Survey participants given a voice in MOC exam content

Responses could improve exam quality.

BY MICHAEL E. NELSON, MD, FCCP, AND THE ABIM PULMONARY MEDICINE BOARD

The American Board of Internal Medicine (ABIM) has emailed diplomates a survey regarding the blueprint for the Maintenance of Certification (MOC) pulmonary exam.

This survey relates to the content of the exam, as opposed to a prior survey that asked diplomates for their opinion about new proposals for 2- and 5-year cycles for the exam. Participating in the survey gives diplomates a voice in determining the content of the MOC exam for pulmonary medicine. If enough individuals participate in the survey and the data support changing the distribution of exam content, it is very likely that ABIM will make improvements to the MOC exam.

The figure on page 24 illustrates the information provided by diplomates that ABIM used to help them decide the exam content for the Hospital Medicine exam. ABIM has heard from practicing physicians and the specialty societies about the need to change MOC exam content.

The American Board of Internal Medicine (ABIM) has emailed diplomates a survey regarding the blueprint for the Maintenance of Certification (MOC) pulmonary exam.

The American Board of Internal Medicine (ABIM) has emailed diplomates a survey regarding the blueprint for the Maintenance of Certification (MOC) pulmonary exam.

The concept behind the PERT is to rapidly mobilize a team with varied expertise helpful for treating patients with pulmonary embolisms (PEs). While the PERT can be activated by any (clinician) for any patient, even low-risk patients ... those with submassive and massive PEs [intermediate- and high-risk patients] are the target patients, said Dr. Mahar of the Cleveland Clinic.

The first PERT was created at Massachusetts General Hospital in Boston in 2012, according to the National

New mechanical ventilation protocols

BY DOUG BRUNK

LOS ANGELES – Acutely hospitalized patients who have been on mechanical ventilation for more than 24 hours, are at high risk for extubation failure, and have passed a spontaneous breathing trial should be extubated to noninvasive ventilation.

The recommendation comes from new clinical practice guidelines from the American College of Chest Physicians and the American Thoracic Society. Moderate-quality evidence suggests that early extubation and a switch to noninvasive ventilation reduces ventilator- and ICU-related complications, including infections and injury to the lungs and other organs. Extubation also cuts costs by reducing ICU stays.

Conditional recommendations are to use inspiratory pressure augmentation during the initial spontaneous breathing trial and to employ protocols to mini...
HELP PRESERVE
MORE LUNG FUNCTION
Reduce lung function
decline with Esbriet™

Indication
Esbriet® (pirfenidone) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

Select Important Safety Information

- Elevated liver enzymes: Increases in ALT and AST >3× ULN have been reported in patients treated with Esbriet. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet had a higher incidence of elevations in ALT or AST than placebo patients (3.7% vs 0.8%, respectively). No cases of liver transplant or death due to liver failure that were related to Esbriet have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiating Esbriet, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary.

- Esbriet delayed progression of IPF vs placebo through a sustained impact on lung function decline in ASCEND2,3
- No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 0062,4
- Safety and efficacy were evaluated in three phase 3, double-blind, placebo-controlled, multicenter trials in 1247 patients randomized to receive Esbriet (n=623) or placebo (n=624)2

- The recommended daily dosage is 3 capsules, 3 times a day (2403 mg/day) with food, titrated to full dosage over a 14-day period2
- Flexible dosing for appropriate modification to help manage potential adverse reactions (patients may require dose reduction, interruption, or discontinuation)2—eg, elevated liver enzymes, gastrointestinal events, and photosensitivity reactions or rash
- Esbriet Access Solutions offers a full range of access and reimbursement support for your patients and practice
- The Esbriet Inspiration ProgramTM motivates patients to stay on treatment with information and encouragement
- Clinical Coordinators are available to provide education to patients with IPF through in-office programs

- Esbriet has been approved outside the US since 20111
- More than 27,000 patients have taken pirfenidone worldwide1

DEMORSTRATED EFFICACY*

- Esbriet had a significant impact on lung function vs placebo in ASCEND2,3
  —48% relative reduction in risk of a meaningful decline in lung function (≥10% decline in %FVC) at 52 weeks for patients on Esbriet vs placebo (17% vs 32%; 15% absolute difference; P<0.001)
  —2.3x as many patients on Esbriet maintained their baseline function at 52 weeks vs placebo (23% vs 10% of patients; 13% absolute difference; P<0.001)
- Esbriet delayed progression of IPF vs placebo through a sustained impact on lung function decline in ASCEND2,3
- No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 0062,4
- Safety and efficacy were evaluated in three phase 3, double-blind, placebo-controlled, multicenter trials in 1247 patients randomized to receive Esbriet (n=623) or placebo (n=624)2
- ATS=American Thoracic Society; ERS=European Respiratory Society; JRS=Japanese Respiratory Society; LAT=Latin American Thoracic Association; %FVC=percent predicted forced vital capacity.

*The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials. In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had %FVC between 50%-90% and %DLco (percent predicted diffusing capacity of lung for carbon monoxide) between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and %DLco ≥35%. The primary endpoint was change in %FVC from baseline to week 72.

†Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences.

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Photosensitivity reaction or rash: Patients treated with Esbriet had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). Patients should avoid or minimize exposure to sunlight (including sunlamps), use a sunblock (SPF 50 or higher), and wear clothing that protects against sun exposure. Patients should avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

Gastrointestinal disorders: Gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported in patients treated with Esbriet. Dosage reduction or interruption for gastrointestinal events was required in 18.6% of patients in the Esbriet 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary in some cases.

Adverse reactions: The most common adverse reactions (≥10%) were nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastroesophageal reflux disease, sinusitis, insomnia, weight decreased, and arthralgia.

Drug interactions: Concomitant administration with strong inhibitors of CYP1A2 (eg, fluvoxamine) significantly increases systemic exposure of Esbriet and is not recommended. Discontinue prior to administration of Esbriet. If strong CYP1A2 inhibitors cannot be avoided, dosage reductions of Esbriet are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet as needed.

Concomitant administration of Esbriet and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to Esbriet. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended. Monitor patients closely when ciprofloxacin is used.

Agents that are moderate or strong inhibitors of both CYP1A2 and CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment.

The concomitant use of a CYP1A2 inducer may decrease the exposure of Esbriet, and may lead to loss of efficacy. Concomitant use of strong CYP1A2 inducers should be avoided.

Specific populations: Esbriet should be used with caution in patients with mild to moderate (Child-Pugh Class A and B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with severe hepatic impairment. Esbriet is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment.

Esbriet should be used with caution in patients with mild (CLcr 50-80 mL/min), moderate (CLcr 30-50 mL/min), or severe (CLcr less than 30 mL/min) renal impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with end-stage renal disease requiring dialysis. Use of Esbriet in patients with end-stage renal disease requiring dialysis is not recommended.

Smoking causes decreased exposure to Esbriet, which may alter the efficacy profile of Esbriet. Instruct patients to stop smoking prior to treatment with Esbriet and to avoid smoking when using Esbriet.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see Brief Summary of Prescribing Information on adjacent pages for additional Important Safety Information.

Team review expedites decisions

CONSORTIUM OF PULMONARY EMBOLISM RESPONSE TEAM’s website.

As of May 2015, the PERT model has been adopted by physicians and health care professionals from more than 40 institutions.

Dr. Mahar reported that the Cleveland Clinic’s PERT is activated through a single pager that resides with a vascular medicine fellow during the day and a critical care fellow at night. When paged, the fellow promptly evaluates the patient and ensures a complete basic work-up, which includes an ECG, cardiac enzymes, N-terminal pro B-type natriuretic peptide, lower-extremity deep vein thrombosis scans, transthoracic echocardiogram, and confirmatory CT/PE protocol or ventilation/perfusion scan.

Based on the simplified Pulmonary Embolism Severity Index and Bova scores, the patient is risk stratified and the patient’s indications, and relative and absolute contraindications to advanced therapies are reviewed. The fellow next sends a

<table>
<thead>
<tr>
<th>BRIEF SUMMARY</th>
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</thead>
<tbody>
<tr>
<td>The following is a brief summary of the full Prescribing Information for ESBRIET® (pirfenidone). Please review the full Prescribing Information prior to prescribing ESBRIET.</td>
</tr>
</tbody>
</table>

1 INDICATIONS AND USAGE

ESBRIET is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Elevated Liver Enzymes

Increases in ALT and AST >3 × ULN have been reported in patients treated with ESBRIET. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with ESBRIET 2403 mg/day in the three Phase 3 trials had a higher incidence of elevations in ALT or AST >3 × ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations >10 × ULN in ALT or AST occurred in 0.3% of patients in the ESBRIET 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST >3 × ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to ESBRIET have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury, that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with ESBRIET in all patients, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary for liver enzyme elevations. [see Dosage and Administration sections 2.1 and 2.3 in full Prescribing Information]

5.2 Photosensitivity Reaction or Rash

Patients treated with ESBRIET 2403 mg/day in the three Phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (3%). The most common (>1%) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction. Photosensitivity reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction. The most common adverse reactions with an incidence of ≥10% and more frequent in the ESBRIET than placebo treatment group are listed in Table 2.

Table 2. Adverse Reactions Occurring in ≥10% of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ESBRIET 2403 mg/day (N = 623)</th>
<th>Placebo (N = 624)</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>18%</td>
<td>16%</td>
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<tr>
<td>Rash</td>
<td>30%</td>
<td>10%</td>
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<tr>
<td>Abdominal Pain1</td>
<td>24%</td>
<td>15%</td>
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<tr>
<td>Upper Respiratory Tract Infection</td>
<td>27%</td>
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<td>Diarrhea</td>
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<tr>
<td>Fatigue</td>
<td>26%</td>
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<td>Headache</td>
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<td>Dyspepsia</td>
<td>19%</td>
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<td>Dizziness</td>
<td>18%</td>
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<td>Vomiting</td>
<td>13%</td>
<td>6%</td>
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<td>Anorexia</td>
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<td>5%</td>
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<tr>
<td>Gastro-esophageal Reflux Disease</td>
<td>11%</td>
<td>7%</td>
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<tr>
<td>Sinusitis</td>
<td>11%</td>
<td>10%</td>
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<tr>
<td>Inflammation</td>
<td>10%</td>
<td>7%</td>
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<tr>
<td>Weight Decreased</td>
<td>10%</td>
<td>5%</td>
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<tr>
<td>Arthralgia</td>
<td>10%</td>
<td>7%</td>
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1 Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.

Adverse reactions occurring in ≥5% to <10% of ESBRIET-treated patients and more commonly than placebo are photosensitivity reaction (9% vs. 1%), decreased appetite (8% vs. 3%), pruritus (8% vs. 5%), asthenia (9% vs. 4%), dysgeusia (8% vs. 2%), and non-cardiac chest pain (5% vs. 4%).

6.2 Postmarketing Experience

In addition to adverse reactions identified from clinical trials, the following adverse reactions have been identified during postapproval use of pirfenidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Blood and Lymphatic System Disorders

Agranulocytosis

Immune System Disorders

Angioedema

Hepatobiliary Disorders

Bilirubin increased in combination with increases of ALT and AST

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of pirfenidone has been evaluated in more than 1400 subjects with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials. ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials (Studies 1, 2, and 3) in which a total of 623 patients received 2403 mg/day of ESBRIET and 624 patients received placebo. Subjects ages ranged from 40 to 85 years (mean age of 67 years). Most patients were male (78%) and Caucasian (95%). The mean duration of exposure to ESBRIET was 62 weeks (range: 2 to 118 weeks) in these 3 trials.

At the recommended dosage of 2403 mg/day, 14.6% of patients on ESBRIET compared to 9.6% on placebo permanently discontinued treatment because of an adverse event. The most common (>1%) adverse reactions leading to discontinuation were rash and nausea. The most common (>3%) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

The most common adverse reactions with an incidence of ≥10% and more frequent in the ESBRIET than placebo treatment group are listed in Table 2.

Adverse reactions occurring in ≥10% of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

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<tr>
<td>Abdominal Pain</td>
<td>12%</td>
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group notification to the PERT via email and text message. The team then convenes online for a virtual meeting and case presentation that includes sharing of lab and test results and images.

The process sounds complex, but the surgeon, interventional radiologist, vascular medicine specialist, and cardiologist are on call and simultaneously get the message and respond, Dr. Mahar said. With a team approach, the decision to use advanced therapies – systemic lytics, surgery, catheter-directed lysis and extracorporeal membrane oxygenation – is expedited. For example, over the last 2 years, four out of five patients who underwent surgical embolectomies had good outcomes without any deaths," he said.

Based on a retrospective chart review from October 2014 through August 2016, Cleveland Clinic’s PERT had been activated for 134 patients, 112 of whom were found to have PEs, Dr. Mahar said during his presentation at the annual meeting of the American College of Chest Physicians (CHEST).

The number of low risk, submassive, and massive PEs were 14 (12%), 76 (68%), and 22 (20%), respectively. Just over half of the PE patients, 55% (60 patients), were treated with anticoagulation therapy alone. Inferior vena cava filters were placed in 32 patients (29%); 14 patients received catheter-directed thrombolysis, 3 received a suction thrombectomy, and 4 received a surgical embolectomy.

Patients with submassive and massive PEs are the targets, Dr. Mahar said.

The 30-day all-cause mortality rate was 9%; the deaths occurred in six patients who had massive PEs, three patients with submassive PEs, and one patient with a low-risk PE. Six of the patients who died had been treated with anticoagulation, two had received catheter-directed thrombolysis, and one had received a full dose of systemic thrombolysis.

Bleeding complications occurred in 10 patients, 6 of whom were treated with anticoagulation alone and 4 of whom underwent catheter-directed thrombolysis.

Cleveland Clinic is a large entity with multiple resources, but the principles of PERT can be applied in smaller facilities, as well, according to Gustavo A. Heresi-Davila, MD, medical director of the Cleveland Clinic’s pulmonary thromboendarterectomy program and the lead researcher for the PERT project at the clinic. “I would emphasize the notion that a PERT has to be multidisciplinary, as people with different backgrounds and expertise bring complementary talent to the discussion.”
NIV failure not reduced with He/O₂ in COPD patients

Inhaling He/O₂ did not result in a lower NIV failure rate than inhaling Air/O₂ in COPD patients requiring noninvasive ventilation, in a randomized, controlled study.

In the study, known as the E.C.H.O. ICU trial, patients either received He/O₂ (a 78%/22% mixture blended with 100% O₂) or a conventional Air/O₂ mixture for up to 72 hours, during both noninvasive ventilation (NIV) and spontaneous breathing.

Previous research had demonstrated that during hypercapnic COPD exacerbations, the He/O₂ mixture reduces airway resistance, partial pressure of carbon dioxide in arterial blood (PaCO₂), intrinsic positive end-expiratory pressure, and work of breathing during both spontaneous breathing and NIV, compared with Air/O₂, said Philippe Jolliet, MD, and his colleagues.

Correction

On page 26 of the November issue of CHEST Physician, the headline was incorrect. The headline should have read “Surgical lung biopsies are unnecessary for most ILDs.”

The two treatment groups in the E.C.H.O. ICU trial had similar NIV failure rates – defined as endotracheal intubation or death without intubation. The rates were 14.7% for the patients who received He/O₂ and 14.5% for the patients who received Air/O₂. The NIV failures for 31 of the patients in the He/O₂ group resulted in intubation; the remaining two patients who were classified as having NIV failure died. All 32 of the patients in the Air/O₂ group who had NIV failures were intubated.

The length of ICU stay was also comparable between the two groups. In the subgroups of patients with severe acidosis (having a pH of less than 7.30) from both the He/O₂ and Air/O₂ groups, the NIV failure rates were again nearly identical (AJRCCM. 2016 Oct 13; doi: 10.1164/rccm.201601-0038OC).

The average times to NIV failure were 93 hours in the He/O₂ group (N = 33) and 52 hours in the Air/O₂ group (N = 32, P = .12). The He/O₂ group achieved a significantly quicker improvement in respiratory acidosis, encephalopathy score, and respiratory rate. Patients intubated following an NIV failure who had received He/O₂ had a shorter ventilation duration and a shorter ICU stay than those intubated following an NIV failure who had received Air/O₂.

Continued from previous page

Small hospitals can draw on their available resources, added Dr. Schilz, director of pulmonary vascular disease and lung transplantation at Case Western Reserve University, Cleveland. “Most hospitals have cardiologists on call 24/7, and many have some flavor of interventional radiology; others have clear referral and transfer schemes. Emergency department personnel at small rural hospitals can rapidly identify patients appropriate for transfer.”

Dr. Mahar added that PERTs are already being utilized in smaller hospitals and that he thinks that, in the next 5 years, having a PERT will be the standard protocol.

Dr. Mahar had no disclosures.

Mary Jo M. Dales contributed to this report.

CHEST Physician is Online

CHEST Physician is available on the Web at chestphysician.org

IN THIS ISSUE

Critical Care Commentary

The big data revolution’s relevance to critical care.

NIV failure not reduced with He/O₂ in COPD patients

Continued on following page
Empirical micafungin failed to boost survival of ICU sepsis

BY SUSAN LONDON
Frontline Medical News

MILAN – Empirical antifungal treatment did not improve the rate of survival free of invasive fungal infection among high-risk colonized patients in the intensive care unit, based on results from the EMPIRICUS randomized controlled trial.

Trial participants were 260 nonneutropenic, nontransplanted critically ill patients with ICU-acquired sepsis, Candida colonization of at least one site, and multiple organ failure who were exposed to broad-spectrum antibacterial agents. They were randomized to 14 days of empirical treatment with micafungin (Mycecum, 100 mg once daily) or placebo.

By day 28, about two-thirds of patients overall remained alive and free of proven invasive fungal infection, with no significant difference between groups, according to data reported at the annual congress of the European Society of Intensive Care Medicine and simultaneously published online (JAMA. 2016 Oct 5; doi: 10.1001/jama.2016.14655). Results were similar in subsets of patients having established risk factors for candidemia.

The EMPIRICUS (Empirical Anti-fungal Treatment in ICUs) findings add to data from other studies suggesting that, in this patient population, sepsis is seldom a result of invasive fungal infection and Candida colonization status is not helpful for guiding treatment, according to the researchers, who were led by Dr. Jean-Francois Timsit of Inserm/Paris Diderot University and department of medical intensive care and infectious diseases, Hôpital Bichat-Claude-Bernard, Paris.

“Altogether, these results call into question the routine use of systematic surveillance for Candida coloniz-ation. Besides sparing unnecessary use of health care resources, it may also avoid inducing resistances to antifungals,” they maintain. “Whether this trial closes 3 decades of clinical research on Candida colonization deserves consideration.”

Patients were recruited to EMPIRICUS from 19 ICUs in France. On average, study participants had three Candida-colonized sites.

A modified intent-to-treat analysis showed that, by day 28 after enrollment, 68% of patients in the micafungin group and 60.2% in the placebo group were alive and free of invasive fungal infection, a nonsignificant difference.

Findings were similar in the subset of patients having high serum levels of (1-3)-beta-D-glucan and in the subset of patients having high Sequential Organ Failure Assessment (SOFA) scores – both risk factors for candidemia – and regardless of the number of colonized sites.

In analyses of secondary outcomes, empirical micafungin was associated with a lower rate of new invasive fungal infection when compared with placebo (3% vs. 12%; P = .008), but the rate of mortality was statistically indistinguishable (30.0% vs. 29.7%).

The groups were statistically indistinguishable with respect to the number of organ failure-free days and the rate of ventilator-acquired pneumonia.

Dr. Timsit disclosed that he receives lecture fees from Gilead, Pfizer, Merck, and Astellas; research grants to his university and research organization from Astellas, Gilead, Merck, and Pfizer companies; a consultancy honorarium from Bayer; and personal fees from Abbott for scientific board participation; additionally, he disclosed participation on a scientific committee of epidemiological studies organized by Astellas and Merck companies outside the submitted work. Astellas provided a research grant to the Grenoble Alpes University Hospital based on the final study protocol. The study was sponsored by the University of Grenoble 1/Albert Michallon University Hospital.

The University of Grenoble provided compensation to the participating hospitals and universities for extra costs associated with the study.

VIEW ON THE NEWS

It’s time to revisit guidelines endorsing empirical antifungal therapy

Taken together, findings from EMPIRICUS and similar trials suggest that empirical antifungal treatment may reduce rates of invasive infection in critically ill patients, but does not improve survival.

These findings highlight two emerging themes in critical care medicine – less is more and targeted therapies are important when treating invasive fungal infection. In particular, the safety and efficacy of the newest antifungal agents are driving greater empirical use, yet this practice increases the cost of care and may contribute to antifungal resistance.

Guidelines have been implemented for empirical treatment of Candida and renal surveillance, yet there are no conclusive mortality benefits for this approach. Data have not ruled out the possibility that some subgroups of patients may see a survival benefit but, in light of the situation, guidelines concerning empirical treatment and surveillance should be revisited.

Like other prophylactic interventions, the risks and potential benefits of empirical echinocandin therapy for critically ill, immunocompetent patients in the ICU need to be studied. Novel biomarkers or clinical risk assessment algorithms may help in identifying those patients who are at highest risk of infection-related morbidity and mortality and would benefit most from targeted preventive therapies.

Trishal Siddharthan, MD, Petros C. Karakousis, MD, and William Checkley, MD, PhD, are with Johns Hopkins University in Baltimore. They made their remarks in an accompanying editorial in JAMA (2016 Oct 5. doi: 10.1001/jama.2016.13801).
CHEST recommends new protocols

New protocols from page 1

mimize sedation in patients ventilated for more than 24 hours. At the annual meeting of the American College of Chest Physicians, one of the six project cochairs, Daniel R. Ouellette, MD, said that the guidelines were intended to address “new territory” from the evidence-based guidelines for weaning and discontinuing ventilator support that were published in 2001.

That effort, chaired by Neil R. MacIntyre, MD, was a landmark article that helped us learn about the steps that we needed to take to liberate patients from mechanical ventilation,” said Dr. Ouellette of the Henry Ford Hospital department of pulmonary and critical care medicine, Detroit. “We hope that this guideline lives up to the importance of that one. We wanted to look over new information and give new recommendations about things that haven’t been addressed in the past.”

Six recommendations from the guideline panel include:

We suggest that the initial spontaneous breathing trial be conducted with inspiratory pressure augmentation rather than T-piece or continuous positive airway pressure. The committee wrote that conducting the initial spontaneous breathing trial with pressure augmentation was more likely to be successful, produced a higher rate of extubation success, and was associated with a trend toward lower ICU mortality.

We suggest protocols attempting to minimize sedation. The committee found that sedation protocols reduced ICU length of stay. However, the protocols did not appear to decrease time on the ventilator or reduce short-term mortality. The authors could not recommend one protocol over another but said the burden of providing sedation by any of the protocols was “very low.”

We suggest protocols for increased ventilator work in patients who were managed by protocol spent on average 25 fewer hours on mechanical ventilation and were discharged from the ICU a day early. However, their mortality rate appeared unchanged.

The guidelines were intended to address “new territory” from the evidence-based guidelines for weaning and discontinuing ventilator support that were published in 2001.

We suggest performing a cuff leak test in patients who meet extubation criteria and are deemed at high risk for postextubation stridor. The committee suggested that the test should be used only in patients with a high risk of stridor (abnormal breathing caused by blockage of windpipe) after extubation. Although patients passing the test had lower stridor and reintubation rates, the authors noted that a high percentage of patients who failed the test could be successfully extubated.

For patients who failed the cuff leak test but are otherwise ready for extubation, we suggest administering systemic steroids at least 4 hours before extubation. The committee said that clinical judgment should take priority over test results, and systemic steroids should be administered to these patients at least 4 hours before extubation. The authors added that the short duration of the steroid therapy was likely to improve success rates without resulting in adverse events.

In a prepared statement, Timothy Girard, MD, of the department of medicine at the University of Pittsburgh and a lead author of the guidelines said the committee hoped the guidelines would help reduce variations in practice that do not benefit patients. “We are not prescribing a specific approach to care for every patient every time,” he said. “But we are trying to summarize the available evidence in as clear and succinct a way as possible so that clinicians know how it applies to most patients.”

Dr. Ouellette disclosed that he has received a research grant from Cardes Pharma for health care–associated pneumonia.

Daniel R. Ouellette, MD, FCCP, comments: Liberation from mechanical ventilation is one of the most important goals in taking care of critically ill patients receiving mechanical ventilation in the ICU. Patients who have a prolonged ventilator course are at risk for many complications and so physicians who work in the intensive care unit must work carefully to liberate patients from the ventilator at the earliest possible moment. That has to be done in a safe fashion so criteria to ensure that this can be done safely are important as well.

Patients often have medical illness that requires sedation, and it is often necessary to sedate patients so that they can tolerate being on mechanical ventilation; however, we know that oversedation can lead to failure to liberate patients from mechanical ventilation expeditiously. Therefore, one of our recommendations’ suggestions is to design protocols for sedation that focus on minimizing sedation so that patients can be extubated expeditiously.

All of the recommendations ultimately focused on a team approach to liberation from mechanical ventilation, because involvement of team members is always important. However, there are a couple of our recommendations that are particularly important in terms of their implications for the team approach and those include recommendations about using protocols to liberate patients from ventilators, in general, and also to use sedation protocols to minimize sedations.

We began to look at developing this topic, because we had initially published guidelines on liberation from mechanical ventilation in 2001. We knew that there was much new information that had emerged since the 2001 guidelines. For that reason we began to think about an update. With the initial inception of this project, we reached out to the American Thoracic Society so as to develop a collaborative effort since this was a topic that interested both societies. This collaboration took nearly 3 years.

When one develops a guideline, one makes an effort to make a guideline as comprehensive and globally applicable as possible. I think the practices in Europe are very similar to practices in North America in terms of mechanical ventilation. Several of our panelists are European and some of the important work that we reviewed came from centers in Europe. It’s my opinion that our guideline will be broadly applicable in both North America and Europe, but there may be regional or local differences. Nevertheless, we recognize in different regions in the world, there are different resource allocations for medical treatment, there are different cultural precepts, and there are other factors that implicate medical problems.

Certainly the European Respiratory Society and other European organizations developed guidelines on related topics … one of the important caveats when CHEST decides to develop a guideline is that we are not reproducing the work that has been done elsewhere and so this guideline represents a project that fills a gap that previously had not been filled.

All guidelines that CHEST develops are living guidelines … it’s hard to envision exactly how often a guideline will be updated. We know that there will be certain areas of our guideline that will stand the test of time, but there will be other areas that will need to be updated, some sooner than others.

The original CHEST guideline on liberation from mechanical ventilation was a very important document that appeared in 2001 and changed the practice of medicine and the practice of managing patients on mechanical ventilation. Nevertheless, the guideline was somewhat limited in scope, because there was only so much information available. … Our goal in developing this guideline was to address some of practitioners’ questions that had emerged in the last decade by looking at newly available data.

In formulating these guidelines, we purposely chose six new questions that were not directly related to any of the questions [that has been answered] in the previous guideline.
The power of flexibility is yours with REVATIO Oral Suspension

With REVATIO you have 3 dosage forms to treat pulmonary arterial hypertension (PAH): oral suspension, tablet, and injection.

Choose your dosage form based on each patient's needs.

To learn more, please visit REVATIOHCP.com

Indication

REVATIO is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with NYHA Functional Class II-III symptoms. Etiologies were idiopathic (71%) or associated with connective tissue disease (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

Important Safety Information

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension.

REVATIO is contraindicated in patients with concomitant use of riociguat, a soluble guanylate cyclase (sGC) stimulator medication. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat.

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any other ingredient in REVATIO. Hypersensitivity, including anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction has been reported in association with the use of sildenafil.

Use of REVATIO, particularly chronic use, is not recommended in children.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with α-blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 5%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors (eg, ketoconazole, itraconazole, and ritonavir) is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with potent CYP3A4 inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, is expected to cause substantial decreases in plasma levels of sildenafil. Treatment with doses higher than 20 mg three times a day is not recommended.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established. In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo.

Patients with retinitis pigmentosa and patients on bosentan did not participate in the preapproval clinical trial. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events were generally transient and mild to moderate. Adverse events of REVATIO injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia, and visual disturbances.

No dose adjustment required for renal impaired.

No dose adjustment required for mild to moderate hepatic impaired. Severe impairment has not been studied.

REVATIO is available in the following dosage forms:
- Tablets: 20 mg
- Injection: 10 mg/12.5 mL in a single use vial
- Oral Suspension: 10 mg/mL (when reconstituted)
INDICATION AND USAGE
REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability, and delay clinical worsening. The delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominantly patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic pulmonary hypertension (71%) or associated with connective tissue disease (CTD) (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

DOSE AND ADMINISTRATION
REVATIO Tablets and Oral Suspension The recommended dose of REVATIO is 5 mg or 20 mg three times a day. Administer REVATIO doses 4–6 hours apart. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg three times a day is not recommended.

Reconstitution of the Powder for Oral Suspension 1. Tap the bottle to release the powder. 2. Remove the cap, 3. Add one measure of 60 mL of water and pour off the water into the bottle. 4. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 5. Remove the cap. 6. Accurately measure out another 30 mL of water and add this to the bottle. You should always add a total of 90 mL of water irrespective of the dose prescribed. 7. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 8. Remove the cap. 9. Press the bottle adapter into the neck of the bottle. The adapter is provided so that you can fill the oral syringe with medicine from the bottle. Replace the cap on the bottle. 10. Write the expiration date of the constituted oral suspension on the bottle label (the expiration date of the constituted oral suspension is 60 days from the date of constitution).

Incompatibilities Do not mix with any other medication or additional flavoring agent.

CONTRAINDICATIONS
REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension [see Warnings and Precautions]. Concomitant use of nicorandil, a guanylate cyclase stimulator, PDE-5 inhibitors, including sildenafil, may potentiate the hypotensive effects of nicorandil. REVATIO is also contraindicated in patients with known hypersensitivity to sildenafil or any component of the tablet, injection, or oral suspension. Hypersensitivity, including anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction, has been reported in association with the use of sildenafil.

WARNINGS AND PRECAUTIONS
Mortality with Pediatric Use In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing REVATIO dose was observed. Deaths were first observed after about 1 year and caused death by respiratory failure. In PAH, Use of PDE-5 inhibitors, particularly use, is not recommended in children [see Use in Specific Populations].

Hypotension REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients on antihypertensive therapy or with resting hypotension [BP less than 90/50], fluid depletion, severe left ventricular outflow obstruction, or automatic dysfunction). Monitor blood pressure when commencing blood pressure lowering drugs with REVATIO.

Worsening Pulmonary Vascular Occlusive Disease Pulmonary vasomotor responses may significantly worsen the cardiovascular status of patients with pulmonary vaso-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with vaso-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

Epistaxis The incidence of epistaxis was 13% in patients taking REVATIO with PAH secondary to CTD. The effect was seen in idiopathic PAH (REVATIO 3%, placebo 2%) patients. The incidence of epistaxis was also higher in REVATIO-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist). The safety of REVATIO is unknown in patients with active peptic ulceration or history of peptic ulcer disease.

Visual Loss When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. Based on published literature, the annual incidence of NAION is 2.5–11.8 cases per 100,000 males aged ≥50 years per year in the general population. An observational study evaluated whether recent, episodic use of PDE5 inhibitors (as a class), typical of erectile dysfunction treatment, was associated with an increase in the risk of NAION. The results suggest an approximately 2-fold increase in the risk of NAION within 5-19 days of use of PDE5 inhibitor. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors, to the patient’s underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE-5 inhibitors, including REVATIO.

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority who have genetic disorders of retinal phosphodiesterase. Prescribe REVATIO with caution in these patients.

Hearing Loss Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in temporal association with the use of PDE-5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have played a role. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient’s underlying vascular risk factors for hearing loss, a combination of these factors, or to other factors. Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE-5 inhibitors, including REVATIO.

Combination with Other PDE-5 Inhibitors Sildenafil is also marketed as VIAGRA®. The safety and efficacy combinations of REVATIO with VIAGRA® or other PDE-5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA® or other PDE-5 inhibitors.

Priapism Use REVATIO with caution in patients with anatomic deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie’s disease) or in patients who have conditions, which predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Vaso-occlusive Crisis in Patients with Pulmonary Hypertension Secondary to Sickle Cell Anemia In a small, prematurely terminated study of patients with pulmonary hypertension (PH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo. The effectiveness and safety of REVATIO in the treatment of PAH secondary to sickle cell anemia has not been established.

ADVERSE REACTIONS
Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data of REVATIO in adults were obtained from the 12-week, placebo-controlled clinical trial (Study 1) and an open-label extension study in 277 REVATIO-treated patients with PAH. WHO Group I.

The overall frequency of discontinuation in REVATIO-treated patients on 20 mg three times a day was 3% and was the same for the placebo group. In Study 1, the adverse reactions that were reported in ≥3% of REVATIO-treated patients (20 mg three times a day) and were more frequent in REVATIO-treated patients than in placebo-treated patients are shown in Table 1. Adverse reactions were generally transient and mild to moderate in nature.

Table 1: Most Common Adverse Reactions in Patients with PAH in Study 1 (More Frequent in REVATIO-Treated Patients than Placebo-Treated Patients and Incidence ≥3% in REVATIO-Treated Patients)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Placebo, % (n=70)</th>
<th>REVATIO 20 mg three times a day, % (n=69)</th>
<th>Placebo-Subtracted, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Headache</td>
<td>39</td>
<td>46</td>
<td>7</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Flushing</td>
<td>4</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Erhyma</td>
<td>1</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Dyspepsia exacerbated</td>
<td>3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Rinitis</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Gastritis</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

At doses higher than the recommended 20 mg three times a day, there was a greater incidence of some adverse reactions including flushing, diarrhoea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately colour-tinge to vision, but also increased sensitivity to light or blurred vision.

The incidence of retinal hemorrhage with REVATIO 20 mg three times a day was 1.4% versus 0% placebo and for all REVATIO doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both 20 mg three times a day and at all doses studied was 1.4% for REVATIO versus 1.4% for placebo. The patients experiencing these reactions had risk factors for hemorrhage including concurrent anticoagulant therapy.

Postmarketing Experience The following adverse reactions have been identified during post approval use of sildenafil (marketed for both PAH and erectile dysfunction). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular Events In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhage have been reported in patients administered REVATIO. Use of sildenafil and REVATIO has been reported in patients with coronary artery disease. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events have been reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after sexual activity without taking REVATIO. The use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient’s underlying cardiovascular disease, or to a combination of these or other factors.

Nervous system Seizure, seizure recurrence.

DRUG INTERACTIONS
Nitrates Concomitant use of REVATIO with nitrates in any form is contraindicated [see Contraindications].

Ritonavir and other Potent CYP3A4 Inhibitors Concomitant use of REVATIO with ritonavir and other potent CYP3A4 inhibitors is not recommended.
Other drugs that reduce blood pressure

Alpha blockers. In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope. Amlopidine. When sildenafil 100 mg oral was co-administered with amlopidine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO® (sildenafil).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D

There are no adequate and well-controlled studies of sildenafil in pregnant women. No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m² basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m² basis).

Labor and Delivery

The safety and efficacy of REVATIO during labor and delivery have not been studied.

Nursing Mothers

It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

Pediatric Use

No studies were less likely to receive a PCC, compared with noncancer patients (64% vs. 21%, respectively; P < .001).

Patients with metastatic cancer were significantly more likely to have received a PCC, compared with noncancer patients (64% vs. 21%, respectively; P < .001).

Patients with a palliative care consult (PCC), with less than .001), while those who had a PCC within 48 hours of admission were 20 times more likely to have a hospital length of stay less than 7 days (P < .019), while those who had a PCC within 48 hours of admission were 20 times more likely to have a hospital length of stay less than 7 days (P < .017). “So if we intervened early, we were able to decrease their length of stay to less than 7 days,” Dr. Kang said at the meeting.

She acknowledged certain limitations of the study, including its small sample size, retrospective design, and lack of follow-up. “This study also has a lot of confounding socioeconomic factors that do not make it applicable to every hospital across the country,” she said. “This is not a homogeneous patient population.”

The study’s principal investigator was Anne Sutherland, MD, who is the medical intensive care unit director at University Hospital. Dr. Kang reported having no financial disclosures.

Few non-ICU patients receive palliative care consults

BY DOUG BRUNK

Frontline Medical News

AT CHEST 2016

LOS ANGELES – A significant percentage of patients who meet criteria for palliative care consultations do not receive a consult during their hospital stay, results from a single-center retrospective analysis showed.

“Physicians need to recognize the palliative care needs of patients with chronic illnesses other than malignancy before they get admitted to the ICU, especially when these patients are admitted repeatedly for the same problem [and] have a significant decline in functional status with a large symptom burden,” Mohileen Kang, MD, said in an interview in advance of the annual meeting of the American College of Chest Physicians. “There is a potential missed opportunity for these conversations to occur with the patients and their families prior to their decompensation and crisis.”

Twenty-nine percent (132) of the patients studied met an indication for a palliative care consult (PCC), with only 35 (27%) of such patients having received one. Patients with metastatic cancer were significantly more likely to have received a PCC, compared with noncancer patients (64% vs. 21%, respectively; P < .001), while those who had a PCC within 48 hours of admission were 20 times more likely to have a hospital length of stay less than 7 days (P < .017). “So if we intervened early, we were able to decrease their length of stay to less than 7 days,” Dr. Kang said at the meeting.

She acknowledged certain limitations of the study, including its small sample size, retrospective design, and lack of follow-up. “This study also has a lot of confounding socioeconomic factors that do not make it applicable to every hospital across the country,” she said. “This is not a homogeneous patient population.”

The study’s principal investigator was Anne Sutherland, MD, who is the medical intensive care unit director at University Hospital. Dr. Kang reported having no financial disclosures.

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A biomarker may show whether acute respiratory distress syndrome (ARDS) is focal or nonfocal, a study showed.

This is an important distinction because some research suggests nonfocal ARDS, characterized by diffuse lung aeration loss, may have a worse prognosis and the two subtypes may respond differently to interventions such as positive end-expiratory pressure and recruitment maneuvers.

At present, the only way to identify focal versus nonfocal ARDS is a computed tomography scan, but that is often impractical because of the risks of moving the patient.

The current research, published in the November issue of CHEST (2016;150:998-1007), revealed that patients with nonfocal ARDS have higher plasma levels of the soluble form of the receptor for advanced glycation end product (sRAGE). At a cutoff of 1,188 pg/mL, the blood test differentiated between focal and nonfocal ARDS with a 94% sensitivity and an 84% specificity.

We might conceive of using sRAGE as a marker for nonfocal ARDS, Dr. Ouellette said.

“Elevated baseline plasma sRAGE is a strong marker of nonfocal CT-based lung-imaging pattern in patients with early ARDS,” reported Jean-Michel Constantin of University Hospital of Clermont-Ferrand (France) and colleagues in the Azerea network.

The researchers recruited 119 consecutive ARDS patients from 10 intensive care units in France. They measured plasma levels of sRAGE, plasminogen activator inhibitor–1 (PAI-1), soluble intercellular adhesion molecule–1, and surfactant protein–D within 24 hours of ARDS onset. Each patient underwent a lung CT scan within 48 hours to assess focal versus nonfocal lung morphology.

Twenty-seven percent of patients had focal ARDS, while 73% were categorized as nonfocal. Mean plasma levels of sRAGE were much higher in nonfocal patients (3,074 pg/mL vs. 877 pg/mL; P less than .001). A cutoff value of 1,188 ng/mL distinguished focal and nonfocal ARDS with a sensitivity of 93% (95% confidence interval, 85%-97%) and a specificity of 84% (95% CI, 66%-95%).

The test’s positive predictive value was 94% (95% CI, 87%-98%), and its negative predictive value was 81% (95% CI, 64%-93%).

The research is still in its early stage, but has a couple possible applications, according to Daniel R. Ouellette, MD, of Henry Ford Hospital, Detroit. “We might conceive of using this as a marker for nonfocal ARDS, and potentially use it to identify patients with worse outcomes. The other thing is, it may be a clue to help us learn about the underlying physiology of the disease,” he said in an interview.

If physicians can confidently categorize a patient, it could inform treatment. “We know that patients who have diffuse disease may be more likely to be treated successfully with advanced ventilator techniques. These techniques would be more useful and likely to lead to recovery in patients that don’t have focal disease,” said Dr. Ouellette. “These results are exciting, but they are very preliminary.”

The study was funded by the Auvergne Regional Council, the French Agence Nationale de la Recherche, and the Direction Generale de l’Offre de Soins, and the University Hospital of Clermont-Ferrand. The authors reported receiving funds from various pharmaceutical companies.
Sepsis survival rates highest in Northeast, metro areas

BY DOUG BRUNK
Frontline Medical News

LOS ANGELES – Compared with other parts of the United States, survival rates for sepsis were highest in the Northeast and in metropolitan areas in the Western regions of the United States, which mirrors the concentration of critical care fellowship programs, results from a descriptive analysis found.

“There must be consideration to redistribute the critical care work force based on the spread of the malady that they are trained to deal with,” lead study author Aditya Shah, MD, said in an interview in advance of the annual meeting of the American College of Chest Physicians. “This could be linked to better reimbursements in the underserved areas.”

Dr. Shah, an internal medicine resident at Advocate Christ Medical Center in Oak Lawn, Ill., and his associates, extracted sepsis mortality data from the National Center for Health Statistics (NCHS) Compressed Mortality File, which aggregates U.S.

M. ALEXANDER OTTO /FRONTLINE MEDICAL NEWS

Dialysis need decreased with fluid administration in sepsis

BY M. ALEXANDER OTTO
Frontline Medical News

LOS ANGELES – Fluid administration of at least 1 L did not increase the incidence of acute respiratory or heart failure in severe sepsis, and actually seemed to decrease the need for dialysis in a review of 164 patients at Scott and White Memorial Hospital in Temple, Tex.

For every 1 mL of fluid administered per kg of body weight, the likelihood of dialysis decreased by 8.5% (odds ratio, 0.915; 95% confidence interval, 0.854-0.980; P = .0111), with no increase in heart or respiratory failure on univariate analysis. The 126 patients (77%) who received at least 1 L had a 68% reduction in the need for dialysis (OR, 0.32; CI, 0.117-0.890; P = .0288).

The findings come from a quality improvement project at the hospital launched after researchers there realized that the benchmark Surviving Sepsis Campaign guidelines weren’t being met. The patients in the study had systolic blood pressures below 90 mm Hg or lactate levels of at least 4 mmol/L. The guidelines would have called for these patients to receive 30 mL/kg of intravenous fluid resuscitation. It turned out that staff in the emergency department – where most of the patients were treated in the critical first 6 hours – were concerned about fluid overload and throwing patients into respiratory, heart, or renal failure, Dr. Jahoor said at the annual meeting of the American College of Chest Physicians. The team didn’t find a difference in mortality when patients received 30 mL/kg – just over 2 L in a 70-kg patient – vs. 20 mL/kg or 1 L. The patients’ in-hospital mortality rates and 28-day mortality rates were 27%, and 32%, respectively.

There also weren’t increased rates of heart failure, acute respiratory failure, or mechanical ventilation when patients received at least 1 L of fluid. “There were [also] lower rates of dialysis, which indicated that we weren’t overloading patients. Even when we looked at fluid as a continuous variable, we still didn’t see” complications, Dr. Jahoor said.

“The No. 1 reason we weren’t meeting benchmarks was fluid administration,” Dr. Aruna Jahoor said.

“Also, the most current data will always lag behind as it is entered retrospectively and needs time to be uploaded online,” he said. “I am still in search of a more real-time database. However, that would require much more intensive time, money, and resources.”

Dr. Shah reported having no financial disclosures.

Dr. Aditya Shah called for consideration to redistribute critical care doctors.

The findings should be reassuring to treating physicians. “When you have pushback against 30-mL/kg administration, you can say ‘well, at least let’s give a liter. You don’t have to worry as much about some of the complications you are citing,’” she said.

For very obese patients, “it can get a little uncomfortable to be given” enough fluid to meet the 30-mL/kg goal, “but you can give at least a liter” without having to worry too much, she said.

The patients in the study were treated from 2010 to 2013; normal saline was the most common resuscitation fluid. The hospital has since added the 30-mL/kg fluid resuscitation to its sepsis admission orders, and compliance has increased significantly. A multivariate analysis is in the works to control for confounders. “We will probably [still] see you are not having increased rates of congestive heart or respiratory failure, or needing dialysis,” Dr. Jahoor said. The protective effect against dialysis might drop out, “but I am hoping it doesn’t,” he said.

The investigators had no relevant financial disclosures.
ECMO patients got relatively low sedative, analgesic doses

BY MARK S. LESNEY
Frontline Medical News

Patients on extracorporeal membrane oxygenation (ECMO) received relatively low doses of sedatives and analgesics while at a light level of sedation in a single-center prospective study of 32 patients.

In addition, patients rarely required neuromuscular blockade, investigators reported online in the Journal of Critical Care.

This finding contrasts with current guidelines on the management of pain, agitation, and delirium in patients on ECMO. The guidelines are based upon previous research that indicated the need for significant increases in sedative and analgesic doses, as well as the need for neuromuscular blockade, wrote Jeremy R. DeGrado, PharmD, of the department of pharmacy at Brigham and Women’s Hospital, Boston, and his colleagues (J Crit Care. 2016 Aug 10;37:1-6. doi: 10.1016/j.jcrc.2016.07.020).

“Patients required significantly lower doses of opioids and sedatives than previously reported in the literature and did not demonstrate a need for increasing doses throughout the study period,” the investigators said. “Continuous infusions of opioids were utilized on most ECMO days, but continuous infusions of benzodiazepines were used on less than half of all ECMO days.”

Their 2-year, prospective, observational study assessed 32 adult intensive care unit patients on ECMO support for more than 48 hours. A total of 15 patients received VA (venoarterial) ECMO and 17 received VV (venovenous) ECMO. Patients received a median daily dose of benzodiazepines (midazolam equivalents) of 24 mg and a median daily dose of opioids (fentanyl equivalents) of 3,875 mcg.

“The primary indication for VA ECMO was cardiogenic shock, while VV ECMO was mainly used as a bridge to lung transplant or in patients with severe acute respiratory distress syndrome. The researchers evaluated a total of 475 ECMO days: 110 VA ECMO and 365 VV ECMO. On average, patients were sedated to Richmond Agitation Sedation Scale scores between 0 and −1. Across all 475 ECMO days, patients were treated with continuous infusions of opioids (on 85% of ECMO days), benzodiazepines (42%), propofol (20%), dexmedetomidine (7%), and neuromuscular blocking agents (13%).”

In total, patients who received VV ECMO had a higher median dose of opioids and trended toward a lower dose of benzodiazepines than did those who received VA ECMO, Dr. DeGrado and his associates reported.

In total, patients in the VA arm, compared with those in the VV arm, more frequently received a continuous infusion opioid (96% vs. 82% of days) and a benzodiazepine (58% vs. 37% of days). These differences were statistically significant.

Adjunctive therapies, including antipsychotics and clonidine, were administered frequently, according to the report.

“We did not observe an increase in dose requirement over time during ECMO support, possibly due to a multimodal pharmacologic approach. Overall, patients were not deeply sedated and rarely required neuromuscular blockade. The hypothesis that patients on ECMO require high doses of sedatives and analgesics should be further investigated,” the researchers concluded.

The authors reported that they had no disclosures.

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Combine qSOFA and SIRS for best sepsis score

BY M. ALEXANDER OTTO
Frontline Medical News

LOS ANGELES – Instead of replacing the Systemic Inflammatory Response Syndrome (SIRS) score with the new quick Sequential Organ Failure Assessment (qSOFA) score to identify severe sepsis patients, it might be best to use both, according to two studies presented at the American College of Chest Physicians annual meeting.

The gold standard 3rd International Consensus Definitions for Sepsis and Septic Shock Task Force recently introduced qSOFA to replace SIRS, in part because SIRS is too sensitive. With criteria that include a temperature above 38°C, a heart rate above 90 bpm, and a respiratory rate above 20 breaths per minute, it’s possible to score positive on SIRS by walking up a flight of stairs, audience members noted at the study presentations noted.

The first study at the meeting session – a prospective cohort of 132 patients scored by both systems within 8 hours of ICU admission at the New York–Presbyterian Hospital – found that qSOFA was slightly better at predicting in-hospital mortality and ICU-free days, but no better than SIRS at predicting ventilator- or organ failure–free days.

However, of the 36% of patients (55) who met only one of the three qSOFA criteria – a respiratory rate of 22 breaths per minute, altered mental status, or a systolic blood pressure of 100 mg Hg or less – 6% (3) died in the hospital. Of those patients, two-thirds (2) were SIRS positive, meaning that they met two or more SIRS criteria.

“Having a borderline qSOFA of 1 point, which is considered negative, with the addition of having SIRS criteria, should raise concerns that patients need further evaluation. SIRS criteria should not be [entirely] discarded” in favor of qSOFA, said lead investigator Eli Finkelstein, MD, of the New York–Presbyterian Hospital.

The second study – a review of 6,811 severe sepsis/septic shock patients scored by both systems within 3 hours of emergency department admission at the University of Kansas Hospital emergency department in Kansas City – found that the two scores performed largely the same when it came to predicting ICU admission and 30-day mortality, but that people who met two or more criteria in both systems were of special concern.

Twenty-five percent of patients (1,713) scored 2 or more on both SIRS and qSOFA. These patients were more likely to be admitted to the ICU and be readmitted to the hospital after a month, compared with those patients who were positive in only one scoring system or negative in both. Additional factors associated with these patients were that they had the longest ICU and hospital lengths of stay. Two hundred (12%) of these patients scoring 2 or more on both SIRS and qSOFA died within 30 days.

“SIRS criteria continue to be more sensitive at identifying severe sepsis, but they are equally as accurate [as qSOFA criteria] at predicting adverse patient outcomes,” said lead investigator and Kansas University medical student Amanda Deis.

SIRS and qSOFA take only a few seconds to assess at the bedside. Using both builds “a clinical picture,” she said.

“Since there is no funding for the work, and the investigators had no relevant financial disclosures.

atto@frontlinemedcom.com

Screen with SIRS, admit with qSOFA

E verybody got fed up with SIRS because it’s overly sensitive, but now we’ve swung in the other direction. It’s absolutely true that qSOFA is more specific, but one of the presenters had a 6% rate of qSOFA missing sick patients.

We want to be somewhere in the middle in terms of not missing too many of these cases. I thought 6% was reasonable, but others may not.

Maybe a combination of the two is best. Using SIRS as ICU screening criteria might be a good idea; the ICU physician could then come in and use qSOFA to determine if someone needs to be admitted to the ICU.

Zaza Cohen, MD, is the director of critical care at Mountainside Hospital in Montclair, N.J. He moderated – but was not involved with – the two studies.
For adult patients with asthma uncontrolled on an ICS or whose disease severity clearly warrants an ICS/LABA. BREO is NOT indicated for the relief of acute bronchospasm.

Important Safety Information

**WARNING: ASTHMA-RELATED DEATH**
- Long-acting beta₂-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths. This finding with salmeterol is considered a class effect of all LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.
- When treating patients with asthma, only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.

**CONTRAINDICATIONS**
- BREO is contraindicated for primary treatment of status asthmaticus or other acute episodes of chronic obstructive pulmonary disease (COPD) or asthma where intensive measures are required.
- BREO is contraindicated in patients with severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients.

Please see additional Important Safety Information on the following pages.
Please see Brief Summary of Prescribing Information, including Boxed Warning, for BREO on the pages following this advertisement.

Reach with Confidence for 24-hour BREO

(FLUTICASONE FURUATE 100 mcg AND VILANTEROL 25 mcg INHALATION POWDER)
BREO offers patients proven efficacy with just one daily dose

In patients uncontrolled on an ICS, BREO has been proven to:

- Deliver 24-hour lung function improvement
- Reduce asthma exacerbations

with one inhalation, once daily*

in patients with a history of exacerbations†

Supporting Clinical Study Information

*In a randomized, double-blind (RDB) study of 1039 patients† symptomatic on a mid- to high-dose ICS, BREO 100/25 once daily (n=312) demonstrated a 108 mL improvement from baseline in weighted mean (wm) FEV1 (0-24 hours) at the end of the 12-week treatment period vs fluticasone furoate (FF) 100 mcg once daily (n=288) (P<0.001).† (In an RDB, placebo-controlled study of 609 patients’ symptomatic on a low- to mid-dose ICS, in a subset of patients, BREO 100/25 once daily (n=108) demonstrated a change from baseline in wm FEV1 (0-24 hours) at the end of the 12-week treatment period vs FF 100 mcg once daily (n=106) of 116 mL [95% CI: –5, 236; P<0.001].†)

†In a 24- to 76-week RDB study of 2019 patients† with ≥1 exacerbations in the prior year, BREO 100/25 once daily (n=1009) reduced the risk of experiencing an exacerbation by 20% (hazard ratio=0.795, P<0.036) vs FF 100 mcg once daily (n=1010). An exacerbation was defined as a deterioration of asthma requiring the use of systemic corticosteroids for ≥3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.

†Studies included patients with asthma ≥12 years of age; BREO is only approved for use in patients ≥18 years of age.

Important Safety Information (cont’d)

WARNINGS AND PRECAUTIONS

- BREO should not be initiated in patients requiring urgent relief of life-threatening episodes of COPD or asthma.
- BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist.
- BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Oropharyngeal candidiasis has occurred in patients treated with BREO. Advise patients to rinse the mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections.
- Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to BREO.

WARNINGS AND PRECAUTIONS (cont’d)

- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, discontinue BREO slowly.
- Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue BREO immediately and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. BREO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.
Have confidence in access

Nationwide, BREO is now covered without restriction§ on:

![Map showing coverage of 90% of commercial health plans]

Individual patient access may vary by geography and plan benefit design.
SOURCE: Managed Markets Insight & Technology, LLC, database as of August 2016.

Important Safety Information (cont’d)

WARNINGS AND PRECAUTIONS (cont’d)
- Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.
- Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents.

ADVERSE REACTIONS
- In a 12-week trial, adverse reactions (≥2% incidence and more common than placebo) reported in subjects taking BREO 100/25 (and placebo) were: nasopharyngitis, 10% (7%); headache, 5% (4%); oropharyngeal pain, 2% (1%); oral candidiasis, 2% (0%); and dysphonia, 2% (0%). In a separate 12-week trial, adverse reactions (≥2% incidence) reported in subjects taking BREO 200/25 (or BREO 100/25) were: headache, 8% (8%); nasopharyngitis, 7% (6%); influenza, 3% (3%); upper respiratory tract infection, 2% (2%); oropharyngeal pain, 2% (2%); sinusitis, 2% (1%); bronchitis, 2% (<1%); and cough, 1% (2%).
- In addition to the adverse reactions reported in the two 12-week trials, adverse reactions (≥2% incidence) reported in subjects taking BREO 200/25 once daily in a 24-week trial included viral respiratory tract infection, pharyngitis, pyrexia, and arthralgia, and with BREO 100/25 or 200/25 in a 12-month trial included pyrexia, back pain, extrasystoles, upper abdominal pain, respiratory tract infection, allergic rhinitis, pharyngitis, rhinitis, arthralgia, supraventricular extrasystoles, ventricular extrasystoles, acute sinusitis, and pneumonia.

For local formulary information about BREO, please contact your GSK sales professional.

What you need to know about this formulary information:

§Covered without restriction means reimbursement from a health plan with no accompanying step edits or prior authorizations. Formulary status may vary and is subject to change. Formulary coverage does not imply clinical efficacy or safety. Benefits designs offered by plans may vary. Actual benefits and out-of-pocket costs are determined by each plan administrator in accordance with its respective policy and procedures. Consumers may be responsible for some out-of-pocket costs based on an individual’s plan. The information provided is not a guarantee of coverage or payment (partial or full). Please verify coverage with and obtain most current information from plan sponsors. GSK does not endorse individual plans.

ADVERSE REACTIONS (cont’d)
- In a 24- to 76-week trial of subjects with a history of 1 or more asthma exacerbations within the previous 12 months, asthma-related hospitalizations occurred in 1% of subjects treated with BREO 100/25. There were no asthma-related deaths or asthma-related intubations observed in this trial.

DRUG INTERACTIONS
- Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- BREO should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists, such as vilanterol, on the cardiovascular system may be potentiated by these agents.
- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may also produce severe bronchospasm in patients with COPD or asthma.
- Use with caution in patients taking non–potassium-sparing diuretics, as electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists.

USE IN SPECIFIC POPULATIONS
- BREO is not indicated for use in children and adolescents. The safety and efficacy in pediatric patients (aged 17 years and younger) have not been established.
- Use BREO with caution in patients with moderate or severe hepatic impairment. Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment. Monitor for corticosteroid-related side effects.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for BREO on the following pages.


Visit BREOhcp.com for more information, including Patient Assistance Programs.

BREO® ellipta®
(fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder)

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5.14 Glaucoma and Cataracts

In clinical trials, the development of localized infections of the mouth and pharynx with BREO was observed with a frequency of 2% or greater in patients aged 18 years and older. LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of infected oropharyngeal ulcerations with a frequency of at least 2% in patients with asthma, physicians should only prescribe BREO for patients who are not adequately controlled on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS [see Warnings and Precautions (5.5)].

5.15 Coexisting Conditions

BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing ICS, as an oral inhalation solution for patients with asthma, physicians should only prescribe BREO for patients who are not adequately controlled on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.

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16% (7%, 7%); headache, 5% (4%, 4%); oropharyngeal pain, 2% (2%, 1%); oral candidiasis, 2% (2%, 0%); and dyspepsia, 2% (2%, 1%). Oral candidiasis includes oral or pharyngeal candidiasis.

In Trial 2, adverse reactions (≥2% incidence) reported in subjects with asthma taking BREO 200/50 in [n=348] or BREO 100/25 in [n=347] are shown in Table 3. Adverse reactions occurring in greater than or equal to 2% of subjects treated with BREO 200/50 included nasopharyngitis, 20%, upper respiratory tract infection, 2%, cough, 1% (2%, 1%), and dyspepsia, 1% (2%, 1%).

24-Week Trial: A 24- to 56-week evaluation of death or asthma-related death or asthma-related cardiac or respiratory deaths was observed. There were no deaths in patients treated with fluticasone furoate 100 mcg and vilanterol 25 mcg daily.

26. All patients were happy and their children were included in the trial.

27. The number of patients with asthma who can be treated with inhaled corticosteroids is limited by their effectiveness in reducing asthma symptoms.

28. The number of patients with asthma who can be treated with inhaled corticosteroids is limited by their effectiveness in reducing asthma symptoms.

29. The number of patients with asthma who can be treated with inhaled corticosteroids is limited by their effectiveness in reducing asthma symptoms.

30. The number of patients with asthma who can be treated with inhaled corticosteroids is limited by their effectiveness in reducing asthma symptoms.

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Home oxygen upped survival in some PAH patients

BY KATIE WAGNER LENNON
Frontline Medical News

AT CHEST 2016

LOS ANGELES – Pulmonary arterial hypertension (PAH) patients with severely impaired diffusing capacity of the lungs for carbon monoxide (DLCO) were much more likely to survive when they received home oxygen therapy, according to a disease registry analysis.

“We all know that supplemental oxygen is widely used with PAH,” said Harrison W. Farber, MD, director of the pulmonary hypertension center at Boston University. But there are practically no data showing that it is successful, and there are even fewer data for patients with PAH who have very low diffusion capacity, he added.

That knowledge gap prompted Dr. Farber and his colleagues to analyze data from REVEAL (the Registry to Evaluate Early and Long-Term PAH Disease Management), the largest disease registry in the world of patients with PAH.

“Patients in that group – the severe DLCO group – who got oxygen had poorer prognostic features but improved overall survival relative to those who didn’t,” Dr. Farber explained during a presentation at the annual meeting of the American College of Chest Physicians. “Based on this, it makes us think that home oxygen, supplemental oxygen treatment, is associated with improved survival in patients, especially those with severe DLCO and PAH.”

The 3,046 patients analyzed by Dr. Farber and his colleagues had World Health Organization Group 1 PAH with right heart catheterization hemodynamic criteria: a mean pulmonary artery pressure greater than 25 mm Hg, a pulmonary capillary wedge pressure less than or equal to 15 mm Hg, and a pulmonary vascular resistance of at least 3 Wood units (WU). Patients were at least 18 years of age and grouped by oxygen use, which was defined as any use at any time from study enrollment to the end of follow-up, and by DLCO group.

A total of 57% of the patients (1,734) received oxygen, and the remaining 43% of the patients (1,312) did not receive oxygen. Among the patients who received oxygen, 71% (1,227) received the therapy continuously, and 24% (408) received oxygen at night only.

Among those patients with severe DLCO impairment, the risk of death was significantly lower in those who received oxygen, compared with those who did not receive oxygen (hazard ratio, 0.56; \( P = .0033 \)). Oxygen use was associated with significant improvements in overall survival in both the newly diagnosed (HR, 0.47; \( P = .029 \)) and previously diagnosed (HR, 0.39; \( P = .026 \)) severe DLCO cohorts, Dr. Farber said.

Patients receiving oxygen were more likely to be treated with PAH-specific medications, regardless of their DLCO group. Among the analysis’s limitations was that the lengths of time patients had been undergoing oxygen treatment were unknown. That prevented adjustments for duration of oxygen treatment, according to Dr. Farber.

Dr. Farber disclosed serving on the steering committees or advisory boards for Actelion, Bayer, Bellerophon, Gilead, and United Therapeutics. He has received research support from Actelion, Gilead, and United Therapeutics, and has been a speaker for Actelion, Bayer, and Gilead.

klennon@frontlinemed.com
Consider mitral valve repair in PH with dyspnea

BY M. ALEXANDER OTTO
Frontline Medical News

LOS ANGELES – Dyspnea in pulmonal hypertension (PH) is caused by mitral valve disease until proven otherwise, according to Paul Forfia, MD, director of pulmonary hypertension, right heart failure, and pulmonary thromboendarterectomy at Temple University, Philadelphia.

Although mitral valve disease is a well-recognized cause of PH, its significance is often underestimated in practice.

“Whether the valve is regurgitant or stenotic makes absolutely no difference. When you delay” repair or replacement, “the patient keeps getting sicker,” he said.

In time, “everyone is standing around wringing their hands going, ‘Oh my god, what are we going to do?’ Are you serious? Fix the valve. We see this type of patient a couple times a month,” Dr. Forfia said at the American College of Chest Physicians annual meeting.

“I have seen lifesaving mitral valve surgery put off for many years in patients with pulmonary hypertension, when all they needed was to have their valve fixed,” he said.

A few things could explain the problem. Prevention of rheumatic fever has made mitral stenosis far less common than in the past, so cardiologists may not be as good at diagnosing it. The increased attention on PH in recent years may also have eclipsed the importance of underlying mitral valve disease and the need to address it, said Dr. Forfia.

Whatever the case, pulmonologists who want the valve fixed often end up playing patient ping pong with cardiologists who want the hypertension controlled beforehand, but “if I treat the pulmonary circulation first, all I am going to do is unmask the left heart failure. There will be no functional improvement whatsoever,” Dr. Forfia said.

Surgery is the best solution as long as patients are well enough to recover. “With pulmonary hypertension in the setting of severe mitral valve regurgitation or stenosis, whether the pulmonary hypertension is related to passive left heart congestion or associated with pulmonary arteriopathy, the only sensible option is to correct the underlying valvar abnormality,” he said. The surgery should be done at an institution capable of managing postop pulmonary arteriopathy, if present.

An expert pulmonology center will spot the mitral valve problem right away. “There is no pulmonary pressure cutoff that should prohibit surgery” in patients able to recover. “There is no such thing as a pulmonary artery pressure too high to be explained by mitral valve disease. The pulmonary pressure can be as high as it wants to be. You will get nowhere by thinking the pressure is too high to address the valve,” Dr. Forfia said.

Often “you hear, ‘I’m afraid the patient is not going to die on the table.’ I always say ‘If the patient is not going to die on the table, they are going to die in their living room of progressive heart failure because you [didn’t] fix their valve. I have never had a patient with pulmonary hypertension not separate from cardiopulmonary bypass. It’s a myth,” he said.

When there’s a ‘question if the dyspnea is coming from the mitral valve, we routinely use exercise right heart catheterization to probe the situation. We have a recumbent bike in the cath lab. You’ll often provoke significant left heart congestion with a low workload. It’s very revealing to the significance of mitral valve disease,” he said. Aortic valve disease is also missed in pulmonary hypertension. “It’s not [a] similar” problem; “it’s the same” problem, Dr. Forfia said.

Dr. Forfia is a consultant for Bayer, Actelion, and United Therapeutics.
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Update on NAMDRC activities

BY CHARLES W. ATWOOD JR., MD, FCCP
NAMDRC President-Elect

The NAMDRC annual meeting will be held March 23-25, 2017, at the Meritage Resort in Napa, California. A variety of excellent speakers and topics of interest to the pulmonary, sleep, and critical care medicine community will be presented, including presentations on the asthma-COPD overlap syndrome, pulmonary hypertension in interstitial lung disease, use of big-data in critical care medicine, cardiovascular risk in obstructive sleep apnea, as well as talks on ICD-10 coding, and updates on practice management and on regulatory topics in pulmonary, critical care, and sleep medicine. Finally, Dr. Mark Kelley, a visiting scholar at the Harvard Business School, will present a special lecture on “What do consumers really value in health care?” Meeting details and a registration form can be found at NAMDRC.org.

On the regulatory front, NAMDRC is having ongoing discussions with the Centers for Medicare & Medicaid Services about new proposed regulations regarding so-called site neutrality affecting outpatient facilities after November 2015. The issue at hand is when a health care facility purchases a physician practice and incorporates it as part of its hospital system and subsequently bills hospital outpatient rates for its services. CMS regulations posted in early November would prevent this practice if the outpatient service is more than 250 yards from the main hospital campus and was not billing as an outpatient service prior to Nov. 2, 2015. Congress instructed CMS to try and curtail the practice of hospital acquisition of physician practices where the hospital is subsequently able to bill Medicare for virtually identical services at notably higher payment rates. The CMS rule, now finalized (with a comment period), would have the effect of requiring hospitals that start new pulmonary rehab programs, or expand existing programs at new locations beyond the 250 yard threshold from the main hospital campus, to bill for the outpatient service at the physician fee schedule rate. That rate, notably lower than the hospital outpatient payment rate, would clearly stifle any growth or expansion of pulmonary rehab.

The costs of starting a pulmonary rehabilitation program are capital intensive and, generally, only hospitals can afford the start-up and ongoing costs, making pulmonary rehabilitation almost always a hospital service. Cost data from CMS demonstrate that the vast majority of billing for pulmonary rehab comes from hospitals and not from physician practices. By stopping the use of hospital-based clinic billing for new or expanded pulmonary rehabilitation services, this has the likely result of severely limiting the development of new pulmonary rehabilitation programs.

If the new site of the rehabilitation program is more than 250 yards away, the hospital must bill under the physician fee schedule for reimbursement. No health care enterprise is likely to expand rehabilitation into new venues with such low reimbursement. The real shame in this scenario is that pulmonary rehabilitation is an effective and very low cost intervention for patients with COPD, and its future is largely being threatened by low reimbursement – making it unattractive for hospitals to open new programs in new space they may have purchased.

What is the fix? NAMDRC has discussed this problem with CMS, pointing out the large likely negative impact on pulmonary rehabilitation. We discussed a possible exemption for pulmonary rehabilitation. The final rule does afford an additional comment period, and we anticipate further discussions with CMS. It is also likely that the American Hospital Association, strongly opposed to this new rule, may seek a legislative fix. A final area of activity is our ongoing discussion with CMS about updating the archaic guidelines created by CMS that govern how patients can be prescribed a bilevel positive airway pressure (PAP) therapy device for different forms of hypoventilation. The guidelines have been so complicated to follow that many clinicians, often at the request of a durable medical equipment company, have obtained home ventilators for patients for whom it was difficult to get a bilevel PAP. To be sure, hypoventilation disorders are complicated. The different patient types have somewhat different equipment pathways but all are overly complicated and are real barriers to getting these patients the necessary ventilatory equipment, which usually can be a bilevel PAP device. The home ventilator pathway has been easier to use to get therapy provided so many physicians have followed it, but it is also a lot more expensive. However, as of October 2015, CMS has effectively shut down the home ventilator pathway unless the patient has an indwelling invasive airway (i.e., a tracheotomy tube). NAMDRC, working with other sister societies, patient organizations, and others, has developed a strategy to oppose this draconian step. We hope to move CMS in a more rational direction regarding ventilator therapy for a variety of patients with hypoventilation. This work is complicated, but we are determined to do our utmost to bring a contemporary approach to this important area of therapy.

Take one section of the survey at a time

MOC from page 1

and to make the certification exam relevant to current clinical practice. The ABIM Pulmonary Medicine Board strongly encourages everyone to take the time to help direct the future of the MOC exam.

Diplomates can find the survey when they log into their respective homepages on the ABIM website at www.abim.org. The survey does not need to be completed in one sitting, but rather can be done one section at a time. It takes approximately 15 minutes to finish each section. A link to the survey is located in the My Reminders tab.

This is a great opportunity for individuals to make their voices heard.
Can we count on you?

CHEST Foundation grant funding for the East African Training Initiative (EATI), for example, will help reduce mortality. Ethiopia bears the burden of high TB and lung disease prevalence. In a country of more than 94 million people, a single pulmonologist was tasked with providing treatment to critically ill patients in a 12-bed ICU. He was armed with a dilapidated facility that had no running water, two functioning ventilators, and no means of performing dialysis. There was no continuity of care at the ICU, and rounds were performed only during the week by rotating departments, few of which were trained in critical care.

This all started to change in 2013, when the EATI, a 2-year fellowship training program in pulmonary and critical care medicine, was launched. With the help of funding from a 2016 CHEST Foundation community service grant, the EATI is establishing infrastructure in Ethiopia to train fellows in pulmonary and critical care medicine for years to come. It is not relief work. The fellows graduating the program go on to set up ICUs in their own hospitals and universities. "As of now, we've already graduated five pulmonologists, and we are on track to graduate fifteen by the year 2020," explained Dr. Joseph Huang, Chairman of Fundraising for the EATI. The drastic results of reduced mortality rates in the medical ICU have caught the attention of the Ethiopian Ministry of Health. By working directly with the EATI, the ministry established a task force in ICU medicine.

Continued on following page

This month in CHEST

Editor’s picks

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


Endobronchial Ultrasound: Clinical Uses and Professional Reimbursements. By Dr. T. R. Gildea and Dr. K. Nicolacakis.


INDICATION
• In adults 18 years of age and older: Prevnar 13® is indicated for active immunization for the prevention of pneumonia and invasive disease caused by Streptococcus pneumoniae serotypes 1, 3, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

Limitations of Use and Effectiveness
• Prevnar 13® will only help protect against S. pneumoniae serotypes in the vaccine

IMPORTANT SAFETY INFORMATION
• Severe allergic reaction (eg, anaphylaxis) to any component of Prevnar 13® or any diphtheria toxoid-containing vaccine is a contraindication
• Immunocompromised individuals or individuals with impaired immune responsiveness due to the use of immunosuppressive therapy may have reduced antibody response
• In adults, antibody responses to Prevnar 13® were diminished when given with inactivated influenza vaccine, trivalent (RV2)
• In adults, the most commonly reported solicited adverse reactions were pain, redness, and swelling at the injection site, limitation of arm movement, fatigue, headache, muscle pain, joint pain, decreased appetite, vomiting, fever, chills, and rash

Please see Brief Summary of Prescribing Information on adjacent page(s).


Please visit www.Prevnar13.com for information and directions.
Continued from previous page

cine with a goal to ultimately establish pneumonia (0.9%, 0.5%) for Prevnar 13® and Prevnar® respectively. The incidence of anaphylaxis following administration of the first dose of Prevnar 13® vaccine was 0.1% (0.1% for Prevnar®). Anaphylaxis was identified in the safety follow-up period. There were no deaths from anaphylaxis following administration of the first dose.

CRITICAL CARE COMMENTARY

The ‘big data’ revolution and its relevance to critical care

BY MATTHEW CHURPEK, MD, PHD

According to IBM, over 2 quintillion bytes of data are generated every day (that’s a 2 with 18 zeros!), with over 90% of the data in the world today generated in the past 2 years alone.

In our private lives, much of this information is generated through online shopping, web surfing, and popular websites such as Facebook and Twitter. Companies are making incredible efforts to collect these data and to use it to improve how they relate to customers and, ultimately, to make more money. For example, companies like Google, Amazon, Facebook, and Netflix collect enormous amounts of data and then use algorithms to provide real-time suggestions for what their customers might want to rent, buy, or click on. These algorithms, which companies use for anything from predicting customer behavior to facial recognition, were developed in the field of machine learning, a branch of computer science that focuses on how to learn from data.

Big data and critical care

Although the “big data” revolution has proliferated across the private sector, medicine has been slow to harness the data available in the EHR to improve patient care, critical care should be one of the specialties that benefits the most. With the variability and frequency of monitoring that critically ill patients receive, there are large swaths of data available to collect, analyze, and harness to improve patient care. The current glut of information results in data overload and alarm fatigue for today’s clinicians, but intelligent use of these data holds promise for making care safer and more efficient and effective.


Furthermore, groups have begun “crowdsourcing” critical care problems by making large datasets publicly available, such as the Multi-parameter Intelligent Monitoring in Intensive Care (MIMIC) database, which now holds clinical data from over 40,000 ICU stays from Beth Israel Deaconess Medical Center. Continued efforts to utilize data from patients in the ICU have the potential to revolutionize the care in hospitals today.

An important area of critical care that has seen a rapid rise in the use of EHR data to create decision support tools is in the early detection of critical illness. Given that many in-hospital cardiac arrests occur outside the ICU and delays in transferring critically ill patients to the ICU increase morbidity and mortality (Churpek MM, et al. J Hosp Med. 2016;11[11]:757-62), detecting critical illness early is incredibly important.

For millennia, clinicians have relied on their intuition and the few clinical trials that their patients would have been included in to make decisions, and evidence-based clinical decision support tools are often not available or not used. The tools and scores we have at our disposal are often oversimplified so that they can be calculated by hand and usually rely on the clinician to manually gather information from the electronic health record (EHR) to calculate the score. However, this is starting to change.

From partnerships between IBM Watson and hospitals, to groups developing and implementing clinical decision support tools in the EHR, it is clear that hospitals are becoming increasingly interested in learning from and using the enormous amount of data that are just sitting in the hospital records.

Although there are many areas in medicine that stand to benefit from harnessing the data available in the EHR to improve patient care, critical care should be one of the specialties that benefits the most. With the variety and frequency of monitoring that critically ill patients receive, there are large swaths of data available to collect, analyze, and harness to improve patient care. The current glut of information results in data overload and alarm fatigue for today’s clinicians, but intelligent use of these data holds promise for making care safer and more efficient and effective.

Dr. Churpek

Editor’s comment

Why should busy ICU clinicians bother with big data? Isn’t this simply a “flash in the pan” phenomenon that has sprung up in the aftermath of the electronic medical records (EMRs) mandated by the Affordable Care Act? Are concerns valid that clinical data–based algorithms will lead to an endless stream of alerts akin to the ubiquitous pop-up ads for mortgage refinancing, herbal Viagra, and online gambling that has resulted from commercial data mining?

In this Critical Care Commentary, Dr. Matthew Churpek convincingly outlines the potential inherent in the big data generated by our collective ICUs. These benefits are manifesting themselves not just in the data populated within the EMR – but also in the novel ways we can now design and execute studies. And for those who aren’t yet convinced, recall that payers already use the treasure trove of information within our EMRs against us in the forms of self-serving quality metrics, punitive reimbursements, and unvalidated hospital comparison sites.

Lee E. Morrow, MD, FCCP, is the editor of the Critical Care Commentary section of CHEST Physician.
NUCALA
THE FIRST TARGETED ANTI-INTERLEUKIN 5 THERAPY FOR SEVERE ASTHMA WITH AN EOSINOPHILIC PHENOTYPE

NUCALA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older with an eosinophilic phenotype.

- NUCALA is not indicated for treatment of other eosinophilic conditions.
- NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

Important Safety Information

CONTRAINDICATIONS
NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions
Hypersensitivity reactions (eg, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration but in some instances can have a delayed onset (ie, days). In the event of a hypersensitivity reaction, NUCALA should be discontinued.

Acute Asthma Symptoms or Deteriorating Disease
NUCALA should not be used to treat acute asthma symptoms, acute exacerbations, or acute bronchospasm.

Opportunistic Infections: Herpes Zoster
In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in subjects treated with NUCALA compared to none in placebo. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA.

Reduction of Corticosteroid Dosage
Do not discontinue systemic or inhaled corticosteroids (ICS) abruptly upon initiation of therapy with NUCALA. Decreases in corticosteroid doses, if appropriate, should be gradual and under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helmith) Infection
It is unknown if NUCALA will influence a patient’s response against parasites. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

ADVERSE REACTIONS
The most common adverse reactions (≥3% and more common than placebo) reported in the first 24 weeks of 2 clinical trials with NUCALA (and placebo) were: headache, 19% [18%]; injection site reaction, 8% [3%]; back pain, 5% [4%]; fatigue, 5% [4%]; influenza, 3% [2%]; urinary tract infection, 3% [2%]; abdominal pain upper, 3% [2%]; pruritus, 3% [2%]; eczema, 3% [<1%]; and muscle spasm, 3% [<1%].
NUCALA IS PROVEN TO:

- **Reduce exacerbations** by **53%** (NUCALA: 0.83/year; placebo: 1.74/year, \(P<0.001\))
- **Reduce daily OCS dose while maintaining asthma control** (\(P=0.008\))
- **Improve quality of life (SGRQ)** with a responder rate of **71%** for NUCALA compared with **55%** for placebo (odds ratio of 2.1; 95% CI: 1.3, 3.2)

- Statistical hierarchy was not met, endpoint is exploratory, and results are descriptive only

In a 32-week study of patients with severe asthma with an eosinophilic phenotype, NUCALA (n=194) and placebo (n=191), each added to high-dose ICS and at least 1 other controller with or without OCS and dosed once every 4 weeks, were compared to evaluate the frequency of exacerbations. In a 24-week study of 135 patients with severe asthma with an eosinophilic phenotype, NUCALA and placebo were each added to high-dose ICS and at least 1 other controller and dosed once every 4 weeks to compare the percent reduction in daily OCS dose (weeks 20 to 24) while maintaining asthma control.

ICS=inhaled corticosteroids; OCS=oral corticosteroids; SGRQ=St. George’s Respiratory Questionnaire.

* Defined as the worsening of asthma that required use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits; for patients requiring maintenance oral/systemic corticosteroids, exacerbations were defined as at least double the existing maintenance dose for at least 3 days.

† The SGRQ is a validated measure of health impairment for chronic respiratory diseases and is able to address the impact asthma has on a patient’s quality of life. Response is defined as a change in score of 4 or more as threshold.

Visit **NUCALAhcp.com** for more information, including patient access programs.

**Important Safety Information (cont’d)**

**ADVERSE REACTIONS (cont’d)**

Systemic Reactions, including Hypersensitivity Reactions: In 3 clinical trials, 10% of subjects who received NUCALA experienced systemic (allergic and nonallergic) and local site reactions compared to 7% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 1% of subjects who received NUCALA compared to 2% of subjects in the placebo group. Manifestations included rash, pruritus, headache, and myalgia. Systemic nonallergic reactions were reported by 2% of subjects who received NUCALA and 3% of subjects in the placebo group. Manifestations included rash, flushing, and myalgia. A majority of the systemic reactions were experienced on the day of dosing.

Injection Site Reactions: Injection site reactions (eg, pain, erythema, swelling, itching, and burning sensation) occurred at a rate of 8% in subjects treated with NUCALA compared with 3% in subjects treated with placebo.

**USE IN SPECIFIC POPULATIONS**

A pregnancy exposure registry monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting www.mothertobaby.org/asthma.

The data on pregnancy exposures from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are progressively transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters of pregnancy.

Reference: 1. Data on file, GSK.
NUCALA®
(mepolizumab) for injection, for subcutaneous use
The following is a brief summary only; see full Prescribing Information for complete product information.

INDICATIONS AND USAGE
NUCALA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. [See Clinical Studies of full Prescribing Information.]

Limitations of Use
• NUCALA is not indicated for treatment of other eosinophilic conditions.
• NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

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WARNINGS AND PRECAUTIONS

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Acute Asthma Symptoms or Deteriorating Disease
NUCALA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use NUCALA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

Opportunistic Infections: Herpes Zoster
In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in subjects treated with NUCALA compared with none in placebo [see Adverse Reactions]. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA.

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Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection
Eosinophils may be involved in the immunological response to some helminth infections. Patients with known parasitic infections were excluded from participation in clinical trials. It is unknown if NUCALA will influence a patient’s response against parasitic infections. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

ADVERSE REACTIONS
The following adverse reactions are described in greater detail in other sections:
• Hypersensitivity reactions [see Warnings and Precautions]
• Opportunistic infections: herpes zoster [see Warnings and Precautions]

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.
A total of 1,327 subjects with asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks’ duration (Trials 1, 2, and 3). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) (Trials 1 and 2), and 135 subjects required daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s) to maintain asthma control (Trial 3). All subjects had markers of eosinophilic airway inflammation [see Clinical Studies of full Prescribing Information]. Of the subjects enrolled, 59% were female, 85% were white, and subjects ranged in age from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 subjects received NUCALA (mepolizumab 100 mg subcutaneous [SC]) for at least 24 weeks. Serious adverse events that occurred in more than 1 subject and in a greater percentage of subjects treated with NUCALA (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 subjects vs. 0 subjects, respectively). Approximately 2% of subjects receiving NUCALA withdrew from clinical trials due to adverse events compared with 3% of subjects receiving placebo.

The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with NUCALA is shown in Table 1.

### Table 1. Adverse Reactions with NUCALA with Greater than or Equal to 3% Incidence and More Common than Placebo in Subjects with Asthma (Trials 2 and 3)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 263)</th>
<th>Placebo (n = 257)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>51 (19%)</td>
<td>18 (7%)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>5 (2%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>30 (12%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (7%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>15 (6%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>12 (5%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>11 (4%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12 (5%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Eczema</td>
<td>12 (5%)</td>
<td>1 (0.4%)</td>
</tr>
</tbody>
</table>

52-Week Trial
Adverse reactions from Trial 1 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with greater than or equal to 3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthma, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in subjects treated with mepolizumab 75 mg IV, compared with 2 subjects in the placebo group.

Systemic Reactions, including Hypersensitivity Reactions
In Trials 1, 2, and 3 described above, the percentage of subjects who experienced systemic (allergic and non-allergic) and local site reactions was 7% in the placebo group and 10% in the group receiving NUCALA. Systemic allergic/hypersensitivity reactions were reported by 2% of subjects in the placebo group and 1% of subjects in the group receiving NUCALA. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of subjects in the group receiving NUCALA and 3% of subjects in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA included rash, flushing, and myalgia. A majority of the systemic reactions in subjects receiving NUCALA (5/7) were experienced on the day of dosing.

Injection Site Reactions
Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in subjects treated with NUCALA compared with 3% in subjects treated with placebo.

Long-Term Safety
Nine hundred ninety-eight (998) subjects have received NUCALA in ongoing open-label extension studies, during which additional cases of herpes zoster have been reported. The overall adverse event profile was similar to the asthma trials described above.

Immunogenicity
Overall, 15/260 (6%) subjects treated with NUCALA developed anti-mepolizumab antibodies. The reported frequency may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. Neutralizing antibodies were detected in 1 subject receiving mepolizumab. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known.

The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

DRUG INTERACTIONS
Formal drug interaction trials have not been performed with NUCALA.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting www.mothertobaby.org/asthma.

Risk Summary
The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was...
no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 30 times the exposure at the maximum recommended human dose (MRHD) of 100 mg SC [see Data].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk: In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data: In a preclinical and postnatal development study, pregnant cynomolgus monkeys received mepolizumab from gestation days 20 to 140 at doses that produced exposures up to approximately 30 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal and external malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to day 178 postpartum. Levels of mepolizumab in milk were less than or equal to 0.5% of maternal serum concentration. In a fertility, early embryonic, and embryo-fetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine interleukin-5 (IL-5), at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryo-fetal development of IL-5-deficient mice has been reported to be generally unaffected relative to wild-type mice.

Lactation

Risk Summary

There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (lgG1 kappa), and immunoglobin G (lgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy [see Use in Specific Populations]. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

Pediatric Use

The safety and efficacy in pediatric patients younger than 12 years have not been established. A total of 28 adolescents aged 12 to 17 years with asthma were enrolled in the phase 3 studies. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2) and had a mean age of 14.6 years. Subjects had a history of 2 or more exacerbations in the previous year despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) with or without oral corticosteroids and had blood eosinophils of greater than or equal to 150 cells/mcL at screening or greater than or equal to 300 cells/mcL within 12 months prior to enrollment. [see Clinical Studies of full Prescribing Information] Subjects had a reduction in the rate of exacerbations that trended in favor of mepolizumab. Of the 19 adolescents who received mepolizumab, 9 received NUCALA and the mean apparent clearance in these subjects was 35% less than that of adults. The adverse event profile in adolescents was generally similar to the overall population in the phase 3 studies [see Adverse Reactions].

Geriatric Use

Clinical trials of NUCALA did not include sufficient numbers of subjects aged 65 years and older that received NUCALA (n = 38) to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Based on available data, no adjustment of the dosage of NUCALA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

OVERDOSAGE

Single doses of up to 1,500 mg have been administered intravenously to subjects in a clinical trial with eosinophilic disease without evidence of dose-related toxicities. There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportive with appropriate monitoring as necessary.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.

Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys treated with mepolizumab for 6 months at IV doses up to 100 mg/kg once every 4 weeks approximately 70 times the MRHD on an AUC basis. Mating and reproductive performance were unaffected in male and female CD-1 mice treated with an analogous antibody, which inhibits the activity of murine IL-5, at an IV dose of 50 mg/kg once per week.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Instruct patients to contact their physicians if such reactions occur.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that NUCALA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

Opportunistic Infections: Herpes Zoster

Inform patients that herpes zoster infections have occurred in patients receiving NUCALA and where medically appropriate, inform patients varicella vaccination should be considered before starting treatment with NUCALA.

Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Pregnancy Exposure Registry

Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUCALA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting www.mothertobaby.org/asthma [see Use in Specific Populations].

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Manufactured by

GlaxoSmithKline LLC
Philadelphia, PA 19112
U.S. License Number 1727

Distributed by

GlaxoSmithKline
Research Triangle Park, NC 27709
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Continued from page 27

scores and many more will likely become commonplace in hospitals to provide an objective and accurate way to identify critically ill patients earlier, which may result in decreased preventable morbidity and mortality.

Future directions

There are several important future directions at the intersection of big data and critical care. First, efforts to collect, store, and share the highly granular data in the ICU are paramount for successful and generalizable research collaborations. Although there are often institutional barriers to data sharing due to surmount, efforts such as the MIMIC database, provide a roadmap for how ICU data can be shared and problems “crowdsourced” in order to allow researchers access to these data for high quality research.

Second, efforts to fuse randomized controlled trials with big data, such as randomized, embedded, multifactorial, adaptive platform (REMAP) trials, have the potential to greatly enhance the way trials are done in the future. REMAP trials would be embedded in the EHR, provide the ability to study multiple therapies at once, and adapt the randomization scheme to ensure that patients are not harmed by interventions that are clearly detrimental while the study is ongoing (Angus DC. JAMA. 2015;314(8):767-8).

Finally, it is important that we move beyond the classic statistical methods that are commonly used to develop decision support tools and increase our use of more modern machine learning techniques that companies in the private sector use every day. For example, our group found that classic regression methods were the least accurate of all the methods we studied for detecting clinical deterioration on the wards (Churpek MM, et al. Crit Care Med. 2016;44[2]:368-74). In the future, methods such as the random forest and neural network should become commonplace in the critical care literature.

The big data revolution is here, both in our private lives and in the hospital. The future will bring continued efforts to use data to identify critical illness earlier, improve the care of patients in the ICU, and implement smarter and more efficient clinical trials. This should rapidly increase the generation and utilization of new knowledge and will have a profound impact on the way we care for critically ill patients.

Editor’s Note

Dr. Lee’s thoughtful piece about why she chose to go into pulmonary–critical care medicine is both inspiring and insightful. She deserves commendation for her willingness to share her story, and I am humbled by her words.

Nitin Puri, MD, FCCP, is the editor of the Pulmonary Perspectives section of CHEST Physician.


dr lee.jpg

Dr. Samantha Lee graduated from American University of Antigua College of Medicine in 2014.
A recently evolved strain of *Mycobacterium* is circulating in hospitals worldwide, causing nearly impossible-to-treat lung infections among patients with cystic fibrosis.

A genome-wide study has determined that *Mycobacterium abscessus* is not transmitted through soil and water, as once thought, but is a nosocomial infection transmitted person to person through droplet and surface contamination, Andres Floto, MD, reported in Science (2016 Nov 11;354[6313]:751-7).

“The bug initially seems to have entered the patient population from the environment, but we think it has recently evolved to become capable of jumping from patient to patient, getting more virulent as it does so,” Dr. Floto of the University of Cambridge, England, wrote in a press statement.

The path of global transmission is not yet entirely clear, the authors noted. But since it first appeared, around 1978, *M. abscessus* has spread globally, strongly suggesting that asymptomatic carriers may be one source of transmission.

“We found no evidence of cystic fibrosis patients or of equipment moving between centers in different countries, indicating that the global spread of *M. abscessus* may be driven by alternative human, zoonotic, or environmental vectors of transmission,” the researchers wrote.

The team conducted whole-genome sequencing

Continued on following page

**CF patients need conscientious infection control**

Aapproximately 30,000 American adults, children, and infants have cystic fibrosis. Non-tuberculous mycobacteria (NTM) are ubiquitous environmental microorganisms, and it has been known for some time that these infections can be transmitted person to person. Any patient, actually, who has preexisting lung disease – and especially those with poor mucociliary clearance – are at risk for a nontuberculous mycobacterial infection. This type of lung infection also can be difficult to diagnose and hard to treat. The U.S. Cystic Fibrosis Foundation in conjunction with the European Cystic Fibrosis Society has developed consensus guidelines for infection control, evaluation, and treatment of this problem. This executive summary was published last January (Floto et al. Thorax.2016;71:i1-i22).

Specifically for nontuberculous mycobacteria, it is recommended to see patients in CF clinic and admit patients to the hospital in an “airborne infection isolation room (AIIR)” if NTM is suspected and until *M. tuberculosis* is ruled out. These AIIRs use engineering controls to prevent airborne transmission of infectious agents that remain suspended in the air and travel long distances along air currents. Rooms that have been renovated or constructed prior to 2001 must have at least six air exchanges per hour and those renovated or constructed since 2001 must at least 12 air exchanges per hour. These rooms should be under negative pressure. Also, even though in a negative pressure room, the patient will be under contact precautions: anyone entering must be gowned, gloved, and wearing an N95 respirator.

At our center, in addition to the standard contact precautions we use for every CF patient, patients with confirmed NTM infections are seen at every clinic visit in an airborne infection isolation room. We also require all CF patients to wear an isolation mask when entering the hospital or clinic facility, when going to a laboratory, or even when going to the bathroom down the hall. Finally, we stress the significant importance of good hand hygiene.

Susan Millard, MD, FCCP, is a pediatric pulmonologist with Spectrum Health/Butterworth Hospital in Grand Rapids, Mich.

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**Hypervirulent *Mycobacterium* infecting CF patients**

**BY MICHELE G. SULLIVAN**

*Frontline Medical News*

**VIEW ON THE NEWS**

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**CHEST 2017 Education Calendar**

> Learn More livelearning.chestnet.org

<table>
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<tr>
<th>Live Learning Courses</th>
<th>Courses held at the CHEST Innovation, Simulation, and Training Center in Glenview, Illinois</th>
</tr>
</thead>
<tbody>
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<td><strong>Mechanical Ventilation: Advanced Critical Care Management</strong></td>
<td>February 17-19, July 28-30</td>
</tr>
<tr>
<td><strong>Comprehensive Bronchoscopy With Endobronchial Ultrasound</strong></td>
<td>February 24-26, September 29 - October 1</td>
</tr>
<tr>
<td><strong>Ultrasoundography: Essentials in Critical Care</strong></td>
<td>March 3-5, September 15-17, December 1-3</td>
</tr>
<tr>
<td><strong>Bronchoscopy Procedures for the ICU</strong></td>
<td>May 6-7</td>
</tr>
<tr>
<td><strong>Advanced Critical Care Echocardiography</strong></td>
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</tr>
<tr>
<td><strong>Difficult Airway Management</strong></td>
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<tr>
<td><strong>Bronchoscopy and Pleural Procedures for Pulmonary and Critical Care Medicine Fellows</strong></td>
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<tr>
<td><strong>Comprehensive Pleural Procedures</strong></td>
<td>August 4-5</td>
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<tr>
<td><strong>Critical Skills for Critical Care: A State-of-the-Art Update and Procedures for ICU Providers</strong></td>
<td>August 11-13</td>
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<tr>
<td><strong>Cardiopulmonary Exercise Testing</strong></td>
<td>September 22-24</td>
</tr>
<tr>
<td><strong>Critical Care Ultrasound: Integration into Clinical Practice</strong></td>
<td>November 10-12</td>
</tr>
</tbody>
</table>

*Calendar subject to change. For most current course list and more information, visit livelearning.chestnet.org.*
ADDITIONAL INDICATION

UPTRAVI is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH. Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms.

PAH associated with congenital heart disease with UHSDLUHGVKXQWV

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Pulmonary Veno-Occlusive Disease (PVOD)
Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue UPTRAVI.
Please see additional Important Safety Information on adjacent page.

The research was funded by the Wellcome Trust and the Cystic Fibrosis Trust in the United Kingdom. There were no financial disclosures.
UPTRAVI® (selalexipag)—
The Only Oral PAH Therapy
Targeting the Prostacyclin Pathway
Proven to Delay Disease Progression

RESULTS FROM GRIPHON, THE LARGEST OUTCOMES TRIAL EVER CONDUCTED IN PAH (N=1156)

GRIPHON was a multicenter, long-term, double-blind, placebo-controlled, parallel-group, event-driven phase 3 study in 1,156 patients (UPTRAVI: n=574; placebo: n=582) with symptomatic PAH (nearly all WHO FC II-III at baseline). The median treatment duration for the UPTRAVI group was 1.4 years.

40% RISK REDUCTION IN DISEASE PROGRESSION IN PATIENTS TREATED WITH UPTRAVI (p<0.0001)

• Reductions in PAH-related hospitalization and other disease progression events* drove the overall reduction

PRIMARY ENDPOINT EVENTS UP TO THE END OF TREATMENT:

A primary endpoint event was experienced by 27.0% of UPTRAVI-treated patients vs 41.6% of placebo-treated patients.

Disease progression primary endpoint comprised the following components as first events (up to end of treatment; UPTRAVI vs placebo): hospitalization for PAH (13.6% vs 18.7%), other disease progression events (6.6% vs 17.2%)* death (4.9% vs 3.1%), initiation of parenteral prostanooid or chronic oxygen therapy (1.7% vs 2.2%), and PAH worsening resulting in need for lung transplantation or balloon atrial septostomy (0.2% vs 0.3%).

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

Adverse reactions occurring more frequently (≥3%) on UPTRAVI compared to placebo are headache (65% vs 32%), diarrhea (42% vs 18%), jaw pain (26% vs 6%), nausea (33% vs 18%), myalgia (16% vs 6%), vomiting (18% vs 9%), pain in extremity (17% vs 8%), flushing (12% vs 5%), arthralgia (11% vs 8%), anemia (8% vs 5%), decreased appetite (6% vs 3%), and rash (11% vs 8%). These adverse reactions are more frequent during the dose titration phase. Hyperthyroidism was observed in 1% (n=8) of patients on UPTRAVI and in none of the patients on placebo.

DRUG INTERACTIONS

Strong CYP2C8 inhibitors

Concomitant administration with strong inhibitors of CYP2C8 (eg, gemfibrozil) may result in a significant increase in exposure to selexipag and its active metabolite. Avoid concomitant use.

DOSAGE AND ADMINISTRATION

Recommended Dosage

Recommended starting dose is 200 mcg twice daily. Tolerability may be improved when taken with food. Increase by 200 mcg twice daily, usually at weekly intervals, to the highest tolerated dose up to 1600 mcg twice daily. If dose is not tolerated, reduce to the previous tolerated dose.

Patients with Hepatic Impairment

For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose is 200 mcg once daily. Increase by 200 mcg once daily at weekly intervals, as tolerated. Avoid use of UPTRAVI in patients with severe hepatic impairment (Child-Pugh class C).

Dosage Strengths

UPTRAVI tablet strengths: 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg

Please see Brief Summary of Prescribing Information on the following page.

* Other disease progression defined as a 15% decrease from baseline in 6MWD plus worsening of Functional Class or need for additional PAH-specific therapy.

6MWD=6-minute walk distance; WHO=World Health Organization.


Visit www.UPTRAVI.com to learn more and download the Patient Enrollment Form.
In an effort to examine the reduction in moderate or severe exacerbations in COPD patients taking indacaterol/glycopyrronium (a combination of a LABA bronchodilator and a LAMA bronchodilator) or salmeterol/fluticasone (a LAMA and an inhaled glucocorticosteroid), researchers compared results from the FLAME and LANTERN trials. The FLAME study evaluated the rate and risk of exacerbations with indacaterol/glycopyrronium versus salmeterol/fluticasone in 3,362 moderate to very severe COPD patients with at least one exacerbation in the previous year (Int J Chron Obstruct Pulmon Dis. 2015;10:1015-26).

Dr. Chapman, professor of medicine at the University of Toronto, reported that, in the FLAME study, which was 52 weeks long, indacaterol/glycopyrronium significantly reduced the annualized rate of moderate or severe exacerbations in patients who had one or more exacerbation in the previous year (a rate ratio of 0.83; P < 0.001), which translated into a clinically meaningful 17% reduction, compared with their counterparts taking salmeterol/fluticasone (RR, 0.89; P = 0.046).

In the LANTERN study, which was 26 weeks long, indacaterol/glycopyrronium also significantly reduced the annualized rate of patients who had 0-1 exacerbation in the previous year, compared with those taking salmeterol/fluticasone (RR, 0.89; P < 0.001).

In FLAME, indacaterol/glycopyrronium significantly delayed the time to first moderate or severe exacerbation, with a clinically meaningful 22% risk reduction, compared with salmeterol/fluticasone (hazard ratio, 0.78; P < 0.001). Similar findings were observed in LANTERN; indacaterol/glycopyrronium significantly delayed the time to first moderate or severe exacerbation, with a clinically meaningful 35% risk reduction, compared with salmeterol/fluticasone (HR, 0.65; P < 0.028).

“These results suggest that LABA/LAMA combinations such as indacaterol/glycopyrronium can be considered as a preferred treatment option for the management of COPD patients, irrespective of exacerbation history,” Dr. Chapman said. He reported having numerous financial disclosures.
Bleeding upped when on antiplatelets during EBUS

BY M. ALEXANDER OTTO  
Frontline Medical News  
AT CHEST 2016

LOS ANGELES – There might be a slight increase in delayed bleeding when patients have endobronchial ultrasound (EBUS) with transbronchial needle aspiration within 5 days of taking oral antiplatelets, according to a review of 404 patients at Riverside Methodist Hospital in Columbus, Ohio.

This study is unusual in that it looked at the 48 hour mark. Previous studies have tended to focus on immediate bleeding events that require the procedure to be stopped; only some of that research has found an increased bleeding risk with antplatelet therapy.

In the study at Riverside Methodist, none of the 20 patients on dual antiplatelet therapy – clopidogrel (Plavix) plus aspirin – bled during the procedure, but one (5%) had a hemoglobin drop of more than 2 g within 48 hours and another was readmitted for procedure-related hemoptysis. Overall, the delayed bleeding event rate for patients using the dual antiplatelet therapy was 10%.

Among the 270 patients not exposed to antiplatelets, the overall bleeding event rate was 2.6%, and the event rate for delayed bleeding was 1.1%. Four patients (1.5%) bled during the procedure, two (0.7%) had hemoglobin drops greater than 2 g within 48 hours, and one (0.4%) was readmitted for hemoptysis.

There were no bleeding events in 101 patients who took only aspirin.

“There was a trend toward delayed bleeding events in patients on clopidogrel or dual antiplatelets. “It’s worth considering a thoughtful pause in decision making. Maybe with the bleeding events we’re seeing, it would be worthwhile, if possible, to defer EBUS with transbronchial needle aspiration “until after the antiplatelet therapy,” said Kevin Swiatek, DO, a medicine resident at Riverside, at the annual meeting of the American College of Chest Physicians.

In a review of 404 patients at Sohag (Egypt) University, retrospectively evaluated 400 COPD patients who were at least 40 years of age. Those who presented with bronchial asthma or other lung diseases were excluded from the analysis. The mean age of patients was 62 years, 69% were male, and 36% were current smokers. Their mean FEV1/FVC ratio (forced expiratory volume in 1 second/forced vital capacity) was 48%, and 57% had two or more exacerbations in the previous year.

Dr. Mohammadien reported that all patients had at least one comorbidity. The most common comorbidities were cardiovascular diseases (85%), diabetes (35%), dyslipidemia (23%), osteopenia (11%), anemia (10%), muscle wasting (9%), pneumonia (7%), osteoporosis (6%), GERD (2%), and lung cancer (2%). He also noted that the association between cardiovascular events, dyslipidemia, diabetes, osteoporosis, muscle wasting, and anemia was highly significant in COPD patients aged 60 years and older, in men, and in patients with stage III and IV COPD. In addition, a significant relationship was observed between a positive CRP level and each comorbidity, with the exception of gastroesophageal reflux disease and lung cancer. The three comorbidities with the greatest significance were ischemic heart disease (P = .0001), dyslipidemia (P = .0001), and pneumonia (P = .0003). Finally, frequent exacerbators were significantly more likely to have two or more comorbidities (odds ratio 2.04) and to have more hospitalizations in the past year (P less than .01).

“Comorbidities are common in patients with COPD, and have a significant impact on health status and prognosis, thus justifying the need for a comprehensive and integrating therapeutic approach,” said Dr. Mohammadien, who reported no conflicts of interest, at the meeting.

Comorbidities common in COPD patients

BY DOUG BRUNK  
Frontline Medical News  
AT CHEST 2016

LOS ANGELES – Comorbidities are common in patients with chronic obstructive pulmonary disease, especially cardiovascular disease, diabetes, anemia, and osteoporosis, results from a single-center analysis showed.

“These affect the course and outcome of COPD, so identification and treatment of these comorbidities are very important,” Hamdy Mohammadien, MD, FCCP, said in an interview in advance of the annual meeting of the American College of Chest Physicians.

In an effort to estimate the presence of comorbidities in patients with COPD and to assess the relationship of comorbid diseases with age, sex, C-reactive protein, and COPD severity, Dr. Mohammadien and his associates prospectively evaluated 250 critically ill ICU patients who were at least 40 years of age. Those who presented with bronchial asthma or other lung diseases were excluded from the analysis. The mean age of patients was 62 years, 69% were male, and 36% were current smokers. Their mean FEV1/FVC ratio (forced expiratory volume in 1 second/forced vital capacity) was 48%, and 57% had two or more exacerbations in the previous year.

Dr. Mohammadien reported that all patients had at least one comorbidity. The most common comorbidities were cardiovascular diseases (85%), diabetes (35%), dyslipidemia (23%), osteopenia (11%), anemia (10%), muscle wasting (9%), pneumonia (7%), osteoporosis (6%), GERD (2%), and lung cancer (2%). He also noted that the association between cardiovascular events, dyslipidemia, diabetes, osteoporosis, muscle wasting, and anemia was highly significant in COPD patients aged 60 years and older, in men, and in patients with stage III and IV COPD. In addition, a significant relationship was observed between a positive CRP level and each comorbidity, with the exception of gastroesophageal reflux disease and lung cancer. The three comorbidities with the greatest significance were ischemic heart disease (P = .0001), dyslipidemia (P = .0001), and pneumonia (P = .0003). Finally, frequent exacerbators were significantly more likely to have two or more comorbidities (odds ratio 2.04) and to have more hospitalizations in the past year (P less than .01).

“Comorbidities are common in patients with COPD, and have a significant impact on health status and prognosis, thus justifying the need for a comprehensive and integrating therapeutic approach,” said Dr. Mohammadien, who reported no conflicts of interest, at the meeting.

Continued on following page

SOFα best predicted in-hospital mortality in acute COPD

BY DOUG BRUNK  
Frontline Medical News  
AT CHEST 2016

LOS ANGELES – The Sequential Organ Failure Assessment (SOFA) score and the Glasgow Coma Scale (GCS) are simple, accurate tools for risk stratification of hospitalized patients with acute exacerbation of COPD, results from a single-center study showed.

“Acute exacerbations of chronic obstructive pulmonary disease often require hospitalization, may necessitate mechanical ventilation, and can be fatal,” Mohamed Metwally, MD, FCCP, said in an interview in advance of the annual meeting of the American College of Chest Physicians. “There are currently no validated disease-specific scores that measure the severity of acute exacerbation. Prognostic tools are needed to assess acute exacerbations of chronic obstructive pulmonary disease.”

Dr. Metwally of Assiut (Egypt) University Hospital noted that scoring models were first introduced for critically ill patients in the ICU in 1980 and subsequently developed for heterogeneous ICU populations, but have not been used to study risk prediction in COPD patients. The purpose of the current trial was to evaluate and compare the performance of general scoring systems commonly used in general ICUs to accurately predict outcomes in hospitalized patients with acute exacerbation of COPD (AECOPD).

For the 2-year study, Dr. Metwally and his associates prospectively evaluated 250 critically ill ICU AECOPD patients, mean age 65 years, at Assiut University Hospital between December 2012 and December 2014. The primary outcome was inhospital mortality while the secondary endpoint was need for intubation and mechanical ventilation. The researchers excluded patients who died less than 24 hours after admission, those with underlying COPD who were admitted with another primary diagnosis such as an accident or a stroke, or for elective hospitalizations such as elective surgery or diagnostic procedures.

Dr. Metwally and his associates collected sociodemographic data, vital signs, and other clinical data.
variables, and collected scores from five tools used to measure mortality prediction: the Acute Physiology and Chronic Health Evaluation (APACHE II), the SOFA score, the Early Warning Score (EWS), the GCS, and the Charlson Comorbidity Index (CCI). To assess performance of the scores, they used area under the receiver operating characteristic curve (AUC) analysis and the Hosmer-Lemeshow goodness-of-fit test for logistic regression.

Of the 250 patients, 43 (17%) died during their hospital stay and 54% required mechanical ventilation. All recorded scores were significantly higher in nonsurvivors, compared with survivors, and the risk of clinical deterioration increased with increasing scores. The discriminatory power of each score varied as measured by AUC analysis. The AUC of APACHE II, SOFA, EWS, GCS, and CCI were 0.79, 0.81, 0.76, 0.69, and 0.68, respectively, and all these models had good calibration in mortality prediction, Dr. Metwally said. The SOFA score was the best in predicting mortality (its predicted mortality was 16%, compared with the actual mortality of 17%), while the APACHE II score overestimated mortality by at least twofold (46% vs. 17%). In addition, the EWS outperformed the GCS in predicting mortality. “This may be due to EWS containing all vital signs plus level of consciousness,” he said in an interview.

The GCS was found to be the most useful in predicting need for mechanical ventilation, with an AUC of 0.81. The AUCs of APACHE II, SOFA, EWS, and CCI were 0.79, 0.80, 0.73, and 0.61, respectively. All of the scores had good calibration in mortality prediction, Dr. Metwally said, with the exception of SOFA.

LABA withdrawal does not worsen asthma control

BY SARA FREEMAN
Frontline Medical News

LONDON – Real-life experience shows that stopping treatment with a long-acting beta-agonist (LABA) does not worsen asthma control, nor does it lead to any immediate decline in lung function.

Spirometric parameters were similar before and 3 weeks after stopping LABA therapy in an observational study of 38 patients who had stable asthma and were being treated with an inhaled corticosteroid (ICS) and a LABA.

The forced expiratory volume in 1 second (FEV1) was 88.8% at baseline and 89.5% at the 3-week visit after stepping down their LABA therapy (P = .55). Patients’ average peak expiratory flow rate was 462 L/min both before and after LABA withdrawal.

In addition, no changes were seen in lung function based on impulse oscillometry, a non-invasive method for measuring airway resistance and reactance (Chest. 2014;146[3]:841-7). Similar levels of fractional exhaled nitric oxide (FeNO, 38 and 36 ppb) were recorded.

The findings were presented at the annual congress of the European Respiratory Society (ERS) and have been published in an early online edition of the Annals of Allergy, Asthma & Immunology (doi: 10.1016/j.anai.2016.07.022).

About 45% of the UK adult asthma population are taking step 3 GINA (Global Initiative for Asthma) therapy, which is ICS/LABA, said Sunny Jabbal, MD, of the Scottish Centre for Respiratory Research at Ninewells Hospital in Dundee, where the study was conducted. Patients should be on the lowest of the five steps in the 2016 GINA guidelines that achieve asthma control and should be regularly reviewed.

To test whether the LABA could be safely withdrawn, that is stepped down to ICS only (GINA step 2), Dr. Jabbal and his colleagues studied 38 patients with a mean age of 39 years. All had well-controlled asthma, and had been receiving ICS/LABA for at least 3 months with no asthma exacerbations requiring treatment. None of the patients were current smokers.

At study entry, patients underwent spirometry, impulse oscillometry, and had FeNO measured. Their LABA was then stopped, and patients were reassessed 3 weeks later. In accordance with GINA, their ICS dose was also reduced by approximately 25%,” Dr. Jabbal said. Patients recorded their symptoms and short-term reliever (albuterol) use on simple diary cards. No adverse events were reported. The mean daily symptom score recorded during the step down process was 0.4, and the mean albuterol usage was one puff per day.
Asthma-COPD overlap syndrome gets missed

BY M. ALEXANDER OTTO
Frontline Medical News

Exacerbations in bronchodilator-responsive asthma–COPD overlap syndrome (ACOS) were more frequent and severe than in chronic obstructive pulmonary disease with emphysema, but only a minority of patients were treated to prevent them, in a review of 1,005 patients from the Annals of the American Thoracic Society.

All subjects were current or former smokers culled from the COPDGene Study, a multicenter observational study looking for the genetic roots of COPD susceptibility; 385 patients met the investigators’ criteria for ACOS with bronchodilator response (ACOS-BDR), which included a history of asthma or hay fever, airflow obstruction with significant bronchodilator responsiveness, and less than 15% emphysema on chest CT.

Another 620 subjects met criteria for COPD with emphysema, including airflow obstruction without bronchodilator reversibility, and more than 15% emphysema on chest CT (Ann Am Thorac Soc. 2016 Sep;13(9):1483-9).

Although the ACOS patients had better lung function, they had similar severity and frequency of exacerbations, compared with the COPD group. After adjustment for forced expiratory volume in 1 second (FEV1) percent predicted and other factors, the patients with ACOS-BDR were actually more likely to have severe and frequent exacerbations. Possible explanations for this are that they were more likely to smoke and have gastroesophageal reflux disease and obstructive sleep apnea, all of which increase the risk of exacerbations.

Even so, ACOS-BDR patients were less likely to be on a long-acting beta-agonist (6.8% vs. 13.9%); a long-acting muscarinic antagonist (20% vs. 60.8%); or a combination long-acting beta-agonist/inhaled corticosteroid (29.9% vs. 55.6%).

“Only a small percentage of them were being treated ... Early and aggressive treatment with combination therapy may help alleviate symptoms and decrease exacerbations,” said investigators led by James Cosentino, DO, of Temple University, Philadelphia. Patients with ACOS “are a particularly high-risk group. They deserve ‘special attention, and practitioners need to be diligent in evaluation of them.”

ACOS is being increasingly recognized as a distinct clinical entity with perhaps a worse prognosis than either asthma or COPD alone. The goal of the study was to better characterize the disease.

To that end, the team found four features that seemed to distinguish ACOS-BDR from COPD with emphysema: ACOS-BDR patients were younger (60.6 vs. 65.9 years old); heavier (body mass index 29.6 vs. 25.1 kg/m²); more likely to be African American (26.8% vs. 14.4%); and more likely to be current smokers (50.9% vs. 20.7%).

It’s “likely that current smoking in subjects with ACOS, coupled with the long duration of asthma, leads to inflammation and small airway remodeling with development of symptoms earlier in the disease course than that seen in those with COPD with emphysema,” the investigators said.

“Early and aggressive treatment with combination therapy may help alleviate symptoms and decrease exacerbations. Recognition and treatment of comorbidities and aggressive smoking cessation may also play a key role in preventing exacerbations and alleviating the morbidity associated with ACOS; however, future studies on the treatment of ACOS are needed,” they said.

The majority of subjects with ACOS-BDR met criteria for Global Initiative for Chronic Obstructive Lung Disease grade B, indicating a high degree of symptoms despite less severe airflow obstruction.

Dr. Cosentino had no conflicts. Other authors disclosed personal fees from Concert Pharmaceuticals, CSA Medical, CSL Behring, Galapagos Therapeutics, and Novartis.

Call it all obstructive airway disease

The importance of this study is that it used readily available metrics to define ACOS in a COPD population. Although diffusion capacity was not reported, quantification of emphysema on chest CT scans combined with history and spirometry provide a reasonable approach to distinguishing ACOS-BDR from COPD with emphysema.

Although subjects with COPD had smoked more heavily as measured by cigarette pack-years, subjects with ACOS were much more likely to be current smokers. Subjects with ACOS also had a higher prevalence of comorbidities such as sleep apnea, diabetes mellitus, hypertension, and hypercholesterolemia as compared with patients with COPD. Having a higher body mass index, to near obesity, and a greater prevalence of gastroesophageal reflux disease raises questions related to diet, lifestyle, and nutrition as potential contributors to ACOS pathophysiology.

In the future, the use of diagnostic terms such as “asthma,” “COPD,” and “ACOS,” will likely give way to the more unifying diagnosis of obstructive airway disease (OAD). ... OAD would be further delineated on the basis of molecular phenotyping, genomic, and systems biology approaches, in combination with more traditional clinical and physiological parameters. This new mindset can help us solve the problem of obstructive airway disease taxonomy and develop not only better treatments, but eventually invent lasting cures – if we are so lucky.

Amir Zeki, MD, is an assistant professor in the division of pulmonary, critical care, and sleep medicine at the University of California, Davis. Dr. Zeki had no disclosures. Nizar Jarjour, MD, is a professor of medicine and head of the allergy, pulmonary, and critical care division at the University of Wisconsin, Madison. Dr. Jarjour reported consulting fees from Astazeneca, Daiichi Sankyo, and Teva. They made their comments in an editorial (Ann Am Thorac Soc. 2016 Sep;13(9):1440-2).
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Few pneumonia incidents with ICS/LABA combo

BY SARA FREEMAN
Frontline Medical News

LONDON – The benefit of a fixed-dose inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA) combination in reducing exacerbations of chronic obstructive pulmonary disease (COPD) far outweighed any risk for pneumonia in a post hoc analysis of the 48-week FORWARD study.

Although there were 13 extra pneumonia events when a fixed-dose combination of beclometasone dipropionate and formoterol fumarate (Foster, Chiesi Farmaceutici SpA) was used, as compared with formoterol fumarate alone, there were 123 fewer moderate to severe COPD exacerbations with formoterol fumarate alone, there were 123 fewer moderate to severe COPD exacerbations over a 342-day analysis period.

“Analysis of pneumonia and exacerbation cumulative number of events shows that the number of incident pneumonia remains very small relative to that of moderate to severe exacerbations,” Massimo Corradi, MD, of the University of Parma (Italy), reported at the annual congress of the European Respiratory Society.

Dr. Corradi added that the new analysis confirms that the ICS/LABA combination has a “positive risk-benefit balance over LABA monotherapy, supporting [the argument that] the benefits of adding an ICS to a bronchodilator significantly outweigh potential risks.”

The FORWARD study was a two-arm trial designed to compare the efficacy and safety of fixed-dose treatment with beclometasone dipropionate and formoterol fumarate versus formoterol fumarate alone in 1,199 patients with severe COPD.

For inclusion in the study, patients had to have a post-bronchodilator forced expiratory volume in 1 second below 50% of predicted and a forced vital capacity ratio of less than 0.7. They also had to have a smoking history of 10 pack-years or more, and a history of at least one COPD exacerbation in the previous 12 months that had required treatment or hospitalization (Eur Respir J. 2013;41[1]:12-7).

After a 2-week run-in period, where all patients received a 24-mcg dose of formoterol fumarate, patients were randomized to continue treatment with formoterol fumarate or to receive the fixed-dose combination of beclometasone dipropionate 400 mcg and beclometasone fumarate 24 mcg for 48 weeks.

A total of 1,186 patients, most of whom were male (69%) with a mean age of 64 years, formed the intention-to-treat population.

Published results (Respir Med. 2014;108[8]:1153-62) showed that the combination of the ICS beclometasone dipropionate and the LABA formoterol fumarate (Chiesi Farmaceutici SpA) was associated with a 28% reduction in the annual rate of moderate to severe exacerbations versus the LABA alone.

The adjusted rate of exacerbations per patient per year was 0.80 in patients treated with the ICS/LABA combination versus 1.12 for those treated with just the LABA, with an adjusted rate ratio of 0.72 (P less than .001).

The published data also showed that pneumonia was reported by 23 patients (3.8%) treated with the ICS/LABA and by 11 (1.8%) treated with the LABA only.

For the new analysis, Dr. Corradi and his coinvestigators looked at the cases of pneumonia and COPD exacerbations in more detail, plotting out the cumulative number of events over time and also characterizing the types of pneumonia in more detail.

All patients had a chest x-ray to confirm the presence of pneumonia, he said, noting that overall there were 35 cases of pneumonia, 24 occurring in patients treated with the fixed-dose beclometasone dipropionate and formoterol fumarate combination and 11 in patients treated only with formoterol fumarate.

Of these cases, 25 required in-hospital treatment – 16 in the ICS/LABA arm and 9 in the LABA-only arm. There were three instances of patients acquiring pneumonia in hospital – two in the ICS/LABA and one in the LABA-only arm.

There were also two fatal cases of pneumonia – one in each treatment group. Neither were thought to be related to either of the treatments.

These findings are in line with a recent review of the use of ICS for COPD by the European Medicines Agency (EMA/488280/2016), which noted that “overall the benefits of inhaled corticosteroid medicines in treating COPD continue to outweigh their risks and there should be no change to the way in which these medicines are used.”

The European Medicines Agency advised that patients and clinicians need to “be alert for signs and symptoms of pneumonia, bearing in mind that the clinical features of pneumonia overlap with those of a worsening (exacerbation) of the underlying disease.”

Dr. Corradi has received speaker fees from Chiesi Farmaceutici SpA, which funded the FORWARD study, and his coauthors are employees of the company.

Optimal management of GERD in IPF unknown

BY DOUG BRUNK
Frontline Medical News

EXPERT ANALYSIS FROM CHEST 2016

LOS ANGELES – The optimal management of gastroesophageal reflux disease (GERD) in patients with idiopathic pulmonary fibrosis (IPF) has yet to be determined, according to Joyce S. Lee, MD.

“We need strong randomized clinical trial data to tell us whether or not medical or surgical treatment of GERD in IPF is indicated,” she said at the annual meeting of the American College of Chest Physicians.

Dr. Lee, director of the interstitial lung disease program at the University of Colorado, Denver, said that GERD is nearly universal in patients with IPF, as there are multiple shared risk factors between the two conditions, including age, smoking, and male gender. A lot of drug discovery and attention is paid to the fibroproliferative state (of IPF), but reflux is an interesting comorbidity in that it could be one of the stimuli for ongoing disease progression in IPF patients,” she said. “So if reflux and treatment of reflux disease is important in patients with IPF, it could truly be a disease-modifying therapy.”

Two proposed hypotheses explain the relationship between reflux and IPF. The first holds that reflux and microaspiration are involved in the pathogenesis of IPF. The second, favored by Dr. Lee, proposes that reflux and microaspiration impact the natural history, either through acute exacerbation, disease progression, or survival. Patients with IPF “have weakening of the lower esophageal sphincter, whether that’s due to the presence of a hiatal hernia, medications, or just aging of the tissue there,” she said. “We know how to diagnose reflux disease, but we don’t know how to diagnose microaspiration, which is defined as subclinical aspiration of small droplets of gastric contents. Reflux is a risk factor for the condition of microaspiration, but it is not a perfect surrogate. Not everybody with reflux will aspirate. There is a potential role for bronchoalveolar lavage pepsin and/or bile salt as a biomarker of microaspiration, but it is not validated or standardized in IPF yet.”

Reflex becomes pathologic when reflux of stomach contents causes troublesome symptoms and/or complications. “Troublesome” is defined as mild symptoms 2 or more days a week or moderate to severe symptoms more than 1 day a week. Dr. Lee said that chest physicians can diagnose GERD in their IPF patients the same way that gastroenterologists and primary care doctors do: with symptoms, barium swallow, 24-hour pH monitoring, impedance testing, and sometimes endoscopy.

The 2015 IPF guidelines recommend that clinicians “use regular antacid treatment for patients with IPF (conditional recommendation, very low confidence in estimates of effect).” It does not extend to surgical treatment...
Inhaled antibiotic promising for bronchiectasis

BY DOUG BRUNK
Frontline Medical News

LOS ANGELES – Long-term inhaled ciprofloxacin therapy appears to be a safe and effective treatment option in patients with bronchiectasis, results from an international phase III trial showed.

“This is really exciting; it’s the first large study of an inhaled antibiotic to show a benefit in this population,” study investigator Kevin Winthrop, MD, said in an interview prior to the annual meeting of the American College of Chest Physicians. “There’s a tremendous unmet need and a lot of these patients have daily struggles and their quality of life is low. To have something that would improve that would be a benefit for patients and physicians alike.”

RESPIRE 1 was a global phase III trial sponsored by Bayer that enrolled adult patients with non-cystic fibrosis bronchiectasis who had at least two exacerbations in the prior 12 months and positive bacterial sputum culture for predefined bacteria. Exacerbations were defined as presence of three criteria: systemic antibiotic treatment; worsening of at least three signs and symptoms for at least 48 hours (dyspnea, wheezing, cough, 24-hour sputum volume, or sputum purulence); and fever or malaise/fatigue. A total of 416 patients in Canada, Germany, Spain, the United Kingdom, and the United States were randomized 2:1 to ciprofloxacin 32.5 mg or placebo administered twice per day using a pocket-sized inhaler as a cyclical regimen of either 14 days on/off drug or 28 days on/off drug, for 48 weeks. The primary endpoints were time to first exacerbation and frequency of exacerbation.

Compared with patients in the placebo arm, those in the ciprofloxacin dry powder for inhalation (DPI) 14-day on/off arm experienced a significantly prolonged time to first exacerbation (a mean of 336 days vs. 186 days, respectively; adjusted hazard ratio, 0.53; \(P = .0007\)) and a significantly reduced exacerbation frequency over 48 weeks (a mean of 0.78 vs. 1.42; adjusted incidence rate of 0.61; \(P = .0061\)). A nonsignificant trend in favor of ciprofloxacin DPI was observed for both primary endpoints among patients in the 28-day on/off arm (time to first exacerbation: HR, 0.73; \(P = .065\); frequency of exacerbations: adjusted incidence rate ratio, 0.98; \(P = .89\)).

Treatment-emergent adverse events and adverse events leading to discontinuation were similar across treatment groups (82% in the ciprofloxacin DPI 14-day on/off arm, 83% in the ciprofloxacin DPI 28-day on/off arm, and 83% in the pooled placebo arm. The rates of serious adverse events were also similar in the three treatment groups (17%, 20%, and 23%, respectively). “Tolerability markers like hoarseness, bronchospasm, shortness of breath, or increased cough were similar between the treatment arms,” said Dr. Winthrop, who is an infectious diseases specialist at Oregon Health and Science University, Portland. “The safety profile looks really good. There were no typical fluoroquinolone types of problems such as tendinopathy reported.”

Dr. Winthrop disclosed that he is a consultant for Bayer.

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Continued from previous page


In an effort to measure the relationship between antacid therapy and change in forced vital capacity, Dr. Lee and her associates evaluated IPF patients from placebo arms of the three Idiopathic Pulmonary Fibrosis Clinical Research Network randomized, controlled trials. They found that, compared with patients who did not take antacid therapy at baseline, those who did experienced a slower decline in their forced vital capacity over time (Lancet Resp Med. 2016 May;4[5]:381-9). Dr. Lee said that both evaluations differed because they were secondary analyses of previously captured data. “There were also differences in the ways the trials obtained GERD history, medication indication, and dosing of the antacid therapy,” she said. “There were also differences in outcomes and different populations studied.”

Dr. Lee’s approach to counseling IPF patients with GERD includes discussing lifestyle modifications and proton-pump inhibitor (PPI) therapy – either daily or twice a day dosing. “Lifestyle modifications include weight loss, smoking cessation, raising the head of the bed 6-8 inches, and avoiding foods that cause acid reflux, including chocolate, alcohol, peppermint, and fatty or spicy foods, and avoiding large and late meals,” she said. “In terms of acid suppression therapy with H2 blockers and PPIs, symptom relief and healing of the esophagus occurs in 85%-90% of patients taking them correctly. This does not alter their risk of having microaspiration.” Laparoscopic antireflux therapy (fundoplication) is indicated only after the failure of medical therapy. “The goal is to correct any hernia and tighten the lower esophageal sphincter,” she said. “Efficacy and symptom relief is reported to be around 95%.” She reported having no financial disclosures.

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