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CRITICAL CARE ALERT®

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Does Pressure-Controlled Ventilation for ARDS Reduce Mortality?

ABSTRACT & COMMENTARY

In a multicenter randomized trial, 79 patients with the acute respiratory distress syndrome (ARDS) received either pressure-controlled ventilation (PCV) or volume-controlled ventilation (VCV), using the same plateau pressure goals. The patients received ventilation with nearly identical plateau pressure, tidal volume, and total positive end-expiratory pressure (PEEP). Hospital mortality was significantly higher (78% vs 51%) in the VCV group, and there were also more extra-pulmonary organ failures (average 3.7 vs 2.6, due to an increase in renal failure) in the VCV patients. A multivariate analysis showed that the mode of ventilation was not associated with mortality, and Esteban and colleagues conclude that the mode of ventilation was not the cause of the increased mortality (Esteban A, et al. *Chest* 2000;117:1690-1696).

COMMENT BY GORDON D. RUBENFELD, MD, MSc

Regardless of how little evidence there is to address many clinical questions in critical care, it is difficult to imagine an intensivist without strong opinions. We all bring clinical experience and preconceptions based on our reading of the existing literature to every new study. As Thomas Kuhn pointed out in *The Structure of Scientific Revolutions*, scientists sometimes go to great lengths to make their data fit their paradigms.

One has the sense that Esteban et al struggled with this problem in trying to interpret the results of their novel study. Esteban et al accepted the "low stretch" ventilator strategy by targeting a plateau pressure of 35 cm H_2O in all patients with ARDS and tried to identify the ideal mode of mechanical ventilation by randomizing patients to PCV and VCV. When total PEEP and plateau pressure are kept constant, the only real difference between the modes is the inspiratory flow pattern. Could this subtle difference in mechanical ventilation really account for the 35% reduction in mortality and the marked reduction in organ failure in the PCV group?

One of the first places we look in randomized trials when the results seem a bit strange is Table 1. In this article, Table 1 provides

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some disquieting information. Although the patients were balanced with regard to severity of illness score and organ failure, there were almost twice as many patients in the VCV group with renal failure at baseline. Perhaps the study turned out the way it did because of an "unlucky" randomization? This is a common concern in clinical trials and can be addressed simply by performing an "adjusted" analysis that incorporates baseline severity of illness. Esteban et al tried to provide this analysis which, they argue, showed that the increased mortality in the VCV group was due to differences in organ failure. Unfortunately, they performed the wrong analysis and, therefore, readers can conclude relatively little from the study results.

When Esteban et al are concerned about an unlucky randomization, they can address this concern fairly simply with an "adjusted" analysis that controls for baseline differences in the patients. Differences that occur after randomization should not be included in the adjusted analysis because they may be caused by the therapy. For example, imagine a study of patients with septic shock that showed a higher mortality in patients treated with corticosteroids. Controlling for differences in baseline severity of illness in this study would be fine. However, an analysis that controlled for infection at any time over the study period would obscure any effect that corticosteroids exerted by increasing infections. Just like in this hypothetical example, Esteban et al relied on an analysis that controlled for "the presence of two or more extrapulmonary organ failures over the study period" to argue that VCV did not increase mortality. The correct way to present the results of this study would be to present the treatment effect adjusting only for baseline differences in organ failure. Their analysis, which adjusts for organ failure after randomization, obscures any influence VCV might exert through its effect on organ failure during the course of ARDS.

The truth is, I share Esteban et al's skepticism that VCV caused the observed increase in mortality and organ failure in this study. My paradigm is that the mode of ventilation has little or no effect on outcome in ARDS if plateau pressure, tidal volume, PEEP, and inspired oxygen concentration are all the same. Since the article comes to the same conclusion, maybe I should stop there? Unfortunately, Esteban et al arrive at this conclusion through a flawed analysis that might obscure either a benefit or a harm of PCV. This article won't change my practice, but it challenges the way I have thought about the effects of mechanical ventilation. ❖

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VICE PRESIDENT/GROUP PUBLISHER: Donald R. Johnston.

EDITORIAL GROUP HEAD: Glen Harris.

MANAGING EDITOR: Robin Mason.

ASSISTANT MANAGING EDITOR: Neill Larmore.

COPY EDITOR: Melissa Lafferty.

MARKETING PRODUCT MANAGER: Schandale Kornegay.

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Customer Service E-Mail Address: customerservice@ahcpub.com

Editorial E-Mail Address: melissa.lafferty@ahcpub.com

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Does Noninvasive Ventilation Lower Risk of Nosocomial Pneumonia?

ABSTRACT & COMMENTARY

Synopsis: *Noninvasive ventilation has been shown to be effective treatment for hypercarbic respiratory failure due to exacerbations of COPD. Compared with intubation, this therapy reduces mortality and costs less to provide. Although there are methodological concerns with this paper, it also appears that noninvasive ventilation is associated with a lower risk of nosocomial pneumonia.*

Source: Girou E, et al. *JAMA* 2000;284:2361-2367.

In order to investigate the association of nosocomial pneumonia (NP) with noninvasive ventilation (NIV), Girou and colleagues retrospectively compared 50 patients who had received NIV for treatment of hypercarbia for at least two hours with 50 individually matched patients managed with intubation. Cases were

matched one to one for diagnosis, age (± 5 years), simplified acute physiology score II (SAPS II) (± 6 points), organ failure score, and absence of contraindications to NIV. All infections were identified; NP was suspected if the patient had a temperature greater than 38 degrees, lung infiltrates on chest X-ray, and sputum macroscopically indicative of infection, all occurring at least 48 hours following ICU admission. PN was confirmed using quantitative cultures from protected samples in intubated patients and in some patients on NIV. However, most PN in NIV patients were confirmed by clinical measures and response to treatment.

During the study period, of the134 patients receiving NIV, 57 met study criteria. Of these only 50 could be successfully matched. The only variable studied that was different between the groups was the percentage of patients on antibiotics prior to ICU admission, which was 78% in the control patients and 40% in the NIV cases. While the difference did not reach statistical significance, cases and controls were also different in location prior to the ICU admission (70% in community cases vs 53% in controls; $P = 0.09$), and the percentage of patients who were infected prior to intubation or NIV (30% in cases, 46% in controls; $P = 0.10$). An equal percentage of patients were treated primarily for cardiac failure in each group (18%).

The total nosocomial infection rate was less in the NIV group (14% vs 38%), NP was also decreased (8% vs 22%). Mortality was greater in the intubated group (26% vs 4%), and both the duration of ventilation and ICU length of stay were also longer. When corrected for mechanical ventilation days, the PN rate remained significantly different.

COMMENT BY CHARLES G. DURBIN, Jr., MD, FCCM

Previous studies have identified the association of PN with endotracheal intubation and suggested that NIV might reduce the PN rate. This study attempts to further evaluate this presumed association. Unfortunately, the case matching in this study may have failed to remove important differences between the studied groups. Specifically, the groups were different in location prior to receiving ventilation, the NIV patients being primarily a community group while the matched, intubated cases more frequently came from another area of the hospital. Many more patients in the intubated group had already been diagnosed with infection and were receiving antibiotics. These variables may be the most important contributors to determining PN rates.

Another serious concern with this study is the fact that patients treated with NIV received this therapy only 4-6 hours per day while the control patients were continuously intubated. If the incidence of infection was calculated per hour of therapy, rather than per 1000 days of ventilation, the NP risks would have been identical. Another concern is that controls were selected from different years rather than cases. Significant changes over time may have affected the results.

The mortality differences suggest that the groups were not comparable in severity of illness at entry, despite similar SAPS II and organ failure scores. This is an important concern with interpretation of the outcome. Girou et al are to be congratulated on providing adequate information to make the judgment that the conclusions of this study must be interpreted with caution. ❖

Face Mask CPAP Fails to Prevent Intubation

ABSTRACT & COMMENTARY

Synopsis: *Despite early improvement in oxygenation, continuous positive airway pressure administered by face mask failed to reduce the need for intubation or survival in patients with hypoxic, nonhypercarbic acute lung injury.*

Source: Delclaux C, et al. *JAMA* 2000;284:2352-2360.

Continuous positive airway pressure administered by face mask (Mask CPAP) is occasionally used to treat patients with acute hypoxic lung injury. The benefits of this approach are believed to be improved oxygenation and a reduced need for invasive ventilation. This intervention has been documented to improve gas exchange parameters, but the actual effect on patient outcome is not well documented. Delclaux and colleagues report the results of a multicenter prospective, randomized, controlled trial of CPAP in patients presenting with non-hypercarbic acute lung injury. They examined the effects of the therapy on oxygenation as well as the need for intubation and survival. Patients with a history of heart failure were included if they had a non-cardiogenic cause for their current illness; a stratified randomization procedure allowed equal distribution of these patients in the study.

One hundred twenty-three consecutive adult patients presenting to one of six hospitals with acute hypoxic respiratory failure were randomized. Entrance criteria included a PaO_2/FiO_2 ratio less than 300 mm Hg on 10 L/min of supplemental oxygen for 15 minutes, plus bilateral diffuse infiltrates on chest radiograph. Patients

were accepted only if less than three hours had passed since meeting entrance criteria. Patients with coma, altered mental status, respiratory acidosis, ventricular arrhythmias, a requirement for vasopressor support, an oxyhemoglobin saturation by pulse oximetry (SpO_2) of less than 80% were excluded. Patients received either standard treatment (mask oxygen) or Mask CPAP. Failure of either treatment arm included any of the following: deceased alertness, agitation requiring sedative medications, signs of exhaustion, hemodynamic instability or cardiac arrest, or refractory hypoxemia (SpO_2 < 85% on 100% O_2). Patients were considered treated successfully when their PaO_2/FiO_2 ratio was greater than 300 mm Hg.

The patients were matched in age (58 years), sex (64% male), and the presence of cardiac disease (18% each group), its cause and severity. One patient in each group had a contraindication to intubation but completed the trial. Within one hour of beginning treatment, the CPAP group had an improved average PaO_2/FiO_2 ratio, decreased respiratory rate and increased pH, as well as feeling subjectively better. During the remainder of the study, however, there were no differences in any of these assessments. There were no differences in rate of intubation (CPAP = 37.5% vs 44% in patients without cardiac disease; CPAP = 27% vs 30% in patients with cardiac disease), length of hospital stay (about 16 days), or hospital mortality (CPAP = 30% vs 27% in patients without cardiac disease; CPAP = 32:% vs 35% in patients with cardiac disease). Intubation occurred earlier in the oxygen alone group. The total number of complications was higher in the CPAP group, but no specific complication difference reached statistical significance.

COMMENT BY CHARLES G. DURBIN, Jr., MD, FCCM

On first blush, this paper seems to demonstrate no effect of CPAP on prevention of intubation or improvement in outcome in patients with hypoxic lung injury. Intubation was performed at a later point in the disease process in the CPAP group. As usual, though, the devil is in the details. The CPAP group had the highest number of complications, including facial skin necrosis, stress ulcer (no prophylaxis), and nosocomial pneumonia. There were four patients who sustained cardiac arrest in the CPAP group, and none in the O_2 alone group. This is interesting because one of these was when the CPAP was accidentally removed during a nursing maneuver during which profound hypoxemia ensued. The other three cardiac arrests were during elective intubation of CPAP patients. It's probable that the delayed intubation in these patients resulted in patients who were in extremis requiring intubation and thus, faring poorly. This suggests that the criteria for intubation were applied differently in the two patient groups, making the comparison unreliable. It also suggests that early rather than late intubation may have benefits in treating hypoxic lung injury. There were no differences in important outcomes, however, so this delay did not create a statistical difference in outcome between the two treatments.

A significant problem with this study is the actual use of CPAP. Patients were treated with face mask CPAP less than continually. In fact, if the patient received only six hours of CPAP in a 24-hour period, this was considered a success. This means that those patients who received CPAP only received it when their gas exchange variables deteriorated to the entrance criteria. It was withdrawn when they improved and was not used therapeutically. With this use pattern in mind, the study demonstrates the value of this therapy in improving oxygenation in the short term with no ultimate outcome worsening.

While this is an interesting study, it really does not answer many of the important questions about using mask CPAP. Does CPAP, continuously used, modify the course of hypoxic lung injury? Is there an increased risk of any particular complication with its use? Does it delay intubation to a point where intubation is more dangerous? And what is the cost (in terms of caregiver time) needed to safely provide this therapy? These and other important questions remain to be evaluated. ❖

Muscle Movement vs. Peripheral Nerve Stimulation During Therapeutic Paralysis

ABSTRACT & COMMENTARY

Synopsis: *In a methods comparison study involving 27 critically ill pediatric patients, poor agreement was found between observed muscle paralysis and corresponding train-of-four scores obtained from peripheral nerve stimulation during and after neuromuscular blocking agent infusion.*

Source: Pena O, et al. *Heart Lung* 2000;29:309-318.

This study was conducted to determine the degree of agreement between observed muscle movement and train-of-four (TOF) scoring obtained

from a peripheral nerve stimulator during a period of therapeutic paralysis. Data were collected from 27 critically ill pediatric patients (mean age 3.5 ± 5.6 years, range, 0.01-17.88 years) at two observation points: 1) during an infusion of a neuromuscular blocking agent (NMBA), and 2) one hour after the infusion was discontinued. At both observation points, patients were observed for any muscle movement in response to eye care or oral care, or to gentle abdominal stimulation. After this observation point, data collectors obtained a TOF stimulation score from the ulnar nerve. If the patient had no response to ulnar nerve TOF stimulation, or if edema was observed, the facial nerve site was used to obtain a TOF score.

Agreement between the two measurement techniques (observed muscle movement and TOF scores) before and after NMBA infusion was evaluated with a Cohen (kappa) statistic, an appropriate statistic to assess an index of agreement. Agreement was defined as a TOF of 0-2 twitches out of four and no muscle movement observed and 3-4 twitches with muscle movement observed. Level of agreement was defined according to the Table below.

Table

Kappa	Level of Agreement
0.81-1.0	Perfect agreement
0.61-0.80	Substantial agreement
0.41-0.60	Moderate agreement
0.21-0.40	Fair agreement
0.01-0.20	Slight agreement
0.00	Poor agreement

Thirty observations were taken from 27 patients (3 patients were observed twice). Twenty-two observations were taken from patients receiving vecuronium bromide and eight were taken from patients receiving cisatricurium besylate infusions. As expected, Pena and colleagues found little observable movement in patients during the NMBA infusion. However, TOF scores did not agree with this observation. Fair agreement was found between observed muscle movement and corresponding TOF scores during the infusion (kappa ranges, < 0.30). During this time, there were patients with low TOF scores (0-2 of 4 twitches) who were observed to have muscle movement and there were patients with high TOF scores (3-4 twitches), with no muscle movement observed in response to tactile stimuli. During the second observation (50-60 minutes after NMBA infusion ceased), patients exhibited more muscle response to tactile stimulation and there was fair-to-moderate agreement (kappa ranges, 0.39-0.70) between observed muscle movement and corresponding TOF scores. The indices of agreement were considerably higher when using the facial nerve site (kappa ranges, 0.34-0.70) to obtain TOF scores than the ulnar nerve site (kappa ranges, 0.06-0.39) in all cases after the drug was discontinued. Pena et al concluded that the disagreement between assessment techniques during the NMBA infusion corroborated the initial observations of their critical care unit's nurses that TOF monitoring was not a reliable indicator of the degree of neuromuscular blockade.

COMMENT BY KAREN JOHNSON, PhD, RN, CCRN

Reports of prolonged paralysis following cessation of neuromuscular blockade infusions emphasized the importance of giving the lowest possible dose of NMBA to achieve desired effects. To more effectively estimate the level of blockade, peripheral nerve stimulation and TOF monitoring protocols have been advocated to prevent prolonged paralysis in critically ill patients of all ages. However, Pena et al found poor agreement between muscular movement and corresponding TOF during NMBA infusion, and substantial agreement between the two techniques after the infusion was discontinued. Pena et al conclude that TOF monitoring may not be a reliable indicator of the level of neuromuscular blockade. Do we now add TOF monitoring to the list of monitoring devices used in critical care units (e.g., pulse oximetry, hemodynamic monitoring), that clinicians find data inaccurate and unreliable?

These results and conclusions raise issues analogous to those that have been raised with respect to the use of the pulmonary artery catheter. In order to fairly evaluate technology, the proper use of the technology must first be controlled. It was Homer who said, "A fool with a tool is still a fool." Optimal use of any technology is dependent upon the clinicians obtaining the data. Pena et al state that "educational training of the investigators and nursing staff in the use of TOF monitoring was provided." However, content and length of the training, experience of the nursing staff, and assessment of competency were not addressed.

Before we conclude that TOF monitoring is not reliable, we must further investigate the following: 1) technical aspects of TOF monitoring (electrode placement, site selection); 2) variables affecting accuracy (edema, site selection); 3) interpretation (visual vs tactile assessment) of the muscle's mechanical response, and 4) drug therapy (when and how much should NMBA use be titrated). Just like with the controversy over the value of

the pulmonary artery catheter in terms of decision making in the care of critically ill patients, the value of TOF monitoring cannot be addressed without first improving the knowledge and practice of the clinicians who use the technology. ❖

Special Feature

Linezolid: New Agent for Old Bugs

By Uday B. Nanavaty, MD

Gram-positive infections are emerging as the most common nosocomial infections in ICUs across the United States. These gram-positive infections are caused by organisms such as staphylococci, streptococci, and enterococci. Recently, there has been increasing concern about drug resistance among these gram-positive cocci. Colonization and infection with vancomycin-resistant enterococci (VRE) are encountered in almost all ICUs. Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* are also commonly seen in the ICU environment. Cases of *S. aureus* with intermediate resistance to vancomycin (VISA) have been reported. Penicillin-resistant *Streptococcus pneumoniae* are found in up to 25% of cases of community-acquired pneumococcal pneumonias throughout the country.

Thus, resistant gram-positive infections are a common problem in the ICU. Until the introduction of quiniprustin/dalfoprostin, vancomycin was the only agent with reasonable activity against a lot of the organisms causing these infections. There was no satisfactory therapy for VRE infections. Quiniprustin/dalfoprostin and linezolid were both developed specifically for gram-positive infections, and have now been introduced to clinical practice. Linezolid in particular is among the newest additions to the list of FDA-approved antimicrobial agents,[1-5] and will surely find increasing use in ICU practice. The drug was developed by Pharmacia and Upjohn and is available with the brand name Zyvox.

History

Linezolid belongs to the oxazolidinone class of drugs. It is a new class of antimicrobial agent, and no other drug from this class has previously been used in clinical practice. Of note, this class of drugs was initially developed for control of bacterial and fungal foliage disease of tomatoes and other plants. Chemical derivatives tried initially were shown to be effective against gram-positive bacteria and *Mycobacterium tuberculosis*, but were not developed for clinical use due to lethality seen in rats.

Subsequent chemical modifications have resulted in safe and effective compounds, one of which, linezolid, has undergone clinical trials. Although several large clinical trials have been performed in patients with community-acquired pneumonia (CAP), skin- and soft-tissue infections, and nosocomial pneumonia, so far most of the data have only been published in abstract form. Most available information is in review articles citing personal communications by their authors with the company.

Mechanism of Action

Linezolid and other oxazolidinone drugs act by inhibiting protein synthesis in susceptible bacteria. The binding site for protein synthesis inhibition is the 50S ribosomal sub unit. It inhibits the formation of the 30S initiation complex, thereby inhibiting protein synthesis in bacteria at a very early step. This is a unique mechanism, as no other antimicrobial class interferes with this initiator complex formation. Because this class of drugs acts early on translation machinery in bacteria, cross resistance with other classes of drugs is less likely than with other types of antimicrobials. The drug is bacteriostatic rather than bacteriocidal, although the clinical implications of this are not clear, as it has been shown to clear bacterial infections successfully.

Pharmacology

Linezolid is 100% bio-available via the oral route, and can also be administered intravenously via peripheral veins. After an oral dose, peak plasma levels are achieved within one to two hours. Although food affects the maximum concentration of the drug, the area of the curve for plasma concentration over time remains largely unchanged. The minimum plasma levels remain above the minimum inhibitory concentration (MIC) after twice daily dosing in healthy volunteers. Excretion in urine seems to be the primary route of clearance. The drug does undergo nonenzymatic oxidation, mediated via reactive oxygen species, in vivo. This oxidation results in metabolites with low antibacterial activity. The elimination half-life was 4.5-5.5 hours under single dose and steady-state conditions in volunteers.

No dose adjustment is warranted based on age. Also, no dose adjustment is recommended for patients with mild to moderate renal or hepatic dysfunction. Supplemental dosing may be necessary for patients undergoing

hemodialysis. The FDA warns against possible interaction with over-the-counter cold remedies. Aztreonam has been administered with linezolid in clinical trials without any untoward interaction.

Laboratory Studies

A large number of bacterial isolates have been tested against linezolid, and its activity has been in general comparable to those of other drugs effective against those bacteria. In vitro data suggest that linezolid is effective against MRSA, VRE (*E. faecium* and *E. faecalis*) penicillin-resistant pneumococci, corynebacteria, some gram-negative anaerobes, and mycobacteria. It is slightly less active against *Legionella* species, *Chlamydia pneumoniae*, and *Haemophilus influenzae*. For most of the gram-positive organisms, the minimum inhibitory concentration for 90% of the strains tested (MIC90) was less than 4 mg/mL.

Clinical Studies

Most of the clinical studies proving efficacy and safety of linezolid have only been published in abstract form. Some small case series and single case reports reporting experience with off-label "compassionate use" have also been published in peer-reviewed journals.

The efficacy of linezolid in skin and soft tissue infections has been established with a study involving about 800 patients. In this study linezolid was compared to oxacillin/dicloxacillin. In another study of soft tissue infection, it has been compared to vancomycin with equal efficacy. In outpatients with CAP, linezolid was as effective as cefpodoxime. In hospitalized patients with CAP, linezolid was as effective as intracenous ceftriaxone followed by orally-administered cefpodoxime. Intravenous linezolid at a twice-daily dose of 600 mg achieved clinical cure in 88.6% patients with VRE infections. In a large group of neutropenic patients (88% of whom had *E. faecium* infections), treated in "compassionate use" protocol, clinical cure was achieved in about 70% of patients. In nosocomial pneumonia, a combination of linezolid and aztreonam was as effective as a combination of vancomycin and aztreonam. At this point, experience with critically ill patients with bacteremia is limited.

Resistance

Two isolates during treatment under "compassionate use" protocols have shown rising MICs against linezolid. Both patients from whom these isolates were recovered had indwelling devices that could not be removed. The clinical implications and mechanisms of this are unknown.

FDA Approval

The FDA has approved the use of linezolid in infections with VRE (*E. faecium*), including bloodstream infections, hospital-acquired pneumonia, and complicated skin and skin-structure infections. It has also been approved for CAP and uncomplicated skin and skin-structure infections.

Dosage

Currently, the recommended dosage of linezolid is 600 mg, orally or intravenously, twice daily. At present, adjustment for mild-to-moderate hepatic or renal dysfunction is not suggested. No dose adjustment is suggested for elderly patients.

Adverse Effects

The most common side effects have been headache, nausea, diarrhea, and vomiting. To date, the most important laboratory changes have been decreases in blood platelet and white blood cell counts. It is unclear at this point how many patients will be unable to tolerate linezolid for one reason or another. Again of note, there is limited experience with the use of this drug in severely ill bacteremic patients.

Summary (*See Table*)

Linezolid [1-5] is a new class of antibacterial agent that works by inhibiting the initiation of protein synthesis at a proximal step. The drug can be given either orally or intravenously. So far in clinical studies the drug has had an excellent safety profile, and it appears to be effective in a wide variety of resistant gram-positive infections, including those caused by MRSA and VRE. Judicious use of this drug may lead to a decrease in the spread of resistant gram-positive infections. So far, limited experience is available for its routine use in ICU. ❖

Table

A Quick Overview of Linezolid

- An oxazolidinone—a new class of antimicrobials
- Either oral or intravenous administration
- Minimal side effects
- Comparable efficacy against a wide variety of gram-positive infections, including MRSA and VRE
- Dosage is 600 mg twice daily
- No adjustment in mild-to-moderate renal or hepatic dysfunction
- No cross resistance with other agents
- Bacteriostatic
- Limited data on use in ICU

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3. Lundsrom TS, Sobel JD. Antibiotics for gram positive bacterial infections. *Infect Dis Clin North Am* 2000; 14:463-474.
4. Chien JW, et al. Use of linezolid, an oxazolidinone, in treatment of multidrug resistant gram positive bacterial infections. *Clin Infect Dis* 2000;30:146-151.
5. FDA talk paper on Zyvox at www.fda.gov.

CME Questions

30. Which of the following analyses will yield misleading results?
a. Adjusting for baseline cholesterol in a study of the effect of a new lipid lowering drug on mortality
b. Adjusting for baseline blood pressure in a study of the effect of a new anti-hypertensive drug on the incidence of stroke
c. Adjusting for baseline tumor size and tumor response over time in a study of the effect of a new chemotherapeutic drug on survival
d. Adjusting for baseline severity of illness score in a study of the effect of parenteral nutrition on ICU mortality
e. Adjusting for baseline pulmonary artery pressure in a study of the effect of a new pulmonary vasodilator on mortality in primary pulmonary hypertension

31. Noninvasive ventilation compared to intubation:
a. is associated with a higher bloodstream infection rate.
b. is associated with a lower nosocomial pneumonia rate.
c. is associated with a higher aspiration pneumonia rate.
d. more deaths from respiratory failure.
e. better post-illness lung function.

32. Case-matched controls:
a. provide the best controls for clinical research.
b. should not be used in clinical research.
c. may have significant bias due to unmatched variables.
d. must be treated contemporaneously with studied cases.
e. are often used and easy to locate by computer database.

33. Mask CPAP is useful in acute hypoxic lung injury because:
a. it improves oxygenation quickly.
b. it improves survival.
c. it hastens the need for intubation.
d. it improves the safety of intubation.
e. it forces more caregivers to remain at the bedside.

34. Mask CPAP improves the outcome in:
a. all hypoxic patients with ALI.
b. only patients without cardiac disease with ALI.
c. only patients with cardiac disease and ALI.
d. patients who are comatose and hypoxic.
e. None of the above

35. Agreement between muscle movement and peripheral nerve stimulation during therapeutic paralysis:
a. is better in children than in adults.
b. may be poor in pediatric patients.
c. is excellent when the ulnar nerve is used.
d. All of the above
e. None of the above

36. Linezolid has been shown to be effective in treating patients with nosocomial pneumonia when:
a. used as a single agent.
b. in combination with cefpodoxime.
c. in combination with vancomycin.
d. in combination with aztreonam.
e. in combination with azithromycin.

37. Which of the following statements about linezolid is correct?
a. It can be switched to oral therapy once patients are able to take drugs by mouth.
b. Dose adjustment is not suggested for mild renal failure patients.
c. It can be used for skin and skin structure infection.
d. It should be given twice daily.
e. All of the above

Attention CME Subscribers

Due to an American Health Consultants error, a mistake has been made with the CME numbering. The numbering should have started over in the October 2000 issue. In the October 2000 issue, questions 44-48 should be 1-5. In the November 2000 issue, questions 49-54 should be 6-11. In the December 2000 issue, questions 55-63 should be 12-20. In the January 2001 issue, questions 64-72 should be 21-29. A reminder will also be sent with your CME scantron in the March 2001 issue. We regret any confusion this may have caused. ❖

CE/CME 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:

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EXPANDING YOUR FOCUS IN INTENSIVE CARE

Creating a Dialogue for End-of-Life Patients

Treatment Preferences Must be Determined Early, Researchers Say

By Julie Crawshaw

A recent study shows that patients who discuss their care with their physicians from the inception of their illnesses greatly improve their odds of getting the kind of medical care they want. Conducted by Joan M. Teno, MD, MS, professor of medicine at Brown University, the study evaluated the decision-making and outcomes of 1494 seriously ill patients who stayed in one of five ICUs for at least 14 days (median stay 35 days) and were enrolled in a larger treatment outcome study. Teno and her fellow researchers interviewed patients, surrogate decision-makers, and physicians about prognosis, communication, and goals of medical care.[1]

"One of the findings from this study is that the doctors are not talking to the patients and patients' families are not talking to the doctors," Teno says. "There's a high rate of people getting care they believe is inconsistent with their treatment preferences."

A New Model for Shared Medical Decision-making

The researchers used their findings to develop a new conceptual model they called Patient-Focused, Family Centered Medical Care. One of the cornerstones of that model is promoting shared medical decision-making. "There is a series of outcome measures we've developed around involving patients in treatment decisions," Teno says.

Elliott Fisher, MD, MPH, another of the study's researchers, says he believes the reason patients and physicians aren't talking more is that the medical model in current use is futility-based. "We start raising the questions when everybody recognizes that there's absolutely no hope," Fisher says. "What we really need to do is start talking about this throughout the patient's illness, not just when everyone sees that the patient is dying."

When patients run out of treatment options—usually when the toxicity of the treatment outweighs its benefits—they reach a point of futility. Both Teno and Fisher perceive a need to move from a futility-based model of decision-making to one that has the patient taking an active role in treatment decisions from diagnosis forward.

"There are always treatment options," Teno says. "Hypertension is an excellent example. There's a veritable slew of anti-hypertensive medications with very different costs, but the majority of patients don't know this because they're not involved in medication decisions."

Mismatched Preferences and Perceptions Spell Trouble

The study found that many seriously ill patients see a mismatch between their treatment preferences and the degree to which they believe those preferences are being honored. Fisher points out that correcting this doesn't necessarily mean that physicians must immediately begin discussing end-of-life measures when a patient is first diagnosed with a potentially fatal illness. "There are ways of having the conversation without really posing that. It's really about understanding the person's values and preferences. Sit and listen and understand where people are in dealing with the illness," Fisher says.

Teno concurs, adding that one of the things the medical community does not do well enough is listen to the patient's concerns. "If we began by listening and then double check by repeating back to the patient what we think we've heard, we'd be a lot better off," Teno says.

Following completion of their study, the Brown researchers designed a toolkit they are making available free of

charge.[2] The toolkit was designed, Teno says, because end-of-life care is different from critical care in which the patient survives. In order to determine what medical decisions are best for patients to live well with a life-defining illness, physicians must:

- Re-engineer advance directives
- Change the culture through education
- Develop measures of and demand quality of care
- Create systems of care that deliver quality medical care
- Develop measures and ways of measuring that work

The overall strategy for the toolkit involves conducting focus groups with dying persons and their loved ones. The information gained is then used to review guidelines for key processes of care. This is followed by reviewing the evidence that indicates that these processes will actually result in quality medical care.

The toolkit emphasizes the importance of family members' perspective in assessing quality of care.

It uses retrospective family interviews and prospective patient interviews in a core module applicable across settings of care. Tests were run with a population of bereaved family members whose loved ones died in a hospital, nursing home, or while under hospice care. Researchers say the instrument is equally reliable and valid in all settings. Interviewers administered the survey either over the telephone or in person.

Different versions of the toolkit are available. The hospital version of the toolkit is based on a longer instrument, and has been tailored to reflect hospital services. That allows hospital staff to obtain that perspective using a measurement tool geared specifically toward hospital care. To maintain consistency across versions, researchers have retained the numbering from the original instrument—which means that the numbering for the hospital version appears out of sequence.

Additional modules are available that allow users to modify the survey to their own particular needs. Reports resulting from toolkit use come with a resource guide that suggests the next steps to improving the quality of care. If users choose to limit the domains of interest, researchers suggest that a useful survey would include the following four domains:

1. physical comfort and emotional support
2. promote shared decision making,
3. focus on individual, and
4. attend to the emotional and spiritual needs of the family.

Using the instrument results in information on seven different aspects (or domains) of quality of care. Domains are color-coded so that the questions pertaining to a specific domain all share the same color.

Users can choose to focus on one or more specific domains. However, researchers stress the importance of including all of the questions within each domain of interest for valid, reliable results. To maintain the validity and reliability of the instrument, the questions must be asked in the order that they appear.

The survey can be used to assess the quality of care received by an individual patient, though it was designed to be used with groups of people. Another study now underway will produce norms for the United States, which should be available this spring.

One of the most dramatic toolkit illustrations shows a photo of a smiling, apparently happy 94-year-old female patient with acute myocardial infarction, low blood pressure, and who is short of breath at rest. A capition asks: "Is she 'terminally ill'? Or is it time to terminate the term terminally ill?"

VA Study Proposes New Health Care Professional

Researchers for another study, conducted by the U.S. Department of Veterans Affairs, concluded that end-of-life conversations should automatically be included in care plans so that critically ill patients can die according to their own values and wishes.[3] The study proposes creating a new health care professional working under physicians whose sole job would be to facilitate and document end-of-life conversations. The VA Health Care Network Upstate New York is using this new model.

Other measures VA researchers suggested include multiple programs to train physicians for end-of-life dialogues and to raise community awareness to facilitate such conversations between health professionals, patients, family members, and caregivers.

Daniel R. Tobin, MD, of the VA Health Care Network Upstate New York, Albany Division, was lead author for the study. Tobin and co-author Dale G. Larson, PhD, professor of counseling psychology at California's Santa Clara University, found that training all health care practitioners in standard communication models for conversations at the end-of-life is essential to providing quality end-of-life care. He and his fellow researchers observed that patient preferences for life-sustaining treatments are often inadequately discussed and documented, and that hospice or home care referrals frequently come too late or not at all. Despite the ability to create a pain free death, many patients still die in unrelieved pain after long hospital stays and intensive care.

Enhancing End-of-Life Conversations

Tobin and Larson say they expect the quantity and quality of end-of-life discussions in the future to be closely linked to improving physicians' communication skills, adopting a patient-centered model of care, focus-

ing on improving the quality of remaining life, and developing clinical models and programs to support such discussions earlier in the health care process.

The VA study found both personal and institutional barriers that presently make meaningful end-of-life conversations difficult in health care settings. Patients with an advanced illness may avoid end-of-life conversations because they can't deal effectively with their emotional pain and fear. Physicians may avoid end-of-life conversations because they are afraid those conversations may cause pain for patients and their families. Also, many physicians are unfamiliar with advance directive laws and fear that talking about whatever medical alternatives might be available could lead to disagreements with the patient or family members.

Further, the study reports that because patients may receive treatment at a variety of health care delivery sites, responsibility for end-of-life discussions may not be clear. Health workers may assume the end-of-life issue has been handled elsewhere and therefore not ask about it. The fact that there is currently no financial compensation for physicians for psychosocial conversations, including those that concern end-of-life, may deter some physicians from initiating an end-of-life dialogue.

Tobin, who advocates randomized trials to test new approaches and models for enhancing end-of-life conversations, is nonetheless excited about the program at his own facility.

"We need to train all health care practitioners in standard communication models for conversations at the end-of-life," Tobin says. "Here, we've also introduced the new role of an advanced illness care coordinator who works in collaboration with the patient, family, and physician to secure dignity and control in the last years of life." ❖

References

1. Teno J, et al. *J Am Geriatrics Soc* 2000;48:S70-S74.
2. To obtain the toolkit, contact Joan_Teno@Brown.edu or her assistant Jeff Edmonds at (401) 863-9630.
3. Tobin D, Larson D. *JAMA* 2000;284:1573-1578.

Pharmacist Involvement Drops ICU Error Rate

Savings Amount to $270,000 Annually

By Julie Crawshaw

Including pharmacists in rounds through the intensive care unit (ICU) can reduce medication errors substantially, according to a study led by researchers at the Harvard School of Public Health (*JAMA* 1999; 282:267-270.) The results translated into a projected savings of $270,000 a year for Massachusetts General Hospital in Boston, where the study was conducted.

Previous studies have shown that when pharmacists review medication orders in the ICU, errors are prevented. But until now, no one had looked at whether including pharmacists at the time the drug is actually prescribed might reduce adverse events.

According to the researchers, past studies found that "the major cause of prescribing errors was physicians' lack of essential drug and patient information at the time of ordering."

The study involved a before-after comparison in the ICU and used a coronary care unit as a control. Pharmacists made daily rounds with the residents, nurses, and attending staff, then remained in the ICU for consultations and were available on call throughout the day.

"[Success] clearly depends on the politics, the individual personality of the pharmacist and how well they communicate with the doctors and nurses. In this study, the doctors and nurses filled out a satisfaction score and they were well satisfied," says co-author David J. Cullen, MD, Chair of the Department of Anesthesiology at St. Elizabeth's Medical Center in Boston and Professor of Anesthesiology at Tufts University School of Medicine.

During the study period, pharmacists made a total of 398 interventions, of which 366 were related to drug orders. Physicians accepted 362, or 99% of the recommendations. Nearly half were clarifications or corrections to an order. The errors found by the pharmacists included wrong doses, wrong frequencies, inappropriate choices, and duplicate therapies.

In 100 instances, pharmacists provided drug use information. They recommended alternative therapies in 47 cases, and several times identified potential problems with drug interactions and allergies.

Overall, the study found that the rate of adverse drug events caused by prescribing errors was reduced by 66% during the six months pharmacists were involved. In the control unit, there was essentially no change in the rate of medication errors during the same period of time.

The authors concluded: "The participation of a pharmacist on rounds with the medical team in an ICU is a powerful means of reducing the risk of adverse drug events caused by prescribing errors."

They wrote that computerized physician order entry also can significantly reduce the rate of serious medication errors. But since most hospitals do not use this technology, they say, "The incorporation of a pharmacist

into the patient care team is a more feasible alternative . . . especially in units with high medication use."

Cullen also notes the practicality of a pharmacist on rounds, which on average, required three hours each day to complete.

"There are clinical pharmacists at many hospitals who have a great deal of knowledge and are not used by physicians as they should be. They are not as accessible as they should be. We felt that having a pharmacist would make a difference, so the pharmacy department found ways to back and fill during the course of the study."

The study was partially funded by a grant from the American Society of Health-System Pharmacists Research and Education Foundation as part of its system changes and outcomes project on adverse drug event prevention.

"Obviously, we were pleased with the results and to some degree were expecting them," says assistant program director for research Helen Waldren.

"It was interesting that, as the author's found, pharmacists were well accepted on the team, more so after the impression by medical staff that [pharmacists] were primarily concerned with cost in their decision making, which is a mindset projected a lot onto different departments by each other these days," she says. "It's also noteworthy that pharmacists reported that developing interpersonal relationships helped a lot on all counts."

(*Additional information is available on the AMA's Web site at www.ama-assn.org. ASHP's grant office can be reached through (301)657-3000.*) ❖

Rewards Will be Reaped by the Safety Conscience

Employers Use the Market to Improve Quality

A coalition of 60 of the country's largest employers who provide health benefits to more than 20 million Americans has agreed to look favorably on health care institutions that have more stringent patient safety measures.

The Business Roundtable, a consortium of Fortune 500 companies and other large private and public health care purchasers, have formed the "Leapfrog Group" to improve American health care and save lives through elimination of avoidable errors. The U.S. Office of Personnel Management, the Health Care Financing Administration, and the Minnesota Departments of Human Services and Employee Relations also participate as liaisons.

These employers, in conjunction with their employees, retirees, and families hope to improve medical care by rewarding hospitals that implement significant safety improvements. Suzanne Delbanco, PhD, the group's executive director, says that Leapfrog plans to reduce preventable medical errors by changing the way members purchase health care. "By encouraging health care providers to adopt three proven safety measures," Delbanco says, "thousands of Americans can be protected from disability and death."

These measures are:

- Computerized physician order entry (CPOE), which requires that physicians enter medication orders via a computer linked to prescribing error prevention software. CPOE has been shown to reduce serious prescribing errors in hospitals by more than 50%.
- Evidence-based hospital referral, which requires doctors to refer patients who need certain complex medical procedures to hospitals that offer the best survival odds based on scientifically valid criteria. This includes the number of times a hospital performs these procedures each year. Research shows can reduce a patient's death risk by as much as 30%.
- Intensive care unit staffing by physicians trained in critical care medicine. Staffing ICUs with physicians who have credentials in critical care medicine has been shown to reduce the risk of patients dying in the ICU by more than 10%.

The program was triggered by a 1999 report by the Institute of Medicine, which found that up to 98,000 Americans die every year from preventable medical errors made in hospitals. New research indicates a more stringent, market-based approach could save up to 58,300 lives and prevent up to 522,000 medication errors annually.

Leapfrog members must agree to:

- Educate and inform enrollees about patient safety and the importance of comparing health care provider performance, with initial emphasis on the Leapfrog safety measures;
- Recognize and reward health care providers for major advances in protecting patients from preventable medical errors;
- Hold health plans accountable for implementing Leapfrog purchasing principles;
- Build the support of benefits consultants and brokers to utilize and advocate for the Leapfrog purchasing principles with all of their clients.

The Business Roundtable is an association of chief executive officers of corporations with a combined workforce of more than 10 million employees in the United States. For more information, contact John Schachter, at the Business Roundtable (202) 872-1260. ❖