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INSIDE

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Extubation to Non-invasive Ventilation for Weaning Reduces Mortality, Morbidity, and Length of Stay

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *This meta-analysis of 12 clinical trials in adult patients with acute respiratory failure showed that extubation directly to non-invasive ventilation before weaning would normally have been attempted decreases mortality, ventilator-associated pneumonia, and length of stay — especially for patients with COPD.*

Source: Burns KE, et al. Use of non-invasive ventilation to wean critically ill adults off invasive ventilation: Meta-analysis and systematic review. *BMJ* 2009 May 21;338:b1574; doi: 10.1136/bmj.b1574.

In 2003, Burns and colleagues published a Cochrane review[1] of available studies examining the effects of early direct extubation to non-invasive ventilation (NIV) in adult patients receiving invasive mechanical ventilation for acute respiratory failure. That review showed significant benefit of the non-invasive approach in terms of mortality, the incidence of ventilator-associated pneumonia (VAP), total duration of mechanical ventilation, and length of hospital stay — although the authors emphasized the small number of available studies on this topic. These same investigators, along with other colleagues in Hamilton, Toronto, and Vancouver, Canada, have now updated their assessment, incorporating the findings of several more recent studies that substantially improve the quality of the evidence base in this important area.

Burns et al conducted an exhaustive search for all studies of NIV in weaning. They conducted duplicate independent citation screening in Medline and several other indexing sources, reviewed abstracts presented at relevant meetings, and contacted investigators of potentially relevant trials to clarify the methods used. They included randomized trials (plus a few carefully screened quasi-randomized trials) of extubation to immediate NIV vs weaning from invasive mechanical ventilation, in adult patients requiring > 24 hours of invasive mechanical ventilation for acute respiratory

failure. The primary outcome variable was mortality; secondary outcomes examined were the incidence of VAP, duration of mechanical ventilation both with and without NIV, and length of stay in both ICU and hospital. The authors carried out extensive analysis for publication bias, heterogeneity among the included studies, and other factors that might influence the results.

Twelve studies met all the inclusion criteria, including 7 subsequent to the 5 in the authors' original meta-analysis. Of the 12 studies (530 patients), 4 were published in Chinese, 2 were published in abstract form, and 1 was an unpublished dissertation. Eight trials included only patients with COPD, and the other 4 included patients with other diagnoses as well as COPD. They used a variety of criteria for patient inclusion as well as for invasive and non-invasive ventilation and weaning; however, the authors judged them similar enough in design to include in the meta-analysis of pooled data.

Use of NIV as an adjunct to weaning was associated with reduced overall mortality (relative risk, 0.55; 95% confidence interval [CI], 0.38-0.79; $P = 0.001$). The incidence of VAP was also substantially reduced, with a relative risk of 0.29 (95% CI, 0.19-0.45; $P < 0.001$). As would have been expected, the duration of intubation was much less in patients managed with NIV for weaning: weighted mean difference, -7.8 days (95% CI, -11 to -4 days; $P < 0.001$). However, total duration of ventilation (invasive + NIV) was also less with NIV (-5.6 days; 95% CI, -9.5 to -1.8 days; $P = 0.004$). Length of stay was shorter with NIV, both in the ICU (-6.2 days; 95% CI, -8.8 to -3.8 days; $P < 0.001$) and overall in the hospital (-7.2 days; 95% CI, -10.8 to -3.6 days; $P < 0.001$). On the basis of these findings, which agree with and strengthen those of their earlier study, the authors conclude that NIV is indeed efficacious in improving all the examined outcomes, and that it should be used preferentially in patients with COPD.

■ COMMENTARY

The evidence base on the use of NIV in acute care has expanded dramatically in the last decade.[2-4] This modality is now standard of care for severe COPD exacerbations and acute cardiogenic pulmonary edema, and its use in certain forms of acute hypoxemic respiratory failure is also supported by considerable evidence. The results of the study by Burns et al clearly indicate that NIV as a bridge to weaning from ventilatory support should be added to this list of "proven indications."

Although the results of this meta-analysis are clear and clinically relevant, it should be emphasized (as it was by the authors) that the available clinical evidence in this area is still not particularly robust. The included studies varied widely in their reported rates of mortality (ranging from 11% to 60%) and VAP (6% to 59%). Because of low event rates, none of the individual clinical trials included in the meta-analysis was adequately powered to demonstrate a difference between the compared weaning strategies. Nonetheless, Burns et al found no evidence of publication bias in the examined studies, and the absence of individual trials with contrary results seems noteworthy.

The figure *(page 35)* provides a conceptual illustration of how NIV should be used — in appropriately selected patients — as discussed here. A multitude of studies now demonstrate that intubation can be avoided in many instances of acute respiratory failure, especially when it occurs in patients with underlying COPD. Staying hands that have become accustomed to reaching for the endotracheal tube in this situation has required a substantial practice change for many clinicians. Moreover, the reality is that intensivists often first become involved in the patient's care after intubation has already taken place, whether in the pre-hospital setting, in the emergency department, or at the hands of another clinician in the hospital. Given the strong evidence that patients with acute respiratory failure com-

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Figure

Schematic comparison of traditional weaning

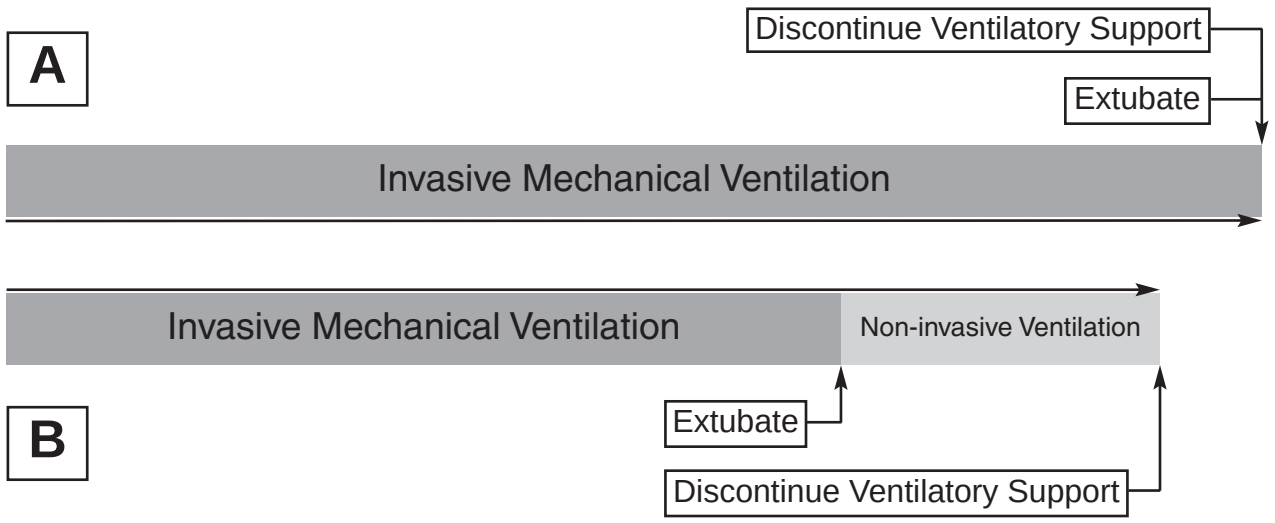

Figure: (A) With traditional weaning, both ventilatory support and intubation are discontinued at the same time, with early conversion to non-invasive ventilation; (B) With early conversion to non-invasive ventilation, ventilatory support is continued following extubation and subsequently weaned as tolerated. Strategy B shortens both the period of intubation and the total duration of ventilatory support.

plicating COPD can usually be managed without intubation,[2-4] such patients are the ideal candidates for early extubation to NIV. The clinician should not be locked into continuing invasive ventilation in patients in whom it might well have been avoided in the first place. In hypoxemic acute respiratory failure (for example, in severe pneumonia or the acute respiratory distress syndrome), the decision is admittedly a bit less clear.

Based on the Burns meta-analysis and the other available evidence,[5] the following guidelines appear reasonable:

Good candidates for early extubation to NIV:

- COPD exacerbation as the reason for acute respiratory failure;
- No major coexistent acute medical conditions;
- Awake, alert, cooperative patient; and
- Minimal or easily manageable airway secretions.

Poor candidates for early extubation to NIV:

- Hypoxemic respiratory failure requiring high FIO_2 and/or PEEP;
- Hemodynamically unstable (e.g., requiring more than minimal pressors);
- Presence of serious coexisting conditions (e.g., multiple organ dysfunction, cardiac ischemia, unstable arrhythmias, or acute brain injury);
- Obtundation or persistent agitation, inability to cooperate, requirement for restraints;
- Copious respiratory secretions;
- Weak or absent cough; and
- Facial or upper airway problems.

In all cases, the patient needs to be cared for in a closely monitored situation, with adequate staffing until NIV is discontinued and clinical stability has been achieved. ■

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Gastric or Duodenal Feeding Tubes: Does It Matter?

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In this randomized study of nasoduodenal vs nasogastric feeding tubes in the medical ICU, patients who received the former met nutritional goals better, had less vomiting, and experienced a lower incidence of ventilator-associated pneumonia.*

Source: Hsu CW, et al. Duodenal versus gastric feeding in medical intensive care unit patients: A prospective, randomized, clinical study. *Crit Care Med* 2009; 37:1866-1872.

In this study examining both the attainment of nutritional goals and the incidence of complications related to enteral feeding, patients in the medical ICU of a university-affiliated tertiary hospital in Taiwan were randomized to nutritional support via nasoduodenal (ND) vs nasogastric (NG) tubes. Patients who did not have any of a substantial list of exclusion criteria, and who were anticipated to require enteral feeding for at least 3 days, were enrolled. Placement of feeding tubes in the stomach or duodenum was confirmed radiographically, and endoscopic positioning was used if duodenal placement could not otherwise be established. Nutritional support was devised and supervised by a clinical dietician, with infusion rates adjusted by a standardized protocol. The primary outcomes were daily caloric and protein intake and time to achievement of nutritional goals. Secondary outcomes included blood glucose levels and complications such as vomiting, diarrhea, tube-related problems, and ventilator-associated pneumonia (VAP).

One hundred twenty-one patients were enrolled during the 2-year study period, and those randomized to ND (n = 59) and NG (n = 62) feeding were not different in terms of demographic or clinical criteria, diagnoses, or drugs received. All patients were mechanically ventilated and the overall hospital mortality rate was approximately 40%. The ND group had higher caloric and protein intakes ($P < 0.05$) beginning on the second day after enrollment. Throughout the study period the ND patients received more calories per day (1658 vs 1426 kcal), more grams of protein per day (68 v 59 g), a higher mean percentage of daily caloric goal (95% vs 83%), and more rapid attainment of goal intake (32 vs 51 hours) than the NG patients, respectively, with all differences being statistically significant. Patients in the NG group had a higher rate of vomiting (13% vs 2%; $P = 0.01$), and also a higher rate of VAP (8.6 vs 3.1 per 1000 ventilator days; $P = 0.01$). No significant differences between the groups were observed for any of the other variables examined. The authors concluded that patients fed by the ND route have higher calorie and protein intake, reach nutritional goals faster, and have fewer complications than patients fed by the NG route.

■ COMMENTARY

How best to provide nutritional support to critically ill patients remains a difficult and contentious topic. Parenteral feeding can commence such support promptly but is invasive and associated with both important complications and high cost. Enteral feeding has many theoretical advantages but is hard to accomplish effectively in everyday practice. Tubes come out or fail to go where they are intended. Trips to the radiology department to assess tube location or for fluoroscopically guided placement are time-consuming, aggravating for staff, and expensive. The feedings are poorly tolerated thanks to the effects of critical illness and drugs, and high gastric residuals increase the likelihood of regurgitation and aspiration. And numerous studies have demonstrated that, unlike the findings reported here, target levels of nutritional support are generally not met with enteral feeding — often by a wide margin — despite our best intentions.

This study, although positive, does not settle the argument about ND vs NG enteral feeding. In an accompanying editorial, Jeejeebhoy nicely summarizes the reasons for this.[1] He lists 15 randomized controlled trials of gastric vs intestinal feeding, nearly all of them too small individually to demonstrate clinically important differences, and cites 2 meta-analyses of largely the same data that draw different conclusions about which route is better. He points out that, although most studies have shown higher caloric delivery to patients fed by the intestinal route, the differences are only about 200-300 kcal/day (as in the present study), and hence unlikely to exert major effects on overall nutritional status. The potential tie-breaker may turn out to be VAP. Even if there proves to be no clear advantage to intestinal feeding in terms of nutritional outcomes, a lower incidence of VAP, if additional studies confirm the findings of Hsu et al, may justify the preferential use of this route. ■

Reference

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Quality of Life Among Survivors of ICU Admission for COPD

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In this British study of patients admitted to the ICU for COPD exacerbations, 6-month survival was better among those successfully treated with non-invasive ventilation, but even among those requiring intubation, quality of life was about what it had been prior to admission, and nearly all of the survivors would want the same treatment again.*

Source: Wildman MJ, et al. Survival and quality of life for patients with COPD or asthma admitted to intensive care in a UK multicentre cohort: The COPD and Asthma Outcome Study (CAOS). *Thorax* 2009; 64:128-132.

THIS PAPER REPORTS ON A COMPREHENSIVE FOLLOW-UP of patients with severe airway obstruction who were admitted to 92 ICUs or to 3 high-dependency respiratory units in the United Kingdom during 2002 and 2003. The purposes were to assess quality of life and functional status among survivors 6 months later, to determine the wishes of these survivors with respect to future similar treatment, and to examine the predictive value of both patient pre-admission functional status and physician outcome prediction on these things.

In all, 832 patients were recruited (mean age, 66 years; 49% men), of whom 78 were judged by their physicians to have "pure" asthma rather than COPD. Of the 754 patients with COPD, 394 (52%) were intubated either prior to or during their ICU stay; 179 were managed successfully with non-invasive ventilation (NIV) but were potential candidates for intubation; and 181 were "do not intubate," although many of these also received NIV. Survival to hospital discharge was 94% among patients treated with NIV who did not require intubation, 61% among those treated with invasive mechanical ventilation, and 60% among the do-not-intubate group. Of the whole cohort of 832 patients, 517 (62%) survived 6 months, and among these, 81% responded to the authors' questionnaire.

Using the EuroQol visual analog scale, on a scale of 1 to 100 with 100 best, the mean rating of survivors of their overall quality of life was 55. This is substantially lower than ratings obtained from members of the general public aged 65-74 years (previously reported to have a mean score of 77), but similar to the mean score of 51 obtained from 132 outpatients of the same age range with severe COPD in a different study. Physician prediction on admission of likely quality of life at 6 months among survivors was pessimistic as compared to the actual results obtained from the patients or their representatives at follow-up (mean predicted score 50 vs 55), and both the agreement and the discrimination of the measures used were poor. About 75% of the survivors judged their quality of life to be the same or better than in the stable period prior to ICU admission, and 95% of them indicated that they would choose the same treatment again if necessary. In keeping with other studies, pre-admission functional status was the best predictor of functional status 6 months after ICU admission, among those patients who survived.

■ COMMENTARY

Most of the COPD patients in this study who survived to 6 months after ICU admission for an exacerbation of their disease had a heavy burden of symptoms as indicated by their quality-of-life scores. Nonetheless, nearly all of them would choose the same treatment again under similar circumstances, and this was true for those who had been intubated as well as for those managed with NIV.

Although this was a well-done study, the generalizability of its findings to COPD patients admitted to American ICUs is unclear. British hospitals have proportionally fewer ICU beds than U.S. hospitals, so that pre-admission selection factors that influenced the results may have been at work. The patients in this study might have been sicker than patients in American ICUs, because ICU entry criteria may have been more stringent. On the other hand, they might have had generally better prognoses, at least in the opinions of their admitting physicians, because of the higher thresholds for ICU admission.

These possible differences notwithstanding, I think this study has the following noteworthy take-home messages:

- Nearly two-thirds of the patients survived for 6 months following ICU admission, including 55% of those intubated for COPD and 48% of the do-not-intubate patients;
- The quality of life of COPD patients who survive 6 months after ICU admission is not very good, but is generally no worse than it was before admission and about the same as that among stable outpatients with severe COPD;
- Functional status in the 2 weeks prior to admission to

ICU was the best overall predictor of quality of life 6 months later, should the patient survive the unit stay;
- The patients would want to do it again; and,
- Their doctors were poor predictors of functional status or overall quality of life in survivors, and tended to be more pessimistic about these things than proved actually to be the case. ■

Special Feature

Get out of Bed and Walk!

By Dean R. Hess, PhD, RRT

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Dr. Hess receives grant/research support from Respironics and Pari; is a retained consultant for Respironics; and receives royalties from Impact.

EARLY IN MY CAREER AS A RESPIRATORY THERAPIST, WE had an unusual piece of equipment in the ICU — the Birdmobile. This distinctive piece of equipment was a souped-up walker with wheels, to which we added a Bird Mark 7 ventilator, oxygen tanks, and a seat. I wish I had a picture, but unfortunately this was long before the days of digital photography. The image remains sharp in my mind. We used this contraption to ambulate mechanically ventilated patients. The patient was removed from the Emerson, BEAR, or MA-1, attached to the Bird, and ambulated in the ICU. If the patient was strong enough, we would venture outside the ICU, and if the weather was good, we would even go outside. The seat allowed the patient to sit down if fatigued and I can remember pushing patients back to the ICU if they were exhausted. I can recall the special relationships that I developed with some of those patients and their families on these "road trips" — their faces come to mind as I write this.

That was in the 1970s. It was a simpler time to be sure. Our mechanically ventilated patients were awake by day and asleep at night. They followed commands and moved around in bed. We did not consider elevating the head of the bed to prevent ventilator-associated pneumonia because many of our patients spent much of the day out of bed in a chair. It was before the time of complicated ventilator modes and propofol. Today, most mechanically ventilated patients are confined to bed, heavily sedated, and physically restrained for their protection.

But are our current practices of bed rest and sedation for mechanically ventilated patients really protective? It has been increasingly reported that quality of life after critical illness is often sub-optimal. This is particularly true in the domain of physical function. The words "critical illness myopathy and neuropathy" were not part of our vocabulary 25 years ago. Today, survivors of ARDS have persistent physical disability for years after ICU discharge. The consequences of these acquired deficits may lead to disability, social isolation, institutionalization, and significant economic burden for society. A variety of factors are responsible for these physical deficits, including severity of illness, acute inflammation, corticosteroid administration, and use of neuromuscular blockers. But perhaps the most important risk factor is prolonged bed rest.[1,2] Now, early in the 21st century, there is renewed interest in physical activity for mechanically ventilated patients.[3]

Mobility in the Medical ICU

Morris et al conducted a prospective cohort study of mobility in medical ICU patients with acute respiratory failure requiring mechanical ventilation on admission; 165 patients were mobilized and another 165 were not.[4] An ICU mobility team initiated the protocol within 48 hours of mechanical ventilation. The team consisted of a critical care nurse, nursing assistant, and physical therapist, but unfortunately did not include a respiratory therapist. Patients who received mobility were out of bed earlier (5 days vs 11 days; $P < 0.001$), had physical therapy initiated more frequently in the ICU (91% vs 13%; $P < 0.001$), and had similarly low complication rates compared with usual care. For the patients who received early mobility, ICU length of stay was 5.5 days vs 6.9 days for usual care ($P = 0.025$). Also, hospital length of stay for patients receiving the mobility protocol was 11.2 days vs 14.5 days for usual care ($P = 0.006$). Importantly, there were no untoward events during any ICU mobility session and no cost differences. The authors concluded that a mobility team initiated earlier physical therapy and that this was feasible and safe, did not increase costs, and was associated with decreased ICU and hospital length of stay.

A methodologic weakness of this study was that ICU nursing unit assignment rather than randomization was used to allocate patients to the study groups. But perhaps a more important shortcoming was the absence of involvement by respiratory therapists. Thus, mobilization was limited to that which could be accomplished within the length of the ventilator circuit. Although patients were transferred from bed to chair and stood at the bedside, full ambulation was not feasible. Moreover,

absence of a respiratory therapist precluded manipulation of the ventilator settings to compensate for any adverse effects on gas exchange (e.g., desaturation) that might occur during mobility.

Bailey et al utilized a team consisting of nurses, respiratory therapists, physical therapists, and critical care technicians to ambulate respiratory failure patients.[5] This was a prospective cohort study to determine whether early activity is feasible and safe in this patient population. They enrolled all consecutive respiratory failure patients who required mechanical ventilation > 4 days who were admitted to their respiratory ICU. During the 7-month study period, they conducted 1449 activity events in 103 patients. The activity events included 233 episodes of sitting on bed, 454 episodes of sitting in a chair, and 762 episodes of ambulation. In patients with an endotracheal tube in place, there were 593 activity events, of which 42% were ambulation. The majority of survivors (69%) were able to ambulate > 100 feet at ICU discharge. Of note, there were < 1% activity-related adverse events including fall to the knees without injury, feeding tube removal, systolic blood pressure > 200 mm Hg, systolic blood pressure < 90 mm Hg, and desaturation to < 80%. It is particularly important to note that no patient was extubated during activity. The authors concluded that early activity was feasible and safe in this patient population. Although this study demonstrated that physical activity among mechanically ventilated patients in the ICU is feasible and safe, the lack of a control group precludes any conclusions related to patient outcomes.

In a recently reported study, Schweickert et al randomly assigned 104 patients to early exercise and mobilization (physical and occupational therapy) during periods of daily interruption of sedation (intervention; n = 49) or to daily interruption of sedation with therapy as ordered by the primary care team (control; n = 55).[6] Every morning, unresponsive patients in the intervention group underwent passive range-of-motion exercises for all limbs. Physical therapy and occupational therapy were then coordinated with interruption of sedation. Sessions began with range-of-motion exercises in the supine position. If this was tolerated, treatment was advanced to bed mobility activities including transfer to upright sitting. Sitting balance activities were followed by activities of daily living and exercises that encouraged increased independence with functional tasks. The session progressed to repetition of sit-to-stand transfers from bed to chair, or bed to commode, and then to pregait exercises and walking. Return to independent functional status at hospital discharge occurred in 59% of patients in the intervention group compared with 35% of patients in the control group ($P = 0.02$). Patients in the intervention group had shorter duration of delirium (median 2.0 days vs 4.0 days; $P = 0.02$), and more ventilator-free days during the 28-day follow-up period than did controls (23.5 days vs 21.1 days; $P = 0.05$). There was only one serious adverse event in the 498 therapy sessions (desaturation to < 80%). Discontinuation of therapy as a result of patient instability occurred in only 4% of all sessions, most commonly for patient-ventilator asynchrony.

Conclusion

So what have we learned about early physical activity of mechanically ventilated patients? First of all, it appears to be safe. However, its safety with widespread application is not assured. Institutional protocols should be implemented to assure adequate monitoring and supervision during physical activity of these patients. Greatest benefit is likely the result of a multidisciplinary approach including intensivists, critical care nurses, respiratory therapists, physical therapists, occupational therapists, and critical care technicians. Each of these disciplines brings specialized expertise to maximize the safety and benefit of physical activity and ambulation. The optimal timing of initiation of physical activity in mechanically ventilated patients is unclear. Undoubtedly, patients should be hemodynamically stable before physical activity is started. It also seems prudent to forego physical activity if the patient requires high levels of ventilator support. Of course, the patient needs to be awake and cooperative, which depends in large part on the amount of pharmacologic sedation administered to the patient. For ambulation, a portable ventilator and monitoring equipment (heart rate and rhythm, blood pressure, pulse oximetry) should be used. At minimum, the patient should receive the same level of ventilatory support when physical activity is initiated and minute ventilation and oxygen levels should be increased as necessary as physical activity and ambulation progress.

Over the past 15 years, we have learned that daily spontaneous breathing trials lead to fewer ventilator days.[7] We then learned that daily awakening also leads to fewer ventilator days.[8] This has led to the practice of daily "wake-up-and-breathe" sessions, in which sedation is stopped and a spontaneous breathing trial is conducted. Such a protocol has been reported to shorten the duration of mechanical ventilation and afford a survival benefit.[9] With the accumulating evidence supporting early physical activity for mechanically ventilated patients, perhaps the new paradigm should be, "wake up, breathe, get out of bed, and walk." ■

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CME / CNE Questions

16. In studies published to date, which of the following has been demonstrated when patients are extubated directly to non-invasive ventilation as an aid to weaning from ventilatory support?
a. Decreased mortality
b. Decreased instances of ventilator-associated pneumonia
c. Decreased ICU length of stay
d. All of the above

17. Which of the following are potential disadvantages to the parenteral nutritional support for patients in the ICU?
a. Difficulty achieving target nutritional goals
b. Increased incidence of ventilator-associated pneumonia
c. High cost
d. Increased incidence of vomiting

18. In the study of quality of life among patients with severe COPD who survived an ICU admission, which of the following was found?
a. Only about 25% of do-not-intubate patients survived 6 months after admission.
b. The patients' physicians accurately predicted post-ICU quality of life.
c. Functional status in the 2 weeks prior to ICU admission was the best predictor of follow-up quality of life among survivors.
d. Most survivors would not want to undergo the same treatment again.

Answers: 16. d, 17. c, 18. c.

CME / CNE Objectives

After reading each issue of *Critical Care Alert*, readers will be able to do the following:

- Identify the particular clinical, legal, or scientific issues related to critical care.
- Describe how those issues affect nurses, health care workers, hospitals, or the health care industry in general.
- Cite solutions to the problems associated with those issues.

In Future Issues:

Is Portable X-ray Equipment Spreading Resistant Bacteria in Your Unit?

PHARMACOLOGY WATCH

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

Meta-analysis Compares Antihypertensive Classes

In this issue: Comparing blood pressure medications, determining optimal length of androgen-deprivation therapy, red yeast rice for LDL reduction, and FDA Actions.

Comparison of antihypertensive classes

All classes of antihypertensive drugs are equivalent in preventing CHD and stroke according to a British study. In the largest meta-analysis of randomized trials of blood pressure reduction to date, researchers reviewed the efficacy of the 5 major classes of blood pressure medications (thiazides, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and calcium-channel blockers). Beta-blockers were found to have a special effect over and above that of blood pressure reduction in preventing recurrent CHD events in people with a history of CHD (29% risk reduction vs 15% with other drugs), although this affect was limited to a few years after myocardial infarction. Otherwise, the 5 main classes and blood pressure-lowering drugs were similarly effective in preventing CHD events and strokes, with the exception of calcium-channel blockers, which have a slightly higher benefit in preventing stroke (relative risk, 0.92; 95% confidence interval, 0.85-0.98). There was benefit in reducing risk of CHD and stroke with BP-lowering treatment regardless of the patient's pretreatment blood pressure, surprisingly even as low as 110 mmHg systolic and 70 mmHg diastolic. Treatment with blood pressure-lowering medications was also associated with a 13% reduction in all-cause mortality, although there was no reduction in cancer or nonvascular related deaths. The authors conclude that blood pressure lowering is important in everyone over a certain age regardless of pretreatment blood pressure and that all classes of blood pressure medications had similar effective in reducing CHD events and stroke (*BMJ* 2009;338:b1665).

Length of androgen-deprivation therapy

Men with locally invasive prostate cancer who have received external beam radiation do better with 3 years of androgen-deprivation therapy compared to 6 months of therapy according to a new study from Europe. After receiving radiation therapy, 970 men were randomly assigned to 6 months of androgen suppression (n = 483) vs 3 years of suppression (n = 487). After mean follow-up of 6.4 years, 132 patients in the short-term group and 90 patients in the long-term group had died. The number of deaths due to prostate cancer was 47 in the short-term group and 29 in the long-term group. The 5-year overall mortality was 19% vs 15.2% for short-term and long-term suppression, respectively, with an observed hazard ratio of 1.42 (P = 0.65 for non-inferiority). The authors conclude that the combination of radiotherapy plus 6 months of androgen suppression provides inferior survival as compared with radiation therapy plus 3 years of androgen suppression in men with locally advanced prostate

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cancer (*N Engl J Med* 2009;360:2516-2527). In an accompanying editorial, Peter Albertson, MD, points out the importance of determining the optimal length of androgen-deprivation therapy because of long-term side effects including weight gain, fatigue, hot flushes, osteoporosis, cardiac disease, and depression. With the high level of regular screening for prostate cancer, most men are diagnosed earlier with much lower grade disease than those addressed in this study, and it is unclear whether these findings can be applied to these men with clinically localized cancer. Radiation plus or minus androgen deprivation vs surgery, age of the patient at diagnosis, and staging of the tumor all are important in determining therapy (*N Engl J Med* 2009;360: 2572-2574).

Red yeast rice and LDL

Patients may be asking about red yeast rice for the treatment of hypercholesterolemia because of a recent study in the *Annals of Internal Medicine*. Patients were recruited from a cardiology practice in suburban Philadelphia who had had a history of statin-associated myalgias. Thirty-one patients were randomized to receive red yeast rice 1800 mg or placebo twice daily for 24 weeks. All patients were also enrolled in a 12-week therapeutic lifestyle program. Red yeast rice was effective in lowering LDL-cholesterol an average of 43 mg/dL from baseline at week 12 and 35 mg/dL at week 24 compared to reductions of 11 mg/dL at week 12 ($P < 0.001$) and 15 mg/dL at week 24 ($P = 0.011$) in the lifestyle-only group. Total cholesterol was also lowered in the treatment group, although there was no change in HDL-cholesterol or triglycerides. Treatment with red yeast rice was not associated with changes in liver enzymes or CPK levels and there was no difference in weight loss or pain severity scores between the two groups. The authors conclude that red yeast rice and therapeutic lifestyle change decreased LDL-cholesterol without increasing CPK or pain levels in patients with a history of statin-related myopathy (*Ann Intern Med* 2009;150:830-839).

The study is interesting because of the large number of patients who do not tolerate statins due to muscle pain and weakness. These patients frequently experience myalgias without myositis (normal CPK levels), and the majority continue to have symptoms despite dose adjustments or changing to a different statin. Red yeast rice is a Chinese supplement known to contain naturally occurring lovastatin (monocolin K) and other monocolins that inhibit HMG-CoA reductase, the same enzyme targeted by statins. It is unclear why red yeast rice is better tolerated than commercial statins, but the authors suggest it may be due to the relatively low dose of the statin, or other, yet undiscovered properties of red yeast rice. The authors also point out that since red yeast rice is a supplement, the chemical composition of different manufacturers is problematic and that patients should be monitored while taking the product. These findings beg the question whether low-dose generic lovastatin may be equally well tolerated, but future studies may help determine if red yeast rice has unique properties that make it an option for the many patients who do not tolerate statins and need to lower cholesterol. In 2007, the FDA issued a warning to consumers to avoid red yeast rice because it contains a pharmaceutical drug, though most products marketed in this country contain negligible amounts of lovastatin.

FDA Actions

The FDA has alerted consumers that 3 Zicam® products may result in long-lasting or permanent loss of smell (anosmia). Zicam Cold Remedy Nasal Gel, Zicam Cold Remedy Nasal Swabs, and Zicam Cold Remedy Swabs Kids Sized are all implicated, and the FDA is recommending that consumers stop using the products and throw them away. All 3 of these products contain zinc, which has not been shown to be effective in reducing the duration or severity of cold symptoms. Other Zicam oral tablets and lozenges have not been included in this advisory. Matrixx Initiatives, the manufacturer of Zicam, is offering refunds for the 3 products noted above. The company is also withdrawing the two adult products from the market — Cold Remedy Swabs Kids Sized had been previously withdrawn. There have been more than 130 reports of anosmia associated with intranasal Zicam product use ranging from 1 dose to long-term use.

The FDA has approved the first formulation of parenteral ibuprofen to treat fever and pain in hospitalized patients. The drug is given intravenously over 30 minutes in doses of 400-800 mg every 6 hours as needed for pain; lower doses are indicated for fever. As with all NSAIDs, caution is warranted when using injectable ibuprofen in patients with heart failure, renal dysfunction, increased risk for thrombosis, or history of ulcers or GI bleeding. Injectable ibuprofen is marketed by Cumberland Pharmaceuticals as Caldolor™. ■