AHC Media

Vol. 19, Issue 7, October 2011
www.ahcmedia.com

Critical Care [ALERT]

A monthly update of developments in critical care and intensive care medicine

SPECIAL FEATURE

Pregnancy and Critical Care Medicine — *Part 11: Acute Respiratory Failure and Pregnancy*

By Andrew M. Luks, MD
Pulmonary and Critical Care Medicine, University of Washington, Seattle

Dr. Luks reports no financial relationship to this field of study.

INTRODUCTION

In Part 1 of this two-part series on Pregnancy and Critical Care Medicine (see *Critical Care Alert*, March 2011, p. 89-93), we reviewed the normal physiologic changes that occur during pregnancy, examining changes occurring across multiple organ systems that affect our management of these patients as well as the ability of the pregnant woman to respond to various forms of stress, such as acute hemorrhage. In the second part of this series, we build on this understanding of pregnancy physiology and examine one of the major reasons critical care physicians are asked to evaluate women around the time of pregnancy — acute respiratory failure. After reviewing some basic frameworks that can be used to sort through the differential diagnosis of women with respiratory failure around the time of pregnancy and other key issues involved in managing these patients, we will consider important issues in airway and ventilator management and then discuss the presentation and management of the most common forms of respiratory failure in this patient population.

DON'T OVERLOOK THE "POSSIBLY PREGNANT" PATIENT

The topics of interest in this Special Feature will be discussed in the context of the woman who is known to be pregnant, actively delivering a baby, or known to have recently delivered a baby. It is important to remember, however, that pregnancy status may not be known to the physician, the patient's family, or possibly even the patient at the time of presentation. This may be due to comorbid conditions, such as morbid obesity, that mask the presence of pregnancy or the fact that the patient

Financial Disclosure: *Critical Care Alert*'s editor, David J. Pierson, MD, nurse planner Leslie A. Hoffman, PhD, RN, and peer reviewer William Thompson, MD, report no financial relationships relevant to this field of study.

[INSIDE]

Patient outcomes after failed extubation
page 55

CME questions
page 56

Critical Care [ALERT]

Critical Care Alert,
ISSN 1067-9502, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road., NE Building 6, Suite 400 Atlanta, GA 30305.

POSTMASTER: Send address changes to Critical Care Alert, P.O. Box 105109, Atlanta, GA 30348.

Copyright © 2011 by AHC Media. All rights reserved. No part of this newsletter may be reproduced in any form or incorporated into any information-retrieval system without the written permission of the copyright owner.

This is an educational publication designed to present scientific information and opinion to health professionals to stimulate thought and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual.

SUBSCRIBER INFORMATION
1-800-688-2421
customerservice@ahcmedia.com

Editorial E-Mail:
neill.kimball@ahcmedia.com

Subscription Prices
United States
1 year with free AMA Category 1 credits: $319
Add $17.95 for shipping & handling. (Student/Resident rate: $120).

Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482. 1-9 additional copies: $215 each; 10 or more copies: $191 each.

Back issues: $40 Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada Add GST and $30 shipping.
Elsewhere Add $30 shipping.

GST Registration Number: R128870672. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

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 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 13.3 nursing contact hours using a 60-minute contact hour. Provider approved by the California Board of Registered Nursing, Provider # 14749, for 13.3 Contact Hours. This CME activity is intended for critical care physicians and nurses. It is in effect for 36 months from the date of the publication.

Table 1. Differential Diagnosis for Acute Respiratory Failure in the Possibly Pregnant Patient

- Acute asthma exacerbation
- Amniotic fluid embolism
- Aspiration pneumonitis
- Decompensated cardiomyopathy (e.g., aortic stenosis)
- Peripartum cardiomyopathy
- Pneumomediastinum/pneumothorax
- Preeclampsia with pulmonary edema
- Pulmonary embolism
- Pulmonary hypertension
- Tocolytic-induced pulmonary edema
- Venous air embolism

has not told any family members about their expected delivery. A recent case report[1] of an obese patient not known to be pregnant who presented with acute pulmonary edema and was subsequently found to be pregnant and suffering from preeclampsia serves as a strong reminder that many of the items on the differential presented in Table 1 must be considered in any woman of child-bearing age who presents with respiratory failure, even if she is not known to be pregnant at that time.

SORTING THROUGH THE DIFFERENTIAL DIAGNOSIS

A basic differential diagnosis for acute respiratory failure in the possibly pregnant patient is provided in Table 1. There are additional ways that this differential diagnosis can be laid out. For example, as shown in Table 2, the causes of respiratory failure in pregnancy can be grouped according to whether the patient has diffuse bilateral opacities on chest imaging. The causes of respiratory failure in pregnancy can also be grouped according to timing relative to delivery (*see Table 3*), as some disorders, such as pulmonary embolism, can occur at any time relative to delivery, while other disorders, including tocolytic-induced pulmonary edema or amniotic fluid embolism, typically occur around the time of delivery. Patients with decompensated pulmonary hypertension may present up to 1 week following delivery while peripartum cardiomyopathy may present for the first time several months following delivery. It is important to remember, however, that these are somewhat artificial distinctions and items should not be taken off the differential diagnosis solely based on timing relative to delivery if other features of the clinical presentation are suggestive of the diagnosis.

CAN I IMAGE THE PATIENT?

There often is reluctance to image pregnant patients for fear of exposing the fetus to harmful radiation. In cases

Table 2. Differential Diagnosis for Acute Respiratory Failure in Pregnancy Grouped by Chest X-ray Findings

Typically Associated with Diffuse Bilateral Opacities on Chest X-ray	Typically Presents with Clear Lung Fields
• Amniotic fluid embolism	• Acute asthma exacerbation
• Aspiration pneumonitis	• Pulmonary embolism
• Decompensated cardiomyopathy	• Decompensated pulmonary hypertension
• Peripartum cardiomyopathy	• Venous air embolism
• Preeclampsia with pulmonary edema	
• Tocolytic-induced pulmonary edema	

of acute respiratory failure, this concern should not lead to withholding of necessary imaging tests. With abdominal shielding, the average radiation dose of a chest CT or CT pulmonary angiogram, for example, is 0.02 mGy, while that of a PA chest x-ray is < 0.01 mGy. These levels are well below the threshold above which the fetus may be at risk for injury (> 50-100 mGy). Fluoroscopy is associated with significantly higher doses of up to 20-100 mGy/min depending on the procedure and duration of each imaging period.[2]

WHAT'S GOOD FOR THE MOTHER IS USUALLY GOOD FOR THE FETUS

Caring for the pregnant patient is different from most situations critical care physicians face, as they are actually caring for two patients at the same time, the mother and the fetus. Decisions about which antibiotics or other medications to use must take into account the possible effects on the fetus and efforts should always be made to include the obstetrician caring for the patient in the decision-making process about these and other major decisions. In general, however, when it comes to managing most critical care issues, a useful principle to remember is that what is good for the mother is usually good for the fetus. For example, improving oxygenation in a severely hypoxemic pregnant mother will improve oxygen delivery to the placenta as will aggressive hemodynamic support in pregnant patients with sepsis. Aggressive management during an acute asthma exacerbation will also prevent possible fetal compromise. The particular tactics used may vary compared to the non-pregnant patient given the fetal concerns, and consultation with the obstetrician can help in such decisions; in general, however, interventions on behalf of the mother are of benefit to the fetus.

AIRWAY AND VENTILATOR MANAGEMENT IN PREGNANT PATIENTS

Depending on the cause and severity of respiratory failure, patients may require more than supplemental oxygen by nasal cannula or face mask in order to maintain adequate respiratory status. Although pregnancy is not an explicit contraindication to use of non-invasive ventilation and numerous case reports document its safe application in pregnant women with pneumonia or during cesarean delivery, for example, extreme care must be used when applying non-invasive techniques of mechanical ventilatory support. As noted in Part 1 of this series, pregnant women are at increased risk of aspiration due to upward pressure of the gravid uterus on the stomach as well as progesterone-induced decreases in lower esophageal sphincter tone. High distending pressures used during non-invasive ventilation may overcome the already less-competent lower esophageal sphincter, increase gastric distention, and further increase the risk of aspiration.

In those patients who require invasive mechanical ventilation, it is important to remember that airway management is fraught with risk in this patient population. Due to their low functional residual capacity and increased oxygen consumption, pregnant women will rapidly develop hypoxemia following cessation of spontaneous ventilation, particularly in the setting of an abnormal lung parenchyma.[3] Multiple factors, including increased mucosal edema, weight gain, and increased breast size, also contribute to difficult airway visualization.[4] Tactics that can be of use in dealing with these issues include ensuring adequate preoxygenation and proper patient positioning, as well as use of short-handled laryngoscopes, smaller endotracheal tubes, and rigid adherence to the principles of rapid sequence intubation. Nasal intubation should be avoided due to an increased risk of epistaxis as a result of capillary engorgement. Further details about managing airways in pregnant women are beyond the scope of this special feature and have been reviewed elsewhere.[4,5]

Table 3. Breakdown of Causes of Acute Respiratory Failure in Pregnancy Based on Timing Relative to Delivery

May Occur at Any Time Prior to or Following Delivery	Risk Increased in Last Trimester of Pregnancy	Typically Occurs Near the Time of Delivery	May Occur Following Delivery of the Fetus
Acute asthma exacerbation	Decompensated cardiomyopathy	Amniotic fluid embolism	Peripartum cardiomyopathy
Venous thromboembolism	Decompensated pulmonary hypertension	Pneumomediastinum/Pneumothorax	Pulmonary embolism
		Preeclampsia with pulmonary edema	Decompensated pulmonary hypertension
		Tocolytic-induced pulmonary edema	
		Venous air embolism	

There is no evidence that one mode of mechanical ventilation is better for pregnant women than another. Because pregnant women have a compensated respiratory alkalosis at baseline, regardless of the mode that is used, minute ventilation should be adjusted to target the typical P_aCO_2 in a pregnant woman of 28-32 mmHg.[3] Overventilation and increased respiratory alkalosis should be avoided as this has the potential to impair uterine blood flow and fetal oxygen delivery, although pregnant women and the fetus tend to tolerate modest degrees of hypercarbia (P_aCO_2 < 60 mm Hg) without difficulty.[3] Finally, static pressures may be elevated in late pregnancy as a result of the large, parturient abdomen, a fact that must be considered when interpreting pressure measurements on the ventilator and deciding how far to lower the tidal volume in pregnant women with acute respiratory distress syndrome.

SPECIFIC CAUSES OF RESPIRATORY FAILURE IN PREGNANCY

Several of the leading items to consider in the differential diagnosis of acute respiratory failure around the time of pregnancy are considered in the following section.

Acute Asthma Exacerbation — Roughly 20%-30% of asthmatic patients have worsening control of their disease in pregnancy, and up to 18% of pregnant asthmatic patients will seek emergency care for an exacerbation.[6] The care of patients who present in exacerbation is largely the same as for nonpregnant patients, including aggressive administration of bronchodilator aerosols, systemic corticosteroids, and supplemental oxygen, but there are several notable differences in management. Systemic epinephrine is avoided if possible as this may cause uterine artery vasoconstriction and impaired fetal oxygen delivery.[6] If arterial blood gases are performed, the clinician's interpretation of those gases must account for the fact that pregnant women have a compensated respiratory alkalosis at baseline. Worsening of that alkalosis can decrease uterine blood flow while the development of maternal respiratory acidosis may impair elimination of carbon dioxide from the fetal circulation by lowering the diffusion gradient across the placenta.

Women who develop progressive respiratory failure despite the measures noted above need mechanical ventilation. Given the increased risk of aspiration in late pregnancy, non-invasive positive pressure ventilation should be avoided and the patient should instead be started on invasive mechanical ventilation. In rare cases that are refractory to aggressive support, termination of the pregnancy can be considered as this may improve the patient's respiratory mechanics in the latter stages of pregnancy, decrease oxygen consumption, and allow use of additional therapies such as systemic epinephrine or permission hypercapnia.[6]

Amniotic Fluid Embolism — This rare but potentially catastrophic complication typically occurs around the time of labor and delivery or in the immediate postpartum period, but it has been described in association with trauma and other forms of uterine manipulation. Cardinal features of the presentation include sudden onset of hypoxemia, cardiovascular collapse, altered mental status, and disseminated intravascular coagulation, with less common presenting signs and symptoms including seizures, constitutional symptoms, agitation, and signs of fetal distress.[7] Although identification of fetal squamous epithelial cells in aspirated pulmonary artery blood has been described as a diagnostic tool, these are nonspecific findings and amniotic fluid embolism remains a clinical diagnosis,[3] with the key feature being the sudden decompensation of the patient in the peridelivery period. Once other potential sources of decompensation such as pulmonary embolism, venous air embolism, and severe preeclampsia have been ruled out, treatment is largely supportive. Aggressive use of fluids and vasopressors is indicated for hemodynamic support, and the degree of respiratory support will vary from oxygen by high flow face mask to invasive mechanical ventilation depending on the degree of hypoxemia and the overall stability of the patient. If onset occurs in the predelivery period, immediate delivery is indicated to prevent further hypoxic insults to the fetus. If the mother suffers a cardiac arrest at any point, standard ACLS protocols are followed and resuscitative medications should not be withheld for fear of harming the fetus.[7]

Peripartum Cardiomyopathy — This entity is defined as the onset of heart failure between the last month of gestation and 5 months following delivery, in the absence of other identifiable causes of heart failure.[8] It can occur at any age and race and with the first pregnancy although it is more common in older, multiparous women. Presentation is similar to other forms of cardiomyopathy, although in the predelivery or immediate postpartum periods, dyspnea, weight gain, and peripheral edema may be difficult to distinguish from normal pregnancy-related changes. Diagnosis is confirmed using echocardiography and treatment is similar to that used in other forms of acute and/or chronic cardiomyopathy, with acute management varying based on the adequacy of systemic perfusion. Those patients with adequate perfusion can be managed with diuretics and vasodilator therapy, while those

with evidence of impaired perfusion will require inotropic support.[8] Continuous positive airway pressure (CPAP) therapy, a commonly used modality for acute cardiogenic edema in non-pregnant individuals, can be considered in peripartum cardiomyopathy but must be used cautiously in the predelivery period due to the increased aspiration risk. Pregnancy usually is continued through term in those patients who present in the last month of gestation and termination is reserved for those with severe hemodynamic instability.

It should also be remembered that not all cardiomyopathy that presents in pregnancy will be of the peripartum type. Patients with known or previously unrecognized stenotic valvular lesions will also develop problems during pregnancy as they do not tolerate the large increases in plasma volume that occur during pregnancy.[3] Given that plasma volume reaches its peak levels around 24 weeks gestation, decompensated cardiomyopathy secondary to such problems will tend to present earlier than peripartum cardiomyopathy, which tends to be seen in the last month of gestation.

Pneumonia — Pregnant women are at risk for developing pneumonia just like the nonpregnant population. The presentation is similar to that in nonpregnant patients, including the causative bacterial organisms, although the physiologic reserve and tolerance of these infections is decreased due to the physiologic demands of pregnancy. Fungal pneumonia is rare in pregnancy, but viral pneumonia should remain on the differential diagnosis, with varicella and influenza being leading considerations.[9] Varicella is of particular concern due to the risk of fetal effects including preterm birth, intrauterine infection, and fetal congenital varicella syndrome. The typical empiric antibiotic therapy used to treat community-acquired pneumonia in non-pregnant patients — ceftriaxone plus azithromycin — is safe in pregnancy but fluoroquinolones should be avoided, if possible, due to concerns about effects on fetal cartilage development.[9]

As noted earlier, pregnant women are at increased risk for aspiration due to decreased lower esophageal sphincter tone and upward pressure on the stomach from the uterus. Aspiration pneumonitis and pneumonia should therefore be considered in pregnant women presenting with focal opacities, particularly in the lower lung zones. Because most aspiration will be gastric in nature, antibiotics may be held unless the patient develops persistent fevers, worsening opacities or hypoxemia, and leukocytosis or other signs of clinical deterioration.

Preeclampsia with Pulmonary Edema — Typically occurring in the third trimester of pregnancy, preeclampsia is defined by the presence of hypertension (SBP > 140 mmHg or DBP > 90 mmHg) and proteinuria (> 300 mg/24 hours)[10] and may be accompanied by peripheral edema, headaches, hepatitis, thrombocytopenia, seizures, and the HELLP syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets).[3] About 3% of patients who develop preeclampsia also develop pulmonary edema.[11] While milder cases of preeclampsia may be managed with blood pressure control alone using hydralazine or labetalol, the presence of pulmonary edema indicates the patient has severe preeclampsia, which warrants delivery of the fetus, provided it is of viable gestational age. Diuretics can be given prior to surgery, although they are often avoided in other cases of preeclampsia due to the fact that many patients have intravascular volume depletion. Magnesium sulfate is typically administered as prophylaxis for seizures while dexamethasone is administered with preterm deliveries to assist with fetal lung maturation.

Pulmonary Embolism — Venous thromboembolism is more common in pregnant women than in the general population and pulmonary embolism remains a leading source of morbidity and mortality in these patients. Of all the disorders described in this review, pulmonary embolism should be considered over the widest time frame relative to delivery, as pregnant women are considered to be at risk from the first trimester well into the post-partum period. Clinical suspicion for the diagnosis must always be high because many of the signs and symptoms of venous thromboembolism, including dyspnea, tachypnea, tachycardia, and lower extremity edema, are common features of normal pregnancy. Diagnosis is made the same way as in non-pregnant patients. Despite the common reluctance to image these patients, CT angiography is a safe modality, as the administered radiation doses are below those felt to create risk to the fetus at all stages of pregnancy.[2] Ventilation-perfusion scanning is also considered safe. Heparin remains the standard treatment for pulmonary embolism in pregnant women. Unfractionated and low molecular weight heparin do not cross the placenta and are not associated with increased bleeding risk or teratogenicity. Warfarin, on the other hand, is relatively contraindicated due to concerns about fetal teratogenicity and risk of fetal hemorrhage. Thrombolytics are also relatively contraindicated, and should only be considered in cases of massive pulmonary embolism where the life of the mother, and therefore the fetus, is at risk.

Pulmonary Hypertension — Regardless of the underlying etiology, pulmonary hypertension

and pregnancy are a bad combination. The basic physiologic problem is that in the setting of high pulmonary artery pressures, the right heart is unable to pump the increasing blood volumes seen at different stages of pregnancy through the high resistance pulmonary circulation. Pregnancy itself does not cause pulmonary hypertension, but preexisting pulmonary hypertension will get worse in pregnancy while previously unrecognized disease may manifest itself for the first time during pregnancy. The risk of decompensated right heart failure rises substantially at around 24 weeks of gestation when circulating blood volume reaches its peak level and persists through the remainder of pregnancy. Labor and delivery also causes problems as uterine contractions lead to auto-transfusion of several hundred milliliters of blood, thereby causing acute increases in right ventricular preload. Importantly, the risk of decompensated right heart failure persists in the first 1-2 weeks following delivery as the pregnant woman mobilizes significant volumes of extracellular fluid into the systemic circulation.[12] The risk of complications and maternal mortality appear to be a function of the stage of the patient's disease with those patients in higher New York Heart Association (NYHA) classes (III and IV) having worse outcomes.[13]

Evidence-based management guidelines are lacking, as the literature consists largely of case reports and small case series of various approaches. The mainstay of therapy remains the use of pulmonary vasodilators with reports in the literature documenting the use of epoprostenol, inhaled iloprost, sildenafil, and nifedipine. Diuresis also may be needed to manage the high intravascular volume. Cesarean and vaginal deliveries are both feasible based on the documented reports, during which care must be given to anesthetic management. Single-shot spinal anesthesia is contraindicated due to a risk of provoking hypotension while epidural anesthesia is preferred due to the lack of significant hemodynamic effects. If patients require general anesthesia, laryngoscopy can transiently raise pulmonary artery pressures while initiation of mechanical ventilation may have a negative impact on right ventricular preload. Mortality risk remains high for these patients with the largest case series reporting maternal mortality of 30%-56%.[12,13] Interestingly, if the mother can be supported through the pregnancy, fetal outcomes are higher than one might expect, with survival ranging from 72% to 88%.[12,13]

Tocolytic-Induced Pulmonary Edema — Patients receiving terbutaline or other β2-agonists for management of preterm labor may develop pulmonary edema either during therapy or within 12 hours of its discontinuation.[3] The presentation is similar to that of other forms of pulmonary edema in non-pregnant patients, including development of hypoxemia and diffuse bilateral opacities on chest radiography, with the key historical features being the onset of these symptoms in close temporal proximity to use of the medication and lack of other complications such as hemodynamic instability or disseminated intravascular coagulation. Treatment involves supplemental oxygen administration, discontinuation of the medication, and diuretic therapy. CPAP would be a reasonable consideration in those patients who remain hypoxemic despite high flow face mask but are otherwise hemodynamically stable and have an empty stomach. Failure to respond to these measures or onset of symptoms outside the time frame described above should lead to consideration of other potential etiologies for the patient's respiratory failure.

Venous Air Embolism — Air can gain entry to the venous circulation under different circumstances in pregnancy and cause obstruction of pulmonary blood flow and, in certain cases, complete right ventricular outflow tract obstruction. Most cases occur during cesarean section with the peak risk occurring between delivery of the infant and closure of the incision. Cases have also been described with tumultuous labor, uterine rupture, and sexual activity in pregnancy.[7] The presentation will vary based on the amount of air that enters the circulation and the degree of obstruction to pulmonary flow. Because many of the symptoms, including chest pain, dyspnea, and hypoxemia, are non-specific and seen with many of the other disorders described above, the key feature that should alert to the possibility of this diagnosis will be the sudden onset of symptoms, including possibly hemodynamic compromise, around the time of a procedure or during labor and delivery. In the operating room, a major clue to the diagnosis may be a decline in end-tidal carbon dioxide tensions, but outside of this arena, diagnosis is difficult and largely relies on a high clinical suspicion.[7] Echocardiography can sometimes be used to visualize the air collections. When the diagnosis is suspected, the patient should be placed in the left lateral decubitus position and started on high flow oxygen with an F_IO_2 of 1.0. In severe cases, consideration can be given to having interventional radiology attempt to aspirate air from the right ventricle or hyperbaric therapy; in less severe cases, treatment with supplemental oxygen alone should lead to slow resolution of the air collection and associated effects.

CONCLUSIONS

Acute respiratory failure is a challenging issue in pregnancy as the unique physiologic and clinical aspects of pregnancy affect the evaluation and management of these patients. The fact that there

are actually two patients being cared for at the same time adds an additional layer of complexity and concern. With careful consideration of the broader differential diagnosis for respiratory failure in this patient population, extreme care during airway management, and effective communication with the obstetricians, it is possible to ensure a safe outcome for both the mother and the fetus. ■

REFERENCES

1. Luks AM. *Emerg Med J* 2007;24:861-862.
2. Wieseler KM, et al. *Radiographics* 2010;30:1215-1229.
3. Lapinsky SE, et al. *Am J Respir Crit Care Med* 1995;152:427-455.
4. Kuczkowski KM, et al. *J Clin Anesth* 2003;15:552-563.
5. Munnur U, et al. *Crit Care Med* 2005;33:S259-268.
6. Hanania NA, et al. *Crit Care Med* 2005;33:S319-324.
7. Gei AF, et al. *Anesthesiol Clin North America* 2003;21:165-182.
8. Murali S, et al. *Crit Care Med* 2005;33:S340-346.
9. Goodnight WH, et al. *Crit Care Med* 2005;33:S390-397.
10. Vidaeff AC, et al. *Crit Care Med* 2005;33:S307-312.
11. Sibai BM, et al. *Am J Obstet Gynecol* 1987;156:1174-1179.
12. Weiss BM, et al. *J Am Coll Cardiol* 1998;31:1650-1657.
13. Bonnin M, et al. *Anesthesiology* 2005;102:1133-1137.

ABSTRACT & COMMENTARY

Patient Outcomes After Failed Extubation

By David J. Pierson, MD, Editor

SYNOPSIS: Failed extubation is more likely to occur in elderly patients with underlying chronic cardiac or pulmonary disease, and patients in whom it occurs have substantially worse clinical outcomes than those who do not require reintubation.

SOURCE: Thille AW, et al. Outcomes of extubation failure in medical intensive care unit patients. *Crit Care Med* 2011;Jul 14. [Epub ahead of print]

In this prospective study carried out in a 13-bed French medical ICU, Thille and associates sought to determine the clinical characteristics and outcomes of patients who experienced extubation failure — the requirement for reintubation within 72 hours of either planned or unplanned extubation. Ventilated patients were evaluated daily according to an established protocol, and all patients in the unit were included unless they underwent tracheotomy or had previously been reintubated. In keeping with accepted evidence-based standards, patients were considered for weaning and extubation when their overall medical condition had improved, their vital signs were stable, their gas exchange and support requirements were acceptable, they did not require excessive airway suctioning, and they were capable of initiating respiratory efforts. They then underwent a spontaneous breathing trial, which if successful was followed by extubation. Also included in the study were all patients who extubated themselves, or whose endotracheal tubes became dislodged during routine care. Criteria for reintubation were standardized, and noninvasive ventilation was not routinely used following extubation.

During the 1-year observational period, 340 adult patients were managed with invasive mechanical ventilation. Their mean age was 59 years and 66% were men. Median total durations of mechanical ventilation and ICU stay were 5 and 9 days, respectively; 60% of the patients survived to the weaning period and ICU mortality was 49%. After exclusion of patients who died on the ventilator and those undergoing tracheotomy, planned and unplanned extubations occurred in 168 and 31 patients, respectively. Extubation failure (requirement for reintubation because of respiratory failure, coma, or shock within 72 hours) occurred in 26 (15%) of the planned and in 20 of the unplanned extubations (48% of self-extubations and 100% of accidental extubations). When planned extubation failed, pneumonia occurred commonly (7/26, 27%) and subsequent mortality was high (13/26, 50%).

Patients who met weaning criteria, had successful spontaneous breathing trials, and were electively extubated, but who subsequently failed and had to be reintubated, had the same duration of ventilatory support prior to weaning, diagnoses, and illness severely as their counterparts who did not require reintubation. However, they were older (65 ± 16 vs 56 ± 17 yr, $P < 0.01$) and were more likely to have underlying chronic cardiac or respiratory disease (65% vs 39%, $P = 0.02$). Extubation failure occurred in 34% of all patients > 65 years old with chronic cardiac or respiratory disease, compared with only 9% of other patients ($P < 0.01$). Failure of both planned and unplanned extubation was associated with rapid worsening of daily organ dysfunction scores. Mortality was 10 times higher in patients with failed extubation than in those with successful planned extubation.

■ COMMENTARY

In keeping with findings from numerous other

EXECUTIVE EDITOR
Leslie Coplin

MANAGING EDITOR
Neill Kimball

EDITOR
David J. Pierson, MD
Professor Emeritus,
Pulmonary and Critical Care Medicine,
University of Washington, Seattle

ASSOCIATE EDITORS
Saadia R. Akhtar, MD, MSc
St. Luke's Idaho Pulmonary
Associates, Boise

Kay Ball, RN, PhD, CNOR, FAAN
Perioperative Consultant/Educator,
K&D Medical Lewis Center, OH

Linda L. Chlan, PhD, RN
School of Nursing,
University of Minnesota

Dean R. Hess, PhD, RRT
Assistant Director of Respiratory Care,
Massachusetts General Hospital,
Associate Professor of Anesthesia,
Harvard Medical School, Boston

Leslie A. Hoffman, PhD, RN
Department of Acute/Tertiary Care,
School of Nursing,
University of Pittsburgh

Andrew M. Luks, MD
Pulmonary and Critical Care Medicine,
University of Washington, Seattle

James E. McFeely, MD
Medical Director Critical Care Units,
Alta Bates Summit Medical Center,
Berkeley, CA

Grant E. O'Keefe, MD
Department of Surgery,
Harborview Medical Center,
University of Washington, Seattle

Richard J. Wall, MD, MPH
Pulmonary Critical Care & Sleep
Disorders Medicine, Southlake Clinic,
Valley Medical Center, Renton, WA

Michael Young, MD
Pulmonary and Critical Care
Wake Forest University
Health Sciences Medical Center
Winston-Salem, NC

PEER REVIEWER
William Thompson, MD
Associate Professor of Medicine,
University of Washington, Seattle

studies, the extubation failure rate in this series after patients fulfilled accepted weaning and extubation criteria was 15%. However, the important contributions of the current study are that: 1) the patients who failed planned extubation were not detectably different from those who did not require intubation with respect to illness severity, initial diagnoses, or duration of ventilatory support at the time of the attempt; 2) despite this lack of differences in the evidence-based assessments used to determine when extubation is appropriate, patients older than age 65 and those with underlying cardiac or respiratory disease were much more likely to fail; and, 3) once they failed, they did very poorly.

Although it is disheartening that the Simplified Acute Physiology II and Sequential Organ Function Assessment scores did not discriminate between successful and unsuccessful extubations, and that using accepted prediction and management practices on patients who were going to fail extubation could not be identified in advance, I find the results useful in at least one important respect. If the results of this study hold up with further investigations and clinical experience, we should consider extubation failure an important event in terms of prognosis when interacting with patients and families — especially when the patient is older than 65 with cardiac and/or respiratory comorbidities. It is encouraging to clinicians and family members alike when a patient passes a spontaneous breathing trial and is initially weaned from ventilatory support after an episode of critical illness. However, when this progress is reversed over the next few days and invasive mechanical ventilation must be resumed, it illustrates the imprecision of our ability to predict how the patient will do, and suggests that the outlook may not be as favorable as we hoped. ■

CME/CNE Questions

1. Which of the following causes of acute respiratory failure in pregnancy is typically associated with diffuse bilateral opacities?

a. Acute asthma exacerbation
b. Preeclampsia with pulmonary edema
c. Decompensated right heart failure
d. Pulmonary embolism

2. Which of the following pregnancy-associated causes of acute respiratory failure may be seen up to 5 months following delivery?

a. Venous air embolism
b. Amniotic fluid embolism
c. Decompensated right heart failure
d. Peripartum cardiomyopathy

3. In comparison with patients who did not require reintubation, patients who met criteria for discontinuation of ventilatory support and were extubated, but required reintubation within 72 hours:

a. had higher Simplified Acute Physiology II scores.
b. had higher Sequential Organ Function Assesment.
c. had been on the ventilator substantially longer.
d. All of the above
e. None of the above

4. Once patients with acute respiratory failure have clinically improved, have stable vital signs, have modest oxygenation and ventilation requirements, do not require frequent suctioning, and pass a spontaneous breathing trial, approximately what proportion of them will fail extubation and require reintubation within 72 hours?

a. 2%
b. 5%
c. 15%
d. 25%

CME/CNE Objectives

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

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

[IN FUTURE ISSUES]

Unintentional discontinuation of medications — A risk of ICU admission

Clinical importance of saddle PE

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Apixaban is Heating Up the Anticoagulation Market

In this issue: Apixaban could soon join the anticoagulation market; Chinese herbs for flu; chronic medication and discontinuation after hospitalization; and FDA actions.

Apixaban trial results look promising

There is soon to be a third player in the anticoagulation wars. Apixaban, an oral factor Xa inhibitor, will likely soon join dabigatran and rivaroxaban as alternatives to warfarin for preventing stroke in patients with atrial fibrillation (AF). Dabigatran, a direct thrombin inhibitor, was approved for this indication last year and rivaroxaban, also a factor Xa inhibitor, is likely to be approved in early September. (Rivaroxaban was previously approved for DVT prevention in patients undergoing orthopedic surgery.) Apixaban also looks very promising based on results of the ARISTOTLE trial, which was published online in the *New England Journal of Medicine* on August 28. ARISTOTLE enrolled 18,201 patients with AF and at least one additional risk factor for stroke. Patients were randomly assigned to apixaban 5 mg twice daily or warfarin with a target INR of 2-3. ARISTOTLE was designed as a noninferiority study with a primary outcome of ischemic or hemorrhagic stroke, or systemic embolism. After median follow-up of 1.8 years, the rate of the primary outcome was 1.27% per year in the apixaban group vs 1.60% in the warfarin group (hazard ratio [HR] 0.79; 95% confidence interval [CI] 0.66 to 0.95; $P < 0.0014$ noninferiority; $P = 0.01$ for superiority). The rate of major bleeding was 30% less with apixaban and the rate of death from any cause was 3.52% with apixaban and 3.94% with warfarin ($P = 0.047$). The rate of hemorrhagic stroke in the apixaban group was about half that in the warfarin group (0.24% per year vs 0.47% per year, $P < 0.001$) and the rate of all other strokes was 0.97% with apixaban vs 1.05% with warfarin ($P = 0.42$). The authors conclude that in patients with AF, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality (*N Engl J Med* published online August 28, 2011). An excellent accompanying editorial discusses the seminal studies that compared the three new anticoagulants to warfarin for stroke prevention in patients with AF: RE-LY — dabigatran; ROCKET AF — rivaroxaban; and ARISTOTLE — apixaban. All three showed that the new drugs were significantly better than warfarin at reducing hemorrhagic stroke and all were at least as effective as warfarin at preventing ischemic stroke. All three drugs were also associated with a significantly lower rate of serious bleeding compared to warfarin. Apixaban was the only drug that showed a significant reduction in overall mortality, although both dabigatran and rivaroxaban showed trends in that direction. ROCKET AF has been criticized because the warfarin comparator group had a time in therapeutic range of only 55% compared to 64% in the RE-LY trial and 62% in ARISTOTLE; however, patients in the ROCKET AF study were at higher risk for stroke than in the other two studies. The bottom line is that all three drugs are effective in preventing stroke in patients with nonvalvular

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

AF and seem to be safer than warfarin as well. The new drugs do not require any laboratory monitoring, which is convenient for patients and also lowers the overall cost of care (although all three drugs will be priced significantly higher than generic warfarin). Rivaroxaban has the advantage of a once daily dose vs the other two drugs, which must be dosed twice daily. None of the three drugs can be quickly reversed in the event of major bleeding or need for surgery. Apixaban is not yet approved in this country but when it is, it is likely that the competition between these three agents will be fierce, and for many purchasers of health care it may come down to cost. ■

Chinese herbs for flu treatment

For the flu season this year, you might consider Chinese herbs instead of antivirals based on the results of a study from China published in the *Annals of Internal Medicine*. More than 400 adults age 15-59 years with confirmed H1N1 influenza were randomized to oseltamivir 75 mg twice daily or a combination of 12 Chinese herbal medicines called maxingshigan-yinqiaosan 200 mL four times a day, a combination of oseltamivir plus maxingshigan-yinqiaosan, or placebo for 5 days. The primary outcome was time-to-fever resolution and the secondary outcomes included symptom scores and viral shedding. Both oseltamivir and maxingshigan-yinqiaosan, as well as the combination, resulted in significant reductions in the estimated median time-to-fever resolution compared to the control group (median time-to-fever resolution — no treatment 26 hours; oseltamivir 20 hours; maxingshigan-yinqiaosan 16 hours; combination 15 hours; all statistically significant at $P < 0.001$). Side effects were similar in all groups. The authors conclude that oseltamivir and maxingshigan-yinqiaosan, alone or in combination with each other, reduce time-to-fever resolution in patients with H1N1 influenza. They go so far as to suggest that maxingshigan-yinqiaosan may be used as an alternative treatment for H1N1 infections (*Ann Int Med* published online August 26, 2011). It may be difficult to obtain maxingshigan-yinqiaosan since it contains ephedra (which is not available in this country) and the authors could not determine if the benefits of maxingshigan-yinqiaosan were due to an antiviral effect or merely an antipyretic effect. ■

Chronic medications and hospitalization

Your patients' chronic medications may be inadvertently discontinued after hospitalization according to a population-based cohort study of almost 400,000 patients published recently in the *Journal of the American Medical Association*. Researchers from Canada reviewed the records of residents age 66 or older who were on statins, antiplatelet/anticoagulant agents, levothyroxine, respiratory inhalers, or gastric acid suppressing drugs on a chronic basis. When compared to nonhospitalized patients, patients admitted to the hospital — especially the ICU — were more likely to have their chronic medications discontinued. Discontinuation rates ranged from a low for levothyroxine of 12.3% discontinuation for hospitalizations vs 11% for controls, to antiplatelet/anticoagulant agents which were discontinued at a rate of 19.4% for hospitalizations vs 11.8% for controls. The discontinuation rates were even higher for patients who were admitted to the ICU. The authors conclude that patients admitted to the hospital are at relatively high risk for potential unintentional discontinuation of chronic medications (*JAMA* 2011;306:840-847). This study points out the importance of medication reconciliation at all post-hospital visits and may validate the role of computerized medical records, especially with regard to medication lists. ■

FDA actions

The FDA has approved a new fixed-dose combination pill for HIV-infected patients. Emticitabibine/rilpirivine/tenfovir DF is approved as a once-a-day pill for treatment of HIV-1 infection in treatment-naïve patients. This is the second triple combination anti-HIV agent approved and differs from the previous agent (Atripla) in that it contains the NNRTI rilpirivine rather than efavirenz. The new combination will be marketed as Complera.

The FDA has approved brentuximab vedotin to treat Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma. The drug is approved for HL patients who have progressed after autologous stem cell transplant or after prior chemotherapy regimens and cannot receive a transplant. This represents the first the drug to treat HL since 1977. Brentuximab will be marketed as Adcetris.

The FDA has approved vemurafenib for the treatment of metastatic and unresectable melanoma, specifically in patients whose tumors have the BRAF V600E mutation. The approval was accompanied by a companion diagnostic test that will determine if a patient's melanoma cells have that mutation (about half of the patients with late stage melanomas). Only patients with the BRAF V600E mutation will respond to the drug since it targets the mutated protein that regulates cell growth. Vemurafenib is marketed by Genentech as Zelboraf. ■