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

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

Use of Normal Saline Instillation with Suctioning: The Debate Continues

ABSTRACT & COMMENTARY

By Ruth Kleinpell, PhD, RN

Director, Center for Clinical Research and Scholarship, Rush University Medical Center; Professor, Rush University College of Nursing, Chicago

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

Synopsis: *This randomized clinical trial compared 130 mechanically ventilated patients who received 8 mL instillation of isotonic saline before tracheal suctioning to a control group of 132 patients who did not in a medical surgical intensive care unit (ICU) in an oncology hospital and found a decrease in the incidence of ventilator-associated pneumonia (VAP) in the saline instillation group. No differences were found in the incidence of atelectasis on daily chest radiography and endotracheal tube occlusions.*

Source: Caruso P, et al. Saline instillation before tracheal suctioning decreases the incidence of ventilator-associated pneumonia. *Crit Care Med* 2009;37:32-38.

THE USE OF NORMAL SALINE INSTILLATION WITH SUCTIONING HAS been debated over the years due to uncertainty about the benefits of use. Caruso and colleagues assessed the use of the instillation of 8 mL of saline before tracheal suctioning and compared VAP rates among control and treatment patients receiving mechanical ventilation for > 72 hours who had an orotracheal or tracheotomy tube. VAP rates diagnosed based on clinical suspicion and confirmed by bronchoalveolar lavage quantitative culture were compared between the groups. The rate of clinically suspected VAP was similar in both groups, while the incidence of microbiologically proven VAP was significantly lower in the saline group ($P = 0.008$).

COMMENTARY

The instillation of normal saline prior to endotracheal suctioning was acknowledged as a common clinical practice several decades

ago. However, research over the past 2 decades has demonstrated adverse physiological effects with the use of normal saline instillation including decreases in oxygen saturation and desaturation,[1-9] increased heart rate,[3,6,8] risk of infection due to dislodgement of bacterial colonies,[10] and subjective patient reports of pain, anxiety, and dyspnea.[11,12] As a result of the evidence from a number of research studies, the routine use of normal saline instillation with suctioning has not been a recommended practice for mechanically ventilated patients. A recent clinical evidence review identified that collectively the research studies examining normal saline instillation provided class III evidence of adverse physiological and psychological effects and support against the routine use of normal saline with suctioning.[13]

The findings by Caruso and colleagues demonstrated lower rates of VAP found in those patients randomized to normal saline instillation before suctioning. These results are contrary to the research evidence that demonstrated a variety of adverse effects of saline instillation with suctioning. However, the results of the study must be interpreted with caution due to a number of limitations, including the use of an oncology population that differs from general ICU patients in terms of incidence of VAP, antibiotic pretreatment, immunosuppression, and mortality rates.[14] Additionally, independent variables with clinical relevance, including antibiotic treatment in the groups, immunosuppression, and age, were excluded as confounding factors.[14] It is also unclear as to whether the researchers controlled for other standard interventions to avoid VAP such as oral care, aspiration of subglottic secretions, and maintenance of cuff pressure on the endotracheal tube.[13] While the results of the study by Caruso and colleagues did demonstrate decreased rates of VAP in those patients randomized to receive normal saline instillation prior to suctioning, it is evident that additional research is needed before this practice is recommended for routine use in ICU patients, especially as the research evidence base had not supported continuation of this practice. ■

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Please call **Paula Cousins,** Senior Managing Editor, at (404) 262-5468.

Neuromuscular Weakness After ARDS

ABSTRACT & COMMENTARY

By Saadia R. Akhtar, MD, MSc

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

Synopsis: *This secondary analysis of a prior prospective randomized controlled trial of methylprednisolone vs placebo for persistent ARDS reveals that although ICU-acquired neuromyopathy is common after ARDS, and associated with worse clinical outcomes, methylprednisolone use does not appear to increase the risk.*

Source: Hough CL, et al. Intensive care unit-acquired neuromyopathy and corticosteroids in survivors of persistent ARDS. *Intensive Care Med* 2009;35:63-68.

HOUGH ET AL SET OUT TO DETERMINE INCIDENCE AND outcomes of early neuromyopathy in patients with persistent acute respiratory distress syndrome (ARDS), and to evaluate the association of neuromyopathy with the use of methylprednisolone in this population. To achieve this aim, they undertook a secondary analysis of a prospective randomized controlled trial of methylprednisolone in late ARDS (LaSRS).[1]

Twenty-five ICUs took part in LaSRS. Eligible patients were > 18 years old and at day 7-28 after the onset of ARDS. Enrolled subjects received methylprednisolone or equivalent placebo as follows: 2 mg/kg IV bolus, then 0.5 mg/kg every 6 hours for 14 days, then 0.5 mg/kg every 12 hours for 7 days, then tapered off over 2-4 days. Chart abstraction was used for data collection; neuromyopathy was identified by notation of "myopathy," "neuropathy," "myositis," "paralysis," or "unexplained muscle weakness." For this secondary analysis, Hough et al evaluated early neuromyopathy, defined as the above findings detected within the first 28 days of entry into LaSRS. The other eligibility criterion was survival to 60 days after enrollment or to hospital discharge. Patients with neuromyopathy prior to admission or entry into LaSRS were excluded for the analysis of association between methylprednisolone and neuromyopathy.

Of 180 patients in LaSRS, 128 (63 in treatment group; 65 in placebo group) were eligible for this analysis. Forty-three (34%) of these patients had neuromyopathy. (Interestingly, only 8 were reported as serious adverse events of neuromyopathy for LaSRS.) Compared to those without neuromyopathy, these 43 subjects had higher serum glucose levels and a trend towards worse oxygenation. They also had longer duration of mechanical ventilation (17 vs 11 days), higher likelihood of re-intubation (23% vs 10%), and longer time to return home (56 vs 34.5 days). After excluding the 6 patients with neuromyopathy present prior to enrollment in LaSRS, the authors found no increased risk of neuromyopathy in the methylprednisolone group (odds ratio, 1.5; 95% confidence interval, 0.7-3.2).

■ COMMENTARY

It is clear that neuromuscular weakness of some sort is a fairly common problem for critically ill patients (with or without ARDS) and may persist for months or longer following the initial ICU stay. A variety of associations has been identified in prior studies.[2,3] However, much remains unknown about this complication. Is it one single entity? How can we more clearly define this (these) condition(s)? What is the true incidence? What are actual causal factors vs associations? What physiological and/or biochemical mechanisms underlie neuromyopathy in critical illness? How can risk be predicted? What simple screening tools can be devised? How can risk be reduced?

Hough et al's work reaffirms the relatively high incidence of neuromyopathy in critically ill patients. It also re-demonstrates interesting associations between neuromyopathy and certain predisposing factors (such as hyperglycemia), and also between neuromyopathy and outcomes (duration of ventilation, for example).

The lack of association between methylprednisolone and neuromyopathy in this analysis is surprising. That may be a reflection of the limitations of the study. First, the relatively small sample size restricts the statistical power to detect differences in outcomes between the study and placebo group. Second, reliance on chart notations regarding weakness makes it likely that case definition is incomplete and imprecise; a significant number of cases may be missed, thus the incidence and associations reported may be inaccurate. Alternatively, the lack of association could be explained by as-yet-unknown dose- or population-dependent effects of methylprednisolone on the development of neuromyopathy.

Although this study by Hough and colleagues may not provide a great deal of new information, its value lies in adding further observational data to the current scant body of knowledge, raising some new questions, and keeping the critical care community's attention on this important and complex topic so that we may continue to consider and investigate it. ■

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Selective Digestive Tract or Oropharyngeal Decontamination and ICU Outcomes

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *This large multicenter study in 13 Dutch ICUs found that regimens of both systemic and limited oropharyngeal decontamination were associated with significant reductions in 28-day mortality when compared with standard care, although the differences were apparent only after adjustment for covariants and the overall prevalence of antibiotic-resistant organisms in the participating institutions was very low.*

Source: de Smet AM, et al. Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med* 2009;360:20-31.

THE EFFECTS OF SELECTIVE DIGESTIVE TRACT DECONTAmination (SDD) and selective oropharyngeal decontamination (SOD; SDD without systemic antibiotics), which are measures for preventing ICU-acquired infections, on patient outcomes and microbial resistance patterns remain unsettled and controversial. This study, carried out in 13 ICUs in the Netherlands in 2004-2006, sought to determine the effects of SDD and SOD on 28-day mortality in comparison with standard therapy. A cluster-randomization, crossover design was used, in which all patients in a given ICU received the same study regimen during a fixed interval, with all 3 regimens being used in each unit in random order with intervening washout periods. Patients admitted to the ICU whose physicians expected them to require more than 48 hours of mechanical ventilation or to remain in the ICU for at least 72 hours were included.

SDD consisted of 4 days of intravenous cefotaxime plus the topical application of a mixture of tobramycin, colistin, and amphotericin B to the oropharynx and stomach. SOD consisted of the same regimen minus the intravenous cefotaxime. When patients were receiving SDD or SOD, other antimicrobial use was discouraged. Surveillance cultures of endotracheal aspirates and oropharyngeal and rectal swabs were obtained on admission and twice weekly. In the standard care group, no routine surveillance cultures were obtained, and there were no restrictions on antimicrobial use by the patients' physicians.

During the 27-month study period, 5939 patients were enrolled, with 2045 receiving SDD, 1904 SOD, and 1990 standard care. This represented 89% of all eligible patients admitted to the study ICUs during that time. Overall 28-day mortality was 27%. Compared to the mortality rate of 27.5% in the standard care group, that in the SOD group was 2.9% lower at 26.9% (relative reduction, 11%; number needed to treat, 34), and that in the SDD group was slightly lower at 26.6% (3.5% absolute reduction; 13% relative reduction; number needed to treat, 29). With model adjustment for age, sex, APACHE II score, intubation status, and other factors, the odds ratio for death in the first 28 days after ICU admission was 0.86 (95% confidence interval [CI], 0.74-0.99) in the SOD group, and 0.83 (95% CI, 0.72-0.97) in the SDD group, as compared to that for patients in the standard care group.

ICU-acquired bacteremia due to *Staphylococcus aureus*, non-lactose-fermenting gram-negative rods, and *Enterobacteriaceae* was significantly reduced in patients receiving either SOD or SDD. No instances of methicillin-resistant *S. aureus* (MRSA) were documented in the 5939 study patients. *Clostridium difficile* was detected in 15 patients (0.8%) in the standard care group, in 5 (0.3%) in the SOD group, and in 9 (0.4%) in the SDD group. For all 3 groups, the rate of antibiotic resistance in bacterial cultures was less than 5%; these rates tended to be lower in the SOD and SDD groups than in the standard care group.

■ COMMENTARY

Despite a number of (mainly European) studies concluding that SDD or SOD reduces the incidence of hospital-acquired infections and improves certain patient outcomes, this therapy has not been recommended in current widely used guidelines,[1] and has not been widely adopted in American ICUs. This new study, while large in scope and carefully conducted, seems unlikely to change this situation despite its significantly better outcomes with SDD or SOD as compared with standard

care. One reason I am hesitant to recommend SDD or SOD for ICU patients in this country is the uncertain generalizability of this study's results with respect to antimicrobial resistance. The low incidence of antimicrobial resistance in surveillance cultures, the very low incidence of *C. difficile*, and the complete absence of MRSA, are in striking contrast to what is found in most North American ICUs. One would expect that the higher the prevalence of these things in the unit, the less likely SDD or SOD would reduce infection rates and improve patient outcomes; in such circumstances, the likelihood of increased rates of resistance would also be a concern.

Debate will likely continue about the potential value of SDD and/or SOD in reducing ventilator-associated pneumonia and other ICU-acquired infections. This study fuels this debate but does not convince me that this intervention should be adopted in my ICU. ■

Reference

1. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171:388-416.

Greater Use of Clinical IT in Hospital Is Associated with Better Patient Outcomes

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In this study of physician use of clinical information technology in relation to 4 common diagnoses in 41 urban hospitals in Texas, inpatient outcomes were better the more extensive the use of computerized order entry, test results, physician charting, and decision support. Increased use of IT was also associated with significantly lower costs for all hospital admissions.*

Source: Amarasingham R, et al. Clinical information technologies and inpatient outcomes: A multiple hospital study. *Arch Intern Med* 2009;169:108-114.

To determine whether relationships existed between the use of clinical information technology (CIT) and measures of patient outcomes, Amarasingham and colleagues conducted a cross-sectional study of urban hospitals in Texas using the questionnaire-based Clinical Information Technology Assessment Tool, which measures a hospital's level of automation based on the interactions of its physicians with the information system. They sent surveys to 7432 randomly selected physicians practicing at 72 hospitals in 10 targeted urban areas in Texas, and included in the data analysis only hospitals from which 5 or more attending physicians returned the questionnaire. They then merged the results with data from a comprehensive hospital claims data file on 167,233 patients older than age 50 who were admitted to those hospitals with any of 4 diagnoses: myocardial infarction, congestive heart failure, coronary artery bypass grafting, and pneumonia. Dependent variables studied in relation to CIT use were inpatient mortality, complications, costs, and length of stay. The aspects of hospital CIT examined were computerized order entry, test results, automation of notes and records, and decision support.

Sufficient responses for inclusion were received from 41 (58%) of the hospitals. Considering the 4 targeted medical conditions together, a 10-point increase in the automation of notes and records was associated with a 15% decrease in hospital mortality (adjusted odds ratio [AOR], 0.85; 95% confidence interval [CI], 0.74-0.97). Hospitals with higher scores on computerized order entry had 55% decreases in hospital mortality for coronary artery bypass grafting, and 9% decreases for myocardial infarction. Higher usage of computerized decision support was associated with a 16% decrease in complications (AOR, 0.84; 95% CI, 0.79-0.90) for all 4 diagnoses. In addition, higher scores on computerization of test results, order entry, and decision support were associated with lower costs per hospital admission (reductions of $110, $132, and $538, respectively; $P < 0.05$). Thus, hospitals with automated notes and records, order entry, and clinical decision support had fewer complications, decreased inpatient mortality, and lower costs.

■ COMMENTARY

While perhaps not surprising, the results of this study provide solid support for the concept that CIT in hospitals is a positive development. An important strength of this study is that the findings were derived not just on the basis of which hospitals had more extensively developed CIT systems, but from data on actual use of these systems by the physicians caring for patients in those hospitals—or, at least, on how those physicians indicated on a questionnaire that they used them.

Of course, the fact that outcomes were better in hospitals with more extensive use of CIT does not establish

causality. In fact, it is very likely that, overall, hospitals with more highly-developed CIT systems are also better at many other things, such as staff recruitment and training, physician continuing education, interdisciplinary interaction, infection control, and provision of up-to-date diagnostic and therapeutic technology. Nonetheless, it is also likely that increasing integration of CIT into daily practice is an important contributor to higher standards of care.

This was not an ICU study, although all 4 of the included medical conditions involve care in the ICU for the majority of patients. One would expect that the advantages accruing from the use of CIT would be amplified in the ICU, where the numbers of assessments and intervention are greater, the quantity of data generated is far greater,[1] and the pace is faster in nearly all respects than that on the regular floors. ■

Reference

1. Manor-Shulman O, et al. Quantifying the volume of documented clinical information in critical illness. *J Crit Care* 2008;23:245-250.

Successful Implementation of a Model Designed to Increase Use of Patient Safety Measures

ABSTRACT & COMMENTARY

By Leslie A. Hoffman, PhD, RN

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

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

Synopsis: *A quality improvement initiative that included a new data collection tool and a "data wall" to display results increased use of patient safety interventions.*

Source: Krimsky WS, et al. A model for increasing patient safety in the intensive care unit: Increasing the implementation rates of proven safety measures. *Qual Saf Health Care* 2009;18:74-80.

THE GOALS OF THIS STUDY WERE FOURFOLD: 1) TO increase implementation rates of evidence-based interventions that have been shown to reduce ICU mortality and morbidity; 2) to design tools to promote team communication and team building; 3) to develop prompts that could be incorporated into an ICU progress note to promote consistent use of these measures; and 4) to provide "real time"' feedback regarding progress.

Subjects were two groups of 40 consecutive patients admitted to the Dartmouth Hitchcock Medical Center ICU before and after the quality improvement initiative. Three evidence-based interventions were identified as targets; prophylaxis against thromboembolic disease, prophylaxis against ventilator-associated pneumonia, and prophylaxis against stress ulcers. The project was led by a quality improvement work group consisting of two fellows, the ICU's clinical nurse educator, two ICU research nurses, the ICU pharmacist, and ICU dietitian. The group identified critical implementation steps, revised the ICU progress note to incorporate a checklist with prompts regarding need for these measures, and constructed a "data wall" that depicted actual vs target implementation rates. To determine compliance, the data collection method rated whether the selected interventions were indicated, ordered when indicated, and in place during the day and night shift.

The model resulted in improved rates of utilization and was credited with fostering a team-based culture to promote patient safety.

■ COMMENTARY

This project, as true of many others, prompted an increase in utilization of several measures that have been proven to impact patient safety. Prior to implementation, a hospital-wide quality assurance improvement initiative identified 5 preventable deaths over a 1-month period, providing the impetus for the project. Three of these deaths were directly attributed to failure to order deep venous thrombosis and/or stress ulcer prophylaxis. The system developed as a result of this quality improvement initiative was unique in two ways. Unlike approaches that defined success as delivery of the intervention, this project assessed whether the intervention was appropriate, ordered, and delivered as indicated over a 24-hour shift. Second, it incorporated a "data wall" that graphically displayed success (or lack thereof) in reaching target goals in a manner that was readily visible to all clinicians.

Prior studies have identified the extensive amount of information that must be reviewed and assimilated by ICU clinicians on a minute-to-minute basis. Although we know that interventions tested in this study are critical in ensuring patient safety, they can easily be overlooked if there are no prompts to serve as reminders. As

well, it appears important to create a visible reminder, such as the data wall, to provide a competitive stimulus to promote consistent adherence to guidelines. ■

Does Chest Physiotherapy Prevent Ventilator-Associated Pneumonia in Brain-Injured Patients?

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *This randomized controlled trial of routine chest physiotherapy, administered 6 times daily in patients with acute brain injury who required mechanical ventilation was unable to demonstrate any effect of this intervention on either the incidence of or the recovery from ventilator-associated pneumonia.*

Source: Patman S, et al. Physiotherapy does not prevent, or hasten recovery from, ventilator-associated pneumonia in patients with acquired brain injury. *Intensive Care Med* 2009;35:258-265.

PATMAN AND ASSOCIATES AT THE LUNG INSTITUTE OF Western Australia in Perth undertook this study to determine whether the routine, intensive administration of chest physiotherapy (PT) to mechanically ventilated patients with severe acute brain injury would prevent the occurrence of ventilator-associated pneumonia (VAP), or speed its resolution once it was present. They randomized 144 patients with acute brain injury from trauma, hypoxia, infection, stroke, or several other causes to receive either standard care or chest PT delivered 6 times daily. To be included, patients had to have an intracranial pressure monitor or drain, be mechanically ventilated, and have an initial Glasgow Coma Scale score of 9 or less. Patients who were hemodynamically or neurologically unstable, who required more than 80% oxygen or 10 cm H_2O of positive end-expiratory pressure, who were comfort-care-only, or who had any of several other features of critical instability were excluded. Chest PT consisted of positioning, manual hyperinflation, and airway suctioning, carried out 6 times in each 24 hours. If unilateral abnormalities were present on the chest X-ray, the affected side was positioned uppermost; sides were alternated in the absence of localizing findings. Each treatment, administered by a physical therapist, took about 30 minutes.

Patients were assessed for the development of VAP each day using the 6-part clinical pulmonary infection score (CPIS), and those with a score of 7 or higher underwent non-bronchoscopic catheter lavage ("mini-BAL"). Although an attempt to semi-quantitate the results was made (grading bacterial growth as "few," "moderate," or "many"), VAP was diagnosed if the mini-BAL culture was positive. In the supplementary electronic data repository for this article, the authors note that the CPIS was actually determined retrospectively for most of the patients.

The chest PT and control groups were well matched. There were 33 cases of VAP (23% overall) using the diagnostic criteria described, 14 (19%) in the treatment group and 19 (26%) in the control group ($P = 0.32$). No differences were detectable in any of the outcome variables studied with respect to chest PT vs standard care, either for the prevention of VAP or for its clinical course and resolution.

■ COMMENTARY

This study found no evidence that an intensive regimen of chest PT, administered to intubated, ventilated patients with severe acute brain injury who would be expected to be at high risk for developing VAP, had any effect on the incidence of this complication or on its rate of resolution. The study has several important limitations. VAP was not diagnosed quantitatively according to the recommendations of current guidelines—although this remains an area of controversy in critical care and similar criteria were employed for all enrolled patients. Because the incidence of VAP was lower than expected in both groups, the authors' second hypothesis (that chest PT hastened clinical recovery from VAP) could not really be tested. And the chest PT itself was somewhat different from that usually used in the United States.

The practice of PT in the ICU is quite different in Australia, where this study was performed, from that employed in North America, primarily because of the absence of respiratory therapists in the former. Consequently, physical therapists do much more chest physiotherapy, airway suctioning, and other respiratory therapy in Australia than in the United States. However, a recent study indicates that PT—including chest physiotherapy in many cases—is very widely used in American ICUs. Hodgin et al surveyed a sample of the membership of the American Physical Therapy Association about their practice of PT in the ICU.[1] Responses were received from 482 physical therapists (50% response rate, representing 49 U.S. states) who

worked in ICUs. Ten percent of the hospitals at which the respondents worked had established criteria for initiating PT in the ICU, although physical therapists routinely evaluated all ICU patients in only 1% of the hospitals.

Although the use of PT in patients with acute brain injury as defined in the study by Patman et al was not assessed, respondents to the Hodgin survey indicated that 87% of patients with strokes received routine physical therapy in the ICU; the odds ratio for receiving PT was 3.7 for patients with strokes in comparison to patients with the 3 included medical conditions. Patients with strokes were about as likely to receive chest PT as those with pneumonia, although they were much more likely to receive passive range-of-motion and positioning therapy. Thus, although accurate data are not available about the numbers of patients in U.S. ICUs with acute brain injury who are administered chest PT, it is safe to say that many of them do.

In the 1960s and early 1970s, inpatients in most U.S. hospitals were routinely administered intermittent positive-pressure breathing (IPPB) treatments, with or without aerosolized drugs, to expand the lungs and prevent pneumonia and other pulmonary complications. This was subsequently shown not only to be extraordinarily expensive, but also completely ineffectual in the huge majority of instances. In many ICUs, the IPPB treatments of the past have essentially been replaced by chest PT as a routine measure for pulmonary hygiene. Given the labor-intensiveness and expense of chest PT, as well as its potential for physiologic compromise and patient discomfort, we should re-think the practice in many ICUs of ordering it routinely for intubated patients, for those with abnormal chest X-rays, or in some cases for anyone with a history of cigarette smoking.

The use of bronchial hygiene measures, including chest PT, is an ideal area for implementation of a therapist-driven protocol,[2] which can increase the likelihood that chest PT will be helpful and reduce its use when it is not. The institution in which I practice has such a protocol. Physicians who are concerned about the adequacy of secretion clearance, or consider a particular patient at high risk for atelectasis or pneumonia, can order this protocol, under which a respiratory therapist evaluates the patient and initiates a therapy regimen tailored to that patient's needs; the effectiveness of the intervention is subsequently assessed so that it can be modified as needed or discontinued if ineffective. The study by Patman and colleagues does not support the routine use of chest PT for the purpose of preventing VAP, at least in the patient population investigated. However, physical measures for facilitating lung inflation and secretion clearance remain an important aspect of respiratory care in the ICU. ■

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2. Shrake KL, et al. Benefits associated with a respiratory care assessment-treatment program: Results of a pilot study. *Respir Care* 1994;39:715-724.

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.

CME / CNE Questions

1. Which of the following effects has been associated with the use of normal saline instillation prior to suctioning?

a. An increase in respiratory rate
b. An increase in endotracheal secretions
c. An increase in blood pressure
d. A decrease in oxygen saturation
e. A decrease in heart rate

2. In their study of neuromuscular weakness following ARDS, Hough et al found neuromyopathy in about what percentage of patients with persistent ARDS?

a. 0%
b. 15%
c. 34%
d. 52%
e. 100%

3. In the Dutch study of selective decontamination of the digestive tract or oropharynx, as compared with standard ICU care, which of the following differed from the situation in most ICUs in the United States?

a. The incidence of methicillin-resistant *Staphylococcus aureus*
b. The overall incidence of antimicrobial resistance
c. The incidence of *Clostridium difficile*
d. All of the above

Answers: 1. d, 2. c, 3. d.

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*.

Warfarin May Be First to Apply Pharmacogenetics

In this issue: Individualization of therapy with pharmacogenetics; the rate vs rhythm debate; the FDA's Risk Evaluation and Mitigation Strategy; FDA actions.

Individualization with pharmacogenetics

Get used to the word "pharmacogenetics" — the discipline of studying genetic variation and its effect on responses to drugs. Warfarin dosing may be one of the first clinical applications of pharmacogenetics as it now appears that genetic testing may help predict an individual patient's response to the oral anticoagulant. Warfarin dosing can vary as much as 10 times from individual to individual, and currently, slow titration with frequent testing is the only way to safely initiate therapy. A new study, however, uses pharmacogenetic testing to estimate the appropriate warfarin dose. Reviewing data from more than 4000 patients, algorithms were developed based on clinical variables only or clinical variables plus genetic information (CYP2C9 and VKORC1). Compared to algorithms employing clinical data alone, algorithms employing genetic information more accurately identified a larger proportion of patients who would require low-dose (49.4% vs 33.3%; $P < 0.001$) or high-dose warfarin (24.8% vs 7.2%; $P < 0.001$). The authors conclude that pharmacogenetic algorithms for estimating the appropriate initial dose of warfarin produces recommendations that are significantly closer to the required stable therapeutic dose than algorithms derived from clinical data alone or a fixed-dose approach, particularly for those that require 49 mg or more per week or 21 mg or less per week. (*N Engl J Med* 2009;360:753-764). Although pharmacogenetic testing is not yet widely available and may be difficult to obtain prior to initiating warfarin therapy, an accompanying editorial states "pharmacogenetics has the potential to increase benefit and reduce harm in people whose drug responses are not 'average.'" (*N Engl J Med* 2009;360:811-813).

The rate vs rhythm debate

Rate control vs rhythm control for atrial fibrillation continues to be debated with most of the evidence falling on the side of rate control in recent years, primarily because of adverse effects from anti-arrhythmics. A new drug may change that however. Dronedarone, a derivative of amiodarone, lowers the hospitalization rate and death rate in atrial fibrillation according to a new phase 3 study. More than 4600 patients with atrial fibrillation and one additional risk factor for death (diabetes, stroke, CHF) were randomized to dronedarone 4 mg twice a day or placebo. The primary outcome was first hospitalization due to cardiovascular event or death. After follow-up of 21 months, 30% of patients in the treatment group and 31% patients in the placebo group stopped the drug prematurely due to adverse events. The primary outcome occurred in 31.9% of patients in the dronedarone group vs 39.4% in the placebo group (hazard ratio, 0.76; 95% confidence interval,

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0.69-0.84; $P < 0.001$). Five percent (5%) of people died in the treatment group vs 6% in the placebo group ($P = 0.18$). Deaths from cardiovascular causes were 2.7% in the dronedarone group vs 3.9% in the placebo group ($P = 0.03$). The treatment group had higher rates of bradycardia, QT interval prolongation, nausea, diarrhea, rash, and increased creatinine levels. Dronedarone was not associated with higher rates of thyroid or pulmonary-related adverse events. The authors conclude that dronedarone reduced the risk of hospitalization due to cardiovascular events or death in patients with atrial fibrillation (*N Engl J Med* 2009;360:668-678). Dronedarone is not yet approved in this country, and is being evaluated for other cardiac arrhythmias as well as atrial fibrillation. A trial in heart failure (ANDROMEDA) was terminated early because of increased mortality associated with dronedarone (*N Engl J Med* 2008;358:2678-2687).

New rules for opioid prescribing

The FDA is considering new tightened restrictions on use of opioid drugs. Manufacturers of these drugs will be required to have a Risk Evaluation and Mitigation Strategy to ensure that "the benefits of the drugs continue to outweigh the risks." The affected opioids include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. This is in response to raising rates of misuse and abuse of these drugs as well as accidental overdoses, which have increased in the last 10 years. The agency plans to have a number of meetings later this year that will include patient groups, federal agencies, and other non-government institutions. Part of the strategy is to make sure that physicians prescribing these products are properly trained in their safe use.

In February, the American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel published clinical guidelines for the use of chronic opioid therapy and chronic noncancer pain. The guideline was commissioned because of the increased use of chronic opioid therapy for noncancer pain and the high risk for potentially serious harm associated with these drugs including opioid-related adverse effects. The guideline's recommendations include: Before initiating chronic opioid therapy (COT), clinicians should conduct a history, physical, and appropriate testing including assessment of risk for substance abuse, misuse, or addiction. A benefit-to-harm evaluation should be performed and documented before starting COT and on an ongoing basis for all patients on COT. Informed consent should be obtained when initiating therapy, and a continuing discussion with the patient regarding therapy should include goals, expectations, risks, and alternatives. Clinicians may consider a written COT management plan. Patients should be reassessed periodically including monitoring of pain intensity and levels of functioning.

For high-risk patients or those who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the plan of care. For patients at risk of addiction, mental health or addiction specialists should be consulted, and if aberrant drug-related behaviors continue, referral for assistance in management or discontinuation of COT should be considered. The guideline also deals with dose escalations, use of methadone, treatment of opioid-associated adverse effects, cognitive impairment associated with COT that may affect driving and workplace safety, use in pregnancy, and state and federal laws that govern the medical use of COT (*J Pain* 2009;10:113-130).

FDA Actions

The FDA has issued a public health advisory regarding the risk of progressive multifocal leukoencephalopathy (PML) associated with use of efalizumab (Raptiva®) for the treatment of psoriasis. Four cases have been reported (3 have been confirmed). The FDA is recommending that health care professionals monitor patients on efalizumab, as well as those who have discontinued the drug, for signs and symptoms of neurologic disease.

The FDA has reaffirmed its position regarding cholesterol-lowering drugs stating that "elevated amounts of low-density lipoprotein … are a risk factor for cardiovascular diseases … and that lowering LDL cholesterol reduces the risk of these diseases." The statement is in response to results from the ENHANCE trial, which indicated that there was no significant difference between simvastatin plus ezetimibe (Vytorin®) vs simvastatin alone (Zocor®) in reducing carotid atherosclerosis. There was, however, a greater reduction in LDL in the Vytorin group vs the Zocor group (56% reduction vs 39% reduction, respectively). The statement from the FDA suggests that the results of ENHANCE do not change the FDA's position that greater LDL lowering is beneficial, and recommends that patients currently on Vytorin or other cholesterol-lowering medications should not change their therapy. The update is available on the FDA's web site at www.FDA.gov. ■