AHC Media

Critical Care [ALERT]

Vol. 24, Issue 4, July 2016
AHCMedia.com

Authoritative, evidence-based summaries for the critical care clinician

SPECIAL FEATURE

Novel Oral Anticoagulants in the Critical Care Setting

By Samuel Nadler, MD, PhD

Critical Care, Pulmonary Medicine, The Polyclinic Center, Seattle; Clinical Instructor, University of Washington, Seattle

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

Coumarin was discovered at the University of Wisconsin through investigations of how ingestion of spoiled sweet clover by cattle caused hemorrhage and death.[1] The name derives from the Wisconsin Alumni Research Foundation, which supported the research and was assigned the patent on a related molecule as rat poison in 1948, and coumarin. It was subsequently understood that warfarin inhibited vitamin K metabolism, preventing the synthesis of clotting factors. Until recently, warfarin was the primary oral anticoagulant for the prevention of stroke in non-valvular atrial fibrillation (AF) as well as the treatment of venous thromboembolism (VTE) and pulmonary embolism (PE). As novel oral anticoagulants (NOACs) have been introduced, their use is becoming widespread. While the risk of major bleeding complications seems less with NOACs, they present unique challenges when patients taking these medications are admitted to the ICU.

SPECIFIC AGENTS

Oral anticoagulants work through inhibition of the clotting cascade. Warfarin inhibits the synthesis of clotting factors II, VII, IX, and X. In contrast, the NOACs directly inhibit the enzymatic activity of specific clotting factors. Dabigatran directly inhibits thrombin (factor II). Rivaroxaban, apixaban, and edoxaban directly inhibit factor X activity. A summary of their pharmacology and pharmacokinetics can be found in Table 1.

The efficacy and safety of dabigatran was demonstrated in the RE-COVER studies.[2,3] The first RE-COVER study showed that in 1,274 patients, dabigatran was non-inferior to warfarin for the treatment of VTE (hazard ratio [HR], 1.1; 95% confidence interval [CI], 0.65-1.84) with similar rates of major bleeding but less bleeding overall (HR, 0.71; 95% CI, 0.59-0.85). Due to the low rate of VTE in the first study, RE-COVER II enrolled an additional 2,589 patients and again demonstrated non-inferiority to warfarin for the treatment of VTE (HR, 1.08; 95% CI, 0.64-1.80) with fewer overall bleeding events. For the treatment of VTE, these studies together generate an HR for dabigatran vs. warfarin of 1.09 (95%

Financial Disclosure: *Critical Care Alert*'s Editor Betty Tran, MD, MSc, Nurse Planner Jane Guttendorf, DNP, RN, CRNP, ACNP-BC, CCRN, Peer Reviewer William Thompson, MD, Executive Editor Leslie Coplin, and Associate Managing Editor Jonathan Springston report no financial relationships relevant to this field of study.

Critical Care [ALERT]
Authoritative, evidence-based summaries for the critical care clinician

Critical Care Alert, (ISSN 1067-9502) is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

Periodicals Postage Paid at Atlanta, GA, and at additional mailing offices.

GST Registration Number: R128870672.
POSTMASTER: Send address changes to *Critical Care Alert*, P.O. Box 550669, Atlanta, GA 30355.

SUBSCRIBER INFORMATION
(800) 688-2421
Customer.Service@AHCMedia.com
AHCMedia.com

Questions & Comments:
Please contact Associate Managing Editor **Jonathan Springston**, at Jonathan.Springston@AHCMedia.com

Subscription Prices
United States
Print: 1 year with free *AMA PRA Category 1 Credits™*: $349
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits™*: $299

Back issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. AHC Media designates this enduring material for a maximum of 2.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

AHC Media is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. This activity has been approved for 2.25 nursing contact hours using a 60-minute contact hour. Provider approved by the California Board of Registered Nursing, Provider #CEP14749, for 27 Contact Hours.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2.25 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

This CME activity is intended for critical care physicians and nurses. It is in effect for 36 months from the date of the publication.

AHC Media

Table 1: Novel Oral Anticoagulants

Name	Mechanism of Action	Half Life (CrCl ≥ 60)	Reversal Agent	Removed by HD?
Dabigatran	IIa inhibitor	12-17 hrs	Idarucizumab	Yes
Rivaroxaban	Xa inhibitor	9-13 hrs	Andexanet alfa	No
Apixaban	Xa inhibitor	8-15 hrs	Andexanet alfa	No
Edoxaban	Xa inhibitor	8-10 hrs	Andexanet alfa	No
Coumadin	Vitamin K antagonist	36-42 hrs	Vitamin K, FFP	No

CI, 0.76-1.57) with similar major bleeding episodes and slightly fewer overall bleeding episodes (HR, 0.7; 95% CI, 0.61-0.79).

The EINSTEIN-VTE and EINSTEIN-PE studies presented the efficacy and safety of rivaroxaban.[4,5] In 3,449 patients, rivaroxaban was non-inferior to warfarin for the treatment of VTE (HR, 0.68; 95% CI, 0.44-1.04) with a similar safety profile. A continued treatment arm of the study, consisting of 1,196 patients, showed lower rates of recurrent VTE (HR, 0.68; 95% CI, 0.44-1.04) without statistically different rates of bleeding. For the treatment of PE, rivaroxaban was shown to be non-inferior to warfarin (HR, 1.12; 95% CI, 0.75-1.68) but demonstrated lower rates of major bleeding (HR, 0.49; 95% CI, 0.31-0.79).

The AMPLIFY investigators presented the safety and efficacy of apixaban.[6] As with rivaroxaban, apixaban was shown to be non-inferior to warfarin for the treatment of acute VTE (relative risk [RR], 0.84; 95% CI, 0.60-1.18). In contrast, apixaban led to lower rates of major bleeding (RR, 0.31; 95% CI, 0.17-0.55) and overall rates of bleeding (HR, 0.44; 95% CI, 0.36-0.55). Similarly, edoxaban was shown to be non-inferior to warfarin for acute VTE (HR, 0.89; 95% CI, 0.70-1.13) with fewer episodes of bleeding (HR, 0.81; 95% CI, 0.71-0.94).[7]

REVERSAL AGENTS

Although data imply NOACs trigger fewer bleeding episodes than warfarin, there were concerns that when these events occur, there were no available agents to reverse their effects. With warfarin, the administration of vitamin K and fresh frozen plasma (FFP) can reverse its anticoagulant effects. In contrast, these measures are much less effective in reversing anticoagulation due to NOACs.[8,9] Prothrombin coagulant concentrates (PCCs), activated PCCs (aPCC), and recombinant factor VIIa have been used to varying effects. Until recently, no specific agents were available for the reversal of NOACs. Currently, two such agents have been described, idarucizumab and andexanet alfa, while a third, ciraparantag, is under development.

Idarucizumab is a monoclonal antibody fragment that binds dabigatran with an affinity 350 times greater than the affinity of dabigatran for thrombin. After administration, it binds both free and thrombin-bound dabigatran and neutralizes the effects. The REVERSE-AD trial examined 90 patients with AF receiving dabigatran for stroke prevention who presented with bleeding.[10] In this trial, 18 patients experienced intracranial bleeding, 20 suffered gastrointestinal bleeding, nine had trauma-related hemorrhage, and 11 weathered other bleeding; all were determined to require emergent reversal of anticoagulation. An additional 39 patients required a procedure that necessitated reversal of anticoagulation. Each received 5 g of IV idarucizumab over 15 minutes. Within minutes after administration, 88-98% of patients showed normalization of bleeding times, and hemostasis was restored up to a median of 11.4 hours. There was one thrombotic event in a patient for whom anticoagulants were not subsequently restarted.

Andexanet alfa is a specific reversal agent for factor Xa inhibitors. It is a recombinant human factor Xa decoy that binds Xa inhibitors but has no intrinsic Xa activity. In a study of 145 healthy participants given either apixaban or rivaroxaban, andexanet reversed the anticoagulant effects within two to five minutes and persisted for about two hours after the infusion ended.[11] Although some mild gastrointestinal upset and hives were reported, there were no serious adverse effects.

Although not yet available, ciraparantag is a novel cationic protein that recently received FDA fast-track designation to treat bleeding related to NOACs. It binds both unfractionated heparin and low-molecular weight heparin, as well as NOACs, and has been shown to reverse the anticoagulation of edoxaban in rat tail transection assays. More recently, it was shown to reverse clotting times in healthy volunteers who had received edoxaban.[12]

CLINICAL CONSIDERATIONS

The most common clinical situations in which NOAC use becomes relevant in the ICU involve the treatment of life-threatening hemorrhage or the need for invasive procedures that require anticoagulant reversal. Few evidence-based guidelines exist for these situations. Practical considerations include the nature of the hemorrhage, the invasiveness of the procedure, and the pharmacodynamics of these agents. Life-threatening bleeding, such as intracranial hemorrhage or variceal bleeding, requires immediate intervention. In contrast, the need for central venous access, thoracentesis, or other invasive procedures may be delayed until the anticoagulant effect of NOACs resolves, as their half-life is relatively short.

Unfortunately, standard coagulation assays are not particularly helpful in judging anticoagulant effects of NOACs.[13,14] While prothrombin time is sensitive for warfarin, it is not useful for NOACs. Similarly, activated partial thromboplastin time features variable sensitivity. For dabigatran, thrombin time and clotting times seem to exhibit the greatest sensitivity. In contrast, chromogenic anti-Xa assays contain the greatest sensitivity for the Xa inhibitors. Ultimately, the degree of hemorrhage, need for reversal, or risk of an invasive procedure may outweigh specific coagulation parameters in considering the best care of patients taking NOACs.

EMERGENCY MANAGEMENT

General management principles for bleeding remain relevant in patients taking NOACs. Minor bleeding can be managed conservatively with the application of pressure, local hemostatic measures, and supportive care with the omission of a single dose of the NOAC. Moderate bleeding may require volume resuscitation and red cell transfusions in addition to conservative measures. Although they have not proven effective at reversing NOAC effects, FFP and cryoprecipitate also may be considered. A full review of the data regarding reversal of NOACs is beyond the scope of this article but may be found in several recent publications.[9,13,15]

For life-threatening hemorrhage, such as intracranial hemorrhage, variceal bleeding, or trauma, consider administering specific reversal agents. A summary of these agents can be found in Table 2. For patients taking dabigatran, idarucizumab may be given. Should this not be available, hemodialysis may attenuate bleeding, as dabigatran is not highly protein bound. Activated protein concentrates and recombinant factor VIIa also may be given, although their benefits have a lesser evidence basis and there are concerns for prothrombotic complications. For the factor Xa inhibitors, andexanet is under development, although it has not yet received FDA approval. As Xa inhibitors are highly protein bound, hemodialysis is not effective at reducing their effects. Activated clotting factors also may be given for hemorrhage exacerbated by Xa inhibition but with less evidence of benefit. Ciraparantag is still under evaluation in clinical trials.

PERIPROCEDURAL MANAGEMENT

There are several reviews of periprocedural management of patients receiving NOACs.[14-16] In general, these recommendations stratify by risk of procedural bleeding and renal function. Low-risk procedures, such as dental extractions, cataract surgery, and skin biopsy, did not require significant interventions other than holding a single dose prior to the procedure.

Table 2: Summary of Reversal Agents for Novel Oral Anticoagulants

Name	Mechanism of Action	Dose	Onset	Duration
Andexanet alfa	Xa decoy	400 mg IV ± 4 mg/mL x 2 hours	2 min	1-2 hrs
Idarucizumab	Monoclonal antibody that binds dabigatran	5 g IV in 15 min	minutes	$T_{½}$ about 45 min but prolonged effects
Ciraparanteg	Cationic binding molecule	100 mg IV	10-30 min	24 hours

Moderate-risk procedures include endoscopy with biopsy, angiography, and catheter ablation. For these procedures, stopping dabigatran one to two days prior to the procedure in patients with normal renal function was suggested and up to five days prior in patients with decreased renal function (CrCl < 50 mL/min). For the Xa inhibitors, researchers recommend stopping one day prior to surgery in patients exhibiting normal renal function and two days prior in those suffering from reduced renal function (CrCl < 30 mL/min). Common ICU procedures, such as central venous catheter placement (internal jugular and femoral vein), thoracentesis/paracentesis, and bronchoscopy with biopsy, likely fall into this category. High-risk procedures include spinal/epidural catheter placement, thoracic or abdominal surgery, major orthopedic surgery, and liver and kidney biopsies. In these cases, hold dabigatran two to three days or four to six days prior in patients with normal or impaired renal function, respectively. Hold Xa inhibitors two to three days prior. Obviously, the need for emergent procedures, such as exploratory laparotomy, thoracotomy, or craniotomy, would necessitate active, immediate reversal as described above. For moderate-risk procedures, restart most agents one to two days post procedure while holding them two to three days after high-risk procedures.

OVERDOSE

In the absence of hemorrhage, the best management of NOAC overdose is unclear. There are data to support the use of activated charcoal within six hours of overdose for all NOACs.[15] However, weigh the benefit against the risk of aspiration and impaction. Hemodialysis can remove dabigatran, but the risk-benefit calculation in individuals without hemorrhage likely favors watchful waiting.

SUMMARY

The newer oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban show promise in the treatment and prevention of venous thromboembolic disease. Studies have shown them to be non-inferior to warfarin in terms of efficacy with similar or reduced bleeding risks. When bleeding occurs, there are fewer evidence-based interventions for reversal of these agents, but research continues. Knowledge of the pharmacokinetics of these agents and potential reversal agents will improve the management of patients taking NOACs when admitted to the ICU. ■

REFERENCES

1. Stahmann MA, Huebner CF, Link KP. Studies on the hemorrhagic sweet clover disease. *J Biol Chem* 1941;138:513-527.
2. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361:2342-2352.
3. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation* 2014;129:764-772.
4. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499-2510.
5. Büller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366:1287-1297.
6. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369:799-808.
7. Büller HR, Décousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369:1406-1415.
8. Hu TY, Vaidya VR, Asirvatham SJ. Reversing anticoagulant effects of novel oral anticoagulants: Role of ciraparantag, andexanet alfa, and idarucizumab. *Vasc Health Risk Manag* 2016;12:35-44.
9. Abo-Salem E, Becker RC. Reversal of novel oral anticoagulants. *Current Opin Pharmacol* 2016;27:86-91.
10. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med* 2015;373:511-520.
11. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med* 2015;373:2413-2424.
12. Ansell JE, Bakhru SH, Laulicht BE, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med* 2014;371:2141-2142.
13. Jackson LR 2nd, Becker RC. Novel oral anticoagulants: Pharmacology, coagulation measures, and considerations for reversal. *J Thromb Thrombolysis* 2014;37:380-391.
14. Weitz JI, Pollack CV Jr. Practical management of bleeding in patients receiving non-vitamin K antagonist oral anticoagulants. *Thromb Haemost* 2015;114:1113-1126.
15. Aronis KN, Hylek EM. Who, when, and how to reverse non-vitamin K oral anticoagulants. *J Thromb Thrombolysis* 2016;41:253-272.
16. Lai A, Davidson N, Galloway SW, et al. Perioperative management of patients on new oral anticoagulants. Br J Surgery 2014;101:742-749.

ABSTRACT & COMMENTARY

A Perspective on Tidal Volume Reduction in Acute Respiratory Distress Syndrome

By Rich Kallet, MS, RRT, FAARC, FCCM

Director of Quality Assurance, Respiratory Care Services, San Francisco General Hospital

Mr. Kallet reports no financial relationships relevant to this field of study.

SYNOPSIS: Less than 20% of acute respiratory distress syndrome patients were treated at any point during mechanical ventilation with a tidal volume at or below the target used during the NIH ARDSNet trials.

SOURCE: Weiss CH, Baker DW, Weiner S, et al. Low tidal volume use in acute respiratory distress syndrome. *Crit Care Med* 2016 March 31 [Epub ahead of print].

Four Chicago area hospitals (one academic, three community facilities) were the subject of a six-month retrospective study reviewing the management of 362 patients meeting the Berlin Definition of acute respiratory distress syndrome (ARDS). The electronic medical record at each institution provided continuous ventilator data from the entire course of mechanical ventilation from intubation to extubation or death. The primary outcome was the percentage of patients who demonstrated at least one tidal volume (V_T) measurement meeting the ARDSNet goal without reference to plateau pressure (Pplat), which was not measured at 50% of the hospitals. Among the secondary outcomes were the percentage of time patients were managed with a V_T < 6.5 mL/kg predicted body weight (PBW) and the time from ARDS onset to the first V_T of < 6.5 mL/kg PBW.

Of the 362 ARDS patients, approximately 20% were classified as severe and 40% as either moderate or mild cases each. Overall, only 19% of patients ever demonstrated a V_T < 6.5 mL/kg, and only 26% among those with severe ARDS. There was no difference between academic vs. community hospitals in this regard. In patients who were managed with the ARDSNet V_T, only about 60% of the time did they actually receive a V_T < 6.5 mL/kg. Only 40% of severe ARDS cases received a V_T < 6.5 mL/kg at some point during mechanical ventilation. Finally, among all ARDS patients who received an ARDSNet V_T, one-third had a delay of more than three days in reaching that threshold.

■ COMMENTARY

This study reflects the inadequacies of utilizing lung-protective ventilation (LPV) 16 years after the landmark ARDSNet trial. By 2013, none of the hospitals had incorporated an LPV protocol or order set as a standard of care. Only 6% of attending physicians initiated rigorous LPV (V_T < 6.5 mL/kg PBW) within a day of ARDS onset in at least 50% of their patients. In contrast, more than half of attending physicians never initiated rigorous LPV within 24 hours of ARDS onset. Furthermore, Pplat had not been universally mandated to guide V_T adjustments. This is very troubling, as alveolar driving pressure (Pplat - PEEP, or positive end-expiratory pressure) is a crucial driver in the development of ventilator-induced lung injury, cor pulmonale, and mortality.

Among the factors the authors cited while explaining the inadequate achievement of LPV, three hint at a common theme of clinical compromise. First, the failure to recognize ARDS in a timely manner partly may reflect a long-standing disagreement with how ARDS was redefined in the mid-1990s. Overcoming this obstacle requires physicians to recognize that most patients intubated for acute respiratory failure usually feature two inherent risk factors for ARDS: a pro-inflammatory state and a reduction in functional residual capacity that magnifies the risk for iatrogenic lung injury. Acknowledging these risk factors renders the interpretation of chest radiographic opacities much less important than expediting effective LPV.

Second, we should acknowledge that in times of high census and acuity, it's unrealistic to expect physicians to manage every aspect of multiple critically ill patients without inadvertently overlooking important details, at least temporarily. The ARDSNet ventilator and fluid management studies demonstrated that respiratory therapists and nurses are eminently capable of executing highly intricate protocols. During the ARDSNet studies, both professions welcomed this responsibility with great pride. The emphasis on patient-centered outcomes driving 21st century healthcare requires an evolution in care delivery that incorporates and develops these professional resources.

The third issue is patient-ventilator asynchrony, which was a topic of frequent discussion during the ARDSNet ARMA study. I distinctly remember Dr. Brower remarking,"eight is easy, six is much harder," an observation that was affirmed many years later.[1] V_T mismatching increases work of breathing and provokes dyspnea. It has long been recognized as a barrier to LPV. Because generous sedation negatively affects patient outcomes, the tendency to liberalize V_T to 7-8 mL/kg appears to be a reasonable compromise, but only in less severe cases and during the recovery phase. However, in the early phase of moderate-to-severe ARDS, strict adherence to LPV goals is likely crucial to improving outcomes and should outweigh other concerns. Finally, the fact most patients were managed at a V_T < 9 mL/kg and only a tiny fraction at > 12 mL/kg is noteworthy. Regardless of the shortcomings found in this study, it still represents a substantial change in practice from 20 years ago. ■

REFERENCE

1. Kallet RH, Campbell AR, Dicker RA, et al. The effects of tidal volume demand on work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome. *Crit Care Med* 2006;34:8-14.

ABSTRACT & COMMENTARY

Can Procalcitonin Predict Need for ICU Admission in Community-acquired Pneumonia Patients?

By Betty Tran, MD, MSc, Editor

SYNOPSIS: In a prospective cohort study of adults hospitalized with community-acquired pneumonia, higher serum procalcitonin levels on admission were associated with an increased risk of invasive respiratory and/or vasopressor support within 72 hours and improved the performance of pneumonia severity scores in identifying high-risk patients.

SOURCE: Self WH, Grijalva CG, Williams DJ, et al. Procalcitonin as an early marker of the need for invasive respiratory or vasopressor support in adults with community-acquired pneumonia. *Chest* 2016 Apr 20 [Epub ahead of print].

There is significant recent interest in studying procalcitonin (PCT) as a biomarker for the management of critically ill patients with sepsis, as its synthesis and secretion are upregulated by bacterial-specific pro-inflammatory cytokines.[1] Several studies have focused on the use of PCT in diagnosing sepsis, as a prognostic marker in sepsis, and as a guide to antibiotic decisions in sepsis. Research by Self et al adds to the growing literature on PCT by examining whether it is helpful in early severity assessment and risk stratification for patients admitted with community-acquired pneumonia (CAP), particularly with regard to ICU admission.

This was a prospective cohort study of 1,770 adults hospitalized with CAP at three centers in Chicago and two hospitals in Nashville, TN, between 2010 and 2012 who had serum PCT measurements. The primary study outcome was the need for invasive respiratory and/or vasopressor support (IRVS), defined as intubation for respiratory failure or vasopressor administration for septic shock within 72 hours of hospital presentation. Overall, 115 patients required IRVS, with 47 requiring both, 37 requiring respiratory support only, and 31 requiring vasopressor support only. The area under the receiver operator curve (ROC) for PCT to discriminate between patients with and without IRVS was 0.69 (95% confidence interval [CI], 0.67-0.71), which the authors noted to be higher than the area for WBC (0.54; 95% CI, 0.51-0.56).

Overall, there was a significant association between PCT level and risk of IRVS. For undetectable levels of PCT (< 0.05 ng/mL), the risk of IRVS was 4.0% (95% CI, 3.1-5.1%). For levels of PCT between 0.05 ng/mL and 10 ng/mL, there was a linear risk of IRVS, with each increase in PCT of 1 ng/mL corresponding to a 1-2% absolute increase in IRVS risk. For PCT levels of 5 ng/mL and 10 ng/mL, the risk of IRVS was 14.2% (95% CI, 11-18.1%) and 22.4% (95% CI, 16.3-30.1%), respectively. The risk of IRVS was observed to plateau when PCT levels reached > 10 ng/mL.

The addition of PCT levels to existing pneumonia severity scoring systems such as the ATS Minor Criteria, Pneumonia Severity Index (PSI), and SMART-COP scores increased the area under the ROC curves and improved the risk stratification ability in predicting IRVS for each severity score.

■ COMMENTARY

The ability to risk stratify patients with sepsis appropriately has important clinical repercussions. Theoretically, accurate prognostication can result in quicker triage for sicker patients to the ICU and expedite crucial interventions such as appropriate antibiotics, searches for occult infection, and methods of source control.

In the Self et al study, PCT levels on admission for patients hospitalized with CAP strongly correlated with the risk of invasive respiratory and/or vasopressor support, interventions that are performed in the ICU. Specifically, patients with PCT levels of 5 ng/mL and 10 ng/mL were three and five times more likely, respectively, to require IRVS than patients with levels < 0.05 ng/mL. When added to ATS minor criteria, PCT levels improved the ability to accurately identify patients at risk for IRVS who would benefit from admission to an ICU.

The authors appropriately acknowledged that the PCT level alone is insufficient in deciding whether to admit a patient with CAP to the ICU. This study suggested yet another unique potential use for PCT in the management of patients with sepsis beyond what has previously been reported in terms of sepsis diagnosis and antibiotic management. There are, however, several issues to consider. First, PCT is mainly upregulated in bacterial infections; its application to non-bacterial pneumonia patients is unclear. Second, its use as a factor in the appropriate triage of sick CAP patients to

the ICU will depend on how quickly the value is made available to healthcare providers, especially in the ED. Third, only a single PCT level on admission was used in this study; it may be more helpful to examine changes in PCT over time, as prior studies have reported that changes in PCT rather than absolute values correlate with patient outcomes such as mortality.[2-4] Finally, it is necessary to note that the decision to admit a patient to the ICU is likely to depend on other clinical and social factors besides the risk of IRVS, and PCT levels may not influence decision-making in these situations. Despite its known limitations, it will be interesting to see if PCT will gain more widespread use similar to how clinicians use BNP, lactate, or D-dimer as part of medical decision-making in specific clinical situations. ■

REFERENCES

1. Nakamura M, Kono R, Nomura S, et al. Procalcitonin: Mysterious protein in sepsis. *J Basic Clin Med* 2013;2:7-11.
2. Karlsson S, Heikkinen M, Pettila V, et al. Predictive value of procalcitonin decrease in patients with severe sepsis: A prospective observational study. *Crit Care* 2010;14:R205.
3. Schuetz P, Maurer P, Punjabi V, et al. Procalcitonin decrease over 72 hours in US critical care units predicts fatal outcome in sepsis patients. *Crit Care* 2013;17:R115.
4. Jensen JU, Heslet L, Jensen TH, et al. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. *Crit Care Med* 2006;34:2596-2602.

ABSTRACT & COMMENTARY

Predicting the Success of Prone Positioning with Lung Ultrasound

By Samuel Nadler MD, PhD

Critical Care, Pulmonary Medicine, The Polyclinic Madison Center, Seattle; Clinical Instructor, University of Washington, Seattle

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

SYNOPSIS: Lung ultrasound may be useful in predicting which patients with acute respiratory distress syndrome would favorably respond to prone positioning.

SOURCE: Prat G, Guinard S, Bizien N, et al. Can lung ultrasonography predict prone positioning response in acute respiratory distress syndrome patients? *J Crit Care* 2016;32:36-41.

Despite increasing adoption of lung protective ventilation, patients with acute respiratory distress syndrome (ARDS) still experience high morbidity and mortality. Many strategies have been studied to improve the care of these patients. The PROSEVA study demonstrated that the early application of prone positioning decreased 28-day and 90-day mortality in patients with severe ARDS.[1] Other strategies include neuromuscular blockade, inhaled pulmonary vasodilators, and alternative ventilation strategies. Which patients could benefit from each strategy may be difficult to determine.

This study tested whether lung ultrasound (L-US) could predict which patients would benefit from prone positioning. Prospectively, 19 patients admitted to a medical ICU with ARDS in whom the attending physician had decided to apply prone positioning were assessed with L-US in 12 different regions. Three ICU physicians with expertise in L-US evaluated each of the 12 segments and classified them as normal (N), with more than two B-lines (B1), with severe loss of aeration (B2), or lung consolidation (C). Researchers placed patients in the prone position and quantified the response. A positive response was defined by an improvement in the PaO_2/FiO_2 ratio of > 20 mmHg at two hours and 14 hours after prone positioning. All patients received lung protective ventilation according to a standardized protocol.

Of the 19 patients enrolled in the study, 12 and 13 met the criteria for positive response at two and 14 hours, respectively. In comparing patients who demonstrated favorable responses to prone positioning to those who did not, there were no significant differences in age, tidal volumes, plateau pressure, lung compliance, lung aeration scores, rates of immunocompromise, or ICU mortality. However, the presence of a normal L-US pattern in the bilateral anterobasal segments produced a positive predictive value of 100% (95% confidence interval [CI], 59-100%) for response to prone positioning and negative predictive value of 58% (95% CI, 28-85%) at two hours. Similar values were observed at 14 hours.

■ COMMENTARY

This study is intriguing in that it proposes a method through which a bedside assessment might predict which patients might benefit from prone positioning. Before adopting this protocol, consider several limitations. First, this was not a prospective study of L-US to determine which patients should undergo prone

positioning. Rather, all patients were placed in the prone position, and there was no difference in the mortality of patients identified as responders vs. non-responders. A prospective trial that decided whether proning should occur based on L-US findings would be needed to determine if this protocol is truly beneficial. Second, 12 ultrasound zones were evaluated, but only the anterobasal segments correlated with beneficial outcomes. Without a correction for multiple comparisons, it may be simple chance that one of the 12 segments correlated with improvement. Third, the assessments were performed by physicians with expertise in L-US. Thus, the generalizability of this protocol remains a question.

Ultimately, the decision whether to place a patient in prone position relates to the risks vs. benefits of this intervention. To this end, the benefits of prone positioning for ARDS are becoming clear. PROSEVA demonstrated a clear mortality benefit of placing all patients with severe ARDS in the prone position early in the course of the disease.[1] Conversely, the risks of prone positioning such as facial edema, skin breakdown, accidental extubation, and catheter displacement can be mitigated by experience with proning. In the Prat et al study, five of the 12 patients who did not experience a favorable L-US pattern in the anterobasal segments still responded favorably to prone positioning at two hours, and six of the 12 patients at 14 hours. Therefore, it becomes difficult to propose deferring prone positioning based on consolidation in the anterobasal segments of the lung as determined by lung ultrasound.

Overall, consider prone positioning in all patients with severe ARDS. Should other factors exist that increase the risk of prone positioning (e.g., trauma, abdominal incisions, obesity, difficult airway), L-US may be useful in determining which patients undergo this intervention. A prospective study to test L-US in determining which patients are placed in prone position would shed light on this question. ■

REFERENCE

1. Guerin C, Reigner J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159-2168.

CME/CE QUESTIONS

1. Which of the following is correct regarding novel oral anticoagulants (NOACs)?
a. NOACs have been shown to be superior to warfarin for the treatment of venous thromboembolism.
b. The anticoagulant effect of NOACs have a longer half-life than that of warfarin.
c. NOACs have been associated with greater risk of major hemorrhage than warfarin.
d. Compared with warfarin, the anticoagulant effect of NOACs are not easily reversed by fresh frozen plasma.

2. Regarding the study by Weiss et al, which of the following statements is false?
a. A V_T of < 6.5 mL/kg was considered appropriate for ARDS management.
b. Only about 20% of patients ever received a V_T < 6.5 mL/kg.
c. None of the hospitals measured plateau pressure.
d. Only a small percentage of patients received a V_T > 12 mL/kg.

3. The addition of procalcitonin concentration to existing pneumonia severity scores resulted in:
a. a significant improvement in risk stratification.
b. reduction in the area under the receiver operator curve.
c. no additional improvement in predicting risk.
d. improved ability to risk stratify patients using the ATS minor criteria only.

4. A normal ultrasound of the anterobasal segment of the lung in patients with ARDS predicted:
a. improved mortality.
b. positive response to prone positioning.
c. positive response to neuromuscular blockade.
d. increased severity of disease.