CRITICAL CARE ALERT®

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

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INSIDE

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Bacteremia During Ventilated-Associated Pneumonia is Associated with Increased Risk of Death

ABSTRACT & COMMENTARY

By Richard J. Wall, MD, MPH

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

Synopsis: *This study showed that developing bacteremia during an episode of ventilator-associated pneumonia (VAP) is associated with increased ICU mortality, and that bacteremia is most likely to occur when VAP is due to methicillin-resistant* Staphylococcus aureus *(MRSA).*

Source: Agbaht K, et al. *Crit Care Med.* 2007;35(9):2064-2070.

THIS SINGLE-CENTER, RETROSPECTIVE STUDY EXAMINED ICU mortality and various risk factors among critically ill patients who developed bacteremia during their VAP episode. The investigators were interested in whether the presence of a positive blood culture at the time of VAP diagnosis was associated with excess mortality. Additional objectives were to compare the organisms seen in bacteremic and non-bacteremic VAP and identify the variables associated with bacteremia.

The study included 199 patients from a medical-surgical ICU who had microbiologically confirmed VAP during a 44-month observation period. Although only 35/199 (17.6%) developed bacteremia during their pneumonia episode, these individuals had a higher ICU mortality rate. In a multivariate model adjusting for severity of illness, bacteriology, and other relevant confounders, the only two variables associated with higher ICU mortality were vasopressor use (hazard ratio 2.43, 95% CI 1.23-4.82) and bacteremia (hazard ratio 2.55, 95% CI 1.25-5.23). In a secondary matched case-control analysis, the odds ratio of death for bacteremic cases compared with non-bacteremic controls was 2.86 (95% CI 1.09-7.51).

The most commonly isolated microorganisms in blood cultures were *S. aureus* (both MRSA and MSSA) and *Pseudomonas aeruginosa*. Although *Haemophilus influenzae* was the second most common organism in respiratory samples, it was never isolated from a single blood culture. In multiple logistic regression, the presence of MRSA as the culprit organism and recent prior hospitalization were both independent risk factors for development of bacteremia. Curiously, in a sub-analysis of individuals with VAP due to MRSA, there was no mortality difference between bacteremic and non-bacteremic patients. The authors propose this finding indicates that while MRSA may be a risk factor for bacteremia, ICU mortality is ultimately due to bacteremia not the MRSA itself.

COMMENTARY

VAP is one of the most commonly acquired infections in the ICU, accounting for >50% of all antibiotic prescriptions in medical ICUs. Understanding the risk factors associated with VAP is important for improving patient care. Reducing VAP is also financially important for hospitals because starting in 2009, the Centers for Medicare & Medicaid Services (CMS) will limit reimbursements for conditions that were not present at admission (eg, infections).[1] Regardless of whether clinicians believe VAP is totally preventable, CMS will likely stop paying for VAP treatment in upcoming years.

Overall, this study shows that bacteremia is an independent risk factor for ICU mortality. The study supports the common sense notion that bacteremic VAP is more dangerous for patients than non-bacteremic VAP. However, it is important to remember that the majority of VAP patients never have bacteremia (in this study only 1/5 VAP patients had a positive blood culture). For this reason, clinicians cannot rely on negative blood cultures to exclude VAP. Quantitative cultures of the lower respiratory tract remain the gold standard for diagnosing VAP. Another key finding of this study is that *S. aureus* causes bacteremia more often than other organisms. The authors provide several theories to explain this interesting finding, but the reasons are still unclear.

This study has several strengths. First, diagnosis and management of VAP were protocolized in this ICU, thereby minimizing biases from variations in clinical care. Second, all cases were microbiologically confirmed using quantitative culture techniques. Unfortunately, the authors did not describe whether they used standardized protocols for ventilator weaning, blood product transfusion, glucose control, and sedation—all of these have been shown to affect VAP rates. Another limitation is that this was a single center study. In addition, "late" VAP episodes (≥10 days after intubation) were more frequent in the bacteremic group and this imbalance may have contributed to the observed mortality differences.

Of note, the Centers for Disease Control and Prevention revised their VAP definitions in May 2007.[2] The most important change is that patients no longer need to be on the ventilator for 48 hours to diagnose VAP. The current study used the older definition (with the 48-hour criterion), but it seems unlikely that the change should affect the study's findings. Nonetheless, readers should be aware of this change, because it may affect interpretation of future VAP studies. ■

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1. Centers for Medicare & Medicaid Services [CMS-1533-FC]. "Changes to the Hospital Inpatient Prospective Payment Systems and Fiscal Year 2008 Rates," page 290ff.
2. Centers for Disease Control and Prevention. The National healthcare safety network manual: Patient safety component protocol (updated May 24, 2007).

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Proactive Palliative Care in the Medical ICU Affects Length of Stay for High-Risk Patients

ABSTRACT & COMMENTARY

By James E. McFeely, MD

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Dr. McFeely Reports no financial relationship to this field of study.

Synopsis: *Using a simple clinical screening tool, patients considered at high risk for death in this closed medical ICU received a basic palliative care consultation. Those with unmet needs received a full consultation with ongoing intervention from the palliative care team. This process shortened ICU length of stay without affecting mortality rates or discharge disposition.*

Source: Norton SA, et al. *Crit Care Med.* 2007;35(6):1530-1535.

Use of specially trained palliative care teams in the ICU has increased in frequency in recent years. Consultation by these teams tends to occur very late in patients' length of stay. Few studies have been performed evaluating outcomes, such as length of stay. This study from the University of Rochester reports the results of prospective evaluation of a performance improvement project in which the goal was to intervene earlier in the patient's ICU course for those high risk patients identified as potentially needing palliative care intervention.

The study was conducted in a 17-bed medical ICU in an academic tertiary care hospital. All patients were screened within 72 hours of admission to identify those with a high adverse burden/benefit ratio and a high risk of death. Patients had to meet at least one of several inclusion criteria, including admission to the ICU following a current hospital stay of greater than a week, age greater than 80 years and the presence of two or more co-morbid diagnoses, diagnosis of stage IV malignancy, status post cardiac arrest, or diagnosis of an intracerebral hemorrhage requiring mechanical ventilation.

Previously palliative care consultations were available through request of the attending physician and occurred relatively infrequently and late in the patient's hospital course. After development of the screening tool, all patients were screened within 72 hours of admission, and anyone who met the inclusion criteria received either a basic or complete palliative care consult. The extent of the palliative care consult was determined after discussions between the palliative care and MICU management team.

During the 4 month long pre-intervention period, an average of 3.8 patients per week screened positive using the High Risk Assessment Tool, but only 5 patients were referred for palliative care consultation using the usual referral process. On average, this consult occurred on day 14 of the ICU stay. During the intervention phase, an average of 4 patients screened positive per week and all were evaluated by the palliative care team.

Baseline demographics of the pre- and post-groups were similar. The total hospital death rates of the two groups were also similar (54% usual care, 59% proactive palliative care). The medical ICU death rate was also unchanged (38% vs 37%). The ICU length of stay for patients dying in the ICU was 5.7 days in the intervention group and 14 days in the usual care group. The ICU length of stay for patients dying elsewhere in the hospital was 9 days in the intervention group and 16 in the usual care group. For those patients who died in the hospital but not in the ICU, there was no difference in their overall hospital length of stay.

COMMENTARY

This study, while having some methodologic flaws, provides further common-sense evidence supporting the value of palliative care early in the course of a high risk patient in the ICU. The study hospital was fortunate enough to have an on-site trained palliative care team. They developed a clinically relevant and easily implementable screening tool and had the resources available to see all these patients within an average of 1.7 days. This aggressive schedule of intervening resulted in a reduction of the ICU length of stay by an average of 8 days while having no net effect on overall mortality rates. This lack of effect on overall mortality suggests that a palliative care consultation did not hasten or otherwise impact patients' death, but rather assisted with appropriate resource utilization for patients who were going to die anyway.

For those hospitals with a palliative care service, the study provides further motivation for using the service early in high-risk patients. For those without a palliative care service, it provides further compelling information that may be used with hospital administrators in order to develop such a program.

BAL Galactomannan to Diagnose Invasive Aspergillosis in the ICU

ABSTRACT & COMMENTARY

By Andrew M. Luks, MD

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

Synopsis: *In immunocompromised ICU patients at risk for invasive aspergillosis, Galactomannan levels in bronchoalveolar lavage fluid are more useful markers for establishing or excluding the diagnosis of invasive aspergillosis than serum galactomannan, BAL culture, or direct examination.*

Source: Meersseman W, et al. *Am J Respir Crit Care Med.* 2008;177:27-34.

Invasive aspergillosis (IA) is increasingly recognized as a source of infection in immunocompromised ICU patients, but accurate diagnosis remains challenging. (See *Critical Care Alert*, October 2007, pp. 50-52). Recent work in neutropenic patients has shown that detection of galactomannan—a polysaccharide fungal-cell wall component released during tissue invasion by aspergillus—in bronchoalveolar lavage (BAL) fluid may facilitate diagnosis in this patient population. Meerseman and colleagues sought to determine if BAL galactomannan levels could play a similar role in the diagnosis of IA in critically ill ICU patients with other forms of immunosuppression.

Patients were included in the study if they had persistent fever despite appropriate empiric antibiotic therapy, clinical signs of invasive mycosis (eg, pleuritic chest pain) or lower respiratory tract infection, and had one of several forms of immunosuppression including hematologic malignancy, cancer with recent chemotherapy treatment, solid organ transplant, recent use of corticosteroids or other immunosuppressive agents such as tacrolimus or methotrexate, cirrhosis or human immunodeficiency virus infection. Patients underwent bronchoscopy and bronchoalveolar lavage upon inclusion and then on a weekly basis, with galactomannan levels, direct microscopic examination and fungal cultures performed on all specimens. Serum galactomannan was performed twice weekly and autopsies were performed in all fatal cases. Antifungal treatment could be started at the discretion of the treating physician and was not protocol-driven.

Patients were classified as having proven, probable IA or possible IA based on previously published case definitions.[1] A variety of statistical analyses were used to compare the results of cultures, serum and BAL galactomannan values between the different groups of patients. Sensitivity of the different techniques was calculated from the proven cases while specificity was determined using a biopsy or autopsy-proven negative group.

A total of 110 patients out of 1109 admissions during the study period were eligible for inclusion in the study, and there were 26 proven cases of IA. All 26 of these cases had at least one BAL galactomannan index > 0.5, the pre-defined cut-point for a positive test, with 23 of these positive levels being found on the first BAL sample. In 11 of 26 proven cases of IA, BAL culture and serum galactomannan remained negative. Thoracic CT scans performed in 15 proven cases showed no evidence of halos or air-crescent signs, classically described features of invasive pulmonary aspergillosis. Using an index cut-off value of 0.5, the sensitivity and specificity of BAL galactomannan were 88% and 87%, compared to 42% and 96%, respectively, for serum galactomannan. Using a cut-point of 0.5, the area under the ROC curve for BAL galactomannan was 0.898 (95% confidence interval 0.811 to 0.985). The specificity of BAL galactomannan remained high even in those patients treated with piperacillin-tazobactam, a widely used antibiotic known to cause false positive results on this assay.

COMMENTARY

One of the striking aspects of this study was the fact that 26 of the 110 ICU patients (24%) with some form of immunosuppression, persistent fevers despite appropriate empiric antibiotics, and/or clinical evidence of lower respiratory tract infections, turned out to have IA. That is a high number that strongly suggests that we need to be looking more closely for this infection among the non-neutropenic immunocompromised patients admitted to the ICU who develop persistent fevers and evidence of pneumonia.

Until recently, proving this diagnosis pre-mortem has been challenging, as the sensitivity and specificity of BAL culture and direct examination have been limited. Radiologic imaging is also of limited utility, as demonstrated by the fact that none of the proven cases in this study had the classically described features of the disease.

The well-conducted study by Meerseman and colleagues strongly suggests that BAL galactomannan assays may alleviate some of these diagnostic problems. It is a minimally invasive test with superior test

characteristics relative to serum galactomannan and BAL culture with a faster turnaround time than either cultures or biopsy specimens. It is also reassuring to know that piperacillin-tazobactam, a widely used broad-spectrum antibiotic, did not affect the specificity of the assay.

Further testing would be useful to confirm these results as this was a single center study and there were a few important methodological issues such as the fact that the authors did not regulate the use of antifungal medications (which can decrease the assay's sensitivity) by the treating physicians. Nevertheless, given the high morbidity and mortality associated with IA infections and the simplicity and minimal invasiveness of BAL galactomannan measurement, we should be using this test more often in immunocompromised patients with evidence of pneumonia and no response to empiric antibiotic therapy. ■

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Special Feature

Managing Critical Hypoxemia in The ICU

By Andrew M. Luks, MD

In the majority of patients who develop the acute respiratory distress syndrome (ARDS), oxygenation can be supported using increased inspired oxygen concentrations (F_IO_2) or higher levels of positive end-expiratory pressure (PEEP). Occasionally, however, patients develop "critical hypoxemia" whereby arterial oxygen tensions cannot be maintained at adequate levels with these standard techniques. It is in these situations that clinicians often use alternative modalities to support oxygenation, including prone positioning, inhaled pulmonary vasodilators, extracorporeal membrane oxygenation, alternative modes of mechanical ventilation and recruitment maneuvers. The purpose of this special feature is to consider these techniques in greater detail. What should be apparent following this brief review is that despite the apparently sound physiologic principles underlying these strategies, the data supporting their use is marginal, at best. As a result, there can be no clear guidelines about when to use the techniques, and clinicians must base their decisions on the needs of the individual patient.

What Constitutes "Critical Hypoxemia?"

Before discussing the options mentioned above, it is worth considering exactly when such options should be considered in the first place. Unfortunately, the literature does not adequately define "critical" or "refractory" hypoxemia and there are no formally established thresholds for using these non-standard measures. ARDS is deemed to be present when the P_aO_2/F_IO_2 ratio is below 200 mm Hg, but clearly not everyone who meets this criterion requires non-standard therapies. It also seems difficult to apply a consistent threshold across all patients because the ability to tolerate a low P_aO_2 may vary between patients. A 20 year-old with ARDS following trauma might tolerate P_aO_2 values in the 50 mm Hg range while this value might be problematic in a 70 year-old with underlying cardiac disease. In general, the decision to initiate non-standard therapies should be tailored to the individual patient and should only be considered when there is impaired oxygenation (eg, P_aO_2 below 50 mm Hg on maximum conventional support) and concurrent evidence of clinical instability or negative effects of hypoxemia (eg, myocardial ischemia, multi-organ dysfunction).

What Else Can Be Done Besides These Measures?

Before initiating non-standard therapies, other interventions warrant consideration. An adequate P_aO_2 is an important objective, but the more important goal is ensuring adequate oxygen delivery. Oxygen delivery is a function of cardiac output, hemoglobin concentration and arterial saturation, with only a minor contribution from the P^aO_2. Table 1 on the following page illustrates the impact on oxygen delivery from manipulating each of these variables in a hypothetical patient with baseline poor cardiac output, anemia and impaired oxygenation. This hypothetical data demonstrates that for a similar 33% increase in each of the variables, there is a greater gain in oxygen delivery from manipulating cardiac output and hemoglobin concentration than there would be from increasing the P_aO_2. As a result, we should be looking to improve these variables before adopting one of the alternative strategies described below.

Table 1: Changes in Oxygen Delivery with Manipulation of Different Parameters

Manipulated Variable	Cardiac Output (L/min)	Hemoglobin (mg/dL)	S_aO_2 (%)	P_aO_2 (mmHg)	O_2 Delivery (ml/min)
Baseline	3	9	75	40	283
Cardiac Output	4	9	75	40	377
Hemoglobin	3	12	75	40	377
P_aO_2	3	9	82	53	310

The values in this table are for a hypothetical patient with impaired cardiac output, anemia and hypoxemia at baseline. A 33% increase in either cardiac output or hemoglobin concentration increases oxygen delivery more than a corresponding 33% increase in the P_aO_2.

In addition to focusing on the supply side of the oxygen equation, efforts should also be directed towards minimizing oxygen demand. Treatment of fever and elimination of shivering are warranted, as are efforts to minimize patient triggering on the ventilator. Breath-stacking, for example, can be minimized with aggressive use of sedation. In rare instances, neuromuscular blocking agents can be considered although there is no data demonstrating a mortality benefit from this practice and these agents increase the risk of critical care polyneuropathy. In the event that paralytics are used, the duration of use should be minimized, and train-of-four monitoring should be employed to ensure an appropriate degree of paralysis.

Prone Ventilation

Prone ventilation is thought to benefit patients by causing favorable changes in regional ventilation and perfusion as well as potentially aiding in secretion clearance and redistribution of extravascular lung water. Studies demonstrate that the technique improves oxygenation but there is still no proof that it improves mortality. Earlier randomized controlled trials,[1, 2] which failed to show a mortality benefit, were criticized due to the short duration of proning and high tidal volumes employed in the studies. A more recent trial,[3] in which patients were proned for an average of 17 hours per day, did show a trend toward decreased mortality but this result was not statistically significant and the mortality rates in the proned group (43%) were still higher than those reported for low tidal-volume ventilation in the ARDSnet trial (30%). Logistical issues must also be considered in the decision to prone a patient. The technique is time and labor intensive, nursing staff lose easy access to lines and tubes, and patients are at increased risk for pressure sores as well as aspiration, among other potential problems. Specialized beds, such as the RotoProne system, are available to facilitate proning and minimize complications but come at a potentially high price. In our region, hospitals pay, on average, $500-700 per day for use of the bed, a high cost in light of the lack of an established mortality benefit.

Inhaled Nitric Oxide

By generating localized pulmonary vasodilation in areas that receive adequate ventilation, inhaled nitric oxide (NO) is felt to improve ventilation-perfusion matching and, as a result, arterial oxygenation. As with prone positioning, the therapy has been demonstrated in randomized trials[4,5] and a meta-analysis[6] to improve oxygenation but there is still no evidence of improved outcomes such as decreased mortality or shortened duration of mechanical ventilation. There are often overlooked risks with the therapy such as the potential for methemoglobinemia, a complication that would, ironically, further impair oxygen delivery, and there remain no reliable markers for predicting which patients will experience improved oxygenation with this treatment. The biggest downside of the therapy, however, is its high cost; our institution currently pays $131/hr for the first 96 hours of use up to a maximum of $12,576; each additional month costs an additional $12,576. Although it has been reported[7] that use of inhaled NO is not associated with increased cost relative to standard treatment, one must recognize that because the therapy is not FDA-approved for this indication, these costs are not reimbursed by insurance or Medicare and the hospitals must absorb the expense.

Inhaled Prostacyclin

Inhaled prostacyclin works by the same mechanism as inhaled NO but has not been studied as extensively. The available data demonstrate improvements in oxygenation and pulmonary hemodynamics comparable to those of nitric oxide,[8,9] but important differences exist between the two therapies. Inhaled prostacyclin is roughly one-tenth the cost of inhaled nitric oxide, but this cost benefit is offset by the fact that administration

is substantially more difficult. There is no reliable delivery mechanism as exists with nitric oxide; the medication is inactivated by room temperature and light and, most importantly, the glyceine diluent used to prepare the inhaled form has been reported to cause tracheitis and has the potential to clog valves in the ventilator circuit. Long-term safety data is also lacking, as is evidence of a mortality benefit from the therapy.

Non-Conventional Modes of Mechanical Ventilation

Multiple modes of mechanical ventilation including pressure control, inverse ratio, airway pressure release and high frequency oscillatory or jet ventilation, have been proposed as alternative strategies when oxygenation cannot be supported using conventional volume control approaches. Space considerations do not permit analysis of the data from trials on all of these modes of ventilation but the general message that comes from these studies is that they fail to demonstrate consistent improvements in oxygenation or benefit in terms of mortality or other important patient outcomes. When one also considers the lack of familiarity clinicians and respiratory therapists might have with these modes, the lack of good data makes it difficult to recommend any of these strategies as viable alternatives.

Recruitment Maneuvers

Increased levels of continuous positive airway pressure (CPAP) for short durations have been used in an effort to open collapsed alveoli and improve oxygenation. Available studies[10] on these maneuvers demonstrate improved oxygenation but the benefits appear to be of short duration (less than 60 minutes). It is unclear whether adding additional PEEP after the recruitment maneuver leads to sustained benefit, as the one study to address this question[11] did not examine oxygenation more than 60 minutes after the maneuver was completed. A further complicating issue with routine use of recruitment maneuvers is the lack of information regarding best practices for these maneuvers including their frequency, magnitude and duration.

Extracorporeal Membrane Oxygenation (ECMO)

Of all the therapies proposed for the management of critical hypoxemia, this is the one with perhaps the weakest data supporting its use. Only two randomized trials[12,13] have examined this technique and both failed to show a mortality benefit, although it should be noted that these studies were conducted before low tidal-volume ventilation became standard therapy for ARDS. More recent studies have been published reporting benefit from the therapy but these have all been either observational[14] or uncontrolled trials,[15] usually from a single institution, and, as a result, provide little useful input into whether this therapy is really of benefit. In some of these reports, the claims of benefit simply do not fit the data. Lewandowski et al,[15] for example, documented a 55% survival in their ECMO treated group in an uncontrolled prospective trial and concluded in their abstract "ARDS can be successfully treated with the clinical algorithm and high survival rates can be achieved." They make this claim even though the non-ECMO group had a much higher survival rate of 89%. There is also no data at present as to whether venoarterial or venovenous methods are more appropriate for patient management. Data collection from a randomized, controlled trial (CESAR trial) examining the use of ECMO in ARDS has been completed in the United Kingdom but the results have yet to be published. Until that data is available, ECMO should not be used for critical hypoxemia in the adult population.

Conclusions

Multiple strategies have been proposed for supporting oxygenation in patients with critical hypoxemia. Unfortunately, the data supporting the use of such strategies is limited and none of the modalities has been associated with a mortality benefit. As a result, any decision to employ these techniques will have to take into consideration the needs of the individual patient with a careful weighing of the risks and benefits of the proposed strategy. ■

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CME / CNE Questions

57. In ventilator-associated pneumonia (VAP), which of the following organisms is most likely to cause bacteremia:
a. *Klebsiella* species
b. *Staphylococcus aureus*
c. *Acinteobacter bumannii*
d. *Streptococcus pneumoniae*
e. *Haemophilus influenzae*

58. In the ICU palliative care consultation study, what was the ICU length of stay for patients in the intervention group as compared to the usual care group?
a. 5.7 days vs 14 days
b. 9 days vs 10 days
c. 12 days vs 14 days
d. 4 days vs 5 days
e. none of the above

59. Which of the following studies has the highest sensitivity for the diagnosis of invasive aspergillosis?
a. fungal culture of bronchoalveolar lavage fluid
b. direct examination of bronchoalveolar lavage fluid
c. bronchoalveolar lavage fluid galactomannan
d. serum galactomannan
e. serum fungal culture

60. Which of the following antimicrobial agents may cause a false positive test for BAL Galactomannan?
a. trimethoprim-sulfamethoxazole
b. piperacillin-tazobactam
c. clindamycin
d. metronidazole
e. levofloxacin

Answers: 57 (b); 58 (a); 59 (c); 60 (b)

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:

Non-Value of Daily Chest X-Rays in 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.

Another Study Implicates Avandia

In this issue: *Rosiglitazone (Avandia) implicated in yet another study; Prilosec and Nexium not associated with cardiac events; Anastrozole (Arimidex) shown more effective than tamoxifen for treatment of early-stage breast cancer; antibiotics show no effect on sinusitis; FDA actions.*

The handwriting may be on the wall for GlaxoSmithKline's rosiglitazone (Avandia) with yet another study implicating the drug with an increased risk of heart failure, cardiovascular events and mortality when compared to other oral hypoglycemic agents. The study was a nested case-control analysis of a retrospective cohort study using health care databases in Ontario. The patient population was nearly 160,000 older (>65 years of age) type 2 diabetics on at least one oral agent. The primary outcome was emergency visit or hospitalization for congestive heart failure, while secondary outcomes were AMI and all-cause mortality. After a mean follow-up of 3.8 years, monotherapy with rosiglitazone was associated with an increased risk of CHF (RR 1.60; 95% CI 2.10; *P*<.001), AMI (RR 1.40; 95% CI, 1.05-1.86; *P*=.02), and death (RR 1.29; 95% CI, 1.02-1.62; *P*=.03). Thiazolidinediones in general were evaluated in the study, but the adverse effects were limited to rosiglitazone. Adverse effects were found in patients who took the drug as a single agent or in combination with other hypoglycemic drugs (*JAMA*. 2007;298:2634-2643). Meanwhile, two large pharmacy benefit managers, Prime Therapeutics and HealthTrans, have dropped rosiglitzone from their formularies and the Department of Veterans Affairs is severely limiting the drug's use. Sales of the drug dropped 27% in the second quarter of 2007 and 39% in the third quarter.

Prilosec and Nexium Cleared

Omeprazole (Prilosec) and esomeprazole (Nexium) are not associated with increased rates of cardiac events, according to statements on the FDA web site. Concern was raised after AstraZeneca submitted data from two long-term studies in patients with severe gastroesophageal reflux to assess treatment with either drug vs surgery. Evaluation of secondary outcomes raised the question of whether long-term use of these drugs increased risk of cardiovascular events including sudden death. In a statement published on the FDA web site (www.fda.gov) on December 10, the agency states that it has completed a comprehensive scientific review of known safety data for both drugs. Based on review of the two studies presented by AstraZeneca and analysis of 14 comparative studies of omeprazole, no evidence of increased rate of cardiac events was seen. "Therefore, FDA continues to conclude that long-term use of these drugs is not likely to be associated with an increased risk of heart problems. The FDA recommends that health-care providers continue to prescribe, and patient's continue to use, these products as described in the labeling for the two drugs."

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Anastrozole over Tamoxifen for Breast Cancer

Anastrozole (Arimidex) is more effective than tamoxifen as adjuvant treatment for early-stage breast cancer according to a study published online as an early release in the *Lancet Oncology*. The study looked at 6241 women with locally invasive breast cancer who were randomized to anastrozole or tamoxifen and followed for a median of 100 months. Primary endpoints were disease-free survival, and secondary endpoints were time to recurrence, incidence of new contralateral breast cancer, time to distant recurrence, overall survival, and death after recurrence. Endpoints were evaluated in the total population and in the hormone-receptor-positive subpopulation. The primary endpoint and all secondary endpoints favored anastrozole except for deaths after recurrence and overall survival for which there is no significant difference. Fracture rates were higher in patients receiving anastrozole compared to tamoxifen. There was no difference in cardiovascular morbidity or mortality between the two treatment groups. The authors conclude that the study "establishes long-term efficacy of anastrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with hormone sensitive, early breast cancer, and provide statistically significant evidence of a larger carryover effect after five years of adjuvant treatment with anastrozole." (*Lancet Oncology* early online publication, 50 December 2007).

Antibiotics and Steroids Not for Sinusitis

Antibiotics and topical nasal steroids are of no benefit for patients with acute maxillary sinusitis according to a new randomized controlled trial of 240 adults. Patients with acute non-recurrent sinusitis were randomized to treatment with antibiotics and nasal steroids, placebo antibiotic and nasal steroid, antibiotic and placebo nasal steroids, or placebo antibiotic and placebo nasal steroid. Amoxicillin 500 mg three times a day for seven days and budesonide spray once daily were the active drug use in the study. The main outcome was proportion of clinically cured at 10 days and the duration of symptoms. Antibiotics made no difference in the proportion of patients with symptoms lasting 10 days or more (29% with antibiotics, 33.6% with no antibiotics). Use of nasal steroid also made no difference for the same measure (31.4% with budesonide, 31.4% with no budesonide). The authors conclude that neither an antibiotic nor topical steroid alone or in combination was effective as the treatment for acute sinusitis in the primary care setting (*JAMA*. 2007;298:2487-2496).

FDA Actions

An expert advisory panel of the FDA has recommended against approving Merck's petition to take lovastatin (Mevacor) over-the-counter. This was the third request in 7 years for OTC status for the cholesterol-lowering drug. The advisers voted 10-2 against approval citing concerns whether patients were capable of determining if they are appropriate candidates for the medication. The FDA generally follows the advice of its advisory panels.

The FDA has approved yet another beta-blocker for the treatment of hypertension. MylanBertek's nebivolol (Bystolic) is a selective beta-1-adrenoreceptor blocker with vasodilating effects. The drug is the 19th beta-blocker approved in the United States.

Wyeth has received an approvable letter for bazedoxifene, a new selective estrogen receptor modulator (SERM) for the prevention of osteoporosis in postmenopausal women. In issuing the letter, the agency asked for more data on the risk of blood clots and stroke, problems that have plagued the other marketed SERM for this indication (raloxifene-Evista). The agency did not ask for new studies however. Wyeth is also seeking the indication for treatment of osteoporosis in postmenopausal women. When approved, bazedoxifene will be marketed as Viviant.

The FDA has issued a safety warning on fentanyl skin patches after several reports of deaths and life-threatening side effects associated with inappropriate use. The warning stresses that the patches are only for patients who are opioid-tolerant and have poorly controlled pain on other narcotic pain medications. The patches are not for postoperative pain or sudden or occasional pain. Patients who used the patch should be aware of the signs of fentanyl overdose. Patients and physicians should be aware of potential drug interactions and physicians and pharmacists need to instruct patients on appropriate use of the patch. Patients also need to be aware that heat sources such as heating pads, electric blankets, saunas, heated waterbeds, hot baths, sunbathing and even fever may result in sudden increases in blood levels of fentanyl.

The FDA has approved a new volume expander for the treatment of volume loss during surgery. German drugmaker Fresenius Kabi's Voluven utilizes a new synthetic starch that is insoluble in water. In clinical trials the product was found to be as safe and effective as Hespan, a currently approved starch solution volume expander. ■