AHC Media

Vol. 24, Issue 8, November 2016
AHCMedia.com

Critical Care [ALERT]

Authoritative, evidence-based summaries for the critical care clinician

SPECIAL FEATURE

Airway Management in the Critically Ill: Challenges, Advances, and Controversies

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

Airway management is a common, high-risk procedure in the ICU. A decade ago, ICU intubation was associated with complications in more than 50% of cases, including prolonged hypoxemia, hemodynamic instability, cardiac arrest, and death.[1] Despite significant improvements in patient safety and outcomes using skilled operators, a systematic approach, and advanced airway tools, more recent publications still report a complication rate in the critically ill that remains unacceptably high. Recent evidence and guidelines help inform best airway practice in the ICU, but challenges and controversies remain.

DEFINING THE PROBLEM

Airway management in the ICU often is emergent and performed in patients with significant cardiopulmonary disease, hemodynamic instability, and upper airway abnormalities. (*See Table 1.*) These factors limit deliberate planning and preparation, decrease the time to perform intubation before hypoxemia develops, and reduce glottic visualization during the procedure. The result is a high incidence of difficult airways — defined as clinical factors that complicate ventilation by facemask or intubation by a skilled operator — reported to be 7-10% in this population.[2,3]

Current studies still report complication rates from ICU intubation of 4.2% to 22%.[3-6] Hypoxemia is the most common cause of serious complications, but post-intubation hypotension also has been associated with poor patient outcomes in a large retrospective, multicenter cohort.[7] ICU patients also present special management challenges for airway management, such as increased intracranial pressure and active coronary ischemia. A recent large cohort study found 47% of the critically ill patients who suffered airway complications in the Royal College of Anesthetists' Fourth National Audit Project were obese, and the incidence of difficult intubation in this population was twice as frequent in the ICU than the OR (16.3% vs. 8.2%; $P < 0.01$).[6,8]

Financial Disclosure: *Critical Care Alert*'s Physician 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 Assistant Editor Jonathan Springston report no financial relationships relevant to this field of study.

[INSIDE]

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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
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AHCMedia.com

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Subscription Prices
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Print: 1 year with free *AMA PRA Category 1 Credits™*: $349
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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.
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Table 1: Challenges, Potential Solutions in ICU Airway Management

Factors	Impact	Solutions
Patient		
Emergent situation, increased difficult airway incidence	Less time for airway assessment, planning	Multiple, skilled operators*
Cardiopulmonary disease	Rapid desaturation	Deliberate preoxygenation* Apneic oxygenation Early extraglottic airway*
Hemodynamic instability	Induction drug limits Increased mortality	Volume loading* Early vasopressor use*
Upper airway edema, secretions, loss of tone	Decreased glottic visualization	Advanced airway tools
Obesity	Decreased glottic visualization, rapid desaturation	Positioning* Preoxygenation*
Staffing, Training		
Low volume, variable training	Less prepared to manage high risk airways	Limit procedure to experts Improve training programs Videolaryngoscopy
Teamwork, communication barriers	Errors, worse outcomes	Dedicated airway teams Teamwork training* Simulation*
Equipment		
Rapid development of new airway devices	Variables availability, expertise in ICU	Standardized airway cart Validate best tools in ICU patients

***Indicates solution is supported by current published best evidence**

Multiple international studies also have documented variable staff training, limited availability of airway equipment in the ICU, and communication and teamwork errors as common causes of adverse outcomes during airway management.[6,9-11] This has led some to call for anesthesiologists alone to perform intubations in the critically ill, but survey data suggest that training and performance gaps in the management of difficult airways in these patients are common, even within this specialty.[12-15]

A SYSTEMATIC APPROACH INCREASES SUCCESS, SAFETY

A systematic approach to airway assessment, patient and equipment preparation, and procedure planning clearly has been shown to increase the rate of intubation success. In a two-phase, multicenter, prospective study of 244 intubations, Jaber et al demonstrated that implementation of a protocolized ICU intubation bundle (*see Table 2*) reduced the incidence of both life-threatening and other complications by 13% and 12%, respectively.[4] Implementation of a standardized, team-based approach to airway management, simulation-based airway skills and teamwork training, and a mandatory bedside procedure checklist also have been shown to improve patient safety with tracheal intubation and to reduce the need for emergent surgical airway procedures.[16,17]

STRATEGIES AND TOOLS TO MANAGE SUCCESS

Preoxygenation can be less effective in patients with significant cardiopulmonary disease, leaving little time for an intubation attempt before hypoxemia develops. Apneic oxygenation is the delivery of supplemental oxygen through the nasopharynx without ventilation, and has shown promise in small, nonrandomized trials examining its use in intubation outside the OR. However, in the first prospective, randomized trial to examine this issue, no difference was observed in 150 critically ill medical

Table 2: An ICU Intubation Bundle Improves Patient Outcomes

Pre-intubation
1. Presence of two operators 2. Fluid loading in absence of cardiogenic pulmonary edema 3. Preparation of long-term sedation 4. Preoxygenation for 3 minutes with non-invasive positive pressure ventilation in case of acute respiratory failure
During intubation
5. Rapid sequence induction: etomidate 0.2-0.3 mg/kg or ketamine 1.5-3 mg/kg combined with succinylcholine 1-1.5 mg/kg in absence of contraindications 6. Sellick maneuver
Post-intubation
7. Immediate confirmation of tube placement by capnography 8. Norepinephrine if diastolic blood pressure remains < 35 mmHg 9. Initiate long-term sedation 10. Initial "protective ventilation:" tidal volume 6-8 mL/kg of ideal body weight for a plateau pressure < 30 cm H_2O
SOURCE: Jaber S, Jung B, Corne P, et al. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: A prospective, multiple-center study. *Intensive Care Med* 2010;36:248-255.

Table 3: ICU Adaptation of Difficult Airway Society Guidelines

Airway Management Steps	Key Points
Plan A: Facemask ventilation, tracheal intubation	• Preoxygenation for all patients • Head-up positioning, ramping • Apneic oxygenation in high-risk patients • Neuromuscular blockade • Consider videolaryngoscopy • Maximum of three laryngoscopy attempts (plus one if skilled operator) • Remove cricoid pressure if intubation difficult
Plan B: Insert extraglottic airway device (EGA)	• Early use to preserve oxygenation • Second-generation EGAs recommended • Maximum of three EGA insertion attempts • Remove cricoid pressure • Use fiberoptic guidance for intubation through EGA
Plan C: Surgical airway	• Scalpel cricothyroidotomy preferred • Bougie assisted placement of 6.0 mm cuffed endotracheal tube • High-pressure oxygenation through narrow-bore cannula discouraged • Regular training for airway managers

patients who received either 15 L/min supplemental oxygen by nasal cannula or no additional oxygen during laryngoscopy attempts. Investigators maintained a high rate of compliance with best practices of preoxygenation, patient positioning, and equipment preparation, which may have reduced the potential additional benefit of this intervention. Further, investigators also excluded patients with anticipated difficult airways, a group in whom apneic oxygenation may produce the best outcome during a prolonged intubation attempt and is recommended in current guidelines.[18,19]

There has been considerable interest in the use of advanced airway tools to increase the success and safety of intubation in the ICU. Videolaryngoscopy (VL), a term used to describe a wide range of intubating devices that employ a video display to provide better glottic visualization, has shown promise in small cohort studies and one randomized, controlled study. However, a recent large, prospective, randomized study comparing standard direct laryngoscopy with videolaryngoscopy in the ICU did not demonstrate a difference in the rate of first attempt success, time to intubation, or complications despite better glottic visualization in the VL group.[20] Methodologic differences in this trial compared to prior positive studies included more aggressive use of neuromuscular blockade, the use of the McGrath MAC video laryngoscope instead of the GlideScope, and the exclusion of patients with anticipated difficult airways who were intubated using video or fiber optic techniques.[21]

Anatomic features continue performing poorly as a tool for identifying patients with a difficult airway, with the MACOCHA score the best validated tool to identify at-risk patients in the ICU.[22,23] In light of this, a practical and informed approach to the unanticipated difficult airway is crucial for critical care providers. The Difficult Airway Society (DAS) published new guidelines for the management of an unanticipated difficult airway in 2015, which are summarized in Table 3.[19]

The guidelines emphasize the importance of adequate sedation and neuromuscular blockade to maximize glottic visualization and first pass success, preoxygenation to maximize time for intubation, and treatment at a facility with videolaryngoscopy in situations in which a difficult airway is anticipated. A gum elastic bougie also is encouraged in situations of incomplete glottic visualization, supported by its major role as a primary rescue device in prior studies.[3]

If initial intubation attempts are not successful, the DAS encourages early use of a second generation extraglottic airway (EGA) to preserve oxygenation, with best current evidence supporting the i-gel (Intersurgical, Wokingham, UK), the ProSeal LMA (PLMA; Teleflex Medical Europe Ltd, Athlone, Ireland), and the LMA Supreme

(SLMA; Teleflex Medical Ltd). Limiting the number of EGA placement attempts to three minimizes airway trauma without reducing overall success rate. Successful placement ensures adequate oxygenation and ventilation and provides time to plan for the next step to manage the failed airway, which in the critically ill patient is most likely fiber optic intubation through the EGA or a surgical airway. For patients in whom EGA placement and repeat bag valve mask ventilation is not successful, the DAS recommends early scalpel cricothyroidotomy with placement of a wide-bore cuffed tube over a bougie as the preferred surgical airway approach.

DIFFICULT AIRWAY RESPONSE TEAMS

Some organizations have developed Difficult Airway Response Teams (DARTs) as a solution to the challenges of standardizing equipment, approach, and training in airway management in large institutions with multiple ICUs. Although DARTs offer the opportunity to deploy a multidisciplinary, well-trained airway team with standardized equipment to the bedside of an anticipated or identified difficult airway, criteria, timing, and coordination of team activation and involvement must be carefully delineated based on the volume of procedures, resources, and capabilities within the various hospital areas in which staff perform intubations. Key factors that have warranted DART activation in one institution's experience include a history of a difficult airway, cervical spine injury or fixation, oropharyngeal and/or supraglottic angioedema, and airway bleeding.[24]

CONTROVERSIES AND FUTURE DIRECTIONS

The rapid evolution of airway devices and increased emphasis on sedation and neuromuscular blockade in recent airway guidelines present challenges and some controversies for many practicing intensivists. Many modern airway devices have been developed for airway management in the OR, and recent literature only further emphasizes that their appropriate roles in an airway management algorithm for the critically ill must be defined better. Although full induction doses of agents, such as propofol, that are recommended in current DAS guidelines have been shown to be safe and effective in the critically ill with preemptive vasopressor administration,[24] many intensivists are less than comfortable with full-dose induction agents, neuromuscular blockers, and rapid sequence intubation protocols in critically ill patients. When and in which patients this strategy should be used also could merit further refinement.

CONCLUSIONS

Airway management remains a high-risk procedure in the ICU. Safety and success rates have significantly improved over the past decade with implementation of a systematic approach that emphasizes preoxygenation, appropriate patient positioning, pre-induction volume loading and vasopressor administration, teamwork and communication between skilled airway operators, and multidisciplinary teams assisting them. Recent guidelines favor early and aggressive neuromuscular blockade to maximize the chances of first-pass intubation success, along with early use of an EGA and, when necessary, scalpel cricothyroidotomy to reestablish adequate oxygenation. How best to apply these guidelines and other advanced airway tools in the critically ill still requires further study, along with an examination of the initial and maintenance training and procedural volume required for an intensivist to maintain competence in this procedure. ■

REFERENCES

1. Jaber S, Amraoui J, Lefrant JY, et al. Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: A prospective, multiple-center study. *Crit Care Med* 2006;34: 2355-2361.
2. American Society of Anesthesiologists. Practice guidelines for management of the difficult airway: An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology* 2003;98:1269-1277.
3. Martin LD, Mhyre JM, Shanks AM, et al. 3,423 emergency tracheal intubations at a university hospital: Airway outcomes and complications. *Anesthesiology* 2011;114: 42-48.
4. Jaber S, Jung B, Corne P, et al. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: A prospective, multiple-center study. *Intensive Care Med* 2010;36:248-255.
5. Simpson GD, Ross MJ, McKeown DW, Ray DC. Tracheal intubation in the critically ill: A multi-centre national study of practice and complications. *Br J Anaesth* 2012;108:792-799.
6. Cook TM, Woodall M, Harper J, et al. Major complications of airway management in the UK: Results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: Intensive care and emergency departments. *Br J Anaesth* 2011;106:632-642.
7. Green RS, Turgeon AF, McIntyre LA, et al. Post-intubation hypotension in intensive care unit patients: A multicenter cohort study. *J Crit Care* 2015;30:1055-1060.
8. DeJong A, Molinari N, Pouzeratte Y, et al. Difficult intubation in obese patients: Incidence, risk factors, and complications in the operating theatre and in intensive care units. *Br J Anaesth* 2015;114:297-306.
9. Porhomayon J, El-Solh AA, Nader ND. National survey to assess the content and availability of difficult-airway carts in critical-care units in the United States. *J Anesth* 2010;24:811-814.
10. Husain T, Gatward JJ, Hambidge ORH, et al. Strategies to prevent airway complications: A survey of adult intensive care units in Australia and New Zealand. *Br J Anaesth* 2012;108:800–806.
11. Lipshutz AKM, Caldwell JE, Robinowitz DL, Gropper MA. An analysis of near misses identified by anesthesia providers in the intensive care unit. *BMC Anesthesiol* 2015;15:93.
12. Clarke RC, Gardner AI. Anesthesia trainees exposure to airway management in an Australian tertiary care teaching hospital. *Anaesth Intensive Care* 2008;36:513-515.
13. Koppel JN, Reed AP, Hagberg CA, et al. Instruction of airway management skills during anesthesiology residency training. *J Clin Anesth* 2003;15:149-153.
14. Rostenstock C, Østergaard D, Kristensen MS, et al. Residents

lack knowledge and practical skills in handling the difficult airway. *Acta Anaesthesiol Scand* 2004;48:1014-1018.
15. Ezri T, Szmuk P, Warters RD, et al. Difficult airway management practice patterns among anesthesiologists practicing in the United States: Have we made any progress? *J Clini Anesth* 2003;15:418-422.
16. Berkow LC, Greenberg RS, Kan KH, et al. Need for emergency surgical airway reduced by a comprehensive difficult airway program. *Anesth Analg* 2009;109:1860-1869.
17. Mayo PH, Hegde A, Eisen LA, et al. A program to improve the quality of emergency endotracheal intubation. *Intens Care Med* 2011;26:50-56.
18. Semler MW, Janz DR, Lentz RJ, et al. Randomized trial of apneic oxygenation during endotracheal intubation in the critically ill. *Am J Respir Crit Care Med* 2016;193 273-280.
19. Frerk C, Mitchell VS, McNarry AF, et al. Difficult Airway Society guidelines for management of unanticipated difficult airways in adults. *Br J Anaesth* 2015;115:824-848.
20. Janz DR, Semler MW, Lentz RJ, et al. Randomized trial of video laryngoscopy for endotracheal intubation in critically ill adults. *Crit Care Med* 2016 June 28 [Epub ahead of print].
21. Silverberg MJ, Li N, Acquah SO, et al. Comparison of video laryngoscopy versus direct laryngoscopy during urgent endotracheal intubation: A randomized controlled trial. *Crit Care Med* 2015;43:636-641.
22. Honarmand A, Safavi M, Yaraghi A, et al. Comparison of five methods in predicting difficult laryngoscopy: Neck circumference, neck circumference to thyromental distance ratio, the ratio of height to thyromental distance, upper lip bite test and Mallampati test. *Adv Biomed Res* 2015;4. Published online 2015 Jun 4. doi: 10.4103/2277-9175.158033.
23. De Jong A, Molinari N, Terzi N, et al. Early identification of patients at risk for difficult intubation in the intensive care unit: Development and validation of the MACOCHA score in a multicenter cohort study. *Am J Respir Crit Care Med* 2013;187: 832-839.
24. Chmielewska M, Winters BD, Pandian V, et al. Integration of a difficult airway response team into the hospital emergency response system. *Anesthesiology Clin* 2015;33:369-379.
25. Koenig SJ, Lakticova V, Narasimhan M, et al. Safety of propofol as an induction agent for urgent endotracheal intubation in the medical intensive care unit. *J Intensive Care Med* 2015;30: 499-504.

FURTHER READING

- Levitan RM, Heitz JW, Sweeney M, et al. The complexities of tracheal intubation with direct laryngoscopy and alternative intubation devices. *Ann Emerg Med* 2011;57:240-247.
- Niforopoulou P, Pantazopoulos I, Demesthia T, et al. Video-laryngoscopes in the adult airway management: A topical review of the literature. *Acta Anaesthesiol Scand* 2010;54: 1050-1061.
- Hernandez MR, Klock PA, Ovassapian A. Evolution of the extraglottic airway: A review of its history, applications, and practical tips for its success. *Anesth Analg* 2012;114:349-368.

ABSTRACT & COMMENTARY

What Influences ICU Admission?

By Eric Walter, MD, MSc

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

SYNOPSIS: There is widespread variability between hospitals in rates of ICU admission. High ICU utilization hospitals were more likely to use invasive procedures and incurred higher costs than low ICU utilization hospitals with no difference in mortality.

SOURCE: Chang DW, Shapiro MF. Association between intensive care unit utilization during hospitalization and costs, use of invasive procedures, and mortality. *JAMA Intern Med* 2016;176:1492-1499.

ICU services comprise 13.4% of total hospital costs and more than 4% of national health expenditures. Yet, the decision as to which patients should be cared for in the ICU largely is subjective. Chang and Shapiro used administrative data to compare ICU use across 94 hospitals in Washington state and Maryland for diabetic ketoacidosis (DKA), pulmonary embolism (PE), upper gastrointestinal bleed (UGIB), and congestive heart failure (CHF). The primary outcomes were risk-adjusted mortality, use of invasive procedures, and hospital costs. Invasive procedures were defined as use of central venous catheters for any of the diagnoses, mechanical ventilation in DKA, thrombolytics in PE, and esophagogastroduodenoscopy in UGIB. Analyses were adjusted for both patient level and hospital level factors. Logistic regression models were used to predict ICU admission rates for each hospital during hospitalizations for each diagnosis. Hospitals also were dichotomized into higher (> 50th percentile for predicted ICU utilization rate) and lower ICU utilization (50th percentile and below) groups.

There was wide variability in rates of ICU admission for each diagnosis (16.3%-81.2% for DKA, 5.0%-42% for PE, 11.5%-51.2% for UGIB, and 3.9%48.8% for CHF). High ICU utilization was associated with increased use of invasive procedures in all four conditions. Increased ICU utilization was associated with higher hospital costs despite comparable lengths of stay. Severity of illness was lower among patients in high ICU utilization hospitals. Hospital mortality did not differ between hospitals with high and low ICU utilization. Correlations between ICU utilization rates for all four conditions were high.

■ COMMENTARY

The ICU is inherently a heterogeneous unit. In the same ICU, we may admit a patient with severe hypotension next to a patient with malignant hypertension. The unit admits a patient presenting with severe bleeding, followed by a patient suffering from portal venous thrombosis. This heterogeneity may explain why so many ICU trials have produced negative results. The variability in admission rates described by Chang and Shapiro highlight another layer of ICU heterogeneity.

In many ways, these results should not be surprising. The decision to admit someone to the ICU is subjective. It will be influenced not only by the patient's severity of illness, but also hospital size, number of ICU beds, bed availability, nurse ratios, physician comfort, reimbursement, and more. Chang and Shapiro found that institutional factors appeared to influence the decision to admit to the ICU more so than patient level factors. High ICU utilization hospitals admitted patients with all four studied conditions frequently to the ICU despite a lower severity of illness. The influence of these institutional factors may be understandable in some circumstances. In this study, smaller hospitals were higher ICU utilizers. It may make sense to admit a patient with DKA to the ICU in a smaller hospital in which floor nurses may not have the time or expertise to manage an insulin drip. However, these results also suggest that many patients may not need ICU care, as there was no difference in mortality between hospitals with high and low utilization. The decision to admit patients to the ICU may expose patients to potential harms, since invasive procedures such as central lines, thrombolytics, intubation, and EGD were used more often by high ICU utilizer hospitals.

These results present significant implications for future studies evaluating ICU outcomes and costs. There may be too much variability from hospital to hospital to compare ICU costs or outcomes directly across hospitals and regions without accounting for both institutional and patient level factors. We simply cannot compare sepsis-related organ failure assessment scores and Charlson comorbidity indices. Future studies must try to better understand the institutional factors that affect the decision to admit a patient to the ICU. At the individual level, ICU physicians and directors must critically consider the reasons why or why not staff chooses ICU level of care for a patient. With a better understanding of the factors that affect the decision to admit to the ICU, clinicians can better determine when ICU level care truly is needed. ■

ABSTRACT & COMMENTARY

Vasopressin as a Single Vasopressor Agent in Patients with Septic Shock

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: The use of vasopressin as a vasopressor for septic shock produced similar outcomes as the use of norepinephrine.

SOURCE: Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of early vasopressin vs. norepinephrine on kidney failure in patients with septic shock: The VANISH Randomized Clinical Trial. *JAMA* 2016;316:509-518.

There has been continuous interest in the use of vasopressin for patients who suffer septic shock. Norepinephrine (NE) continues to be the recommended first-line vasopressor, but since the VASST trial in 2008, the use of vasopressin as an adjunct vasopressor has become widespread.[1] That trial demonstrated that the addition of low-dose vasopressin (0.03 U/min) improved the mortality of patients in a subgroup of patients with less severe septic shock (defined as need for NE < 15 mcg/min). Other studies have implied that vasopressin may produce a synergistic effect with corticosteroids to prevent renal dysfunction. The Vasopressin as Initial Therapy in Septic Shock (VANISH) trial sought to determine if early vasopressin use as compared with standard NE infusions would improve patient outcomes.

The VANISH trial was a factorial (2 x 2), multicenter, double-blind, randomized, controlled trial that included 421 adult patients with sepsis as defined by systemic inflammatory response criteria with suspected or known infection. All patients underwent adequate fluid resuscitation yet required vasopressors. Patients were randomized to vasopressin (up to 0.06 U/min) or NE (up to 12 mcg/min) as a first vasopressor. If this intervention did not restore mean arterial pressure > 65 mmHg, patients also were randomized to receive hydrocortisone (50 mg intravenously every six hours for five days, then tapered) or placebo as an additional treatment. If patients remained hypotensive despite administration of both study drugs, additional open-label vasopressors were added. Exclusion criteria included previous vasopressor use during hospitalization, need for steroid treatments, endstage renal failure, known mesenteric ischemia, or vasospastic diseases such as systemic sclerosis. The primary outcome was kidney failure-free days up to 28 days. Secondary outcomes included renal replacement therapy, mortality and organ failure-free days, and Sequential Organ Failure Assessment scores.

Overall, the treatment groups were well balanced at baseline and received similar amounts of fluid. Study drugs were started within three hours of diagnosis, and the mean arterial pressures were similar in all groups. Two patients in the NE group received open-label vasopressin and were included in the intent-to-treat analysis. There were no significant differences in kidney failure-free days, mortality, new organ failure, or the need for renal replacement therapy in comparisons of vasopressin vs. NE or with the use of hydrocortisone. There also were no differences in duration of mechanical ventilation, ICU length of stay, hospital length of stay, time to shock reversal between groups, and no significant increase in adverse events.

■ COMMENTARY

The VANISH trial did not detect a statistically significant difference in primary or secondary endpoints. In the study's power calculations, the sample size was chosen to detect a 20-25% relative risk reduction of kidney failure assuming an incidence of acute kidney failure of 30-50%. There was an incidence of renal failure of 40.6-49.5% in the four study groups. The absolute difference in kidney failure in the vasopressin vs. NE groups was -5.1% (95% confidence interval, -15.2% to 5%), which represents a relative risk reduction of 11.3%. Thus, this study was not powered to detect this degree of renal protection. Interestingly, the greatest benefit in terms of use of renal replacement, incidence, and duration of kidney failure (although not statistically significant, either) was in non-survivors.

Compared with NE, this study also showed that vasopressin statistically and non-significantly trended toward higher 28-day mortality (30.9% vs. 27.5%), ICU mortality (28.4% vs. 25.0%), and hospital mortality (33.3% vs. 29.4%). The time to shock reversal tended to be longer with vasopressin by six hours, the use of

United States Postal Service

Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication Number	3. Filing Date
Critical Care Alert	1 0 6 7 _ 9 5 0 2	10/1/16
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$349.00

7. Complete Mailing Address of Known Office of Publication *(Not printer) (Street, city, county, state, and ZIP+4)*
950 East Paces Ferry Road NE, Ste 2850, Atlanta
Fulton County, GA 30326-1180

Contact Person: Regenia Sims
Telephone: 404-262-5473

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not printer)*
950 East Paces Ferry Road NE, Ste 2850, Atlanta, GA 30326-1180

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do not leave blank)*

Publisher *(Name and complete mailing address)*
AHC Media LLC, David Fournier, President and CEO
950 East Paces Ferry Road NE, Ste 2850, Atlanta, GA 30326-1180

Editor *(Name and complete mailing address)*
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PS Form **3526,** October 1999 *(See Instructions on Reverse)*

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15.	**Extent and Nature of Circulation**	**Average No. Copies Each Issue During Preceding 12 Months**	**No. Copies of Single Issue Published Nearest to Filing Date**
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g.	Total Distribution *(Sum of 15c. and 15f)* ►	142	135
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i.	Total *(Sum of 15g. and h.)* ►	152	145
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16. Publication of Statement of Ownership
☑ Publication required. Will be printed in the November 2016 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner
David R. Fournier Publisher & CEO
Date: 09/12/2016

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonme nt) and/or civil sanctions (including civil penalties).

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PS Form **3526,** October 1999 *(Reverse)*

inotropes was greater by 6.7%, and there were greater rates of digital ischemia and acute coronary syndrome. Thus, while it may be expected that a larger trial may detect a small change in renal protection with vasopressin, it is equally likely that it will show increased mortality, length of stay, and complication rates that seem to be more important endpoints. If the benefit is greatest among non-survivors, as previously suggested, this is not truly an overall benefit.

The VANISH trial may be interpreted in the context of the prior VASST study. VASST added vasopressin to NE infusions and was a larger trial (n = 802). A notable difference in baseline demographics in this study was that the vasopressin arm was statistically younger (59.3 vs. 61.8 years; $P = 0.03$). Despite this difference, no statistically significant improvement was observed in the primary endpoints of 28-day mortality or secondary endpoints of 90-day mortality, days free of organ dysfunction, mechanical ventilation, use of renal replacement therapy, corticosteroid use, length of stay, or serious adverse events. Given that both VASST and VANISH did not demonstrate efficacy in their primary or secondary endpoints, reconsider the widespread use of vasopressin. ■

REFERENCE

1. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008;358:877-887.

CME/CE QUESTIONS

1. **Which of the following airway management strategies has been shown to reduce complications in the critically ill?**
   a. Apneic oxygenation
   b. Fluid loading
   c. Videolaryngoscopy
   d. Awake intubation
   e. All of the above

2. **Current Difficult Airway Society guidelines recommend that:**
   a. blind intubation through an extraglottic airway is a preferred strategy.
   b. videolaryngoscopy has replaced the role of direct laryngoscopy.
   c. neuromuscular blockade should be used in difficult airways.
   d. cricothyroidotomy should be performed using a Seldinger technique.
   e. None of the above

3. **Compared to hospitals with low ICU utilization, hospitals with high ICU utilization:**
   a. demonstrated lower mortality.
   b. charged more fees for service providers.
   c. featured a shorter length of stay.
   d. used invasive procedures more frequently.
   e. treated patients with a higher severity of illness.

4. **In the study of ICU admission rates by Chang and Shapiro:**
   a. wide variability in rates of ICU admission for each diagnosis suggest that institutional factors influence the decision to admit a patient to the ICU.
   b. the decision to admit a patient to the ICU is made on objective criteria alone.
   c. smaller hospitals were less likely to admit a patient with one of the studied conditions to the ICU.
   d. the rate of admission to the ICU for patients with diabetic ketoacidosis was very similar across all studied hospitals.
   e. ICU admission rates across hospitals in California were studied.

5. **Which of the following were observed in the VANISH trial?**
   a. Vasopressin use was associated with improved 28-day mortality.
   b. Vasopressin use was associated with statistically significant improvement in rates of renal failure.
   c. Vasopressin was associated with statistically significant increased adverse events.
   d. Vasopressin infusions of 0.06 U/min were more effective than 0.03 U/min.
   e. None of the above

CME/CE OBJECTIVES

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

- identify relevant topics in the practice of critical care medicine;
- utilize recommendations from current clinical guidelines; and
- manage common critically ill patient and ICU administration scenarios.