Update in Pulmonary, Sleep, and Critical Care Medicine: Evidence Published in 2013

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This article summarizes studies published in 2013 that influence the practice of pulmonary, sleep, and critical care medicine. Key studies were identified from *ACP Journal Club* and ACP JournalWise and were among the highest-ranked and most-accessed articles in 2013.

In pulmonary medicine, an analysis of data from the National Lung Screening Trial (NLST) suggested that using a risk stratification model for computed tomography (CT) screening of lung cancer significantly improved the rate of false-positive results per cancer death prevented. For chronic obstructive pulmonary disease (COPD), a randomized trial reported that for acute exacerbations, a 5-day course of oral prednisone was noninferior to a 14-day course, and a large, observational case–control analysis reinforced prior findings that inhaled long-acting β-agonists (LABAs) and dry-powder–delivery long-acting muscarinic antagonists (LAMAs) conferred small but significant increases in cardiovascular risk to older patients with COPD.

For treatment of acute venous thromboembolism (VTE), a double-blind, placebo-controlled study demonstrated that apixaban, a fixed-dose oral factor Xa inhibitor, was equivalent to warfarin and was associated with a lower risk for clinically significant bleeding. For non–cystic fibrosis (CF) bronchiectasis, 2 randomized trials evaluating macrolide therapy with azithromycin or erythromycin found each to be more effective than placebo. These observations must be balanced against the macrolide-related risks for hearing deficits and cardiovascular mortality as well as increases in macrolide resistance.

In sleep medicine, a randomized crossover trial evaluated the effectiveness of custom-fitted mandibular advancement devices (MADs) for the treatment of obstructive sleep apnea (OSA). Although oral appliances were not as effective as continuous positive airway pressure (CPAP) at reducing the apnea–hypopnea index (AHI), patients used oral appliances more than CPAP, and resulting improvements in daytime sleepiness, sleep quality, and blood pressure were noninferior. In another study, primary care management of uncomplicated OSA was shown to be a reasonable and possibly cost-effective alternative to sleep specialist management, provided that there are ample educational and nursing resources for practitioners.

In critical care medicine, a large multicenter randomized study demonstrated that colloid fluids are equivalent to crystalloid fluids for acute resuscitation of hypovolemic shock. A randomized, placebo-controlled study suggested that the addition of methylprednisolone and vasopressin to epinephrine during in-hospital cardiac arrest was associated with significantly improved survival. For acute upper gastrointestinal bleeding with a high risk for rebleeding, a transfusion trigger of a hemoglobin level less than 7 mg/dL with a goal level of 7 to 9 mg/dL was associated with increased survival, fewer cases of recurrent bleeding, and fewer in-hospital complications than a more liberal trigger of less than 9 mg/dL. Clinicians should be aware that patients with massive exsanguination and active cardiovascular or cerebrovascular disease were excluded from this study.

A randomized trial demonstrated that universal decolonization of all intensive care unit (ICU) patients with chlorhexidine and mupirocin was more effective at reducing nosocomial infection than were methicillin-resistant *Staphylococcus aureus* (MRSA)–specific screening and isolation policies. Finally, a multicenter randomized study in patients with severe acute respiratory distress syndrome (ARDS) showed that early transition to prone positioning is a useful adjunctive therapy, provided that there is adequate staffing to perform the maneuver and monitor for complications.

Pulmonary Medicine

Risk Stratification Before CT Screening for Lung Cancer Improves the Risk–Benefit Ratio

Kovalchik SA, Tammemagi M, Berg CD, et al. Targeting of low dose-CT screening according to risk of lung-cancer death. N Engl J Med. 2013;369:245-54. [PMID: 23863051]

Background: The NLST results first published in 2011 (1) demonstrated that screening with low-dose chest CT led to a 20% reduction in lung cancer death among current or former smokers, particularly among older patients with greater smoking exposure. With more than 90 million current or former smokers in the United States, determining which patients to screen has high priority.

Findings: The investigators developed an a priori risk prediction tool based on factors known to be associated with lung cancer death: age, pack-years of smoking, years since smoking cessation, body mass index, presence of emphysema, and family history of lung cancer. On the basis of these factors, the NLST population was divided into 5

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quintiles of increasing risk. By screening the 3 highest-risk quintiles instead of all patients, the number of patients who would have to undergo CT screening to prevent 1 lung cancer death decreased from 302 to 161, and the ratio of false-positive results to CT-prevented deaths from lung cancer (a measure of the risk–benefit ratio) decreased significantly (from 108 false-positive results per CT-prevented death to 65).

Cautions: Other than false-positive results, potential harms of CT screening were not assessed. The study was underpowered to assess the efficacy of CT screening in patients with multiple pulmonary comorbidities, which was increasingly prevalent across risk quintiles.

Implications: Although this study suggests that low-dose CT for lung cancer screening might be more effective if more restrictive criteria are applied than those set forth by the NLST, this model will need to be validated in a general population before being applied broadly. Until then, this analysis highlights the varied risk–benefit profile of CT screening for lung cancer, even among higher-risk groups.

A 5-Day Course of Oral Prednisone Is Effective for Patients With Acute COPD Exacerbation

Leuppi JD, Schuetz P, Binssinger R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. JAMA. 2013;309:2223-31. [PMID: 23695200]

Background: Acute exacerbations occur at least once annually in almost one half of patients with COPD, resulting in substantial health consequences. Consensus guidelines suggest a 10- to 14-day course of oral glucocorticoids (2). However, up to 1 in 10 patients experiences frequent exacerbations and is therefore susceptible to the risks of increased cumulative glucocorticoid exposure, raising the question of whether a shorter course would be effective.

Findings: Adults with COPD presenting to the emergency department of 5 centers in Switzerland were randomly assigned to receive a 5-day versus a 14-day course of oral prednisone, 40 mg/d. All patients received antibiotics, inhaled glucocorticoids, LABAs, and tiotropium.

The 5-day course did not differ from the 14-day course in terms of repeated exacerbations of COPD within 6 months and lung function. Furthermore, patients in the short-course group had 65% less cumulative steroid exposure over 6 months (median prednisone exposure, 200 mg vs. 560 mg).

Cautions: Patients may have been relatively overtreated—all received inhaled glucocorticoids, LABAs, and antibiotics in addition to oral prednisone, which may have led to underpowering of this noninferiority study.

Implications: This study provides compelling evidence that for most patients with acute COPD exacerbations, a 5-day course of oral glucocorticoids, in addition to optimization of other COPD therapies, is sufficient.

Long-Acting Bronchodilators May Increase Cardiovascular Risk Among Older Patients With COPD

Gershon A, Croxford R, Calzavara A, et al. Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease. JAMA Intern Med. 2013;173:1175-84. [PMID: 23689820]

Background: Inhaled LABAs and LAMAs are cornerstones of treatment in COPD but have cardiovascular effects that may be deleterious. This study assessed the association of these medications with adverse cardiovascular events in a real-world heterogeneous group of patients.

Findings: This nested case–control study analyzed approximately 191 000 elderly patients with COPD from a Canadian health care database. New prescription of either a LABA or LAMA was associated with an equivalent, higher risk for cardiovascular event–related hospitalizations and emergency department visits (adjusted odds ratio, 1.31 [95% CI, 1.12 to 1.52] with LABAs and 1.14 [CI, 1.01 to 1.28] with LAMAs), even after adjustment for sex, preexisting cardiovascular disease, and COPD severity.

Cautions: Because of the observational nature of the study, the possibility of hidden confounders cannot be ruled out. The analysis did not distinguish between use of LABA alone and a LABA in combination with an inhaled corticosteroid; it is possible that the addition of an inhaled corticosteroid may modulate the LABA-related cardiovascular risk.

Implications: This study suggests that among older patients with COPD, LABAs and LAMAs confer equivalently small but significant increases in cardiovascular risk. The small increased population risk suggests that individualized attention to cardiovascular risk and increased monitoring are critical in high-risk patients with COPD who are receiving LABA or LAMA therapy.

Oral Apixaban Is a Reasonable Alternative in Uncomplicated Patients With Acute VTE

Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369:799-808. [PMID: 23808982]

Background: Parenteral anticoagulation followed by oral warfarin is the mainstay of therapy for VTE but poses many challenges, including the need for injections initially and close monitoring of the coagulation profile. Prior work by these investigators (3) demonstrated that apixaban, an oral factor Xa inhibitor with rapid onset of action and fixed-dose administration, is effective for preventing recurrent VTE with low rates of major bleeding. The current study was done to assess whether oral apixaban was similar to warfarin for acute VTE treatment.

Findings: 5400 adult patients with confirmed proximal deep venous thrombosis or pulmonary embolism were randomly assigned to receive apixaban or warfarin therapy. After 6 months, there was no significant difference in the occurrence of recurrent VTE (2.3% of apixaban recipients

vs. 2.7% of warfarin recipients), and the risk for significant bleeding was reduced by more than 60% in the apixaban group (4.3% vs. 9.7%).

Cautions: This study included few patients with extremes of body weight or age and few patients with cancer or poor kidney function, therefore limiting the generalizability of the results. Owing to the close follow-up in the study, adherence to apixaban therapy may have been higher than in clinical practice. Because apixaban has a short half-life, missed doses may have very significant consequences.

Implications: Apixaban seems to be a reasonable alternative for patients with acute VTE without contraindications to therapy, especially those who want to avoid injections and blood monitoring. Patients should be selected with the inclusion criteria from this and other recent trials in mind. Close follow-up and counseling about the effects of missed doses are necessary.

Macrolides Reduce Exacerbations in Patients With Non-CF Bronchiectasis

Altenburg J, de Graaff CS, Stienstra Y, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA. 2013;309:1251-9. [PMID: 23532241]

Background: Bronchiectasis exacerbations have deleterious consequences on lung function, morbidity, and quality of life. Long-term macrolide therapy has been demonstrated to have beneficial effects in CF-induced bronchiectasis (4); this study was done to assess whether long-term azithromycin therapy would have a similar effect in non-CF bronchiectasis.

Findings: 83 adult patients with non-CF bronchiectasis and at least 3 infectious exacerbations in the prior year were randomly assigned to receive azithromycin, 250 mg/d, or placebo for 1 year while being monitored by pulmonary specialists and providing sputum samples every 3 months. The azithromycin group had more clinical stability than the placebo group (46.5% vs. 80%, respectively, had $\geq$1 exacerbation), but of note, the azithromycin group developed a significantly higher rate of macrolide resistance (88% vs. 26% of cultured strains).

Cautions: Hearing loss, an important adverse effect of macrolide therapy, was assessed only by subjective report. Furthermore, the study was underpowered to adequately detect toxicities associated with long-term therapy. Evidence indicates that patients with very high cardiovascular risk may be at increased risk for cardiovascular death with azithromycin use (5).

Implications: This study, along with a similar study published concurrently (6), sheds light on an oft-ignored but prevalent pulmonary disease. In patients with non-CF bronchiectasis who experience frequent exacerbations, long-term macrolide therapy is effective in improving clinical stability when linked to pulmonary specialist referral and sputum-culture monitoring. The benefit of macrolide therapy needs to be balanced with the potential for increased antibiotic resistance and adverse medication events.

Sleep Medicine

Custom-Fitted Oral Appliance Therapy Is a Reasonable Option for Mild to Moderate OSA

Phillips CL, Grunstein RR, Darendeliler MA, et al. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med. 2013;187:879-87. [PMID: 23413266]

Background: Adherence to CPAP therapy for OSA remains challenging over the long term owing to many varied factors. Although custom-fitted MADs are known to be less efficacious than CPAP therapy at reducing the AHI, tolerance of MADs is significantly higher in general, and this balance may lead to equivalent functional outcomes.

Findings: 126 adult patients with at least mild, symptomatic OSA were enrolled and treated with 4 weeks of CPAP therapy and 4 weeks of MAD therapy in a randomized, crossover fashion. The patient sample was, on average, normotensive (mean blood pressure, 123/80 mm Hg) with moderate OSA (mean AHI, 25 events/h).

Although CPAP was more effective than MADs in reducing AHI (4.5 vs. 11 events/h, respectively), self-reported adherence with use of MADs was higher (6.5 vs. 5.2 h/night for CPAP use). There was no overall difference between MADs and CPAP with respect to improvement in blood pressure, daytime sleepiness, or quality of life.

Cautions: Patients with baseline severe OSA (AHI >30 events/h) who used MADs continued to have moderate OSA despite therapy (mean AHI, 19 events/h). Adherence to therapies was subjectively reported, potentially leading to bias. Because neither intervention reduced blood pressure among these normotensive patients, the study cannot claim true noninferiority for this outcome.

Implications: This study supports a broader role for the use of MADs in the treatment of mild to moderate OSA. Patients with severe OSA should still be offered a trial of CPAP as initial therapy, although MAD seems to be a reasonable "salvage" option in these patients.

Highly Trained Primary Care Practitioners Can Be Effective in Treating Uncomplicated OSA

Chai-Coetzer CL, Antic NA, Rowland LS, et al. Primary care vs specialist sleep center management of obstructive sleep apnea and daytime sleepiness and quality of life: a randomized trial. JAMA. 2013;309:997-1004. [PMID: 23483174]

Background: The increasing prevalence of OSA has increased the demand for sleep medicine services, and cost-saving initiatives have spawned interest in ambulatory models of OSA management. It remains unclear whether a primary care–based ambulatory approach to OSA manage-

ment would be a reasonable alternative to sleep specialist center–based care.

Findings: 155 adults with presumptive OSA on the basis of a screening questionnaire and overnight oximetry were enrolled. Patients were randomly assigned to receive primary care, nurse-based management or standard care offered at a sleep center. Before the study, primary care practitioners underwent extensive training regarding OSA management.

After 6 months of OSA therapy, improvements in daytime sleepiness, sleep quality, and blood pressure were similar in the primary care group and sleep specialist group. Primary care management was also associated with cost savings per patient of almost 60%. Sleep specialist care was associated with less therapy discontinuation and greater use of non-CPAP therapies.

Cautions: Patients with cardiac or respiratory comorbidities were excluded, thus limiting the generalizability of the findings. In the primary care group, the supervising nurse had more than 15 years of sleep medicine experience; it is arguable that this may not be representative of most primary care models with respect to proficiency in OSA management.

Implications: Increased participation by primary care physicians is critical for managing such an increasingly prevalent yet underdiagnosed condition as OSA. This study suggests that for the management of uncomplicated OSA, a primary care model is reasonable and cost-effective, provided that practitioners have sufficient sleep medicine education and community-based nursing support.

Critical Care Medicine

Colloids and Crystalloids Are Largely Equivalent for Fluid Resuscitation of Hypovolemic Shock

Annane D, Siami S, Jaber S, et al; CRISTAL Investigators. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock. JAMA. 2013;310:1809-17. [PMID: 24108515]

Background: Both colloids and crystalloids may have theoretical benefits in the management of hypovolemic shock, but early data from small studies suggested that they may not be equivalent in practice (7). The CRISTAL (Colloids Versus Crystalloids for the Resuscitation of the Critically Ill) study is the latest entry in recent years to address this area of clinical uncertainty.

Findings: 2857 adults in hypovolemic shock were studied. Patients were randomly assigned to receive any colloid versus any crystalloid for initial acute resuscitation of hypovolemic shock in the ICU. Those treated with colloids received significantly less fluids than those treated with crystalloids (median volume administered in first 7 days, 2000 vs. 3000 mL, respectively). There was no difference in 28-day mortality (25.4% in the colloid group vs. 27.0% in the crystalloid group), although the colloid group had more vasopressor-free and ventilator-free days.

Cautions: Clinicians were not blinded to the use of study fluids, leaving the study susceptible to potential bias. Specific colloid and crystalloid agents were not compared, allowing comparison only of 2 large classes, and possible adverse effects with specific agents may have been missed.

Implications: This study suggests that, in general, colloids are noninferior to crystalloids for the acute resuscitation of hypovolemic shock. Nonetheless, an individualized approach to each patient is still warranted, because other studies have raised agent-specific concerns, such as the potential for kidney injury with use of hydroxyethyl starch (8), or have suggested situation-specific caution, such as use of albumin in the setting of traumatic brain injury (9). Given cost differences, crystalloids may still be preferable to colloids for initial resuscitation of these patients.

Addition of Steroids and Vasopressin Improves Neurologically Favorable Survival After In-Hospital Cardiac Arrest

Mentzelopoulos SD, Malachias S, Chamos C, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial. JAMA. 2013;310:270-9. [PMID: 23860985]

Background: The survival rate after in-hospital sudden cardiac arrest requiring vasopressors is very poor. These investigators did a previous study in which the combination of vasopressin, epinephrine, and methylprednisolone given during in-hospital cardiac arrest was associated with increased survival to hospital discharge (10). The current study was conducted to extend those findings and assess survival with favorable neurologic function.

Findings: 364 adult patients with sudden in-hospital cardiac arrest were consecutively enrolled and randomly assigned to receive vasopressin and steroid (methylprednisolone) with epinephrine (VSE group) or placebo with epinephrine. The VSE recipients who survived resuscitation with postresuscitation shock also received stress-dose hydrocortisone. The VSE group had significantly increased return of spontaneous circulation and increased survival to hospital discharge with favorable neurologic recovery (survival rate, 14% vs. 5.1% in the placebo group), as well as more days free of neurologic or renal failure.

Cautions: The control group had a greater number of cardiac arrests due to respiratory and metabolic causes, which are known to have worse outcomes than arrest due to cardiac causes. Not all patients with ventricular tachycardia or fibrillation arrest received therapeutic hypothermia; more uniform application of this therapy may have altered the benefits seen with VSE therapy.

Implications: Although the results of this well-designed study demonstrate that the addition of vasopressin and steroids strikingly improved survival in patients who develop

in-hospital cardiac arrest, this finding will need to be validated in different settings before broad application. Until then, systematic consideration of proven therapies, such as therapeutic hypothermia, should be pursued.

Restrictive Transfusion Strategy Reduced Mortality in Patients With Acute Upper Gastrointestinal Bleeding

Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368:11-21. [PMID 23281973]

Background: Meta-analyses of trials comparing restrictive red blood cell transfusion strategies with liberal transfusion strategies have shown no significant differences in outcomes (11), but nearly all trials have excluded patients with acute gastrointestinal bleeding. This study was performed to address this gap in evidence.

Findings: 921 adult patients with severe acute upper gastrointestinal bleeding and high risk for rebleeding were recruited from a single hospital in Spain and randomly assigned to receive a restrictive transfusion strategy (at a hemoglobin level <7 g/dL) or a liberal strategy (at a hemoglobin level <9 g/dL). Patients with massive exsanguination or active cardiovascular or cerebrovascular disease were excluded. The restrictive transfusion group had a 45% reduction in all-cause mortality (5.2% vs. 9.2%, respectively), fewer episodes of recurrent bleeding (10% vs. 16%), and fewer in-hospital complications (40% vs. 48%).

Cautions: The transfusion strategy was broken at the discretion of clinicians when such circumstances as massive bleeding or surgical intervention occurred; this ensued more often in the restrictive strategy group than the liberal strategy group (8% vs. 3%, respectively) and may have influenced results. Exclusion criteria were extensive and limit the generalizability of this study; of note, patients with lower gastrointestinal bleeding were excluded.

Implications: Most patients with upper gastrointestinal bleeding and high risk for rebleeding should be managed with a restrictive red blood cell transfusion strategy, with transfusion occurring when the hemoglobin level falls to less than 7 g/dL. Modification of this threshold should be considered in patients with massive exsanguination and those with active or recent cardiovascular or cerebrovascular disease.

Universal Decolonization Prevents More ICU Infections Than MRSA Screening and Isolation

Huang SS, Septimus El, Kleinman K, et al; CDC Prevention Epicenters Program; AHRQ DECIDE Network and Healthcare-Associated Infections Program. Targeted versus universal decolonization to prevent ICU infection. N Engl J Med. 2013;368:2255-65. [PMID: 23718152]

Background: Health care–associated infections caused by MRSA are a significant source of morbidity and mortality, particularly in the ICU. The current strategy of polymerase chain reaction assay–based detection and contact isolation is resource-intensive and may have adverse effects on patient care.

Findings: The study was conducted in 78 U.S. community-based adult ICUs with preexisting infection prevention procedures. The investigators followed 48 390 patients during a baseline period and compared them with 74 256 patients during the intervention period. During the intervention period, participating ICUs were randomly assigned to 1 of 3 groups: standard MRSA screening plus contact isolation, MRSA screening plus targeted decolonization of MRSA-colonized patients with intranasal mupirocin and chlorhexidine bathing, or empirical mupirocin plus chlorhexidine decolonization of all patients admitted to the ICU. Universal decolonization was associated with a 37% reduction in MRSA-positive blood cultures and a 44% reduction in bloodstream infections by any organism.

Cautions: The differential effect of intranasal mupirocin versus chlorhexidine bathing was not examined. Monitoring for resistance to mupirocin and chlorhexidine was not performed.

Implications: Universal decolonization with chlorhexidine bathing and adjunctive therapy may be more effective at reducing nosocomial ICU infection than MRSA-specific screening and isolation policies. More generally, these findings suggest that broadly applicable population-based interventions, such as hand hygiene or bundled care, offer more promise for infection control than individualized, disease-specific strategies, such as pathogen-specific screening and isolation.

Prone Positioning Improves Survival Among Selected Patients With Severe ARDS

Guérin C, Reignier J, Richard JC, et al; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368:2159-68. [PMID: 23688302]

Background: Management of severe ARDS can be challenging; in many cases, lung injury is heterogeneous, such that volume and pressure applied by the mechanical ventilator may be unequally distributed throughout the lung. This study was performed to assess the effect of early use of prone positioning, which has been shown to improve ventilation–perfusion matching (12).

Findings: In a prospective trial in 27 European ICUs with experience in prone positioning, 576 patients with severe ARDS and no contraindications were randomly assigned (out of 1434 patients who were screened) to prone positioning instituted within 36 hours of ARDS recognition versus standard supine care. Prone patients spent 73% of available time in the prone position, with an average of 17 hours per prone session and a mean of 4 sessions per patient.

Patients in the prone position had higher oxygenation and better lung mechanics by day 3 and, compared with the control group, had significantly lower 28-day mortality

(16% vs. 32%) and 90-day mortality (24% vs. 41%). There was no significant increase in the number of adverse events from prone positioning.

Cautions: Patients were highly selected; less than 15% of all patients with ARDS were randomly assigned. All staff performing prone positioning had more than 5 years' experience with these procedures. Patients in the study received a lower positive end-expiratory pressure strategy, even though a recent meta-analysis suggests that higher positive end-expiratory pressure strategies may be better in patients with moderate to severe ARDS (13).

Implications: Early consideration should be given to prone positioning during ventilation for patients with moderate to severe ARDS and persistent hypoxemia despite ventilator optimization. Application of prone positioning requires staff training and adequate personnel to perform the maneuver, as well as appropriate monitoring for complications of this position.

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