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INSIDE

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Predictors of PTSD in Ventilated ICU Patients

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *Among survivors of critical illness requiring mechanical ventilation who were followed up at 6 months, symptoms of PTSD were more common in women, in those under age 50, and in those who had received higher doses of lorazepam during their ICU stay.*

Source: Girard TD et al. *Crit Care.* 2007 Feb 22;11(1):R28 [Epub ahead of print].

This pilot study from the medical and coronary ICUs at Vanderbilt University Medical Center sought to identify factors associated with the development of symptoms of post-traumatic stress disorder (PTSD) following critical illness. The authors prospectively evaluated all English-speaking patients without underlying neurological impairment who required mechanical ventilation during the study period. In those enrolled, they recorded demographics, ICU admission diagnoses, APACHE II score, and Charlson Comorbidity Index, and evaluated them daily for delirium using the CAM-ICU scale previously developed by the authors. They also recorded all doses of sedatives and narcotic analgesics administered to the patients. They then followed the patients up at 6 months using a validated 2-part questionnaire (the PTSS-10) for assessing symptoms of PTSD.

A total of 280 of the 555 patients potentially eligible for inclusion in the study were excluded according to a priori criteria, leaving 275 enrolled patients, 96 of whom died during hospitalization and 179 were potentially eligible for follow-up. Of the 179, 86 were lost to follow-up, 23 died within 6 months, and 27 were judged too ill at 6 months to participate or declined to participate. Thus, 43 patients (24% of those eligible at discharge) were included in the follow-up study. Of these, 6 (14%) scored more than 35 points on the PTSS-10, consistent with a diagnosis of PTSD. These 6 patients were compared to the others who were evaluated at 6 months to look for associations and potential predictors of the disorder.

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Female patients had more PTSD than males on multivariable analysis. High levels of PTSD symptoms were less likely to occur in older patients, with these symptoms significantly less likely in those older than age 50. Although overall the amount of sedatives (benzodiazepines and/or propofol) and opioids administered to the patients did not correlate with development of PTSD, the total dose of lorazepam was positively associated with PTSD by both univariate and multivariable analysis. The duration of delirium did not differ among patients who did and did not develop PTSD.

COMMENTARY

This small but carefully done prospective study found PTSD in 14% of patients who survived a critical medical illness requiring mechanical ventilation. PTSD symptoms were more likely to occur in women, in patients older than age 50, and in patients who received higher cumulative doses of lorazepam.

Only 6 patients met diagnostic criteria for PTSD in this study. Thus, it should be regarded as a pilot study, as the authors emphasize, and its results should be interpreted cautiously. For example, one must not read too much into the association between lorazepam dose and PTSD, given the small numbers involved and the fact that no association was evident for midazolam, the other benzodiazepine commonly used. However, it is becoming increasingly clear from this and other studies that PTSD occurs in a significant minority of patients who survive a critical illness. As the authors point out, patients and their families should be made aware of this complication, and clinicians following patients after hospital discharge should be prepared to recognize and deal with PTSD if it occurs. ■

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Family Conferences in the ICU Infrequently Address The Patient's Prognosis for Survival

ABSTRACT & COMMENTARY

By Leslie A. Hoffman, PhD, RN

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

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

Synopsis: *Although the majority (> 85%) of conferences included statements about functional ability and quality of life, prognosis for survival was not mentioned in one third of conferences.*

Source: White DB, et al. Prognostication during physician-family discussions about limiting life support in intensive care units. *Critical Care Med.* 2007;35:442-448.

ALTHOUGH PROGNOSTIC INFORMATION IS VIEWED as very important to family members of incapacitated, critically ill patients, little is known about what prognostic information clinicians provide during family conferences. This study presents an analysis of 51 patient-family conferences that involved deliberations about major end-of-life treatment decisions. The study was conducted in four Seattle area hospitals, including two community hospitals, one inner city hospital and one university hospital.

Of the 68 families approached, 51 (75%) agreed to participate. Mean duration of the conferences was 32.0 ± 14.8 min (range 7-74 min). The majority of conferences (86%) contained discussions about the patient's anticipated functional status or quality of life, compared with 63%

in which the chances for survival (short or long term) were discussed. Four factors were associated with a greater number of prognostic statements about survival, including a longer duration of the conference ($p < .001$), increased amount of conflict between the physician and family about withdrawing life support ($p < .001$), the physician's race being white ($p = .009$) and higher educational level of the family ($p < .001$). There was considerable physician-to-physician variability in the amount of prognostic information provided but consistency in information provided by individual physicians.

COMMENTARY

ICUs admit critically ill patients with the goal of providing technically sophisticated care that leads to their recovery. Despite advances in care provision, surveys indicate that many patients do not respond to treatment or experience complications that suggest they have limited potential for survival, either short- or long-term, or will have severe limitations in functional status, quality of life, or neurological outcome. In such situations, surveys suggest that the majority of families indicate they want to actively participate in end-of-life decision-making. In order do this, it is important that that they clearly understand the patient's expected prognosis.

A positive aspect of this study was the finding that, with one exception, all recorded conferences included at least one statement about prognosis, and the overwhelming majority (86%) included statements about functional outcomes or quality of life. There was a strong positive association between the length of the conference and the number of prognostic statements. While most included statements about prognosis for survival, such comments were missing from approximately one-third of family conferences. Prior studies have shown that families with the most optimistic expectations tend to opt for more aggressive treatment. Consequently, this finding has implications for decision-making.

Moral distress is defined as a situation in which an individual feels a certain way about the appropriate ethical choice but is constrained from taking this action. In a recent study of nurse-physician perceptions of moral distress, the three situations ranked as most troubling were "being expected to continue life support because of a family decision when not in the patient's best interests"; "initiating lifesaving actions that only prolong death"; and "avoiding the decision to pull the plug".[1] Continuing aggressive interventions when the patient has no chance of recovery risks adverse consequences for all involved—patients, families, and clinicians. Although prognostication is admittedly inexact, it is possible to introduce the topic in general terms, eg, "I'm afraid that things may not turn out well" and then proceed to more specific statements, eg, "I don't see her surviving more than a few months." Findings of this study suggest that it is important to ensure that prognostic information is shared and understood by families with less education, who may not ask leading questions, and to allow a reasonable period of time for the discussion. ■

Reference

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Can Procalcitonin Distinguish Sepsis from Other Causes of SIRS?

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: *A meta-analysis of 18 studies that have examined the usefulness of procalcitonin measurement in the diagnosis of sepsis finds that the diagnostic performance of this measurement is low and that the test cannot reliably distinguish sepsis from other causes of the systemic inflammatory response syndrome.*

Source: Tang BMP, et al. *Lancet Infect Dis.* 2007;7(3):210-217.

Several studies have suggested that procalcitonin may be a useful biochemical marker to differentiate sepsis from other, non-infectious, causes of the systemic inflammatory response syndrome (SIRS), such as pancreatitis. Tang and colleagues conducted a meta-analysis of these studies in order to evaluate the diagnostic accuracy of procalcitonin in the diagnosis of sepsis and to determine whether the increasing reliance on the test in clinical practice is, in fact, justified.

Out of a total of 39 candidate studies, 18 investigations encompassing 2097 patients were included in the

final meta-analysis. Studies were excluded if they lacked a well-defined gold standard for the diagnosis of sepsis, provided insufficient information to create 2 X 2 contingency tables and examined patients without SIRS or critical illness or examined too narrow a spectrum of critically ill patients. The 18 studies were divided into two groups: phase 2 studies which examined how the test discriminates between patients with and without sepsis, and phase 3 studies that evaluate the test's performance in patients suspected to have the disorder. Performance characteristics including sensitivity and specificity, positive and negative likelihood ratios, diagnostic odds ratio (the ratio of the odds of a positive test in a patient with sepsis compared with the odds of a positive test in a patient without sepsis) and summary receiver operator characteristic (SROC) curves were determined for these separate groups and then for all 18 studies combined.

In the 14 phase 2 studies, procalcitonin had a positive likelihood ratio of 3.03, a negative likelihood ratio of 0.43, a diagnostic odds ratio of 7.79 (values greater than 100 indicate high accuracy while values less than 25 point to a lack of utility for the test) and an area under the curve of 0.79. Statistical analysis could not be performed on the 4 phase 3 studies due to a high level of statistical heterogeneity resulting from variations in sample sizes, but the larger studies in this group did trend toward a lack of diagnostic accuracy. When statistical analysis was performed on all 18 studies combined, test performance remained low; the mean values for sensitivity and specificity were 71% (95% confidence interval 67 to 76%) and the area under the SROC curve was only 0.78.

COMMENTARY

The study by Tang and colleagues should give pause to clinicians who are considering adding procalcitonin measurements to their diagnostic protocols in the ICU; in a meta-analysis that appears methodologically sound, they demonstrate that the test characteristics for procalcitonin are not of sufficient quality to warrant reliance on this test in critically ill patients. In addition to the low mean sensitivity and specificity and somewhat low area under the ROC curve across the 18 studies included in the meta-analysis, the low positive and negative likelihood ratios are a concern.

The clinician standing at the bedside will not be looking for help from a diagnostic standpoint when his or her pre-test probability of the patient having sepsis is on the very low or very high side. Instead, such a clinician needs assistance when the pre-test probability is in the intermediate range. However, with a positive likelihood of 3 and a negative likelihood ratio of 0.43, the procalcitonin measurement is unlikely to change the pre-test probability enough to alter one's decisions as to whether or not to start antibiotics.

Another question to consider in deciding whether to incorporate this test into diagnostic protocols is how well the test performs relative to our current strategies. Among the studies in the meta-analysis, very few of them actually examined how the procalcitonin test performed when compared to a clinician's bedside assessment. Even if the test has a good sensitivity, specificity and other test characteristics, it is not clear that we need to use it if it does not perform any better than clinicians already perform in its absence. For example, it might be worthwhile to know whether procalcitonin-based decision strategies decrease the inappropriate use of antibiotics, much the same way that bronchoalveolar lavage in the diagnosis of ventilator-associated pneumonia was shown to lead to more rational antibiotic use.

Until such data becomes available or consistent data emerges from large studies on broad ranges of critically ill patients with better test characteristics than those found by Tang and colleagues, clinicians should avoid using procalcitonin in the diagnosis of sepsis. ■

Managing ARDS: Steroid Saga Sequel

ABSTRACT & COMMENTARY

By Saadia R. Akhtar, MD, MSC

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

Synopsis: *This multicenter, randomized, double-blind, placebo-controlled trial finds that early initiation of low-dose, prolonged glucocorticosteroid therapy for ARDS results in improved lung injury scores and a greater likelihood of successful extubation by day 7. Other clinical outcomes may also be favorably impacted.*

Source: Meduri GU, et al. *Chest.* 2007;Apr;131(4):954-963.

SYSTEMIC AND PULMONARY INFLAMMATION ARE KEY in the development and progression of the acute res-

piratory distress syndrome (ARDS). Lack of improvements in inflammatory markers and in the lung injury score (LIS) by day 7 are associated with higher mortality.[1] Some small studies have suggested that low-to-moderate-dose, prolonged corticosteroid infusion may reduce inflammatory markers, LIS, and duration of mechanical ventilation.[2] With this foundation, Meduri et al set out to determine whether early initiation of low-dose prolonged glucocorticosteroid replacement for ARDS leads to improvement in LIS (1 point reduction) and greater success of extubation by day 7.

A randomized double-blind placebo-controlled study was conducted at 5 hospitals in Memphis, Tennessee, over 5 years. Adult patients meeting usual criteria for ARDS within 72 hours of initiation of mechanical ventilation were eligible. Once enrolled, patients were randomized 2:1 to receive methylprednisolone vs placebo: a bolus dose of 1 mg/kg was followed by daily doses of 1 mg/kg/day from day 1-14 (or until extubation, whichever came first), and then a taper (0.5mg/kg/day for 1 week, 0.25mg/kg/day for 4 days, and 0.125mg/kg/day for 3 days). Low-tidal-volume ventilation per the ARDSnet protocol was utilized once the data from the ARDS Network's initial trial became available. Screening for ventilator-associated pneumonia was performed prior to initiation of drug, then every 5-7 days until extubation. Neuromuscular blockers were not permitted. Finally, patients whose LIS did not improve between study day 7-9 were removed from the study and treated unblinded with 2mg/kg/day methylprednisolone. Intention-to-treat analysis was performed, and other standard statistical techniques were employed. Interim data analyses were done after enrollment of every 30 patients.

Over 5 years, 500 patients were screened. Of these, 91 (63 methylprednisolone, 28 placebo) met inclusion criteria and agreed to participate. At baseline, patients in the 2 groups were similar in all ways (including precipitating factor for ARDS) except that there were a larger number of subjects in the placebo group with catecholamine-dependent septic shock. At day 7, there were marked, statistically significant differences between the corticosteroid and placebo groups in 1-point reduction in LIS (69.8% vs 35.7%) and successful liberation from mechanical ventilation (54% vs 25%). A variety of other clinical parameters were similarly impacted: C-reactive protein level, PaO_2/FIO_2, multiple organ dysfunction score, length of ICU stay and ICU mortality (hospital and post-discharge mortality up to 12 months) were not significantly different.

Interestingly, patients whose initial short cosyntropin stimulation test revealed relative adrenal insufficiency had less improvement in both study arms. There were less nosocomial infections in the methylprednisolone group and no difference in number of patients who developed neuromuscular weakness. Five patients in the control group and 10 in the methylprednisolone group were transitioned to open-label glucocorticosteroids when LIS did not improve significantly at days 7-9.

COMMENTARY

Short-term high-dose corticosteroid infusions do not improve and in fact may worsen outcomes in patients with ARDS.[3] As noted above, some small studies have suggested that low-to-moderate-dose prolonged glucocorticosteroid infusion reduces inflammatory markers, LIS and duration of mechanical ventilation.[2] Such work motivated a recent large multicenter study of low-dose glucocorticosteroids for late ARDS (beginning at day 7 or later, for a total of 21 days of therapy). Investigators found that there was no overall mortality benefit at 60 or 180 days; furthermore, there was the suggestion of worse outcome in those patients started on glucocorticosteroids at day 14 or later but a trend towards improved survival in those patients started on glucocorticosteroids between days 7-13.[4] Thus, interest remains in using glucocorticosteroids early in ARDS. Supportive evidence for this was also provided by a post hoc analysis of a study using glucocorticosteroids for septic shock, which suggested an association between ARDS and mortality benefit with glucocorticosteroids.[5]

Meduri et al's investigation of methylprednisolone infusion beginning (at 1mg/kg/day) within 72 hours of onset of ARDS and tapering off over 2-4 weeks finds a marked difference in the primary endpoints of LIS and successful extubation by day 7. Although these are interesting and exciting results, they are not, as the authors themselves acknowledge, definitive but rather hypothesis-generating for a larger clinical trial. That is, whether these findings signify that long-term outcomes such as mortality will be similarly improved with this treatment in most patients with ARDS remains unknown. The critical care community has learned from multiple prior experiences that surrogate markers of long-term outcomes may not be reliable or accurate predictors. This current data should be assessed with that information in mind.

This work has limited generalizability as the patient population was fairly specific. This was a regional rather than national or international cohort. In addition, as with the recent trial by the ARDSnet investigators,[4] a large percentage of screened patients were excluded from enrollment by the predefined study criteria. The study was not powered to assess important clinical out-

comes such as hospital length of stay or mortality (the placebo group in particular was quite small). Furthermore, the results and analysis are complicated by several factors. There was a significant baseline difference between the treatment arms in numbers of patients with catecholamine-dependent septic shock.

Based on other evidence about glucocorticosteroids in septic shock, we must question the conclusions about the basis of the outcome differences in this study. Due to the time period during which this trial was conducted, some patients did not receive a low-tidal-volume ventilation protocol, and there was no consistent weaning protocol in place. Both of these practices may have impacted the magnitude of difference in outcomes between the 2 treatment groups. The fact that some patients were taken off the study to receive glucocorticosteroids may change the results in a variety of unpredictable ways. (I am intrigued and surprised by the fact that the investigators used a study of 24 patients to take current study patients off protocol for failure to improve LIS at day 7-9 [2].)

Thus, contrary to Annane's recommendation (in the editorial accompanying this paper)[6] that all patients with ARDS (except those at > 2 weeks) be treated with prolonged glucocorticosteroids as Meduri et al have proposed, I suggest caution until other larger studies examine this protocol. The findings are promising but I believe additional evidence is needed to more clearly guide our usage of glucocorticosteroids in patients with ARDS. Those physicians who decide to use the therapy recommended by Meduri et al now must at least carefully monitor their patients for infection and neuromuscular weakness, aggressively manage blood glucose, and use low-tidal-volume ventilation. ■

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Should We Use Intensive Insulin Therapy to Prevent Critical Illness Polyneuropathy?

ABSTRACT & COMMENTARY

By Andrew M. Luks, MD

Synopsis: *A prospectively planned sub-analysis of data from a randomized trial of intensive insulin therapy in the medical ICU reveals that in patients in the ICU for greater than 7 days, intensive insulin therapy decreases both the incidence of critical illness polyneuropathy / myopathy and the frequency of prolonged mechanical ventilation.*

Source: Hermans G, et al. *Am J Respir Crit Care Med.* 2006;175:480-489.

Van den Berghe et al have recently reported the results of intensive insulin therapy (IIT) on morbidity and mortality in medical intensive care unit patients.[1] In the study discussed below, Hermans and colleagues performed a prospectively planned sub-analysis on data from that trial to determine whether IIT had any effect on the incidence of critical illness polyneuropathy/myopathy (CIP/CIM) and the frequency of treatment with prolonged mechanical ventilation in medical patients who were in the ICU for 7 or more days.

A total of 443 patients met criteria inclusion in this sub-analysis. Out of the 420 patients for whom complete data was available, 212 had been randomly assigned to receive conventional insulin therapy (CIT) while the remaining 208 patients were randomized to the IIT arm. IIT was aimed at blood glucose levels between 80 and 110 mg/dL while the CIT protocol mandated that insulin be given when blood glucose levels were above 215 mg/dL and that insulin doses be decreased or held if the blood glucose fell below 180 mg/dL. The diagnosis of CIP/CIM was made using electroneuromyography (ENMG) while prolonged mechanical ventilation was defined as greater than or equal to 14 days on the ventilator.

Mean glucose levels in the IIT group were 102 mg/dL vs 159 mg/dL in the CIT group. Within the IIT group, 81 out of the 208 patients (38.9%) met ENMG criteria for CIP/CIM compared to 107 out of 212 patients in the CIT group (50.5%). The authors

also found that IIT reduced the incidence of treatment with prolonged mechanical ventilation from 99 of 212 patients in the CIT group (46.7%) to 72 of 208 patients (34.6%) in the IIT group. Furthermore, IIT increased the cumulative chance of successful weaning from mechanical ventilation and decreased the number of days on the mechanical ventilation from a median of 14 (interquartile range 9-22) in the CIT group to 12 days (inter-quartile range, 8-20 days) in the IIT group.

In their analysis of risk factors for the development of CIP/CIM, the authors report that while neuromuscular blocking agents increased the risk of CIP/CIM, corticosteroids actually had a protective effect with regard to this outcome, as did increasing patient age. When risk factors for prolonged mechanical ventilation were assessed, however, the number of days of treatment with corticosteroids was found to increase the duration of treatment with mechanical ventilation.

COMMENTARY

Debate continues as to whether intensive insulin therapy should be standard practice in the ICU. Herman and colleagues make a useful contribution to the growing literature on this issue by providing data on important endpoints—the incidence of critical illness polyneuropathy and duration of mechanical ventilation—which affect the clinical outcomes for critically ill patients. Their additional finding that corticosteroids may exert a protective effect against CIP/CIM is particularly intriguing and runs counter to much previous work which has demonstrated that corticosteroids exerted a deleterious effect in this regard. Unfortunately, their results do not provide any insight into the potential mechanism for this finding beyond the fact that better control of blood glucose levels in the setting of steroid use may be the key factor.

While the article provides useful data in this important debate, it is not clear that these results are enough to convince those on the fence about the usefulness of IIT to switch their practice and incorporate it into ICU protocols. This reservation derives from several methodological issues with the study. First, although the two groups were well-matched with respect to most variables, maximum sequential organ failure assessment (SOFA) scores were lower in the IIT group than in the CIT group. To the extent that severity of illness affects the likelihood of developing CIP/CIM or prolonged mechanical ventilation, this mismatch is potentially of great significance. Second, CIP/CIM was diagnosed solely on the basis of ENMG and it is not clear that this measure correlates well with other markers of patient strength or neurologic function.

A more important concern, however, is the fact that the authors only included patients who had been in the intensive care unit for seven or more days. It is not clear why patients with shorter ICU duration were not included and it is worthwhile to question whether the inclusion of these patients' stay may have, in fact, altered the observed results of the study. This omission is also of importance for clinical practice. If IIT is only of benefit in patients treated in the ICU for greater than seven days, in the absence of useful prognostic factors to identify a priori which patients will fall into that category, clinicians are left wondering in whom and when they should start IIT following ICU admission.

A final concern in considering whether to implement this therapy is the fact that the only positive trials for IIT[1,2] have come from this one research group conducting their studies out of a single center; at the same time, several large studies from other centers have been stopped early due to a lack of efficacy or concerns about the safety of IIT. Until positive results emerge from other multi-center trials, it is reasonable to resist the urge of Hermans and colleague's intriguing data and hold off on implementing such protocols until the results of further studies become available.

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CME / CNE Questions

11. What proportion of surviving patients met criteria for post-traumatic stress disorder 6 months after an ICU admission requiring mechanical ventilation?

a. 4%
b. 9%
c. 14%
d. 26%
e. 42%

12. Which of the following were associated with post-traumatic stress disorder 6 months after an ICU admission requiring mechanical ventilation?
a. female sex
b. the quantity of midazolam administered
c. age over 50 years
d. all of the above
e. none of the above

13. In family conferences, physicians were significantly more likely to share prognostic information about survival when:
a. The family requested the conference.
b. The family had already agreed to a DNR order.
c. The family member was female.
d. The family member was > 65 years of age.
e. Family members had more years of education.

14. Family conferences included prognostic information about the patient's chances of survival:
a. 98% of the time
b. 86% of the time
c. 63% of the time
d. 25% of the time
e. 10% of the time

15. Which of the following is true regarding the test characteristics of the procalcitonin assay in critically ill patients?
a. The sensitivity approaches 95%.
b. The specificity approaches 95%.
c. The positive likelihood ratio is about 7.
d. The negative likelihood ratio is 0.8.
e. The area under the SROC curve was 0.78.

16. Meduri et al's protocol of low dose prolonged methylprednisolone infusion beginning early in ARDS led to
a. increased nosocomial infections in the treatment group
b. decreased hospital mortality in the treatment group
c. decreased hospital mortality in the placebo group
d. increased likelihood of successful extubation in the treatment group
e. increased likelihood of successful extubation in the placebo group

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17. Which of the following statements are true regarding Hermans and colleagues' data on risk factors for the development of critical illness polyneuropathy/myopathy or prolonged mechanical ventilation?
a. Corticosteroids increase the risk of developing critical illness polyneuropathy/myopathy.
b. Neuromuscular blocking agents increase the risk of developing critical illness polyneuropathy/myopathy.
c. Increasing age increases the risk of developing critical illness polyneuropathy/myopathy.
d Corticosteroids decrease the risk of prolonged mechanical ventilation.
e. None of the above.

Answers: 11(c); 12(a); 13(e); 14(c); 15(e); 16(d); 17(b)

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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.

Risk With Preventative Antibiotics Outweighs Benefit for Most

Sweeping new changes have been made to the guidelines for prevention of endocarditis in patients undergoing dental procedures. The new recommendations dramatically reduce the indications for dental prophylaxis and reduce the number of patients who need preprocedure antibiotics. The guideline was issued by the American Heart Association in conjunction with the American Dental Association, Infectious Diseases Society of America, and the Pediatric Infectious Diseases Society and was published online April 19, 2007, in *Circulation*. The guidelines reflect evidence that the risk of taking preventative antibiotics outweighs the benefit for most patients. It is also been found that infectious endocarditis (IE) is more likely to result from frequent exposure to random bacteremias from activity such as flossing and brushing than from dental work. Specifically, the guidelines say that prophylactic antibiotics are no longer required for patients with mitral valve prolapse, rheumatic heart disease, bicuspid valve disease, calcified aortic stenosis, or congenital heart conditions such as ventricular septal defect, atrial septal defect, and hypertrophic cardiomyopathy. There are still patients who are at extremely high risk of IE who should continue to receive prophylactic antibiotics: patients with artificial heart valves, a history of infective endocarditis, congenital heart disease including unrepaired or incompletely repaired cyanotic congenital heart disease, including those with palliative shunts and conduits, those with a completely repaired congenital heart defect with prosthetic material during the first 6 months after the procedure, repaired congenital heart defect with residual defect at the site or adjacent to the site of a prosthetic patch or prosthetic device, or a cardiac transplant patient with a cardiac valvulopathy. Antibiotic prophylaxis is no longer recommended for any other form of congenital heart disease. Dosing regimens are essentially the same as previous recommendations and include oral amoxicillin 2 gm 30 to 60 minutes prior to procedure. Oral alternatives include cephalexin, clindamycin, azithromycin or clarithromycin. Parenteral regimens include ampicillin, cefazolin, ceftriaxone, and clindamycin. The guideline also no longer recommends antibiotics to prevent IE in patients undergoing genitourinary or gastrointestinal tract procedures (*Circulation* 2007, doi:10.1161/CIRCULATIONAHA.106.183095). The full guideline is available at http://www.ada.org/prof/resources/ topics/infective_endocarditis_guidelines.pdf. ■

Gonococcal Infections, CDC's Updated Treatment

The CDC has issued updated treatment recommendations for gonococcal infections and associated conditions due to the high level of resistance of gonorrhea to fluoroquinolones. The agencies Gonococcal Isolate Surveillance Project demonstrates that fluoroquinolone-resistant gonorrhea is continuing to spread and is now widespread

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throughout United States. Therefore, fluoroquinolones such as ciprofloxacin, ofloxacin, or levofloxacin are no longer recommended. Current recommended regimens for gonococcal infections of the cervix, urethra, and rectum are ceftriaxone 125 mg IM and a single dose or cefixime 400 mg orally in a single dose plus treatment for chlamydia if chlamydial infection is not ruled out. Uncomplicated gonococcal infections of the pharynx should be treated with ceftriaxone 125 mg IM plus treatment for chlamydia, if chlamydial infection is not ruled out. Disseminated gonococcal infection should be treated with ceftriaxone 1 g IM or IV every 24 hours. Pelvic inflammatory disease may be treated with parenteral and oral therapy. Parenteral therapy regimens include cefotetan or cefoxitin plus doxycycline or clindamycin plus gentamicin. An alternative regimen is ampicillin/sulbactam plus oral doxycycline. Oral therapy can be considered in women with mild to moderate disease. With the loss of fluoroquinolones, cephalosporins are the mainstay of most regimens. For patients who are highly allergic to cephalosporins, spectinomycin may be considered although it is not generally available in this country. Another option is azithromycin, however, prescribing should be done in consultation with an infectious disease specialist due to concerns over emerging antimicrobial resistance to macrolides. The CDC's full recommendations are available online at www.cdc.gov/std/treatment/2006/updated-regimens.htm. ■

Head Lice — Malathion First-Line Treatment

Malathion should be first-line treatment for children who have lice according to a new review in the journal *Pediatrics*. Head lice have become resistant to nearly all first-line treatments in United States including permethrin, which has been considered first-line treatment for years. Malathion, in the formulation containing isopropyl alcohol and terpineol, is safe and effective for lice and all existing points within the life cycle, and generally requires a single treatment, reducing the duration of infestation, and lost time from school and work. Concern about flammability seems to be over emphasized, as there have been no reported cases of bodily injury related to burns (*Pediatrics* 2007. 119:965-974).

Statins, May Cut the Risk of Cataracts

Statins, the cholesterol wonder drugs, have been associated with a number of other benefits including reduction of inflammation within the arteries, improved bone density, reduction in the risk of colon cancer, renoprotective effects, and reduction in the risk of Alzheimer's disease and other dementias. Now, a new study suggests that the drugs may also cut the risk of cataracts by 50%. Researchers from Australia reviewed the rate of cataract development in 3,654 elderly patients. After 10 years, after controlling for age, gender and others factors, the hazard ratio for any type of cataract in statin users was 0.52. In subgroups, there was a decreased risk of nuclear cataracts (HR = 0.66) and cortical cataracts (HR =0.76), but neither of these reached statistical significance. The authors conclude that there may be a protective influence of statins on cataracts and this needs to be further explored (*Am J Ophthalmol* 2007; 143:687-689). ■

FDA Actions

Sanofi Aventis has been approved to produce a vaccine to prevent bird flu in humans. The vaccine against the H5N1 virus will not be produced commercially, but will instead be stockpiled by the U.S. government for distribution in case of the outbreak. The FDA admits that the vaccine is not optimal, requiring a higher dose than normal flu vaccine, and 2 shots which must be given 28 days apart. But until other vaccines are developed, this vaccine will be used as the "interim measure."

The FDA is recommending updating black box warning regarding suicidality in young adults (under age 24) starting on antidepressants, calling for appropriate monitoring and close observation. The new recommendation should also include the statement that there was no increase in suicidality in adults over the age of 24, and a decrease in the risk in adults over the age of 64.

The FDA has approved generic versions of 2 of the most popular drugs of the last decade, Ambien (zolpidem) and Zoloft (sertraline). Zolpidem will be available in 5 mg and 10 mg immediate-release tablets. Thirteen manufactures have received approval to market the product. Sertraline is approved in the 25 mg, 50 mg and 100 mg strengths, and will be produced by Ranbaxy Laboratories.

The FDA has issued a warning about the health risks of dietary supplements touted as sexual enhancement products and treatments for erectile dysfunction that have been distributed under the trade names True Man and Energy Max. Both drugs have been sold throughout United States. Energy Max was found to contain an analogue of sildenafil, the active ingredient in Viagra, while True Man was found to contain an analogue of sildenafil and vardenafil, the active ingredient in Levitra. Both drugs can have serious interactions with nitrates. ■