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INSIDE

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MRSA Ventilator-associated Pneumonia: Vancomycin or Linezolid?

ABSTRACT & COMMENTARY

By Andrew M. Luks, MD

Pulmonary and Critical Care Medicine, University of Washington, Seattle

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

Synopsis: *This open-label, multicenter trial showed that treatment of MRSA ventilator-associated pneumonia with linezolid was associated with non-statistically significant improvements in microbiologic cure, clinical cure, survival, duration of mechanical ventilation, and ICU length of stay when compared to therapy with vancomycin.*

Source: Wunderink RG, et al. Early microbiological response to linezolid vs vancomycin in ventilator-associated pneumonia due to methicillin-resistant *Staphylococcus aureus*. *Chest* 2008;134:1200-1207.

Methicillin-resistant Staphylococcus aureus (MRSA) is a common cause of ventilator-associated pneumonia (VAP). Several studies have shown that linezolid is associated with higher clinical cure and survival rates when compared with vancomycin in the treatment of MRSA nosocomial pneumonia.[1,2] Wunderink and colleagues sought to build on these data and determine if treatment with linezolid was also associated with a faster microbiologic response than vancomycin for patients with MRSA VAP.

They conducted a prospective, randomized, open-label multicenter study at 36 sites over a 3-year period. Patients were eligible for inclusion if they were ≥ 18 years of age with suspected VAP based on the presence of purulent sputum, fever or hypothermia, hypotension, or leukocytosis, leukopenia, or bandemia. Patients had to have been in the hospital > 5 days, have been on mechanical ventilation for at least 48 hours, and be expected to need mechanical ventilation for at least 72 hours following enrollment. Patients were excluded if they had received antimicrobial agents with activity

against the patient's MRSA isolate for ≥ 48 hours prior to enrollment. Bronchoalveolar lavage (BAL) was performed anywhere from 24 to 72 hours post-study enrollment, and patients were deemed to have MRSA VAP if the quantitative culture yielded > 10^4 cfu/mL of the organism.

Patients were randomized to receive linezolid 600 mg IV every 12 hours or vancomycin 1 g every 12 hours for 7-14 days. Seventy-two to 96 hours later, a repeat BAL was performed from the same lung subsegment as in the initial collection. After 4 days or following the second bronchoscopy, patients receiving linezolid could be switched to oral therapy (600 mg every 12 hours). Patients were withdrawn from the study due to non-compliance or protocol violations, if it was deemed medically necessary, or if the baseline quantitative cultures yielded < 10^4 cfu/mL for MRSA. Using intention-to-treat analysis, the authors examined differences in microbiologic cure rates between linezolid- and vancomycin-treated patients with microbiologic cure defined as a repeat BAL containing < 10^2 cfu/mL for MRSA. Secondary outcomes included clinical outcome, mortality, the duration of mechanical ventilation, and hospital and ICU length of stay.

The authors identified only 50 patients (30 linezolid and 20 vancomycin) who had a MRSA concentration of 10^4 cfu/mL on the baseline BAL sample. Of these patients, only 23 linezolid patients and 19 vancomycin patients underwent follow-up BAL at 72-96 hours. Patients treated with linezolid had a non-statistically significantly higher microbiologic cure rate than patients treated with vancomycin (56.5% vs 47.4%). None of the 10 linezolid patients with microbiologic treatment failure died, as compared with 5 of 10 patients with microbiologic failure in the vancomycin group. Regarding the secondary outcomes, patients treated with linezolid had higher clinical response rate (66.7% vs 52.9%), greater survival at the end of the study (86.7% vs 70%), fewer days on mechanical ventilation (10.4 days vs 14.3 days), shorter hospitalization (18.8 days vs 20.1 days), and shorter ICU length of stay (12.2 days vs 16.2 days), but none of these differences reached statistical significance. The incidence of treatment-related adverse events was similar between the two groups.

■ COMMENTARY

Vancomycin has long been the standard treatment for MRSA VAP. While it is generally effective in this regard, the entire course of therapy must be administered intravenously, which usually mandates central or PICC line placement. Linezolid offers a potential advantage in this respect, as an oral form of the medication is available and patients can be switched to this route after several days on the intravenous form. Clinical use of the medication is not as widespread as is vancomycin, however, and one plausible reason might be the lack of randomized, prospective trials establishing its efficacy relative to vancomycin for VAP. The earlier studies of these two agents all examined patients with nosocomial pneumonia, not just patients with VAP, and several were retrospective in nature.

By focusing on patients with VAP and collecting data in a prospective manner, this study attempts to address these issues and puts forth some intriguing results. However, the study has some methodological issues, the most important of which is the very low number of patients who completed the study protocol. Given the prevalence of MRSA and of VAP, it is unclear how a multicenter study conducted at 36 sites over a 3-year period could only enroll 50 patients. As a result, the study was clearly underpowered, and none of the results reached statistical significance. The study was also open-label, although blinding a study in which the dose and frequency of administration of one of the medications must be adjusted based on drug-levels is admittedly difficult. It is also not clear to me that the authors' definition of microbiologic cure (repeat BAL with < 10^2 cfu/mL at 72-96 hours) is a valid endpoint that has any correlation with meaningful clinical outcomes.

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Questions & Comments

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Finally, it is noteworthy that the lead author, who is also the lead author on several other studies comparing linezolid with vancomycin, is a paid consultant for Pfizer, Inc., the maker of linezolid, while all but two of the other authors are either employees of or consultants to the company. In fact, there are surprisingly few studies in the literature comparing these two agents in adults that are not authored by the lead author in this study, and one of the few studies in adults for which he is not an author has similar issues with relationships between the paper's authors and linezolid's manufacturer.[3]

The question of which medication is the better option for patients with MRSA VAP is an important one. The existing literature suggests that linezolid may be as effective as, if not more effective than, vancomycin, but before we make wholesale changes in our practice and adopt linezolid as the treatment of choice for this problem, we need larger, prospective trials conducted with less influence from the company with a stake in the outcome of the study. ■

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Benefits of a Dedicated ICU Clinical Pharmacist

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In this large epidemiology study using a previous survey and 2004 Medicare data focusing on serious infections in the ICU, hospitals with dedicated ICU clinical pharmacists had lower ICU mortality rates, shorter ICU stays, and reduced charges.*

Source: MacLaren R, et al. Clinical and economic outcomes of involving pharmacists in the direct care of critically ill patients with infections. *Crit Care Med* 2008;36:3184-3189.

In 2004, the authors of this study conducted a survey of U.S. hospitals with ICUs to assess the prevalence and use of dedicated ICU clinical pharmacists.[1] That survey indicated that 62% of hospitals had clinical pharmacists with at least a portion of their full-time equivalent position specifically dedicated to direct involvement in patient care in the ICU rather than drug dispensing and other more traditional pharmacist roles. For the current paper, the authors used the results of that survey, along with ICD-9 diagnostic data, mortality, lengths of stay, total charges, drug charges, and laboratory charges obtained from the Expanded Modified Medicare Provider Analysis and Review (MEDPAR-Hospital-National) for the year 2004, to examine associations between having an ICU clinical pharmacist and those variables for 3 categories of ICU infections: nosocomial-acquired infections, community-acquired infections, and sepsis.

Because of the nature of the databases used, the numbers of hospitals and patients, as well as of variables such as case mix, varied for each infection category. Of the 382 institutions responding to the original survey, 272 had Medicare patients with nosocomial infections; the corresponding numbers for community-acquired infections and sepsis were 265 and 276 hospitals, respectively. Numbers of patients in the different categories ranged from 8927 (community-acquired infections) to 54,042 (sepsis). In each instance, the studied outcomes were better in hospitals with ICU clinical pharmacists than in institutions without pharmacists in this role. For nosocomial infections, community-acquired infections, and sepsis, respectively, hospital mortality rates with and without ICU clinical pharmacists were 14.61% vs 18.05%, 11.43% vs 13.28%, and 18.54% vs 19.43%, all statistically significant with P values of 0.008 or less. Compared to ICUs with clinical pharmacists, mortality rates in ICUs without them were 23.6% higher for nosocomial infections (386 extra deaths), 16.2% higher for community-acquired infections (74 extra deaths), and 4.8% higher for sepsis (211 extra deaths).

ICU lengths of stay were longer in hospitals without ICU pharmacists, by 7.9% (14,248 extra days), 5.9% (2855 extra days), and 8.1% (19,215 extra days), for the 3 infection categories, respectively (all differences significant; at least $P = 0.03$). ICUs that did not have dedicated clinical pharmacists had greater total Medicare billings: by 12% for nosocomial infections, by 11.9% for community-acquired infections, and by 12.9% for

sepsis (all, $P < 0.001$). Differences for Medicare drug and laboratory charges were similar. The authors conclude that, if these results "were extrapolated to all 933,638 Medicare patients in an ICU with the studied infections, the involvement of a clinical pharmacist could save 7409 patient lives, 390,921 ICU days, and $4,168,278,242 in total charges."

■ **COMMENTARY**

This study has some important limitations, the most important of which in my opinion relates to the 2004 survey[1] from which the participating institutions for the present investigation were selected. In that survey, only 382 (11.8%) of 3238 U.S. hospitals with ICUs (1034 ICUs) responded, and these institutions had some potentially relevant differences from the non-responding hospitals. Compared to the 88% of institutions that did not respond to the survey, more responding hospitals were not-for-profit, non-governmental hospitals, and fewer were in all the other categories (government, for-profit, and so on). In the responding hospitals, 52% of the ICUs were open (patient managed by private non-intensivist attending), 28% were transitional (patient co-managed by private attending and intensivist), and 20% were closed (patient managed by intensivist). Thus, whether the present study's results apply to a particular practice environment is unclear, and extrapolating the findings to include all U.S. hospitals in 2009 — and especially the authors' generalizations about lives and money saved — seems pretty dubious.

Previous studies have shown that hospital mortality correlates inversely with the ratio of pharmacists to occupied beds, and that involving pharmacists directly in the care of ICU patients is associated with fewer adverse drug-related events, greater efficiency of care, and lower drug-related costs. Using hospitals with and without ICU pharmacists as identified from a previous survey, the present study documents positive associations between having ICU clinical pharmacists and patient mortality, ICU length of stay, total charges, drug charges, and laboratory charges.

I think it is important to phrase this study's findings in this way, because the authors have not demonstrated that having an ICU pharmacist per se reduces mortality, length of stay, and charges. Whether they have dedicated ICU clinical pharmacists is likely only one of many ways in which the study hospitals differ. A number of aspects of the process of care in the ICU are similarly associated with improved patient outcomes. For example, hospitals with ICU pharmacists are probably also more likely also to have closed ICUs, trained intensivists, greater implementation of protocols and care bundles, multidisciplinary rounds, palliative care services, and other dedicated ICU personnel such as specialist respiratory therapists, nutritionists, and social workers.

Having said that, I am convinced that MacLaren and colleagues are justified in their recommendation that "hospitals should consider employing clinical ICU pharmacists." For decades, the institution in which I work has been fortunate to have specialist clinical pharmacists assigned to each of its main ICUs — including medical, trauma/surgical, and neurosurgical units. The presence of these experts on daily work rounds has improved adherence to clinical practice guidelines and unit protocols, facilitated matching of antibiotic therapy to local microbial susceptibility patterns, identified and prevented adverse drug reactions and interactions, and aided in efforts to prevent oversedation and drug withdrawal. And the educational impact of our ICU clinical pharmacists for physicians, nurses, and others on the staff has been immeasurable. ■

Reference

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Mobilizing Patients in the ICU Is Safe and Cost-effective

ABSTRACT & COMMENTARY

By Leslie A. Hoffman, RN, PhD

Department of Acute / Tertiary Care School of Nursing, University of Pittsburgh

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

Synopsis: *Earlier physical therapy in the ICU led to a shorter ICU and hospital length-of-stay with no untoward events and no cost difference, inclusive of mobility team costs.*

Source: Morris PE, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med* 2008;36:2238-2243.

THIS STUDY COMPARED OUTCOMES IN 330 PATIENTS WHO were managed with mobility therapy (n = 165) vs usual care (n = 165) in a medical ICU. Patients were prospectively enrolled within 48 hours of intubation and 72 hours of ICU admission. Exclusion criteria included

inability to speak (nonverbal) or walk prior to ICU admission (use of a cane or walker was not an exclusion), neuromuscular disease that could impair weaning, acute stroke, body mass index > 45 kg/m^2, unstable fractures, cardiopulmonary resuscitation or do-not resuscitate status at ICU admission, and preadmission steroid administration (prednisone > 20 mg/day for 2 weeks). The mobility team rotated in a set order among 7 ICUs that admitted MICU patients, recruiting patients over 24 consecutive months. Usual care patients were recruited from units where the team was not currently assigned. The mobility protocol was administered 7 days a week and included four levels of activity: Level 1 = passive range of motion and turning every 2 hours; Level 2 = those activities plus active resistance physical therapy and moving to a sitting position; Level 3 = the prior activities plus sitting on the edge of the bed; and Level 4 = prior activities plus active transfer to a chair, weight shifting in place, and ambulation.

At baseline, intervention patients did not differ from usual care patients with respect to any measured variable. APACHE II scores were 21.6 ± 8.0 for usual care patients and 23.5 ± 8.8 for intervention patients (P = 0.092). Intervention patients were out of bed earlier (5 vs 11 days; $P < 0.001$), had therapy more frequently (91% vs 13%; $P < 0.001$), and experienced a shorter length-of-stay (LOS) in the ICU (5.5 vs 6.9 days; P = 0.025) and hospital (11.2 vs 14.5 days; P = 0.006). There was a trend toward a lower incidence of ventilator-associated pneumonia (P = 0.087) and deep vein thrombosis (P = 0.078) in intervention patients. There were no adverse events. Costs, inclusive of the mobility team, averaged $41,142 for intervention patients and $44,302 for usual care patients (P = 0.262).

■ COMMENTARY

An increasing body of recent literature has reported positive benefits from early mobilization of ICU patients, accompanied by few or no adverse events. Early mobilization of patients in the ICU is not new. In the 1970s, several centers reported their experience with ambulation of mechanically ventilated patients, including excellent patient acceptance, improved strength, and earlier weaning from mechanical ventilation. More recently, Needham reported a conversation with a 56-year-old man who experienced a complicated 2-month medical ICU stay that included aspiration, sepsis, and nutritional depletion.[1] His rehabilitation included walking laps around the medical ICU while still ventilator-dependent. When interviewed after discharge, he described bed rest as "unbearable" and walking while ventilator-dependent as "wonderful" and "not uncomfortable."

The present study found that implementation of a step-wise early mobility protocol resulted in more physical therapy sessions, shorter ICU and hospital stays, and, importantly, no adverse events. Although there was no significant difference in costs, the absolute difference was less for the mobility group. The authors attribute the benefits they describe to several factors, including the step-wise protocol and delivery by an independent multidisciplinary team (physical therapist, critical care nurse, nursing assistant). The team began passive range of motion when the patient was unconscious and, freed from other responsibilities, was able to insure that sessions were delivered as prescribed.

Bed rest has known detrimental effects that include changes in muscle fibers, inflammatory markers, and metabolic parameters. Laboratory studies have demonstrated insulin resistance and microvascular dysfunction after 5 days of bed rest in healthy volunteers.[1] Findings of this and other studies suggest the need for a protocol-driven focus in ICU patient care that includes target sedation levels, daily sedation interruption, daily assessment of weaning readiness, and mobility therapy with the latter directed by an evidence-based protocol that identifies who to enroll, when to begin, and when to progress through various levels culminating in ambulation, if possible. ■

Reference

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Straining to Predict Fluid Responsiveness

ABSTRACT & COMMENTARY

By Andrew M. Luks, MD

Synopsis: *This prospective clinical study demonstrates that arterial pressure changes during a 10-second Valsalva maneuver can be used to predict fluid responsiveness in spontaneously breathing, non-intubated patients.*

Source: Monge García MI, et al. Arterial pressure changes during the Valsalva maneuver to predict fluid responsiveness in spontaneously breathing patients. *Intensive Care Med* 2008 Oct 2; Epub ahead of print.

Despite the prominent role that volume challenges play in the management of hypotensive patients, we lack simple, reliable methods to determine which patients will respond to such challenges. Monge Garcia and colleagues sought to address this problem by investigating whether a Valsalva maneuver could predict volume responsiveness in spontaneously breathing patients.

The authors studied patients in a multidisciplinary intensive care unit (ICU) at a single institution who had radial artery catheters in place and were deemed to require fluid administration for hypotension, tachycardia, or oliguria. Patients were excluded if they had arrhythmias, a history of syncope, or could not execute satisfactory Valsalva maneuvers. After obtaining baseline data, including measurement of the stroke volume index (SVI) using a FloTrac™ sensor connected to the arterial line, subjects were placed in the supine position and asked to perform a 10-second Valsalva maneuver during which they maintained a constant expiratory pressure of 30 cm H_2O.

Central venous pressure, arterial pressure, and airway pressure were monitored continuously before, during, and after the maneuver. These data were used to calculate two primary variables including: 1) Valsalva pulse pressure variation (ΔVPP), the percent variation between the highest pulse pressure during Phase 1 of the Valsalva pressure response and the lowest pulse pressure during Phase 2, and 2) Valsalva systolic pressure variation (ΔVSP), the percent variation between the highest systolic pressure during Phase 1 and the lowest systolic pressure during Phase 2. Subjects were then administered a 500 mL bolus of 6% hydroxyethylstarch over 30 minutes, after which time the Valsalva maneuver and hemodynamic measurements were repeated. Patients were labeled as being volume responders if the SVI increased by > 15% following the fluid bolus. A variety of statistical analyses were then used to compare hemodynamic responses between responders and non-responders.

Of the 30 patients who participated in the study, there were 19 responders and 11 non-responders. It is important to note that prior to volume expansion, mean systolic blood pressures in the responders and non-responders were over 120 mm Hg while mean diastolic blood pressures were roughly 60 mm Hg. These average pressures did not change with volume expansion in either the responders or the non-responders. There were positive linear correlations between volume expansion-induced changes in the SVI and pre-infusion values of ΔVPP ($r^2 = 0.71$; $P < 0.0001$) and ΔVSP ($r^2 = 0.60$, $P = 0001$). There was no correlation between pre-infusion CVP and changes in SVI. A threshold ΔVPP of 52% predicted fluid responsiveness with a sensitivity of 91% and specificity of 95%. The positive and negative predictive values were 91% and 95%, respectively. A ΔVSP of 30% of greater predicted fluid responsiveness with a sensitivity of 73% and a specificity of 90%. ■

■ COMMENTARY

Critical care clinicians repeatedly face the question of whether to administer fluids or vasopressors to hypotensive patients, but lack reliable means for determining which strategy is indicated for a particular patient. Static measures of volume status such as CVP and pulmonary capillary wedge pressure have proven to have little utility in this regard, while other proposed tactics such as passive leg raising are infeasible because they require echocardiographic measures of left ventricular outflow to determine whether the patient is in fact volume responsive.[1] On the surface, the notion of using a Valsalva maneuver to predict volume responsiveness is very appealing. It is inexpensive, simple to perform, and the protocol described by Monge Garcia and colleagues does not require complicated measurement tools such as echocardiography as part of the formal assessment.

Unfortunately, the trial described above falls short in many important respects, and does not tell us whether this is a valid tool for determining volume responsiveness in our patients. First, even though hypotension is perhaps the most common reason for which we must decide whether to give fluids or vasopressors, the patients in this study were far from hypotensive, with mean blood pressures in the 120/60 mm Hg range prior to the volume infusion. As a result, we have no idea if this tactic has any predictive capability in the patients in whom we are most concerned about its utility. Second, to apply this tactic, patients must be cooperative and able to execute a 10-second Valsalva maneuver. Leaving aside the fact that most true Valsalva maneuvers require a longer duration expiratory pressure hold than 10 seconds, many if not most of the patients in the ICU in whom we want to assess volume responsiveness are not able to complete Valsalva maneuvers because they are either intubated or have pain, altered mental status, or other problems that limit patient cooperation.

Finally, there is an important item in the study protocol that limits the study's applicability. Rather than measuring hemodynamic responses to crystalloid administration, the study authors used 6% hydroxyethylstarch for volume resuscitation. Even before recent data suggested volume resuscitation with hydroxyethylstarch is associated with adverse side effects such as acute renal failure and increased need for renal

replacement therapy,[2] volume resuscitation with colloid solution was uncommon in many ICUs. Because of this protocol issue, we do not know whether the Valsalva maneuver predicts hemodynamic responses to the more commonly used crystalloid solutions. Clinicians who use such solutions for volume resuscitation should not rely on this maneuver to predict volume responsiveness until further studies address this limitation. ■

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Rapid Response Team Did Not Reduce Hospital-Wide Codes or Mortality

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *With the largest cohort and longest follow-up yet reported, this prospective single-center study found that implementing a rapid response team reduced codes outside the ICU, but had no effect on either hospital-wide code rates or overall patient mortality.*

Source: Chan PS, et al. Hospital-wide code rates and mortality before and after implementation of a rapid response team. *JAMA* 2008;300:2506-2513.

CHAN AND ASSOCIATES PERFORMED A PROSPECTIVE before-and-after cohort study of the effects of implementing a rapid response team (RRT) in a 404-bed tertiary-care academic hospital in Kansas City, MO. They tracked cardiac arrests (codes) both in and out of the ICU as well as overall hospital mortality during two 20-month periods, January 2004 through August 2005 and January 2006 through August 2007. The intervention — implementation of a 3-member ICU-based RRT and an extensive educational effort for ward staff — took place from September through December 2005. Patients were thus enrolled in the study during the same seasonal time periods before and after the intervention. The primary outcome measures were hospital-wide code rates and mortality. The authors undertook extensive measures to adjust for pre-intervention trends and to look for potential confounders that might affect the study variables.

The study included 24,193 patient admissions in the pre-RRT period and 24,978 patient admissions in the post-RRT period. There were clinically small but statistically significant differences in the two populations: Patients admitted during the post-intervention study interval were slightly older, more likely to be male, and more likely to be African-American, and the case-mix estimate was slightly higher. Post-intervention there were 376 RRT activations, for altered mental status (27%), tachycardia (23%), tachypnea (13%), hypotension (12%), and other a priori-determined triggers. Forty-six percent of RRT episodes resulted in transfer to a higher level of care (ICU 41%, telemetry 4%, operating room, or other procedure 1%).

After RRT implementation, non-ICU codes decreased (adjusted odds ratio [AOR], 0.59; 95% confidence interval [CI], 0.40-0.89) relative to ICU codes (AOR 0.95; 95% CI, 0.64-1.43; $P = 0.03$ for interaction), but there was no change in the rate of hospital-wide codes (AOR 0.76; 95% CI, 0.57-1.01). Hospital-wide mortality did not differ between the pre- and post-intervention periods (3.22 vs 3.09 per 100 admissions; AOR 0.95; 95% CI, 0.81-1.11; $P = 0.52$). A careful search for response team undertreatment or underuse that might have affected the mortality findings revealed very few instances.

■ COMMENTARY

This large single-institution study showed that RRT implementation was not associated with reductions in hospital-wide code rates or mortality, although it did document a reduction in codes outside the ICU. One might suggest that, had they included just a few more patients, the small observed differences would have reached statistical significance. However, using post-hoc power calculations the authors determined that, based on the differences observed, a pre-intervention and post-intervention population of 148,000 patients during each period would have been required to have 80% power to detect a 5% mortality reduction at the $P = 0.05$ level.

The authors discuss several possible reasons for their failure to demonstrate improved survival and reduced hospital-wide code rates after RRT implementation in their hospital. One is that the RRT tended to be called for patients who were not, in fact, about to code, and that those who did go on to cardiopulmonary arrest could not have been helped. Another is that patients triaged by the RRT to the ICU received heightened

surveillance by unit staff, such that when they did arrest preparations had been made and a hospital-wide code did not have to be called. A third is that many patients initially treated by the RRT were subsequently made DNR (do-not-resuscitate) as a result of that interaction. As the authors note, it may be that the RRT episode catalyzed end-of-life care discussions in patients that might not otherwise have taken place. However, based on the observed code case-fatality rates prior to implementing the RRT, the authors calculated that as many as 59 more hospital-wide codes would have occurred if the 73 RRT patients who subsequently were made DNR had not been seen by the RRT.

A fourth possible reason for the RRT's failure to improve hospital-wide mortality might be a higher prevalence of DNR status during the second part of the study. Data were not available to the investigators on the numbers of patients designated DNR during the different study periods. Of course, it may also be that no reductions in hospital-wide code rates or mortality occurred after implementing the RRT because such teams do not in and of themselves actually affect these outcomes.

Following studies showing that many codes occur after hours of deterioration that could potentially have been detected and preventive actions taken, the Institute for Healthcare Improvement recommended that hospitals implement RRTs as one of the 6 strategies of the 100,000 Lives Campaign.[1] This de facto mandate sent hospitals scrambling nationwide to create, implement, and track the results of RRTs, and a number of before-and-after studies have concluded that these teams both reduce the number of codes and save lives.[2] However, while the premise for RRTs appeared sound, the evidence base substantiating their effectiveness has been called into question.[3,4] Given the prevalence of medical error, practice variation, and poor adherence to evidence-based practice guidelines, there can be little doubt that better care results in better outcomes. However, this new study will hardly be reassuring to the advocates of RRTs as a means for improving overall quality of health care in hospitals. ■

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CME / CNE Questions

40. Which of the following statements is *true* regarding the relative efficacy of linezolid and vancomycin in the treatment of MRSA VAP?
- a. Linezolid is associated with a higher rate of microbiologic failure than vancomycin.
- b. Linezolid is associated with longer hospital and ICU length of stay than vancomycin.
- c. Linezolid is associated with a non-statistically significant decrease in mortality compared to vancomycin.
- d. Linezolid is associated with a statistically significant increase in adverse events compared to vancomycin.

41. Hospitals with a dedicated ICU clinical pharmacist also had which of the following?
- a. Lower mortality
- b. Shorter ICU length of stay
- c. Lower total Medicare charges
- d. All of the above

42. Mobility therapy implemented in a medical ICU:
- a. resulted in improved outcomes but higher costs.
- b. significantly reduced the incidence of VAP.
- c. significantly reduced the incidence of deep vein thrombosis.
- d. resulted in two cases of accidental extubation.
- e. resulted in a shorter ICU and hospital length of stay.

43. Pulse pressure variation during a 10-second Valsalva maneuver predicts hemodynamic response to administration of 6% hydroxyethylstarch.
- a. True
- b. False

44. In the study by Chan et al on the effects of implementing a rapid response team in their large tertiary-care hospital, which of the following was found?
- a. A reduction in the number of codes outside the ICU
- b. No change in the number of hospital-wide codes
- c. No change in hospital mortality
- d. All of the above

Answers: 40. c, 41. d, 42. e, 43. a, 44. d.

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.

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*.

How Best to Control Hypertension?

In this issue: Drug combinations for hypertension; tenecteplase for out-of-hospital cardiac arrest; CAM most commonly used for back, neck, and arthritis pain; FDA Actions.

Combination therapy for hypertension

What's the best drug combination with an ACE inhibitor for treatment of hypertension in patients at risk for cardiovascular disease? Current guidelines recommend a diuretic, as witnessed by the number of ACE inhibitor/diuretic combination products that are currently marketed. However, a new study suggests that the calcium channel antagonist may be a better selection than a diuretic. Researchers from several medical schools in the United States and Sweden randomized 11,506 patients with hypertension who were at high risk for cardiovascular events to receive treatment with either benazepril plus amlodipine or benazepril plus hydrochlorothiazide. The primary endpoint was a composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. The average patient was 68 years old at entry and the group included patients with a history of ischemic heart disease, peripheral vascular disease, stroke, LVH, and diabetes. The study was terminated early after 3 years when it was found that the benazepril/amlodipine group had a significantly lower risk of the primary endpoint: 9.6% vs 11.8% (hazard ratio 0.80; 95% confidence interval, 0.72-0.92; $P = 0.002$). This represents a 2.2% absolute risk reduction and a 19.6% relative risk reduction in the benazepril/amlodipine group vs benazepril/hydrochlorothiazide. The authors conclude that the combination of benazepril/amlodipine is superior to benazepril/hydrochlorothiazide in reducing cardiovascular events in patients with hypertension who are at risk (Jamerson K, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high risk patients. *N Engl J Med* 2008;359:2417-2428). An accompanying editorial from the chair of the seventh report of the Joint National Committee on hypertension suggests it is time to re-examine the recommendation of initial therapy with a thiazide-type diuretic. He also states, however, that regardless of the drugs chosen for treatment of hypertension, the most important factor is reducing blood pressure to goal levels (Chobanian AV. Does it matter how hypertension is controlled? *N Engl J Med* 2008;359:2485-2488).

A survival benefit with tenecteplase?

Thrombolytic therapy during out-of-hospital cardiac arrest does not improve outcomes according to a new study. There has been considerable interest in thrombolytic therapy during cardiopulmonary resuscitation since it has been shown that 70% of these arrests are due to acute myocardial infarction or pulmonary embolism. European researchers randomized 1050 patients with witnessed out-of-hospital cardiac arrest to tenecteplase or placebo during cardiopulmonary

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resuscitation. The primary endpoint was 30-day survival and the secondary endpoints were hospital admission, return of spontaneous circulation, 24-hour survival, survival to hospital discharge, and neurologic outcomes. The trial was discontinued early when it was found that there was no survival benefit with tenecteplase. Thirty-day survival was 14.7% with tenecteplase and 17% with placebo. Secondary outcomes similarly showed no benefit from tenecteplase. The authors conclude that when tenecteplase was used during advanced life support for out-of-hospital cardiac arrest there was no improvement in outcomes in comparison to placebo (Bottiger BW, et al. Thrombolysis during resuscitation for out-of-hospital cardiac arrest. *N Engl J Med* 2008;359:2651-2662).

CDC report on CAM use

There is a 40% chance that your patients are using complementary and alternative remedies according to new report from the Centers for Disease Control & Prevention. Not including vitamins and minerals, the use of a complementary and alternatives medicine (CAM) in adults and children has increased in the last 5 years. Treatments include non-vitamin, non-mineral natural products (fish oil, flaxseed oil, echinacea), chiropractic or osteopathic manipulation, deep breathing exercises, massage, and meditation. Children are also using alternative treatments, especially if their parents use them. Despite lack of evidence of efficacy, echinacea is the most common remedy used by children. In adults, use of CAM treatments for URIs is actually down, perhaps indicating better patient education. Back pain, neck pain, and arthritis pain are the most common reasons why people turn to CAM, according to this recent survey. These results point out the need to query patients about the use of complementary and alternative medicines.

FDA Actions

The FDA is requiring a boxed warning on sodium phosphate bowel-cleansing products because of the risk of acute phosphate nephropathy associated with use of these products. Sodium phosphate cleansing products are most commonly used as bowel preparation for procedures such as colonoscopy. According to the warning, the products Visicol® and OsmoPrep® should be used with caution in people older than age 55; those suffering from dehydration, kidney disease, colitis, or delayed bowel emptying; and people taking other medications that may affect kidney function. These products should also not be used in conjunction with other oral laxatives containing sodium phosphate, and over-the-counter products, such as Fleet® Phospho-Soda®, should also be used with caution if given in a high dose to the patient population at risk.

The FDA is requiring a warning on all anti-epileptic drugs regarding the risk of suicidal thoughts and behavior. The warning is based on review of nearly 200 studies that showed that patients on anti-epileptic drugs were at almost twice the risk of suicidal behavior or thoughts compared to patients on placebo. Along with the warning, the agency is also requiring a Medication Guide for patients as part of its Risk Evaluation and Mitigation Strategy. Over 20 drugs will be required to change their labeling including the commonly used agents phenytoin, carbamazepine, divalproex, gabapentin, lamotrigine, primidone, and topiramate.

The FDA is considering a ban on the long-acting beta agonists salmeterol (Serevent®) and formoterol (Foradil®) for the treatment of asthma. An expert committee comprised of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee voted unanimously to withdraw the indication for the treatment of asthma for the two drugs based on evidence from meta-analyses showing increased risk of death associated with use of long-acting beta agonist when not paired with a steroid inhaler. The committee did not vote to ban Advair® or Symbicort®, inhalers that combine a long-acting beta agonist with a steroid. If the FDA follows the subcommittee's recommendations, the drugs would no longer be indicated for treatment of asthma but would remain on the market to treat chronic obstructive pulmonary disorders. The FDA has not indicated when it will act on the subcommittee's recommendations.

The FDA has approved fenofibric acid (Trilipix™) for use with a statin for the treatment of dyslipidemia. This is the first fibrate approved for use with statins. The approval is based on a large trial in which the drug was used in combination with rosuvastatin (Crestor®), atorvastatin (Lipitor®), and simvastatin (Zocor®). There have been safety concerns about using fibrates and statins together, particularly gemfibrozil, but the newer generation fibrates appear safer. Abbott, the manufacturer of Trilipix, is collaborating with AstraZeneca to develop a fenofibric acid/rosuvastatin fixed combination product within the next year. ■