AHC Media

Vol. 20, Issue 5, August 2012
www.ahcmedia.com

Critical Care [ALERT]

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

SPECIAL FEATURE

Research Results, Pathophysiologic Reasoning, and Clinical Experience: How Should Critical Care Practice be Guided?

By David J. Pierson, MD, Editor

A middle-aged man with community-acquired pneumonia complicated by underlying cardiomyopathy develops the acute respiratory distress syndrome (ARDS). He is intubated and ventilated according to the institution's lung-protective ventilation protocol, but as positive end-expiratory pressure (PEEP) is increased in response to worsening hypoxemia he becomes hypotensive and tachycardic. Boluses of intravenous crystalloid produce only transient improvement, and an infusion of norepinephrine is started. On 70% oxygen and 14 cm H_2O PEEP, the patient's PaO_2 is 70 mmHg. The resident asks the attending intensivist whether a pulmonary arterial catheter (PAC) should be inserted to guide this patient's management. She is told:

• No. Multiple large studies have shown that PACs do not improve outcomes in patients with sepsis or ARDS.

Or

• Yes. The persistent tachycardia, underlying cardiac dysfunction, and high PEEP make accurate clinical assessment of the patient's volume status very difficult, and data from a PAC may clarify the issue. If the filling pressures are low, then giving more fluid may permit further PEEP increases without compromising cardiac function, and allow the FIO_2 to be decreased as oxygenation improves. On the other hand, if the wedge pressure turns out to be high, then interventions to improve cardiac contractility are needed, and giving more fluid would be inadvisable.

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

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Critical Care Alert,
ISSN 1067-9502, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road, NE Building 6, Suite 400 Atlanta, GA 30305.

POSTMASTER: Send address changes to Critical Care Alert, P.O. Box 105109, Atlanta, GA 30348.

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Subscription Prices
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1 year with free AMA Category 1 credits: $319
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This hypothetical scenario introduces a topic of fundamental importance in today's practice of critical care: how the results of published studies, pathophysiologic reasoning, and other forms of knowledge should be used in guiding clinical decision-making. The intensivist's first response rests on a seemingly secure foundation of evidence-based medicine (EBM), given the extensive literature on PACs and clinical outcomes indicating that their routine use in the ICU fails to improve mortality and tends to increase complications and costs. But does the available evidence include results from patients demographically or physiologically like the one described, managed according to other aspects of current best evidence? His second response seems very sound, given the stated pathophysiologic rationale along with the mutually exclusive approaches to management that the PAC's data might indicate. But will more numbers and more complete physiologic characterization of the situation really benefit the patient in a way that would matter to him in addition to (presumably) enlightening his physicians?

In addition to choosing one of the options given, the attending intensivist might have chosen any of a number of alternative therapeutic interventions — each of them supported by at least some clinical research and/or pathophysiologic evidence, and each within the "accepted scope of practice" in many institutions. These might include different approaches to ventilatory support — such as recruitment maneuvers, airway pressure release ventilation, or high-frequency oscillatory ventilation — or prone positioning, neuromuscular blockade, or extracorporeal membrane oxygenation. The fact that the benefits and hazards of these and other interventions in critical care remain uncertain, as applied to patients with potentially fatal illness by clinicians whose personal experience often gives them strong but divergent preferences for management, makes reconciling the different types of clinical knowledge and the variation encountered in ICU practice critically important.

This special feature is based largely on the recent report of a multi-society working group on the role of clinical research results in the practice of critical care medicine.[1] I will summarize some of the issues and arguments addressed by the group as these relate to the ICU clinician, although the published statement discusses many aspects of these and other things in more detail than can be presented here.

EVIDENCE-BASED MEDICINE IN PERSPECTIVE

The era of EBM began 20 years ago with a paper by Guyatt and colleagues.[2] The goal of EBM is to apply the best available evidence gained from the scientific method to clinical decision making. Ideally, through the use of EBM, clinicians will incorporate all available and relevant medical knowledge in making decisions about how best to manage an individual patient.[1] In pursuit of this goal, EBM seeks to assess the strength of the evidence of risks and benefits of treatments and diagnostic tests. Numerous hierarchies of the various forms of clinical evidence have been put forth in pursuit of this assessment. The following is one such hierarchy:[3]

- Evidence from randomized controlled trials.
- Systematic reviews of observational studies.
- Physiologic studies.
- Unsystematic clinical observations.

Ranked even higher than individual randomized, controlled trials are meta-analyses of multiple such trials; evidence from personal experience would fall somewhere below the last category on the list.

Criticism of and disagreement with the precepts of EBM have been advanced ever since its introduction. Although its proponents have always stressed the need to place best evidence in the context of the individual patient, and to evaluate

the populations, interventions, and practice settings of published studies for relevance to each clinician's circumstances, EBM has been criticized as "cookbook medicine" that robs the practitioner of individual choice and clinical freedom. Its value and applicability in critical care have been hotly debated,[4,5] and remain controversial with respect to the importance of other kinds of evidence besides the results of clinical trials in guiding patient management.[1]

To address this situation, in 2009 the American College of Chest Physicians, the American Thoracic Society, and the Society of Critical Care Medicine assembled the working group that produced the recent official multi-society statement.[1] Besides the then-presidents of the three societies and the first author (an intensivist-educator and ethicist), the group included several experts in critical care research and education who were known to represent a spectrum of viewpoints on the issues under discussion, plus a philosopher and a patient advocate. Their purpose was to identify and clarify the issues involved, and then to create a conceptual framework for clinicians with respect to incorporating the results of clinical research into the practice of critical care medicine. Over a 2-year period the group had a series of face-to-face meetings, conference calls, and electronic communications, leading to unanimous consensus on the statements contained in the published document.[1] There was no intent to accept or reject the principles of EBM, nor to resolve any of the controversies related to specific interventions or practices in the ICU. Instead, the goal was to provide clinicians with a conceptual framework for evaluating discordant information and conflicting claims when caring for critically ill patients.

DIFFERENT TYPES OF KNOWLEDGE IN CRITICAL CARE: PROS AND CONS

A central message of the working group's document is that clinical knowledge comes in several forms, that each of these is important, and that none of them is sufficient by itself for optimal clinical decision-making. The main types of knowledge discussed are the results of clinical research, pathophysiologic reasoning, and knowledge gained from experience.[1]

Clinical research, via properly designed randomized clinical trials (RCTs), can yield data to address specific clinical questions and has the advantage of controlling and minimizing the bias that inevitably comes with personal experience. However, with the strengths of clinical research also come its weaknesses when it comes to applying the results to the individual patient at hand. Researchers in clinical trials study populations, and in order to focus on the variables of interest, they tend to define those populations narrowly, excluding those with atypical features or comorbidities. The protocols used are necessarily very specific, rigid, and rigorously administered. In addition, the results of RCTs are fixed in time and place, and may become less applicable as technical capabilities, other aspects of practice, and the culture of the ICU change. Knowledge gained in RCTs thus cannot be directly and indiscriminately applied to individual patients without careful examination of the circumstances, populations, and protocols used. Attesting to this problem is the frequently demonstrated difference between efficacy (results obtained in the constrained context of an RCT) and clinical effectiveness (what happens when the intervention is employed in routine clinical practice).[6] Apparently similar RCTs can yield contradictory results, and the lack of comparability among different studies leads to disagreement and controversy, even when there is considerable evidence available.[7-10]

A central — and attractive — feature of our field is the prominent role played by physiology in the presentation and evolution of critical illness. It permits a degree of understanding, as well as opportunities for assessment and intervention that are often not possible in other specialties and practice contexts. However, using pathophysiologic reasoning to guide the management of critically ill patients has several shortcomings. Some patients manifest illness and respond to interventions differently from others. There may be important disconnects between desired physiologic effects and improved clinical outcomes. For example, effective suppression of arrhythmias after acute myocardial infarction using flecainide and similar agents resulted in increased mortality.[11] Ventilating patients with ARDS using larger tidal volumes and inflation pressures improved arterial oxygenation but worsened mortality.[12] And while prone positioning improves oxygenation in patients with hypoxemic respiratory failure, meta-analysis of RCTs showed no effect on survival.[13] In addition, as pointed out by the working group, our understanding of the mechanisms involved in critical illness may not be as accurate or as complete as we think.[1]

While emphasis has been placed on the results of clinical research and on pathophysiologic reasoning, experiential knowledge is also an irreplaceable component of clinical practice, and

a legitimate basis for medical decision-making. The source of experiential knowledge may be the individual clinician but can also be derived from other expert clinicians. The problem with this form of knowledge, besides the limited personal experience of individual clinicians in comparison with what can be found in the literature, is the inevitability of bias and the impossibility of its avoidance when used to guide patient care. Better control of bias is a main advantage of clinical research over experiential knowledge, which is an important reason the latter cannot serve as the only source in medical decision-making. Relying on experience tends to make practice patterns more static. And while experience may increase the clinician's levels of comfort and confidence, it may not guarantee greater expertise.

PRACTICE VARIATION: GOOD OR BAD?

While much attention has been given to reducing practice variation by means of clinical practice guidelines and protocols, and numerous studies have shown improved outcomes with their implementation, practice uniformity comparable to that achieved by airline pilots and others in industry is unlikely to occur in critical care. The working group offers a number of reasons why, even in the presence of evidence from RCTs and other relevant knowledge, intensivists are likely to demonstrate considerable variation in how they use their knowledge. These reasons include the following:[1]

- Whether the evidence is consistent with the clinician's prior knowledge or belief.
- Biologic plausibility of the evidence in relation to the clinician's prior knowledge.
- Similarity of patient population and/or intervention to those in the clinician's practice.
- Size of reported effect or benefit.
- Whether the benefit or outcome is perceived to be of high value.
- How rapidly the effect or benefit is likely to occur.
- Perceived costs and safety.
- Relative ease or difficulty of implementation in the clinician's practice setting.

Just as they vary with respect to natural caution vs aggressiveness, clinicians also vary in their tendencies to adopt and adhere to protocols and routines. There are also "early adopters" who quickly embrace new technology and interventions, and those who are reluctant to change established practice patterns. Because of these and other factors, different intensivists will inevitably use the available evidence differently and there will be practice variation.

THE IMPORTANCE OF EXPLICITNESS IN CLINICAL DECISION-MAKING

In one of its key and most emphatic statements, the working group emphasizes the importance of explicitness and transparency in the context of this practice variation.[1] "While there may be important elements of clinicians' knowledge that are tacit, clinicians should be able to identify and articulate the sources and kinds of knowledge that are being invoked in support of a particular clinical decision." Further, the clinician "ought to be able to concisely outline and justify the process of clinical reasoning, elucidating the facts and reasoning supporting a particular decision, such as in the assessment portion of a clinical note, in a presentation to a colleague or trainee, or in discussion with the patient or family."

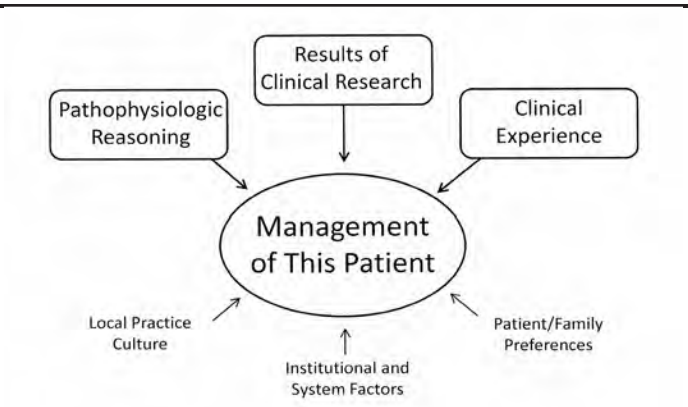
"Because I say so" is not an acceptable explanation for a management decision in the care of a critically ill patient, particularly when that decision varies from protocol or when not all members of the team agree. Disagreement is to some extent inevitable in the high-stakes environment of the ICU, but everyone involved in the patient's care needs to know what the plan is and why — hence the importance of explicitness, as described above.

RECONCILING THE DIFFERENT TYPES OF KNOWLEDGE IN CRITICAL CARE: THE TAKE-HOME MESSAGE

In summarizing their discussion of the various types of knowledge and the factors weighing on their use by clinicians, the working group reached consensus on the following points:

- Clinical research results, pathophysiologic reasoning, and clinical experience each represent a different kind of medical knowledge, and each is crucial for effective clinical decision-making.
- When utilized in the care of individual patients, each kind of medical knowledge has different strengths and weaknesses: none is by itself sufficient to guide clinical decisions, and none takes precedence over the others.
- Patient and/or family preferences and features of the system in which care is delivered also represent important considerations in medical decision-making.
- Clinical research will be more or less compelling to individual clinicians depending on various factors that are independent of study design and statistical validity.
- Practice variation may be acceptable when based on different weighting of conflicting medical knowledge or different patient or clinician values.
- Explicitness is a hallmark of sound clinical reasoning and is necessary in assessing the causes and appropriateness of practice variability.

Figure. Role of Different Kinds of Medical Knowledge in Critical Care Decision Making



In managing an individual critically ill patient, each of the kinds of medical knowledge depicted at the top is important, and none is completely sufficient. Similarly, the factors shown at the bottom of the figure are also important, and must be taken into consideration in clinical decision-making.

The accompanying figure depicts graphically the concepts developed in this important publication and summarized in the above list. ■

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ABSTRACT & COMMENTARY

Antibiotic Resistance Patterns in Medical vs Surgical Patients in the Same ICU

By David J. Pierson, MD, Editor

SYNOPSIS: Over a 2.5-year period, antibiotic resistance patterns of organisms recovered from medical and surgical patients managed by the same intensivist team in the same ICU were indistinguishable. This suggests that reported differences are more likely due to geographic factors and differences in antibiotic usage than to some inherent difference between medical vs surgical ICU patients.

SOURCE: Akulian JA, Metersky ML. Antibiotic resistance patterns in medical and surgical patients in a combined medical-surgical intensive care unit. *J Crit Care* 2012; Mar 27. [Epub ahead of print.]

In the ICU at the University of Connecticut Health Center, adult patients with both medical and surgical problems are primarily managed by the same team of intensivists. The 234-bed teaching hospital does not manage serious trauma, burns, or organ transplants; patients in the ICU

represent general and cardiothoracic surgery, neurosurgery, orthopedics, and non-surgical (that is, medical) patients. This study retrospectively examined the antimicrobial resistance patterns of all bacterial isolates from patients who had been in this unit for more than 1 day during a 2.5-year period. Isolated organisms were categorized in four groups: *Staphylococcus aureus*; *Enterococcus faecalis* and *E. fecium*; non-lactose fermenting gram-negative bacilli; and lactose-fermenting gram-negative bacilli. Antibiotic sensitivities were analyzed for each of these groups, for medical vs surgical patients.

Of 1551 eligible ICU admissions, 265 patients had positive cultures and were included in the study: 171 medical patients with 242 positive cultures and 94 surgical patients with 175 positive cultures. Patient demographics and comorbidity status were not different between the two groups, although surgical patients had been in the hospital and in the ICU substantially longer before the positive culture appeared (3.5 and 2.4 days, respectively, for medical patients, vs 13 and 6.6 days for surgical patients, both $P < 0.001$). No significant difference in antibiotic resistance was found between medical vs surgical patients for any of the four bacterial groups.

COMMENTARY

Similar patients with ICU-associated infections in different institutions and in different regions may have markedly different causative organisms. A number of studies have found important differences in antimicrobial resistance patterns in organisms recovered from medical vs surgical ICU patients in the same hospital. However, as the authors of the present study point out, those studies have come from institutions with physically separate units and different management teams. This study found similar patterns of antimicrobial resistance in medical and surgical patients managed in a combined medical-surgical ICU by a common intensivist team.

Together, these findings suggest that the antimicrobial resistance patterns manifested by ICU-acquired bacteria in a given unit are more likely to reflect local epidemiologic conditions and antibiotic usage patterns than any inherent differences among patients with surgical and non-surgical illnesses. For the clinician, the message with respect to antimicrobial usage in patients with suspected ICU-acquired infection seems little changed by the findings of this study: Select empirical coverage according to your unit's current bacterial prevalence and antibiogram, as well as the patient's risk factors and clinical condition, and modify it promptly once culture and sensitivity results are available. ■

ABSTRACT & COMMENTARY

Are There Effective, Evidence-Based Strategies That Can be Implemented in Practice to Prevent Unplanned Extubations?

By Linda L. Chlan, RN, PhD
School of Nursing, University of Minnesota

Dr. Chlan reports that she receives grant/research support from the National Institutes of Health.

SYNOPSIS: Recommendations from the small number of lower-quality studies cited in this review article that examined strategies to prevent unplanned endotracheal extubations include: continuous quality improvement programs to standardize care including weaning readiness; application of physical restraints only when deemed necessary to prevent device removal; standardized practices for securing the endotracheal tube; sedation protocols; and appropriate nurse/patient ratios.

SOURCE: da Silva Lucas PS, Fonseca MC. Unplanned endotracheal extubations in the intensive care unit: Systematic review, critical appraisal, and evidence-based recommendations. *Anesth Analg* 2012;114:1003-1014.

The purpose of this article was to provide a systematic review and critical appraisal of the literature on the incidence and risk factors for unplanned endotracheal extubations, factors associated with reintubations, and outcomes of unplanned extubations. Several evidence-based recommendations were presented to prevent unplanned extubations.

The search strategy used by the two Brazilian

authors included searching a number of key databases from January 1950 to May 2011, with an extensive list of key search terms pertaining to adult ICU patients. Criteria for selection of studies included the incidence of unplanned extubations, outcomes and risk factors of unplanned extubations, the incidence of reintubations, and strategies to prevent unplanned extubations. A variety of study designs were considered, including cohort, case-control, or cross-sectional. The Newcastle-Ottawa Scale[1] was used to assess the quality of nonrandomized studies. The Oxford Centre for Evidence-based Medicine's Level of Evidence[2] was used for assessing grades of recommendation. The search initially yielded 44,766 potentially relevant studies, 103 of which were reviewed. From this number, 50 studies met the inclusion criteria. Overall, the papers included in the review were deemed to be of lower methodological quality as no randomized trials were included.

The incidence of unplanned extubations is reported in the literature as either the number per 100 ventilated patients, or as the number per 100 days of mechanical ventilation. This varying method of reporting a key statistic is problematic. Overall, over the last 10 years the median rate of unplanned extubation was 7.3 per 100 ventilated patients, or a median of 0.9 unplanned extubations per 100 intubation days. A majority of unplanned extubations were patient self-extubations. Risk factors associated with unplanned extubations among the studies reviewed were inconsistent across the studies. Some studies reported that patients who were restless or agitated self-extubated more often, whereas others reported patients at a higher level of consciousness self-extubated. Patients who received midazolam had a greater risk for self-extubations, as did those with a higher acuity level, and those without a nurse at the bedside. The application of physical restraints was found in 25-87% of patients who self-extubated.

Not surprisingly, complications of unplanned extubations include airway and vocal trauma, respiratory distress, tachycardia, and emesis. Reintubation rates were 1.8-88% overall. Outcomes of unplanned extubations included prolonged mechanical ventilation and longer ICU and hospital stays, particularly in those patients who required reintubation, which was associated with increased mortality. Very few studies included preventive measures for reducing unplanned extubations. Most effective were quality improvement programs targeted with staff education, surveillance, and management of high-risk patients.

Physical restraints do not prevent self-extubation and should only be used when other strategies to prevent device removal have been exhausted. Methods for safely securing the endotracheal tube should be used on all patients. The role of sedation remains controversial. Patients who are sedated still self-extubate, which the authors concluded was an indicator of inadequate sedation. Given that most patients tolerate unplanned extubations, weaning readiness should be actively assessed in patients. The role of appropriate nursing staff ratios and experience remains unclear in the prevention of unplanned extubations.

COMMENTARY

This well-done, high-quality systematic review critically appraises the state of the science in regards to the incidence, risk factors, outcomes, and preventive strategies surrounding unplanned endotracheal extubations. While unplanned extubation can be a serious occurrence, most patients who self-extubate do not require re-intubation. Most times, these patients were ready to wean. A complicating factor in this review is that some studies report unplanned extubation rates per 100 patients, while others report them per 100 patient days. A standard report metric is needed.

The role of sedation and physical restraints in unplanned extubations remains unclear. This author does not agree with the comments made by da Silva Lucas and Fonseca that inadequate sedation is tied to self-extubations. Given the complexity of factors, delirium and agitation may play a prominent role. Patients who are anxious may require a different approach to symptoms management. Tailored sedative regimens are needed for mechanically ventilated patients. Likewise, the use of physical restraints does not prevent self-extubation. The literature demonstrates that the application of physical restraints can contribute to patient agitation and thus lead to self-extubation. The practice of routine application of physical restraints to prevent treatment interference is unwarranted and needs to cease.

Many of the recommendations for prevention of unplanned extubations are based on sound clinical practice, such as implementing standardized protocols for weaning readiness and securing endotracheal tubes. Clinicians are advised to actively include these strategies in their practice to prevent unplanned extubations. ■

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To earn credit for this activity, please follow these instructions:

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CME/CNE Questions

1. Which of the following kinds of medical knowledge is most valuable in clinical decision making?

a. The results of clinical research
b. Pathophysiologic reasoning
c. Either a or b depending on the clinical situation
d. Personal experience
e. None of the above

2. Which of the following characteristics of the results of clinical research may cause different clinicians to use those results differently in managing patients?

a. Whether the benefit or outcome is perceived to be of high value
b. How rapidly the effect or benefit is likely to occur
c. The perceived costs and safety of the intervention
d. The relative ease or difficulty of implementation in the clinician's practice setting
e. All of the above

3. The study of antimicrobial resistance in organisms from medical vs surgical ICU patients found which of the following?

a. More methicillin-resistant *Staphylococcus aureus* in medical patients
b. More lactose-fermenting gram-negative rods in surgical patients
c. More vancomycin-resistant *Enterococcus* species in surgical patients
d. a and b but not c
e. None of the above

4. Which of the following is true about the antimicrobial resistance patterns in ICU-acquired organisms from medical vs surgical patients?

a. Medical patients in the study were older and had more comorbidities
b. Surgical patients had more antimicrobial resistance in all four bacterial groups studied
c. Surgical patients were in the unit longer before having a positive culture
d. All of the above
e. None of the above

5. A most common risk factor for unplanned endotracheal extubations is:

a. younger age.
b. higher illness acuity.
c. absence of physical restraints.
d. presence of sedation protocols.
e. None of the above

6. Evidence-based strategies to prevent unplanned endotracheal extubations include:

a. standardized protocols to secure the endotracheal tube.
b. protocols to restrain all patients.
c. use of midazolam as the sedative of choice for all patients.
d. minimal interruption of patients by nursing staff.
e. None of the above

CME/CNE Objectives

Upon completion of this educational activity, participants should be able to:

- identify the particular clinical, legal, or scientific issues related to critical care;
- describe how those issues affect physicians, nurses, health care workers, hospitals, or the health care industry; and
- cite solutions to the problems associated with those issues.

[IN FUTURE ISSUES]

Is pulmonary oxygen toxicity still a clinically relevant issue?

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.*

FDA Approves First New Anti-Obesity Drug in Years

In this issue: Lorcaserin for weight loss; statins and fatigue; treatment-resistant gonorrhea; hydrocodone classification changes; USPSTF recommendations; and FDA actions.

Magic bullet for weight management?

The FDA has approved lorcaserin, the first new weight loss medication in more than a decade. The drug is approved for chronic weight management in adults with a body mass index of 30 or greater, or 27 or greater in those with weight-related conditions such as high blood pressure, type 2 diabetes, or hypercholesterolemia. Lorcaserin works by activating the serotonin 2C receptor in the brain, which promotes satiety. Approval was based on the results of three randomized, placebo-controlled trials of nearly 8000 obese and overweight patients with and without type 2 diabetes. All participants received lifestyle modification and reduced-calorie diets as well as exercise counseling. Lorcaserin was associated with an average weight loss of 3-3.7% compared to placebo over 1 year. Those with type 2 diabetes experienced favorable changes in glycemic control. There is no evidence of valvulopathy associated with the drug; although serotonin syndrome is a concern, especially when the locaserin is taken with an SSRI or some migraine drugs. The most common side effects include headache, dizziness, fatigue, nausea, dry mouth, and constipation as well as hypoglycemia in diabetic patients. Lorcaserin will be marketed by Arena Pharmaceuticals as Belviq. ■

Do statins cause fatigue?

Statins may be associated with fatigue and exertional intolerance, according to a small study from UC San Diego. Researchers randomized just over 1000 patients (692 men and 324 women) to simvastatin 20 mg (lipophilic statin), pravastatin 40 mg (hydrophilic statin), or placebo for 6 months. The outcomes were self-ratings of change in baseline in "energy" and "fatigue with exertion." Statin users were more likely to report worsening energy and fatigue compared to placebo ($P = 0.002$) Fatigue and exertional intolerance was worse with simvastatin compared to pravastatin (simvastatin, $P = 0.03$; pravastatin, $P = 0.01$). Women were more severely affected than men. The authors acknowledge that these findings are based on small numbers and findings are provisional. However, they also state that "this is the first randomized evidence of affirming unfavorable statin effects on energy and exertional fatigue." They further suggest that these effects "germane to quality of life, merit consideration when prescribing or contemplating use of statins, particularly in groups without expected morbidity/mortality benefit." (*Arch Intern Med* published online June 11, 2012. doi: 10.1001/archinternmed.2012.2171). The study also raises the potential issue of increased adverse effects of lipophilic statins such as simvastatin. The various risks and benefits of lipophilicity have been debated for years. It is clear that highly lipophilic statins, such as the now removed cerivastatin (Baycol), may have more muscle toxicity, and may have more CNS adverse effects as well. Of currently marketed statins, simvastatin is the most lipophilic, while pravastatin and rosuvastatin are the least. ■

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Call to action for resistant gonorrhea

The World Health Organization (WHO) is calling for urgent action to prevent the spread of "untreatable gonorrhea" around the world. The concern is based on reports from several countries, including Japan, United Kingdom, Australia, France, Sweden, and Norway, of gonorrhea that is resistant to cephalosporin antibiotics — the last remaining treatment option. According to WHO, more than 100 million people are infected with gonorrhea annually, and the world is faced with "dwindling treatment options." WHO is calling for greater vigilance on the correct use of antibiotics and more research into alternative treatment regimens for gonococcal infections. The agency also calls for increased monitoring and reporting of resistant strains as well as better prevention, diagnosis, and control of gonococcal infections. Single-dose treatment to assure adherence is also important as is the treatment of partners. WHO also stresses education and prevention, with special attention to high-risk groups such as sex workers and men who have sex with men. Cephalosporin-resistant gonorrhea has not been reported in the United States yet, but surveillance systems are in place. According to a recent CDC editorial in the *New England Journal of Medicine,* "It is time to sound the alarm. During the past 3 years, the wily gonococcus has become less susceptible to our last line of antimicrobial defense..." (*N Engl J Med* 2012; 366:485-487). ■

Changes on horizon for hydrocodone drugs

Could Vicodin soon be a Schedule II drug? The answer may be yes depending on congressional action this summer. The U.S. Senate recently passed The FDA Safety and Innovation Act (S 3187) with an amendment to classify all hydrocodone-containing products from Schedule III to Schedule II. The House of Representative's version of the bill did not contain similar language, and the proposal is under consideration for the final bill to be sent to the President for signature later this summer. Meanwhile, lawmakers in New York are moving forward with legislation that would make all hydrocodone-containing drugs Schedule II. If enacted, these laws would categorize hydrocodone containing drugs, such as Vicodin and Norco, in the same group with morphine, oxycodone, and methadone. Schedule II drugs cannot be phoned in, and patients are required to receive a new prescription for each refill. The proposed tightened regulations are in response to the explosion of prescription opioid abuse nationwide. Meanwhile, pharmacy groups, such as the American Pharmacists Association, are opposed to the legislation and are actively lobbying against it, arguing that it is unnecessarily restrictive to patients who legitimately need access to these drugs. ■

Vitamin D and calcium supplements

The U.S. Preventive Services Task Force (USPSTF) has now recommended that vitamin D and calcium supplements above the usual recommended daily allowances are of no benefit to help prevent bone fractures in healthy older women, and may actually cause harm. In a draft recommendation statement issued in early June, the USPSTF concluded that there is insufficient evidence to recommend vitamin D for prevention of cancer or combined vitamin D and calcium for the prevention of fractures in postmenopausal women or men. They further recommend against daily supplementation of more than 400 IU of vitamin D and 1000 mg of calcium carbonate. Older adults who are at risk for falls may continue to take vitamin D (www.uspreventiveserviestaskforce.org/draftrec3.htm). The draft recommendation was issued just after a study was published showing calcium plus vitamin D supplements appear to be associated with lower mortality in older individuals. In a large meta-analysis, patients receiving both calcium and vitamin D had a 9% reduction in mortality (hazard ratio, 0.91; 95% confidence interval, 0.84-0.98), although vitamin D alone did not affect mortality (*J Clin Endocrinol Metab* published online May 17, 2012, doi: 10.1210/jc.2011-3328). ■

FDA actions

The FDA has issued opinions on two oral novel anticoagulants. The agency turned down Janssen's application for approval of rivaroxaban (Xarelto) for the treatment of acute coronary syndrome, at least for now. The FDA did not release the reasons for the decision, but speculation is they want more information from the ATLAS-ACS trial. Rivaroxaban was approved last year for prevention of venous thromboembolism after hip or knee replacement surgery, and also for stroke prevention in patients with non-valvular atrial fibrillation (AF). The FDA also delayed the approval of apixaban (which would represent the third novel oral anticoagulant along with dabigatran and rivaroxaban) for the prevention of stroke and systemic embolism in patients with non-valvular AF. It had been widely speculated that the drug would be approved this spring, especially given that the FDA had granted a priority review for apixaban last November. The delay is similarly due to the need for additional information from the ARISTOTLE trial. Once approved apixaban will be marketed by Bristol-Myers Squibb as Eliquis. ■