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

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INSIDE

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Can We Accurately Predict Fluid Responsiveness?

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 non-randomized, prospective trial demonstrated that passive leg raising can be used to predict fluid responsiveness in non-intubated, spontaneously breathing patients with severe sepsis or acute pancreatitis.*

Source: Préau S, et al. Passive leg raising is predictive of fluid responsiveness in spontaneously breathing patients with severe sepsis or acute pancreatitis. *Crit Care Med* 2010;38:819-825.

PASSIVE LEG RAISING (PLR), A RAPIDLY REVERSIBLE MANEUVER that simulates rapid volume expansion by putting several hundred milliliters of fluid back into the circulation, has been shown to predict fluid responsiveness in mechanically ventilated patients. Préau and colleagues sought to determine whether the same maneuver could be used in spontaneously breathing patients and whether there were any differences between three potential means of assessing the hemodynamic response to the PLR: stroke volume changes measured by echocardiography, pulse pressure variation on arterial pressure monitoring, and Doppler flow measurements in the femoral artery.

The authors enrolled consecutive, non-intubated patients with sepsis or acute pancreatitis at a single center in France. Patients were eligible for participation if the attending physician decided to perform a fluid challenge based on the presence of signs of inadequate tissue perfusion including hypotension, decreased urine output, mottled skin, or tachycardia. Patients on non-invasive ventilation or those with poor echocardiographic images or high-grade aortic insufficiency were excluded. Enrolled patients were placed in the supine position. Systolic, diastolic, and mean arterial pressure

(SAP, DAP, MAP) as well as pulse pressure (PP) were measured using an arterial catheter while blood flow velocity in the femoral artery (VF) was assessed with continuous Doppler and stroke volume (SV) was measured with transthoracic echocardiography. The measurements were then repeated within 5 minutes of raising the patients' legs to 30°-45° relative to the trunk. Following a 5-minute period with legs back in the flat position, patients then received a 500 mL infusion of 6% hydroxyethylstarch over < 30 minutes and a final set of measurements was completed. Individuals whose SV rose > 15% following volume expansion (VE) were labeled as responders, while those with < 15% change in SV were labeled non-responders. Changes in each variable in response to PLR were then compared to changes observed following volume expansion. Observed changes were also compared between responders and non-responders.

Of 890 patients admitted to the ICU in the two-year study period, only 34 met inclusion criteria and had suitable echocardiographic windows to permit SV measurements, including 28 patients (82%) with severe sepsis and six (18%) with acute pancreatitis. In the entire group, PLR increased SV from 47 ± 14 to 50 ± 14 mL ($P < 0.01$) while VE increased SV from 47 ± 14 to 53 ± 15 mL. SV positively correlated with PP ($r^2 = 0.4$) and VF ($r^2 = 0.62$). Among the 14 patients (41%) determined to be VE-responders, SV, PP, and VF were significantly higher than in the non-responders and also showed positive and statistically significant correlations with SV changes seen following VE. A SV ≥ 10% predicted volume responsiveness with a sensitivity of 86% and specificity of 90%, while PP ≥ 9% (sensitivity 79%, specificity 85%) and VF ≥ 8% (sensitivity 86%, specificity 80%) were also found to be useful in this regard.

■ COMMENTARY

Just about every critical care physician has been at the bedside of a hypotensive patient and wondered whether to give fluids or start a vasopressor. A reliable tool for answering this question and predicting volume responsiveness remains one of the "holy grails" of critical care medicine. The clinician can always stand there and give more fluid to see if the patient is volume-responsive but in non-intubated patients this simple strategy may provoke worsening respiratory failure and create a need for intubation that may not have been there otherwise. Central venous pressure measurements are often relied upon to guide decisions, but studies have consistently shown that such static measures of preload are poor predictors of volume responsiveness. In the face of such issues, PLR and other "dynamic" measures have been proposed as an alternative means for guiding these decisions.[1]

At first glance, the technique sounds exceedingly simple. Place the patient in the supine position, raise their legs to 30°-45°, during which time about 300-500 mL of fluid reenters the circulation, and observe the response. The devil is in the details, however, as the response to PLR and, therefore the determination of volume responsiveness, is not made by simply looking at whether the patient's blood pressure improves, but rather requires the use of techniques such as echocardiography or esophageal Doppler monitoring to assess the hemodynamic response to the maneuver. These requirements limit the utility of PLR a great deal as clinicians may either lack the skills to do the measurements themselves or may not have access to the tools in the short time they have to make a decision about treating the hypotensive patient.

The study by Préau and colleagues moves PLR a bit closer to being a useful bedside technique because it demonstrates that PP changes on an arterial catheter correlate to a reasonable degree with echocardiographic measurements of the change in SV and, as a result, can be used as a surrogate measure of the hemodynamic response to PLR. However, while the study does move us closer, it does not get us all the way there. The authors only looked at non-intubated patients in their

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Questions & Comments

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study, a significant limitation when one considers the high percentage of patients with severe sepsis and acute pancreatitis who end up on mechanical ventilation. Further study will be needed in these patient groups using a PLR protocol similar to that used by Préau and colleagues before we can rely on this technique to guide our assessments of volume responsiveness. ■

Reference

1. Pinsky MR. Hemodynamic evaluation and monitoring in the ICU. *Chest* 2007;132:2020-2029.

Colistin and Acute Respiratory Failure

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *Colistin, a 50-year-old polymyxin antibiotic that recently has been reintroduced to treat multidrug-resistant hospital-acquired* Acinetobacter *or* Pseudomonas *pneumonia, can cause acute neuromuscular weakness and precipitate acute hypercapnic respiratory failure, as illustrated by this case report.*

Source: Wahby K, et al. Intravenous and inhalational colistin-induced respiratory failure. *Clin Infect Dis* 2010;50:e38-e40.

Wahby and colleagues in Detroit report the case of a 33-year-old woman with *Acinetobacter baumannii* pneumonia complicating a prolonged ICU stay after a peripheral blood stem cell transplant. The organism was resistant to all antibiotics except ampicillin-sulbactam (in very high concentrations) and colistin. After 5 days of intravenous colistin at 2.5 mg/kg every 12 hours (in the usual recommended dose range), the patient developed respiratory distress and was found to have severe acute respiratory acidosis, requiring intubation and mechanical ventilation. No other drugs or disease processes likely to have precipitated neuromuscular weakness were identified, and the patient improved within 24 hours after the colistin was switched to ampicillin-sulbactam. Extubated with a normal arterial PCO_2 after 5 days and transferred to the floor, she was begun on colistin by inhalation, 75 mg nebulized every 12 hours, in addition to the ampicillin-sulbactam. After 3 days on this regimen, hypercapnia was again noted, although the inhaled colistin was continued. Twenty-four hours later the patient was found unresponsive in severe acute respiratory acidosis, which again resolved after 3 days of mechanical ventilation after the inhaled colistin was stopped. The patient recovered from her acute illness and the neuromuscular weakness did not recur.

■ COMMENTARY

Colistin (also called polymyxin E) belongs to the polymyxin group of antibiotics, and first became available for clinical use in about 1960. It was given as an intramuscular injection for the treatment of gram-negative infections, but fell out of favor after aminoglycosides became available because of its adverse effects, principally nausea, vomiting, and nephrotoxicity. It later found wider clinical use as topical therapy as part of selective digestive tract decontamination, and in aerosolized form for patients with cystic fibrosis. More recently, a number of centers around the world have used colistin intravenously as a last-line therapy for otherwise pan-resistant ventilator-associated pneumonia (VAP), especially due to *Pseudomonas* and *Acinetobacter* species.[1]

An additional adverse effect of polymyxin antibiotics including colistin — one mostly forgotten as use of these agents largely disappeared in the 1970s — is acute neuromuscular weakness precipitating hypercapnic respiratory failure. Lindesmith et al in Denver reported a series of 11 patients with colistin-induced respiratory paralysis and acute hypercapnic respiratory failure.[2] Most of them also had underlying renal abnormalities (apparently absent in the present case) and had received the drug intramuscularly. As in this case, the weakness resolved quickly once the drug was stopped, with a mean duration of ventilatory support of 27.5 hours.

With aerosolized tobramycin used routinely for serious airway infections in patients with cystic fibrosis, and increasing use of nebulized colistin in this population, it should not be surprising that this agent would be tried in the treatment of VAP in non-cystic-fibrosis patients when the causative organism is resistant to other agents. Administration of colistin by aerosol, which is neither FDA-approved for this indication nor supported by data from controlled trials, appears to be occurring more frequently in the last few years.

Although acute neuromuscular paralysis due to aerosolized colistin has not previously been reported, the present case should alert ICU clinicians to its possibility. Colistin toxicity, whether the drug is administered parenterally or by nebulization, should be added to the list of potential causes for neuromuscular weakness in critically ill patients. ■

References

1. Linden PK, Paterson DL. Parenteral and inhaled colistin for treatment of ventilator-associated pneumonia. *Clin Infect Dis* 2006;43(Suppl 2):S89-S94.
2. Lindesmith LA, et al. Reversible respiratory paralysis associated with polymyxin therapy. *Ann Intern Med* 1968;68:318-327.

Special Feature

Evidence Is Not Enough: Knowledge Translation in the ICU

By David J. Pierson, MD, Editor

With increased emphasis on evidence-based medicine during the last dozen years has come the implicit assumption that the availability of more and better evidence on how disease should be diagnosed and managed will lead to better patient care. Unfortunately, however, this assumption is wrong. A large body of evidence shows that many (if not most) patients do not receive care according to best available evidence or current standards of care. The result is needless suffering, many lost lives, and enormous waste. This is true for health care as a whole, and also in critical care.

There are many examples of excess morbidity, mortality, and costs resulting from the failure of clinicians and institutions to adhere to evidence-based guidelines and other forms of accepted best practice. A familiar illustration is the use of lung-protective ventilation (LPV) in managing patients with acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS). As everyone who manages critically ill patients must surely know, the original ARDS Network study[1] and other clinical trials have demonstrated that limiting delivered tidal volume (VT) to about 6 mL/kg predicted body weight (PBW), and end-inspiratory static airway pressure to not more than 30 cm H_2O, other aspects of management being the same, substantially improves survival in ALI-ARDS, with a number-needed-to-treat of 11 patients so managed to save one life.[2] No special equipment or techniques are required to achieve this benefit, and LPV can readily be applied in any ICU, using any critical care ventilator. Given this information, the relative simplicity of implementing LPV, and the thousands of lives at stake, one might expect that this therapy would have been put into near-universal use. Yet numerous studies demonstrate that this is far from being the case.[3,4]

In a study of 398 patients with ALI-ARDS managed between 1994 and 2001, Weinert et al found that the VT used decreased only from a mean of 11.2 mL/kg PBW prior to publication of the ARDS Net study to 10.1 mL/kg PBW afterward.[5] Only 0.9% of their patients received a VT of 6.2 mL/kg PBW or less.[5] Young et al compared the VT used before and after publication of the ARDS Net study in 300 patients with ALI-ARDS at their institution.[6] They found that mean VT fell from 12.3 to 10.6 mL/kg PBW in the later study interval, but that there was no change in inspiratory plateau pressure, and that only 16% of ALI-ARDS patients were ventilated with VTs of 8 mL/kg PBW or less following publication of the ARDS Net study.[6]

In another study in which VT was recorded three times daily in patients with ALI-ARDS managed during 2003, Wolthuis and colleagues found that 85% of the delivered volumes exceeded 8 mL/kg PBW, and that 39% of them were greater than 10 mL/kg PBW.[7] More recently, Umoh et al reported that only 46% of patients with ALI-ARDS who were managed at three Baltimore teaching hospitals received VTs of 6.5 mL/kg PBW or less.[8] These and other studies consistently show that clinicians have failed to adopt the VT and plateau pressure settings of LPV for many patients — even in institutions that participated in the ARDS Net study showing that this approach was life-saving.[4]

Why Don't Clinicians Use Best Evidence?

The LPV story is only one of many documenting the failure of clinicians to adopt evidence-based best practices in critical care.[3,4] Why is this so? In a widely cited paper, Cabana and associates reviewed the existing literature on barriers to the adoption of clinical practice guidelines.[9] They classified the barriers into seven separate categories, falling generally under the areas of knowledge, attitudes, and behavior. The Cabana study dealt with health care in general, but Kahn subsequently discussed the barriers it identified within the context of critical care.[3] Table 1 *(see page 5)*, adapted from these two articles,[3,9] lists these barriers and provides some ICU-relevant examples.

Following publication of the first studies showing that clinicians were not adopting LPV as widely as might have been hoped, Rubenfeld and colleagues carried out a study to find out why this was the case.[10] They surveyed experienced ICU nurses and respiratory therapists (RTs) at all 10 of the ARDS Net VT study's participating institutions to determine the perceived barriers to LPV adoption.[10] Identified barriers to the initiation of LPV includ-

ed physician unwillingness to relinquish control of the ventilator to an LPV protocol, failure of the managing physician to recognize that the patient had ALI or ARDS, and difficulty calculating PBW for setting the appropriate VT. Barriers to continuing LPV once it was initiated included concerns over patient discomfort and tachypnea, the frequent occurrence of hypercapnia and acidosis, and the fact that arterial oxygenation tends not to be as good on LPV as when higher VTs and plateau pressures are used. Although studies of actual drug usage on LPV vs traditional ventilatory management have not shown an increased need for sedation with the former,[4] concerns about this were cited as an additional barrier to LPV use, as was difficulty adhering to the ARDS Net LPV protocol.[10]

In general, studies have shown that the wider the practice variation among individual clinicians, the less the care delivered tends to conform to accepted practice standards. In addition, the ICU physician staffing model in use correlates with various measures of the quality of care, including practice variation: "closed" units (in which trained intensivists participate in the management of all patients) generally perform better. That physician staffing and other aspects of ICU operation vary widely in different geographic areas and among institutions in a given region was recently emphasized in a study by Dodek et al.[11] These investigators surveyed all ICUs in each of the five health care regions of British Columbia, examining the physician staffing model (open vs closed units, and the presence of trained intensivists), staffing and coverage by RTs, and the use of practice guidelines for nutrition, prophylaxis against deep venous thrombosis, and weaning from mechanical ventilation. They documented wide geographical variations in all variables examined, as well as major variation by ICU size. In the different regions, 20%-71% of the ICUs had

Table 1

Barriers to implementation of best practice in the ICU[3,9]

Category	Individual Barrier	Examples
Knowledge	• Lack of awareness of the evidence (volume of information is too great; insufficient time to keep up with literature)	• Clinicians unaware that elevating head of bed could reduce incidence of VAP; clinicians unaware that tidal volume should be set according to predicted body weight
	• Lack of familiarity with current guidelines (unaware of recommendations)	• Clinicians believe they are following guidelines but their actual practice differs from recommendations
Attitudes	• Lack of agreement with current guidelines (dispute study findings; guidelines too "cookbook" or too rigid)	• Clinicians do not believe LPV study findings are valid, or that recommended measures actually reduce incidence of VAP; guidelines do not apply to their patients
	• Lack of self-efficacy (do not believe that guideline recommendations can actually be achieved in their practices)	• RTs believe that physicians will not want to surrender control of ventilator to implement LPV
	• Lack of motivation to change (inertia of established practice; habit; comfort of routine)	• Culture of the ICU is inherently resistant to change
Behavior	• External barriers to adoption of practice as recommended in guidelines (factors beyond immediate control of ICU clinicians)	• ED physicians too busy to initiate goal-directed sepsis protocol; inability to reconcile patient/family preferences/values with recommended therapy
	• Barriers related to the guidelines themselves (organization; presentation; accessibility; conflicting recommendations in different guidelines)	• Guideline for conservative fluid management strategy in ALI-ARDS too complex for convenient implementation by staff; requirements of one guideline interfere with or contradict another guideline in local setting
	• Environmental factors (organizational constraints in local practice setting; lack of time or resources)	• Equipment and materials required for procedure to be done according to guidelines not conveniently at hand; poor communication among physicians, nurses, and RTs about LPV

Key: ALI = acute lung injury; ARDS = acute respiratory distress syndrome; ED = emergency department; LVP = lung-protective ventilation; RT = respiratory therapist; VAP = ventilator-associated pneumonia.

trained intensivists, whose presence also varied with ICU size, from 7% in the smallest hospitals to 100% in those with more than 10 beds. The largest ICUs were also more likely to have 24-hour RT coverage, but this varied dramatically: 60% of the units in one region had no RT coverage at all. Similarly, there was variable use of practice guidelines, with those for ventilator weaning being present in 20%-80% of the ICUs in the different regions. Although this study did not examine specific outcomes of ventilator management or other individual critical care therapies, one might assume that these also varied widely in the different ICUs in the province.

What Is Knowledge Translation?

Knowledge translation (KT) is the process of putting the results of research and other evidence into use in everyday practice.[4,12] Also known by numerous other terms such as dissemination and diffusion, research uptake, research utilization, and knowledge-to-action, KT is a burgeoning field in health care. A PubMed search on Feb. 3, 2010, using the terms "knowledge translation" or "knowledge transfer" yielded 705 citations, 293 of them published in the last two years. However, adding "critical care" to the search terms reduced the total to only 16 citations in the last 10 years. Thus, the ICU has been the focus of relatively little work in KT to date.

One reason for the difference between what the evidence says should be done and what actually happens is the real-world distinction between efficacy and clinical effectiveness.[4] Efficacy is what is demonstrated in clinical trials. It shows what can be achieved under controlled research conditions, in carefully selected patients who generally have no serious comorbidities and who are managed with a rigidly controlled protocol overseen by research staff. In contrast, clinical effectiveness is what is experienced in everyday practice: The patients are unselected, they typically have comorbidities and other complicating factors that would have excluded them from the clinical trials, and their care is not scrutinized by research nurses or others to assure adherence to the protocol. And, given that protocols need to be tailored to local institutions, patient populations, and practice traditions, certain aspects of management may vary from what was done in the study demonstrating efficacy.

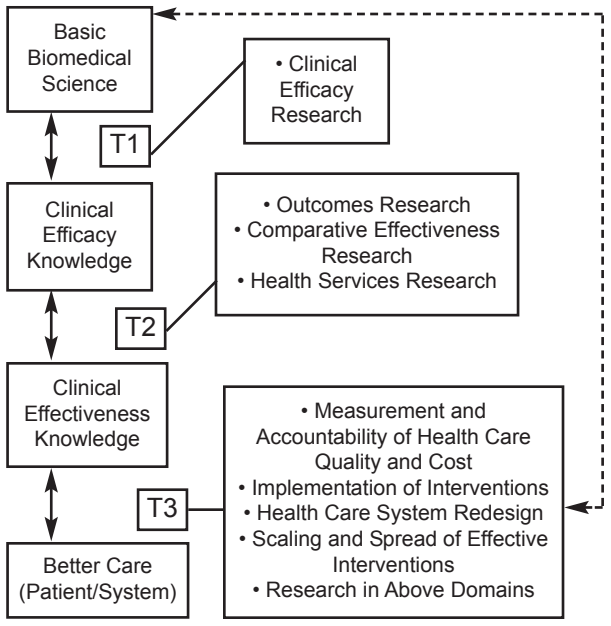
Knowledge translation is a complex, global process that involves an entire health care system, not just individual clinicians. The Figure *(right)*, adapted from the work of Dougherty and Conway,[13] shows one approach for clarifying the process and better understanding what has to be done to implement KT effectively. It seeks to improve not only the care of individual patients, but also the health status of the whole population, as well as efficiency and cost-effectiveness for the system. The "3-Ts" in the "road map" model shown in the figure represent separate translational steps. The first T (T1) is clinical efficacy research, to determine what treatments are effective and how to apply them under controlled conditions. T2 comprises activities to move from efficacy to clinical effectiveness, including the development of evidence-based clinical practice guidelines for applying the knowledge gained in the first step to the care of individual patients. The third T (T3) deals with the "how" of health care delivery, at both individual and system-wide levels.

Implementing Knowledge Translation in Critical Care

Although the 3-Ts road map is helpful for gaining an overall understanding of what KT aims to do in health care, it does not translate intuitively to the ICU or to a practical action plan for those working in the clinical trenches. A more accessible scheme whose implementation is easier to visualize is that offered by Pronovost and colleagues of the Johns Hopkins Quality and Safety Research Group,[14] which is summarized in Table 2 *(see page 7)*.

Figure

The 3-Ts road map for knowledge translation in health care[13]



Legend: T1, T2, and T3 represent the major translational steps in this model, with activities at each step testing the discoveries of prior research in progressively broader application. Double-headed arrows indicate the need for feedback loops among the various parts of the transformation network.

Table 2

Overall strategy for translating evidence into practice[14]

Global concepts guiding the process

- Envision the problem within the larger health care system
- Engage collaborative multidisciplinary teams

Measures to be taken at the system level

- Summarize the evidence
- Identify local barriers
- Measure performance

Measures to be taken at the local level (the 4-Es)

- *Engage:* Explain why the intervention is important
- *Educate:* Share the evidence supporting the interventions
- *Execute:* Create an intervention "tool kit" focused on the barriers as the intervention is implemented
- *Evaluate:* Assess regularly for performance measures and unintended consequences

That group's model for translating evidence into practice focuses on systems (how work is organized) rather than the care of individual patients.[14] It stresses collaborative action by interdisciplinary teams, and tailoring of the structure of the effort as well as the details of the intervention to the characteristics and needs of the institution involved. Central to its implementation is the creation of a collaborative culture in the institution, something that may represent a substantial change. This model applies primarily to large scale projects, as the resources required to develop, implement, and evaluate the program it describes are substantial.

Once the program has been conceived and support has been obtained from the highest levels of the organization, three system-level steps are involved. First, the relevant research pertaining to the specific outcome to be sought is reviewed using a rigorous, formalized approach. Interventions associated with the improved outcome sought are identified, and several of those that are likely to yield the greatest benefit to the organization are selected. These interventions are then converted into specific behaviors.

Next, local barriers to implementation are identified. Pronovost et al emphasize the value of direct observation of the staff as the target interventions (for example, the insertion of central lines) are performed, to identify defects in each step in its implementation. All stakeholders involved in the intervention (for example, physicians, nurses, and supply personnel) are observed and queried about problems and potential improvements related to that intervention. Measurement of performance of the target interventions is key in this process.[14] Both process measures (how often patients actually receive the therapy or other intervention as intended) and outcome measures (whether relevant results actually improve) are incorporated into the assessment.

Whereas the above measures are system-wide, actual implementation of the intervention must succeed at the ground level. The model described uses what Pronovost and colleagues call the "4-Es": engage, educate, execute, and evaluate. Although initially these are undertaken in sequence, the authors emphasize that their operation is cyclical and ongoing rather than a linear, one-time process. Engaging the staff involves providing actual data on baseline performance (for example, for central line infections, the number of infections and patient deaths in the unit attributable to those infections); the investigators also engage the staff by sharing real-life stories of individual patients to put a human face on the issue. Education involves summarizing the relevant literature and providing checklists of the evidence to members of the staff at all levels. Execution of the plan is based on a "tool kit" for surmounting the identified barriers to implementation, which standardizes care processes, provides checklists, and incorporates learning from mistakes. Evaluation includes comparing ongoing performance measures to baseline data from the unit. Two additional "Es", endure (incorporating the project into the hospital's quality improvement program) and extend (expanding the project into other areas of the institution, such as the emergency department), have subsequently been added to the model.

The model summarized in Table 2 and described above has been used in a large-scale research study of infections associated with the insertion of central lines.[15] In that study, which took place in 103 ICUs, the median infection rate per 1000 catheter-days decreased from 2.7 (interquartile range, 0.6-4.8) to 0 (interquartile range, 0-2.4) in the 18 months following the intervention.[15] These results, requiring implementation of the program of Pronovost and associates on a wide scale throughout the state of Michigan, are most impressive from both clinical and economic perspectives.

Knowledge translation is complex and demanding of both human and material resources. However, there can be little doubt of the need for it in critical care, or of its potential benefits for everyone from individual patients to society as a whole. An excellent series of articles dealing with different aspects of KT in health care has recently been published in the *Canadian Medical Association Journal* (*CMAJ* 2010;182:E68-E98), and has also appeared in book form.[16] More studies and

other resources pertaining directly to critical care are sure to appear in the coming months. ■

References

1. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-1308.
2. Petrucci N, Iacovelli W. Lung protective ventilation strategy for the acute respiratory distress syndrome. *Cochrane Database Syst Rev* 2007;(3):CD003844.
3. Kahn JM. Disseminating clinical trial results in critical care. *Crit Care Med* 2009;37(1 Suppl):S147-S153.
4. Pierson DJ. Translating evidence into practice. *Respir Care* 2009;54:1386-1401.
5. Weinert CR, et al. Impact of randomized trial results on acute lung injury ventilator therapy in teaching hospitals. *Am J Respir Crit Care Med* 2003;167:1304-1309.
6. Young MP, et al. Ventilation of patients with acute lung injury and acute respiratory distress syndrome: Has new evidence changed clinical practice? *Crit Care Med* 2004;32:1260-1265.
7. Wolthuis EK, et al. Feedback and education improve physician compliance in use of lung-protective mechanical ventilation. *Intensive Care Med* 2005;31:540-546.
8. Umoh NJ, et al. Patient and intensive care unit organizational factors associated with low tidal volume ventilation in acute lung injury. *Crit Care Med* 2008;36:1463-1468.
9. Cabana MD, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282:1458-1465.
10. Rubenfeld GD, et al. Barriers to providing lung-protective ventilation to patients with acute lung injury. *Crit Care Med* 2004;32:1289-1293.
11. Dodek PM, et al. Structure, process, and outcome of all intensive care units within the province of British Columbia, Canada. *J Intensive Care Med* 2010 Jan 21; Epub ahead of print.
12. Straus SE, et al. Defining knowledge translation. *CMAJ* 2009;181:165-168.
13. Dougherty D, Conway PH. The "3T's" road map to transform US health care: The "how" of high-quality care. *JAMA* 2008;299:2319-2321.
14. Pronovost PJ, et al. Translating evidence into practice: A model for large scale knowledge translation. *BMJ* 2008;337:a1714; doi: 10.1136/bmj.a1714.
15. Pronovost P, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006;355:2725-2732; Erratum in: *N Engl J Med* 2007; 356:2660.
16. Straus S, et al. *Knowledge Translation in Health Care. Moving from Evidence to Practice.* Maiden, MA: Wiley Interscience; 2009.

CME / CNE Questions

1. Following passive leg raise, what percentage change in pulse pressure predicts volume responsiveness in non-intubated patients with severe sepsis or acute pancreatitis?
a. ≥ 9
b. ≥ 15%
c. ≥ 20%
d. ≥ 25%
e. ≥ 30%

2. Colistin and other polymyxin-type antibiotics can cause acute respiratory failure due to:
a. increased carbon dioxide production.
b. acute upper airway obstruction.
c. diffuse bronchospasm.
d. carbonic anhydrase inhibition.
e. neuromuscular weakness.

Answers: 1. a, 2. e.

CME / CNE Objectives

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

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

PHARMACOLOGY WATCH

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

Thiazolidinediones and Risk of Heart Failure

In this issue: FDA is reviewing safety of TZDs; SSRI use with tamoxifen; Metformin smells like fish; FDA Actions.

FDA reviews TZD safety

Thiazolidinediones (TZDs) have been under intense scrutiny in recent years after rosiglitazone (Avandia®) was linked to increased cardiovascular morbidity and mortality in several studies. In recent weeks, *The New York Times* has reported that some FDA staffers are recommending that rosiglitazone be removed from the market. According to the story in the *Times*, a "confidential government report" states that about 500 heart attacks and 300 cases of heart failure per month could be averted if patients were switched from rosiglitazone to pioglitazone (Actos®). Congress has even gotten involved, specifically the Senate's Committee on Finance, which in January issued a 350-page report on rosiglitazone, focusing on GlaxoSmithKline's handling of evidence of possible cardiac risks associated with use of the drug. Now the American Heart Association and the American College of Cardiology have weighed in on the issue suggesting there is insufficient evidence to support the use of pioglitazone over rosiglitazone and that both drugs increase the risk for heart failure and should not be initiated in patients with class III/IV heart failure. They further state that the drugs should not be used with an expectation of benefit with respect to ischemic heart disease events (*Circulation*, published on-line Feb. 23, 2010). Meanwhile, the FDA web site reports that the Agency is reviewing data on rosiglitazone and is planning a public meeting in July 2010 to present all known heart-related safety data on the drug and provide an updated assessment of the risks and benefits of rosiglitazone and the treatment of type 2 diabetes. ■

SSRI use with tamoxifen

The SSRI paroxetine (Paxil®) reduces the effect of tamoxifen in women with breast cancer leading to higher breast cancer mortality according to a new study in the *British Medical Journal*. Concern about SSRIs interfering with the metabolism of tamoxifen was raised last June at the American Society of Clinical Oncology meeting. Tamoxifen is converted from its prodrug to the active metabolite via the cytochrome P450 pathway, specifically CYP2D6. Paroxetine is an exceptionally strong inhibitor of CYP2D6, the strongest inhibitor of all the SSRIs. In the study, Canadian researchers looked at more than 2400 women from Ontario treated with tamoxifen for breast cancer along with a single SSRI. After adjustment for confounders, absolute increases of 25%, 50%, and 75% in the proportion of time on tamoxifen with overlapping use of paroxetine were associated with 24%, 54%, and 91% increases in the risk

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of death from breast cancer, respectively ($P < 0.05$, for each comparison). No such risk was seen with any other antidepressant. The authors conclude that paroxetine use during tamoxifen treatments is associated with an increased risk of death from breast cancer, supporting the hypothesis that paroxetine can reduce or abolish the benefit of tamoxifen in women with breast cancer (*BMJ* 2010;340:c693). The study is important because up to one-quarter of women diagnosed with breast cancer experience a depressive disorder, and antidepressants are commonly used during tamoxifen treatment for not only depression, but also for treatment of hot flashes and other symptoms. It is evident that paroxetine should never be prescribed to women taking tamoxifen for treatment of breast cancer and that preference should be given to antidepressants that show little or no inhibition of CYP2D6. Among the SSRIs, the strongest inhibitors of CYP2D6 besides paroxetine are fluoxetine (Prozac®), duloxetine (Cymbalta®), and to a lesser extent sertraline (Zoloft®). Among non-SSRI antidepressants, bupropion (Wellbutrin®) also is a strong CYP2D6 inhibitor. Drugs that are not inhibitors of the enzyme include citalopram (Celexa®) and venlafaxine (Effexor®). ■

Generic metformin smells fishy?

If your patients tell you their pills smell like fish, they may be taking generic metformin. A letter to the *Annals of Internal Medicine* describes two patients who stopped taking generic metformin because of a fishy taste that caused nausea. The fishy smell is a property of metformin and is well known to pharmacists. Apparently the film-coated extended-release formulations have less smell and may be better tolerated (*Ann Intern Med* 2010;152:267-268). ■

FDA actions

A new FDA warning states that **long-acting beta agonists** (LABAs) should never be used alone in the treatment of asthma in children or adults. The LABAs salmeterol (Serevent®) and formoterol (Foradil®) have been associated with severe worsening of symptoms when used without a controller medication such as an inhaled corticosteroid. Both products will be required to include warnings on the product label that states:

- Use of LABAs is contraindicated without the use of an asthma controller medication;
- LABAs should only be used long term in patients whose asthma cannot be adequately controlled on asthma controller medications;
- LABAs should be used for the shortest duration of time required to achieve control, and should be discontinued once asthma control is achieved;
- Pediatric and adolescent patients who require an LABA in addition to an inhaled corticosteroid should use a combination product containing both an inhaled steroid and a LABA to ensure compliance with both medications.

The FDA has approved **rosuvastatin (Crestor®)** for primary prevention in patients without elevated LDL-cholesterol but who have an elevated C-reactive protein (2 mg/L or higher) and at least one additional cardiovascular risk factors such as low HDL, hypertension, or family history of premature heart disease. The approval was based on the JUPITER trial, which showed a 44% reduced relative risk of cardiovascular events in patients with normal LDL cholesterol but elevated CRP.

The FDA has approved a new **pneumococcal vaccine** for infants and children. Wyeth Pharmaceuticals' **Prevnar 13™** is a 13-valent conjugate vaccine that will replace the currently available 7-valent Prevnar®. It is approved for the prevention of invasive disease caused by 13 different serotypes of *S. pneumoniae*.

The FDA has approved the **monoclonal antibody rituximab (Rituxan®)** to treat certain patients with chronic lymphocytic leukemia (CLL). Rituximab is approved for CLL patients who are starting chemotherapy for the first time and also for those who have not responded to other CLL therapies. It is administered with fludarabine and cyclophosphamide for the treatment of CLL. Rituximab is manufactured by Genentech.

The FDA is initiating a risk-management program for **erythropoiesis-stimulating agents** (ESAs) for the treatment of chemotherapy-related anemia. The drugs, which include epoetin alfa (Procrit®, Epogen®) and darbepoetin alfa (Aranesp®), have been associated with accelerated tumor growth and higher mortality rates in some cancer patients. The Risk Evaluation and Medication Strategy (REMS) requires that patients receive a medication guide on safety issues associated with the drugs and requires training and certification of health care professionals who administer chemotherapy to patients with cancer and counseling of patient regarding the risks of the drugs. The REMS does not currently apply to patients being treated with an ESA for anemia due to other conditions, specifically renal failure. ■