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Critical Care [ALERT]

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

SPECIAL FEATURE

Update on Rescue Therapies for Hypoxemic Respiratory Failure

By David J. Pierson, MD, Editor

Critical hypoxemia in acute respiratory failure may be defined as a degree of impairment in tissue oxygenation that — in and of itself, and separately from the primary cause of the respiratory failure — threatens the life of the patient. How this conceptual definition translates to objective measurements has not been standardized. Several clinical trials of different ventilation strategies for managing patients with severe acute respiratory distress syndrome (ARDS) have included the option for the managing physician to employ "adjunct" or "rescue" therapies over and above the study interventions. The thresholds for such interventions generally have consisted of measures of arterial oxygenation, such as a PaO_2/FIO_2 ratio of less than 60-80 mm Hg on a specified amount of positive end-expiratory pressure (PEEP). What has emerged from all such studies is the fact that, whatever the study's designated threshold for considering rescue therapies, participating clinicians have employed such interventions substantially more often than the thresholds recommend. This has definitely been my observation in clinical practice. Thus, a pragmatic definition for critical hypoxemia is "that level of arterial oxygenation in a patient with acute respiratory failure that prompts the managing physician to do something different," such as a change in ventilator management or the addition of some additional intervention, over and above conventional lung-protective ventilation (LPV).

This newsletter published a concise review of rescue therapies for critical hypoxemia in 2008.[1] In this essay, I provide an update on the topic, comparing the available interventions and summarizing their current status in the management of patients with hypoxemic acute respiratory failure. In the past year, several excellent, more comprehensive reviews

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[INSIDE]

Critical Care [ALERT]

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have been published on this topic.[2-6] In 2011, the standard of care for patients with ARDS — the clinical setting in which rescue therapies for critical hypoxemia are most often considered — is LPV. All patients should receive low-tidal-volume ventilation; delivered tidal volume should be set according to predicted (not actual) body weight, and be not more than 8 mL/kg, preferably 6 or less; and alveolar distending pressure (end-inspiratory plateau pressure in most instances) should be closely monitored and kept below 30 cm H_2O. These things have been established by high-quality evidence: they save lives and are no longer optional at the discretion of the clinician. Beyond the components of conventional LPV, the evidence that other interventions improve patient outcomes in ARDS is much less convincing.

A clinical trial in which patients with early ARDS were heavily sedated for the initial 48 hours and given either the nondepolarizing muscle relaxant cisatracurium or placebo[7] found improved survival and a shorter duration of mechanical ventilation in the experimental group. It has been proposed that cisatracurium has anti-inflammatory properties separate from its action as a muscle relaxant, which may alter the evolution of acute lung injury.[8] This concept is consistent with the fact that the survival curves in the two groups did not begin to diverge until the second week after completion of the infusion. Because of the many negative aspects of the use of paralytic agents in patients with acute respiratory failure,[9] changing practice on the basis of this intriguing study is inadvisable at this point. In any event, the investigators did not study cisatracurium as a rescue therapy, and its effects on arterial oxygenation, if any, are not reported.[7]

Aside from the study just mentioned, no clinical trial has demonstrated a survival benefit when any of the rescue therapies listed in the accompanying table[9-18] has been compared or added to conventional LPV. However, as discussed in the most recent review of these modalities,[6] subsequent subset analyses and meta-analyses of the findings in multiple trials have uncovered some significant differences. In a patient-level meta-analysis of three clinical trials, higher PEEP was associated with slightly improved survival among patients with ARDS as opposed to those with less severe hypoxemia,[10] although the 95% confidence interval (CI) for the relative risk included 1.00. Another meta-analysis, of three clinical trials of prone positioning, found a significant survival benefit in the subset of patients with PaO_2/FIO_2 < 100 mm Hg (relative risk, 0.84; 95% CI, 0.74-0.96).[19] Similarly, a meta-analysis of eight randomized trials of high-frequency oscillatory ventilation (none of which individually showed a survival benefit compared to conventional LPV) found a relative risk of death of 0.77, 95% CI, 0.61-0.98, with that ventilation modality.[20] How clinicians should interpret these survival benefits derived from individually negative studies is uncertain.

The table compares the main rescue therapies currently available for treating critical hypoxemia. These interventions vary a great deal in ease of application, invasiveness, cost, and local availability. The lack of convincing evidence from clinical trials that these interventions reduce mortality in all comers with ARDS should not be interpreted to mean that they may not be beneficial for certain patients, nor should it necessarily imply that they should never be used. However, it suggests that careful consideration of the potential advantages and disadvantages of each modality is appropriate, and that clinicians should not feel compelled to deviate from conventional LPV in managing their most severely ill patients.

Walkey and Wiener recently examined the utilization patterns and patient outcomes associated with the use of rescue therapies in six clinical trials conducted by the ARDS Network between 1996 and 2005.[21] Such therapies were allowed according to the study protocols, at clinician discretion, and had been employed in 166 of the 2632 patients in the trials. The interventions used were prone positioning (97 patients, or 58% of

Table. Characteristics of Currently Available Rescue Therapies for Refractory Hypoxemia in ARDS Patients*

Intervention	Rationale for Use	Beneficial Effects	Disadvantages; Potential for Harm	Added Monetary Cost
Use of higher PEEP[10,11]	Keep atelectatic or poorly inflated alveoli open throughout the respiratory cycle; prevent atelectrauma	Increased PaO_2	May decrease venous return and cardiac output, requiring more fluid and/or vasopressor administration and potentially increasing risk for barotrauma	None (but may require more aggressive hemodynamic monitoring)
Inverse I:E ratio ventilation (either volume- or pressure-controlled)	Keep poorly inflated alveoli open for more of the respiratory cycle; increased mean airway pressure	Increased PaO_2, usually with increased auto-PEEP	Decreased venous return and cardiac output; variable auto-PEEP in different lung regions; increased risk for pneumothorax and other barotrauma	None (but requires more aggressive hemodynamic monitoring and heavy sedation)
Esophageal pressure monitoring[12]	Determine actual trans-pulmonary pressure in face of high chest-wall pressure, and adjust PEEP accordingly	Usually leads to use of higher PEEP, with corresponding increase in PaO_2	Catheter may be difficult to place; data can be misleading when sensor not in proper position	Requires special catheter and monitoring system
Airway pressure release ventilation[13]	Higher mean airway pressure with lower peak pressure; permits spontaneous breathing	As effective as conventional ventilation in supporting oxygenation and ventilation; may require less sedation	Tidal volume may exceed LPV goals with spontaneous breathing	None (but not available on all current critical care ventilators)
Recruitment maneuvers[14,15]	Open atelectatic alveoli; maintain lung inflation at lower end-expiratory pressure	Increased PaO_2, although effect less with time requiring repeated maneuvers	Hypoxia, hypotension, alveolar rupture (but generally safe); Increased risk for VAP if breaking ventilator circuit is involved	None

Continued on page 4

those who received at least one rescue therapy), inhaled vasodilators (mainly nitric oxide, 47 patients, 28%), high-frequency ventilation (12 patients, 7%), and extracorporeal membrane oxygenation (ECMO, 10 patients, 6%). With multivariate analysis, predictors of the use of a rescue therapy were patient age (odds ratio per 10 years, 0.88; 95% CI, 0.78-0.99; $P = 0.049$), the amount of PEEP used (OR per 5-cm H_2O increase, 1.33; 95% CI, 1.05-1.69; $P = 0.019$), and peak airway pressure (OR per 5-cm H_2O increase, 1.11; 95% CI, 0.001-1.237; $P = 0.047$). Thus, clinicians managing the patients enrolled in the ARDS Network studies used rescue therapies more often in younger patients who had worse oxygenation defects and stiffer lungs. In their analysis, Walkey and Wiener found no evidence for a survival benefit among patients who received rescue therapies.[21]

Space does not allow a more in-depth discussion of the different aspects of using rescue therapies for critical hypoxemia. However, considering the above discussion, the information in the table, my own observations in the medical and surgical ICUs of a level-1 trauma center, and the literature available to date on this subject, I draw the following conclusions:

- There is great practice variation in the use of rescue therapies — regionally, among different institutions, and among individual clinicians, as well as with respect to which patients are offered such therapies;
- Regardless of local practice guidelines or study threshold criteria, individual clinicians decide when to use rescue therapies, and they tend to use them in more patients than the guidelines or study protocols would indicate;
- Rescue therapies often improve arterial oxygenation, but few studies have been done in patients with critical hypoxemia, and no rescue therapy has been clearly shown to have a favorable impact on survival;
- Because of the power of anecdotal experience, this lack of evidence is unlikely to deter clinicians from using them;
- Clinicians should bear in mind that an increased PaO_2/FIO_2 ratio is no guarantee of an improved clinical outcome, and in fact that some interventions that improve oxygenation — such as larger tidal volumes — actually worsen outcomes;
- Which rescue therapies are used in a particular institution or ICU will be determined largely by

Table. Characteristics of Currently Available Rescue Therapies for Refractory Hypoxemia in ARDS Patients* (continued from page 3)

Intervention	Rationale for Use	Beneficial Effects	Disadvantages; Potential for Harm	Added Monetary Cost
High-frequency oscillatory ventilation[13]	"Ultimate lung-protective ventilation"; mean airway pressure maintained with minimal increase during cycle	Generally as effective as conventional ventilation in supporting oxygenation and ventilation	Requires specific, very different ventilator, with unique requirements for monitoring and skills on part of staff	Separate ventilator used only for this purpose; costs associated with staff training
Neuromuscular blocking agents (therapeutic paralysis)[9]	Reduce oxygen consumption from skeletal muscle activity; eliminate breath-stacking; improve ventilation distribution	Eliminates patient-ventilator asynchrony and breath-stacking; variably improves PaO_2; no outcome data when used as rescue therapy	Loss of neurologic exam; increased risk for pressure ulcers; increased duration of mechanical ventilation; increased risk for subsequent neuromuscular weakness and PTSD in survivors	Cost of paralytic agent and train-of-4 monitoring
Prone positioning[16]	Improve regional ventilation and perfusion; aid in redistribution of extravascular lung water; facilitate secretion clearance	Usually improves PaO_2	Cannot be used in patients with severe obesity, intracranial hypertension, open abdomen, multiple drains, etc; time- and labor-intensive; increased risk for pressure ulcers; oxygenation benefits tend to wane over time	Added cost if commercial proning system used; vendor charges $1295 per day at my institution
Inhaled nitric oxide[17]	Vasodilation in ventilated lung regions; improved ventilation-perfusion matching	Increases PaO_2 in most patients; relatively easy to administer and generally safe	May increase risk for renal impairment; may be difficult to wean; use in this clinical setting is not FDA-approved	Vendor charges hospital $119 per hour used ($2859/day) at my institution; this cost to hospital is not reimbursed
Aerosolized prostacyclin[18]	Same as with nitric oxide	Increased PaO_2; same benefits as with nitric oxide at lower cost	Clogs filters in ventilator circuits; requires close monitoring and frequent filter changes	Costs of drug, administration system, and frequent circuit filter changes
ECMO	Maintain tissue oxygenation and CO_2 removal while lung recovers	Fully supports gas exchange	Available only at specialized centers; many patients are not candidates because of comorbidities, etc.	Equipment and personnel for specialized life-support system

*Note: Improved survival and other patient-relevant outcome benefits are not included in the table, since none has been demonstrated for any of these interventions in appropriately rigorous clinical trials.

local availability and practice culture;

- Because the available rescue therapies vary a great deal in invasiveness, discomfort, and costs, patients and families should be given the opportunity to help decide what interventions beyond conventional LPV should be used in a particular case. ■

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ABSTRACT & COMMENTARY

Mechanical Ventilation: A Marker of the End-of-Life or Loss of Independence for the Elderly?

By Michael Young, MD

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

SYNOPSIS: This study of outcomes among more than 50,000 elderly Medicare beneficiaries found that activities of daily living and mobility had deteriorated substantially more among those who had been hospitalized the previous year, and that only 27% of those who had received mechanical ventilation were alive 1 year after hospitalization.

SOURCE: Barnato AE, et al. Disability among elderly survivors of mechanical ventilation. Am J Respir Crit Care Med 2010; Nov 5. [Epub ahead of print].

A recent examination of the Medicare database[1] illustrates that survival rates after in-hospital cardiopulmonary resuscitation (CPR) remained unchanged from 1992 to 2005. In fact, the proportion of patients discharged to home after CPR decreased over time. These discouraging results occurred despite the numerous improvements in CPR and ICU care and the development of Rapid Response Teams. Clinician response to these data that confirm poor outcomes after in-hospital CPR appears divided. One perspective is that these findings indicate a compelling need for additional research to develop more effective resuscitation techniques. An alternative view is that the outcomes of CPR will remain poor unless we limit the application of CPR to populations with a better chance of a good outcome.

In a similar fashion, the long-term survival rates of elderly patients who require mechanical ventilation for acute respiratory failure appear disappointing[2] despite many exciting advances in ICU care. These data may be at odds with the impression of many clinicians, patients, and families of the ability of mechanical ventilation to save the lives of our elderly ICU population. When artificial ventilation was first used 60 years ago during the polio epidemic in Scandinavia, the mortality rate of respiratory failure among polio victims dropped from 87% to 40%.[3] These impressive results likely helped stimulate the growth of ICU care and the widespread application of mechanical ventilation. In the past two decades, a number of studies have identified patient characteristics that predict higher risk of death among populations of ICU patients who require mechanical ventilation. Less is known about the long-term functional status and quality of life of elderly survivors of mechanical ventilation.

The present study by Barnato et al of Medicare recipients who require mechanical ventilation adds to our understanding of outcomes of mechanical ventilation in the elderly beyond the dichotomous outcome of who lived vs who died at the time of hospital discharge. Using data from the Medicare Beneficiary Survey from 1996-2003, Barnato and colleagues compared the level of disability in the following three groups of patients: 1) patients

Table. Functional Outcomes and Mortality among Elderly Medicare Beneficiaries

	No hospitalization (n = 42,890)	Hospitalized, no mechanical ventilation (n = 11,347)	Hospitalized with mechanical ventilation (n = 534)
ADL disability score (95% CI)	6 (5-6)	15 (14-16)	23 (19-29)
Mobility Difficulty (95% CI)	22 (22-22)	38 (37-39)	46 (43-50)
Dead at one year follow-up (%)*	3,831 (9)	2,717 (24)	387 (73)

*Censored from analysis were patients who died before first outpatient follow-up interview that occurred in the fall post-discharge from the hospital.

ADL, activities of daily living; CI, confidence interval

requiring hospitalization without mechanical ventilation (n = 11,347), 2) patients hospitalized who received mechanical ventilation (n = 534) and 3) patients who were not hospitalized (n = 42,890).

To compare disability levels between groups the authors use a scoring system that relied on patient reported mobility and the validated Katz Activities of Daily Living (ADL) Scale score, weighted from 0 (no disability) to 100 (completely disabled). Among patients who received mechanical ventilation, only survivors were used in the study set. The authors also excluded both patients who resided in nursing homes at the time of study entry and patients enrolled in group health plans. Demographic information included age, sex, race, marital status, income, baseline cognitive score, ADL, and mobility score. The not-hospitalized patients were statistically significantly younger at 76 ± 7 years (SD) vs the hospitalized patients without mechanical ventilation at 78 ± 7 years, but similar to the hospitalized patients with mechanical ventilation at 76 ± 7 years. The demographic baselines were otherwise similar for all three groups. The time interval between hospital discharge and post-hospital assessment for patients hospitalized with or without mechanical ventilation was a mean of 128 ± 96 and 162 ± 102 days, respectively.

The main outcomes are summarized in the Table. The ADL disability and mobility difficulty scores worsened among patients who were hospitalized without mechanical ventilation and deteriorated still further among patients who were hospitalized with mechanical ventilation. Among patients who were hospitalized with mechanical ventilation, the death rate was alarmingly high at the time of the outpatient follow-up. Patients who died before the first outpatient follow-up evaluation were censored from analysis. Thus, the true proportion of patients who died within days to several months after receiving mechanical ventilation is likely much higher than the 73% noted in Table 1.

COMMENTARY

Limitations of this study include reliance on patient or family self-reported information to calculate pre- and post-ADL and mobility scores. In addition, the time that the first assessment post-hospitalization occurred varied. The authors also suggest that survivor bias and non-response bias likely underestimates the true magnitude of the post-hospitalization disability. The demographic information available to compare the baselines between the three groups is limited, raising the possibility that important baseline differences between groups exist but were not measured. Also these data do not provide insight into what patient factors predict a higher vs lower risk of death and disability among patients who received mechanical ventilation. Finally, the number of patients in the group who received mechanical ventilation is limited and the authors did not include sample size calculations to determine the number of patients required to avoid both Type I and Type II errors.

Despite its limitations, this study provides us with at least three important insights. First, it confirms previous observations that mechanical ventilation in the elderly is associated with an extremely high risk of death within days to months of receiving mechanical ventilation. Second, this study indicates that elderly survivors of mechanical ventilation are at great risk to suffer significant increases in disability. Third, this study should prompt investigators to examine populations of elderly patients who receive mechanical ventilation for patient types most likely to benefit from mechanical ventilation and the type of clinical care that reduces the risk of death and significant disability among those who survive.

This study also should stimulate physicians to be circumspect about reflexively providing mechanical ventilation for the elderly. The outcome of mechanical ventilation in the elderly appears worse than the poor outcomes described when dialysis is initiated among residents of nursing homes.[4] Although precise comparisons are not available, the risk of death and disability among elderly patients who receive mechanical ventilation appear grossly similar to the extraordinary risk of death and

disability of patients who receive inpatient CPR.

If the goal of mechanical ventilation is survival for weeks to months after a stay in the ICU and return to pre-hospital baseline function, from a population perspective, mechanical ventilation is largely a failed therapy. Clearly we need better science so we may identify the elderly patients most likely to benefit from a trial of mechanical ventilation and a better understanding of the clinical care required to improve the outcomes of elderly patients who receive mechanical ventilation. Arguably, an even higher priority is to provide elderly patients, their families, and clinicians with viable alternatives to mechanical ventilation which is so often associated with death within days to weeks, or possibly worse, survival with great disability. ■

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ABSTRACT & COMMENTARY

A Risk Factor for Hospital-Acquired Infections: Hand Contamination by Anesthesia Providers

By Leslie A. Hoffman, RN, PhD

SYNOPSIS: Bacterial transmission to the IV stopcock set was documented in 19/164 cases (11.5%); 47% of these cases were of provider origin and linked to hands of anesthesia providers.

SOURCE: Loftus RW, et al. Hand contamination of anesthesia providers is an important risk factor for intraoperative bacterial transmission. Anesth Analg 2011;112:98-105.

In a prior study, investigators at Dartmouth-Hitchcock Medical Center linked intraoperative contamination of patients' IV stopcocks with an increase in patient mortality. The present study was conducted to test the hypothesis that bacterial contamination of anesthesia provider hands before patient contact was an important risk factor for intraoperative bacterial transmission. The first and second operative cases in each of 82 randomly selected operating rooms (OR) were used for analysis, yielding 164 cases. Prior to the start of the first case, cultures were obtained from two sites on the anesthesia machine (APL valve and agent dial) and the patient's IV stopcock. Concurrently, the hands of the assigned anesthesia provider, e.g., anesthesiologist, resident physician, or CRNA, were sampled as they entered the OR but before patient contact. At completion of the first case and before the start of the second case, the two sites (anesthesia machine, stopcock) were again sampled. Hands of anesthesia providers were also sampled when they entered the OR before the start of the second case. Transmission events were defined as potential pathogens present at the end of a case not present at the beginning of the case. Using biotype analysis, comparisons were then made with samples from the hands of anesthesia providers. To be identified as transmitted, an organism was required to have an identical biotype to the same organism found on the providers' hands.

Overall, 66% of provider hands were contaminated with one or more major pathogens, e.g., methacillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), etc. Bacterial transmission to the IV stopcock was identified in 19/164 cases (11.5%); of these cases; 9/19 (47%) were of provider origin. Bacterial transmission to anesthesia equipment was identified in 146/164 (89%) of cases; of these cases, 17/146 (12%) were of provider origin. Contamination of the environment before the start of case two (a measure of decontamination efficacy) occurred in 6/82 (7%) of the ORs and was linked to stopcock contamination in 1/19 (5%) of cases. Anesthesiologists had significantly less overall hand contamination than residents and CRNAs. The number of rooms supervised by the atending anesthesiologist, age of the patient, and patient discharge from the OR to an ICU were independent predictors of bacterial transmission not linked directly to providers.

■ COMMENTARY

We are constantly reminded by old and new studies

that health care provider actions place patients at risk for infection. Although we know that hand hygiene is critical to preventing hospital-acquired infections, we often take shortcuts that can expose patients to risk. In confirmation, this study documented a case of intraoperative horizontal transmission that involved: 1) provider negative at the start of case one; 2) stopcock contamination by organisms brought by second provider; 3) ineffective decontamination, and; 4) contaminated stopcock during case two attributed to the original organism.

This study included many steps to rigorously isolate sources of contamination. Baseline bacterial cultures were obtained after active decontamination of the equipment sites by the investigators. All patients received fresh IV stopcocks immediately before the first case began. Anesthesia providers were asked to use the stopcock set identified by the investigators for all medication administration. Hand samples were not obtained if the anesthesia provider had physical contact with the patient. Finally, all transmitted organisms were compared using biotype analysis.

Findings of this study target hand contamination from organisms brought into the OR at the time of the first case as a major problem. As well, findings suggested modifiable risk factors. It might be expected that contamination would increase over time as providers moved from room-to-room during cases. Instead, the first case was associated with the larger magnitude of contamination. Strategies to insure adherence to established hand hygiene practices before first entering the OR would thus likely eliminate a substantial portion of the problem. The solution could be a simple as a surgical scrub for all anesthesia providers and institution of rigorous monitoring practices to objectively identify success of this strategy or additional risk factors. The cost of surgical site infections to patients, families and the nation is enormous. Greater attention placed on the simple things, e.g. explicitly following hand hygiene practices, takes limited time and has great potential benefits. ■

CME/CNE Questions

1. Which of the following rescue therapies for refractory hypoxemia acts primarily as a vasodilator in the lung?

a. Nitric oxide
b. High-frequency oscillatory ventilation
c. Therapeutic paralysis with neuromuscular blocking agents
d. Prone positioning
e. None of the above

2. What proportion of elderly Medicare beneficiaries who received mechanical ventilation during hospitalization were alive 1 year later?

a. 9%
b. 27%
c. 42%
d. 61%
e. 73%

3. Hand contamination by anesthesia providers occurred more frequently when samples analyzed were obtained from:

a. patients undergoing surgery who were older or admitted from an ICU.
b. IV infusion tubing.
c. hands of the attending anesthesiologist.
d. hands of resident physicians or CRNAs.

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]

Family rounds in the ICU

Ionized calcium and ICU outcomes

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 and Rivaroxaban Near Approval for Nonvalvular AF

In this issue: Apixaban and rivaroxaban near approval for nonvalvular atrial fibrillation; fidaxomicin for *C. difficile* infections; guideline for intensive insulin therapy; and FDA Actions.

Dabigatran for stroke in patients with nonvalvular atrial fibrillation

Dabigatran, a direct thrombin inhibitor, recently was approved for prevention of stroke in patients with nonvalvular atrial fibrillation. The evidence for its benefit is strong enough that the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society recently upgraded their atrial fibrillation guidelines to include dabigatran (*Circulation* published online February 14, 2011). Meanwhile, the direct factor Xa inhibitor rivaroxaban is working its way through the FDA approval process for the same indication, with approval expected later this year. The latest player in the field is apixaban, also a direct factor Xa inhibitor. Apixaban was studied in a double-blind Phase 3 study of 5599 patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable. Patients were randomized to receive apixaban 5 mg twice daily or aspirin 81-324 mg per day with a mean follow-up of 1.1 years. The primary outcome was occurrence of stroke or systemic embolism. The study was terminated early because of a clear benefit in favor of apixaban. There were 51 events (1.6 % per year) in the apixaban group vs 113 events (3.7% per year) in the aspirin group (hazard ratio with apixaban 0.45, 95% confidence interval 0.32-0.62; P < 0.001). The death rate was 3.5% in the apixaban group vs 4.4% in the aspirin group (P = 0.07). The rates of major bleeding or intracranial hemorrhage were similar; however, the risk of first hospitalization for cardiovascular causes was significantly lower with apixaban. The authors suggest that apixaban is more effective than aspirin. In indirect comparisons, apixaban is more effective than aspirin plus clopidogrel and at least as effective as warfarin in preventing stroke or systemic embolism in patients with atrial fibrillation (*N Engl J Med* published online February 10, 2011). Apixaban is currently being studied head-to-head with warfarin in the ARISTOTLE trial. If the data from that trial looks favorable, it is likely that both apixaban and rivaroxaban also will be approved for this indication in the not-too-distant future. Dabigatran and apixaban are both dosed bid while rivaroxaban is a once-a-day drug. The extent to which these drugs gain general usage at the expense of warfarin in large part will be due to patient preference and cost. ■

Fidaxomicin for *C. difficile* infections

A new option may soon be availiable for treating *Clostridia difficile* infections. Fidaxomicin (not yet approved in this country) is a non-systemic (poorly absorbed) narrow spectrum macrolide antibiotic that is bacteriocidal against *C. difficile* infections. It recently was compared to vancomycin in a head-to-head Phase 3 noninferiority study of 629 adults. Patients with a positive stool toxin test to *C. difficile* were randomized to

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fidaxomicin 200 mg twice a day or vancomycin 125 mg four times a day. The primary endpoint was clinical cure and the secondary endpoint was recurrence within 4 weeks and global cure (no recurrence). Fidaxomicin was noninferior to vancomycin in both the intention-to-treat (88.2% cure rate with fidaxomicin vs 85.8% with vancomycin) and per-protocol analysis (92.1% and 89.8%, respectively). Significantly fewer patients had recurrence with fidaxomicin in both groups (15.4% vs 25.3%, $P = 0.005$ intention-to-treat, and 13.3% vs 24.0%, $P = 0.004$ per protocol) although the lower rate of recurrence was in the less virulent strains. For the more virulent strains, the recurrence rate was about 25% for both drugs. Fidaxomicin was associated with a higher rate of hyperuricemia and elevated transaminases (*N Engl J Med* 2011;364:422-431). An accompanying editorial points out that the incidence and virulence of *C. difficile* infections is increasing at an alarming rate in this country. Fidaxomicin inhibits vegetative forms of *C. difficile* while preseving intestinal flora, a combination that holds promise, and if borne out "this new agent could become a recommended therapy for *C. difficile* infection" (*N Engl J Med* 2011;364:473-475). ■

Guideline for intensive insulin therapy

A guideline from the American College of Physicians (ACP) recommends against aggressively controlling blood glucose in hospitalized patients. Intensive insulin therapy (IIT) is no longer recommended for patients in intensive care units, regardless of whether they have diabetes. Specifically, the ACP recommends not using IIT to strictly control blood glucose or even normalized blood sugar in surgical ICU or medical ICU patients, and recommends a target blood glucose level of 140-200 mg/dL if insulin therapy is used. The recommendation is based on multiple studies that show no reduction in mortality with a blood glucose target of 80-180 mg/dL compared with higher targets using a variety of intensive insulin regimens. This includes treatment of patients with myocardial infarction, stroke, acute brain injury, or those under perioperative care. The guideline further recommends that avoiding targets less than 140 mg/dL should be a priority because harm is likely with lower blood glucose targets (*Ann Intern Med* 2011;154:260-267).

FDA actions

The FDA is warning against the use of terbutaline for prevention or prolonged treatment of preterm labor in pregnant women. The drug, which is approved for treatment of asthma, has been used off label for treatment of preterm labor and uterine hyperstimulation; however, the agency has received postmarketing reports of serious adverse reactions, including heart problems, and even maternal deaths, associated with the drug. The FDA has added a Boxed Warning and Contraindication to the labeling of the drug warning against these uses. This extends to both the IV and oral forms of terbutaline.

The FDA has approved hydroxyprogesterone caporate injection to reduce the risk of preterm delivery before 37 weeks of pregnancy in a pregnant woman with a history of at least one spontaneous preterm birth. The drug is not intended for use in women with a multiple pregnancy, such as a twin pregnancy, or other risk factors for preterm birth. The drug was approved under the FDA's accelerated approval regulations, and, as such, additional studies will be required after approval to show that the drug does indeed have clinical benefit. Hydroxyprogesterone caproate is given once a week by injection into the hip beginning at week 16 and no later than week 21. The drug is marketed by Hologic Inc. as Makena.

The FDA has issued a drug safety alert regarding the risk of serious liver injury with dronedarone (Multaq). The drug — which is approved for prevention of atrial fibrillation/flutter — has been associated with multiple cases of severe liver injury, including two cases that required liver transplantation. Dronedarone previously was found to double the risk of death in patients with severe heart failure and was approved with a REMS designed to prevent its use in that patient population. Physicians are reminded to advise patients to contact a health care professional immediately with any signs of hepatic injury or toxicity. All patients on dronedarone should get periodic hepatic serum enzymes especially during the first 6 months of therapy.

The FDA has approved a new treatment for head lice. Spinosad is an insecticide originally derived from a naturally occurring soil bacterium. The 0.9% topical suspension was shown to be effective in two Phase 3 active-control, randomized studies in which 86% of patients treated with the active drug were lice free after 14 days compared to 44% of controls. The product should not be used in children under 6 months of age because it contains benzyl alcohol. Spinosad is applied as a single 10-minute application which may be repeated in one week if lice are seen. It will be marketed by ParaPro LLC as Natroba. ■