CRITICAL CARE ALERT®

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

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INSIDE

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Why Are We Giving Our Patients Blood?

ABSTRACT & COMMENTARY

By Andrew M. Luks, MD

Pulmonary and Critical Care Medicine, University of Washington, Seattle

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

Synopsis: *This retrospective analysis of data on patients with acute lung injury shows that transfusion of red blood cells in such patients is associated with increased in-hospital mortality, and that the risk is highest with transfusion of non-leukoreduced blood and transfusion following the onset of acute lung injury.*

Source: Netzer G, et al. *Chest.* 2007;132(4):1116-1123.

Multiple recent studies have demonstrated that red blood cell (RBC) transfusion may be deleterious to critically ill patients, as it has been found to be associated with increased mortality following coronary artery bypass surgery, increased rates of ventilator-associated pneumonia and worse outcomes in patients with burn injury and trauma. Netzer and colleagues sought to build on this literature and determine if RBC transfusion had an effect on in-hospital mortality in patients with acute lung injury (ALI). They performed a retrospective analysis on previously collected data from a cohort of 248 patients with ALI or acute respiratory distress syndrome (ARDS) at a single center between 1999 and 2002. All patients over the age of 13 admitted to the medical or surgical ICU at this center were enrolled if they met American European Consensus criteria for ALI/ARDS. They did not include patients with heart failure, respiratory diseases such as diffuse alveolar hemorrhage mimicking ARDS, significant burns or transplant recipients.

RBC transfusion was the primary exposure variable and this was evaluated dichotomously (any transfusion) as well as linearly (total number of RBC units transfused). The primary outcome was in-hospital mortality. Because mechanical ventilation strategies changed over the course of the study due to the results of the ARDSNet trial, and because the use of leukore-

duced blood increased over the same time period, appropriate adjustments were made in the statistical analysis to account for these changes in practice. The authors also investigated whether the timing of transfusion relative to the onset of ALI had any effect on mortality.

Overall mortality among the 248 patients analyzed in the study was 39%, consistent with that seen in the placebo group of the ARDSNet trial. Transfusion was associated with an increased risk of mortality. Transfusion of any RBC was associated with an unadjusted odds ratio (OR) for mortality of 2.90, a value that remained significant when adjusted for various factors such as age, gender and APACHE III score. The mortality risk per unit of RBC transfused adjusted for length of stay was 1.06. Put in other terms, a patient who received 4 units of blood over the course of admission had a 24% increase in mortality risk. With regard to timing of the transfusions, transfusion of blood after the onset of ALI was associated with an OR of mortality of 1.13 per unit transfused while administration prior to ALI onset was not a risk factor for mortality. The risk of mortality was higher, however, with non-leukoreduced blood; the OR for non-leukoreduced RBC per unit transfused was 1.14 compared to only 1.04 for the leukoreduced products. Finally, when adjusted for RBC transfusion, platelet administration was not associated with a higher risk of mortality.

COMMENTARY

The study by Netzer and colleagues is yet another entry in a growing list of studies that leaves one wondering why it is that we are transfusing RBC in critically ill patients. Basic cardiopulmonary physiology teaches us that increasing a patient's hemoglobin levels improves oxygen delivery, a key goal in the critically ill. Yet, studies on a wide variety of critically ill patients, such as post-cardiac surgery, burn, trauma and now ALI patients, demonstrates that RBC transfusion may have deleterious effects such as increased mortality, increased ventilator-associated pneumonia and decreased organ function. The etiology of these effects has not been definitively established but may relate to transfusion-related amplification of lung injury or immunosuppressive effects.

It should be noted that there are some methodological issues of concern in the paper such as the fact that the authors were not able to separate cases of Transfusion-Related Acute Lung Injury (TRALI) from pure ALI, and the fact that it was a retrospective analysis, but in light of all the previous studies with similar conclusions, this paper's results warrant consideration.

The Transfusion Requirements in Critical Care (TRICC) trial[1] has previously demonstrated that using a restrictive transfusion strategy in which patients are only transfused when their hemoglobin values fall below 7 mg/dL is not associated with increased morbidity or mortality when compared to a more liberal transfusion threshold. Given the large number of studies noted above demonstrating potential deleterious effects of RBC transfusion, increased attention should be devoted to stricter transfusion practices along the lines of those used in this important, prospective-randomized trial. There are situations in which RBC transfusion is likely to be beneficial, warranting deviation from strict thresholds—acute coronary syndrome and early goal-directed therapy[2] are two good examples—but in general the growing evidence now indicates that we need to be more careful about our use of RBC transfusions in the ICU. ■

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Steroids for COPD Exacerbations: Oral or IV?

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *This study of oral versus intravenous prednisolone in patients hospitalized with exacerbations of COPD showed no differences in any outcome variable between the two forms of administration.*

Source: de Jong YP, et al. *Chest.* 2007 Jul 23; [Epub ahead of print] DOI 10.1378/chest.07-0208.

De Jong and colleagues in The Netherlands conducted a prospective, randomized, double-blind, double-dummy, placebo-controlled, parallel-group clinical study of intravenous vs oral corticosteroids in the treatment of patients hospitalized because of an exacerbation of chronic obstructive pulmonary disease (COPD). All patients with known COPD who were admitted to a single institution during the 2-year study period were considered for inclusion. Patients were excluded if they had asthma, significant comorbidity, poor compliance, or previous study enrollment, and also if the exacerbation was severe, as defined by arterial pH 7.25 or less or PCO_2 70 mm Hg or more. Patients received 5 days of either intravenous or oral prednisolone, 60 mg, as the active medication; they also received nebulized ipratropium and albuterol 4 times daily and oral amoxicillin-clavulanate. Prednisolone was given orally to all patients after the first 5 days, with the daily dose tapered to zero over the next week.

Treatment failure, the primary outcome, was defined as death, admission to ICU, readmission for COPD, or intensification of pharmacological therapy during a 90-day follow-up. The study was designed as a non-inferiority trial, with sample sizes calculated to detect a difference of 15% in the primary outcome. Secondary outcomes included spirometry, length of hospital stay, health status as measured by the St George's Respiratory Questionnaire, and a measure of health-related quality of life.

During the study period 435 potentially eligible patients were admitted 581 times. After exclusions, 210 patients (48%) were included, 107 of whom received prednisolone intravenously and 103 of whom received it by mouth. Final data analysis included 99 and 94 of these patients, respectively. The patients were demographically and clinically similar: three-fourths were men, with mean age 70 years and mean FEV_1 approximately 1.0 L (37% of predicted, or GOLD stage 3). Most of them had received oral corticosteroids in the month prior to admission, although only about 10% took them chronically. About 12% were on long-term oxygen therapy at home.

Mean duration of hospitalization was about 11 days, and 7 patients died. Treatment failure, the primary study outcome, occurred in 62% of the patients who received steroids intravenously, as compared to 56% in those who received them orally, with no differences in early vs late treatment failure. No differences in secondary outcome variables—including changes in FEV_1, health status, quality of life, or duration of hospitalization—achieved or approached statistical significance. The authors conclude that orally-administered prednisolone is not inferior to its intravenous counterpart, and that the former is preferable because of its lower cost and greater convenience.

COMMENTARY

As confirmed by a Cochrane review of numerous published placebo-controlled studies,[1] the systemic administration of corticosteroids to patients with COPD exacerbations hastens physiologic recovery, reduces morbidity, and improves other outcomes, both in ambulatory patients and those ill enough to be admitted to the hospital. In exacerbations, steroids also decrease the incidence of treatment failure and the likelihood of relapse in the succeeding 1 to 3 months. Thus, a short course of systemic steroids is the current standard of care for this condition.

Although once-daily prednisone (or prednisolone, as used in this study) is generally used in treating exacerbations in outpatients, it has been common practice to administer steroids intravenously when patients are sick enough to be admitted to the hospital—despite the fact that they are virtually 100% bioavailable when taken by mouth. Nearly all studies of corticosteroids in hospitalized COPD patients have used intravenous administration, and such patients typically receive the drug in 2 or 4 divided daily doses.

Hospitalization for exacerbations accounts for the largest component of health care costs for COPD. In the United States, some 750,000 hospitalizations for COPD

exacerbations occur each year. Thus, if the findings of this study are valid, oral rather than intravenous administration could have important implications in terms of the use of monetary and other resources.

This study's results agree with my own personal bias that hospitalized patients with COPD exacerbations can be treated as effectively with oral as with intravenous steroids, as long as they can take medication by mouth and are not actively vomiting. However, the present study falls short of being the final word on the subject. The authors acknowledge that their own *a priori* criteria for the non-inferiority of oral administration were not met because of insufficient patient enrollment during the study period: they achieved only 74% power (vs the planned 80%) to assure non-inferiority of oral prednisolone. And they excluded patients with severe hypercapnia or acidemia, which is the population of greatest interest to intensivists. In addition, although there are no good data to suggest that higher steroid doses are more effective in this condition, the 60 mg daily prednisolone dose is lower than that initially used by many American clinicians in treating hospitalized patients.

As a side note, I know of no data supporting the use of inhaled steroids in COPD exacerbations. Given the lower overall potency of these agents as compared to usual doses of systemically-given preparations, for patients already receiving inhaled steroids prior to the exacerbation, it would make sense to discontinue them until the daily oral prednisone dose is reduced below about 15-20 mg. It has also become commonplace in some intensive care units to administer inhaled steroids to intubated patients who have COPD, whether exacerbated or not. To my knowledge this practice, which is both expensive and time-consuming for staff, is supported by no evidence at all. Given the inefficiency of aerosol delivery via endotracheal tube (which reduces drug delivery by a factor of 5 to 10 in comparison with optimal oral technique), it is most unlikely that the administered agent reaches the patient's lungs in any biologically significant amount. ■

Reference

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Should We Be Using Oral Decontamination with Ventilated Patients?

ABSTRACT & COMMENTARY

By Andrew M. Luks, MD

Synopsis: *This systematic review and meta-analysis demonstrates that oral decontamination with antiseptic preparations decreases the risk of ventilator-associated pneumonia but has no effect on mortality, duration of mechanical ventilation or length of stay in the ICU.*

Source: Chan EY, et al. *BMJ.* 2007;334(7599): 889-900.

Previous work demonstrates that selective gut decontamination decreases the risk of ventilator-associated pneumonia (VAP), but the practice has been limited by concerns about promoting antibiotic resistance. Oral decontamination alone has been proposed as an alternative, but the data on its efficacy have been mixed. Chan and colleagues conducted a meta-analysis to further investigate this issue and to determine whether oral decontamination with antibiotic or antiseptic preparations decreases the risk of VAP.

Two reviewers searched the literature for published and unpublished randomized trials testing the effects of oral decontamination on the incidence of pneumonia and evaluated the quality of these trials. Studies were grouped into two broad categories including those that tested oral antibiotics vs placebo and those that tested oral antiseptics against placebo. No trials compared oral antibiotics with oral antiseptics or selective gut decontamination. The primary outcome measures in their meta-analysis were the incidence of VAP and mortality. They used each included study's definition of pneumonia rather than applying their own standard definition across the included studies. Secondary outcomes included the duration of mechanical ventilation and duration of stay in the intensive care unit.

Eleven trials including a total of 3242 patients were included in the meta-analysis. Four trials (1098 patients) examined oral antibiotics while the remaining seven trials (2144 patients) looked at oral antiseptic solutions. While the oral antibiotic solutions had no effect on the risk of VAP, oral antiseptic solu-

tion was, in fact, associated with decreased risk (RR = 0.56, 95% confidence interval 0.39-0.81). When the 11 trials were combined in a single analysis, the relative risk of pneumonia with oral decontamination was 0.61 (95% confidence interval 0.45-0.82) and the number needed to treat to prevent one case of pneumonia was 14 (95% confidence interval 10-31). Oral decontamination with either antibiotics or antiseptics had no effect on mortality, duration of mechanical ventilation or duration of stay in the intensive care unit.

COMMENTARY

Given the high morbidity and mortality associated with VAP, identifying effective strategies for preventing this complication should be a high priority. The study by Chan and colleagues suggests that oral decontamination with antiseptic solution may be effective for this purpose but does not provide strong enough evidence of benefit or low risk to justify widespread adoption of the practice.

There are several issues that prevent broad application of these results. First, there were important methodological differences between the trials included in the meta-analysis, such as the manner in which they defined VAP and the manner in which they did or did not control for important variables, which may make comparison between the included studies difficult. Second, although the meta-analysis examines a large number of patients and points to a benefit for oral antiseptic solutions, important clinical questions remain unanswered. For example, with the exception of one trial that examined the use of povidone iodine, the remaining trials used chlorhexidine, but in varying concentrations. As a result, we have no idea which is the best antiseptic preparation or its optimum concentration for use in decontamination.

More importantly, we still lack information about perhaps the most important question of all regarding this practice: what role, if any, will it have on rates of antibiotic resistance in the ICU? We may prevent VAP, but if we end up concurrently creating resistant bacteria that will make ICU care more problematic in the future, have we really done ourselves or our patients any favors? Until this issue is resolved, we should focus on other proven techniques for preventing VAP, such as elevating the head of the bed, that do not pose this risk. ■

Special Feature

Rapid Response Systems: Update and Critique

By David J. Pierson MD, Editor

In an attempt to enhance what it considered a sluggish nationwide response to the Institute of Medicine's calls for reducing error and improving patient outcomes in hospital care, the Institute for Healthcare Improvement (IHI) initiated in 2004 an ambitious, highly visible, 18-month program. Called the 100,000 Lives Campaign, it was based on the implementation of "evidence based practices" in 6 clinical areas or "Planks" (Table 1).[1] Eighteen months later, IHI pronounced the program a resounding success, announcing that 122,300 lives had been saved as a result of the program. Bolstered by this success, IHI promptly extended its goals to the saving of 5 million lives by the end of 2008, using the "planks" of the 100,000 Lives Campaign and other interventions.[2]

Table 1:
The Six "Planks" in the Institute for Healthcare Improvement's 100,000 Lives Campaign[3]

- Rapid response teams
- Medication reconciliation
- Prevention of central line infections
- Prevention of surgical site infections
- Prevention of ventilator-associated pneumonia
- Evidence-based care for acute myocardial infarction

While the evidence base supporting several of the "planks" in Table 1 is strong, that for rapid response teams—and the increasing mandate for their establishment in all hospitals—has been called into question.[3,4] This brief essay examines the rapid response system (RRS) phenomenon and the current evidence that initiation of such systems in hospitals reduces mortality and events such as cardiac arrest and unanticipated transfers to the ICU.

What Are Rapid Response Teams?

Hospitalized, acutely-ill patients who are not in ICUs are at risk for serious adverse effects such as

cardiac arrest, unplanned admission to the ICU, and death. Although these events may occur suddenly and without warning, in many if not most instances they are preceded by warning signs—tachypnea, tachycardia, oxyhemoglobin desaturation, or mental status changes, for example—that could alert staff to intervene and potentially prevent the adverse outcome. The RRS concept emerged from an appreciation of this potential: recognition or suspicion of a patient's critical unmet need would trigger a rapid sequence in which a pre-established team came to the bedside, assessed the patient, and either intervened directly or facilitated such intervention.[5]

Teams operating within an RRS can have different structures and memberships, and in fact the literature has been somewhat confusing with respect to their composition and terminology. The most commonly described types of team are the medical emergency team (MET), the rapid response team (RRT), and the critical care outreach team (CCO), which are somewhat distinct:

- A MET is usually headed by a physician. It can prescribe therapy, manage the airway, place central lines, and initiate ICU-level care on the ward, in the angiography suite, or wherever the emergency occurs.[5]
- An RRT is typically headed by an ICU nurse or other non-physician, usually includes a respiratory therapist, and generally has quick access to a designated in-house intensivist or other physician (in teaching hospitals, commonly an ICU fellow or senior resident) when needed.
- As described in the literature, CCO teams encompass one of the above structures but also include a more prospective, proactive component aimed more specifically at prevention rather than response.

The nomenclature used to designate these and other variations of RSS has been a source of confusion, and a consensus group recently made recommendations intended to reduce this.[5]

A Systematic Review of the Evidence

To examine the strength of the evidence supporting the use of RRSs, Winters and colleagues at Johns Hopkins performed a systematic review of studies that had been published on this topic through mid-2005.[4] Using accepted methodology for such analyses, they identified 10,228 abstracts of publications in English that were potentially relevant. Studies were subjected to the formal analysis if they included data on outcomes in both intervention and control groups, and if they reported mortality and/or the incidence of cardiac arrest. Reports of out-of-hospital interventions and of restricted populations within the hospital (such as patients transferred out of an ICU to the general ward) were excluded. The investigators attempted to evaluate potential bias by collecting comparison data on intervention and control groups, and assessing the degree to which the reported measures and outcomes were explicitly defined.

Using the criteria described, 46 studies were evaluated more thoroughly. Of these, 38 were rejected according to the investigators' *a priori* criteria, and 8 studies were included in the formal review. Six of these 8 were observational in nature, 5 employing historical controls and 1 a concurrent control group. Two other studies were interventional, 1 a cluster-randomized trial within a single institution[6] and the other a large, multi-center study also using a cluster-randomized design.[7]

None of the 8 studies had a control group that Winters et al considered to be truly comparable to the intervention group; half of the studies made some attempt to adjust for differences between intervention and comparison groups, but the attempts varied and their effectiveness could not be determined with certainty. With varying detail and objectivity, the 8 included studies listed the "alert criteria" used to activate the RRS in the intervention group (see Table 2 below).

Table 2:
Criteria used to activate the rapid response systems in the 8 included studies (data from reference 5)

Alert Criterion	Number of studies In which it was reported
Respiratory rate	8
Heart rate	8
Blood pressure	8
Change in mental status	8
Desaturation (pulse oximetry)	5
"Worry" (staff concern)	5
Other symptoms	5
Urine output	4
Laboratory values	1

Seven studies (5 observational, 2 cluster-randomized) reported hospital mortality data. The relative risk for mortality with the use of RRSs among the 5 observational studies was 0.87, with 95% confidence interval 0.73-1.04. The corresponding relative risk in the 2 clus-

ter-randomized trials was 0.76 (95% CI, 0.39-1.48), and the p value for heterogeneity in these studies was 0.01, suggesting a high degree of heterogeneity. Neither result for a reduction in hospital mortality was statistically significant, with the 95% CI in each instance surpassing 1.

Five of the 8 included studies (4 observational, 1 cluster-randomized) reported cardiac arrest data. For the observational studies the pooled relative risk for cardiac arrest in the hospital was 0.70 (95% CI, 0.56-0.92) in comparison with controls, which was statistically significant (albeit with a high degree of heterogeneity at p <0.01). In the cluster-randomized study reporting cardiac arrest data the relative risk was 0.94 (95% CI, 0.79-1.13) compared with control.

With respect to unanticipated transfer to the ICU from a general inpatient floor, 3 observational studies that reported these data had a pooled relative risk for such transfer of 0.84 (95% CI, 0.55-1.26) with the RRS. In the multicenter cluster-randomized trial,[7] the relative risk for unanticipated ICU admission with a RRS was 1.04 (95% CI, 0.89-1.21) vs control.

Winters et al concluded from their systematic review of published studies that the evidence supporting the use of RRS is "weak to moderate" with respect to their primary objectives—reducing hospital mortality and cardiac arrest rates and the incidence of unanticipated admission to an ICU.[5] The authors could not find strong support for considering RRSs to be standard of care, or for mandating their institution in all hospitals.

Conclusions and Current Unknowns

When deficiencies of care exist, improvement in the quality of care will lead to better outcomes. The introduction of RRSs has been one means for improving the quality of care, targeting serious adverse events such as cardiac arrest, unplanned ICU admission, and death. Insofar as preventable adverse events can be detected and effective interventions brought to bear to head them off, initiation of an RRS should be expected to decrease their incidence. However, as the systematic review by Winters et al[5] shows, objective, rigorous evidence documenting such a decrease is scant. The more rigorous the study design (and thus the higher on the hierarchy of evidence quality), and the farther removed from anecdotal, purely observational reports, the less compelling is the support from the current literature. Also lacking is demonstration that an RRS is necessarily the best way to bring about the desired improvements. Table 3 summarizes some of the current unknowns in this era.

Table 3:
Remaining Unknowns about Rapid Response Systems in Hospitals

- What is the optimal composition for such a team?
- Should it be led by an ICU physician or by a nurse?
- Would increased nurse staffing and education on the wards accomplish the same goals?
- What is the effect of a hospitalist service?
- Would automatic monitoring systems be as effective?
- What are the optimal "alert criteria" for triggering an assessment by the RRS?
- What is the relative importance of subjective "staff concern" vs physiologic monitoring data?
- What should be the role of the RSS team at the bedside—brief triage, coordination of care with the primary or ICU team, or some sort of ongoing assessment?

To a certain extent this discussion is academic, since establishment of RRSs (especially in the form of RRTs) is being thrust upon hospitals by the Joint Commission and other forces. However, it is unlikely that the final word on RRSs is in from the standpoint of evidence-based medicine, and future studies will probably shed additional light on their benefits and costs as well as on how they or future modifications should best be employed. ■

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CME / CNE Questions

51. Which of the following statements is true regarding transfusion of red blood cells or platelets in critically ill patients with acute lung injury?

a. RBC transfusion is associated with decreased mortality.
b. Transfusion of leukoreduced blood carries a lower mortality risk than non-leukoreduced blood.
c. Transfusion prior to the onset of acute lung injury is a risk factor for mortality.
d. Patients who receive 4 units of blood during their admission have a 50% increase in mortality.
e. Platelet transfusions are associated with increased mortality.

52. According to the results of the Transfusion Requirements In Critical Care (TRICC) trial, for patients not in the early phase of septic shock or experiencing acute coronary syndrome, which of the following transfusion thresholds should be applied in the intensive care unit?

a. 3 mg/dL
b. 5 mg/dL
c. 7 mg/dL
d. 9 mg/dL
e. 11 mg/dL

53. Which of the following statements about the use of corticosteroids in COPD exacerbations is true?

a. Intravenous administration results in more rapid recovery of lung function as compared to oral.
b. Intravenous administration shortens hospitalization in comparison to oral.
c. Intravenous administration improves quality of life more than oral.
d. All of the above.
e. None of the above.

54. Compared to placebo, which of the following have been shown to result from administration of systemic corticosteroids to patients with COPD exacerbations?

a. More rapid physiologic recovery in hospitalized patients but not in ambulatory patients.
b. More rapid physiologic recovery in both hospitalized and ambulatory patients.
c. An increased incidence of treatment failure.
d. No change in the incidence of relapse in the succeeding 3 months.
e. None of the above.

55. Oral decontamination with antiseptic solution is associated with which of the following outcomes in patients on mechanical ventilation?

a. decreased hospital length of stay
b. decreased ICU length of stay
c. decreased ventilator-associated pneumonia
d. decreased in-hospital mortality
e. decreased all-cause mortality

56. Which of the following were included in the 6 basic "planks" of the 100,000 Lives Campaign?

a. rapid response teams
b. medication reconciliation
c. prevention of central line infections
d. prevention of ventilator-associated pneumonia
e. all of the above

Answers: 51 (b); 52 (c); 53 (e); 54 (b); 55 (c); 56 (e)

CME / CE Objectives

After reading each issue of *Critical Care Alert*, readers will be able to do the following:

- Identify the particular clinical, legal, or scientific issues related to critical care.
- Describe how those issues affect nurses, health care workers, hospitals, or the health care industry in general.
- Cite solutions to the problems associated with those issues.

In Future Issues:

Palliative Care Consultation in the ICU

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

FDA Warnings Dominate Pharmaceutical News

In this issue: *FDA warnings for existing drugs dominate pharmaceutical news this month. The FDA and its advisory committees have issued warnings on erythropoiesis-stimulating agents, oseltamivir (Tamiflu) and zanamivir (Relenza) for the treatment of influenza, rosiglitazone (Avandia) for the treatment of type 2 diabetes, varenicline (Chantix) to help stop smoking, the beta agonist salmeterol (Serevent), and modafinil (Provigil) for use in children. The FDA has also asked for marketing suspension of Bayer's aprotinin (Trasylol). These warnings represent a new push by the FDA to regulate existing drugs for safety after they have been approved for marketing. It also comes at a time when the FDA is cleaning up its advisory committee processes, especially with regard to limiting potential conflict of interest by advisory committee members. A summary of the new committee processes can be found at www.FDA.gov.*

Erythropoiesis-stimulating agents (ESAs) are the subject of new warnings from the FDA. The drugs, Aranesp, Epogen, and Procrit are used to treat anemia associated with cancer chemotherapy and chronic kidney failure. For cancer patients, several studies have shown that the drugs promote tumor growth and decrease survival rates in patients with advanced breast, head neck, lymphoid, and non-small cell lung cancer when given in doses that achieve a hemoglobin level of 12 g/dl or greater—the target in clinical practice. There is currently no evidence to know whether the ESA's promote tumor growth or shorten survival in patients who achieve hemoglobin levels less than 12 g/dl. The warning also specifically states that ESA's should only be used in cancer patients to treat chemotherapy-related anemia, not other causes of anemia associated with cancer and stress, and that the drug should be discontinued once chemotherapy is discontinued. For patients with chronic kidney failure, the new warnings states that ESA's should be used to maintain hemoglobin levels between 10 to 12g/dl. Higher hemoglobin levels increase risk for death and serious cardiovascular events such as stroke, heart attack, or heart failure. Finally, the new labeling emphasizes that there is no data that demonstrates that ESA's improve symptoms associated with anemia such as quality of life, fatigue, or patient well-being for patients with cancer or for patients with HIV undergoing AZT therapy.

An FDA panel is recommending new warnings on the flu drugs oseltamivir (Tamiflu-Roche) and zanamivir (Relenza-Glaxo) regarding abnormal psychiatric behavior associated with the drugs. This issue came up last year with a number of reports from Japan of erratic behavior including jumping from buildings resulting in deaths in patients taking the

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drugs. Many of the cases involved children. Japan has already taken the step of warning prescribers not to use the drugs in those aged 10 to 19. The panel reports 700 cases of psychiatric adverse events associated with both drugs, and 25 potential deaths in patients taking Tamiflu. No fatalities have been reported with Relenza. Both companies insist their drugs are safe and suggest that it is difficult to know if symptoms are caused by influenza or by medications. In the meantime Roche has agreed to stronger warnings for Tamiflu. Both medications reduce the symptoms of influenza and reduce the duration by approximately one-and-a-half days.

The manufacturers of rosiglitazone (Avandia-GlaxoSmithKline) have agreed to add new information to the existing black box warning regarding the potential increased risk of heart attacks associated with drug. The FDA's press release states that "People with type 2 diabetes who have underlying heart disease or who are at high risk of heart attack should talk with their health-care provider about the revised warning as they evaluate treatment options. FDA advises health-care providers to closely monitor patients who take Avandia for cardiovascular risks." Rosiglitazone is approved for treatment of type 2 diabetes as single therapy or in combination therapy with metformin, sulfonylureas or other oral anti-diabetes treatments. GSK has been asked by the FDA to conduct a long-term study to evaluate the potential cardiovascular risks of rosiglitazone.

The FDA has issued an "Early Communication" regarding varenicline (Chantix), Pfizer's prescription medication to help adults stop smoking. Pfizer has received reports describing suicidal ideation and erratic behavior in some patients taking the drug which have been submitted to the FDA. The Agency is soliciting any additional similar cases from Pfizer and will complete analysis when more data is available and then communicate conclusions and recommendations. In the meantime the FDA recommends health-care providers monitor patients taking Chantix for behavior and mood changes.

An expert panel of the FDA is also recommending a new warning for the long acting beta agonist salmeterol (Serevent-GlaxoSmithKline) regarding use in children. Nine new adverse event reports including five deaths in children using the drug had been reported in the last year as well as reports of increased hospitalizations and asthma-related deaths in children. Before a final recommendation is made by the FDA, review of other long-acting beta agonists will also be included, including formoterol (Foradil), Novartis' long-acting beta agonist and GlaxoSmithKline's Advair which is a combination inhaler of salmeterol and fluticasone. There is some evidence that steroid inhalers mitigate the risk of asthma-related deaths in patients taking long-acting beta agonists.

An FDA panel is recommending stronger warnings for use of modafinil (Provigil) in children. The drug is approved to treat certain sleep disorders in adults, and is not approved for use in children, but is occasionally used off label for the treatment of attention deficit hyperactivity disorder. The drug's labeling was recently updated to warn of serious skin reactions and psychological problems such as hallucinations and suicidal ideation.

Bayer Pharmaceuticals is complying with the FDA's request for a marketing suspension of aprotinin (Trasylol). The drug, which is used to control bleeding during heart surgery, is the subject of a large Canadian study, the preliminary results of which have shown an increased risk of death associate with the drug.

FDA Actions

The FDA has approved over-the-counter sales of cetirizine 5 mg plus pseudoephedrine HCL 120 mg (Zyrtec-D) for adults and children aged 12 years and older. The product has been available as a prescription drug since 2001 for the treatment of upper respiratory allergies.

The FDA has approved several new generics for marketing. Oxcarbazepine (Trileptal) will soon be available as a generic in 150, 300, and 600 mg strengths the treatment of partial seizures in adults and children. Hydrocodone/ibuprofen (Vicoprofen) is also approved as a new generic. The drug is approved for short-term treatment of acute pain. Rivastigmine (Exelon) will be available in generic 1.5, 3, 4 .5, and 6 mg strengths for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia assisted with Parkinson's disease. ■