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# Critical Care [ALERT]

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

SPECIAL FEATURE

# Reducing Patient Discomfort During Mechanical Ventilatory Support — An Integrated Approach

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

## INTRODUCTION

Patients have referred to receiving mechanical ventilatory support as, "the most inhumane ever experienced"....[1] While mechanical ventilation is one of the most commonly used treatment modalities in the ICU, this life-saving modality causes great anxiety, distress, and discomfort in patients. The purpose of this article is to present to the reader patient perceptions of being mechanically ventilated, and how those experiences can be used to inform the implementation of selected, low-tech interventions to reduce discomfort and distress in critically ill patients receiving mechanical ventilatory support. This article is intended to serve as a reminder to clinicians that the ICU environment is "foreign" to a majority of patients and their loved ones. It is an environment that induces great fear and anxiety, which is easily forgotten by clinicians who are accustomed to the high-tech, life-and-death nature of the ICU.

This article is not intended to be an exhaustive review; it will focus on selected non-pharmacologic interventions for which there is evidence of effectiveness that can be integrated into the usual medical plan of care to reduce discomfort, including communication. All clinicians desire that their patients be comfortable. However, reducing discomfort can be an immense challenge in this complex patient population.

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## DEFINITION OF KEY TERMS

To begin with, the key terms of discomfort, comfort, and pain need to be defined. Discomfort can be defined as to make uncomfortable or uneasy; distress, grief, mental or physical uneasiness; annoyance.[2] Comfort, on the other hand, can be defined as a feeling of relief or encouragement; contented well-being; a satisfying or enjoyable experience; to give hope and strength.[2] In contrast, pain is defined by the International Association for the Study of Pain[3] as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Alleviation of pain and suffering are important goals for clinicians, and many articles have already been written on this salient topic. However, this article will not address pain management interventions per se, but will focus only on interventions for reducing discomfort in critically ill patients receiving mechanical ventilatory support given the frequency with which discomfort is reported by patients. The appropriate use of very simple and effective interventions can be implemented at times to relieve discomfort without pharmacologic means.

## SOURCES OF DISCOMFORT FOR PATIENTS RECEIVING MECHANICAL VENTILATORY SUPPORT

It can be argued that the goal of mechanical ventilation is for weaning to take place as soon as medically possible, in order to facilitate the removal of mechanical ventilatory support to avoid lung injury, ventilator-associated pneumonia, and other adverse sequelae associated with this treatment modality. However, this can be a challenge at times as evidenced by the increasing population of patients requiring prolonged mechanical ventilatory support, which can be defined as support for more than 96 hours.[4] The need for prolonged mechanical ventilatory support is not projected to decrease in the next 10 years. In fact, a recent study reported that by 2020 there will be an increased need for prolonged ventilatory support in adults, most prominently in those 18-64 years of age.[4] Given the complexity and intensity of services surrounding the care of these patients, effective symptom management approaches will be needed that do not prolong ventilator days or ICU stays, nor induce adverse sequelae in these high-intensity patients.

Patients receiving mechanical ventilatory support report a number of distressing and bothersome symptoms. Bothersome and distressing symptoms recalled by ICU patients include both physiological and psychological sources for this distress. These symptoms include anxiety, thirst, fear, discomfort and pain, fatigue, restlessness, inability to sleep, lack of control, loneliness,[5] and immense communication challenges to name but a few.[5-7] Despite receiving intravenous sedative and analgesic agents, a majority of patients vividly recall their ICU experiences.[5,8] Specifically, intubated patients have recalled spells of terror, feeling nervous when left alone, and poor sleeping patterns.[5] In fact, patients who had prolonged periods of ventilatory support and ICU stay report being most bothered by the endotracheal tube.[8] Patients who received the highest cumulative doses of sedatives and opioids were bothered quite a bit by nightmares, and they also had fewer periods of wakefulness and more agitation that was quite distressing.[8] The significance of these findings is that patients still report distressing and uncomfortable symptoms associated with ventilatory support despite the receipt of sedative and opioid medications that are intended to palliate these symptoms. There is much opportunity for improvement in the area of symptom management for these patients.

While this statement is not intended to criticize ICU caregivers, patients receiving mechanical ventilatory support feel as though clinicians pay more attention to the machine (ventilator) and not to them as a person.[8] Patients report that they feel "invisible," that they are merely an extension of the apparatus (ventilator system) reduced to organs, objects, or diagnoses.[9] Further, patients desire to have their loved ones with them in their immediate presence during

this fearful time, as family generally are a source of great comfort and reassurance for patients. Patients desire to know what is happening and require frequent reassurance and reorientation given memory issues with the receipt of sedative and opioid medications. This does not mean that patients desire to be so sedated that they are not aware of their surroundings. This is further from the truth as patients report that they do not like having fragmented memories or not being able to recall their ICU experiences factually.[8]

## INTEGRATED APPROACH TO REDUCE DISCOMFORT AND SYMPTOMS OF DISTRESS ASSOCIATED WITH MECHANICAL VENTILATORY SUPPORT

While the extensive list of distressful patient experiences may seem overwhelming and daunting to manage, there are options other than relying solely on the sometimes automatic, stand-by administration of sedative and opioid medications. While warranted at times, these medications are limited in their effectiveness, given that patients continue to report discomfort and distressing symptoms.[5] It is not the intent of this article to discount the practice of medication administration to manage symptoms. Medications are indicated at times to promote synchrony with the mechanical, artificial breaths delivered by the ventilator and reduce the stress response. What is needed is an integrated approach to manage and treat these bothersome symptoms. For the purpose of this article, integrated is defined as the best of pharmacologic therapy and the best of non-pharmacologic therapy to realize the best outcomes for patients. Given the extensive attention in the literature over the recent past on sedation practices and protocols, the remainder of this article will focus on suggested areas for non-pharmacologic interventions to promote an integrated approach to symptom management.

Many ICU patients can remain awake or lightly sedated if they are comfortable.[10] There are several "low-tech," non-pharmacologic interventions that can be integrated into ICU care practices to reduce patient discomfort and promote patient comfort. The first area for consideration is that of the many integrative therapies that might be safely implemented with mechanically ventilated patients. Integrative therapies can be defined as those complementary and alternative medicine treatments, modalities, and practices that are combined with conventional medical treatment, and for which there is some evidence of safety and efficacy.[11]

A recent review article advanced several suggestions for implementing integrative therapies in the ICU beginning with an appraisal of the physical environment.[12] Simple enhancements can promote a more healing environment such as noise reduction from alarms, telephones, and clinicians' conversations; promoting day-night cycles with access to natural lighting and less use of artificial lighting during night-time hours; and uninterrupted sleep periods including refraining from performing unnecessary care interventions, such as bathing, during the middle of the night. Other suggestions for managing anxiety and agitation associated with mechanical ventilatory support include uncovering possible causes for these symptoms and appropriate administration of pharmacologic agents coupled with non-pharmacologic adjunctive therapies such as listening to preferred relaxing music, massage, or animal-assisted therapy. Other overlooked "low-tech" integrative interventions include presence and reassurance in a calming manner, given the common symptom of fear reported by these ICU patients.[12]

## DON'T OVERLOOK COMMUNICATION

Compounding the plethora of distressful and bothersome symptoms reported by mechanically ventilated patients are the immense challenges experienced by these non-verbal patients surrounding communication. Communication difficulty is a common, distressing symptom for mechanically ventilated patients.[13] Patients report immense frustration, along with increased anxiety and distress, with inadequate communication.[14,15] To reduce discomfort through the appropriate management of the myriad of symptoms experienced by these patients, the assessment of symptoms and the effectiveness of interventions must be documented. Just because a patient is mechanically ventilated does not mean that an assessment cannot be performed. There are several communication aids that can be implemented to enhance communication. To reduce patient discomfort, the clinician needs to know or attempt to discern what is bothersome to an individual patient in order to treat and manage symptoms appropriately.

At the core of performing any assessment is communication. Effective communication can be achieved, even in the non-vocal mechanically ventilated patient with a concerted effort, patience, and the assistance of very inexpensive communication aids. While indeed communication attempts can be frustrating to the clinician, several simple and low-cost strategies are proposed to promote effective communication.[16] One strategy is to establish a communication-friendly environment

that includes speaking directly to the patient and minimizing background noise. Being aware of a patient's visual and hearing acuity, as well as handedness and muscle strength for writing, are important. Clinicians should refrain from speaking rapidly and asking more than one question at a time. They should focus on "yes-no" type questions and supplement verbal communication with letter boards, note-writing, or communication boards.[16] Assistive and augmentative devices are available to facilitate communication.[16] The clinician is advised to refer to a recent article for more detailed strategies to promote effective communication with mechanically ventilated patients, including a communication assessment tool, communication kit, and picture board with communication symbols.[16]

## SUMMARY AND KEY POINTS

The purpose of this article was to call the clinician's attention to the discomfort and distress reported by patients receiving mechanical ventilatory support, and to offer suggestions for an integrated approach to effectively reduce discomfort and promote comfort for these patients. An integrated approach includes the judicious use of sedatives and analgesics, implementation of safe and effective integrative therapies, such as preferred relaxing music, and the central importance of communication. Patients receiving mechanical ventilatory support report communication difficulties as immensely bothersome and stressful, which only compounds discomfort and distress when clinicians cannot discern the source(s) of these many symptoms. The clinician is advised to keep in mind that the ICU environment is extremely fearful and stressful for patients and their loved ones; communication difficulties compound these experiences. ■

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## ABSTRACT & COMMENTARY

# Treating VAP: The Importance of Getting Initial Antibiotic Coverage Right

*By David J. Pierson, MD, Editor*


**SYNOPSIS: In this study in which all patients with clinically suspected ventilator-associated pneumonia were given prompt empiric antibiotic therapy, whether that therapy turned out to be appropriate for the organisms recovered turned out to be an important determinant of patient outcomes.**



SOURCE: Muscedere JG, et al for the Canadian Critical Care Trials Group. The adequacy of timely empiric antibiotic therapy for ventilator-associated pneumonia: An important determinant of outcome. *J Crit Care* 2011;Nov 30. [Epub ahead of print.]


This study was a secondary analysis of data from an earlier randomized clinical trial comparing one antibiotic vs two (meropenem alone or meropenem plus ciprofloxacin) as early empiric therapy for ventilator-associated pneumonia (VAP). In

that study, once the clinical suspicion of VAP (CSVAP) had been established, lower-airway culture specimens were obtained (by endotracheal suction in half the patients and bronchoalveolar lavage in half, via a stratified design) and empiric antibiotics begun within a median of 9 hours. Here, the authors examined outcomes in that study (ICU and hospital mortality, days of mechanical ventilation, and ICU and hospital lengths of stay) among the 47% of the originally enrolled patients who were proven microbiologically to have VAP, according to whether the recovered organisms were sensitive to the antibiotics used. Bacteriologic results from the two diagnostic procedure groups were combined for the purposes of this study, and all patients determined in the earlier trial to have had VAP were adjudicated by the authors to confirm this diagnosis clinically and microbiologically.

Thus, this was a retrospective analysis of outcomes in the 350 patients with positive cultures from among 739 with CSVAP who were begun promptly on empiric broad-spectrum antibiotic therapy. The 37 patients (10.6%) with one or more organisms that were not sensitive to the initially administered antibiotics (inadequate therapy, IT) were compared to the 313 patients (89.4%) whose infecting organisms were sensitive to what they received (appropriate therapy, AT).

The IT group had statistically higher mortality, both in the ICU (35.1% vs 11.8%; $P = 0.0001$) and in the hospital (48.7% vs 19.5%; $P = 0.02$). They also spent more days on mechanical ventilation (15.8 vs 16.8 days; $P = 0.0005$), in the ICU (13.5 vs 8.4 days; $P = 0.02$), and in the hospital (42.2 vs 27.9 days; $P = 0.04$), than those in the AT group. In a separate 3:1 case-control analysis, the odds ratio of in-hospital mortality with IT was 3.00 (95% confidence interval, 1.24-7.24; $P = 0.01$).

## COMMENTARY

In previous studies of CSVAP in which empiric broad-spectrum antibiotic treatment has been given initially and then tailored to the results of microbiologic studies among patients who prove to actually have VAP, worse outcomes have been documented in those who do not initially receive AT. However, in those studies empiric therapy in patients with initial IT has often been both microbiologically inappropriate and delayed. This is the first study to look specifically at the issue of appropriate empiric antibiotics in the context of all patients having received antibiotics promptly once CSVAP was identified. Thus, the authors were able to take the confounding variable of the timing of initial antibiotic therapy out of the equation. They demonstrate that the microbiologic appropriateness of the initial antibiotic(s) given is a significant determinant of patient outcome.

The selection of an appropriate initial empiric antibiotic regimen, once a critically ill ventilated patient is clinically suspected of having VAP, remains a complicated and controversial task. The original clinical trial from which this secondary analysis was performed found no differences in outcomes among patients who had *Pseudomonas* as the causative organism with the two antibiotic regimens used. However, the number and choice of antibiotics in patients with CSVAP cannot be approached as a "one-size-fits-all" proposition. Local practice patterns and preferences enter into it, as do the patient's immune status and recent antibiotic history, plus local VAP organism prevalence, resistance patterns, and the institution's current "antibiogram." This study's findings, though, support the concept that initial empiric antibiotic therapy for CSVAP needs to be begun promptly and be broad enough to cover the likely causative organism(s), in that context and for that patient. Once culture results are available, coverage can be narrowed appropriately. ■

## ABSTRACT & COMMENTARY

# Critical Care Clinicians Require Critical Communication Skills

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

SYNOPSIS: This article provides many excellent suggestions and strategies for improving communication among the members of the critical care team to reduce medical errors.

SOURCE: Brindley PG, Reynolds SF. Improving verbal communication in critical care medicine. *J Crit Care* 2011;26:155-159.

The purpose of this article was to apply aviation communication principles and strategies to the field of critical care medicine, particularly crisis communication situations. Given the number of medical errors that contribute to patient mortality, most stemming from poor communication, this paper offers several excellent suggestions and simple strategies for improving communication among the critical care team, and includes both speaking as well as listening skills.

Effective communication is at the core of leadership, teamwork, and crisis management. Functioning as a good team or effective leader parallels good communication. The authors describe several effective leadership and communication goals that include the ability to establish a shared mental model, to coordinate tasks, to centralize the flow of information, to establish a structure, and to stabilize emotions. The authors note that medical teams rarely achieve a shared mental model, which they refer to as an understanding of the situation, task, and resources.

One manner in which to achieve a shared mental model is by addressing the culture of a unit/group in order to improve communication. Commercial airlines are one example of an effectively communicating team that functions well in a crisis to avert error or disaster by promoting a culture of horizontal authority, whereby subordinates are empowered to speak up and senior members listen. In the medical arena, nurses usually delay in sharing identified problems with the team because they are viewed as subordinate to physicians in most organizations. Physicians, on the other hand, tend not to communicate what they are doing and why, and usually only communicate with other physicians rather than the entire health care team.

Fortunately, the authors offer several practical strategies from the literature to promote verbal communication, improve assertiveness, improve understanding, and improve task completion. Promoting verbal communication involves using speech best suited for a situation and communicating clearly and assertively, particularly in a crisis. Improving assertiveness includes graded strategies that range from least direct to most direct — hint, preference, query, shared suggestion, statement, command. For subordinates, if hints are ignored they rarely will escalate their assertiveness. Another example to improve assertiveness is the Situation, Background, Assessment, and Recommendation (SBAR) communication, which originated in the military. The SBAR approach allows all members of the ICU team to speak clearly and comprehensively. For improving understanding, the authors note that overly aggressive or passive speech is not appropriate in any situation as this style shifts the focus to power rather than the task at hand. “Heard is not understood” strategies to improve in this area include “call out” and “speaking up,” so colleagues know not to interrupt an individual while completing complex, and many times, concurrent tasks. Lastly, strategies to improve task completion include the 3 Cs of communication: clear instructions, citing names, and closing the loop, which is similar to the repeat-back method for confirm understanding of the delivered message.

## COMMENTARY

Much has been written over the past years with regard to patient safety and the need to improve it. The "Silence Kills” study (2005), conducted by VitalSmarts, the Association of periOperative Registered Nurses, and the American Association of Critical-Care Nurses,[1] revealed that 84% of health care professionals have observed colleagues take dangerous shortcuts when working with patients, and yet fewer than 10% spoke up about their concerns. While checklists and safety tools are important, the crux of the matter lies with respectful and effective communication to prevent errors and promote patient safety. In general, health care professionals are not taught how to communicate in their basic education or training programs. Further, role models are needed in all organizations where a culture that contains a horizontal hierarchy is modeled among leadership.

To promote optimal patient safety in the ICU, all members of the ICU care team need to acquire and practice effective communication skills. Sending and receiving accurate messages can be a matter of life and death, particularly in highly stressful situations such as during patient resuscitation. Educators, preceptors, fellowship directors, and managers are all challenged to model, inform, and promote excellent communication skills, as these skills are just as important as technical skills and knowledge in caring for critically ill patients. ■

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ABSTRACT & COMMENTARY

# Do Macrolide Antibiotics Improve Survival in Acute Lung Injury?

*By David J. Pierson, MD, Editor*

SYNOPSIS: In a retrospective examination of data from the original ARDS Network low-tidal-volume study, patients who had received a macrolide antibiotic had lower 180-day mortality and got off the ventilator faster than patients who did not receive a macrolide; other antibiotics had no detectable association with the study variables.

SOURCE: Walkey AJ, Wiener RS. Macrolide antibiotics and survival in patients with acute lung injury. *Chest* 2011;Nov 23. [Epub ahead of print.]

This is a report of a secondary analysis of data from the original Acute Respiratory Distress Syndrome (ARDS) Network low-tidal-volume study, which demonstrated improved survival with ventilator tidal volumes of 6 (vs 12) mL/kg predicted body weight in patients meeting the American-European consensus definition of acute lung injury (ALI) or ARDS. In a 2-by-2 factorial design, that original study also investigated the effect of lysophylline in ALI/ARDS. Because no effect of lysophylline was demonstrated, all the data (that is, from both 6- and 12-mL/kg PBW tidal volumes, and both lysophylline and placebo) were used in the present study of the possible effect of macrolide antibiotics (not part of the original study, but recorded in the database) on patient outcomes.

Virtually all of the 235 patients in the study (232/235, 99%) had received one or more antibiotics within 24 hours of study enrollment. Macrolides had been used in 47 (20%) of the patients — erythromycin in 27 (57%), azithromycin in 19 (40%), and clarithromycin in 1 patient. Eleven of the patients who received a macrolide (23%) died prior to the a priori 180-day survival cutoff, as compared to 67/188 (36%) of the patients who did not receive a macrolide. The difference was not significant ($P$ = 0.11), but after adjustment for confounding covariates, mortality in the macrolide group was significantly lower (hazard ratio, 0.46; 95% confidence interval, 0.23-0.92; $P$ = 0.028). In addition, time to discontinuation of mechanical ventilation was significantly lower among patients who received a macrolide ($P$ = 0.009). These associations were unaffected by the diagnosis predisposing to ALI/ARDS or by tidal volume randomization group. The authors could detect no effects of fluoroquinolones in the 90 patients who received this class of antibiotics, nor of cephalosporins in the 93 patients who received them.

## COMMENTARY

By no means does this retrospective analysis demonstrate that macrolide antibiotics reduce mortality and shorten the need for mechanical ventilation in ALI/ARDS. That will require much more rigorous, prospective investigation. However, the results of this study are intriguing, both on theoretical grounds and in light of recent studies of this class of antibiotics in other pulmonary disorders.

Macrolides have anti-inflammatory properties in addition to their antimicrobial action. Studies using animal models have shown beneficial effects of macrolide antibiotics against ALI induced by a variety of drugs and toxins. Clinically, macrolides have been shown to be effective in treating diffuse panbronchiolitis, a chronic airway disease seen primarily in Japan and elsewhere in Asia. Studies in cystic fibrosis, non-CF bronchiectasis, bronchiolitis obliterans, and other chronic airway disorders have also produced encouraging preliminary results.[1] And, in a study recently reported in the *New England Journal of Medicine*, daily administration of low-dose azithromycin for 1 year reduced the frequency of exacerbations and improved some measures of quality of life in patients with chronic obstructive pulmonary disease (COPD).[2]

While it seems a long way from COPD and diffuse panbronchiolitis to ALI/ARDS, there is at least biologic plausibility to the notion that macrolides could be effective in the latter. We should not start treating all our ALI/ARDS patients with macrolides on the basis of the study by Walkey and Wiener, but we should keep our eyes open for further developments. ■

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## CME/CNE Questions

**1. Which of the following is true concerning patient wishes while receiving mechanical ventilatory support in the ICU?**

a. They want to "sleep" through the entire experience
b. They want to be frequently reassured and reoriented
c. The endotracheal tube is not at all bothersome
d. They would like to receive more sedative medications to be more calm
e. All of the above

**2. Which of the following is true concerning effective communication strategies with mechanically ventilated patients?**

a. The use of high-tech talking devices that mimic speech are essential to promote effective communication.
b. To prevent patient fatigue, the clinician should ask many questions at once to determine how the patient is feeling.
c. It is recommended that the clinician speak directly to the patient when asking questions.
d. Only a speech-language specialist can effectively communicate with patients.
e. All of the above

**3. Compared to those whose initial therapy proved to be appropriate, patients with clinically suspected ventilator-associated pneumonia who received prompt empiric antibiotic therapy to which the recovered organisms proved to be resistant:**

a. did just as well clinically but had higher treatment costs.
b. had higher ICU and hospital mortality.
c. were weaned from ventilatory support more rapidly.
d. spent fewer days in the ICU and in the hospital.

**4. Which of the following should be taken into consideration in the initial antibiotic treatment of suspected ventilator-associated pneumonia?**

a. The timing of the first dose
b. The patient's immune status
c. Recent organism prevalence and resistance patterns in the institution
d. Recent antibiotic exposure in that patient
e. All of the above

**5. Previous studies of empiric antibiotic therapy for suspected ventilator-associated pneumonia:**

a. showed that the choice of antibiotic is not as important as the timing of initiation.
b. showed that the correctness of the initial antibiotic used is more important than the timing.
c. did not distinguish between antibiotic choice and timing when therapy was inappropriate.
d. showed that the antibiotic sensitivities of cultured organisms were not clinically important.
e. None of the above

**6. A shared mental model is one in which:**

a. the attending physician is in charge and is not questioned about decisions.
b. nurses communicate their thoughts to physicians in a written format.
c. all members of the team are encouraged to speak up during a crisis.
d. encourages vertical authority among the team members.

**7. A horizontal hierarchy is one that:**

a. empowers all members of the team to speak freely and assertively.
b. promotes one individual to provide orders to the remainder of the team members.
c. promotes a physician-centric communication model.
d. promotes the use of authoritative language in all situations.

**8. Which of the following statements is true about the findings of the original ARDS Network study of tidal volume and lysophylline in acute lung injury?**

a. Survival was improved in the low-tidal-volume group
b. Lysophylline had no effect on survival
c. After statistical adjustments, survival was improved in patients who received macrolide antibiotics
d. All of the above

**9. Which of the following effects of macrolide antibiotics provides biologic plausibility for a favorable effect on patient outcomes in acute lung injury?**

a. Antimicrobial effects
b. Anti-inflammatory effects
c. Surfactant effects
d. Anti-fibrotic effects

### 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]

Gender and ICU burnout

Making ICUs less noisy

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.*

# Dutasteride and Low-Risk Prostate Cancer

***In this issue:*** New treatment for prostate cancer; avastin and breast cancer; new CMS disclosure rule; and FDA actions.

## Adjunct to active surveillance?

Low-risk prostate cancers are nonpalpable, low-grade tumors associated with prostate-specific antigen (PSA) levels less than 10 ng/mL. For these patients, active surveillance is an option, allowing a period of observation to help decide who should be treated or not treated. Generally, this involves repeated biopsy sampling with the option to treat more aggressively if higher grade tumors are found. Active surveillance is more frequently utilized in Europe and Canada than in the United States, where more aggressive treatment is the norm. A new study from the U.S. and Canada investigates the safety and efficacy of the 5α-reductase inhibitor dutasteride on prostate cancer progression in men with low-risk disease. A total of 302 men ages 48-82 with low-volume Gleason score 5-6 prostate cancer were randomized to dutasteride 0.5 mg per day or placebo. Patients were followed for 3 years with prostate biopsies done at 18 months and 3 years with the primary endpoint being time to prostate cancer progression. After 3 years, 38% of men in the dutasteride group and 48% of men in the control group had prostate cancer progression (hazard ratio 0.62; 95% confidence interval [CI], 0.43-0.9; $P = 0.009$). Dutasteride was not associated with an increase in adverse events. There were no prostate cancer-related deaths and no incidence of metastatic disease in either group. The authors conclude that "dutasteride could provide a beneficial adjunct to active surveillance for men with low-risk prostate cancer" (*Lancet* published online January 23, 2012). An accompanying editorial points out the appeal of a safe oral drug that can prevent prostate cancer progression, but the author cannot recommend the drug based on this study due to several limitations — short duration, no evidence of mortality difference, and, most importantly, the risk that 5α-reductase inhibitors may decrease the volume of low-grade, but not high-grade, cancers. (*Lancet* published online January 23, 2012). This study comes at a time when physicians are actively debating the pros and cons of screening for prostate cancer. The recently published PLCO trial showed that PSA screening does not lower the risk for death from prostate cancer while there is evidence of harm (*J Natl Cancer Inst* 2012;104:125-132). Some would argue that rather than treating low-grade prostate cancers, it may be better not to diagnose it at all. This issue is sure to be a topic of discussion at the FDA if GlaxoSmithKline requests approval for dutasteride (Avodart) for the management of low-risk prostate cancer. ■

## More to the avastin/breast cancer story?

In November 2011, the FDA revoked the approval of Genentech's bevacizumab (Avastin) for the treatment of breast cancer. The somewhat controversial decision was based on lack of evidence of improved survival with the drug, even though several studies have shown improvement in progression-free survival. This has sparked a debate regarding surrogate clinical endpoints, such

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as progression-free survival or pathological complete response, which is the endpoint used in two new studies recently published in the *New England Journal of Medicine*. The first study from Germany randomly assigned 1948 women with medium-sized tumors to receive neoadjuvant epirubicin and cyclophosphamide, followed by doxetaxel with or without bevacizumab, in patients with HER2-negative breast cancers. Rates of pathological complete response were 14.9% without bevacizumab and 18.4% with the drug (odds ratio 1.29; 95% CI, 1.02 to 1.65; $P = 0.04$). Patients with hormone receptor-negative ("triple negative") tumors did better while patients with hormone receptor-positive tumors saw no improvement (*N Engl J Med* 2012;366:299-309). The other study, supported by the National Cancer Institute, looked at about 1200 patients with operable HER2-negative breast cancer. Patients were given neoadjuvant therapy with docetaxel plus capecitabine or paclitaxel plus gemcitabine followed by doxorubicin-cyclophosphamide. They were further randomized to receive bevacizumab for the first six cycles. Adding capecitabine or gemcitabine to docetaxel had no effect and increased toxicity; however, adding bevacizumab increased the rate of pathological complete reponse (28.2% without bevacizumab vs the 34.5% with bevacizumab, $P = 0.02$). Bevacizumab increased the rates of hypertension, left ventricular systolic dysfunction, hand-foot syndrome, and mucositis. The authors conclude that bevacizumab significantly increased the rate of pathological complete response (*N Engl J Med* 2012;366:310-320). An accompanying editorial points out that the ongoing controversy regarding bevacizumab for the treatment of breast cancer revolves around the issue of using surrogate endpoints in clinical trials as well as broader economic issues in the treatment of cancer. Although the study showed improvement in the surrogate endpoint of pathological complete response (defined as absence of residual tumor in the breast and nodes in the European study and a less stringent criteria of absence of residual tumor in the breast only in the American study), neither study was powered to show differences in survival — the criteria the FDA used to withdraw the approval for bevacizumab (*N Engl J Med* 2012;366:374-375). It is unlikely that either of these studies will influence the FDA to change its decision until more definitive survival data are available. ■

## Disclosure rule open for comments

The Centers for Medicare and Medicaid Services is requesting comments on a proposed rule that would require drug and device companies to report all financial relationships with physicians. The new rule is part of the Affordable Care Act. It would require disclosure of payments for food, entertainment, gifts, consulting fees, honoraria, research funding for grants, education or conference funding, royalties or licenses, and insurable contributions. Physicians would also need to disclose stock ownership in pharmaceutical and device companies, with all this information provided on a public website. Failure to disclose this information would mean substantial fines for physicians. Comments will be accepted until mid-February with the final rule expected later in 2012. ■

## FDA actions

Responding to concerns about increasing antibiotic resistance, the FDA has issued an order that prohibits the use of cephalosporins in cattle, swine, chickens, and turkeys effective April 15, 2012. This rule is intended to limit the indiscriminate use of cephalosporins and preserve the effectiveness of the drugs in humans.

The FDA has approved a once-weekly, extended-release formulation of exenatide for treatment of type 2 diabetes. The drug is a glucagon-like peptide-1 receptor agonist and is indicated as an adjunct to diet and exercise for improved glycemic control. It is the first once-weekly diabetes drug to be approved. The approval was based on the DURATION-5 trial, which compared once-weekly exenatide with twice-daily exenatide injection. Exenatide extended-release is approved with a Risk Evaluation and Medication Strategy (REMS) because of concerns regarding acute pancreatitis and the potential risk for medullary thyroid cancer, as well as concerns about QT prolongation and cardiovascular risk. Exenatide extended-release will be marketed by Amylin Pharmaceuticals and Alkermes plc as Bydureon.

The FDA has approved vismodegib to treat adult patients with advanced basal cell carcinoma who are not candidates for surgery or radiation, and for patients with metastatic disease. The drug was approved under the agency's priority review program and is the first approved drug for metastatic basal cell carcinoma. The once-a-day oral pill inhibits the Hedgehog pathway, a molecular pathway found in basal cell carcinomas but few other normal tissues. The approval was based on a single, multicenter trial of 96 patients in which 30% of patients with metastatic disease experienced a partial response and 43% patients with locally advanced disease experienced a complete or partial response. Vismodegib is marketed by Genentech as Erivedge. ■