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Critical Care [ALERT]

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

ABSTRACT & COMMENTARY

Doxycycline May Protect Against *Clostridium Difficile* Infection

By Betty Tran, MD, MS

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Dr. Tran reports no financial relationships relevant to this field of study.

SYNOPSIS: This retrospective study of hospitalized patients receiving ceftriaxone found that additional treatment with doxycycline compared to other antibiotics was associated with a lower risk of *Clostridium difficile* infection.

SOURCE: Doernberg SB, et al. Does doxycycline protect against development of *Clostridium difficile* infection? *Clin Infect Dis* 2012;55:615-620.

Doernberg and colleagues sought to determine whether receipt of doxycycline was associated with protection from development of *Clostridium difficile* infection (CDI) in hospitalized patients being treated with ceftriaxone, a known high-risk antibiotic for CDI. They retrospectively identified 2734 hospitalizations involving 2305 adult patients at San Francisco General Hospital who received ceftriaxone during their hospitalization. Of these, 1066 (39%) patients also received doxycycline; these patients tended to be older, were more likely to have pneumonia on admission, were less likely to be surgical patients, had higher Charlson Comorbidity Index scores, and received shorter courses of additional antibiotics. The duration of treatment with ceftriaxone, the number of hospital days before development of CDI, and total length of hospital stay, however, were similar between the group that received doxycycline and the group that did not. The primary outcome of interest was development of CDI within 30 days of receiving ceftriaxone.

During the 2005-2010 study period, the overall incidence of CDI was 5.60 per 10,000 patient-days, a rate that is lower than reported in other studies. The incidence of CDI in patients who

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received doxycycline was 1.67 per 10,000 patient-days compared to 8.11 per 10,000 patient-days in patients who did not receive doxycycline. For each day that a patient received doxycycline, there was a 27% lower risk of CDI compared to a patient who was not receiving doxycycline (95% confidence interval [CI], 0.56-0.96; $P = 0.03$). When the authors directly compared common therapies for community-acquired pneumonia (CAP), a 5-day course of ceftriaxone plus doxycycline was associated with an 85% lower rate of CDI (95% CI, 0.03-0.77) compared to a 5-day course of ceftriaxone plus a macrolide, and an 87% lower rate of CDI (95% CI, 0.03-0.62) compared to a 5-day course of ceftriaxone plus a fluoroquinolone. Because of the uncertainty of capturing all data on antibiotic exposure and CDI cases after discharge, a sensitivity analysis was performed using only hospital data up until discharge with similar results, according to the authors.

COMMENTARY

Given the increasing morbidity and mortality of CDI, especially among hospitalized patients, and the high prevalence with which inpatients receive at least one dose of antibiotics, this article poses a fascinating question and springboard for further clinical and laboratory investigations.

San Francisco General Hospital, the study site, presented a unique opportunity for investigators as doxycycline was the recommended first-line therapy for CAP in non-ICU inpatients. Current American Thoracic Society and Infectious Diseases Society of America guidelines, however, recommend doxycycline as an alternative to either a macrolide or a fluoroquinolone as part of a treatment regimen for CAP based only on level III evidence. Findings from this study suggest that further research is needed to revisit the use of doxycycline as a preferred antibiotic in CAP treatment. Doxycycline may reduce the burden of CDI in already vulnerable patient populations, but widespread recommendations for its use may be tempered by differences in clinical outcomes of CAP depending on the setting (outpatient vs inpatient vs ICU).

[A 5-day course of ceftriaxone plus doxycycline was associated with an 85% lower rate of CDI compared to a 5-day course of ceftriaxone plus a macrolide, and an 87% lower rate compared to a 5-day course of ceftriaxone plus a fluoroquinolone.]

The mechanisms to explain the association between receiving doxycycline and having a lower risk of CDI also need to be explored. The authors posit a few possibilities, including doxycycline's in vitro activity against *C. difficile*, its attenuation of *C. difficile* toxin production, and its minimal effects on bowel flora due to maximal absorption in the upper gastrointestinal tract. These hypotheses sound plausible, although further data will be informative, especially to ensure that doxycycline use does not result in inadvertent but unwanted outcomes such as the selection of rarer but more virulent strains of *C. difficile*.

Although further data are needed to support the findings reported, this study is encouraging and also highlights an approach to reducing the rate of CDI by using "lower-risk" antibiotics, a method that may prove to be a valuable weapon in the antibiotic stewardship arsenal. ■

ABSTRACT & COMMENTARY

Lie Still, Sleep Becalmed: The Effects of Deep Sedation in the First 48 Hours of ICU Care

By Saadia R. Akhtar, MD, MSc
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Dr. Akhtar reports no financial relationships relevant to this field of study.

SYNOPSIS: This multicenter prospective study found that deep sedation in the first 48 hours of mechanical ventilation and ICU care is associated with delayed extubation and increased risk of hospital and 180-day mortality.

SOURCE: Shehabi Y, et al; Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators and the ANZICS Clinical Trials Group. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *Am J Respir Crit Care Med* 2012;186:724-731.

The authors note a paucity of literature on early (0-48 hours of ventilation and ICU admission) sedation practices and their impact on outcomes; thus they performed this multicenter prospective cohort study with the hypothesis that early sedation is associated with delirium, time to extubation, and hospital and 180-day mortality. Twenty-five Australian and New Zealand ICUs participated. Over a 3-month period in 2010, up to 20 patients were recruited from each study site. Inclusion criteria were age ≥ 18 years, need for mechanical ventilation and sedation for 0-24 hours at enrollment, and expected ongoing need for this support. Exclusions included neurological impairment, psychiatric illness, dementia, burns, or palliative care. Usual demographic and clinical data were recorded. Richmond Agitation Sedation Score (RASS) and a pain score were measured every 4 hours ("deep sedation" defined as RASS -3 to -5). Confusion Assessment Method for ICU (CAM) was assessed daily. Cumulative doses of sedatives, analgesics, and antipsychotics were recorded. Patients were followed to ICU discharge or death (up to 28 days), and 180-day survival data were obtained from medical records or national death registries. Standard statistical methods were applied.

The study cohort consisted of 251 patients. A total of 629 met the initial inclusion criteria; however, the majority were excluded for neurological impairment, 72 due to study staff not being available for enrollment, and 27 were discharged or died within 24 hours. The cohort had mean APACHE II score 21; median ventilator days 5.1; ICU length of stay 8.5 days; and ICU, hospital, and 180-day mortality of 16.7%, 21.1%, and 25.8%, respectively. Midazolam and propofol were used with similar frequency; fentanyl was slightly preferred to morphine. Delirium was quite common, with at least 50% of patients being CAM positive for at least 1 day. About two-thirds of these patients received haloperidol, dexmedetomidine, or diazepam for delirium or agitation; these drugs were also given to about 28% of patients without delirium or agitation. Specific sedation targets were only ordered on 25% of patients and met just 35% of the time; routine sedation holidays occurred rarely (3.1% of all study days). Most patients were maintained with deep sedation early on (76% at 4 hours into mechanical ventilation and 68% at 48 hours), but this decreased to 24% at ≥ 5 days. After adjusting for nine variables defined a priori, early deep sedation was associated with longer time to extubation (7.7 vs 2.4 days; each 4-hour measure of deep sedation delayed extubation 12.3 hours); cumulative doses of midazolam and fentanyl were predictive as well but propofol or morphine doses were not. Early deep sedation was associated with delirium at 48 hours but not later. Finally, hospital and 180-day mortality risk were increased by early deep sedation but not the choice of agent.

COMMENTARY

Patients in the ICU often have pain, anxiety, and/or delirium for a variety of reasons. It is essential that health care providers treat these symptoms and provide comfort, and continuous infusions of sedative medications are frequently the most effective way to accomplish this. At the same time, it is clear that excessive sedation leads to increased time on mechanical ventilation and ICU length of stay.[1] Shehabi et al's study further corroborates this by correlating time spent in deep sedation in the first 48 hours of ICU stay with longer time to extubation as well as higher hospital and 180-day mortality; there is an association with delirium at 48 hours as well. Although these results are not surprising, prior studies have generally addressed

impact of sedation beyond the first 48 hours; the authors note this study is unique in focusing on this early time period.

It is also well-established that less sedation, achieved by using protocol-driven sedation administration and daily interruption of sedation (i.e., sedation holidays), is associated with improved outcomes without adverse psychological effects.[2] Despite good evidence supporting this, implementation rates of such an approach remain quite low as noted again here. This multicenter Australasian report found no clear sedation protocols, no apparent guidelines for triggers for specific medications (implied from the description of antipsychotic use for patients without delirium or agitation), limited use of sedation targets (and when given, usually not met), and appallingly rare sedation holidays (occurring on only 3.1% of study days).

This study is interesting for three reasons. First, it describes current ICU sedation practices in Australia and New Zealand, which I suspect may not differ from practices in other developed areas of the world. Second, it adds further evidence to the literature on adverse effects of excessive sedation and the high frequency of delirium in ICU patients. Third, and perhaps most importantly, it reminds us of how difficult it can be to implement evidence and change clinical practice.

If the Australasian experience sounds familiar, then it is time to take action today because previous well-designed, randomized, controlled studies and ongoing reports like this one leave little doubt of the harm of excessive sedation and the potential benefits of changing our approach to management of sedation in the ICU. ■

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ABSTRACT & COMMENTARY

Psychological Distress Decreased When Families Completed Daily ICU Diary

By Leslie A. Hoffman, RN, PhD

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

SYNOPSIS: Family members who received a diary written during their family member's ICU admission had lower levels of symptoms related to post-traumatic stress disorder.

SOURCE: Jones C, et al. Intensive care diaries and relatives' symptoms of posttraumatic stress disorder after critical illness: A pilot study. *Am J Crit Care* 2012;21:172-176.

Family members of patients recovering from critical illness may experience psychological problems, including anxiety, depression, and post-traumatic stress disorder (PTSD). Jones and colleagues reasoned that provision of an ICU diary, written in everyday language by ICU staff, would be beneficial to family members by providing an explanation of daily events and opportunity for expression of feelings and contribution to the plan of care. Subjects were family members of patients who were admitted to the ICU for > 72 hours and mechanically ventilated for > 24 hours. The recruitment sites were two general adult ICUs in England and Sweden. The median ICU stay for patients enrolled in the study was 14 days (range, 4-50 days).

Each patient had a diary written for them by staff while they were in the ICU and family members contributed if they wished. At discharge from the ICU, patients and family members were randomized into two groups: one received the diary as soon as they wished but within 2 months of discharge (n = 15), and the second group at 3 months after discharge (n = 15). There were no significant differences between groups in age, length of ICU stay, hours of mechanical ventilation, or APACHE II scores. Family members completed a standardized questionnaire designed to detect PTSD symptoms 1 and 3 months following ICU discharge. At 3 months, scores reflecting PTSD symptoms were significantly lower (P = 0.03) in the group that received the diary within 2 months of discharge, indicating fewer PTSD symptoms.

■ COMMENTARY

This study, conducted in two European ICUs, provides interesting information regarding potential benefits of a simple intervention that may decrease psychological distress following ICU admission. The authors relate that ICU diaries are in "wide use" in Scandinavia and the United Kingdom, but the benefits of this practice have rarely been evaluated. Findings of their study are similar to those reported by a French group[1] from a study enrolling a similar-sized sample (n = 49) followed over a longer period. In the French study, scores reflecting PTSD symptoms were decreased at 12 months, but not at 3 months.

Both studies had a number of limitations: sample size was small and reported benefits did not occur until months after ICU discharge, raising the potential that intervening events were responsible for the change. Nevertheless, provision of the diary was not reported to cause any ill effects and patients and family members had the option of not reading its content. The structure of the French diary was similar to an information booklet; it included an organizational chart of the ICU with staff photos and a photo of an empty ICU bed with explanations of equipment and monitoring systems. Photos of a mechanical ventilator and other equipment were added if used. The first entry was contributed by the ICU physician who summarized the patient's medical history and condition. ICU staff contributed to the following pages by writing a daily narrative in everyday language that provided a status update. Family members contributed as they wished. At discharge, an ICU staff member wrote a conclusion expressing wishes for a good recovery. This intervention merits consideration as a means to reduce patient distress: it is simple to implement, has potential benefit, and has no apparent untoward effects. ■

REFERENCE

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ABSTRACT & COMMENTARY

The Cuff-Leak Test for Predicting Post-Extubation Stridor: Are We Focusing on the Wrong Question?

By Richard H. Kallet, MS, RRT, FAARC, FCCM

Director of Quality Assurance, Respiratory Care Services, San Francisco General Hospital

Mr. Kallet reports no financial relationships relevant to this field of study.

SYNOPSIS: This prospective, single-center, observational study investigated whether the presence of deterioration in the results of cuff-leak tests done immediately post-intubation as compared to the same test repeated just prior to extubation would improve sensitivity for detecting subsequent stridor. There was no difference between the testing strategies in sensitivity (86%), whereas the specificity of the pre-extubation test was much higher (76%) than the comparison method (48%).

SOURCE: Gros A, et al. Intra-individual variation of the cuff-leak test as a predictor of post-extubation stridor. *Respir Care* 2012; May 4. [Epub ahead of print.]

The cuff-leak test (CLT) was performed prospectively in this study using the volume technique whereby the difference between inspired and expired tidal volume before and after cuff deflation is used to detect the presence of laryngeal edema and the likelihood of developing post-extubation stridor.[1] The rationale for performing the CLT immediately post-intubation is to control for a false-positive test (that is, little or no leak and subsequent absence of stridor) that may occur when the endotracheal tube is too large relative to laryngeal diameter. The authors determined the change in CLT as the difference between pre-extubation and post-intubation results, so that a negative value (i.e., deterioration in leak volume) would signify a positive test for possible upper airway edema. Data were collected from 104 adult ICU patients requiring more than 48 hours of mechanical ventilation who were deemed ready for an extubation trial. Determinations of sensitivity, specificity, positive, and negative predictive values for stridor were made for each test strategy. The change in CLT using a pre-hoc cutoff of 0 mL was compared to

the pre-extubation CLT in which the cutoff was determined post-hoc.

There were seven incidents of post-extubation stridor and respiratory distress (6.7%), all of which occurred within 12 hours, and reintubation was required in six. The CLT comparison method was not better than using a single pre-extubation CLT for detecting stridor. Post-hoc analysis demonstrated that using a cutoff value of 130 mL for the pre-extubation CLT produced the same sensitivity (86%) and a higher specificity (76% vs 48%). Likewise, the positive predictive value was higher for the single CLT vs the CLT comparison method (21% and 11% respectively), whereas the negative predictive values were essentially the same (99% and 98%, respectively).

COMMENTARY

Post-extubation stridor is a relatively rare but frequently life-threatening event with a reported incidence between 2-16%.[2] There are several indirect risk factors (female gender, height, obesity, and neurologic injury) as well as direct risk factors (duration of endotracheal intubation, history of difficult or traumatic intubation, unplanned traumatic extubation, upper airway infection, trauma, or surgery). The ability to accurately predict post-extubation stridor is limited by crude measurement techniques and questionable inter-observer reliability. More importantly, the low prevalence of stridor limits the ability to establish a reliable positive predictive value for the CLT.

We addressed this issue at our institution following a sentinel event in which a patient with several unrecognized risk factors developed severe post-extubation stridor and subsequently suffered a cardiac arrest. Although we had been using various CLT techniques over the years, these were not standardized, nor were absolute cutoff criteria agreed upon. Also, patients were not routinely screened for risk factors. Since then, we have systematically screened all intubated patients for risk factors and stratified the number and type of risk factors that would automatically trigger a CLT.

Our institution has also incorporated the volume CLT introduced by Miller et al.[1] The advantage of the volume CLT is that it uses standardized ventilator settings to minimize inter-observer variability. Pressure-based techniques typically rely on a manual resuscitator with an inline pressure manometer. The airway pressure at which a leak becomes "audible" (if at all) is used to assess whether upper airway edema is likely to be present. However, neither the specific amount nor the delivery technique of applied airway pressure is standardized. An acceptable cutoff value for airway pressure has never been established and therefore is arbitrary. In addition, the "quality" of the audible air leak has never been addressed. For example, should clinicians make the same decision regarding extubation at a leak pressure of 20 cm H_2O when they hear a brief high-pitched squeak as in the case of a sustained sonorous sound?

More importantly, when we compared the volume CLT to our traditional pressure CLT, we discovered that approximately 100 patients had a negative-volume CLT despite having a positive-pressure CLT. Only four of these patients developed post-extubation stridor and only one required reintubation. Also, we found that the positive predictive value for our volume CLT is only about 50%, whereas our negative predictive value is 95%. Therefore, we have become more liberal with extubation trials in our unit despite a poor volume CLT, although this is done with an anesthesiologist at the bedside as a precaution.

The conditions under which the CLT is performed are important. Originally, the CLT was devised by anesthesiologists and done under general anesthesia when both the laryngeal and abdominal muscles are relaxed. This is important because laryngeal muscle adduction may produce a false-positive result, whereas forced expiration potentially may produce a false-negative result. When the CLT is done in sedated, relaxed patients test results are highly reproducible with little inter-observer variability.[3] Clinicians are reluctant to sedate a patient just prior to extubation to perform a CLT. We have largely circumvented this by performing the CLT during the night prior to a planned extubation when extra sedation can be given. For patients who require 2 or more days of mechanical ventilation, it seems unlikely that upper airway edema would suddenly develop within a few hours prior to extubation.

The take-home message is that the volume CLT has a high negative predictive value and therefore is a useful screening tool for reliably predicting the absence of stridor. A positive test result is sufficiently sensitive to warrant more thorough airway evaluation prior to extubation. It behooves clinicians to extubate patients with a positive CLT under close scrutiny with reintubation equipment readily available at the bedside. Finally, from my experience I concur with the authors that because of the low incidence and known risk factors associated

with post-extubation stridor, the CLT should be performed only in patients with significant or multiple risk factors. ■

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ABSTRACT & COMMENTARY

Can We Predict Long-Term Cognitive Impairment in Survivors of Critical Illness?

By Linda L. Chlan, RN, PhD

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

SYNOPSIS: In survivors of critical illness with documented cognitive impairment at discharge, commonly used cognitive screening tests do not predict which of these patients will experience long-term cognitive impairment.

SOURCE: Woon FL, et al. Predicting cognitive sequelae in survivors of critical illness with cognitive screening tests. *Am J Respir Crit Care Med* 2012; 186:333-340.

As more patients are surviving critical illness, there is documentation of serious cognitive, physical, and psychiatric consequences arising from lengthy ICU stays in these patients. Numerous studies have demonstrated new cognitive impairments in ICU survivors, yet there is no evidence available as to which patients are likely to experience long-term cognitive impairments after hospital discharge. The study by Woon and colleagues was conducted to address this knowledge gap. The researchers wanted to determine if commonly used cognitive screening tests administered at hospital discharge could be used to predict cognitive impairments, termed cognitive sequelae, 6 months later.

The baseline cognitive screening tests were the Mini-Mental State Examination (MMSE), which is the "gold standard" for cognitive status screening, and the Mini-Cog used to detect cognitive impairments; both were administered at hospital discharge. A battery of cognitive tests was administered 6 months after discharge from the hospital, including the Wide Range Achievement Test-3 Reading subtest (WRAT-3) and the Wechsler Abbreviated Scale of Intelligence (WASI). A number of neuropsychological tests were also administered 6 months after discharge to look for the presence of cognitive sequelae, including attention, upper extremity motor speed, language, memory-delayed recall, long-delay recall, mental processing speed, and executive function. Detailed information on this extensive battery of cognitive and neuropsychological tests can be found in the article by Woon et al.

Patients receiving mechanical ventilation for > 48 hours who were 18-85 years of age were recruited from the Shock Trauma ICU and Respiratory ICU at LDS Hospital and Intermountain Medical Center in Salt Lake City, Utah, from August 2007, through December 2008. Of the 319 patients who initially met the study inclusion criteria, only 70 (50% male) participated in the cognitive assessments at hospital discharge. Of these 70 participants evaluated at hospital discharge, 10 died between discharge and the 6-month follow-up period, three declined to participate, and four were lost to follow-up contact. A final sample of 53 participants completed the 6-month follow-up, with an average age of 54 years, mean hospital length of stay of 25 days, mean ICU length of stay of 13.3 days, and mean duration of mechanical ventilation of 8.8 days.

At hospital discharge, 39% of the participants were impaired on both the MMSE and the Mini-Cog; 64% were impaired on the MMSE only with 45% impaired only on the Mini-Cog. Perhaps not surprisingly, only 28% of the patients had normal scores on both cognitive screening tests. At 6 months post-hospital discharge, controlling for pre-ICU cognitive function, education, depression, and days of mechanical ventilation, the MMSE and Mini-Cog scores were not found to predict cognitive sequelae in this sample. However, a number of the measured cognitive sequelae were found in these ICU survivors at the 6-month follow-up including, most prominently, impaired memory (38%), executive dysfunction (36%), and slow upper extremity motor

speed (26%). Of note, the researchers did not assess for the presence of delirium at any time in this study.

■ COMMENTARY

The primary aim of the study by Woon and colleagues was to determine if the MMSE and the Mini-Cog could predict cognitive sequelae in survivors of prolonged critical illness. While the findings addressing the primary aim were not found to be statistically significant, the most clinically significant finding from this article is the marked cognitive sequelae in this sample of ICU survivors. Of note, this sample of study participants was relatively young (54 years of age) with impairments in memory and executive function 6 months after hospital discharge. These findings have important implications for quality-of-life outcomes in survivors of prolonged critical illness and their ability to return to work.

The small sample of only 53 participants out of an initial group of more than 300 patients limits the generalizability of these findings to ICU survivors in general. However, the marked cognitive impairments in these patients should give pause to all ICU clinicians when discussing post-ICU outcomes with patients and their family members. Surviving a prolonged critical illness may come with significant cognitive, physical, and psychiatric consequences that can directly impact quality of life. ■

CME/CNE Questions

1. Compared to other antibiotics, the use of doxycycline in conjunction with ceftriaxone resulted in a:

a. higher rate of community-acquired pneumonia treatment failure.
b. higher rate of nosocomial infections.
c. lower rate of *Clostridium difficile* diarrhea.
d. lower rate of medical non-adherence.
e. higher rate of antibiotic-associated diarrhea.

2. In Shehabi et al's study, early use of deep sedation was associated with:

a. no change in mortality.
b. increased patient satisfaction.
c. low rates of delirium.
d. longer time to extubation.
e. increased rates of ventilator-associated pneumonia.

3. When an ICU diary was implemented:

a. PTSD symptoms were unchanged for older patients.
b. family members had fewer PTSD symptoms in the first week after ICU discharge.
c. patients had fewer PTSD symptoms in the first week after ICU discharge.
d. diary entries proved problematic because they contained confidential information.
e. PTSD symptoms were decreased but not until months after ICU discharge.

4. Risk factors for developing post-extubation stridor include all of the following *except*:

a. extended duration of endotracheal intubation.
b. history of COPD.
c. gender.
d. neurological injury.
e. unplanned "traumatic" extubation.

5. Based on the findings from the study by Woon et al, which of the following statements is true about the predictive value of the Mini-Mental Status Exam (MMSE) in ICU survivors?

a. The MMSE is a significant predictor of long-term cognitive function.
b. The MMSE is a significant predictor of long-term physical dysfunction.
c. The MMSE is a significant predictor of long-term depressive symptoms.
d. The MMSE is a significant predictor of psychiatric consequences.
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]

Benefits of rapid response teams

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.*

Menopausal Hormone Therapy and the Risk for VTE, AD

In this issue: Menopausal hormone therapy and risk of VTE and AD; patients' understanding of chemotherapy benefits; and FDA actions.

Hormone therapy and VTE risk

The different drug formulations of menopausal hormone therapy (HT) may determine the risk of venous thromboembolism (VTE), according to a new study. It is known that combined estrogen-progesterone therapy has a higher risk of VTE than estrogen-only therapy, and oral therapy has a higher risk than transdermal therapy. Now, a follow-up study from the Million Women Study with more than 3.3 million patient-years of follow-up looks at the varying risks of different HT combinations. The risk of VTE was again found to be significantly higher for combination estrogen-progesterone therapy compared to estrogen-only therapy (relative risks [RR] = 2.07 [95% confidence intervals (CI) 1.86-2.31] vs 1.42 [1.21-1.66]). Transdermal estrogen-only therapy resulted in no excess risk for VTE (RR 0.82 [0.64-1.06]). Among users of combination estrogen-progesterone, the risk of VTE varied by progestin type with significantly greater risk for preparations containing medroxyprogesterone compared to other progestins (2.67 [2.25-3.16] vs 1.91 [1.69-2.17]; *P* heterogeneity = 0.0007). The risk of VTE was significantly higher (2 times the risk) in the first 2 years after starting combination HT than later years. Five-year risks for pulmonary embolism (PE), both fatal and nonfatal, were calculated as: 1 in 664 for never users of hormone therapy, 1 in 475 for current users of oral estrogen-only, 1 in 390 for users of estrogen-progesterone containing norethisterone/norgestrel, and 1 in 250 for users of estrogen-progestin therapy containing medroxyprogesterone. The authors conclude that VTE risk varies considerably by HT formulation and is greatest in users of oral estrogen-progesterone therapy containing medroxyprogesterone. One case of PE could be avoided for every 1295 current users of oral HT if estrogen-only rather than estrogen-progesterone was used. Among combined HT users, one PE in 700 women could be avoided by use of a progestin other than medroxyprogesterone (*J Thromb Haemost* published online Sept. 10, 2012. doi: 10.1111/j.1538-7836.2012.04919.x). These data follow on the Women's Health Initiative, which also showed a higher risk of breast cancer for combination hormone replacement therapy vs estrogen-only therapy, but this risk is offset by the risk of endometrial cancer in women with an intact uterus on unopposed estrogen. ■

Hormone therapy and AD risk

Does the timing of menopausal HT affect the risk of Alzheimer's disease (AD)? Several studies have suggested the timing of postmenopausal HT is critical, especially during the first 5 years after menopause when hormones appear to be somewhat neuroprotective. The Women's Health Initiative (WHI) study clearly showed that starting HT after age 65 had no effect on cognition and in fact may be harmful. Now a new study confirms that starting HT immediately after menopause may have neuroprotective benefits. In a follow-up from the Cache

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County study, 1768 women provided a detailed history on age at menopause and use of HT between 1995 and 2006. During this interval, 176 women developed AD. Women who used any type of HT within 5 years of menopause were at 30% less risk of AD (95% CI, 0.49-0.99), especially if they used it for 10 years or more. By contrast, woman who started HT 5 or more years after menopause did not have a decreased rate of AD. Confirming the WHI findings, rates of dementia were nearly doubled among those who began combination estrogen-progesterone compounds later in life. The authors conclude that the association of HT and the risk of AD may depend on the timing of use. HT appears to be beneficial during the critical window near menopause, but may be associated with an increased risk if initiated later in life. (*Neurology* 2012;79:1846-1852). An accompanying editorial suggests that AD and coronary heart disease share common risk factors. WHI data show that women assigned to HT close to menopause had a reduction in the risk of coronary heart disease, whereas women given HT later in life had increased risk. The same seems to be true for the risk of AD. Two soon-to-be published studies will provide evidence regarding hormone effects on cognition in younger postmenopausal women (*Neurology* 2012;79:1840-1841). The decision to initiate HT in postmenopausal women is generally based on severity of symptoms, risk of breast cancer, risk of venous thromboembolic disease, and other factors. Benefits on cognition and potential protection against AD may now need to be added to the equation. ■

Chemotherapy often misunderstood

Chemotherapy for metastatic lung or colon cancer may provide palliation and prolongation of life by weeks or months, but a new study shows that most patients with these diseases erroneously think that chemotherapy is curative. Researchers studied nearly 2000 patients in the Cancer Care Outcomes Research and Surveillance study who were alive 4 months after diagnosis of stage IV lung cancer or colorectal cancer. All patients received chemotherapy. Overall, 69% of patients with lung cancer and 81% of those with colorectal cancer did not report understanding that chemotherapy "was not at all likely to cure their cancer." This misunderstanding about the benefits of chemotherapy was more prevalent among nonwhite and Hispanic patients as compared to non-Hispanic white patients (odds ratio [OR] for Hispanic patients 2.82, 95% CI, 1.51-5.25; OR black patients 2.93, 95% CI, 1.80-4.78). Patients who rated communication with their physician favorably also had a higher OR (1.90; 95% CI, 1.33-2.72). Educational level, functional status, and the patient's role in decision making were not associated with inaccurate beliefs about chemotherapy. The authors conclude that "many patients receiving chemotherapy for incurable cancers may not understand that chemotherapy is unlikely to be curative." This misunderstanding suggests that patients "have not met the standard for true ongoing informed consent" and may not accept toxic treatment with no reasonable hope of cure. The data also suggest that patients rate their doctors as better communicators if they are more optimistic. The authors suggest that honest communication is "a marker of quality of care" but may cause lower patient ratings (*N Engl J Med* 2012;367:1616-1625). ■

FDA actions

The FDA has approved a new drug for the treatment of chronic myelogenous leukemia (CML). Omacetaxine mepesuccinate is a protein translation inhibitor that was originally identified in the 1970s as a potential treatment for CML as well as other hematologic conditions and even solid tumors. It was eventually dropped from development as the tyrosine kinase inhibitors (TKIs) became the mainstay of therapy. Emerging resistance to imatinib and other TKIs has led to renewed interest in the drug. It was recently approved for chronic, accelerated, or blast-phase Philadelphia-chromosome-positive CML that is resistant or in patients who are intolerant of other therapies including TKIs. Approval was based on a study of patients in chronic or accelerated-phase CML who had been treated with two or more TKIs. Omacetaxine is administered by subcutaneous injection. It is marketed by Teva Pharmaceuticals as Synribo. It joins Pfizer's bosutinib (Bosulif), which also was recently approved for the same indication.

The FDA has approved perampanel as adjunctive treatment for partial onset seizures in patients 12 years of age and older. The drug is the first in its class of noncompetitive AMPA receptor antagonists that are taken orally once daily. Approval was based on data from three Phase 3 studies of nearly 1500 patients with partial-onset seizures which found that perampanel, when used as an adjunctive therapy with other anti-seizure medications, significantly reduced seizure frequency. The drug comes with a boxed warning regarding serious neuropsychiatric events including agitation, aggression, anxiety, paranoia, euphoria, anger, and irritably. Perampanel is marketed by Eisai Inc. as Fycompa. ■