CRITICAL CARE ALERT®

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

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INSIDE

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Why Nurses Want to Leave the ICU: Work Environment and Clinical Competence

ABSTRACT & COMMENTARY

By Leslie A. Hoffman, PhD, RN

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

Synopsis: *ICU nurses who stated a desire to leave were influenced by their perceptions of the work environment and clinical competence of other nurses in their unit.*

Source: Stone PW, et al. Organizational climate and intensive care unit nurses' intention to leave. *Crit Care Med*. 2006;34:1907-1912.

THIS STUDY REPORTS FINDINGS FROM A SURVEY OF 2,323 ICU nurses regarding their intention to leave due to working conditions and factors predicting this intention. The sample was part of a larger study of patient safety that involved 110 ICUs from 66 hospitals across the United States. The study excluded step-down, intermediate care, and telemetry units. The average RN was 39 ± 9 years old, had 16 ± 9 years experience in health care, and was employed in his or her current position for 8 ± 8 years.

In this stable, experienced workforce, 391 (17%) of the RNs indicated their intention to leave within 1 year. Reasons included working conditions (n = 202; 52%), positive career move (n = 87; 22%), personal or family reasons (n = 44; 11%), retiring (n = 10; 3%) and no reason (n = 48; 12%). There were no significant differences in demographics or characteristics of the setting (region, type of ICU, bed size) between nurses who stated they intended to leave due to working conditions compared to other reasons. Those who indicated they would be leaving due to working conditions rated all organizational climate factors significantly lower ($P < .001$) than other nurses. Differences were largest in "support for professional practice," defined as opportunities for advancement and involvement in hospital governance. The smallest difference was found in perceptions of nurse/physician collaboration.

When analyzed using logistic regression, three items were signif-

icantly related to the intention to leave. A one unit increase in the professional practice score decreased the odds of intention to leave by 48% (Odds Ratio [OR], 0.52; 95% CI, 0.42-0.64; $P < .01$). Perceptions of high nursing competence of other nurses employed in the ICU setting were also associated with reduced likelihood of an intention to leave (OR, 0.61; 95% CI, 0.44-0.83; $P < .01$). A one-year increase in the current position decreased the odds of citing an intention to leave by 3% (OR, 0.97; 95% CI, 0.94-0.99; $P < .05$).

COMMENTARY

It is encouraging that, in this stable, experienced sample of ICU nurses, the majority (83%) indicated that they did not intend to retire or resign their current ICU position in the coming year. Slightly more than half (52%) of those who indicated an intention to leave cited "working conditions," with professional practice rated most highly as the factor influencing this decision. Other important factors were perceptions of the clinical competence of nurses employed with them in the ICU and the number of years in the current position. Factors cited in past studies, eg, nurse/physician collaboration, staffing, scheduling were not rated as highly in influencing this decision.

One possible explanation for these findings relates to the sample selection process. Nurses included in this study were employed in hospitals who were invited to participate in an ongoing national study on patient safety. It is possible that, given the selection process, the hospitals that volunteered represented the "cream of the crop" in regard to practices known to impact retention of valued critical care nurses. If so, the message of this study is that ICU nurses in these settings need to be challenged with new opportunities for career advancement within the bedside career ladder and be given a role in unit governance.

One method of achieving this recognition is through attaining Magnet Status. The Magnet Recognition Program was developed by the American Nurses Credentialing Center to recognize health care organizations that provide the very best in nursing care. A Magnet hospital is stated to be one where nursing delivers excellent patient outcomes, job satisfaction is high, and turnover low. Magnet status is also said to indicate that nursing is involved in decision-making in patient care delivery, changing nursing practice through research, and are encouraged and rewarded for advancing in nursing practice. Organizations that exhibit these characteristics have found that they have decreased nursing turnover, perhaps due to the greater challenges and recognition they provide to those who wish to improve the quality of care through adoption of best practices and the generation of new research findings. ■

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Keeping HIT on Our Radar Screens

ABSTRACT & COMMENTARY

By Saadia R. Akhtar, MD, MSc

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Dr. Akhtar does research for Eli Lilly.

Synopsis: *A meta-analysis of 10 studies of heparin used either for prophylaxis or for treatment suggests that venous thromboembolism related to heparin-induced thrombocytopenia occurs frequently in patients previously treated with unfractionated heparin, but uncommonly in those on low molecular weight heparin.*

Source: Levine RL, et al. How frequently is venous thromboembolism in heparin-treated patients associated with heparin-induced thrombocytopenia? *Chest.* 2006;130:681-687.

A SYSTEMATIC SEARCH OF THE LITERATURE FROM 1984 to 2004 was conducted in order to answer the

question posed by the title of this article: How frequently is venous thromboembolism in heparin-treated patients associated with heparin-induced thrombocytopenia (HIT)? Randomized controlled trials and cohort studies (retrospective or prospective) of unfractionated or low-molecular-weight heparin (UH or LMWH), for either prophylaxis or treatment of venous thromboembolism (VTE), were included if they clearly defined and objectively tested for HIT and new or recurrent VTE. In addition, qualifying studies had to have at least one VTE occur in the relevant patient group.

Initial search terms identified 673 citations on MEDLINE. Of these, 41 were pertinent based on title and abstract. A supplemental search of bibliographies of review articles and texts on the subject was also conducted. A total of 10 articles (6 randomized controlled trials, 3 prospective cohorts, 1 retrospective study) met all inclusion criteria. Data were taken from these studies and tabulated as VTE occurring in patients with HIT and without HIT. The authors further evaluated VTE with HIT in those treated with UH vs LMWH, intravenous vs subcutaneous heparin therapy, and in medical vs surgical patients. Standard statistical methods were employed.

There were several differences between the studies, including types of patients (at varying risks for HIT), duration of treatment (5 to > 20 days), laboratory test used for identifying HIT, and follow-up for recurrent VTE (hospital length of stay to 90 days). HIT was defined either as a platelet count < 100,000/mL or as a 40-50% decrease from baseline level. The 10 studies provided data from 6219 patients (3792 received UH and 2427 LMWH): 386 patients developed VTE and 32 had HIT. VTE was more likely to occur in surgical patients than in medical patients. There was no difference in the risk of HIT-associated VTE between patients receiving intravenous UH vs. subcutaneous UH. However, the frequency of HIT-associated VTE was markedly higher in patients who had received UH compared to those who had received LMWH (12.8% vs 0.7%).

COMMENTARY

HIT is a potentially life-threatening immune-mediated condition associated with recurrent VTE (and arterial thromboses), even after cessation of heparin. Antibodies are formed to the heparin-platelet factor 4 complex, and these lead to platelet activation. Multiple mechanisms increase thrombin generation and clotting. Clearance of aggregated platelets results in thrombocytopenia. HIT is usually readily recognized in patients who develop severe thrombocytopenia (with or without VTE) within the usual time frame of 5-10 days after initiation of heparin. However, it may be easily missed in patients with a mild and relative thrombocytopenia or those with normalized platelet counts presenting with VTE after a recent brief exposure to a heparin product.

As the authors note in their discussion, there is a reasonably large literature on the incidence of HIT following UH or LMWH (0.2-3%, lowest for LMWH).[1,2] Furthermore, the incidence of thrombosis in the first few weeks after development of HIT is also fairly well-described (20-75% if alternative anticoagulation is not added). With these considerations in mind, the authors sought to answer a slightly different question: "What is the risk that a patient presenting with VTE during or following heparin therapy has HIT?" They found that 1 out of every 8 patients who developed VTE following exposure to UH had HIT. For LMWH, it was < 1 out of every 100 patients.

The studies included in the analysis have several limitations, such as limited follow-up and screening period for VTE and the use of laboratory tests for HIT that may have relatively low sensitivity. The analysis itself is limited by the dissimilarities between the included studies and lack of any sort of adjustment for these. However, such deficiencies would most likely result in an underestimation of risk.

Thus, although this publication may not provide the most accurate estimation of risk of HIT in patients presenting with VTE after recent heparin therapy, it provides an important reminder that the risk is quite substantial. Evaluation for HIT must be considered as part of the routine diagnostic evaluation of every patient with VTE. ■

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Ventilator Weaning: RT-Driven or R2D2-Driven?

ABSTRACT & COMMENTARY

By Saadia R. Akhtar, MD, MSc

Idaho Pulmonary Associates, Boise

Dr. Akhtar does research for Eli Lilly.

Synopsis: *This multicenter, randomized trial demonstrated that a computerized protocol, when compared with usual physician-driven weaning, reduced duration of mechanical ventilation and ICU length of stay.*

Source: Lellouche F, et al. A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation. *Am J Respir Crit Care Med*. 2006;174:894-900.

A PREVIOUSLY DESCRIBED "CLOSED-LOOP KNOWledge based system" placed into a standard ventilator may be used to guide weaning via the pressure support mode. The system uses continuously recorded patient data on respiratory rate, tidal volume and end-tidal CO_2 to adjust the pressure support (PS) level. Once a specified minimum level of PS is reached, a spontaneous breathing trial is completed and the computer makes a recommendation for or against extubation. Noting that there are excellent data supporting protocol-driven ventilator weaning,[1] but that protocols may be difficult to implement, the authors hypothesized that a computerized approach may be superior to usual care.

The study was conducted in 5 European medical-surgical ICUs. Patients were mechanically ventilated for ≥ 24 hours on ≤ 50% oxygen with a variety of criteria including positive end-expiratory pressure ≤ 8 cm H_2O, hemodynamic stability and minimal sedation. Exclusion criteria included poor neurological or overall prognosis, presence of a do-not-resuscitate order or a tracheostomy. At study entry, patients were placed on PS 15 cm H_2O for 30 minutes. Once tolerated, they were randomized to computer-driven (CDW) or usual weaning. The primary end points were time to successful extubation (defined as 72 hours without ventilator support) and duration of mechanical ventilation. An estimated sample size of 75 per group was necessary to detect reduction in weaning time of 2 days with power 0.8 and $P \leq 0.05$. Usual statistical methods were employed.

Over 10 months, 1014 mechanically ventilated patients were screened, 147 met study criteria and 144 were randomized (74 CDW, 70 controls). Patients in the 2 groups were similar with respect to demographics, severity of illness, organ dysfunction, comorbidities and duration of mechanical ventilation prior to study entry (about 4 days). Weaning time was decreased from median 5 days in the control group to 3 days in the CDW group. (There was a median delay of 1 day between the CDW system recommending extubation and physicians proceeding with this.) Total duration of ventilation was 7.5 days vs 12 days; and ICU length of stay was 12 days vs 15.5 days.

There were no significant differences between the groups in extubation failure, hospital length of stay, mortality, or ventilator-associated pneumonia. Need for non-invasive ventilation after extubation was significantly less in the CDW group. There was no significant difference in sedation or paralytic use between the groups or in the period before entry into the study vs afterwards. Finally, 10 patients were removed from the CDW system due to clinical worsening.

COMMENTARY

There is good evidence that weaning time or time on mechanical ventilation can be safely reduced by use of weaning protocols driven by nurses or respiratory therapists.[1-3] Data also suggest that standardized practice in closed units with formal rounds and adequate levels of intensivist staffing may yield outcomes similar to those seen with specific protocols.[4]

CDW is an interesting and novel alternative approach to liberation from mechanical ventilation. There are reasons to hypothesize that CDW may be superior to protocols (or standardized and consistent practice patterns) that rely on human beings. It ensures more complete compliance: there are considerable data in the literature on the difficulty of achieving compliance with 'human-driven' protocols.[5,6] CDW may be faster than a human-driven approach in that it operates and weans PS continuously for 24 hours a day (as compared to intermittent assessment for reduction of PS or just a once a day spontaneous breathing trial). (Even CDW has its limitations: in this study when patients met extubation criteria per CDW recommendations, humans added on average a perhaps-unnecessary day to the time on mechanical ventilation.)

Lellouche et al's work does address their primary hypothesis, demonstrating that CDW is superior to their 'usual care.' The study however does not answer the question of whether CDW is superior to the currently recommended standardized protocol-driven weaning methods. The centers in question relied on physician direction for weaning. Although we are told that many had formal protocols or structured practices in place for

weaning, there is no information available on the means/degree of implementation.

This study does demonstrate that CDW may be incorporated relatively easily and provides motivation for future comparisons with more clearly established "protocolized" weaning methods. I await such further studies and suspect that CDW may ultimately be found to be the best choice for some units: even if shown to be equal rather than superior to current best care, CDW may work well for intensive care units without an adequate number of support staff trained in the use of weaning protocols and/or those units with limited numbers of physicians trained in critical care. ■

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Special Feature

Update on the Management of Sepsis

By James E. McFeely, MD

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

SEVERE SEPSIS WITH ORGAN FAILURE HAS ONE OF THE highest mortality rates of any diagnosis commonly treated in the Intensive Care Unit. Recent clinical trials have provided some positive results with reductions in overall mortality from sepsis. This is a welcome change from the recent past when all clinical trials were negative. As a result, we now have some interventions that can be applied at the bedside with proven efficacy in this group of patients.

Eleven of the relevant medical societies have reviewed the most recent set of data and developed guidelines for the management of sepsis as part of a joint undertaking called the Surviving Sepsis Campaign.[1] However, Eli Lilly's sponsorship has generated controversy about the guidelines, given that the company has the only drug approved for this indication and provided over 90% of the funding and supportive development of the project.[2] In addition, Eli Lilly has recently begun awarding unrestricted grants for an "Implementing the Surviving Sepsis Campaign" program, the main goal of which is the creation of performance bundles based on recommendations from the campaign guidelines.

This article includes a summary of the primary research on which the guidelines are based, to facilitate review of the guidelines as submitted and to provide supporting evidence should local modification of those guidelines seem appropriate.

The Magnitude of the Problem

Sepsis is a common problem in the United States, with an estimated 750,000 cases per year and an overall mortality rate of 30-50%, depending on the number of organs involved and previous conditions existing in the patients. Sepsis is difficult to study because it is a complex response to infection involving a number of different pathways, including the patient's immune, coagulation, and inflammatory responses to the initial insult. Organ failures can occur due to a failure of a host response as well as from an over-reaction of the host response system. Over the years numerous trials attempting to manipulate each of these pathways have turned out to be negative for a variety of reasons, some having to do with underlying physiology and others related to clinical trial design.

More recently, various therapies have had positive clinical trials and these can be grouped into broad categories. Some of these interventions have been clearly shown to work; others have suggestive data that they might work with varying levels of risk (*see Table*). Other therapies have clearly been shown not to be effective and should not be implemented.

Early Goal-Directed Therapy

Early identification and resuscitation of patients with suspected sepsis and shock, as performed by Rivers and

Table

Current Status of Therapies for Sepsis

Beneficial	Might help; moderately risky	Helps selected populations; higher risk	Not beneficial
Rapid antibiotic administration	Stress-dose corticosteroids	Activated Protein C	Renal-dose dopamine
Lung-protective ventilation for ALI/ARDS	Tight glycemic control		Bicarbonate for lactic acidosis
Early goal-directed therapy			High-dose corticosteroids
Source control of infection			

ALI: acute lung injury; ARDS: acute respiratory distress syndrome

colleagues,[3] was shown to be at least as effective as activated protein-C (absolute risk reduction, 16% vs 6%) in reducing mortality from sepsis. Early goal-directed therapy requires implementation in the emergency room and involves 6-hour resuscitation through administration of fluids, vasopressors, inotropes, and transfusion to preset end points that include a mean arterial pressure greater than 65 mm Hg, central venous pressure of 8-12 mm Hg, hematocrit greater than or equal to 30%, and central venous oxygen saturation greater than 70%.

For most hospitals, this therapy requires a change in practice in the emergency room setting, with an increase in utilization of central venous catheters, measurement of serum lactate level, and frequent reassessment and adjustments in fluid and vasopressor therapy. When these procedures were implemented as a group, Rivers et al were able to show a reduction in mortality from 49 to 33%, the highest overall mortality reduction of any sepsis intervention to date.[3]

Rapid Antibiotic Administration

No placebo-control trials have been performed to date to document the role of antibiotic administration in treatment of sepsis due to a lack of clinical equipoise in the control group. Common sense suggests the administration of appropriate antibiotic therapy as a cornerstone of treatment of sepsis. A recent retrospective cohort study showed that rapid treatment with appropriate antibiotics (within the first hour of identification of septic shock) does result in a significant reduction in overall mortality.[4] Delays in antibiotic administration of even one hour resulted in a significant increase in mortality.

Low Tidal-Volume Ventilation

Use of a low-tidal-volume ("lung-protective") ventilation strategy for patients with acute respiratory failure in a setting of sepsis has also been shown to reduce mortality.[5] The magnitude of the mortality reduction is slightly less than that seen with early goal-directed therapy, but greater than with activated protein C administration. Use of a "ventilator bundle" in this setting, including prophylaxis against deep-venous thrombosis and peptic ulcer, elevation of the head of the bed, and scheduled interruptions of sedative drugs ("sedation vacations"), would also be appropriate.

Corticosteroids

The use of corticosteroids in patients with severe sepsis and organ failure continues to be controversial. What is known is that early short courses of high-dose steroids failed to improve mortality in sepsis.[6,7] Two small randomized trials of low-dose steroids have shown a decreased need for vasopressor support in patients with sepsis, but these studies did not show a reduction in overall mortality. Only one trial has shown a survival benefit in patients who failed to respond to an ACTH stimulation test and were treated with low-dose corticosteroids.[8] Problems with implementation include variability in cortisol assays from hospital to hospital, as well as frequent lack of correlation between a total serum cortisol level and serum free cortisol levels, which can be affected by serum albumen. Well-known complications of the use of corticosteroids include development of hyperglycemia, myopathy, and immunosuppressive effects, some of which can be mitigated by use of low-dose hydrocortisone. The current trend is toward use of low-dose hydrocortisone in patients with refractory shock, at least until the results of a random serum cortisol or ACTH-stimulated cortisol level can be obtained.

Tight Glycemic Control

To date, no randomized control trials have been conducted of tight glycemic control in patients with sepsis, despite a recent resurgence and interest in this therapy. The most frequently cited research involved critically ill surgical patients and showed that tight glycemic control decreases mortality in patients staying in the ICU for at least five days.[9] A subsequent trial by the same group in medical ICU patients showed an increased mortality rate among patients with an ICU stay of less than 3

days, but improvement in mortality rates for patients staying longer.[10] There are theoretical reasons why intensive insulin therapy might be beneficial, including the known complications of hyperglycemia such as impairment in neutrophil function with increased risk of infection, decreased wound healing, and pro-coagulant effects. Initial concerns about increased risk of hypoglycemia have eased primarily through use of continuous glucose infusions and frequent rechecking of blood glucose values. Clearly, a randomized control trial of tight glycemic control in sepsis is badly needed.

Activated Protein C

The role of activated protein-C in treatment of sepsis with organ failure continues to evolve. After the initial positive results of the PROWESS trial, a series of negative trials with the same compound have raised questions about the appropriate use of the drug and the subset of patients for which it is indicated.[11,12] For safety reasons, the PROWESS trial did not include several subsets of patients who become septic, including dialysis patients, those with liver failure, children, and transplant recipients.

Subsequent to the somewhat controversial approval of activated protein-C by the FDA, the manufacturer, Eli Lilly, conducted a trial on pediatric patients with severe sepsis with organ failure that failed to show a mortality benefit.[13] In addition, a large trial in patients with single-organ failure and sepsis was stopped, again because of a lack of mortality benefit.[14] A study of tissue factor pathway inhibitor (TFPI), an additional coagulant pathway inhibitor, was also negative.[15] These negative results have raised questions within the medical community about the results of the initial PROWESS trial and have prompted calls for that trial to be repeated. For now, use of activated protein-C should be strictly limited to patients who meet the inclusion and exclusion criteria of the original PROWESS trial (eg, patients at a high risk of death with at least two organ failures), and should not be extrapolated to any other patient population without further supporting data.

Failed Therapies

A number of other compounds have been tested in sepsis and have failed to show any benefit. Most of these never came to market. Commonly utilized agents shown not to work include 'renal dose' dopamine and sodium bicarbonate for treatment of lactic acidosis.[16,17] Neither of these has a place in current practice guidelines for treatment of sepsis—a fact that may require some re-education of the more senior members of the treatment team.

Management of sepsis continues to be an active area of investigation and over the last few years positive clinical trials have resulted in some real improvements in patient outcomes. Your development of local guidelines and goals for therapy should be based strictly on the data that is available in the medical literature and should be constantly revised as new information becomes available. ■

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CME / CE 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 Questions

9. ICU nurses who indicated an intention to leave their positions in one year:
a. were significantly older.
b. had fewer years of nursing experience.
c. related their nurse manager less positively.
d. rated collaboration between nurses and physicians negatively.
e. rated all organizational climate factors lower.

10. Among surveyed ICU nurses in a large, stable workforce, what proportion indicated an intention to leave within the next year?
a. 6%
b. 17%
c. 31%
d. 45%
e. 62%

11. Heparin-induced thrombocytopenia:
a. has never been reported with low molecular weight heparins.
b. poses a very low risk of recurrent venous thrombosis.
c. may present with only mild thrombocytopenia.
d. is a clinical diagnosis without available confirmatory laboratory tests.
e. is only a concern in patients on continuous heparin drips.

12. Heparin-induced thrombocytopenia-related venous thromboembolism is more common in:
a. medical patients than surgical patients.
b. children than adults.
c. patients who have previously received IV unfractionated heparin compared to those who have received subcutaneous unfractionated heparin.
d. patients who have previously received unfractionated heparin compared to those who have received low molecular weight heparin.
e. None of the above

13. Computer-driven weaning systems:
a. use pressure support mode for weaning.
b. require input of arterial blood gas data.
c. have been tested primarily in pediatric populations.
d. use intermittent mandatory ventilation for weaning.
e. None of the above

14. In Lellouche et al's study, computer-driven weaning was found to:
a. be superior to respiratory therapist-driven weaning.
b. increase ICU length of stay.
c. reduce sedative use.
d. increase sedative use.
e. reduce weaning time by 2 days.

15. Which of the following have definitively been shown to be of no benefit in treatment of patients with sepsis?
a. drotrecogin alpha (activated protein C)
b. low-dose corticosteroids
c. renal-dose dopamine
d. low tidal volume ventilation
e. early goal directed therapy

Answers: 9 (e); 10 (b); 11 (c); 12 (d); 13 (a); 14 (e); 15 (c)

In Future Issues:

Reversing Lung Collapse in ARDS

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.

Sweeping Changes Needed for US Drug Safety System

In response to several high-profile drug misadventures including the rofecoxib (Vioxx®) withdrawal from the market, the FDA's Center for Drug Evaluation and Research (CDER) asked the Institute of Medicine (IOM) to assess the drug safety system in the United States. The recommendations, published in the October 26 *New England Journal of Medicine*, call for sweeping changes, especially in the post-marketing surveillance of new drugs.

The report suggests that the FDA has acted to accelerate drug approvals without ensuring the safety of these drugs once they are approved and on the market. Direct-to-consumer advertising is also partially to blame, especially when aggressive marketing campaigns lead to sudden widespread use of a new drug. Chronic under funding and a poor work environment at the FDA are also partially to blame. But the biggest culprit is the lack of an effective mechanism of continued evaluation of new drugs once they're on the market, which currently amounts to little more than reports of adverse events from practitioners. The IOM's report recommends changes in the FDA's committee structure, which strengthens conflict-of-interest restrictions and recommends that the FDA commissioner be appointed for a fixed term of 6 years. They also recommend labeling new drugs with a symbol such as a black triangle for up to 2 years to signify "the uncertainty associated with new drugs" and a moratorium on direct to consumer advertising during that period. Five years after a drug's launch, the FDA should perform a review of the risk/benefit status of all approved drugs (*N Engl J Med*. 2006;355:1753–1755).

An accompanying editorial points out that much of the money provided to the CDER is for drug approval, and much of it derives from industry, whereas little funding is earmarked for monitoring of the safety of drugs after they've been approved and introduced onto the marketplace. The editorialists recommend that all clinical trials beyond phase I must be registered in the public database, as has been recommended previously. The editorial also endorses the black triangle indication in the first 2 years after the drug's approval in a moratorium on direct-to-consumer advertising during that time. Most importantly, the editorialists ask for better funding and more transparency in the FDA, and urges Congress to implement the recommendations (*N Engl J Med.* 2006;355:1821).

Antiaging Supplements Proven Ineffective

Dehydroepiandrosterone (DHEA) and testosterone are not effective antiaging supplements, according to 2 new studies. Both compounds have been widely marketed as antiaging supplements. The first study from the *New England*

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Journal of Medicine was a 2-year, placebo-controlled, randomized, double-blind study involving both women and men.

Among the men, 29 received DHEA, 27 received testosterone, and 31 received placebo. Among women, 27 received DHEA and 30 received placebo. After 24 months the men showed no significant effect of DHEA on body-composition measurements. Neither DHEA nor testosterone affected oxygen consumed per minute, muscle strength, or insulin sensitivity. Testosterone resulted in a slight increase in fat-free mass, and both DHEA and testosterone resulted in an increase in bone mineral density at the femoral neck. Women who received DHEA had an increase in bone mineral density at the ultradistal radius. There was no difference in quality-of-life issues in either group with any intervention. The authors conclude that neither DHEA nor low-dose testosterone replacement in elderly people has physiologically relevant beneficial effects on body composition, physical performance, insulin sensitivity, or quality of life (*N Engl J Med*. 2006; 355:1647–1659).

The second study was also a double-blind, randomized, controlled trial that included a hundred men age 70 and over. Subjects were randomized to receive DHEA 50 mg/d, the anti-estrogen atamestane 100 mg/d, the combination of the 2, or placebo for 36 weeks. No differences were found in either treatment arm compared with placebo on a battery of tests, which included isometric grip strength, leg extensor power, and physical performance (*J Clin Endocrinol Metab*. 2006;91:3988–3991).

The Three Most Common Culprits of ADE

Three drugs are responsible for a third of the estimated 700,000 outpatient adverse drug events per year in this country, according to a new study. A collaborative effort of the FDA, CDC, and US Consumer Chronic Safety Commission developed the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project several years ago to assess the risk of adverse drug events (ADEs) in the outpatient setting. During the 2-year study period, 21,298 ADEs were reported that resulted in patients presenting to the emergency departments of the 63 reporting hospitals. This extrapolates to over 700,000 cases annually in this country. Individuals age 65 or older were more likely than younger individuals to suffer an ADE. Drugs for which regular outpatient monitoring is used to prevent toxicity accounted for 41.5% of hospitalizations, and 50% of hospitalizations were in people age 65 and older. Of those drugs, insulin, warfarin, and digoxin were responsible for one in 3 estimated ADEs treated in emergency departments. The authors conclude that adverse drug events are an important cause of morbidity in the United States, especially among the elderly, and that ongoing population-based surveillance may help target prevention strategies (*JAMA*. 2006; 296:1858–1866).

New Guidelines for Lyme Disease Prevention

The Infectious Disease Society of America has issued new guidelines for Lyme disease (LD) prevention. Of note, guidelines state that routine use of antimicrobial prophylaxis or serologic testing is not recommended after a recognized tick bite; however, a single dose of doxycycline 200 mg may be given to adults and children over the age of 8 if 1) the attached tick is recognized as a potential carrier of LD and has been attached for least 36 hours; 2) the dose can be given within 72 hours of tick removal; 3) the patient is in an endemic area; 4) doxycycline is not contraindicated. Testing of ticks is not recommended. Even if patients have been prophylaxed, they should be monitored for signs and symptoms of tick-borne illness for up to one month (*Clin Infect Dis*. 2006:43—published online October 2, 2006).

FDA Actions

The FDA has approved a new agent for the treatment of hepatitis B infections. Telbivudine (Tyzeka™), from Novartis, has been approved for the treatment of adults with chronic hepatitis B infections. In clinical trials, the drug was shown to suppress replication of hepatitis B virus and reduce liver inflammation.

The FDA has approved Merck's sitagliptin (Januvia™), a new oral antidiabetic for the treatment of type 2 diabetes. The drug is a DPP-4 inhibitor, a new class of medications that prolongs the action of incretin hormones, resulting in improved glycemic control. The drug is approved for monotherapy or as add-on with metformin or a thiazoldinedione. Sitagliptin has the theoretical advantages of not causing weight gain or increasing the risk of hypoglycemia. It is supplied as a 100 mg tablet that is given once a day. ■