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SPECIAL FEATURE

Treatment of Pulmonary Embolism in the ICU

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Dr. Walter reports no financial relationships relevant to this field of study.

Venous thromboembolism (VTE) is the third most common cardiovascular condition behind myocardial infarction and stroke, with an incidence rate of about one per 1000 person-years.[1,2] Nearly 5% of the population will experience VTE in their lifetime.[3] VTE encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE treatment has changed significantly over the past several years. As recently as a few years ago, both DVT and PE required hospitalization for observation and treatment with IV anticoagulants. Today, DVT is commonly treated in the outpatient setting.[3] PE may also be treated as outpatient, but inpatient treatment is still the norm, primarily because of the potential morbidity and mortality. In a population-based study, the 30-day mortality from PE was 16% and 19% depending on whether the diagnosis was probable or definite. One-year mortality was 29% and 32%, respectively.[1] ICU clinicians are frequently involved in the treatment of acute PE. This review will focus on the acute phase of PE treatment, the time when ICU clinicians are most likely to be involved.

INITIAL TREATMENT

The initial objectives of PE treatment are to prevent clot extension and/or recurrence through the use of systemic anticoagulation. Although this may change as newer anticoagulants become available, heparin is still the anticoagulant of choice for the initial treatment of PE. Heparin therapy is classified as low molecular weight (LMWH) or unfractionated heparin. In the absence of renal insufficiency, fixed-dose LMWH is recommended over unfractionated heparin for all forms of VTE.[3,4] LMWH has a lower risk of death (odds ratio [OR], 0.76) and major hemorrhage (OR, 0.57), and lower rates of recurrent VTE (OR, 0.68), compared to unfractionated heparin.[5] Vitamin K antagonists (e.g., warfarin) should be started in parallel with heparin therapy and continued until the international normalized ratio (INR) is therapeutic for 24-48 hours.[2-4] Vitamin K antagonists should not be started without heparin, as

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this practice increases the risk of recurrent clots compared to combination therapy.[6]

HIGH-RISK PE

High-risk, or massive, PE is generally defined as PE complicated by hemodynamic compromise as a result of right heart failure (usually defined as systolic blood pressure < 90 mm Hg).[2] Some authors include the need for mechanical ventilation in this definition.[7] Fortunately, high-risk PE is not common. In a large retrospective study from U.S. hospitals, only 3.4% of acute PE diagnoses were classified as high-risk (defined as in shock or ventilator dependent).[7] Similar to previous studies, mortality was high, with an in-hospital mortality of 37%. Other studies have shown similar rates of high-risk PE (~ 5%) with similar risks of death.[4]

In patients with high-risk PE, thrombolytic therapy appears to decrease mortality, but at the risk of increased bleeding. As opposed to anticoagulation, which prevents clot extension and recurrence, thrombolytic therapy leads to more rapid clearing of clot, vein patency, and improved right ventricular (RV) function. In a retrospective, population-based study, mortality was 15% in high-risk patients who received thrombolytics compared to 47% in high-risk patients who did not receive thrombolytics (relative risk, 0.31; 95% confidence interval [CI], 0.30-0.32; $P < 0.0001$). Of note, patients in this study who received thrombolysis were younger and had fewer comorbidities than patients who did not receive thrombolysis. This may have biased the results to some degree. Several meta-analyses have reviewed the use of thrombolytics in high-risk PE, and the bulk of evidence suggests thrombolytic therapy for high-risk PE is associated with a reduction in mortality and recurrent PE, with an increased risk of major bleeding. However, the strength of the evidence is considered to be weak.

The 2012 American College of Chest Physicians (ACCP) Task Force on Antithrombotic Therapy for VTE disease gives a weak recommendation for the use of thrombolysis in patients with high-risk PE who do not have a high risk of bleeding (grade 2C).[4] Others have given stronger recommendations.[2,3,7] Some suggest it be considered even in the presence of an increased risk of bleeding (except for an increased risk of central nervous system bleeding).[2] When thrombolytics are used, a short infusion duration (≤ 2 hours) is recommended due to a decreased risk of bleeding compared to longer infusions. Additionally, the use of a peripheral vein is recommended over infusion directly into the pulmonary artery, as the latter is associated with more bleeding complications as well. Both of these are grade C recommendations.[4]

INTERMEDIATE-RISK PE

By far the most controversial arena in the treatment of acute PE involves the use of thrombolytics in intermediate-risk patients. Intermediate-risk PE, also termed submassive PE, is usually defined as patients with acute PE who are hemodynamically stable but with signs of right ventricular (RV) dysfunction.[2,3] RV dysfunction can be assessed with imaging and/or lab testing. Signs of RV dysfunction on chest CT or echocardiography include RV dilation, increased right-to-left ventricular diameter ratio, or hypokinesis of the RV free wall. Elevated brain natriuretic peptide (BNP) and troponin levels are lab markers suggesting RV dysfunction. Many different scoring systems, using variations of imaging and lab results, have been proposed to help risk stratify patients with acute PE. To date, there is no universally accepted, well-discriminating scoring system.

Thrombolytic therapy in patients with intermediate-risk PE was studied in a 2002 randomized, controlled trial comparing heparin plus alteplase (n = 118) with heparin alone (n = 138).[8] The primary outcome of death, or need for treatment escalation, occurred less frequently in the heparin plus alteplase group compared with those who received heparin alone. However, there was no difference in mortality (3.4% vs 2.2%, $P = 0.71$). The major difference in outcome was an increased need for treatment escalation among patients given heparin alone. The majority of treatment escalations included the use of thrombolytics in response to a clinical deterioration (hypotension or worsening respiratory failure). For years, both proponents and critics of

thrombolysis in intermediate-risk PE have used this publication to defend their point of view. Critics argue that thrombolytics do not change mortality, and that rather than preemptively giving thrombolytics to all intermediate-risk patients, only those patients who develop shock or respiratory failure need treatment. Proponents argue that thrombolytics prevent this clinical deterioration. The 2012 ACCP guidelines addressed this question and concluded the increased risk of bleeding outweighed the "less-certain" benefits of thrombolytics. They recommend against their use for most patients with acute PE not associated with hypotension (grade 1C).[4]

In 2014, the publication of a new randomized, controlled trial[9] and meta-analysis[10] provided additional data but did not quell the controversy. Meyer et al reported results from the Pulmonary Embolism Thrombolysis (PEITHO) trial, a large trial that randomized intermediate-risk patients with acute PE to either tenecteplase plus heparin (n = 506) or heparin plus placebo (n = 499).[9] Patients had to be normotensive but with signs of RV dysfunction (via echo or chest CT) and myocardial injury (positive troponin I or T test). The primary outcome of death or hemodynamic decompensation within 7 days occurred less frequently in the tenecteplase group compared to the placebo group (2.6% vs 5.6%; OR 0.44; 95% CI, 0.23–0.87). However, similar to the previous trial in this population, the difference was driven almost exclusively by more hemodynamic decompensation in the placebo group, as 7-day mortality did not differ between groups (1.2% vs 1.8%; OR 0.65; 95% CI, 0.23–1.85). There was also no difference in 30-day mortality (2.4% vs 3.2%). The tenecteplase group did have significantly more major extracranial bleeding (6.3% vs 1.2%) and hemorrhagic stroke (2.0% vs 0.2%).

Since this trial was published, Chatterjee and colleagues published a meta-analysis of thrombolysis for PE.[10] They pooled results from 16 randomized, controlled trials (including PEITHO) comparing thrombolytic therapy vs anticoagulant therapy for acute PE. They concluded that thrombolytic therapy was associated with a decreased all-cause mortality (2.17% vs 3.89%; OR 0.53; 95% CI, 0.32-0.88). As expected, major bleeding occurred more frequently in the thrombolytic cohort (9.24% vs 3.42%; OR 2.73; 95% CI, 1.91-3.91). These results equate to a number needed to treat of 59 (to prevent one death) and a number needed to harm of 18 (to cause one major bleed). When the analysis was limited to trials specifically enrolling intermediate-risk patients (70.9% of all patients), thrombolytic therapy was still associated with a significant reduction in mortality (1.39% vs 2.92%; OR 0.48; 95% CI, 0.25-0.92). Thrombolytics remained associated with a more than three-fold greater risk of major bleeding (7.74% vs 2.25%; OR 3.19; 95% CI, 2.07-4.92). In a prespecified analysis, this risk of bleeding did appear to be greatest in patients older than 65 years.

Thus, the decision to use thrombolytic therapy in patients who are hemodynamically stable remains challenging. For every one life saved, the tradeoff could be up to three patients with major bleeding events. It would be helpful to have a clearer understanding of what types of major bleeding events occurred, as the long-term consequences of a gastrointestinal bleed requiring transfusion and intracranial bleeding can be dramatically different. Unfortunately, the Chaterjee meta-analysis does not provide this level of detail. However, at least for the intermediate-risk patients, we can look at PEITHO to try to address this question. PEITHO accounted for 40% of the weighted analysis among the intermediate-risk patients. Hemorrhagic stroke occurred in 10 patients (2.0%) who received thrombolysis, as compared to one patient (0.2%) who received placebo. Of these 10 patients, four died, and most of the remaining patients had persistent mild-to-moderate disability.[9] Consequently, it is prudent to strongly consider the potential morbidity associated with the bleeding risk that comes with thrombolytic therapy. Two reviews this year have taken the same stance as the ACCP guidelines and have recommended against the routine use of thrombolytic therapy in normotensive patients.[2,3] Of note, these reviews were published prior to the Chatterjee meta-analysis.

OTHER ISSUES

Inferior Vena Cava Filters

The use of retrievable inferior vena cava (IVC) filters among patients with VTE is increasing.[11] There is a general consensus that IVC filters should be used in patients with VTE and contraindications to anticoagulation.[2-4] The use of IVC filters in other patient populations is debated. Several large, retrospective epidemiologic studies using hospital discharge data (all from the same group, Stein et al) have reported that IVC filters were associated with lower mortality among unstable patients (independent on the use of thrombolytic therapy), stable patients who received thrombolytics, and patients who had pulmonary artery embolectomy.[7,11,12] An accompanying editorial recommended that IVC filters (and thrombolytics) be used in all unstable patients who do not have contraindications.[13] Others feel additional studies are needed before this recommendation can be made.[2] The 2012 ACCP guidelines only recommend an IVC filter in patients with contraindications to anticoagulation. It is worth mentioning that these guidelines were published prior to the Stein studies.

Table 1. Clinical Signs and Treatment of Acute Pulmonary Embolism

	Low risk	Intermediate risk	High risk
Clinical Signs	Normotensive Normal right Ventricular function	Normotensive Right ventricular dysfunction	Hypotension and/or mechanical ventilation
Initial Treatment	Anticoagulation	Anticoagulation	Anticoagulation
Thrombolysis	Not indicated	Remains controversial May reduce mortality Increased risk of bleeding	Generally recommended Probably reduces mortality

Pulmonary Artery Embolectomy

Pulmonary artery embolectomy is rarely performed for acute PE. From 1999 to 2008, only 0.18% of acute PE was treated with surgical embolectomy.[12] Evidence for both catheter-based and surgical embolectomy is weak. The 2012 ACCP guidelines give a weak recommendation (grade 2C) for these techniques when there is a contraindication to thrombolysis, failed thrombolysis, or shock that is likely to cause death before thrombolysis can take effect (usually a few hours).[4] Outcomes after thrombectomy are difficult to assess, as studies are small and use different patient populations. Using nationwide hospital discharge data from 1999-2008, the case fatality rate among stable patients with acute PE who underwent thrombectomy was 24%. If the patients were unstable, mortality was 40%.[12] Mortality was decreased if an IVC filter was placed in addition to embolectomy. The authors noted that these results reflected a nationwide average mortality and that outcomes may be better at select centers with more expertise. Supporting this argument is a more recent single-center series that reported excellent outcomes after embolectomy in a combination of 20 intermediate and high-risk patients (5% mortality).[14] A criticism of these small case series, however, is that we do not know what mortality would have been had patients only been treated with anticoagulation or thrombolysis and not embolectomy.

Newer Anticoagulants

Over the past 5 years, several newer anticoagulants have become available. These drugs are direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) and direct factor IIa inhibitors (dabigatran). All except for edoxaban have received FDA approval for the treatment of VTE, and it is likely that edoxaban will be approved soon. Several phase 3 clinical trials have shown these anticoagulants to be at least as effective as, and probably safer than, heparin therapy followed by warfarin.[2,3] Unlike warfarin, these new agents have the distinct advantage of not needing monitoring — a potential cost savings and quality of life benefit for patients. An ongoing concern has been the lack of a reversal agent. However, at least in short-term trials (3-12 months), this was not a significant clinical problem, as major bleeding occurred less frequently than with warfarin. These agents may not be appropriate for patients with renal impairment. Cost is a significant barrier, but the use of newer anticoagulants is likely to increase over the next several years.

SUMMARY

Pulmonary embolism is a common and potentially life-threatening disorder. Immediate anticoagulation is first-line therapy (*see Table*). High-risk PE is usually defined as PE with hemodynamic compromise or need for mechanical ventilation. Thrombolysis is indicated for high-risk PE. Intermediate-risk PE is defined as PE with signs of RV dysfunction, and the use of thrombolysis in this population is controversial. Thrombolysis may decrease the risk of mortality, but is associated with a substantial increase in the risk of major bleeding. IVC filters are uniformly recommended when there are contraindications to anticoagulation. There is limited evidence to guide the use of IVC filters in other clinical settings. Similarly, there are limited data for thrombectomy, but this is generally recommended for unstable patients if there is a contraindication to thrombolysis. Newer anticoagulants are likely to gain increasing clinical acceptance. In short-term trials, they have been shown to be as effective as heparin plus vitamin K antagonist therapy, and they may be safer. ■

REFERENCES

1. Tagalakis V, et al. Incidence of and mortality from venous thromboembolism in a real-world population: The Q-VTE Study Cohort. *Am J Med* 2013;126:e13-e21.
2. Konstantinides S, et al. Management of venous thromboembolism: An update. *Eur Heart J* 2014;35:2855-2863.
3. Wells PS, et al. Treatment of venous thromboembolism. *JAMA* 2014;311:717-728.
4. Kearon C, et al. Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e419S-e4194S.
5. Erkens PM, et al. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev*. 2010:CD001100.

6. Brandjes DP, et al. Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. *N Engl J Med* 1992;327:1485-1489.
7. Stein PD, et al. Thrombolytic therapy in unstable patients with acute pulmonary embolism: Saves lives but underused. *Am J Med* 2012;125:465-470.
8. Konstantinides S, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med* 2002;347:1143-1150.
9. Meyer G, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014;370:1402-1411.
10. Chatterjee S, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: A meta-analysis. *JAMA* 2014;311:2414-2421.
11. Stein PD, et al. Impact of vena cava filters on in-hospital case fatality rate from pulmonary embolism. *Am J Med* 2012;125:478-484.
12. Stein PD, et al. Case fatality rate with pulmonary embolectomy for acute pulmonary embolism. *Am J Med* 2012;125:471-477.
13. Dalen JE. Thrombolytics and vena cava filters decrease mortality in patients with unstable pulmonary embolism. *Am J Med* 2012;125:429-430.
14. Worku B, et al. Pulmonary embolectomy in the treatment of submassive and massive pulmonary embolism. *Cardiology* 2014;129:106-110.

ABSTRACT & COMMENTARY

Clinical Practice Guidelines for Platelet Transfusion

By Betty T. Tran, MD, MSc

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Dr. Tran reports no financial relationships relevant to this field of study.

SYNOPSIS: Based on a recent systematic review of the literature, clinical guidelines were developed by the American Association of Blood Banks with the goal of providing platelet transfusion thresholds for adult patients in common clinical scenarios.

SOURCE: Kaufman RM, et al. Platelet transfusion: A clinical practice guideline from the AABB. *Ann Intern Med* 2014 Nov 11 [Epub ahead of print].

The American Association of Blood Banks (AABB) commissioned a panel of 21 experts to develop guidelines on the appropriate administration of platelet transfusion in adult patients based on the best available published evidence. The guidelines were based on a recent systematic review of the literature searching PubMed from 1946 to September 2014 and the Cochrane Central Register of Controlled Trials and Web of Science from 1900 to September 2014. Seventeen randomized, controlled trials and 53 observational studies were included in the final review. The authors aimed to identify platelet thresholds in common clinical situations at which prophylactic platelet transfusion would likely improve hemostasis and benefit the patient.

In summary, the AABB had six recommendations of varying strengths based on the availability of quality evidence. The AABB recommends the prophylactic transfusion of platelets in the following clinical scenarios:

1. Hospitalized adults with therapy-induced hypoproliferative thrombocytopenia with a platelet count of <= 10 x 10^9 cells/L (10,000 cells/μL) to reduce the risk of spontaneous hemorrhage. Low-dose platelet transfusions (equal to one-half a standard apharesis unit) are equally effective in decreasing bleeding risk but require more frequent transfusions; however, high-dose platelet transfusions (double the standard dose) do not provide additional hemostatic benefit (quality of evidence: moderate, strength of recommendation: strong).
2. Patients having elective central venous catheter (CVC) placement with a platelet count < 20 x 10^9 cells/L (20,000 cells/μL) (quality of evidence: low, strength of recommendation: weak).
3. Patients having elective diagnostic lumbar puncture (LP) with a platelet count < 50 x 10^9 cells/L (50,000 cells/μL) (quality of evidence: very low, strength of recommendation: weak).
4. Patients having major elective non-neuraxial surgery with a platelet count < 50 x 10^9 cells/L (50,000 cells/μL) (quality of evidence: very low, strength of recommendation: weak).
5. The last two recommendations focus on clinical scenarios in which the AABB does not recommend routine prophylactic platelet transfusion:
6. The AABB recommends against routine prophylactic platelet transfusion for patients who are nonthrombocytopenic and have cardiac surgery with cardiopulmonary bypass. Transfusion is suggested if these patients exhibit perioperative

bleeding with thrombocytopenia and/or evidence of platelet dysfunction (quality of evidence: very low, strength of recommendation: weak).
7. The AABB cannot recommend for or against platelet transfusion in patients receiving antiplatelet therapy who have traumatic or spontaneous intracranial hemorrhage (quality of evidence: very low, strength of recommendation: uncertain).

■ COMMENTARY

Given that most platelet transfusions are ordered prophylactically to reduce the risk of bleeding in patients with hematopoietic disorders and/or prior to invasive procedures, these recommendations are a helpful guide in managing thrombocytopenia in commonly encountered clinical scenarios. The authors duly note that these guidelines are not meant to be universal standards of care; clinical scenarios can be quite complex, and platelet counts are not representative of platelet function. Development of these guidelines highlights the need for further investigation in this field, as data are limited beyond the indication for prophylaxis against spontaneous hemorrhage in patients with hypoproliferative thrombocytopenia (recommendation #1). The AABB recommendations are mostly based on observational data, often from a single center's experience, and, thus, rely heavily on the panel's expert interpretation and consensus (or lack thereof) on the topic. Although this can result in more biased data, one can envision the potential ethical challenges of doing randomized trials involving prophylactic platelet transfusions prior to procedures. It is reassuring, however, that severe or life-threatening bleeding complications (WHO modified bleeding scale grade 3 or 4) are quite rare in the setting of invasive procedures such as CVC placement or LP. Therefore, the higher platelet transfusion recommendations for interventions involving the central nervous system (< 50,000 cells/μL for LP, < 80,000-100,000 cells/μL for surgeries traditionally) are largely based on the potential for devastating neurologic complications as a result of bleeding rather than actual observed outcomes. ■

ABSTRACT & COMMENTARY

Statins Not Helpful in Treating ARDS

By David J. Pierson, MD, Editor

SYNOPSIS: Although studies in animals and preliminary reports in patients with ARDS suggested that statin administration might be beneficial in patients with the syndrome, this multicenter, double-blind clinical trial showed no benefit from simvastatin by any measure examined.

SOURCE: McAuley DF, et al. Simvastatin in the acute respiratory distress syndrome. *N Engl J Med* 2014;371:1695-1703.

To obtain better evidence about the recent suggestion that statins might be beneficial in managing patients with the acute respiratory distress syndrome (ARDS), McAuley and colleagues carried out a rigorous clinical trial in the ICUs of 40 hospitals in the United Kingdom and Ireland. Mechanically ventilated patients with ARDS (diagnosed using current consensus criteria) who were within 48 hours of syndrome onset and were not already receiving statins were randomized to receive simvastatin, 80 mg, or placebo, enterally, daily for up to 28 days. Clinical outcomes examined were ventilator-free days to day 28, days free of non-pulmonary organ failure, mortality, and safety.

Of the 539 patients (mean age 54 years, 56% male, 75% with sepsis as underlying predisposition), 259 received simvastatin and 280 received placebo. The groups were well matched. No significant differences were found in ventilator-free days (mean, 12.6 vs 11.5 days in statin vs placebo groups), days free of non-pulmonary organ failure (19.4 vs 17.8), 28-day mortality (22% vs 27%), or incidence of serious adverse effects related to the study drug. The authors concluded that simvastatin therapy, although safe, did not improve clinical outcomes in patients with ARDS.

■ COMMENTARY

Despite biological plausibility and promising findings in early-phase clinical trials of statins for treatment of ARDS, these things have not translated into improvements in patient-centered outcomes once subjected to rigorous clinical research. This is unfortunate given the ready availability and favorable safety profiles of these agents. Statin therapy can thus be added to the list of management interventions for ARDS that, while initially promising, have ultimately been demonstrated to be ineffective or even harmful. Although manuscripts describing negative clinical trials have tended to be less attractive to journal editors than reports of benefit in anecdotal observations or highly preliminary studies, the former are more important in the long run, once such initial reports have been disseminated, with respect to variables that patients care about. ■

ABSTRACT & COMMENTARY

Should Long-acting Bronchodilators Be Used in Acute Exacerbations of COPD?

By David J. Pierson, MD, Editor

SYNOPSIS: In this study of administrative data from patients admitted to 421 U.S. hospitals with acute chronic obstructive pulmonary disease (COPD) exacerbations, 41% received long-acting bronchodilators, which are not recommended in this setting. Comparison with patients who did not receive the long-acting agents showed no evidence for clinical or economic benefit from their use.

SOURCE: Lindenauer PK, et al. Use and outcomes associated with long-acting bronchodilators among patients hospitalized for chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2014 Aug 28. [Epub ahead of print].

This was a retrospective cohort study of 421 U.S. hospitals participating in the Premier Inpatient Database. It focused on patients hospitalized with exacerbations of chronic obstructive pulmonary disease (COPD) between January 1, 2010 and June 30, 2011. Its purpose was to determine the frequency with which long-acting bronchodilators (LABDs, which are approved and recommended for use in long-term management of stable patients) are used in this setting.

The Premier Inpatient Database includes approximately 15% of admissions to acute care U.S. hospitals, and it has been used extensively in comparative effectiveness research for COPD. The authors reviewed data for all patients older than age 40 with a principal discharge diagnosis consistent with acute COPD exacerbation, who were also treated with systemic corticosteroids. Patients were excluded if they were intubated (in which case LABDs could not be administered), transferred, or discharged within 2 days. The primary outcome variable was a composite measure of treatment failure (invasive mechanical ventilation, in-hospital death, or readmission within 30 days); secondary outcomes included length of stay and hospital costs. The authors used propensity score analysis to compare patients who received LABDs to those who did not, in addition to multiple other statistical means for reducing confounders.

Of the 77,378 patients included in the analysis (mean age 69; 58% female; 77% white), 31,725 (41%) received LABDs during their hospital stay. Of the patients, 48% of these received long-acting beta agonists alone, 21% received tiotropium alone, and 31% received both. Treatment failure, as defined for this study, occurred in 13.4% of patients, including 2.2% who required invasive mechanical ventilation, 3.4% who received noninvasive ventilation, 1.8% who died, and 8.6% who were readmitted within 30 days. Patients treated with LABDs tended to be younger, to have a slightly lower comorbidity score, and to have been admitted previously for COPD exacerbations (all statistically significant differences). These patients also received inhaled corticosteroids in the hospital much more often than patients not treated with LABDs (82% vs 12%; $P < 0.0001$).

In the propensity-matching analysis (which could be done for 81% of the LABD-receiving patients) there were no significant differences in treatment failure, a composite measure of complications, length of stay, or hospital costs between the two groups. Secondary analysis revealed no outcome associations for either type of LABD, separately or in combination, nor for cardiovascular complications, in comparison with patients receiving short-acting bronchodilators alone. The authors conclude that LABDs are commonly prescribed to patients hospitalized with acute COPD exacerbations, but that this is not associated with improved clinical or economic outcomes.

■ COMMENTARY

Drugs shown to be effective in, and FDA-approved for, use in one pulmonary condition tend to metastasize to other conditions with similar features for which both evidence for clinical effectiveness and approval for use are lacking. The widespread prescription of montelukast for patients with COPD, and of anticholinergic agents in the long-term management in asthma, come to mind as examples. Long-acting bronchodilators — both beta agonists and anticholinergics — have been shown effective in the long-term management of COPD, but not in acute exacerbations. The present study's finding that 41% of COPD patients hospitalized for acute exacerbations received long-acting agents suggests that this is another example of this "indication creep".

A natural tendency to step up pharmacologic management — adding new agents while continuing those already in use — during a worsening of the patient's condition, as well as administrative pressure to make sure that established outpatient regimens are not lost track of when patients are hospitalized, may contribute to this disappointingly high rate of non-recommended drug administration. ■

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CME QUESTIONS

1. **The American College of Chest Physicians 2012 Task Force on Antithrombotic Therapy for VTE disease:**

   a. recommends the use of thrombolysis in patients with high-risk PE who do not have a high risk of bleeding.

   b. recommends an inferior vena cava filter in patients at high-risk of clinical deterioration.

   c. recommends thrombectomy as first-line treatment for patients with acute PE and hypotension.

   d. does not recommend thrombolysis for intermediate-risk PE because it is not effective in this population.

2. **Which of the following statements is true with respect to treatment of acute PE?**

   a. All patients with acute PE should be hospitalized for initial treatment.

   b. Unfractionated heparin is recommended as the first-line anticoagulant of choice for the initial treatment of acute PE as it is associated with a lower risk of bleeding compared to low molecular weight heparin.

   c. There is a general consensus that IVC filters should be used in patients with VTE and contraindications to anticoagulation but IVC filter use in other populations is debated.

3. **Based on the American Association of Blood Banks clinical practice guidelines on platelet transfusions, which of the following patients should receive a platelet transfusion?**

   a. A patient with AML receiving chemotherapy and a platelet count of 5 x 10^9 cells/L (5,000 cells/µL).

   b. A patient with septic shock needing central venous access and a platelet count of 30 x 10^9 cells/L (30,000 cells/µL).

   c. A patient with acute encephalopathy needing a lumbar puncture and a platelet count of 80 x 10^9 cells/L (80,000 cells/µL).

   d. All of the above

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- identify the particular clinical, legal, or scientific issues related to critical care;
- describe how those issues affect physicians, nurses, health care workers, hospitals, or the health care industry; and
- cite solutions to the problems associated with those issues.

[IN FUTURE ISSUES]

Impact of Diagnostic Criteria on Incidence of VAP

Statins Not Helpful in Treating ARDS

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Cumulative Index
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