infection that could be causing it and the organ dysfunction that could be associated with it. The specificity of SIRS derives from the population in which it is witnessed, and its sensitivity is to be respected.

To quote a friend, the remarkable CEO of a small Kansas hospital, “If a patient with an infection feels bad enough that they climb up on that gurney and place themselves at our mercy, we

Continued on following page

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owe it to them to prove why they don't have sepsis, rather than why they do."

Editor's Comment

The progress made in the last several years emphasizes the importance of early identification and aggressive treatment of sepsis. The

Third International Consensus Definitions (Sepsis-3) have sparked great controversy in the sepsis community, because they delay the recognition of sepsis until organ damage occurs. In this Critical Care Commentary, Dr. Steven Q. Simpson asserts with solid argu-

ments that the use of a screening tool with higher specificity for mortality, at the expense of sensitivity, is not a step in the right direction. Moving away from criteria that have been widely adopted in clinical trials and quality improvement initiatives throughout the

world can be a setback in the battle to improve sepsis outcomes. Until prospectively validated criteria that allow earlier identification of sepsis are developed, there is no compelling reason for change.

Angel Coz, MD, FCCP
Section Editor

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Adult bronchiectasis, asthma therapy, frailty in ILD

Clinical Research

New guidelines for adult bronchiectasis

Clinically significant bronchiectasis is a combination of

radiologic bronchial dilatation with clinical symptoms. Guidelines on management of adult bronchiectasis were recently published (*Eur Respir J.* 2017; Sep 10;50[3]).

For all adult patients with clinically significant bronchiectasis, the guidelines suggest standardized minimum testing with differential blood count, serum immunoglobulins, and testing for allergic bronchopulmonary aspergillosis with any further workup on an individual basis. Annual sputum surveillance is suggested for clinically stable adult patients; however, the evidence for this recommendation came from studies done on patients with cystic fibrosis.

Inhaled bronchodilators are suggested as the first-line treatment in symptomatic patients. Long-term antibiotics (greater than 3 months) are recommended in patients with greater than 3 exacerbations/year after optimizing airway clearance and disease-specific treatment.

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In Memoriam

CHEST has been informed of the following members' deaths. We extend our sincere condolences.

Nagesh V Salian, MD, FCCP (2016)
Ted A Calinog, MD, FCCP (2017)
Azam Ansari, MD (2017)
Arthur E. Schmidt, MD, FCCP (2017)

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Pseudomonas aeruginosa infections are to be treated with inhaled antibiotics (colistin or gentamicin) (Charles SH, et al. *Am J Respir Crit Care Med*. 2014;189[8]:975; Murray P, et al. *Am J Respir Crit Care Med*. 2011;183[4]:491; and nonpseudomonal infections are to be treated with macrolides (Conroy W, et al. *Lancet*. 2012;380[9842]:660; Altenburg J, et al. *JAMA*. 2013;309[12]:1251), although interchangeable for intolerance. Sputum cultured early will guide therapy among poor responders. Long-term mucolytic agents are suggested in appropriate tolerating patients. Pulmonary rehabilitation for 6-8 weeks is strongly recommended in adult bronchiectasis with impaired exercise capacity. Surgical interventions for bronchiectasis are reserved for a small group of patients who have localized disease and high exacerbation rates despite maximal medical therapy. Inhaled corticosteroids are suggested not to be used in adult bronchiectasis. Guidelines recommend against the use of statins

and recombinant human DNase as it increases exacerbations (*Chest*. 1998;113[5]:1329. The task force acknowledged the low quality of evidence for their recommendations requiring more research in the field of adult bronchiectasis.

Bharat Bajantri, MD
Fellow-in-Training
Member



DR. BAJANTRI

Airways Disorders ICS/LABA combo therapy: black box

warning removed

Publication of the Salmeterol Multicenter Asthma Research Trial (SMART) in 2006 caused panic among asthmatics and the physicians who treat them (Nelson et al. *Chest*. 2006;129[1]:15). The study suggested that the long-acting beta-2-agonist (LABA) salmeterol leads to an increased risk of asthma/respiratory-related deaths compared with placebo. This finding was more pronounced in the African American subpopulation. The study left many questions unanswered, including whether or not this risk is present when

LABA therapy is combined with inhaled corticosteroids (ICS) (O'Byrne. *Chest*. 2006;129[1]:3). Subsequent meta-analyses con-

*Now that tiotropium is included
in the 2017 GINA guidelines,
it's only a matter of time
before we're debating whether
LABA/long-acting muscarinic
antagonist is safe for asthmatics.*

firmed the increased risk with LABA monotherapy but not with LABA/ICS (Salpeter et al. *Ann Intern Med*. 2006;144[12]: 904; Jaeschke et al. *Am J Respir Crit Care Med*. 2008;178[10]:1009). Still, a black box warning relating LABA to asthma-related death was applied to LABA/ICS products.

In 2011, the Food and Drug Administration (FDA) mandated large, randomized controlled trials be performed for LABA/ICS products to assess safety. These trials were recently completed, showing no difference in asthma-related deaths between LABA/ICS and ICS alone. There were 41, 297 patients across four trials, three included

teenagers and adults (age ≥ 12) and one enrolled children (ages 4-11). These studies prompted the FDA to remove the black box warning from salmeterol/fluticasone, formoterol/budesonide, and formoterol/mometasone (<https://www.fda.gov/downloads/Drugs/DrugSafety/UCM589997.pdf>).

Conclusion: Because LABA/ICS therapy is effective for asthma, most pulmonologists continue to prescribe it despite the SMART study results and FDA warning. In a practical sense, we don't expect the FDA findings to radically change asthma care. Still, it seems we can finally put this question to rest – LABA/ICS is indeed safe for asthmatics. Most physicians will continue to avoid LABA monotherapy, and now that tiotropium is included in the 2017 GINA guidelines, it's only matter of time before we're debating whether LABA/long-acting muscarinic antagonist (LAMA) is safe for asthmatics.

Aaron Holley, MD, FCCP
Steering Committee Member

Navitha Ramesh, MD, MBBS
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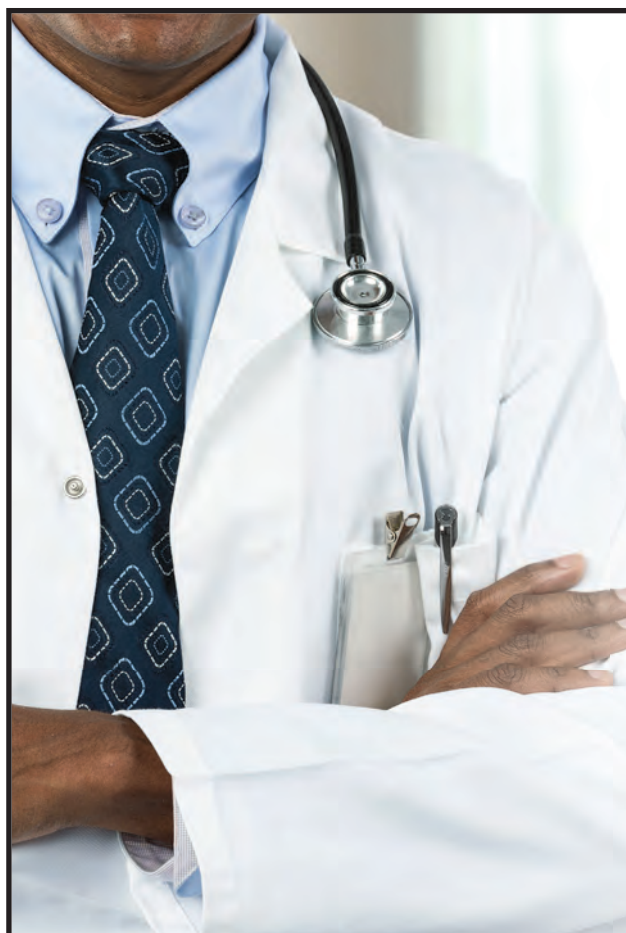
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Critical Care**Standardized handoffs in the ICU: room for improvement?**

Transitions in patient care are commonplace in the ICU. But handoffs are particularly susceptible to error given the complexity of the patient population. Impacts of less-than-ideal handoffs likely include adverse events, delays in medical diagnosis and treatment, redundant communications, redundant activities such as additional procedures and tests, lower provider and patient satisfaction, higher costs, longer hospital stays, more hospital admissions, and less effective training for health-care providers. Yet, there is great heterogeneity in handoff practiced, and the impact of standardized handoffs in the ICU is unclear (Cochran A. *JAMA Surg.* 2018 Jan 3. doi: 10.1001/jamasurg.2017.5468. [Epub ahead of print]).

In a survey of over 600 academic intensivists, 55% of the participants stated that attending handoffs in the ICU should be standardized, yet, only 13% of those participating in handoffs reported using a standardized process (Lane-Fall M. *Crit Care Med.* 2016;44[4]:690). Clinician miscommunication contributes to an estimated 250,000 deaths in US hospitals per year (Makary M. *BMJ.* 2016 May 3;353:i2139. doi: 10.1136/bmj.i2139). Standardized handoffs may improve outcomes in the ICU.

In many ICUs that do use standardized sign-out templates, higher clinician satisfaction and fewer unexpected patient events have been reported (Bavare AC. *J Healthc Qual.* 2015;37[5]:267; Nanchal R. *BMJ Qual Saf.* 2017;26[12]:987). In a recent randomized controlled trial, use of a standardized handoff curriculum in the ICU resulted in a significant 3% decrease in communication errors, without any change in the duration of the handoff. There also was a clinician-reported improvement in team communication and patient safety; but no changes in ICU length of stay, duration of mechanical ventilation, or number of re-intubations were noted (*JAMA Surg.* 2018 Jan 3. doi: 10.1001/jamasurg.2017.5440. [Epub ahead of print]).

Unfortunately, despite interest in improving patient handoffs, there are few tools to evaluate the

effectiveness of different hand-off strategies. Most studies report clinician perceptions rather than patient-centered outcomes. Further research is required to examine the optimal approach to handover communication. However, based on the available evidence, a standardized approach to handoffs is likely better than a nonstandardized format.

Shruti Gadre, MD
Fellow-in-Training
Member

Christopher Carroll,
MD, FCCP
Vice-Chair



DR. GADRE

Home-Based Mechanical Ventilation and Neuromuscular Disease Update on two recent FDA-approved therapies for ALS and SMA

Amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) are neuromuscular diseases often deteriorating to progressive respiratory failure. Two medications received recent FDA approval and are now available in clinical practice – edaravone for ALS and nusinersen for SMA. We present a balanced overview of the favorable data along with realistic challenges.

Edaravone (Radicava) is the second FDA-approved medication for management of ALS (Riluzole was approved over 20 years ago). Edaravone is a free radical scavenger that reduces oxidative stress, resulting in a protective effect on neuronal cells. It originally showed promise in acute ischemic stroke in Japan and was subsequently studied for ALS. A phase 3 randomized, double-blind placebo-controlled study performed in Japan (*Lancet Neurol.* 2017;16[7]:505) compared ALSFRS-R scores of a specific subset of ALS patients receiving edaravone vs placebo. This study revealed that patients with early ALS (2 years duration or less) with rapid progression (ALSFRS-R score of 7.5 in 6 months) had a 33% decrease in their degree of progression (reducing their ALSFRS-R score to 5) in the edaravone group. Of note, there was also slowing in the decline of FVC, though not clinically significant. Although the drug was rapidly

approved by the FDA, there are obvious challenges that must be recognized. First, it is unclear if patients will discern such a mild degree of slowing of disease progression. In addition, the annual cost may be prohibitive, and lifelong IV administration of the medication for 10 days every month may pose logistical barriers.

Nusinersen (Spinraza) is the first FDA-approved therapeutic medication for spinal muscular atrophy (SMA). SMA is a hereditary neuromuscular disorder leading to degeneration of motor neuron cells and ultimately diffuse muscle weakness and often respiratory failure. Nusinersen is an antisense oligonucleotide that modifies splicing of the SMN-2 gene to increase production of normal, full-length SMN protein, which is deficient in SMA. The ENDEAR trial (Finkel RS, et al. *N Engl J Med.* 2017;377[18]:1723) was a phase 3, multicenter, double-blind study that enrolled SMA infants to receive nusinersen vs sham. Infants who received treatment had improvements in motor milestones (41% vs 0%) and less permanent-assisted ventilation or death in the nusinersen group (39% vs 68%), a 47% reduction in risk of death. The therapy is safe and

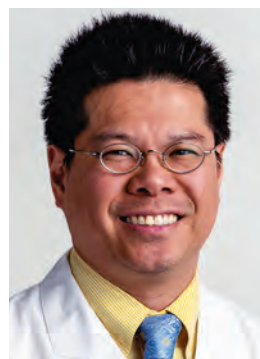
tolerable, although there is reported risk of bleeding abnormalities, renal toxicity, and constipation. Administered intrathecally, there is a series of four loading doses, followed by maintenance doses every 4 months – presumably lifelong. Although FDA approved all three SMA subtypes, the eventual impact is uncertain, especially in cases of advanced

muscle weakness. There are realistic challenges: the high cost (\$125,000/dose), limited longitudinal evidence, technical administration, and limited access.

Pulmonologists should be aware of both medications as new therapeutic options for ALS and SMA; however, the long-term impact is yet to be determined.

Ashraf Elsayegh, MD, FCCP
Steering Committee Member

Won Y. Lee, MD
Steering Committee Member



DR. LEE

Interstitial and Diffuse Lung Disease Frailty as a measure of disease activity in ILD

Frailty is a systemic geriatric syndrome characterized by age-related

accumulation of physiologic deficits across several systems with an attenuated response to biological stress. Considering that interstitial lung disease (ILD), particularly, idiopathic pulmonary fibrosis (IPF), is a disease of the aging population, frailty is an emerging area of clinical interest. The biological pathways driving the association of frailty with worse prognosis are complex but hinge on cellular senescence, systemic inflammation, and sarcopenia.

There is a high prevalence of frailty in adults with chronic lung diseases and is associated with worse prognosis. The current literature, though, is mostly derived from patients with COPD. Frailty

Frailty is an emerging area of clinical interest. The biological pathways driving the association of frailty with worse prognosis are complex but hinge on cellular senescence, systemic inflammation, and sarcopenia.

measured using the 42-item patient-reported frailty index is associated with dyspnea severity in patients with fibrotic ILD (Milne et al. *Respirology.* 2017;22[4]:728) and systemic sclerosis-associated ILD (Guler et al. *Respir Med.* 2017 Aug;129:1-7. doi: 10.1016/j.rmed.2017.05.012. Epub 2017 May 25.). The SHARE-Frailty and the Edmonton Frail Scale instruments utilized to measure frailty in the University of Alabama at Birmingham IPF cohort detected a high-percentage of frail and pre-frail patients (Luckhardt et al. *Am J Respir Crit Care Med.* 2017;195:A7012). However, there are differences in targeted domains between the various frailty instruments, and this could affect the identification of the frailty syndrome in patients.

Frailty as a measure of disease activity and progression is not currently employed in clinical trials for ILD, primarily due to lack of standardized tools for this patient population. Future studies designed to utilize the frailty syndrome as outcome measures may further our understanding of the clinical manifestations and underlying mechanisms, as well as identify potential therapeutic interventions for patients with ILD.

Tejaswini Kulkarni MD, MPH
Fellow-in-Training Member



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² Piazza, G., et al., A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: the Seattle II study." *Journal of the American College of Cardiology: Cardiovascular Interventions* 2015; 8: 1382-92.

³ Tapson, et al, "Optimum Duration and Dose of r-tPA with the Acoustic Pulse Thrombolysis Procedure for Submassive Pulmonary Embolism: OPTALYSE PE," American Thoracic Society (ATS) Meeting, Washington, DC, May 2017.

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