

# Critical Care [ALERT]

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

## ABSTRACT & COMMENTARY

### High Mortality in Patients with COPD Exacerbations Who Fail Noninvasive Ventilation

By David J. Pierson, MD, Editor

**SYNOPSIS:** Wider use of noninvasive ventilation in managing severe COPD exacerbations has improved overall outcomes, but this study of a large nationwide database shows that increasing numbers of patients fail NIV and require intubation. This subset of patients has substantially higher mortality and hospital costs.

**SOURCE:** Chandra D, et al. Outcomes of non-invasive ventilation for acute exacerbations of COPD in the United States, 1998-2008. *Am J Respir Crit Care Med* 2011;Oct 20. [Epub ahead of print.]

Until now, getting a handle on the utilization and outcomes of noninvasive ventilation (NIV) in the management of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in the United States has been hampered by the absence of a nationwide database on this important condition.<sup>1</sup> With this study, Chandra and colleagues have gone a long way toward correcting this deficiency. They used a nationwide database to examine more than 7 million hospitalizations for AECOPD between 1998 and 2008, looking at patient demographics,

the use of both NIV and invasive mechanical ventilation (IMV), and patient outcomes. Although the article provides a general overview of their findings, I will focus primarily on what their data reveal about an important subset of AECOPD patients — those in whom NIV is unsuccessful, necessitating intubation and the use of IMV.

The authors used data from the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project (HCUP-NIS), which collects information from about 20% of all U.S. hospitals

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## Critical Care Alert,

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and includes all areas of the country, insurance categories, and hospital sizes. For all admissions for AECOPD, Chandra et al determined whether NIV or IMV had been used and identified all patients who were started on NIV and subsequently received IMV; against these data they examined in-hospital mortality (adjusted for patient demographics, hospital characteristics, and comorbidities), length of stay, and total charges for the hospitalization.

Of the 7,511,267 admissions for AECOPD to the participating hospitals from 1998 through 2008, 612,650 (8.1%) received ventilatory support, with NIV progressively increasing (from 1.0% to 4.5% of admissions) and IMV decreasing (from 6.0% to 3.5%) during the study period. The proportion of patients who started on NIV and were switched to IMV remained the same at about 4.6%, but because of the steady increase in patients in whom NIV was used, their absolute numbers climbed steadily. Overall, 9681 patients transitioned from NIV to IMV, of whom 2595 (27%) died. This compares to 17,436 deaths (9%) among 198,375 patients managed initially on NIV who were not switched to IMV. Adjusted odds ratios for mortality in NIV patients who were switched to IMV were substantially increased in comparison with those who remained on NIV, for every year starting in 2000. In 2008, a patient requiring IMV after unsuccessful NIV had 61% greater odds of death than a patient placed directly on IMV at the start, and 677% greater odds of death compared to a patient treated with NIV without transition to IMV. Charges for hospitalization increased steadily from 1998 through 2008, but the increase was steepest for patients who required a transition from NIV to IMV. Hospital length of stay was longest for the latter group and did not fall over time, whereas length of stay gradually decreased among the other groups.

## ■ COMMENTARY

This study demonstrates that whether ventilatory support was required was strongly correlated with outcomes among patients hospitalized with

AECOPD. The mortality rate among those in whom neither NIV nor IMV was used remained in the 2-3% range throughout the 11-year data period. For patients who received NIV only, in-hospital mortality started at 11 or 12% and fell gradually to 7% or 8% (estimates from Figure 3, since precise data are not provided in the paper). Patients who received only IMV (no NIV) had an overall mortality rate of 23%, whereas, as mentioned, 27% of the patients who started out on NIV and had to be intubated for IMV died. Of course, these groups of patients undoubtedly varied a great deal in terms of severity of underlying COPD, the acute illness, comorbidities, and other factors, so that the mortality differences cannot be interpreted as simply reflecting differences in ventilatory support. Still, I think some conclusions can be drawn.

The steady increase in NIV use nationwide during the study period probably reflects increased awareness of the compelling evidence supporting it and the recommendations of practice guidelines, and the progressive decrease in mortality among patients who did not require intubation is consistent with increasing experience and expertise with this therapy over time. That the proportion of patients receiving IMV fell by nearly half during the study period likely also reflects increasing awareness that this complication-laden intervention is not necessary as often as we used to believe; the mortality rate among this decreasing proportion of patients who required IMV stayed about the same.

The group of greatest concern, whose outcomes actually worsened over time in terms of absolute patient numbers, is those patients who were initially managed with NIV and subsequently required intubation. Some of these patients likely developed new complications or experienced a progression of the primary problem. However, it is also likely that others were unsuitable for NIV in the first place, or received NIV in an ineffective or suboptimal manner. Carrying out NIV effectively

is both a science and an art, with a substantial learning curve not only for the physician in knowing when to use it but also for the respiratory therapist in tailoring it to the patient's needs and toleration over time. The findings of the present study are very encouraging in their documentation of more widespread use of NIV for AECOPD. Hopefully, the overall

improvement in patient outcomes will continue with increasing experience, and the subset of patients who fail initial NIV will be better understood and more successfully managed. ■

#### REFERENCE

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## ABSTRACT & COMMENTARY

# Detecting Airflow Obstruction in the Mechanically Ventilated Patient

By David J. Pierson, MD, Editor

**SYNOPSIS:** Examination of expiratory flow-volume tracings obtained from passively ventilated patients during manual compression of the abdomen showed a pattern ascribed to expiratory flow limitation in those with a history of COPD or asthma, and also in obese patients.

**SOURCE:** Lemyze M, et al. Manual compression of the abdomen to assess expiratory flow limitation during mechanical ventilation. *J Crit Care* 2011;Jul 26. [Epub ahead of print.]

Lemyze and colleagues studied a simple bedside procedure for detecting expiratory airflow obstruction in intubated, mechanically ventilated patients. They recorded inspiratory and expiratory flow tracings on the ventilator's digital monitor screen with and without pressing manually on the patient's abdomen throughout expiration. They reasoned that expiration in patients who had no expiratory airflow limitation would be augmented throughout the expiratory phase, whereas the flow tracings in obstructed patients (as in severe chronic obstructive pulmonary disease [COPD] or asthma) would demonstrate a different pattern and not show increased flow throughout the whole exhalation. They tested this in a series of ventilated patients with and without previously known obstructive lung disease.

The patients were studied during controlled mechanical ventilation (sedated; no triggering), with simultaneous recording of expiratory waveforms and measurement of esophageal pressures via gastric balloon. Separately, the first 13 patients also had expiratory waveforms recorded with 5 cm H<sub>2</sub>O continuous negative airway pressure, using a technique for detecting airflow limitation during mechanical ventilation described by Valta et al in 1994.<sup>1</sup> The authors studied 44 patients (28 men; mean age 56 years) in a medical ICU who had been ventilated for a mean of 4.7 days (primary causes for respiratory failure not given). Seventeen patients were

diagnosed with COPD (defined according to GOLD criteria; severity of obstruction by forced expiratory volume in the first second [FEV<sub>1</sub>] not given), and three carried a diagnosis of asthma. The other patients were not known to have underlying airway disease.

Using the authors' technique, expiratory flow limitation was detected during abdominal compression in 31 of 44 patients, or 70%. This included all 20 patients with a clinical history of obstructive lung disease, plus 11 others, 10 of whom were obese and several of whom were elderly. Of the first 13 patients studied, in whom airflow limitation was assessed by both abdominal compression and negative expiratory pressure, seven demonstrated such limitation, with complete agreement by both techniques. There was good correlation between the presence of the obstruction pattern and the detection of auto-PEEP. The authors conclude that manual compression of the abdomen during exhalation, with examination of the expiratory waveform on the ventilator's monitor, "provides a simple, rapid, and safe bedside reliable maneuver to detect and quantify expiratory flow limitation during mechanical ventilation." They hypothesize that the apparent airflow obstruction in the 25% of their patients who were not known to have airway disease may have been due to obesity (airway closure from ventilation at low lung volumes), airway edema (from excessive fluid administration), or advanced age.

## ■ COMMENTARY

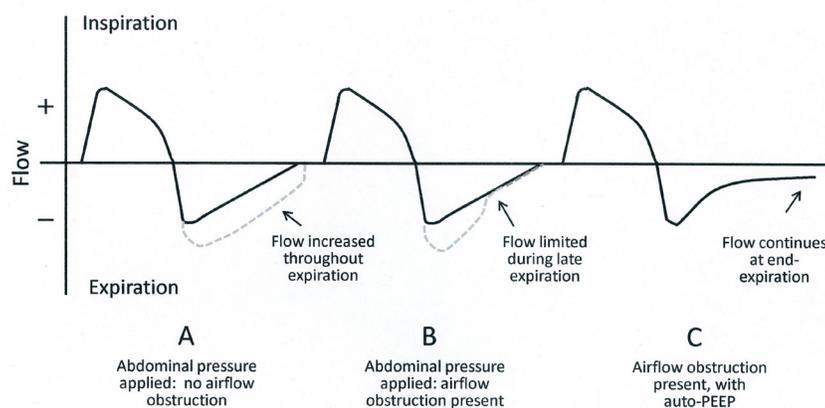
Methodologically, this study has several important shortcomings that affect the confidence with which their recommendations can be accepted. Chief among these is the lack of validation of the new technique with accepted measurements of airflow obstruction in the patients studied. The authors used a previously reported technique, the application of negative airway pressure during expiration, as their “gold standard” to confirm that obstruction was present, but used it in only 13 of the 44 patients studied. In validating the negative-pressure technique, Valta et al had correlated its results with spirometric measurements in the obstructed patients in their study.<sup>1</sup> The absence of FEV<sub>1</sub> data or other confirmation of the diagnosis of obstructive lung disease, as well as the apparent presence of airflow limitation in patients without known airway disease, diminishes the confidence with which the present study’s conclusions can be accepted. In addition, because the patients were sedated and not interacting with the ventilator, whether this technique might be useful in spontaneously triggering patients or those on spontaneous modes such as pressure support will require further study.

The above cautions notwithstanding, this paper highlights a clinically important issue in the management of mechanically ventilated patients. Obstructive lung disease is very common in all adult ICU populations, and predisposes patients to potentially life-threatening complications

during mechanical ventilation if not detected and appropriately managed. Patients with severe underlying COPD, especially, are particularly vulnerable to air trapping, dynamic hyperinflation, and auto-PEEP during positive-pressure ventilation, which if undetected may lead to diminished venous return, hypotension, and pulseless electrical activity, as well as to alveolar rupture and clinical barotrauma. In addition, the presence of dynamic hyperinflation exacerbates patient-ventilator asynchrony and is one of the most common reasons for unsuccessful attempts at weaning.<sup>2</sup>

Despite multiple clinical practice guidelines and the ready availability of the means of assessment, the diagnosis and staging of COPD are notoriously inaccurate.<sup>3</sup> Cigarette smokers who are middle-aged or elderly have a high prevalence of COPD, but the proportion of them who have it is still considerably less than 50%. Only measurements of vital capacity and FEV<sub>1</sub> can confirm the diagnosis in patients with chronic respiratory symptoms and an appropriate exposure history. However, studies have shown that the majority of patients who carry a diagnosis of COPD have never had pulmonary function tests. Conversely, studies of medical patients hospitalized for other reasons have shown that the prevalence of undiagnosed COPD in such individuals is high.<sup>3</sup> Thus, both because of its clinical importance during mechanical ventilation and the unavailability of accurate diagnostic information in many patients, accurate detection

Figure. Detection of Expiratory Airflow Obstruction During Mechanical Ventilation



Cartoon illustrating inspiratory and expiratory flow patterns, as typically shown on the ventilator’s monitor screen during volume-targeted ventilation with a decelerating inspiratory wave form, during individual breaths under three different circumstances. In breath A, in the absence of airflow obstruction, applying abdominal pressure produces higher flows throughout expiration. With severe expiratory airflow obstruction (breath B), applying abdominal pressure increases expiratory flow only initially, with the rest of the expiration flow-limited. Dynamic hyperinflation and auto-PEEP in the presence of severe airflow obstruction can be detected without abdominal compression by examining the expiratory waveform (breath C) in a passively exhaling patient: the ventilator breath is incompletely exhaled before the next inspiration is due, as shown by failure of the expiratory flow tracing to return to zero.

of airflow obstruction in all ventilated patients is a problem of great practical importance.

Current ICU ventilators incorporate automated assessment of auto-PEEP, although the measurement must be initiated each time by the clinician and it cannot be carried out meaningfully if the patient is actively making either inspiratory or expiratory efforts. Although it is not a quantitative measurement, the presence of auto-PEEP can be detected at the bedside via the ventilator's graphics display.<sup>4</sup> The figure (see p. 84) illustrates schematically both the abdominal compression technique for detecting airflow obstruction, as used by Lemyze et al in this study, and the detection of dynamic hyperinflation utilizing the ventilator's expiratory waveform.

In ventilated patients with severe asthma, significant airway obstruction can often be detected during the inspiratory phase by an increased difference between peak and plateau

pressures, the former reflecting decreased airway caliber and the latter the degree of air trapping. Changes in both peak-minus-plateau pressure difference and the auto-PEEP level can be used as indicators of the effectiveness of bronchodilator therapy in the management of acute severe asthma. Auto-PEEP is the most direct monitor of dynamic hyperinflation in COPD. Because airway obstruction in COPD is primarily expiratory, the inspiratory peak-minus-plateau airway pressure difference is a less useful monitor in that condition than in asthma. ■

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## ABSTRACT & COMMENTARY

# Patients Placed in Contact Isolation Are at Increased Risk for Delirium

By David J. Pierson, MD, Editor

**SYNOPSIS:** This retrospective study of all non-psychiatric patients admitted to an academic medical center found that although those placed in contact isolation from the time of admission had no increased risk for delirium, patients moved into isolation after admission were twice as likely to develop delirium during the hospital stay.

**SOURCE:** Day HR, et al. Association between contact precautions and delirium at a tertiary care center. *Infect Control Hosp Epidemiol* 2012;33:34-39.

To examine the association between being placed in contact isolation and delirium, Day and colleagues at the University of Maryland Medical Center reviewed administrative data on all patients admitted during a 2-year period ending in 2009. They excluded patients with underlying schizophrenia or bipolar disorder, those admitted to the psychiatry service, and alcohol-related admissions, as well as patients under age 18. Patients placed into contact isolation during hospitalization were stratified into those assigned this status on admission (because of pre-existing risk or documented infection) and those subsequently moved into isolation (because of positive surveillance or clinical cultures, acquired risk, or other factors). Because delirium is underdiagnosed and incompletely identified by

its direct ICD-9 code, the authors also used as proxy measures the otherwise-unexplained use of haloperidol or other antipsychotic drugs and the use of physical restraints during the admission. They performed selected chart reviews to assure that the variables under study were recorded in the administrative database with acceptable accuracy.

Of 70,275 admissions during the study period, 60,151 (in 45,266 unique patients; 9869 ICU admissions) were evaluated after *a priori* exclusions. Contact precautions were used in 9684 admissions (15%), 58% of them from the time of admission and 42% commencing at some point following admission. The authors' criteria for delirium were met in 7721 admissions (13.5%). Overall, patients placed in contact isolation at

any time during hospitalization were twice as likely to have delirium compared to non-isolated patients (16.1% vs 7.6%, respectively; odds ratio [OR], 2.4; 95% confidence interval [CI], 2.2-2.5%). There was no relationship between contact precautions and delirium among patients who were placed in isolation immediately on admission. However, being moved into isolation sometime after admission because of identification of a multiple-drug-resistant bacterium was associated with increased risk for delirium (OR, 1.75; 95% CI, 1.60-1.92;  $P < 0.01$ ). Although ICU patients had significantly more delirium than non-ICU patients, being placed in contact isolation had no independent effect.

#### ■ COMMENTARY

Delirium, which occurs in about 15% of all hospitalized patients and is considerably more common in the ICU, is associated with numerous bad outcomes, including increased mortality, morbidity, and length of stay. Under current recommendations by the Centers for Disease Control and Prevention, contact precautions — including the use of gloves and gowns and isolation in a private room — are now used in a substantial number of hospitalized patients. Several studies have documented that physicians, nurses, and other clinicians interact with patients in isolation less often than non-isolated patients, and that those in isolation have more symptoms of depression and anxiety. Because decreased environmental stimuli predispose to delirium, it is hardly surprising that patients

placed in isolation are more likely to develop this important disorder.

This study does not show that isolation causes delirium. Patients placed in isolation had increased mortality and lengths of stay, were more likely to be admitted to the ICU, and had more positive cultures suggesting clinical infections with resistant organisms than patients who were never placed in contact precautions. Thus, delirium was likely influenced by some or all of these and other factors that could not be controlled for in a retrospective study. The fact that patients placed in isolation from the time of admission — because of a past history of colonization with resistant organisms or the presence of specific risk factors — did not have a higher risk for delirium suggests that those who required the institution of contact precautions subsequent to admission were sicker and perhaps more predisposed to delirium in the first place. These points are acknowledged by the authors.

I think the important contribution of this study is the spotlight it shines on contact isolation as a marker for the development of delirium. Regardless of the contribution of isolation per se to this development, knowing that isolated patients are at increased risk can help — at the level of the individual clinician as well as for hospital policy — with respect to efforts at early detection, appropriate treatment, and prevention of this important complication of acute illness. ■

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## ABSTRACT & COMMENTARY

# Perceived Inappropriateness of Care Among ICU Clinicians

By David J. Pierson, MD, Editor

**SYNOPSIS:** In this 1-day survey of clinicians working in 82 ICUs in 10 countries, one in four nurses and one in three physicians reported that they delivered inappropriate care to at least one patient that day. Perceived inappropriateness of care was less likely when there was effective interdisciplinary collaboration and teamwork in the unit.

**SOURCE:** Piers RD, et al; APPROPRICUS Study Group of the Ethics Section of the ESICM. Perceptions of the appropriateness of care among European and Israeli intensive care unit nurses and physicians. *JAMA* 2011;306:2694-2703.

**T**his study was a survey of all the physicians and nurses working in 82 adult ICUs on a particular day in 2010. It was conducted by a study group of the Ethics Section of the European Society of Intensive Care Medicine, and the ICUs involved were in nine European countries

plus Israel. The objective was to determine the prevalence of perceived inappropriateness of care (that is, a specific patient-care situation in which the clinician acts in a manner contrary to his or her personal and professional beliefs), using a series of questionnaires.

The ICUs studied had a median of 11 beds each and 95% of them managed both medical and surgical patients. Hospitals ranged from fewer than 250 beds (11%) to more than 750 beds (34%), and were mainly university or university-affiliated (56%), most of the rest (38%) being public hospitals. Seventy-four percent of the ICUs were closed units, and trained intensivists were present in all, with a median patient-to-intensivist ratio of 3.3. Of 99 ICUs eligible for participation in the study, 82 did so, and of 1953 clinicians working on the day of the study, median participation per ICU was 100% for physicians and 93% for nurses.

Perceived inappropriateness of care of at least one patient was reported by 439 ICU clinicians (27%; 25% of nurses and 32% of physicians). In ICUs for which patient data could be linked to the clinicians working there, inappropriateness of care was reported in 23% of the beds on that day. Of the potential types of inappropriate care listed on the questionnaire, the one most commonly reported (in 65% of instances) was “disproportionate care,” broken down into “too much care” (in 89% of situations) followed by “other patients would benefit more” (in 38%). When symptom control decisions were solely in the hands of physicians, this was strongly associated with perceived inappropriateness of care among both nurses and physicians. The latter was significantly less common when nurses were involved in end-of-life decision making, when good collaboration existed between nurses and physicians, and when there was individual clinician freedom in deciding how to perform work-related tasks. Nurses — but not physicians — who perceived their workloads to be excessive were also more likely to report inappropriate patient care. In both groups of clinicians, perceived inappropriateness of care was positively associated with higher intent to leave a job.

Study participants generally reported end-of-life decisions as being made too late or too infrequently. Among those reporting inappropriate care, a perceived failure to observe distributive justice (that is, allocating care to those who need it most and not to those who do not need it) was common, especially

among physicians. However, in two-thirds of the instances in which a given patient received care from more than one participant in the study, only one of them perceived that the care was inappropriate. The prevalence of perceived inappropriateness of care varied widely across countries, and also across ICUs and among individual clinicians within a given country. No severity-of-illness-related measure, such as mortality or length of stay, correlated with perceived inappropriateness of care.

#### ■ COMMENTARY

This large-scale observational study found that one in four ICU nurses and one in three physician intensivists believed that they delivered inappropriate care to at least one of their patients on the day of the survey. This belief was strongly correlated with certain features of the ICUs in which they worked, particularly with respect to collaboration and teamwork among physicians and nurses. Both physicians and nurses who reported that they provided inappropriate care were more likely to express the intention to leave the job in the near future.

The study also found wide variation in the prevalence of perceived inappropriateness of care — among the 10 participating countries, in different ICUs within countries, and even among clinicians in a particular ICU — as well as disagreement between clinicians caring for a given patient as to whether the care was inappropriate. This emphasizes the subjective nature of perceived inappropriateness of care, as well as the importance of individual differences, potentially influenced by cultural and other factors.

This study was carried out in Europe — omitting Scandinavia, Spain, and the United Kingdom — as well as in Israel, and the applicability of its findings to American ICUs and the clinicians who work in them is uncertain. Certainly there are substantial organizational and cultural differences. However, the finding that perceived inappropriateness of care was less likely in ICUs where there was collaboration, teamwork, and shared decision making certainly seems applicable everywhere. ■

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## CME/CNE Questions

**1. Which of the following statements is true about the management of hospitalized patients with acute exacerbations of COPD?**

- a. Noninvasive ventilation is more widely used than in the past.
- b. Fewer patients are now being managed with invasive mechanical ventilation.
- c. Outcomes for patients transitioned from noninvasive to invasive mechanical ventilation are just as good as for patients initially ventilated invasively.
- d. All of the above
- e. a and b but not c

**2. Among patients with acute exacerbations of COPD, the mortality rate of those treated with noninvasive ventilation who do not subsequently require intubation is about:**

- a. 3%.
- b. 9%.
- c. 16%.
- d. 23%.
- e. 36%.

**3. Which of the following is the most important component in the accurate diagnosis of COPD in patients with chronic respiratory symptoms and an appropriate exposure history?**

- a. Physical examination
- b. Chest X-ray
- c. Chest CT
- d. Spirometry
- e. Echocardiography

**4. Mechanically ventilated patients with severe COPD are particularly predisposed to development of which of the following?**

- a. Dynamic hyperinflation
- b. Air trapping
- c. Auto-PEEP
- d. Alveolar rupture
- e. All of the above

**5. In the study by Lemyze et al, manually pressing on the abdomen in mechanically ventilated patients revealed a pattern suggestive of airflow obstruction in patients with which of the following?**

- a. COPD

- b. Asthma
- c. Obesity
- d. All of the above
- e. None of the above

**6. The development of delirium during acute hospitalization increases the risk for which of the following?**

- a. Mortality
- b. Morbidity
- c. Increased length of stay
- d. All of the above
- e. None of the above

**7. Which of the following patient groups was found to have a higher incidence of delirium?**

- a. Patients admitted to the ICU
- b. Patients moved into contact isolation at some point following admission
- c. Patients placed in contact isolation at the time of admission
- d. All of the above
- e. a and b but not c

**8. In the 1-day study of ICUs in 10 countries, what proportion of physicians reported delivering care to at least one patient that was inappropriate?**

- a. 8%
- b. 16%
- c. 32%
- d. 48%
- e. 64%

**9. Which of the following were more likely also to be present when ICU clinicians perceived that inappropriate care was being delivered on their shift?**

- a. Involvement of nurses in end-of-life decision making
- b. Interdisciplinary collaboration and teamwork
- c. Agreement among all the clinicians working in that ICU
- d. Increased likelihood of a stated intention to leave their present job
- 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]

Macrolide antibiotics and acute lung injury

Is that hospital's VAP rate really zero?

# 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.*

## New, Shorter Treatment Regimen for Tuberculosis

**In this issue:** New treatment for TB; safety of dabigatran; quality of antidepressants; systolic hypertension treatment; and FDA actions.

### Short course treatment for latent TB

Three months of two drugs administered once weekly is as effective as 9 months of daily isoniazid (INH) for the treatment of latent tuberculosis infection (LTBI), according to a new study. An international team of researchers randomized nearly 8000 patients with latent tuberculosis (TB) to 3 months of directly observed once-weekly therapy with rifapentine 900 mg plus INH 900 mg or 9 months of self-administered daily INH 300 mg. The primary endpoint was confirmed TB after 33 months of follow-up. In the modified intention-to-treat analysis, TB developed in 0.19% of the once-weekly combination group and in 0.43% of the INH only group. Rates of completion were much higher with the short course, once-weekly regimen (82.1% in the combination-therapy group and 69.0% in the INH only group,  $P < 0.001$ ). Rates of hepatotoxicity were higher in the INH only group. The authors conclude that use of rifapentine plus INH given once a week for 3 months is as effective as 9 months of INH in preventing tuberculosis and has a higher treatment-completion rate (*N Engl J Med* 2011;365:2155-2166). Based on this study and others, the CDC has issued a new recommendation on the use of short-course combination therapy for latent TB infection. The recommendation states, "The new regimen is recommended as an equal alternative to the 9-month INH regimen for otherwise healthy patients  $\geq 12$  years who have LTBI and factors that are predictive of TB developing (e.g., recent exposure to contagious TB)." It also recommends that the new regimen may be

considered for other categories of patients when it offers advantages. Daily INH continues to be the preferred regimen for children between the ages of 2 and 11 (*MMWR Morb Mortal Wkly Rep* 2011;60:1650-1653). ■

### Bleeding concerns with dabigatran

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Aliskiren (Tekturna), Novartis' direct renin inhibitor, should not be combined with an ACE inhibitor or angiotensin receptor blocker (ARB) to treat hypertension, according to the manufacturer. Novartis recently terminated the ALTITUDE trial when it was found that patients with type 2 diabetes or impaired renal function who were given the combination of aliskiren with an ACEI or ARB had a higher incidence of nonfatal stroke, renal complications, hyperkalemia, and hypotension. More information can be found at [www.novartis.com/newsroom/media-releases/en/2011/1572562.shtml](http://www.novartis.com/newsroom/media-releases/en/2011/1572562.shtml). ■

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**The FDA has approved Prevnar 13 for adults age 50 and older to prevent pneumonia and invasive disease caused by *Streptococcus pneumoniae*.** The vaccine was previously approved for children up to 5 years of age. The approval was based on head-to-head studies with Pneumovax 23 which is already approved for use in adults. According to the FDA, "for the 12 common serotypes, Prevnar 13-induced antibody levels were either comparable to or higher than the levels induced by Pneumovax 23." Prevnar 13 is manufactured by Wyeth Pharmaceuticals.

**Dronedarone (Multaq) should not be prescribed to patients with permanent atrial fibrillation (AF), based on results from the PALLAS trial which showed that the drug doubles the risk for cardiovascular death, stroke, and heart failure in such patients.** The FDA is requiring revised labeling for the antiarrhythmic drug and has issued a Drug Safety Communication after a safety review was completed. If dronedarone is to be prescribed, the FDA recommends ECGs every 3 months and immediately stopping the drug if the patient is found to be in AF. The drug is indicated to reduce hospitalization for AF in patients in sinus rhythm with a history of non-permanent AF (paroxysmal or persistent AF). Dronedarone is manufactured by Sanofi-Aventis. ■

# 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.*

## New, Shorter Treatment Regimen for Tuberculosis

**In this issue:** New treatment for TB; safety of dabigatran; quality of antidepressants; systolic hypertension treatment; and FDA actions.

### Short course treatment for latent TB

Three months of two drugs administered once weekly is as effective as 9 months of daily isoniazid (INH) for the treatment of latent tuberculosis infection (LTBI), according to a new study. An international team of researchers randomized nearly 8000 patients with latent tuberculosis (TB) to 3 months of directly observed once-weekly therapy with rifapentine 900 mg plus INH 900 mg or 9 months of self-administered daily INH 300 mg. The primary endpoint was confirmed TB after 33 months of follow-up. In the modified intention-to-treat analysis, TB developed in 0.19% of the once-weekly combination group and in 0.43% of the INH only group. Rates of completion were much higher with the short course, once-weekly regimen (82.1% in the combination-therapy group and 69.0% in the INH only group,  $P < 0.001$ ). Rates of hepatotoxicity were higher in the INH only group. The authors conclude that use of rifapentine plus INH given once a week for 3 months is as effective as 9 months of INH in preventing tuberculosis and has a higher treatment-completion rate (*N Engl J Med* 2011;365:2155-2166). Based on this study and others, the CDC has issued a new recommendation on the use of short-course combination therapy for latent TB infection. The recommendation states, "The new regimen is recommended as an equal alternative to the 9-month INH regimen for otherwise healthy patients  $\geq 12$  years who have LTBI and factors that are predictive of TB developing (e.g., recent exposure to contagious TB)." It also recommends that the new regimen may be

considered for other categories of patients when it offers advantages. Daily INH continues to be the preferred regimen for children between the ages of 2 and 11 (*MMWR Morb Mortal Wkly Rep* 2011;60:1650-1653). ■

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