CRITICAL CARE ALERT®

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

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INSIDE

Hospital Mortality with Different Days and Times of ICU Admission: Up and Running 24/7

ABSTRACT & COMMENTARY

Synopsis: *Among 56,250 British ICU patients, hospital mortality rates were higher among those admitted on the weekend or at night, but the differences disappeared when confounding by illness severity and other aspects of case mix were eliminated.*

Source: Wunsch H, et al. *Intensive Care Med*. 2004:30:895-901.

Wunsch and colleagues examined data from 75,621 consecutive admissions to 102 ICUs in England, Wales, and Northern Ireland to determine whether the day of the week or the time of the day patients were admitted affected hospital mortality. They excluded patients who spent less than 8 hours in the ICU, were younger than 16, were admitted after burns or cardiac surgery, were transferred from another ICU, or had insufficient data for determination of APACHE II scores. This left 56,250 patients for evaluation. The 24-hour day was divided into day (8 AM-6 PM), evening (6 PM-midnight) and night (midnight-8 AM) periods, to correspond with usual working schedules in ICUs in the United Kingdom.

There were almost twice as many ICU admissions on any given weekday as on Saturday or Sunday, mainly reflecting differences in scheduled surgery. In addition, substantially more patients were admitted during the day than in the evening, and during the evening than at night. Patients admitted on weekends had higher crude hospital mortality than patients admitted mid-week (Saturday vs weekends, 35% vs 27%; crude odds ratio, 1.41; 95% confidence interval 1.32-1.52). Night admissions were also associated with higher mortality compared with daytime admissions (crude mortality 34% vs 27%; OR, 1.43; 95% CI, 1.37-1.51). The differences diminished in each instance when adjusted using the overall UK APACHE II model, but remained statistically significant. However, when adjustment was carried out using individual components of the APACHE II model, the differences disappeared for both day of week and time of day. Thus, after appropriate adjustment for case mix, the day of the week, and time of day patients were admitted to the ICU were

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not associated with significant differences in hospital mortality.

COMMENT BY DAVID J. PIERSON, MD

Patients admitted to the ICU on weekends, or at night regardless of the day of the week, are more likely to die in the hospital than patients admitted during the week or during the day. However, interpreting these differences is tricky. It is tempting to assume that fewer physicians, nurses, and support personnel are around at night and on the weekend, that diagnostic and other procedures would be less available, and that these things might lead to worse patient outcomes. But such does not turn out to be the case, at least in this study. Instead, patients admitted during the week and during the day tended to be postoperative and other elective admissions, with less severity of illness and less likelihood of dying in the hospital. Patients admitted on Saturday or Sunday, or in the middle of the night on any day of the week, are sicker and thus more likely to die.

There are limitations to this study with respect to the application of its findings to your practice and mine. It reflects what happens in ICUs in England, Wales, and Northern Ireland, which differs in important ways from critical care in North America. It does not include patients readmitted to the ICU (bounce-backs). And it does not sort out what happens on the ward after ICU discharge. Nonetheless, the findings of Wunsch et al support the concept that staffing in ICUs tends to be more constant around the clock and throughout the week than that on the general inpatient ward. Whether the ICUs involved were "open" or "closed," and the extent to which care was provided by trained and/or board-certified intensivists, both of which have been shown to affect patient outcomes,[1,2] is also not specified in the paper. However, this study provides reassurance that concerns about the quality of care at different times of the 24-hour day and on different days of the week may be unfounded in the 24/7 environment of the ICU. ■

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Decision Analysis of Treatment Strategies for Ventilator-Associated Pneumonia

ABSTRACT & COMMENTARY

Synopsis: *In late-onset VAP, survival improved and costs decreased using initial coverage with 3 antibiotics. Mini-BAL did not improve survival, but decreased costs and antibiotic usage.*

Source: Ost DE, et al. *Am J Respir Crit Care Med*. 2003;168:1060-1067.

THE OPTIMAL STRATEGY FOR MANAGING VENTILATOR-associated pneumonia (VAP) remains controversial. To clarify the tradeoffs, Ost and colleagues developed a decision analysis model to simultaneously examine outcomes of 16 diagnostic and treatment strategies. The subjects were a cohort of immunocompetent critically ill patients with the following characteristics: 1) intubated for 7 days; 2) evidence of late-onset VAP

based on Centers for Disease Control and Prevention (CDC) criteria of fever, purulent secretions, leukocytosis and radiographic infiltrates; and 3) estimated mortality of 20%. Five assumptions were built into the model. First, antibiotics would be chosen based on American Thoracic Society guidelines adapted to local formularies and ICU pathways. Second, antibiotics would be given immediately after the patient met CDC criteria for VAP, and continued until diagnostic test results returned. Third, antibiotics would be adjusted to cover any identified pathogens and unnecessary antibiotics discontinued. Fourth, if all cultures were negative and the patient had ongoing severe sepsis or was unstable, antibiotics would be continued. Fifth, if the patient was stable, antibiotics would be discontinued.

There were 4 treatment strategies (zero, 1, 2, or 3 antibiotics) and 4 diagnostic strategies: 1) no diagnostic testing; 2) endotracheal tube aspirate quantitative cultures, 3) bronchoscopic cultures; or 4) non bronchoscopic mini-BAL quantitative cultures. Initial coverage with 3 antibiotics was better than expectant management (zero antibiotics) or 1 or 2 antibiotics, leading to both improved survival (54% vs 66%) and decreased costs ($55,447 vs $41,483 per survivor). Testing with mini-BAL did not improve survival but did decrease costs ($41,483 vs $39,967) and antibiotic use (63 vs 39 antibiotic days per survivor). From the perspective of minimizing cost, minimizing antibiotic use, and maximizing survival, the best strategy was 3 antibiotics with mini-BAL.

COMMENT BY LESLIE A. HOFFMAN, PhD, RN

VAP frequently complicates the course of critically ill patients on mechanical ventilation and is associated with a high mortality. Survival is highly dependent on selecting the appropriate initial antibiotic. Although diagnostic tests often lead to a change in therapy, it requires time to obtain the results, and when they become available it may be too late to alter survival. Therefore, many advocate that high-risk populations be initially treated with broad-spectrum antibiotic therapy. The decision model that Ost et al used was developed from a literature search that returned 555 citations, later reduced to 111 articles based on search criteria. The final model analyzed multiple outcomes including survival, cost, cost per survivor, antibiotic use, antibiotic use per survivor, and the combined perspective of financial and antibiotic cost per survivor. From a combined perspective, a 3 antibiotic plus mini-BAL strategy was superior to all 1 and 2 antibiotic strategies, irrespective of diagnostic technique, in terms of minimizing antibiotic use and financial cost per additional survivor. Diagnostic testing alone had little impact on survival, but was cost-effective because decreased unnecessary antibiotic usage.

Often overlooked as a technique, decision analysis offers a useful perspective on complex management challenges, such as those presented by VAP. The technique allows simultaneous testing of more options than is possible in a clinical trial. It is ideally suited to situations with multiple clinical options, a large literature base, and continuing uncertainty about the best approach. Decision analysis is subject to accuracy of the basic assumptions used to build the analytic model and unable to project the consequences of future events, such as the emergence of antibiotic resistance and the consequence of this outcome. Given these limitations, it provides an interesting approach to the analysis of a very complex problem. ■

The Forgotten Art and Science of Hand Hygiene

ABSTRACT & COMMENTARY

Synopsis: *This concise review makes a compelling case for a change in the healthcare worker's behavior. Helpful hints including increasing the use of alcohol-based formulations to reduce the time constrains are provided throughout the article.*

Source: Trampuz A, et al. *Mayo Clin Proc*. 2004;79: 109-116.

Nosocomial infections have become the Achilles heel for the healthcare industry. Numerous scientific and lay public articles cite the increasing frequency of nosocomial infections. The problem and the solution, however, have been known for a long time. As Trampuz and colleagues review in the article, Semmelweis proposed more than 150 years ago that the results of hospital care (in that case, a maternity ward) could be dramatically improved by using careful hand washing with a 4% solution of chlorinated lime. The microbiology of skin flora was not well defined at that time. It is now known that there are normal resident flora, a group of organisms (coagulase-negative staphylococci, corynebacteria, etc) that colonize the deeper layers of skin. These organisms are hard to get rid of by hand washing, but they prevent colonization of deeper tissues by more virulent or pathogenic microorganisms. Transient flora, a group of organisms that colonize more

superficial layers of skin, are responsible for most health care related infections and the spread of antimicrobial resistance. This group includes organisms such as *Staphylococcus aureus*, Gram-negative bacilli and *Candida* species amongst them.

There are 2 different methods for hand hygiene. In the traditional method, hands should be washed thoroughly with soap and water for at least one minute, and a disposable towel should be used to dry hands and perhaps to close the faucet. With mechanical friction, microorganisms are removed from the skin and hair follicles. It is now thought that such careful hand washing is essential only when hands are soiled with body fluids. In general, it takes approximately 2 minutes to complete such a hand-washing task. It is estimated that if good hand washing is performed for 3 episodes per hour, nurses may have to spend about one fifth of their time washing hands during an 8-hour shift.

The emerging alternative is alcohol-based hand rubbing solutions and gels. The use of alcohol-based hand rubs is being recommended in most other circumstances in which hand hygiene is required. Alcohol has bactericidal properties that most hand washing soaps do not have. A much shorter time is needed to achieve a significant reduction in bacterial colony counts when using alcohol based hand rubs. These products also have some important virucidal activity. Also, alcohol-based hand rubs can be used while traveling between the points of contact with the patient to other areas of work, or even while traveling to the next patient.

The use of powder-free gloves reduces the need for hand washing; however, it does not obviate the need for hand hygiene. Alcohol-based hand rubs should be used after removing gloves. Needless to say, a new pair of gloves should be used for each patient contact. Trampuz et al suggest that alcohol-based hand rubs are also easier on hands than repeated washing with soap and water. Alcohol rubs should be stored away from high temperatures. At present, it is thought that the emergence of microbial resistance is less likely against alcohol-based formulations. It is important to remember that alcohol based hand rubs are to be used only when direct contamination of hands with body fluids has not occurred. The risk of wearing rings and artificial fingernails, which may act as harbingers of bacterial contamination, is highlighted in the article. Based on the available scientific evidence, Trampuz et al suggest that alcohol-based hand rubs should be used liberally and regularly to reduce nosocomial infections.

COMMENT BY UDAY B. NANAVATY, MD

Good hand hygiene by health care personnel is vital to reduce nosocomial infection rates. Maintaining good hand hygiene is a moral duty as well. Unfortunately, routine compliance rates with good hand hygiene are ridiculously low. Most studies suggest that hand hygiene compliance rates in hospital settings are between 20 to 40%. Hospital and system wide projects including education and surveillance by camera and other electronic devices improve compliance rates. Unfortunately, even with these expensive interventions, compliance rates approach only about 70% at best. Imagine if restaurant workers had hand hygiene rates of 40% or less! The country would be reeling with gastrointestinal morbidity and the food industry would be out of business. Before the bugs on our hands get us out of our business, it is important that we get rid of them, as best and as frequently as possible. ■

Special Feature

Hospital Mortality and ICU-Acquired Infection

By Jun Takezawa, MD

Risk Factors for the ICU-Acquired Infection

SEVERAL FACTORS ARE CONSIDERED TO BE ASSOCIATED with the development of nosocomial infections in the ICU (*see Table 1*). Among them, indwelling devices that directly contact the blood and mucosal membrane such as the central venous catheter, urinary tract catheter and endotracheal tube are considered to be the most responsible risk factors in the development of nosocomial infections. These devices are placed into the patient and manipulated by the medical practitioner, and referred to as external risk factors. These device-related external risk factors are associated with the length of

Table 1

Risk Factors for the Development of ICU-Acquired Infection

Risk	
Internal risk	Age, Gender, Original disease, Severity of illness, Comorbidity
External risk	• Device: Central venous catheter, Ventilator, Urinary tract catheter • Drugs: Antibiotics, immunosuppressives • Intervention/Operation Infection Control: hygienic procedure, Manual, Surveillance, Education • Therapeutic and nursing capability Monitoring Organizational characteristics: Open/Closed, Staffing

time the device remains in the patient. However, they are also associated with the frequency of manipulations of the device, such as bolus injection and exchanges of the infusion bottles and lines, especially for indwelling central venous catheters. In addition to the length and/or frequency of exposure to the risk device, the hygienic management, behavior pattern of antibiotic administration, level of infection control, and patient management (therapeutic, nursing, monitoring, staffing, and organizational) also play a role, along with the external risk factors, in the development of nosocomial infections. On the other hand, the risk factor inherent to the patient is referred as an internal risk factor. Such internal risk factors include age, gender, severity of illness, immunological competence, comorbidity, and so on.

In order to accomplish an inter-institutional comparison on infection rate, both internal and external risk factors should be adjusted. Among the risk factors indicated above, the internal risk may be adjusted by using measures of illness severity such as the APACHE score, but the external risk can only be adjusted by device utilization days. Therefore, the difference in infection rates adjusted by the above two risk factors is attributable to the other remaining external risk factors, most of which are related to both the patient and ICU management.

Purpose of Surveillance

The purpose of the surveillance is 1) to identify the outbreak of nosocomial infections (although outbreaks are usually readily noticed by ICU practitioners); 2) to provide data on infection control to be pursued by ICU practitioners in quality improvement; 3) to obtain the incidence and prevalence of nosocomial infections from the viewpoint of public health; and 4) to provide for inter-institutional comparisons with respect to preventive programs and practice in managing nosocomial infections by the respective institutions.

When surveillance is conducted for the purpose of inter-institutional comparison of the nosocomial infection rate, all risk factors for ICU-acquired infections should be adjusted. The National Nosocomial Infection Surveillance (NNIS) system, which is run by the US Centers for Disease Control and Prevention (CDC), apparently uses only external risk-adjusted infection rates for inter-institutional comparison. The severity of illness in NNIS employs the device utilization ratio, which is calculated as the length of days the devices are in use divided by the number of patient days. Use of this ratio is based on the assumption that the severely ill patient requires long-term use of the devices for efficient and safer management. However, the device utilization ratio, as well as APACHE and SAPS scoring systems, which are frequently used for stratifying severity of illness in terms of mortality, are not proved to be related to the acquisition of nosocomial infections in the ICU, in part because the most severely ill patients die quickly. Therefore, patients who die within 24 hours after admission to the ICU are excluded for inter-hospital comparison of the performance of ICUs.

In the NNIS system, risk-adjusted infection rate is compared within the individual types of ICUs, such as neuro-ICU, coronary-CU, and surgical-ICU, which implies that the original disease is taken into account as an internal risk factor. However, because all the internal risk factors are not included in the NNIS system, the exact effect of ICU-acquired infections on

Table 2

The Effect of ICU-Acquired Infections on Hospital Mortality

	# of pts	drug-susceptible	drug-resistant	*P*-value
Ventilator associated pneumonia				
Alive	5756	230	84	—
Dead	1101	140	63	—
% of dead	16.1	37.8	42.9	< 0.001
Urinary tract infection				
Alive	6042	25	3	—
Dead	1289	15	0	—
% of dead	17.6	37.5	0	< 0.01
Catheter-related bloodstream infections				
Alive	6049	18	3	—
Dead	1277	18	3	—
% of dead	17.4	50.0	50.0	< 0.001
Sepsis				
Alive	6038	24	8	—
Dead	1230	52	22	—
% of dead	16.9	68.4	73.3	< 0.001
Surgical site infection				
Alive	6009	44	17	—
Dead	1263	28	13	—
% of dead	17.4	38.9	43.3	< 0.001

The total numbers of the patients are different among the ICU-acquired infections because of a lack of available data.

Adapted from: Suka M, et al. Environ Health Prev Med. (in press).

hospital mortality is unknown.

ICU-Acquired Infection and Hospital Mortality

Although the incidence of ICU-acquired infection is recognized as an important determinant of outcome for ICU patients, the precise relationship between ICU-acquired infection and hospital mortality has yet to be defined. A 1-day point-prevalence study for 1417 ICUs from 17 western European countries, called the EPIC study, showed that a prevalence rate of infection in ICUs was 44.8%, and almost half of the infections were acquired in the ICU (20.6%).[1] The EPIC study showed that the impact of ICU-acquired infection on ICU mortality might vary according to the types of infection; the highest odds ratio was found in sepsis (3.50), followed by pneumonia (1.91) and blood stream infection (1.73). Moreover, several studies showed that inadequate treatment of infections might be an important determinant of hospital mortality.[2,3]

There have been few cohort studies in which the patients discharged from the ICU were followed up until hospital discharge. One cohort study involving 28 ICUs from 8 countries showed that the hospital mortality rate in patients with ICU-acquired infection was 32.1%, compared with 12.1% in patients without ICU-acquired infections.[4] These rates were crude and not adjusted for potential confounders (eg, age, underlying disease, and severity of illness).[5,6] Moreover, the impact of ICU-acquired infection on hospital mortality might be affected by drug-resistant pathogens.[7]

Table 3

Factors Associated with Hospital Mortality[8]

	HR	95% CI (lower-upper)
Sex (vs Man)	1.06	(0.95-1.19)
Age (years)*		
45-54	1.19	(0.94-1.49)
55-64	1.06	(0.85-1.31)
65-74	1.11	(0.91-1.35)
75-	1.33	(1.09-1.62)
APACHE II score**		
11-15	1.68	(1.37-2.06)
16-20	2.66	(2.18-3.25)
21-25	4.28	(3.48-5.27)
26-30	5.92	(4.76-7.37)
31-	7.88	(6.23-9.97)
Operation		
Elective	0.29	(0.24-0.34)
Urgent	0.68	(0.59-0.77)
Ventilator	1.78-	(1.49-2.12)
Urinary catheter	0.70	(0.54-0.90)
CV catheter	1.23	(1.04-1.47)
ICU-acquired infection		
Drug-susceptible	1.11	(0.94-1.31)
Drug-resistant	1.42	(1.15-1.77)

HR = hazard ratio, CI = confidence interval,

* = compared to 16-44 years, ** = compared to 0-10.

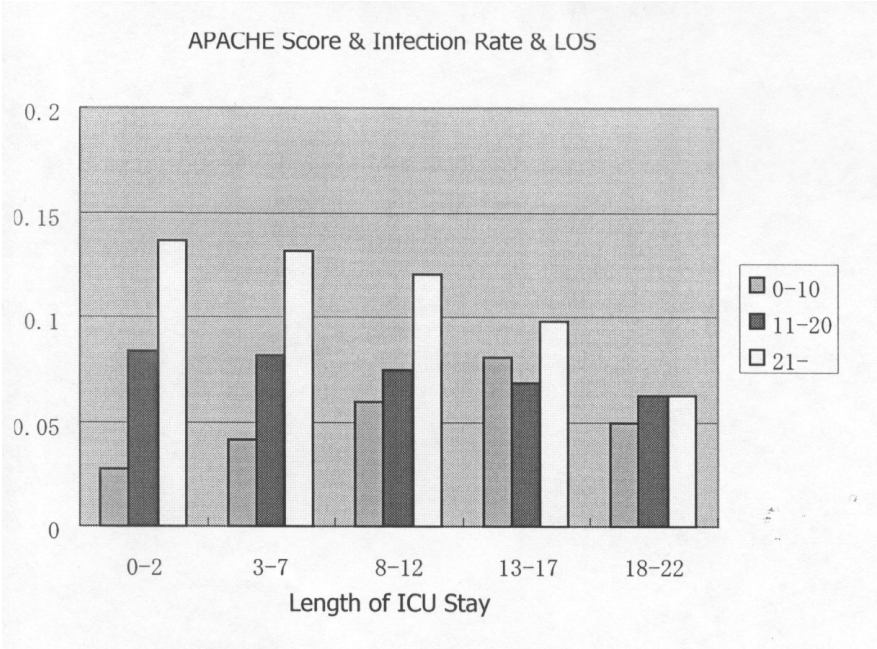
JANIS Database Analysis

The Japanese Nosocomial Infection Surveillance (JANIS) system, started in 2000 by the Ministry of Health, Labor, and Welfare, collected data on 7374 patients admitted to the 34 participating ICUs between July 2000 and May 2002. The data used for their analysis is from patients discharged from ICU who were aged 16 years or older, whose ICU stay was from 48 to 1000 hours, who had not transferred to another ICU, and who had no infection diagnosed within 2 days after ICU admission. These patients were followed up until hospital discharge or the 180th day after ICU discharge. Adjusted hazard ratios (HRs) with their 95% confidence intervals (CIs) for hospital mortality were calculated using a Cox's proportional hazard model.[8]

Table 2 shows the effect of ICU-acquired infections on hospital mortality in the JANIS data. Overall, 678 patients (9.2%) had at least one ICU-acquired infection. Drug-resistant pathogens were detected in 201 patients. The most common ICU-acquired infections were ventilator-associated pneumonia (VAP, 517 cases, 64%), followed by sepsis (106 cases, 13%), surgical site infections (102 cases, 13%), urinary catheter-related infections (43 cases, 5%), and catheter-related blood stream infections (42 cases, 5%). All types of ICU-acquired infections were significantly associated with hospital mortality. Compared to patients who had no infection, those infected by drug-susceptible and drug-resistant pathogens had significantly higher rates of hospital mortality (shown as *P* value). The mortality rate with drug-resistant pathogens was higher than that with drug-susceptible pathogens, except for urinary tract infection in which few cases of drug-resistant pathogens were observed (not shown here).

Table 3 shows hazard ratios and their corresponding 95% confidence intervals for hospital mortality. After adjusting for sex, age, and APACHE II score, significantly higher HR for hospital mortality was found in respirator, central venous catheter, and ICU-acquired infection caused by drug-resistant pathogens, with significantly lower HR for elective and urgent operation and

Figure



Adapted from: Suka M, et al. Environ Health Prev Med. (In Press).

urinary catheter. The impact of ICU-acquired infection on hospital mortality was different between drug-sensitive pathogens (HR, 1.11; 95% CI, 0.94-1.31) and drug-resistant pathogens (HR, 1.42; 95% CI, 1.15-1.77).

Severity of Illness and ICU-Acquired Infection

It is still unknown whether severity of illness is related to the development of ICU-acquired infections. When the incidence of ICU-acquired infections is evaluated in terms of severity of illness along with the ICU stay, the incidence of ICU-acquired infections along the ICU days is different among the severity of illness (*see Figure*).[8] In the most severely ill patients, the incidence of ICU-acquired infections is highest in the early phase of ICU admission, while in the least severely ill patients, the incidence of ICU-acquired infections is low in the early phase, but is increased along the ICU stay up to 20 days. In moderately ill patients, the incidence ICU-acquired infections do not change markedly along the ICU stay. Therefore, severity affects the incidence ICU-acquired infections; however, this effect on ICU-acquired infections is inversed depending on the severity of illness. In this sense, the general concept that the more severely ill the patients are, the more they develop nosocomial infections is not verified.

Performance Measurement of ICUS

Performance of the ICU is usually measured in terms of outcome and process. The incidence of ICU-acquired infection is classified as the process evaluation, while hospital mortality is classified as outcome evaluation. However, the sensitivity of the outcome measurement by hospital mortality is low, because the relatively small numbers of the patients die during the hospital admission. Additionally, so many confounders are associated with the hospital mortality of ICU patients, which include original disease, severity of illness, development of complications (medical errors and nosocomial infections), patient management (therapeutic, nursing and monitoring capabilities), demographical characteristics (age and gender of the patients), and organizational characteristics (open or closed ICU, staffing). Because the magnitude of contribution of those confounders on mortality is not prioritized, it is extremely difficult to evaluate ICU performance on an individual confounder (risk factor) basis. It is of most importance to develop a new statistical model to measure both overall and individual confounder-based performance of the ICU. The ICU-acquired infection is one of the most important confounders (risk factors) for the measurement of ICU performance. It is concluded that performance of the ICU is improved by improving the individual risk factors; however, it is extremely difficult to achieve it by just monitoring the overall risk-adjusted hospital mortality of the patients discharged from the ICU. ■

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CME / CE Questions

8. **Patients admitted to the ICU at night or on a weekend are more likely to die during that hospitalization because:**
   a. board-certified intensivists are less likely to be immediately available then;
   b. staffing of ICU nurses and respiratory therapists is less;
   c. important diagnostic tests and consultations are less immediately available;
   d. all of the above
   e. their severity of illness is greater

9. **Which of the following statements is true about hospital mortality in relation to when patients are admitted to the ICU?**
   a. Mortality is higher in patients admitted at night.
   b. Mortality is higher in patients admitted on weekends.
   c. Both of the above
   d. None of the above

10. **Based on a decision analysis model, the best strategy for managing late onset VAP in patients who had been mechanically ventilated for 7 days was:**
   a. mini-BAL and 2 antibiotic coverage.
   b. bronchoscopy and three antibiotic coverage.
   c. mini-BAL and three antibiotic coverage.
   d. 3 antibiotics, no diagnostic testing.
   e. antibiotics after results of diagnostic tests are available.

11. **As compared to culturing endotracheal aspirates or bronchoscopically obtained bronchoalveolar lavage (BAL) fluid, the non-bronchoscopic mini-BAL technique for diagnosing VAP:**
   a. decreased both costs and antibiotic use.
   b. decreased costs but increased antibiotic use.
   c. increased both costs and antibiotic use.
   d. increased costs but decreased antibiotic use.
   e. had no effect on either cost or antibiotic use.

12. **With the goal of reducing nosocomial infection rate in mind, good hand washing is required. All the following are true about hand washing *except*?**
   a. Good hand washing can be accomplished in 20 seconds with use of bactericidal soaps.
   b. Good hand washing should be followed by drying of hands with disposable towels.
   c. Good hand washing works mostly by the mechanical removal of organisms.
   d. Good hand washing would require at least one minute of hand washing.
   e. All of the above

13. **All the following are advantages of alcohol-based hand rubs *except* which statement?**
   a. They completely eliminate the need for hand washing.
   b. They reduce the time required for hand hygiene in certain situations.
   c. Alcohol-based hand rubs may be more gentle to the skin than soaps.
   d. Alcohol based hand rubs have bactericidal and virucidal properties.

14. **Which of the following are internal (as opposed to external) risk factors for ICU-acquired infection?**
   a. Monitoring
   b. Antibiotics administered
   c. Severity of illness
   d. All of the above
   e. None of the above

Answers: 8 (e); 9 (c); 10(c); 11 (a); 12 (a); 13 (a); 14 (c)

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: **Hyperoxia Ineffective in Preventing Infection**

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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.*

Missing Link Between Vaccines and Diabetes

A large cohort study from Denmark suggests no link between childhood vaccines and type 1 diabetes. The potential for such a link has been of concern for years because of the association between certain infections and the development of type 1 diabetes in children. Epidemiologists also noted that the incidence of type 1 diabetes has increased in developed countries along with a widespread use of vaccines in those countries. Danish researchers studied the records of children born in Denmark between 1990 and 2000, which represented 4,720,517 person-years of follow-up. In the cohort, 681 cases of type 1 diabetes occurred. The rate ratios for developing diabetes among children who received at least 1 vaccine compared to unvaccinated children were: 0.91 for *Haemophilus influenzae* type B vaccine, 1.02 for diphtheria/tetanus/polio vaccine, 0.96 for diphtheria/tetanus/pertussis/polio vaccine, 1.06 for whole cell pertus! sis, 1.14 for measles/mumps/rubella vaccine, and 1.08 for oral polio vaccine. No clusters of diabetes cases were found at any age level. The authors conclude that the data do not support the causal relationship between childhood vaccine and type 1 diabetes (*N Engl J Med*. 2004; 350:1398-1404).

Breast Cancer and the Use of Statins

Adding to the considerable evidence regarding the safety and efficacy of statins, it now appears that statins may slightly reduce the risk of breast cancer. Published in the "Early View" online journal *Cancer*, this case-control study was designed to assess whether statins were associated with an increased risk of breast cancer. At least 1 previous study has suggested an increased risk of breast cancer with statin use. The study looked at 975 women in Washington state who were diagnosed with primary invasive breast carcinoma, and were between 65 and 79 years old at the time of diagnoses. The comparison group was 1007 randomly selected women from the same residence area. Compared with non-users, current users, or ever-users of statins were not found to be at an increased risk for breast carcinoma. And in fact, the odds ratio of statin users was 0.9 compared to non-statin users (95% CI, 0.7-1.2). Long-term statin use of > 5 years was related to an even lower odds ratio of 0.7. The authors conclude that statins are not associated with an increase risk of breast carcinoma, and may in fact impart a reduced risk among long-term users (*Cancer* April 26, 2004).

Warnings Issued for IBS Drugs

Tegaserod (Zelnorm-Novartis), the heavily promoted serotonin 5-HT4 partial agonist for the treatment of irritable bowel syndrome (IBS), is the subject of new warnings by the FDA. The drug is indicated for women with IBS whose pri-

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mary symptom is constipation. The warning is the result of reports of diarrhea leading to hypovolemia, hypotension, and syncope in a small number of patients. There have also been rare cases of bowel ischemia in patients taking tegaserod, although no causal relationship has been found. Novartis has issued a "Dear Doctor" letter regarding the change in labeling dated April 26 (for more information see www.FDA.gov/medwatch). This is the second IBS drug to come under FDA scrutiny. The serotonin 5-HT3 antagonist alosetron (Lotronex-GlaxoSmithKline), for the treatment of IBS in women with severe diarrhea, was briefly withdrawn from the market in June 2002 because of over 80 cases of ischemic colitis associated with use of the drug. Alosetron became available again in December 2002 under a restricted use program.

What is the risk of a re-prescribing penicillin to penicillin allergic patient? The risk may be quite low according to a new study. Researchers looked at a database from the UK General Practice Research Database which included over 3.3 million patients who received penicillin. More than 6000 patients reported an allergy to the initial prescription, however, 48.5% of those patients were given the second prescription for penicillin at least 60 days later. Of those 3014 patients, only 57 (1.89%) had another event after the second prescription. This was much higher than the rate of reactions in patients who had not had an initial reaction (odds ratio, 11.2; [95% CI 8.6-14.6]), however, the absolute rate of reactions in patients who had an initial allergic reaction was quite small (*J Allergy Clin Immunol.*2004:113; 764-770). An accompanying editorial pointed out that even anaphylactic reaction had a low rate of recurrence with repeat exposure (1 out of 16) (*J Allergy Clin Immunol.*2004:113;605-606). And, while no one is recommending rechallenging patients with penicillin allergies, the low rate of repeat reactions is a far cry from the reported 60% rate of previous studies

FDA Actions

The FDA has removed the warning for lactic acidosis from metformin (Glucophage) and metformin extended release (Glucophage XR). Once considered the most serious side effect associated with metformin, a recent meta-analysis showed that there were no reports of lactic acidosis during more than 20,000 patient years use of the drug (*Arch Intern Med.*2003;163:2594-2602).

The FDA has approved apomorphine injection (Apokyn-Bertek) for hypomobility associated with Parkinson's disease. Hypomobility or "off periods" become more frequent with advanced Parkinson's disease and may occur at the end of a dosing interval or may occur spontaneously. A subcutaneous injection of apomorphine is effective for both types of “off periods.” However, because the drug causes severe nausea, it must be taken with an anti-emetic—although, not a 5HT3 antagonist because the combination may cause hypotension and syncope.

Aventis has received approval to market insulin glulisine (Apidra), a new rapid-acting insulin. The drug is a novel recombinant DNA human insulin analogue that is designed to be given 15 minutes before a meal or within 20 minutes after starting a meal. With a rapid onset and short duration of action, it is designed to cover mealtime blood sugar spikes. Aventis is marketing insulin glulisine to be used in combination with insulin glargine (Lantus), the company's long-acting basal insulin preparation.

The FDA has approved changes in prescribing information for finasteride (Proscar-Merck) that include concomitant use of the alpha-blocker doxazosin for the treatment of benign prostatic hyperplasia. Finasteride is a 5-alpha-reductase inhibitor. The combination was recently found to be better than either drug alone in reducing the overall clinical progression of benign prostatic hyperplasia (NEng J Med.2003;349:2387-2398).

Telithromycin (Ketek-Aventis) has been approved by the FDA for marketing for the treatment of community-acquired pneumonia including pneumonia caused by drug-resistant pneumococcus, sinusitis, and acute exacerbations of chronic bronchitis. Telithromycin represents the first of a new class of antibiotics known as ketolides. It is an oral tablet that is given once a day. ■