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Ventilator-associated Pneumonia and the Gastropulmonary Route of Infection

A Pendulum

Ventilator-associated pneumonia (VAP) is one of the most frequently occurring nosocomial infections, responsible for considerable antibiotic use and associated with increased duration of length of stay and, probably, with a higher mortality risk (1). Prevention of VAP is among the best studied and most intensely debated issues in intensive care medicine. Many episodes of VAP are caused by *Enterobacteriaceae*, and colonization of the upper respiratory tract almost always precedes lung infection (2). Observational studies more than 20 years ago identified gastric colonization and gastric acid–modifying drugs (such as Histamine type-2 antagonists and antacids) as risk factors for VAP (2). Moreover, experimental studies with radioactive-labeled enteral nutrition suggested the occurrence of intratracheal aspiration of gastric contents, especially in supine position (3). These findings supported the concept of the gastropulmonary route of infection: reduced intragastric acidity (either because of age, severe illness, medication, or enteral nutrition) facilitates gastric colonization, which, after aspiration, leads to pulmonary infection.

Based on this concept, at least four types of intervention have been proposed and evaluated: modulation of gastric colonization with different approaches of stress ulcer prophylaxis, the semirecumbent patient position, subglottic aspiration, and finally, maintaining tracheal cuff pressure.

STRESS ULCER PROPHYLAXIS

In "pre–proton-pump inhibitor times" critically ill patients received H2-antagonists or antacids for stress ulcer prophylaxis. As both agents aimed to reduce levels of intragastric acidity (either through reduced acid production or through alkalizing gastric contents), sucralfate seemed a logical alternative to

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prevent VAP, as it presumably offered stress ulcer prophylaxis without modifying intragastric acidity. Indeed, first studies suggested that sucralfate was associated with lower rates of VAP (4, 5), confirming the importance of the gastropulmonary route of infection. Yet subsequent double-blind placebo-controlled studies failed to confirm these observations (6, 7), and the use of sucralfate for stress ulcer prophylaxis to prevent VAP is no longer recommended in guidelines (8, 9). In contrast, stress ulcer prophylaxis with other agents (proton-pump inhibitors) is now part of different VAP bundles (10). If anything, this may increase the occurrence of VAP.

SEMIRECUMBENT PATIENT POSITION

Aspiration of gastric contents is promoted by gastric volume overload, which may occur during continuous gastric feeding. Placing a patient in semirecumbent position—with the head elevated in a 45° position—seemed a logical solution to prevent VAP. In the first randomized study, 86 patients were randomized to a complete supine position (0° head elevation, n = 47) or the semirecumbent position (45° head elevation, n = 39), and the latter was associated with a 26% reduction in the occurrence of VAP (11). Both the supine position and receiving continuous gastric nutrition were significant risk factors for VAP. Yet, the complete supine position while receiving gastric feeding was not standard care practice in most ICUs, and the 45° position was determined once daily only, leaving questions about the feasibility of this intervention. In a subsequent multicenter study, 221 patients were randomized to a "do-nothing scenario" or to semirecumbency, with an aimed position of 45° (12). In both groups head elevation was measured automatically every 60 seconds during the first week of ventilation, and special efforts were taken to place patients in their randomized position in case of deviation. Nevertheless, although all "semirecumbent patients" were in the 45° position at least once daily, their average position was close to 30°. The average position of the "do-nothing" group was around 12°, and there was no reduction in the occurrence of VAP. Since other studies also reported that an average position of 45° is not feasible, maintaining a 30–45° head elevation position is now recommended in most guidelines (8, 9). Based on the available evidence it is uncertain whether this truly prevents VAP.

DEVICES TO PREVENT ASPIRATION

After aspiration, fluids must pass the inflated cuff to reach the lungs. Accumulation of fluids, containing bacteria residing in the oropharynx and stomach, above the inflated endotracheal cuff is common in mechanically ventilated patients. Continuous aspiration of this fluid, with a specially designed tube, also serves as a logical approach to prevent VAP. In a meta-analysis of 13 studies, its use was associated with a 45% reduction in VAP, as well as reduced lengths of ICU stay and ventilation (13). An alternative approach to prevent aspiration is to maintain appropriate cuff pressure, without continuous aspiration. In this issue of the *Journal*, Nseir and coworkers (pp. 1041) report their findings of a randomized single-center study of 122 patients (14). Using a pneumatic device they achieved higher intracuff pressure, which was associated with a 75% reduction in microaspiration of gastric fluids (as determined by frequently measuring pepsin in tracheal aspirates), lower bacterial concentrations in tracheal aspirates, and a 70% reduction in VAP. Importantly, higher intratracheal cuff pressure was not associated with tracheal ischemia, which was investigated with bronchoscopy within 24 hours after detubation in 78% of the patients. This study revitalizes the concept of the gastropulmonary route. But again, there is conflicting evidence. In another Spanish study the same approach tested in an almost identical study design was not associated with a determinable reduction in the incidence of VAP (15). An important difference, though, might have been the routine use of chlorhexidine oropharyngeal decontamination in all patients in the latter study (15). A recent systematic review and meta-analysis summarizes the effectiveness of this intervention to prevent VAP (16).

The role of gastric colonization *per se* in the pathogenesis of VAP, therefore, remains uncertain, and larger studies are needed to unequivocally demonstrate that modulation of bacterial colonization in the stomach can prevent VAP and that subglottic aspiration and maintaining intratracheal cuff pressure improve patient outcome.

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Early-Onset Pneumonia after Cardiac Arrest: An Unintended Consequence of Therapeutic Hypothermia?

Over 225,000 out-of-hospital cardiac arrests (OHCA) occur each year in Europe and in the United States, and despite major advances in both pre-hospital and hospital treatments, survival rates to hospital discharge with favorable neurologic status remain low (1). In 2002, two landmark randomized trials demonstrated that therapeutic mild hypothermia (32–34°C) administered for 12 to 24 hours was able to significantly improve survival and neurologic outcome in patients with OHCA due to ventricular fibrillation (2, 3). The clinical benefits of therapeutic hypothermia are achieved through multiple pathways, such as mitigation of the intense inflammatory response associated with the post–cardiac arrest syndrome, which is the combination of hypoxic brain injury, circulatory dysfunction, and systemic ischemia/reperfusion lesions (4). However, hypothermia by itself may have unintended consequences and adverse effects, particularly bleeding, electrolyte disturbances, and infections (4–6). While early-onset pneumonia, which is due to loss of airway protection during coma and inhalation of gastric and oropharyngeal secretions, is the most frequent infectious complication of patients with OHCA, no studies to date have attempted to carefully evaluate the impact of therapeutic hypothermia on the frequency and morbid consequences of this infection.

In this issue of the *Journal*, Perbet and colleagues (pp. 1048) report on the incidence, risk factors, causative agents, and impact on outcomes of early-onset pneumonia on a large retrospective cohort (n = 641) of patients successfully resuscitated from OHCA in the erea of therapeutic hypothermia (2002–2008) and treated in two tertiary referral medical intensive care units in Paris, France (7). They also evaluated the specific contribution of therapeutic hypothermia, which was applied to 75–80% of the patients, on the occurrence of the disease.

The first major finding of this study is that therapeutic hypothermia was associated with an increased risk of early-onset pneumonia after OHCA (odds ratio, 1.90; 95% confidence interval [CI], 1.28–2.80). The authors made great efforts to ascertain that this association was not the result of confounding factors. Multivariable analyses revealed that hypothermia remained the single independent risk factor for the disease after adjustment on a propensity score for receiving hypothermia, on the prescription of antibiotic prophylaxis, and over the time of the study. Furthermore, when the analysis was restricted to bacteriologically proven infections, the odds ratio of hypothermia as a risk factor for early-onset pneumonia peaked to 2.38 (95% CI, 1.54–3.68). Although the occurrence of early-onset pneumonia was independently associated with prolonged durations of mechanical ventilation and ICU stay, it did not alter neurological outcomes and ICU survival. Hypothermia may indeed exert "Ying-Yang" effects in patients recovering from OHCA. While hypothermia-induced altered immune function may protect the brain subjected to hypoxia and ischemia/reperfusion (8), it may also be responsible for higher rates of infections (5, 6, 9) by suppressing the secretion of proinflammatory cytokines and impairing leukocyte migration and phagocytosis (4, 8, 10). In addition, hypothermia is known to promote insulin resistance and hyperglycemia, which may further increase risks of infection (4).

Other relevant information derived from this study relates to the epidemiology, microbiology, and treatment strategies of early-onset pneumonia after OHCA. First, the infection was frequent in this setting: 419/641 (65%) patients had a clinical diagnosis of pneumonia that was later bacteriologically confirmed in 314 (49%). In agreement with previous studies describing bacterial flora responsible for community-acquired aspiration pneumonia (11–13), the most frequent pathogens grown from lung secretions were *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and Enterobacteriaceae, while anaerobes were never isolated. Pneumonia was polymicrobial in 55% of the cases. It should also be noted that initial empiric antibiotic therapy was inappropriate in 89 (21%) cases, bacteria being resistant to prescribed amoxicillin-clavulanate or penicillin G in 84 cases. Inappropriate initial treatment was associated with prolonged length of ICU stay, but did not impact on mortality. Since resistance to third-generation cephalosporin was observed in only 3% of the pathogens grown from distal pulmonary samples, this antibiotic may be used preferentially when direct examination of tracheobronchial secretion reveals gram-negative bacteria. Although not recommended in this situation, antibiotic prophylaxis was administered to 176 (27%) of the patients, and 62 (10%) patients received antibiotics without confirmed infection.

There are several limitations to this study by Perbet and colleagues that warrant critical evaluation. The main problem with this study is the somewhat loose definition used for early-onset pneumonia and specifically the fact that despite negative culture of distal pulmonary samples, pneumonia was still diagnosed based only on purulent tracheal aspirates, infiltrates on chest X-ray, and hypoxemia in 90 (> 20%) patients. Indeed, the incidence of early-onset pneumonia following OHCA in this study was among the highest reported in the literature (11–13), and some of the pneumonia diagnosed herein might in fact be chemical or acid-induced pneumonitis, since aspiration of the gastric fluid is almost constant after cardiac arrest. Second, the rate of bacterial resistance to prescribed antibiotics (in particular 42 cases of pneumonia with bacteria resistant to amoxicillin-clavulanate) is surprisingly high. Detailed analysis of patients' case-mix and of their exposition to antibiotics in the weeks before OHCA might have provided useful information on risk factors associated with bacterial resistance. Finally, due to the retrospective design of this study, major confounding factors not taken into account in multivariable models predicting early-onset pneumonia may