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Critical Care [ALERT]

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

ABSTRACT & COMMENTARY

Gender Composition of ICU Staff May Serve As a Buffer to Caregiver Burnout

By Linda L. Chlan, RN, PhD
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Dr. Chlan reports that she receives grant/research support from the National Institutes of Health.

SYNOPSIS: The results from this multicenter Swiss survey on burnout and stress among ICU caregivers (nurses, physicians, nurse assistants) showed that an increased proportion of female nurses was associated with decreased risk for high burnout, but high stress was not consistently associated with high burnout in study participants.

SOURCE: Merlani P, et al for the STRESI Group. Burnout in ICU caregivers: A multicenter study of factors associated to centers. *Am J Respir Crit Care Med* 2011;184:1140-1146.

The intensive care unit (ICU) can be immensely stressful for caregivers and can lead to burnout that results from chronic emotional and interpersonal stressors in the environment. This article reports on the findings of a nationwide survey involving all certified ICUs in Switzerland to determine if center-related characteristics of these ICUs are associated with burnout and job stress. Questionnaires were sent to all Swiss ICU centers inquiring about their ICUs' patient-related factors (mortality, length of stay) and staff composition (physicians, nurses, nurse assistants). Physicians, nurses, and nurse assistants completed a questionnaire that contained items on demographic characteristics as well as personal and professional characteristics. Respondents also completed the Maslach Burnout Inventory and a perceived evaluation of stress ("I feel stressed: never, sometimes, often, very often"). Odds ratios and logistic regression were

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Critical Care [ALERT]

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the main analyses reporting results of individual characteristics and multiple characteristics that contributed to an increased or decreased risk for burnout and perceived stress.

The overall response rate by individual ICU center was a respectable 72%. A response rate of 69% was realized for physicians, 73% for nurses, and 46% for nurse assistants, for a total of 2996 respondents. Among those who responded, 29% showed a high degree of burnout, with 33% and 39% medium and low burnout, respectively. Presence of burnout was highest in the nurse assistants (41%), followed by physicians (31%) and nurses (28%). Overall, 37% of Swiss ICU professionals felt highly stressed. A higher proportion of female nurses and physicians decreased the risk of burnout. Increased risk of high stress was associated with working in university hospitals and pediatric ICUs, with the number of ICU beds, and with a higher proportion of female physicians. Not surprising was that both mortality rate and lengthy ICU stays increased risk of high burnout and high stress. Surprisingly, being male increased the risk of high burnout but decreased the risk of high stress. Nurse assistants had an increased risk of high burnout. The findings from the numerous analyses in this study suggest that a higher proportion of female ICU nurses decreased risk of high burnout among the entire ICU team.

COMMENTARY

Stress and burnout are inherent in the work environment of the ICU and are worldwide phenomena. The finding that the presence of a higher proportion of female ICU staff nurses may decrease the risk for high burnout is interesting and also not surprising. Given that a majority of nurses worldwide are of the female gender, perhaps this group of ICU nurses has more years of experience and personal tools for dealing with stressful workplaces and the many factors that can contribute to burnout. That the presence of males in the nursing workforce has only begun to increase in the recent past suggests that men may not have gender-specific support systems in their places of employment if they are not represented in the staff in adequate numbers. Further, they may be lacking mentors or positive role models. Men may experience an increased risk for burnout because there are fewer of them in the nursing workforce.

As with any survey, the characteristics of the one-third of staff members who did not complete the survey are unknown. It is not known if these ICU professionals are at higher or lower risk for burnout and stress. One of the more interesting findings from this study is that high stress is not always associated with high burnout. This suggests that stress perception and risk for burnout may be associated more with personality styles and personal, effective coping patterns than the actual physical ICU environment.

Given the worldwide shortage of ICU professionals, stress and burnout are an important consideration as quality of care can suffer and contribute to professionals leaving the ICU work setting. This in turn only intensifies the chronic stress for those in the work setting and can contribute even more so to burnout. A respectful work environment for all professionals is an important factor in job satisfaction. The American Association of Critical-Care Nurses has several suggestions for creating and sustaining healthy work environments.[1] Skilled ICU professionals are needed to provide care in this high-acuity setting where individuals need to take responsibility to self-monitor their own risk for stress and burnout. ■

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ABSTRACT & COMMENTARY

Aerosolized Antibiotics in the Management of Ventilator-Associated Pneumonia

By David J. Pierson, MD, Editor

SYNOPSIS: This retrospective review of patients with ventilator-associated pneumonia caused by *Pseudomonas aeruginosa* or *Acinetobacter baumannii* at the authors' institution found that survival, ventilator days, and lengths of stay were better among those who had received aerosolized tobramycin or colistin in addition to systemic antibiotic therapy. The numbers were small, however, and the potential use of adjunctive aerosolized antibiotic therapy comes with a number of important caveats.

SOURCE: Arnold HM, et al. Use of adjunctive aerosolized antimicrobial therapy in the treatment of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* ventilator-associated pneumonia. *Respir Care* 2012;Feb 17. [Epub ahead of print.]

Arnold and colleagues at Barnes-Jewish Hospital in St. Louis performed a 6-year retrospective cohort study of patients with bronchoalveolar lavage (BAL) documented ventilator-associated pneumonia (VAP), diagnosed by accepted clinical and quantitative culture criteria, that was caused by either *Pseudomonas aeruginosa* (PA) and *Acinetobacter baumannii* (AB). The purpose of the study was to compare outcomes among patients who had received adjunctive aerosolized antibiotics (AAA) to those in patients who were treated with only systemic antibiotics (NAAA). Included in the study were all adult patients without cystic fibrosis who were ventilated for at least 48 hours, had new or progressive infiltrates on chest X-ray, had at least two of three clinical indicators (fever/hypothermia, leukocytosis/leukopenia, and purulent secretions), had at least 10^4 colony-forming units/mL of one of the target organisms on BAL fluid culture, and received at least 72 hours of treatment with antibiotics to which the recovered organism was sensitive. In addition to microbiologic data and clinical outcomes, the authors recorded patient age, comorbidities, APACHE II score on the day of bronchoscopy, and modified Clinical Pulmonary Infection Score.

During the 2004-2009 period covered by the study, 150 patients initially met the authors' criteria for inclusion. After exclusion of 57 of these for a priori reasons such as withdrawal of life support, antibiotic treatment for less than 72 hours, and missing data, there were 19 patients who received AAA and 74 who did not (NAAA). All patients received systemic antibiotics to which their organisms were sensitive. Of the 19 patients treated with AAA, 10 received tobramycin, 300 mg twice daily for 11.0 ± 3.9 days, and 9 received colistin, 150 mg twice daily for 8.9 ± 6.7 days. AAA patients had higher initial APACHE II scores. NAAA subjects experienced a shorter time from VAP onset to appropriate intravenous antibiotic initiation (0.5 ± 0.9 vs 2.6 ± 5.4 days, $P = 0.038$), but the length of intravenous therapy was similar in the two groups (12.8 ± 8.5 vs 17.8 ± 13.3 days, $P = 0.163$). Other aspects of the patients' demographics and management were similar.

Thirty-day mortality was 0.0% in the AAA group vs 17.6% among NAAA patients ($P = 0.063$). When patients transitioned to palliative care were included in the mortality analysis, this suggested difference in hospital mortality disappeared (32.1% vs 33.3%; $P = 0.907$). However, Kaplan-Meier curves depicting the probability of 30-day survival from VAP onset demonstrated that patients receiving AAA had a statistically greater survival ($P = 0.030$ by the log rank test). Patients who received AAA spent fewer days on the ventilator (18.9 ± 15.9 vs 38.4 ± 32.4 days, $P < 0.001$), in the ICU (37.5 ± 42.5 vs 56.3 ± 31.3 days, $P = 0.001$), and in the hospital (39.0 ± 42.5 vs 58.3 ± 33.4 days, $P = 0.001$), and these differences persisted after excluding those who died. No outcome differences were found in AAA patients who received tobramycin vs colistin. The authors conclude that patients with VAP due to PA or AB may experience improved survival when AAA is added to the antibiotic regimen. However, they also refer to recent reports of increased microbial resistance to both tobramycin and colistin when administered by aerosol, and call for large randomized clinical trials to settle the issue of whether AAA is beneficial in VAP.

COMMENTARY

Like all studies based on a retrospective chart review, this report tells us what clinicians did in managing a series of patients but not why they did it. That is, why some patients with VAP due to the organisms in question received AAA and others did not is unknown, although it is unlikely that the treatment

assignment was random. And while the patients were similar according to the factors the authors examined, there may have been other important aspects of their underlying health status, the acute illness, or the ways in which they were managed that varied enough to cast doubt on whether the findings reflected effects of the treatment of interest. However, this article focuses attention on an important topic — the role of aerosolized antibiotics in intubated, critically ill patients.

Despite ongoing administrative and clinical efforts to decrease the incidence of VAP, it is exceedingly unlikely that this complication of critical illness can ever be completely eliminated because of its predispositions and pathogenesis. In most instances, VAP develops in patients who require at least several days of intubation and whose lower airways have been colonized by bacteria not normally found there. These organisms gain entry around or through the endotracheal or tracheostomy tube, and their proliferation in the lower airways precedes tissue invasion and clinical illness. It therefore stands to reason that antimicrobial agents delivered to the airways would be useful in preventing bacteria from proliferating there, and potentially also in treating tissue invasion and clinical illness when they occur. Antibiotics have been administered via aerosol for these purposes for 40 years, but whether they are clinically effective remains far from certain.

In a thoughtful discussion of the pros and cons of using AAA to prevent or treat VAP,[1] MacIntyre and Rubin list a number of reasons why this should be beneficial:
• Airway colonization precedes clinical infection in the great majority of cases.
• Reducing airway bacterial load reduces the development of VAP.
• Aerosolized antibiotics deposit directly in the airways and kill bacteria there.
• Aerosolized and other topically-applied antibiotics have been shown to decrease airway infections in certain settings (as, for example, with selective decontamination of the digestive tract).
• Numerous case reports and small series suggest clinical effectiveness.

However, these authors also point out numerous potential adverse effects and other disadvantages of using aerosolized antibiotics for VAP:
• Antibiotics applied to the airway mucosa penetrate poorly to the deeper tissues.
• Airway bacteria are typically encased in biofilms, into which the agents may not penetrate.
• Resistance develops rapidly when antibiotics are applied topically.
• Bronchospasm, hypersensitivity pneumonitis, and systemic toxicity may occur.
• There are numerous technical aspects to delivering these drugs via artificial airways that may greatly reduce their effectiveness.
• No drugs or delivery systems are currently FDA-approved for this use.

The practical technical difficulties involved in aerosolizing drug preparations that are not intended to be applied in this manner deserve special mention. Using the wrong diluent or concentration, or mixing agents for nebulization, can result in ineffective particle sizes, drug precipitation, and other problems. The literature on optimal administration of aerosols during mechanical ventilation is extensive. Many types and brands of nebulizers are in current use, and their aerosol delivery characteristics vary dramatically. Large quantities of drug typically deposit in the artificial airway, greatly reducing the delivered dose. Drug delivery is decreased by rapid inspiratory flows and also by humidification of the inspired gas, both of which are typically needed in ventilating critically ill patients with VAP. Reducing the inspiratory flow rate improves aerosol delivery but increases the risk of expiratory air trapping and hyperinflation, while turning off the humidification system facilitates aerosol delivery but can lead to airway drying and the inspissation of secretions; the consequences of forgetting to readjust these variables after each treatment could be dire.

With the emergence of multiple drug resistance among the organisms that may cause VAP, and the relative dearth of new, effective antibiotics, the increasing interest in AAA is understandable. Recent reviews[2,3] emphasize the sound rationale for using AAA in VAP, particularly when resistance limits the systemic agents that can be used, but conclude that insufficient evidence currently exists to support this approach for managing patients. The potential role for AAA remains uncertain, and the availability of data from well-designed, large clinical trials in this important area of critical care would be of great value. ■

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ABSTRACT & COMMENTARY

Respiratory Arrest: An Adverse Effect of Polymyxins

By David J. Pierson, MD, Editor

SYNOPSIS: Two ICU patients experienced respiratory arrest while receiving polymyxin. Given the recent resurgence of use of this antibiotic and its close relative colistin to treat gram-negative infections resistant to newer agents, clinicians should be aware of this infrequent but long-known and potentially fatal adverse effect.

SOURCE: Wunsch H, et al. Polymyxin use associated with respiratory arrest. *Chest* 2012;141:515-517.

Wunsch and associates describe two patients who suffered respiratory arrest requiring intubation and mechanical ventilation while receiving polymyxin B. The first was a liver-transplant patient with normal renal and respiratory function who developed bacteremia due to *Klebsiella pneumoniae* that was resistant to carbapenem but sensitive to polymyxin B. One hour after the first intravenous dose of polymyxin B was started, the patient was found unresponsive and apneic. After intubation, he had normal sensorium and respiratory mechanics. The second patient had a polymicrobial perinephric abscess following renal transplantation, and developed respiratory distress and acute respiratory acidosis, followed by apnea, shortly after the start of his fourth intravenous infusion of polymyxin B. This patient subsequently reported having been unable to breathe or move his arms at the time of the incident. Re-challenge with a polymyxin B infusion in this patient, considered indicated in the setting of recurrent, resistant infection 2 weeks later, was again followed by respiratory arrest 2 hours after the infusion was begun. Both patients recovered from these episodes promptly and completely after intubation, and the authors were unable to identify other potential causes for the sudden respiratory arrests.

COMMENTARY

Polymyxin B and polymyxin E — also known as colistin — are bactericidal polypeptide antibiotics introduced in the late 1940s and formerly widely used in treating gram-negative infections. The drugs have prominent renal and neurological toxicity, however, and with the introduction of gentamycin and other aminoglycosides in the 1960s, their use declined. Over the next 3 decades, the polymyxins were rarely used as other antibiotics effective in treating gram-negative infections became available. However, with the emergence of organisms resistant to newer antimicrobials over the last 10 years, polymyxin B and colistin have seen increasing use, particularly in critically ill patients. In reporting their cases, Wunsch et al also document a steady increase in the use of polymyxin B in their institution since 2000, a 10-fold increase from about one per 1000 hospital admissions to one in 100. The experience at many institutions appears to be similar, particularly referral centers managing immunocompromised patients and individuals with infections due to multidrug-resistant organisms. In addition to intravenous administration, polymyxin B and colistin are increasingly being aerosolized in the treatment of ventilator-associated pneumonia and other serious respiratory infections.

As mentioned, the polymyxins have prominent neurological side effects. These include dizziness, paresthesias, visual disturbances, hearing loss, and neuromuscular blockade, presenting as an acute myasthenia-like syndrome.[1] The latter can cause acute ventilatory failure and respiratory arrest. In what may be the largest reported series of this complication, Lindesmith et al described 11 patients who developed reversible respiratory paralysis after receiving colistin (9 patients) or polymyxin B (2 patients) during the mid-1960s.[2] The drugs had been administered in usual doses, in all but one instance intramuscularly, and respiratory arrest had occurred at widely varying times. Four patients experienced respiratory paralysis 1 to 8 hours after the initial dose, but others had received up to 29 previous doses and the muscle weakness developed at varying periods after a dose. Nearly all of the patients were weaned and extubated within 1-2 days after the event. All 11 of these patients, as well as most of the other reported cases, had underlying renal disease.

This is the first report in decades of neuromuscular blockade from polymyxins causing respiratory arrest. However, the long interval since the last reported cases may well be because of the markedly decreased use of these drugs from the 1970s through the 1990s. With increasing current use of these antibiotics in multiple-drug-resistant infections, however, clinicians should be aware of this

potentially life-threatening adverse effect. Whether neuromuscular blockade can also occur with aerosol administration is uncertain but entirely reasonable, particularly in the presence of underlying renal disease. This complication could be difficult to detect in patients already on mechanical ventilation and receiving polymyxin B or colistin for ventilator-associated pneumonia, but it is at least a theoretical cause for inability to wean in such patients. ■

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ABSTRACT & COMMENTARY

Can Anything Really be Done to Make Intensive Care Units Less Noisy?

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

SYNOPSIS: Best practices that combine work setting noise reduction policies and engineering controls are needed to reduce noise levels in ICUs to the 45-dBA level recommended by the Environmental Protection Agency — roughly equivalent to sound levels in a normal work environment with casual conversation or from a radio playing in the background.

SOURCE: Konkani A, Oakley B. Noise in hospital intensive care units — A critical review of a critical topic. *J Crit Care* 2011;Oct 25 [Epub ahead of print.]

This paper reports on the findings of a systematic literature review on noise and noise-reduction strategies in the intensive care unit (ICU). The goal of the literature review was to determine the best ways to ameliorate sound/noise in the ICU. A search on PubMed and the ISI Web of Knowledge of research articles written in English through May 2011, was conducted using the key words ICU, noise, and hospital. Citations were reviewed and those that examined sources of noise levels, current noise levels in the ICU, and methods to reduce noise were included in the review. Articles were excluded from the review if they measured noise in general hospital areas or overall hospital noise. The search yielded 29 articles, and 10 papers meeting the authors' inclusion criteria were included in the review.

The findings on sound/noise levels in the ICU, noise sources, effects of noise on staff performance, and patient perception of noise were presented in the review paper. Not surprisingly, since 1960, average daytime noise/sound levels in hospitals have increased from 57 dBA to 72 dBA. One of the most significant findings was that night-time noise levels have increased from 42 dBA to 60 dBA, which is about as loud as a noisy lawnmower. Peak sound levels have been measured at > 85 dBC, which is similar to a chainsaw heard 10 meters away. The major sources of ICU noise were staff and visitor conversations; equipment alarms; activities such as opening and closing storage drawers or equipment packages; telephones, pagers and television; and closing doors and falling objects. A full 34% of noise was deemed to be totally avoidable.

Two articles documented the effect of noise on staff, concluding that noise can contribute to nurses' stress, higher heart rates, feelings of irritation, and tension. However, there was no documented association between noise and work performance. Patients reported that mornings are the most annoying and that people talking was the source of noise they found most annoying. The Environmental Protection Agency (EPA) recommends sound levels not exceed 45 dBA, as anything higher than that causes persons to raise their voices when conversing. Unfortunately, none of the studies reviewed found ICU sound levels within this recommended level. The authors noted that there was no consistent measurement of noise among the studies reviewed, as some measured average sound levels at one point in time while others only reported peak sound levels. Some studies reported noise/sound levels at only one point in time whereas others measured sound/noise levels over a number of days. These measurement discrepancies made it a challenge for the authors to draw any meaningful conclusions from their review.

The authors concluded that there is no single solution to reduce noise levels in the ICU. Efforts

need to fall into the category of "avoidable" noise levels, such as unnecessary staff conversations outside patient rooms. The authors commented that general behavior modification strategies like enforced "quiet time protocols" and simple low-cost environmental modifications on doors can be helpful in reducing noise in the ICU.

COMMENTARY

Given the high-tech, high-demand, 24/7 nature of the environment, it is not surprising that ICUs are noisy, which can be a source of annoyance for patients. Noisy environments can impede efficient work if crucial conversations cannot be heard due to excessive background sounds in the environment. Can a less noisy ICU environment be attained without sacrificing patient safety given the demands for care delivery in the sometimes chaotic environment? For the health of patients and staff, the response should be, "We need to try and reduce those avoidable sources of noise in the ICU."

Equipment and monitoring devices will need to alarm. The review by Konkani and Oakley provided several best practices that can be tailored by individual ICUs to reduce annoying sound levels on their respective units. Suggestions include simple, low-tech interventions such as staff education on the adverse effects of noise and those areas patients find the most annoying (i.e., unnecessary, loud staff conversations), quiet-time protocols tailored to individual ICUs, and fixing noisy doors and other pieces of equipment. While the EPA ideal sound limit may not be consistently achievable, there is room for improvement by all clinicians to reduce unnecessary noise in their work environments. ■

ABSTRACT & COMMENTARY

Neuroprognostication in Patients Receiving Therapeutic Hypothermia Following Cardiac Arrest

By David J. Pierson, MD, Editor

SYNOPSIS: Although current guidelines recommend delaying neuroprognostication during therapeutic hypothermia following resuscitation from cardiac arrest, this review of 55 consecutive patients so managed found that a "poor prognosis" designation was arrived at during the hypothermia period in most of them, including six patients who were eventually discharged with a favorable neurologic outlook.

SOURCE: Perman SM, et al. Timing of neuroprognostication in postcardiac arrest therapeutic hypothermia. *Crit Care Med* 2012;40:719-724.

Therapeutic hypothermia (TH) has been widely adopted as a management strategy for patients who remain comatose after return of spontaneous circulation following cardiac arrest, as the only therapeutic intervention shown to favorably influence neurologic outcomes. Because sedation and paralysis are used, and because hypothermia itself depresses neurologic function, current guidelines recommend deferring neuroprognostication until the TH period is completed. In this retrospective review of patients managed with post-cardiac arrest TH in the medical and cardiac ICUs of two University of Pennsylvania hospitals, the authors sought to determine when neuroprognostication took place, how it was done, and what the patient outcomes were.

During the 3.5-year period covered by the study, TH was carried out by means of a protocol. Adult patients who had return of spontaneous circulation following cardiopulmonary resuscitation after primary cardiac arrest and whose Glasgow Coma Scale scores were less than 6 were included, so long as they did not have do-not-resuscitate status or another specific contraindication. Hypothermia (32-34° C) was induced using cold intravenous saline and external cooling body wraps, and was maintained for 24 hours once the target temperature was attained. Active rewarming at 0.25-0.50° C/h was then undertaken. Sedating and paralyzing agents were used throughout the TH period, the latter being discontinued once normothermia was reached. For this study, the "intra-TH" period was defined as extending from resuscitation through 15 hours following attainment of normothermia. Patients who survived to discharge were designated according to cerebral performance category as good (full function), moderate cerebral disability (disabled but independent), severe cerebral disability (conscious but disabled and dependent), coma/vegetative state (unconscious), or dead or brain dead.

Of 55 patients who initially met entry criteria and whose charts were reviewed, six were excluded

for various a priori reasons, leaving 49 patients (59% male, mean age 56 years). Of these, 28/49 (57%) had documentation of an "intra-TH" poor prognosis in the chart. Documentation occurred prior to achievement of target hypothermia in five patients, during the 24-hour hypothermia period in eight, during rewarming in five, and within the first 15 hours after rewarming in 10. Of the 28 patients assigned a poor prognosis during the TH protocol, 18 (64%) were still receiving sedation and paralytic drugs at the time. Neurology consultation was obtained in 21 of the 28 "poor prognosis" patients, 24 of whom also underwent head computed tomography. Most of the "poor prognosis" designations were assigned by the primary managing team, while the neurology consultant advised waiting until post-TH for prognostication in 43% of instances. Most of the patients assigned an "intra-TH" poor prognosis had a do-not-resuscitate order signed within 48 hours thereafter. Of the 28 patients given an "intra-TH" poor prognosis, 20 (71%) did not survive to discharge, while six (21%) of them were eventually discharged with a cerebral performance score of "good."

COMMENTARY

This study found that, in the authors' institution, patients managed with post-arrest TH were often assigned a poor prognosis before completion of the TH regimen, which included sedation and muscle relaxation as part of the protocol. The timing and mechanism of prognostication varied greatly. As the authors point out, further research is clearly needed to determine how best to evaluate the neurological prognosis in patients treated with TH.

In addition to anoxic brain injury, which is the primary target for neurologic assessment following cardiac arrest, sedatives, and paralytics, the effects of hypothermia on their metabolism and clearance, and the hypothermia itself may all contribute to assignment of an inappropriately poor prognosis. The fact that several patients who were discharged in good neurologic condition were initially assigned a poor prognosis prior to completion of the TH protocol emphasizes the importance of not concluding too hastily that the patient has little or no chance of meaningful recovery in the context of TH and its associated interventions. ■

CME/CNE Questions

1. Which of the following is true based on the findings from the Swiss study?

a. High stress and high burnout risk are always associated with one another.
b. A higher proportion of female ICU nurses can decrease risk for burnout.
c. Physicians across all ICU settings have the highest risk for burnout.
d. ICU staff in community-based ICUs have the highest risk for burnout.

2. Aerosolized antibiotics have been shown to:

a. kill bacteria in the airways.
b. prevent ventilator-associated pneumonia.
c. cure ventilator-associated pneumonia.
d. All of the above

3. Which of the following is most likely to predispose patients to neuromuscular blockade associated with polymyxin therapy?

a. Penicillin allergy
b. Underlying renal insufficiency
c. Underlying liver disease
d. Concomitant use of aminoglycosides

4. The single most effective strategy for reducing noise in the ICU is:

a. turning pagers to vibrate mode.
b. immediate silencing of alarms.
c. reprimanding staff if they are speaking too loudly.
d. None of the above

5. Which of the following components of a therapeutic hypothermia protocol for managing post-arrest patients could interfere with accurate neuroprognostication during the hypothermia period?

a. Sedatives
b. Paralytic agents
c. Hypothermia
d. All 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.

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.*

Statins and the Risk of Diabetes

In this issue: Statins and diabetes risk; new treatment guideline for diabetes; new pertussis vaccine recommendation; antibiotics and rhinosinusitis; fluoroquinolones and cystitis; and FDA actions.

Do statins increase the risk of diabetes?

Studies have suggested that statins may increase the risk of diabetes in the elderly, women, and Asians. A new study reviews data from the 162,000 postmenopausal women enrolled in the Women's Health Initiative to investigate whether the incidence of new onset diabetes mellitus (DM) is associated with statin use among these women. This study reviewed records from women who were enrolled between 1993 and 1998 through 2005. More than 7% of the women in the study reported taking statins. Statin use at baseline was associated with an increased risk of DM (hazard ratio, 1.71; 95% confidence interval, 1.61-1.81). This association remained after adjusting for other potential confounders, including obesity, and was observed for all types of statin medications. The authors conclude that statin medication use in postmenopausal woman is associated with an increased risk for DM and that this may be a medication class effect (*Arch Intern Med* 2012;172:144-152). As pointed out in a brief comment in the same issue, observational data are potentially susceptible to "bias (confounding) by indication." In other words, women who would be prescribed statins may be inherently at risk for DM. This study did a good job of evaluating women with and without a history of cardiovascular disease and found that there was still an increased risk of DM. This finding "may have important implications for the balance of risk and benefit of statins in the setting of primary prevention in which previous meta-analyses show no benefit on all-cause mortality." The FDA has issued a new warning about statins and the risk of diabetes (see FDA actions). ■

Oral medications for diabetes

The American College of Physicians has published a new guideline for the "Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus" in the February 21 issue of the *Annals of Internal Medicine*. The guideline suggests that if diet, exercise, and weight loss fail to improve hyperglycemia, oral drug therapy should be initiated. Most diabetes medicines lower HbA_{1c} levels to a similar degree, and none of the medications have compelling outcomes data to suggest one class is superior to another class with regard to cardiovascular or all-cause mortality. But metformin "was more effective than other medications as monotherapy as well as when used in combination therapy with another agent for reducing HbA_{1c} levels, body weight, and plasma lipid levels (in most cases)." Therefore, the guideline recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy for most patients with type 2 diabetes. Metformin is effective at reducing glycemic levels and is not associated with weight gain. Additionally, the drug helps reduce LDL cholesterol and triglyceride levels. Metformin is contraindicated in patients with impaired kidney function, decreased tissue perfusion or hemodynamic instability, liver disease, alcohol abuse, heart

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failure, and any conditions that might lead to lactic acidosis. For patients with persistent hyperglycemia despite metformin, a second drug should be added. No good evidence supports one combination over another. Sulfonylureas have a higher risk for hypoglycemia and thiazolidinediones are associated with an increased risk for heart failure. There are no specific recommendations for the use of the glinides (nateglinide or repaglinide) or the DPP-4 inhibitors (linagliptin, saxagliptin, or sitgliptin). The guideline does not make a recommendation for combinations of more than two oral agents. Injectables, such as the various insulins and GLP-1 analogs, were not addressed in the guideline. (*Ann Intern Med* 2012; 156:218-231). ■

New recommendation for Tdap vaccine

The Advisory Committee on Immunization Practices, a division of the Centers for Disease Control and Prevention, is recommending that all adults get immunized against pertussis (whooping cough). Previously the committee had recommended that only adults who spend time around infants or young children should be immunized. The goal of the expanded recommendation is to prevent teenagers and adults from spreading the disease to infants. In 2010, California experienced a pertussis outbreak that infected 9000 people and resulted in 10 infant fatalities. The adult vaccine combines tetanus, diphtheria, and acellular pertussis (Tdap). ■

Antibiotics not needed for rhinosinusitis

Physicians now have more ammunition for not treating patients with acute rhinosinusitis with antibiotics, based on the results of a new study that shows amoxicillin is of no benefit in these patients. Researchers at Washington University in St. Louis randomized 166 adults with uncomplicated, acute rhinosinusitis to a 10-day course of amoxicillin 500 mg three times a day or matching placebo. The main outcome (change in the Sinonasal Outcome Test) was not significantly different between the two groups at day 3 or day 10. There was a slight improvement in the antibiotic group at day 7. The authors conclude that "treatment with amoxicillin for 10 days offers little clinical benefit for patients clinically diagnosed with uncomplicated acute rhinosinusitis." Patients with symptoms indicative of serious complications were excluded from the trial (*JAMA* 2012;307:685-692). ■

Fluoroquinolones for cystitis

Cefpodoxime is inferior to ciprofloxacin for short-course treatment of acute uncomplicated cystitis in women, according to new study. In a randomized, double-blind trial, 300 women ages 18-55 with uncomplicated cystitis were randomized to ciprofloxacin 250 mg orally twice daily for 3 days or cefpodoxime 100 mg twice daily for 3 days. The overall clinical cure rate with the intent-to-treat approach in which patients lost to follow-up were considered as having a clinical cure was 93% for ciprofloxacin compared to 82% for cefpodoxime. For the intent-to-treat approach in which patients lost to follow-up were considered as not having responded to treatment, the clinical cure rate was 83% for ciprofloxacin compared to 71% for cefpodoxime. The microbiological cure rate was 96% for ciprofloxacin compared with 81% for cefpodoxime. At follow-up, 16% of women in the ciprofloxacin group had vaginal *Escherichia coli* colonization compared with 40% in the cefpodoxime group. The authors conclude that cefpodoxime did not meet criteria for non-inferiority to ciprofloxacin for treating uncomplicated cystitis in women (*JAMA* 2012;307:583-589). The study is somewhat disappointing given the increasing rates of fluoroquinolone resistance in the community and the need for effective alternatives. ■

FDA actions

The FDA has issued a new warning and is requiring label changes to all statins regarding the risk of elevated blood sugar and reversible cognitive changes. The agency is making these changes after a comprehensive review of multiple studies that show increases in blood sugar associated with the drugs. A separate labeling change warns that cognitive effects have been reported with statin use, including transient memory loss and confusion — symptoms that are reversible with stopping the medication. There is no evidence that statins are associated with long-term cognitive changes or dementia. Statins affected by these warnings include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. In a separate warning, lovastatin is now contraindicated with strong CYP3A4 inhibitors, such as itraconazole and erythromycin. This is a similar warning to that issued for simvastatin in 2011.

In one of the strangest stories of the year, the FDA is warning oncologists that a counterfeit version of bevacizumab (Avastin) may have been purchased and used by some medical practices in the United States. The counterfeit version does not contain any active drug and may have resulted in patients not receiving needed therapy. Counterfeit bevacizumab was purchased from a foreign supplier known as Quality Specialty Products or Montana Health Care Solutions. The FDA is recommending that physicians stop using bevacizumab purchased from the suppliers and call the FDA immediately. ■