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INSIDE



## Annie, Annie, Are You OK? Does Anyone Know CPR?

ABSTRACT & COMMENTARY

***Synopsis:*** *This single-center, prospective, observational study of resuscitation for in-hospital cardiac arrest reveals that the performance of cardiopulmonary resuscitation is inconsistent with current guidelines.*

**Source:** Abella BS, et al. *JAMA*. 2005;292(3);305-310.

The study objective was to assess compliance of cardiopulmonary resuscitation (CPR) for in-hospital arrest with national and international guidelines by measuring several surrogate parameters of CPR quality (compression rate, compression depth, ventilation rate, no-flow time). Inpatients older than 18 years of age experiencing cardiorespiratory arrest at the study hospital were eligible. Those having arrest in the emergency department or operating room and those not resuscitated with the study monitor/defibrillator were excluded. The study monitor/defibrillator was modified by Laerdel Medical Corporation to record presence or absence of pulse, rate and depth of chest compressions and rate and volume of ventilations. This device has been tested and validated previously.

Compression rate, compression depth, ventilation rate and no-flow time (time without compressions and thus without blood flow to vital organs) were recorded for the first 5 minutes of CPR. American Heart Association guidelines were used to define expected values (compression rate 100/minute, compression depth 1.5-2.0 inches, ventilation rate 12-16/minute, no-flow time 10 seconds/minute of CPR). A no-flow fraction (NFF, fraction of cardiac arrest time without compressions) was then calculated (expected value 17%). CPR quality parameters were compared for patients who died vs those who had return of spontaneous circulation (ROSC). Standard statistical methods were employed.

Over 16 months, 67 patients were enrolled. Mean age was 62 years. Two-thirds of patients were men and nearly the same number were black. Half (52%) of the cardiac arrests occurred


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in an intensive care unit. The initial rhythm was identified as pulseless electrical activity in 60%, pulseless ventricular fibrillation/tachycardia in 15%, and asystole in 10%. Forty percent of patients had ROSC and 10% survived to hospital discharge. Mean compression rate was < 90/minute 28% of the time and compression depth was < 1.5 inches 37% of the time. Mean ventilation rate was > 20/minute 61% of the time. In regards to ventilation volume, Abella and associates report "[this] did not appear to deviate greatly from physiological ranges." Mean NFF was 24%. No significant associations were seen between these parameters and ROSC.

## COMMENT BY SAADIA R. AKHTAR, MD, MSC

Standardized, internationally accepted adult CPR certification courses and guidelines exist.[1] Nearly every health care professional is required to complete such a course and to maintain CPR certification. Despite this, compliance with guidelines appears to be poor. This report from Abella et al is the latest to demonstrate that compression rate and depth and ventilation rate during real-world in-hospital CPR deviate considerably from recommendations: the ultimate and most important impact of this is prolonged no-flow time. In addition to this report, a recent European observational study of quality of CPR during out-of-hospital arrest (published in the same issue of *JAMA*) found inadequate chest compressions nearly half of the time.[2] Neither of these studies was designed to measure the effect of CPR quality on outcomes. There are no randomized controlled human trials of impact of CPR provision according to guidelines on the outcomes of cardiac arrest. However, it is clear from animal and other observational human studies that providing adequate and continuous compressions and limiting no-flow time significantly improves survival and neurological outcomes.[3] In addition, hyperventilation may worsen survival.[4]

As health care professionals in intensive care medicine, we focus much time and attention on maximizing outcomes by employing sophisticated therapies, technologies and artificial life-support mechanisms for all patients, including those post-cardiorespiratory arrests. This study is an important reminder that without initial effective resuscitation, other interventions may be futile; the quality of CPR we are providing currently must be improved. On a personal and local scale, I recommend sharing these findings, re-training frequently and monitoring resuscitation events at our own institutions for compliance with guidelines: I believe that if we start by focusing on one thing, the essence of continuous and adequate compressions, we can make an impact. On a larger scale, future studies must eval uate what optimal CPR is, how it impacts outcomes and how to best teach and implement it. ■

## References


1. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. *Circulation*. 2000;102 (Suppl):I1-I403.
2. Lars W, et al. *JAMA*. 2005;292(3):299-305.
3. Gallagher EJ, et al. *JAMA*. 1995:274(24):1922-1925.
4. Aufderheide TP, et al. *Crit Care Med*. 2004;32:345-351.



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# Heat and Moisture Exchangers and Ventilator-Associated Pneumonia

ABSTRACT & COMMENTARY

***Synopsis:*** *This meta-analysis of published trials comparing HMEs and heated humidifiers found a significant reduction in VAP when they were used, particularly among patients who required more than 7 days in the ICU.*

**Source:** Kola A, et al. *Intensive Care Med*. 2005; 31(1):5-11.

KOLA AND ASSOCIATES IN HANNOVER, GERMANY, carried out a systematic review of randomized controlled trials examining the effects on the incidence of ventilator associated pneumonia (VAP) by using a heat and moisture exchanger (HME) rather than a heated humidifier to condition inspired gases during mechanical ventilation. They sought reports of clinical trials published between 1990 and 2003 using Medline and the bibliographies of individual reports. They also searched the Cochrane Central Register of Controlled Trials. Published trials were included if they used HMEs in the treatment group and heated water humidifiers in the control group, provided specific definitions for pneumonia, and reported its incidence. Meta-analysis was then performed on the results of the identified trials.

Of 197 articles initially identified, Kola et al found 8 that met all their *a priori* inclusion criteria. These 8 trials included a total of 1368 patients, 693 managed with HMEs and 675 who had heated humidifiers. Only one individual trial reported a significant difference in VAP rate when comparing HMEs to heated humidification.[1] However, pooling the results from all the studies revealed a reduction in the overall risk ratio of VAP in the HME group (0.69; 95% CI, 0.51-0.94). A test for homogeneity showed no evidence of significant heterogeneity in the pooled results, so that considering all 8 studies as one large cohort for the purposes of meta-analysis appeared justified.

Kola et al performed 2 subanalyses of their data, assessing the effect of duration of mechanical ventilation and of how pneumonia was defined. Only in studies with a duration of mechanical ventilation of 7 days or longer was there a significant difference in VAP incidence with the 2 humidification systems: for ventilation > 7 days the risk ratio of VAP was 0.57 (95% CI, 0.38-0.83), as compared to 0.99 (0.59-1.62) for ventilation < 7 days. The significant overall reduction in VAP incidence with HME use was found in the 4 studies using a clinical definition for VAP (RR, 0.64; 95% CI, 0.44-0.92), but not in the 4 studies using a microbiologically confirmed diagnosis (RR, 0.83; 95% CI, 0.49-1.42).

## COMMENT BY DAVID J. PIERSON MD

Next to urinary tract infection, VAP is the second most common ICU-acquired infection. It accounts for increased morbidity and mortality as well as enormous increases in the costs of ICU management. Risk factors for acquiring VAP, as listed by the authors of this paper, relate both to the patient and to management in the ICU, as shown in Table 1. Because of the magnitude of the problem of VAP, anything clinicians can do to decrease its incidence would seem worthwhile, especially if the intervention is easy to implement and inexpensive in comparison with alternatives.

For several reasons, HMEs are attractive substitutes for the traditional heated humidifiers used to warm and moisten inspired gases during mechanical ventilation. HMEs are passive and incorporated into the ventilator circuit, and do not require frequent circuit interruption (which increases the risk for VAP). HMEs reduce costs, most prominently because they require less attention from respiratory therapists and other personnel. However, HMEs cannot be used in all patients. Kola et al list 4 contraindications, as shown in Table 2.

Because they are essentially filters through which the patient's inhaled and exhaled breath must pass, circumstances must be avoided in which they may become clogged. Thus, the presence of copious, tenacious, or grossly bloody secretions is a contraindication to their use. Even in the absence of obstruction from secretions, HMEs add resistance to the circuit. As a result, they

**Table 1**

**Risk Factors for Ventilator-Associated Pneumonia, as Cited by Kola et al.**

| Related to the Patient | Related to Management |
|---|---|
| Increased age | Duration of mechanical ventilation |
| Chronic lung disease | Reintubation |
| ARDS | Frequent circuit changes |
| Polytrauma | Low intra-cuff pressures |
| Burns | Tracheostomy |
| Neurosurgery | Enteral nutrition |
| Aspiration | Supine position |
| | Use of H2 receptor antagonists |

could interfere with spontaneous breathing during partial ventilatory support, and might add unacceptable work of breathing in patients with severe underlying lung disease. Patients with obstructive lung disease were excluded from most of the studies included in the meta-analysis by Kola et al. HMEs could also impair the efficiency of the ventilator at high minute ventilations, and they are less effective under these circumstances. For this reason, at the institution at which I practice, HMEs are not used in patients with minute ventilations exceeding 15 L/min.

The possible effect of HMEs on the incidence of VAP has been examined previously with meta-analysis. Cook and colleagues looked at several aspects of airway management, including HMEs, in an article published in 1998.[2] They concluded that, although the study of Kirton et al[1] was the only randomized trial published to date to have a statistically positive overall result, the use of HMEs probably was associated with lower rates of VAP. The present meta-analysis included 4 additional trials not examined in the earlier review, and its findings make the case for a favorable effect of HMEs on VAP more strongly.

The fact that HMEs reduced the incidence of VAP only in studies using a clinical definition of pneumonia, and not when microbiological confirmation was used, is troubling. How best to diagnose VAP remains a hotly debated issue, but most authorities are not only leaning toward microbiological confirmation but also increasingly relying on quantitative cultures from bronchoalveolar lavage (BAL) or mini-BAL catheter.[3] More studies, using precise and standardized definitions for VAP, will be required before this issue can be settled more objectively.

The advantages of HMEs, at least with respect to the incidence of VAP, apply mainly to patients requiring prolonged mechanical ventilation, and they cannot be used in some patient groups. However, it seems justified to use HMEs instead of heated humidifiers whenever feasible. ■

### References


1. Kirton OC, et al. *Chest*. 1997;112:1055-1059.
2. Cook D, et al. *JAMA*. 1998;279:781-787.
3. Chastre J, et al. *Am J Respir Crit Care Med*. 2002;165(7):867-903.


**Table 2**

**Contraindications to the Use of Heat and Moisture Exchangers during Mechanical Ventilation**

- Hemoptysis
- Tenacious secretions
- Increased airway resistance
- Hypothermia

# Hydrocortisone for Severe Community-Acquired Pneumonia

ABSTRACT & COMMENTARY


***Synopsis:*** *In this multicenter clinical trial of patients with severe community-acquired pneumonia, a 7-day course of low-dose hydrocortisone infusion was associated with decreased signs of inflammation and significant reductions in duration of mechanical ventilation, hospital length of stay, and in-hospital mortality.*


**Source:** Confalonieri M, et al. *Am J Respir Crit Care Med*. 2005;171:242-248.

CONFALONIERI AND ASSOCIATES REPORT THE results of a 6-center Italian clinical trial of hydrocortisone vs placebo in patients hospitalized with severe community-acquired pneumonia (CAP). Patients admitted to the ICUs or respiratory intermediate care units of the participating centers with CAP were considered for the trial. Patients were determined to have severe CAP if they had 2 minor criteria or 1 major criterion from the Table.

Patients were excluded if they had nosocomial pneumonia, were immunosuppressed, had a life expectancy of less than 3 months because of underlying medical illness, had a recent history of gastrointestinal hemor-

**Table**

**Clinical Criteria for Severe Community-Acquired Pneumonia**

| |
|---|
| **Minor Criteria** |
| Respiratory rate > 30 breaths/min |
| $PaO_2/FIO_2$ < 250 mm Hg |
| Bilateral or multilobar radiographic involvement |
| Systolic BP < 90 mm Hg |
| Diastolic BP < 60 mm Hg |
| **Major Criteria** |
| Requirement for mechanical ventilation |
| 50% or more increase in radiographic involvement at 48 hr |
| Requirement for vasopressors for > 4 hr |
| Serum creatinine 2.0 mg/mL or more |

**Source:** Ewig S, et al. *Am J Respir Crit Care Med*. 1998;158:1102-1108.

rhage, or were receiving more than 0.5 mg/kg/day of prednisone. All patients received protocol-guided antibiotic therapy, plus either hydrocortisone (200 mg initially followed by 10 mg/hr for 7 days) or placebo intravenously in a double-blind fashion. Primary end points were improvement in $PaO_2/FIO_2$ and multiple organ dysfunction syndrome (MODS) score by day 8; secondary end-points were duration of mechanical ventilation, length of ICU and hospital stays, and survival to hospital discharge.

During the 33 months of the study, 121 patients were evaluated for study entry at the 6 centers and 48 were randomized, of whom 46 (23 in each group) completed the protocol. The patients were mostly male (32/46) and elderly (mean age, 63 years), with admission APACHE II scores of approximately 18. Those randomized to receive hydrocortisone had lower initial $PaO_2/FIO_2$ (141 vs 178 mm Hg; $P = 0.03$), higher admission C-reactive protein levels (55 vs 29 mg/dL; $P = 0.04$), and more extensive radiographic opacities (chest radiograph score 2.9 vs 2.4; $P = 0.03$).

Patients randomized to receive hydrocortisone had more rapid improvement in $PaO_2/FIO_2$ ($P = 0.002$), chest radiograph score ($P < 0.0001$), C-reactive protein levels ($P = 0.01$), and MODS score ($P = 0.003$) by day 8. Fewer hydrocortisone-treated patients developed delayed septic shock (0 vs 9; $P = 0.001$). Patients in the hydrocortisone group requiring ventilatory support (n = 6) spent 4 days on mechanical ventilation (range, 1-27 days) as compared to 10 days (range, 2-44 days) for the 15 patients in the placebo group who were ventilated ($P = 0.007$). Hospital length of stay was significantly less among patients who received hydrocortisone ($P = 0.03$). Survival to hospital discharge was 70% in the placebo group and 100% in the hydrocortisone group ($P = 0.009$).

### COMMENT BY DAVID J. PIERSON, MD

This study showed that a 7-day course of low-dose intravenous hydrocortisone to patients admitted to the ICU with severe CAP who were managed according to current antibiotic guidelines was associated with more rapid physiologic improvement, shorter duration of ventilatory support, less progression to MODS and septic shock, and better overall survival. Unfortunately, several limitations tend to blunt my enthusiasm for the results. It took 33 months for 6 ICUs to enroll 48 patients with a fairly common condition; the patients in the hydrocortisone and placebo groups differed in initial severity of illness; and allocation to the two groups was uneven at the various participating centers. Patients who received placebo tended to receive invasive mechanical ventilation and those on hydrocortisone were mainly ventilated noninvasively.

The corticosteroid saga continues. High-dose steroids given early in patients with septic shock or acute lung injury appear to be bad, whereas lower-dose steroids given to patients with relative adrenal insufficiency complicating critical illness appear to be good-although identifying which patients those are and knowing when to stop steroids in the patients who do not qualify remain problematic. This study is strongly positive for the use of low-dose hydrocortisone, starting early in hospitalization, in patients with CAP who require ICU admission. Whether subsequent, larger studies will bear out these findings, at this point giving hydrocortisone to patients like those in this study and in the manner used by Confalonieri et al does not appear to be harmful. ■

*Special Feature*

# Antibiotic Cycling in the ICU

*By Jun Takezawa, MD*

## Introduction

ONCE INTENSIVE CARE PRACTICES HAVE BEEN WELL standardized, patient safety becomes one of the biggest issues in the ICU in terms of management of health care quality (affecting the outcomes of patients admitted to the ICUs). The quality of health care in the ICU is related to 1) organizational characteristics (such as staffing, open vs closed systems, workforce); 2) standardization of treatment and care process; 3) competence of the ICU staff in providing treatment and care; and, 4) risk hedging capability against medical errors which include acquisition of nosocomial infections. The acquisition of nosocomial infections in the ICU is known to significantly affect patient outcomes such as ICU and hospital mortality and length of ICU and hospital stays.

## Risk Factors for ICU-Acquired Infections

Environmental risk factors in the development of ICU-acquired infections include widespread use of broad-spectrum antibiotics, increased utilization of the ICU by more seriously-ill patients, increased use of

invasive medical devices, lack of well-trained nurses and their increased workload, and the increased numbers of patients who stay in the ICU due to chronic and severe illness. The risk factors for ICU-acquired nosocomial infections, which are preventable, are insufficiency in hygiene practice, uncontrolled antibiotic usage, delays in administration of the appropriate antibiotic, and emergence of antibiotic-resistant organisms. Although hygiene practice is standardized by various guidelines published by the professional societies such as APIC and NCRQ and governmental health care agencies, the use of antibiotics is not well standardized, and the numbers of nosocomial infections caused by antibiotic-resistant organisms is still increasing.

## Prevention of Emergence of Antibiotic-Resistant Organisms

Several attempts have been made to promote the judicious use of antibiotics in preventing the emergence of antibiotic-resistant organisms, in hopes of decreasing the number of ICU-acquired infections caused by the antibiotic-resistant organisms. One strategy is limiting or restricting the number of antibiotics used in the ICU. Although a large scaled randomized controlled trial in order to obtain a definitive conclusion on this issue would be difficult to do, it is rational to believe that a decrease in the total number of antibiotics used in a given hospital would result in improvement of the antibiotic susceptibility of the organisms which inhabit the hospital environment.

## Antibiotic Cycling

Another strategy to reduce the emergence of antibiotic-resistant bacteria is the use of various antibiotic classes. This has been accomplished by alternating or cycling antibiotics used in the ICU during predetermined periods.

The background rationale for antibiotic cycling is that selective pressure by the antibiotic is reduced during the restricted period, and susceptibility to the antibiotics on the part of resistant organisms is improved. Additionally, the chance for emergence of resistant organisms may be decreased if susceptibility to the antibiotics remains stable. As far as susceptibility of the antibiotics being reversible, and the baseline susceptibility improved by restricting the use of a certain class of antibiotics, this strategy may be effective in reducing the average resistance rate of the antibiotics during cycling. Therefore, if the baseline susceptibility is not improved or does not return to the baseline level, this strategy is ineffective.

## Reported Experiences with Antibiotic Cycling

The antibiotic cycling strategy was first introduced by Gerding et al[1] where gentamicin and amikacin were cycled alternatively. This strategy was designed in response to increased resistance of Gram-negative bacteria to gentamicin. During the first 4-month period, in which gentamicin was predominantly used, resistance to gentamicin and amikacin was 12% and 3.8%, respectively. During the next 26 months, amikacin was predominantly used. Resistance to gentamicin decreased to 6.4%, but that to amikacin increased to 9.2%. Then gentamicin was re-introduced for the next 12 months. The resistance to gentamicin increased to 9.2%, while the resistance to amikacin was 3.9% which is the same resistance rate as was found in the pre-cycling period. Finally, amikacin was re-introduced for 12 months. The resistance to gentamicin and amikacin was 5.4% and 2.8%, respectively. These results suggested that antibiotic cycling reduced the resistance to the cycled antibiotic when the baseline resistance had already increased, and the resistance level remained stable as far as cycling was continued.

Young et al[2] cycled the use of gentamicin and amikacin because of the increased resistance to gentamicin in 14 US hospitals. During the baseline period where gentamicin was primarily used and amikacin was restricted, resistance to gentamicin was 14% and that to amikacin was 2.4%. In the next 15 months, gentamicin was restricted and amikacin was used as a first line aminoglycoside. The resistance to gentamicin was significantly decreased to 9.2%, while resistance to amikacin remained at the same level of 2.2%. During the subsequent period when cycling and restriction were terminated, the resistance to gentamicin significantly increased to 15.3%, and that to amikacin was also significantly increased to 4%.

Because of the increased incidence of Gram-negative bacterial infections, especially for ventilator-associated pneumonia (VAP), Kollef et al[3] predominantly used antibiotics from ceftazidime to ciprofloxacin for 6-month intervals in treating Gram-negative bacterial infections. They found that the incidence of VAP due to Gram-negative bacteria was significantly reduced when ciprofroxacin was used and ceftazidime was restricted.

Gruson et al[4] controlled antibiotic use for the treatment of VAP by restricting both ceftazidime and ciprofloxacin for empiric and therapeutic uses. When the Gram-negative bacteria responsible for VAP were identified, cefepime, piperacillin-tazobactam, imipenem, and ticarcillin-clavulanic acid were sequentially changed for one-month intervals. They found that the

number of antibiotic-resistant Gram-negative bacteria responsible for VAP was significantly reduced. The susceptibility of the gram-negative bacteria to this antibiotic regimen was also significantly improved. In addition, the prevalence of methacillin-sensitive strains of *Staphylococcus aureus* responsible for VAP was also increased from 40% to 60%.

Kollef et al[5] subsequently rotated 3 different classes of antibiotics used for treating Gram-negative infections in a surgical and medical ICU consecutively for a 6-month period. They found that inadequate administration of antibiotics to nosocomial infections caused by Gram-negative bacteria was reduced and hospital mortality was significantly improved in patients whose APACHE scores were more than 15. However, they also found that the resistance of the bacteria to the antibiotics used during cycling was significantly increased compared to the resistance when they were restricted during the cycling periods.

Because of the increased incidence of colonization of vancomycin-resistant Enterococcus species (VRE) in hematological malignancy unit, Bradley et al[6] rotated the use of antibiotics; ceftazidime and piperacillin-tazobactam. During the initial 4 moth period, where ceftazidime was used, the incidence of VRE colonization was 57%; during the subsequent 8-month period, in which ceftazidime was replaced with piperacillin-tazobactam, the incidence of VRE colonization was significantly decreased to 29%. When ceftazidime was introduced again, the incidence of VRE colonization returned to 36%.

Raymond et al[7] rotated the empirical use of antibiotics every 3 months in the surgery-trauma ICU for one year. Ciprofloxacin+/-clindamycin, piperacillin/tazobactam, carbapenem, and cefepime+/-clindamycin were rotated, and the effects of antibiotic rotation on patient outcomes were evaluated in comparison with those during non-protocol driven antibiotic use for a period of one year. The incidence of Gram-negative bacterial infections and mortality associated with infection were significantly decreased by the antibiotic rotation. However, during the protocol driven period, formulary change from ceftazidime to cefepime occurred and both antibiotic surveillance and a new hygiene practice were started.

Toltzis et al[8] conducted a clinical trial to evaluate whether antibiotic cycling decreased the incidence of colonization of multidrug-resistant Gram-negative bacteria in patients admitted to a neonatal intensive care unit. Study patients received empirical antibiotic therapy on a one-month rotation basis, employing gentamicin, piperacillin-tazobactam, and ceftazidime. The control patients received empirical antibiotics according to the preference of the physician. There was no significant difference in the amount of antibiotics used between the study and control patients. Also, no difference was found in the incidence of colonization of multidrug-resistant Gram-negative bacteria or in clinical outcome.

From these observations, antibiotic cycling was effective in reducing the incidence of colonization of antibiotic-resistant bacteria and ICU-acquired infections caused by antibiotic-resistant bacteria. The susceptibility of the cycling antibiotics was also improved during the withdrawal period. However, the rate of resistance to the initial antibiotics returned to the baseline level, when the same antibiotics were re-introduced.

## Difficulties in Clinical Trials

There are several problems inherit to the antibiotic cycling strategy in conducting clinical trials:

- The susceptibility of the antibiotics used in a certain ICU is different among the ICUs, and choice of antibiotics cycled as well as optimal duration of antibiotic cycling may be different among the ICUs. Thus, the positive result obtained from one ICU may not be applicable to other ICUs.
- The baseline antibiotic susceptibility is always monitored to confirm that antibiotic cycling improves the average susceptibility of the cycled antibiotics during the whole cycling phases.
- It always takes a long period of time to accomplish an antibiotic cycling trial, and during this period it is likely that many confounders such as new infection control practices and new devices could be introduced into clinical practice, which may affect the result of antibiotic cycling strategy.
- It is highly possible that resistant bacteria can be introduced into ICUs as community-acquired or ward-acquired infections. This may affect the baseline susceptibility of the antibiotics used for cycling.
- Although randomized, controlled trials can be organized to exclude confounders and biases associated with clinical trials, this type of clinical trial is expensive and labor-intensive, especially in view of the fact that, ideally, cycling antibiotics should be blinded.
- The biggest problem is which outcome measure should be adopted, such as baseline resistance, incidence of ICU-acquired infections, ICU or hospital mortality, length of ICU or hospital stay, and cost.
- To measure performance of infection control practice, a risk adjustment is required. However, risks for each outcome are different and it is not evaluated thoroughly.

## Current Recommendation

Although antibiotic cycling seems to be effective in reducing the baseline resistance of the causative organisms which are responsible for ICU-acquired infections, this strategy has not been verified by clinical trials with any strong evidence. This strategy may be beneficial when the baseline resistance is already high. However, the baseline resistance should be carefully monitored, to confirm that it is stable or not increasing. The best practice for prevention of ICU-acquired infection is early and sufficient administration of optimal antibiotics to the infected patient, and more importantly, having both the incidence of ICU-acquired infections and the amount of antibiotics used in the ICU also low. In order to accomplish this goal, however, sound daily infection control practice is most important. Therefore, antibiotic-cycling is not recommended as a routine clinical practice for prevention of emergence of antibiotic-resistance bacteria and ICU-acquired infections caused by them. ■

### References


1. Gerding DN, et al. Am J Med. 1985;79 (Suppl 1A):1-7.
2. Young EJ, et al. Am J Med Sci. 1985;290:223-227.
3. Kollef MH, et al. Am J Respir Crit Care Med. 1997;156:1040-1048.
4. Gruson D, et al. Am J Respir Crit Care Med. 2000;162:837-843.
5. Kollef MH, et al. Crit Care Med. 2000;28: 3456-3464.
6. Bradley SJ, et al. J Antimicro Chemother. 1999;43:261-266.
7. Raymond DP. Crit Care Med. 2001;29:1101-1108.
8. Toltzis P. Pediatrics. 2002;110:707-711.


# CME / CE Questions

**28. Which of these parameters did Abella et al use as a surrogate measure of CPR quality?**
a. Length of code and CPR
b. Ventilation rate
c. Time to intubation
d. Successful central line placement
e. Neurological recovery

**29. The *expected* values of CPR quality parameters were derived from American Heart Association guidelines and included all of the following *except*:**
a. compression rate >100/minute.
b. ventilation rate 12-16/minute.
c. compression depth 1.5-2 inches.
*d. ventilation tidal volume 3-5 mL/kg.
e. no-flow fraction 17%.

**30. There was a statistically significant association between ventilation rate during CPR and:**
a. compression rate.
b. compression depth.
c. return of spontaneous circulation.
d. survival to hospital discharge.
e. None of the above

**31. According to the article by Kola et al, which of the following is a contraindication to the use of heat and moisture exchangers during mechanical ventilation?**
a. COPD
b. ARDS
c. Fever
d. Hemoptysis
e. All of the above

**32. A 7-day course of low-dose intravenous hydrocortisone had which of the following effects in patients admitted to the ICU with severe community-acquired pneumonia?**
a. Lower mortality
b. Shorter duration of ventilatory support
c. More rapid improvement in arterial oxygenation
d. All of the above
e. b and c but not a

**33. Which of the following are criteria for defining severe community-acquired pneumonia?**
a. Respiratory rate > 20/min
b. Systolic BP < 100 mm Hg
c. Leukocyte count > 20,000 or < 2000
d. Serum creatinine > 2 mg/dL
e. None of the above

**Answers:** 28 (b); 29 (d); 30 (e); 31 (d); 32 (d); 33 (d)

# 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:

PHARMACOLOGY WATCH

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

# The Risk of Aspirin Withdrawal in ACS Patients

Stopping aspirin may be hazardous to your health, according to recent research. Patients with heart disease who developed acute coronary syndrome (ACS) were questioned to determine whether their aspirin therapy had recently been interrupted. Thirteen percent of patients with recurrent ACS had stopped aspirin within the previous month. The incidence of ST-segment elevation ACS was higher in those who stopped aspirin, compared to those who did not stop aspirin (39% vs 18%; *P*=0.001). The risk of stopping aspirin was particularly high for patients who had uncoated stents. The mean delay between aspirin withdrawal and acute coronary event was 10 days. Patients withdrew from aspirin for a number of reasons including minor surgery, endoscopy, dental treatment, bleeding, and noncompliance. The authors conclude that aspirin withdrawal in patients with coronary disease represents a risk for the occurrence of a new coronary event (*J Am Coll Cardiol.* 2005;45:456-459). The risk of ischemic stroke may be as much as 3 times higher with interruption of aspirin therapy, according to presentation at the International Stroke Conference. Researchers from Switzerland noted that the odds ratio for stroke or TIAs associated with aspirin discontinuation was 3.25 (95% CI). Seventy-seven percent of ischemic strokes related to aspirin discontinuation occurred in the first 8 days after aspirin was stopped, with remaining strokes occurring from day 9 to day 30. The reasons cited for discontinuing aspirin were primarily minor bleeding and minor surgical procedures—many of which can safely be performed (many dental procedures, cataract surgery among others) while patients are taking aspirin (strokeconference.americanheart.org /portal /strokeconference/sc/02.02.05c).

## *Neuropsychiatric Symptoms of Dementia*

Treatment of neuropsychiatric symptoms in patients with dementia represents one of the biggest challenges in primary care. Dementia is diagnosed by the loss of cognitive function, but other symptoms are often more prominent including agitation, aggression, delusions, hallucinations, repetitive vocalizations, and wandering, among others. Many classes of psychiatric medications are used to treat neuropsychiatric symptoms in dementia including antidepressants, anxiolytics, anticonvulsants, cholinesterase inhibitors, typical antipsychotics, and atypical antipsychotics. Often these drugs are used in combination, and the cocktail can get confusing and even dangerous for patients and caregivers alike. A new review of the topic in the "Clinician's Corner" section of the February 2nd *Journal of the American Medical Association* helps clarify treatment options. The authors reviewed 29 articles that met their inclusion criteria. Among typical antipsychotics, which

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include haloperidol, thiothixene, chlorpromazine, trifluoperazine, and acetophenazine, there was no difference in the efficacy among these drugs in treating neuropsychiatric symptoms. Haloperidol may be somewhat more effective for treating aggression but not agitation. Side effects including extrapyramidal symptoms and somnolence are common with these agents. Antidepressants, including the SSRIs, were also relatively ineffective, except for treatment of depression associated with dementia. The best evidence for efficacy was found in the atypical antipsychotic group, especially risperidone (Risperdal) and olanzapine (Zyprexa). These drugs were found to have a modest effect on agitation/aggression, hallucinations, and delusions. A higher risk of stroke was found in the most recent trial (prompting a "Dear Doctor" letter from Janssen in April 2003). The cholinesterase inhibitors group including galantamine (Reminyl), donepezil (Aricept), and rivastigmine (Exelon) were somewhat disappointing with regard to neuropsychiatric symptoms, with minimal improvement of questionable clinical benefit. Memantine, the relatively new N-methly-D-asparte antagonist was seen to improve cognitive and functional parameters, but also did not improve neuropsychiatric symptoms. The authors stress that the management of neuropsychiatric symptoms in dementia "should always begin with an assessment of the medical (eg, pain and delirium) and environmental causes of the behavior." They also recommend starting with a cholinesterase inhibitor if the patient is not already receiving one, because they are relatively well tolerated and may benefit cognition and function (*JAMA.* 2005;293:596-608).

## FDA Actions

Pfizer has received FDA approval to market pregabalin (Lyrica) for the treatment of painful diabetic neuropathy and post-herpetic neuralgia, the 2 most common types of neuropathic pain. Pregabalin was shown to be effective in a company-sponsored study of 338 patients with a 1-5 year history of painful, diabetic, peripheral neuropathy who were randomized to receive the drug at 1 of 3 doses or placebo for 5 weeks. Patients in the 300 and 600 mg/day doses showed improvements in mean pain score vs placebo ($P = 0.0001$ ), but no improvement was seen at the 75 mg/day dose. The higher doses also resulted in improvements in weekly pain score, sleep interferes score, patient global impression of change, clinical global impression of change, and lifestyle surveys. The most common side effects were dizziness and somnolence (*Neurology.* 2004;63:2104-2110). Pregabalin is a 3-substituted analogue of gamma-amino butyric acid (GABA), and is closely related to Pfizer's gabapentin (Neurontin), which recently lost its patent and is now available as a generic. Pregabalin is currently under review by the FDA for the treatment of partial seizures.

The FDA has also approved palifermin (Kepivance-Amgen) to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies undergoing chemotherapy, with or without radiation, in preparation for bone marrow transplantation. The drug, which is the first agent to be approved for this indication, stimulates epithelial cell growth in mucous membranes. It is given prior to fractionated total body irradiation and high dose chemotherapy, and repeated after bone marrow transplantation. The drug's efficacy in non-hematologic malignancies has not been shown.

Citalopram (Celexa) is now available in generic tablets and liquid. The liquid formulation recently joined the tablet formulation for the popular SSRI antidepressant.

Extended release buproprion (Wellbutrin SR) is now available as a generic in the 200 mg strength.

Fosinopril/HCTZ (Monopril) has also joined the generic ranks in 10/12.5 mg and 20/12.5 mg strengths.

The FDA has also approved a generic fentanyl transdermal system (Duragesic) for the treatment of severe chronic pain. The new generic, which is produced by Mylan technologies, provides a constant dose of the drug for 72 hours.

Canada has suspended marketing of Adderall and Adderall XR because of reports of sudden unexplained death (SUD) in children taking the drugs. SUD has been associated with amphetamine abuse and has been reported in children with heart disease taking prescribed doses of amphetamines, including Adderall and Adderall XR. These latest reports of SUD have been in children without structural heart disease who were taking the drugs as prescribed. The FDA is looking at these reports, but “does not feel that any immediate changes are warranted in the FDA labeling or approved use of this drug.” More information is available on the FDA web site at FDA.gov.