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Critical Care [ALERT]

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

ABSTRACT & COMMENTARY

Nighttime Intensivist Coverage May Not Benefit All ICUs

By Betty Tran, MD, MS
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Dr. Tran reports no financial relationships relevant to this field of study.

SYNOPSIS: This retrospective, multicenter study found that nighttime intensivist staffing is associated with lower patient mortality only in ICUs that lack mandatory daytime intensivist staffing.

SOURCE: Wallace DJ, et al. Nighttime intensivist staffing and mortality among critically ill patients. *N Engl J Med* 2012;366:2093-3101.

Supporters of 24-hour intensivist staffing in the ICU cite potential benefits to the patient as a result of more timely and accurate diagnostic evaluation, consistent provision of complex treatment, and overall higher quality, safer care. Previous studies, however, have reported conflicting results with regard to patient outcomes in ICUs with nighttime intensivist staffing. This study by Wallace and colleagues sought to examine the relationship between nighttime intensivist staffing and mortality in patients admitted to the ICU.

The authors conducted a retrospective study using data obtained for 65,752 patients admitted to 49 ICUs in 25 hospitals (74% of all surveyed sites) participating in the Acute Physiology and Chronic Health Evaluation (APACHE) clinical outcomes database from 2009 through 2010. The hospitals were diverse with regard to academic status, geographic location, and number of ICU beds, and there were no significant differences between hospitals participating in the study and those that did not. Of the 49 ICUs that participated, 12 had nighttime intensivist staffing, contributing data for 14,424 admits (22%), and 37 had no nighttime intensivist for 51,328 admits (78%). There were no significant differences between patients admitted to ICUs with or without nighttime intensivists.

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Critical Care [ALERT]

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Nighttime intensivist staffing was associated with a reduction in risk-adjusted in-hospital mortality only in ICUs with low intensity (i.e., optional consultation) daytime intensivist coverage (odds ratio [OR] 0.62, $P = 0.04$). In ICUs with high intensity (i.e., mandatory consultation or primary care by an intensivist) daytime intensivist staffing, there was no additional mortality benefit associated with an in-hospital nighttime intensivist (OR 1.08, $P = 0.78$). These results were supported by sensitivity analyses in subgroup populations most likely to benefit from in-house nighttime intensivist staffing: patients receiving active treatment on admit, undergoing mechanical ventilation, admitted at night, with the highest acute physiology scores, and admitted with sepsis. Similar results were also found in a separate verification cohort using data from the Pennsylvania Health Care Cost Containment Council (PHC4). An additional finding was that when the definition of nighttime intensivist staffing was modified to include a resident physician, nighttime staffing was associated with lower mortality in all ICUs, although the addition of a nighttime intensivist to an ICU already staffed by residents offered no extra benefit in outcomes.

COMMENTARY

As more hospitals contemplate moving toward 24-hour intensivist staffing, the potential benefits of such efforts will need to be weighed against the inherent costs and requisite expansion of the intensivist workforce necessary to build such programs. Crucial to this decision is the need for solid data supporting better outcomes in patients admitted to ICUs with nighttime intensivist staffing compared to other ICU models.

This study has important implications for addressing this dilemma. The findings suggest that ICUs already staffed by an intensivist either as a consultant or as the primary person responsible for the patient's care or that have resident physician nighttime coverage do not benefit from the addition of a nighttime intensivist in the hospital in terms of reducing patient mortality. On the other hand, ICUs in which daytime intensivist input is merely optional may benefit from nighttime intensivist staffing. This latter observation is not surprising, as mandatory intensivist staffing in the ICU is associated with lower ICU and hospital mortality.[1]

[Overall, the findings of this study argue against widespread implementation of 24-hour intensivist staffing as standard of care.]

Overall, the findings of this study argue against widespread implementation of 24-hour intensivist staffing as standard of care. Specific to academic teaching hospitals, there is added concern for loss of resident and fellow physician autonomy when a 24-hour intensivist is present. There are, however, other potential benefits to nighttime intensivist staffing. These include reduced intensivist burnout, increased allied health staff satisfaction, reduced patient ICU length of stay, and fewer procedural complications. Further studies on all these outcomes are warranted. In the meantime, individual ICUs will need to define carefully the anticipated benefits they hope to derive from 24-hour intensivist coverage and at what costs prior to expanding their staffing. ■

REFERENCE

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ABSTRACT & COMMENTARY

High-Flow Nasal Cannula Oxygen Therapy in Acute Respiratory Failure: What Do We Know?

By Eric C. Walter, MD, MSc

Pulmonary and Critical Care Medicine, Northwest Permanente and Kaiser Sunnyside Medical Center, Portland

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

SYNOPSIS: Limited data on the use of high-flow nasal cannula oxygen therapy suggests it is associated with improvement in physiologic parameters.

SOURCE: Sztrymf B, et al. Impact of high-flow nasal cannula oxygen therapy on intensive care unit patients with acute respiratory failure: A prospective observational study. *J Crit Care* 2012;27:324.e9-324.e13.

High-flow nasal cannula oxygen therapy (HFNC) is a generic name for oxygen delivery devices that provide oxygen nasally at higher flow rates than conventional nasal cannulae. Conventional ventilation usually can only provide flow rates up to 15 L/min, while HFNC can deliver flow rates up to 60 L/min. Both flow rate and fraction of inspired oxygen (FiO_2) are titratable. HFNC has been successfully used in the neonatal intensive care unit (ICU) for neonates with acute respiratory failure (ARF). Although there are substantially fewer published studies outside the neonatal ICU, it is now being used with increasing frequency in adults with ARF.

This small, prospective study reported outcomes from 20 patients with ARF admitted to the ICU and placed on HFNC. ARF was diagnosed as pulse oximetry < 96% and/or a respiratory rate ≥ 25 while receiving oxygen through a facemask at an estimated FiO_2 > 50%. The median age of enrolled patients was 59 years and the median SAPS2 score was 33 (estimating a 16% risk of hospital mortality). Pneumonia was the most common diagnosis (11/20). Following initiation of HFNC, median respiratory rate decreased from 28 to 24.5, with a significant increase in oxygen saturation (93.5% vs 98.5%). Both results were statistically significant. PaO_2 increased from 65.5 to 114.5 mmHg with no significant change in pH. Six patients were ultimately intubated and two patients died.

COMMENTARY

This small study is one of a handful of studies beginning to critically evaluate HFNC. HFNC may represent another case of the adoption of technology in advance of the data. Small studies similar to that of Sztrymf et al have been published showing similar improvements in physiologic parameters and/or patient comfort. While many changes are statistically significant, one can argue the clinical significance of a respiratory rate improving from 28 to 24.5. Many of these studies lack a control arm so we do not know how patients would have done had HFNC not been started. However, taken together, the direction of clinical changes in this study, and others, does seem to suggest that HFNC can provide improvements in oxygenation and respiratory effort for patients.

There are a variety of mechanisms proposed to explain how HFNC may help to improve ARF. Patients with ARF often have very high inspiratory flow rates. Conventional oxygen delivery devices often only provide oxygen at flow rates up to 15 L/min, and thus a significant amount of room air may be entrained. HFNC is hypothesized to better match oxygen delivery with inspiratory flows. HFNC has been shown to provide low-level positive airway pressure, theoretically providing some alveolar recruitment as well. Furthermore, HFNC may wash out carbon dioxide from the nasopharynx, decreasing the rebreathing of carbon dioxide and increasing the amount of oxygen that reaches the lungs.

HFNC is relatively easy to use but there are some important considerations. Both FiO_2 and flow rate are titratable. It is important that everyone on the medical team is aware of what changes are being made. For example, a patient who has gone from 70% to 50% oxygen may seem to be improving until it is discovered this occurred in the setting of increasing flow rates from 30 to 60 L/min. Arguments are being made that HFNC may prevent or delay intubation in patients with hypoxic ARF. It remains to be seen if this is a good or bad thing. Few would argue

that preventing intubations is a bad thing but delaying a necessary intubation too long may actually be harmful.

In summary, HFNC appears to be here for good. It is relatively easy to use and early data suggest it improves physiologic parameters in patients with ARF. Data related to more clinically significant outcomes, such as length of stay, intubation rates, and mortality, are currently lacking. We should not let our excitement for new technology cause us to forget that only after critical evaluations can we be sure we are helping, and not hurting, our patients. ■

ABSTRACT & COMMENTARY

Medical Emergency Team Calls in the Radiology Department

By David J. Pierson, MD, Editor

SYNOPSIS: This study of potentially life-threatening changes in patient condition during trips to the radiology department of a large academic medical center found that such events occurred about once a week, involved both ward and ICU patients who had comorbidities and high overall mortality, and were often unanticipated by vital sign changes or other recognized warnings.

SOURCE: Ott LK, et al. Medical emergency team calls in the radiology department: Patient characteristics and outcomes. *BMJ Qual Saf* 2012; 21:509-518.

Ott and colleagues at the University of Pittsburgh reviewed all medical-emergency team (MET) calls to the radiology department involving adult inpatients during a 2-year period. They sought to identify the characteristics of the patients involved, and to find any relationships between these characteristics and patient outcomes. Activation of the hospital's well-established MET system occurs when patients experience deterioration in respiratory, cardiovascular, or neurological status, or develop other predefined alterations in symptoms, signs, or interventions, using standardized criteria. MET calls originating during transport to or from the radiology department were not considered in the study. The authors recorded the timing and circumstances of each MET call, the patient's origin (e.g., ward or ICU), demographic and diagnostic data, the Charlson Comorbidity Index, plus vital signs and level of care needs in the 12 hours prior to the call. In addition, the level of care given in the radiology department was sought from the electronic medical record, as was information on the level of care required following the call and whether the patient died in the hospital after the event.

During the 2-year study period, there were 111 MET calls to the radiology department. Patients were sent for CT (44%), MRI (22%), interventional radiology (15%), and other imaging. Calls happened more frequently on days near the middle of the week and during the hours from 8 a.m. to noon, although they also occurred at other times. Almost half (43%) of the MET calls occurred on the patients' first day in the hospital. Forty percent of the patients came to the radiology department from an ICU, and 60% from the wards. Fifteen percent were mechanically ventilated, 12% were on an oxygen facemask, and 38% had nasal oxygen, while only 35% of the patients arrived in radiology on no respiratory support. After the MET call, most patients (78/111, 70%) required a higher level of care than before, including 38 of the 67 non-ICU patients; 26% of those not on mechanical ventilation before the call required it afterwards.

Patients generating MET calls in the radiology department tended to be middle-aged, and there was no gender difference. They were evenly distributed across diagnostic categories, and tended to have comorbidities (renal 61%, cerebrovascular 28%, diabetes 22%, myocardial infarction 21%, cardiopulmonary disease 20%), with a mean Charlson Comorbidity Index of 4. During the 12 hours preceding the MET call, 16% had reached or exceeded the institution's MET vital sign threshold. More than half of the patients received continuous monitoring while in the radiology department.

Twenty-five percent of patients who experienced a MET call in the radiology department died. Mortality was higher among ICU-originating patients than in those coming from the ward (57% vs 43%; $P = 0.03$). Aside from this, the

only association with a fatal outcome following the MET call was for having received inotropic medications and/or fluid resuscitation in the 12 hours prior to the call (39% vs 17% of the patients who died; $P = 0.02$).

COMMENTARY

This study is helpful in that it provides a systematic look at a large consecutive series of patients in a tertiary referral center for whom the MET system was activated while they were in the radiology department for imaging or procedures. Intensivists and other hospital clinicians dread the "stat" page to the radiology department, and they know that the acute patient deterioration that triggers such calls occurs not infrequently. A hope in conducting a study like this is that patterns and predispositions can be identified that will permit effective preventive measures to be implemented. However, Ott et al had no such good fortune. In documenting the wide variety of patient characteristics and clinical factors present in this series, the authors are careful to point out that nothing can be concluded about causation or specific measures to take in the future. Nonetheless, they have better described a clinical scenario that is both frequent and associated with high patient mortality. One may hope that future studies can identify ways in which the incidence of radiology department MET calls can be reduced and their outcomes improved.

As pointed out in the accompanying editorial by Staples and Redelmeier,[1] there are a number of possible explanations for acute patient deterioration in the radiology department. Of these, the two most likely are, first, that seriously ill patients are likely to need complex studies requiring imaging, and are also predisposed to complications associated with both intrahospital transport and the performance of the procedures. Imaging procedures may be ordered because of patient deterioration or suspicion of a new medical process, settings in which adverse events may be particularly likely. And, second, caring for a complicated, potentially unstable patient during transport and imaging-related interventions presents major challenges, including the following:

- The procedure and associated waiting can take considerable time.
- The patient must be moved, positioned, and otherwise physically manipulated.
- The administration of various contrast agents and sedatives may be required.
- Lines may come out, infusions may be interrupted, and scheduled medication doses may be missed.
- Physicians and other caregivers may be distracted by aspects of the procedure.
- Patients may experience anxiety, agitation, claustrophobia, or other distress.

Although the present study does not tell us how to prevent MET calls to the radiology department or how to improve outcomes when they occur, it casts light on an important problem affecting all who work in the ICU. ■

REFERENCE

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ABSTRACT & COMMENTARY

Hand Hygiene Exemplars: Lead the Followers

By Leslie A. Hoffman, RN, PhD
Department of Acute/Tertiary Care, School of Nursing, University of Pittsburgh

SYNOPSIS: Hand hygiene was more likely to be performed when the first person entering the room or the attending physician (regardless of order) performed hand hygiene.

SOURCE: Haessler S, et al. Getting doctors to clean their hands: Lead the followers. *BMJ Qual Saf* 2012;21:499-502.

In this study, a research assistant who was already embedded in patient care teams to observe the process of care during bedside rounds was recruited to document hand hygiene compliance by nine internal medicine teams over a 3-month period. The teams consisted of one attending, one post-graduate year 3 (PGY-3) resident, two PGY-1 residents, one medical student, and one pharmacy student. The research assistant recorded order of entry and exit from the room, training level, and adherence to hand hygiene using a data collection tool encrypted to maintain secrecy.

During the study, there were 718 observed hand hygiene opportunities when the team entered patient rooms and 744 opportunities when leaving the room. Overall, hand hygiene compliance was 52% before entering and 70% before leaving the room. Compliance by training level ranged from 47%-67% before entering and 64%-87% on leaving ($P < 0.001$). Simply being first, second, or last did not impact the likelihood of performing hand hygiene. However, if the first person entering or leaving the room performed hand hygiene, compliance of the other team members increased significantly ($P = 0.002$). If the attending physician performed hand hygiene on entering the room, overall team member compliance also increased significantly ($P < 0.001$). This observation held regardless of who entered or left the room first. Mean compliance was 74% if the attending physician performed hand hygiene compared to 51% if not done ($P = 0.016$).

COMMENTARY

Adherence to good hand hygiene is considered essential for infection protection. With the emergence of highly resistant organisms, rigid adherence to this simple practice becomes even more important. However, it is well known that compliance remains poor, despite multiple attempts to change this outcome. Findings of this study are especially intriguing because they suggest that a simple, no-cost intervention can improve hand hygiene compliance, i.e., role modeling and peer pressure. In this study, hand hygiene compliance was significantly improved when the attending physician performed this routine on entering and exiting the patient's room and, as well, when the first person to enter or exit the room performed this step.

Interestingly, hand hygiene compliance was greater on exiting the patient's room than when entering. The authors attributed this finding to "self protection" and questioned whether this finding implied that "self protection" may be a stronger driver of behavior than patient protection. In more than half of the patient encounters in this study, the attending physician was the first person to enter the room, suggesting that if senior clinicians made hand hygiene an integral part of bedside teaching, they need to do little more than perform the task themselves to motivate others to follow their example. This study was conducted on general medical wards, rather than in an ICU; however, there would appear to be no reason why the same findings would be expected in critical care settings. ■

ABSTRACT & COMMENTARY

Does Aspirin Reduce Mortality in the Systemic Inflammatory Response Syndrome?

By David J. Pierson, MD, Editor

SYNOPSIS: In this retrospective study, patients with systemic inflammatory response syndrome who had received aspirin had a lower mortality rate than those who had not. The groups were different in numerous ways, although propensity analysis to account for confounding variables and make the groups more comparable failed to completely eliminate the mortality difference.

SOURCE: Eisen DP, et al. Acetyl salicylic acid usage and mortality in critically ill patients with the systemic inflammatory response syndrome and sepsis. *Crit Care Med* 2012;40:1761-1767.

In this retrospective cohort study of patients with the systemic inflammatory response syndrome (SIRS) in an Australian ICU, those with SIRS who received acetyl salicylic acid (ASA; aspirin) were compared to those who did not receive aspirin. Using the hospital's electronic medical records, the authors identified all patients admitted to the ICU during a 9.5-year period who met two or more of the four SIRS criteria proposed by the 1992 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference:[1] temperature > 38° C, heart rate > 90 beats/min, respiratory rate > 20 breaths/min (or $PaCO_2$ < 32 mmHg), and white blood cell count > 12,000/mL (or < 4000/mL or > 10% band forms). For all such patients, they determined whether aspirin or another non-steroidal anti-inflammatory drug (NSAID), such as ibuprofen, had been administered during the same 24-hour period in which the SIRS criteria were met, along with patient demographics, diagnoses, selected laboratory data, and in-

hospital mortality. The investigators then performed covariable and propensity analyses to decrease the effect of confounding variables in comparing aspirin and non-aspirin patients with respect to mortality, documented bleeding complications (not further specified), and a decrease in renal function (defined as a doubling of initial serum creatinine level).

During the interval reviewed, there were 7945 admissions to the study ICU. Of these, 6131 met the authors' SIRS inclusion criteria. Excluding repeat admissions, 2082 patients with SIRS received aspirin and 3441 did not. Overall in-hospital mortality in the two groups was 9% and 20%, respectively. Seven percent of all patients with SIRS received an NSAID other than aspirin, and these patients were about evenly distributed between the aspirin and non-aspirin groups. The patients in the aspirin-receiving and non-aspirin groups were quite different: the former were older by a mean of 8 years, more likely to be male (71% vs 59%), and had cardiac-related comorbidities, 48% of them having been admitted for coronary artery bypass grafting vs 15% of the non-aspirin-receiving patients. Propensity analysis, in an attempt to eliminate these differences, matched 1445 of the aspirin-receiving patients with an equal number of non-aspirin patients.

The difference in mortality among aspirin and non-aspirin patients with SIRS was less pronounced after the propensity analysis, but remained statistically significant (10.9% mortality vs 17.2%), with an absolute difference of -6.2% (95% confidence interval [CI], -9.5% to -3.5%). After propensity matching, the investigators also found a higher risk of developing renal impairment (6.2% incidence vs 2.9%; absolute risk difference, 3.3%; 95% CI, 2.5% to 5.0%) in patients who received aspirin, but a lower risk for bleeding (8.8% incidence vs 17.6%; absolute risk reduction, -8.8%; 95% CI, -11.1% to -7.3%).

COMMENTARY

In the discussion, the authors point out that because it is retrospective and thus quasi-experimental, "this study cannot establish a causal association between ASA and death from SIRS or sepsis. Despite efforts to adjust for confounding factors, the difference in mortality between ASA users and nonusers could potentially be attributable to residual confounding." This is the crux of the matter for all readers of this article, and especially for clinicians wishing to determine whether the findings are relevant to their practices.

This study prompts consideration of the hypothesis that aspirin might have a mortality-reducing effect on SIRS. However, two issues make me reluctant to embrace this hypothesis. The first has to do with how different the patient groups turned out to be, as illustrated by likely explanations for the renal and bleeding effects. Renal toxicity is not a common adverse effect of aspirin in therapeutic doses, and the authors state in the discussion that the patients in this study "had been using ASA before admission to the ICU." Thus, it is difficult to generate an aspirin-related hypothesis as to the decline in renal function after ICU admission. In addition, bleeding is one of the common adverse effects of aspirin use and the study found the rate of bleeding to be twice as high in the non-aspirin-receiving patients. These things suggest to me that the renal and bleeding rates were most likely the results of factors other than the use of aspirin, and they weaken the assertion that the mortality difference was due to this agent.

The second issue is that ibuprofen, an NSAID like aspirin whose effects in SIRS and sepsis would be expected to be similar, has already been subjected to a multicenter, randomized, controlled trial in patients with sepsis,[2] as mentioned in the introduction. That study was negative with respect to an effect of ibuprofen on mortality.

Aspirin is cheap and very widely used, and administering it to patients with SIRS who do not have contraindications would likely be safe. Nonetheless, I agree with the authors' call for caution in interpreting their findings, quoted above, and also with their statement in the abstract that "the effect of acetyl salicylic acid on mortality of patients with systemic inflammatory response syndrome and sepsis needs to be evaluated with prospective randomized intervention studies." ■

REFERENCES

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2. Bernard GR, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. *N Engl J Med* 1997;336:912-918.

CME/CNE Questions

1. ICUs that benefitted, in terms of mortality reduction, from the addition of a nighttime intensivist:

a. consisted primarily of post-surgical patients.
b. were predominantly located in tertiary centers.
c. had disproportionately sicker and more complex patients.
d. had optional consultations by daytime intensivists.
e. had a higher patient to physician ratio.

2. Based on available evidence, the addition of an in-house nighttime intensivist to an ICU already covered by a nocturnal resident physician:

a. resulted in decreased complications secondary to central line placement.
b. conferred no additional patient mortality benefit.
c. decreased resident opportunities for learning.
d. improved patient and family satisfaction.
e. reduced ICU recidivism.

3. High-flow nasal oxygen has been best studied in:

a. adults with acute respiratory failure in the emergency room.
b. adults with acute respiratory failure in the intensive care unit.
c. adults with acute respiratory failure on the hospital wards.
d. adults with chronic respiratory failure.
e. infants in the neonatal intensive care unit.

4. High-flow nasal oxygen may improve oxygenation by:

a. increased washout of carbon dioxide from the nasopharynx.
b. providing low-level positive airway pressure.
c. better matching delivered oxygen flow rates with patient's inspiratory rates.
d. All of the above
e. None of the above

5. Which of the following were characteristics of patients for whom a medical emergency team call was initiated while they were in the radiology department?

a. Most such patients were women.
b. They were most common in patients with underlying cardiopulmonary disease.
c. They happened most often on the weekends.
d. All of the above
e. None of the above

6. In the study of patients for whom a medical emergency team call originated in the radiology department, which of the following was associated with higher mortality?

a. Being on supplemental oxygen prior to the call
b. Coming to the radiology department from the ICU rather than the ward
c. Coming from a surgical floor rather than a medical floor
d. All of the above
e. None of the above

7. Compliance with hand hygiene was increased when:

a. hand hygiene products were readily accessible.
b. participants attended an educational event about hand hygiene.
c. nurse team members performed hand hygiene on entering the room.
d. the attending physician was part of the rounding team.
e. the person first entering the room performed hand hygiene.

8. Hand hygiene appeared to be influenced by:

a. role modeling.
b. peer pressure.
c. desire for self-protection.
d. a and b but not c
e. All of the above

9. Patients with systemic inflammatory response syndrome who received aspirin had which of the following?

a. Lower in-hospital mortality
b. Higher rates of renal dysfunction developing in the ICU
c. Lower incidence of bleeding
d. All of the above
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]

Do medical and surgical ICU patients have different bacterial resistance patterns?

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.*

Does Azithromycin Cause Cardiovascular Death?

In this issue: Azithromycin and cardiac risk; warfarin and heart failure; aspirin and VTE; effectiveness of long-acting contraceptives; and FDA actions.

New study finds increased risk

Is azithromycin proarrhythmic? Macrolide antibiotics are associated with an increased risk of sudden cardiac death, but azithromycin (Zithromax), the popular "Z pack" macrolide, has been considered safe. That may change based on the results of a new study from Vanderbilt. Researchers reviewed the records of patients in the Tennessee Medicaid cohort to detect an increased risk of death related to short-term cardiac effects of azithromycin and several control antibiotics. Patients with serious noncardiovascular illness and hospitalized patients were excluded. Over the study period, there were almost 350,000 patients who took azithromycin, 1.35 million patients who took amoxicillin, 265,000 patients who took ciprofloxacin, nearly 200,000 patients who took levofloxacin, and nearly 1.4 million control patients. Five days of therapy with azithromycin compared to no antibiotics significantly increased the risk of cardiovascular death (hazard ratio [HR] 2.88, confidence interval [CI], 1.79 to 4.63; $P < 0.001$) and death from any cause (HR 1.85; 95% CI, 1.25 to 2.75; $P = 0.002$). Use of amoxicillin was not associated with increased risk of death. Relative to amoxicillin patients, patients taking azithromycin were at 2.5 times higher risk of cardiovascular death and 2 times higher risk of death from any cause, although the absolute risk was low with an estimated 47 additional cardiovascular deaths per million courses. Patients at risk for cardiovascular disease were at higher risk, with an estimated 245 additional cardiovascular deaths per 1 million courses. Cardiovascular death risk was higher with azithromycin compared to ciprofloxacin, but the death rate from levofloxacin was roughly the same. The authors conclude that 5 days of azithromycin was associated with a small but absolute increased risk of cardiovascular death, which was most pronounced in patients with a high baseline risk for cardiovascular disease (*N Engl J Med* 2012;366:1881-1890). Soon after this study was published, the FDA issued a statement urging patients to continue taking azithromycin unless instructed otherwise by their health care professional. The FDA will review the results of the study and will communicate any new information on azithromycin, including the potential risk of QT interval prolongation, to health care professionals and the public. Health care professionals are urged to report any adverse effects related to the use of azithromycin to the FDA's MedWatch Safety program. ■

Warfarin doesn't prevent death

Warfarin is no more effective than aspirin in preventing mortality in patients with heart failure who are not in atrial fibrillation (AF), according to a new study. More than 2300 patients with a left ventricular ejection fraction less than 35% (average 25%) and a mean age of 61 years were randomized to warfarin with a target INR of 2.0-3.5 or

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

aspirin 325 mg per day. The primary outcome was ischemic stroke, intracerebral hemorrhage, or death from any cause. Patients were followed for up to 6 years with a mean follow-up of 3.5 years. There was no difference in the primary outcome (7.47 events per 100 patient years for warfarin, 7.93 for aspirin; HR with warfarin 0.93, CI, 0.79 to 1.10, $P = 0.40$). Warfarin was associated with a significant reduction in the rate of ischemic stroke but was associated with a higher rate of hemorrhage. The authors conclude that among patients with heart failure who are in sinus rhythm, there was no difference in outcome between warfarin and aspirin, but note that since warfarin was associated with a lower risk of ischemic stroke, the choice between the two drugs should be individualized (*N Engl J Med* 2012;366:1859-1869). An accompanying editorial asks, "Could there be some patients with heart failure who would benefit from warfarin?" Those with AF, a history of cardioembolic stroke, history of left ventricular thrombus, and perhaps those with atherothrombotic coronary artery disease may benefit, but in general, warfarin cannot be recommended for patients with heart failure who are not in AF (*N Engl J Med* 2012;366:1936-1938). ■

Aspirin and venous thromboembolism

Aspirin may be protective in patients who have had an unprovoked venous thromboembolism (VTE) to prevent recurrence after they finish oral anticoagulant therapy. In a double-blind study, patients with first-ever unprovoked VTE who had completed 6-18 months of oral anticoagulant treatment were randomly assigned to aspirin 100 mg daily or placebo for 2 years. The primary endpoint was recurrent VTE with major bleeding being the primary safety outcome. Recurrent VTE occurred in 6.6% of patients on aspirin and 11.2% of patients on placebo (HR 0.58; 95% CI, 0.36 to 0.93). One patient in each group had a major bleeding episode. The authors conclude that aspirin reduces the risk of recurrence in patients with unprovoked VTE after they have finished anticoagulant therapy, with no apparent increase in risk of major bleeding (*N Engl J Med* 2012;366:1959-1967). This study is important because about 20% of patients with unprovoked VTE have a recurrence within 2 years. It also shows that taking low-dose aspirin safely reduces that risk by nearly half. An accompanying editorial points out that a similar but larger study is currently ongoing in Australia and New Zealand with results due later this year (*N Engl J Med* 2012;366:2028-2030). ■

Long-acting contraceptives are better

Long-acting contraceptives, such as IUDs and implants, are up to 20 times more effective than oral contraceptives and other short-acting contraceptive methods, according to a new study. In a large, prospective cohort study, women participants were provided with the reversible contraception of their choice at no cost for 3 years. The endpoint was failure of long-acting reversible contraception (IUDs and implants) compared with commonly prescribed contraceptive methods, including oral contraceptive pills, transdermal patches, contraceptive vaginal rings, and depot medroxyprogesterone acetate injection (DMPA). In the nearly 7500 women participants, there were 334 unintended pregnancies. The failure rate among participants who used pills, patch, or ring was 4.55 per 100 participants years as compared with 0.27 among participants using long-acting reversible contraception (HR after adjustment for age, educational level, and history with respect to unintended pregnancy 21.8; 95% CI, 13.7 to 34.9). The rate for DMPA was also low at 0.22. Younger women (< 21 years) who used a short-acting contraceptive had a pregnancy rate almost twice as high as older participants. The pregnancy rate among women who used DMPA, an IUD, or implant were similarly low regardless of age. The authors conclude that the effectiveness of long-acting reversible contraception is superior to that of contraceptive pills, patch, or ring and is not altered in adolescents or young woman (*N Engl J Med* 2012;366:1998-2007). This study not only points out the reliability of long-acting contraceptives, but also the surprisingly high failure rate of short-acting contaceptives, especially in young women. ■

FDA actions

In the biggest generic launch since last year's atorvastatin (Lipitor), the FDA has approved generic clopidogrel (Plavix). The popular antiplatelet drug, with sales of more than $9 billion last year, will be available from seven generic manufacturers in the 75 mg strength and four manufacturers in the 300 mg strengths. The immediate "multisource" status of the generic approval should result in dramatic cost reductions for patients, from an average of $200 per month to about $40 per month. The drug is approved for treatment of acute coronary syndrome and prevention of thrombotic events in patients who have had a recent myocardial infarction, recent stroke, or peripheral artery disease. ■