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NOSOCOMIAL INFECTION IN THE CRITICALLY ILL

The Lung as a Target Organ

In this issue of Anesthesiology, Fabregas et al. provide compelling evidence that the lungs of many critically ill patients dying in the intensive care unit after a prolonged period of mechanical ventilation are massively colonized and extensively infected by nosocomial microorganisms. They also report the presence of high concentrations of pathogens in lung regions free of histologic lung infection and question the validity of bacterial quantitative analysis for differentiating bronchial colonization from true lung infection. These disturbing results, confirming previous suspicions, 2-4 are based on the simultaneous bacteriologic and histologic analysis of 375 postmortem pulmonary biopsies obtained from various pulmonary lobes in 25 critically ill medical patients. In addition, the study confirms, emphasizes, and extends the results of three others, 5-6 showing that, although disseminated within all pulmonary segments, lung infection is located predominately in lower lobes, frequently is polymicrobial, and is associated with a variety of noninfectious pulmonary lesions.

An important result of the study is that bacterial concentrations $\geq 10^5$ cfu (colony forming unit)/g of lung tissue were found in the absence of any histologic evidence of lung infection. In biopsy samples demonstrating bronchopneumonia, no clear relationship could be established between lung bacterial burden and evolution phase or histologic grade of lung infection. This "histobacteriologic" discrepancy was observed not only in patients receiving antibiotics but also in those with no antimicrobial therapy. Massive contamination related to the delay between death and sampling was unlikely to be the explanation, because postmortem thoracotomy was performed within 30 min after death in the majority of patients. Although bronchiolitis was observed in many patients, as previously shown, 5,6 it accounted for less than 10% of the positive lung cultures observed in lung regions free of histologic pneumonia. The presence of high concentrations of microorganisms without histologic evidence of parenchymal or bronchial infection is highly suggestive of massive colonization of the distal bronchial tree by nosocomial pathogens. By analogy with observations reporting bacterial concentrations $\geq 10^5$ cfu/ml in distal bronchi of patients whose lungs were mechanically ventilated and without suspected pneumonia, 7 high concentrations of microorganisms were likely to have been present in distal bronchioles of noninfected pulmonary lobules. Although Fabregas et al. 1 always sampled peripheral zones of the lung, the size of their biopsy sample—about 8 cm$^3$ divided into two pieces, one for quantitative microbiology culture, the other for histopathology processing—implies that alveolar spaces were cultured with distal bronchioles. This occurs unavoidably in any study comparing histology and bacteriology on relatively large biopsy samples. In studies with smaller superficial lung tissue specimens (≤1 cm$^3$) excised, 2,6,8,9 a reasonably good correlation was found between lung bacterial burden and histologic grade of lung infection. 6 In addition, noninfected lung parenchyma was always characterized by negative lung cultures 2 or bacterial concentrations $<10^3$ cfu/g. 2 Although one can understand the authors' statement that bronchial colonization (i.e., colonization of the proximal part of the bronchial tree) could not account for positive cultures of lung parenchyma free of histologic infection, it is highly likely that colonization of bronchioles (i.e., colonization of the most distal part of the bronchial tree) was the culprit.

If these data are considered with the results of four other studies, 2,3,5,6 ventilator-associated bronchopneumonia can be seen as the result of a massive bacterial inoculum penetrating distally into the bronchial tree and producing patchy areas of alveolar and bronchiolar infection, depending on the status of local antibacterial defenses. The bronchogenic origin of alveolar infection is strongly supported by several characteristics of ventilator-associated bronchopneumonia. Histologically, foci of bronchopneumonia are defined as infected alveolar spaces connected to one or several infected bronchioles. 1,2 Bronchiolitis is the histologic grade immediately preceding alveolar infection. 2 In critically ill patients, dependent segments are the most frequently infected segments, suggesting that gravity plays

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An important role in the pathophysiology of ventilator-associated bronchopneumonia \(^1\) has been emphasized by experimental \(^1\) and clinical studies \(^1\) that have shown that the administration of antibiotics significantly reduces the incidence of ventilator-associated bronchopneumonia. It is likely that, in patients with ventilator-associated bronchopneumonia, the same bacterial inoculum is present in bronchioles leading to infected and noninfected alveolar spaces. As a consequence, Fàbregas et al. \(^1\), being unable to identify infected lung territories using the quantitative culture of their biopsy samples, \(^1\) logically conclude that quantitative lung bacteriology is not a reliable "gold standard" for the diagnosis of bronchopneumonia, and only lung histology should be taken into account.

Two important questions then arise. First, what is the clinical significance of quantitative cultures of distal bronchial samples performed daily at the bedside in critically ill patients whose lungs are mechanically ventilated? Second, is there a quantitative threshold above which the diagnosis of ventilator-associated bronchopneumonia is almost certain? Bacterial concentration measured on a distal bronchial sample (e.g., a protected specimen brush or a bronchoalveolar lavage) depends on the method of sampling and the bacterial concentration present at the sampling site. Because the protected specimen brush retrieves approximately 0.001 ml of bronchial secretions, a 10^5 cfu/ml concentration corresponds approximately to 10^5 cfu/ml of bronchial secretions. \(^1\) Because the protected minibronchoalveolar lavage represents a tenfold dilution of bronchoalveolar secretions, a 10^6 cfu/ml concentration corresponds approximately to 10^5 cfu/ml of bronchoalveolar secretions. \(^1\) It has been shown that the onset of bronchopneumonia is frequently preceded by an increase in bronchial quantitative cultures to above 10^5 cfu/ml. \(^1\) Several studies have shown that nonprotected blind bronchial sampling using a bacterial threshold \(\geq 10^5\) cfu/ml is at least as effective as protected specimen brush for diagnosing ventilator-associated bronchopneumonia. \(^1\) Indirect evidence is accumulating to show that alveolar infection is likely to occur above a bacterial inoculum of 10^5 cfu/ml in distal bronchi. Therefore, techniques of distal sampling should collect bronchial secretions as far distal as possible in the bronchial tree; and quantitative bacterial analysis should be systematically performed before any administration of antibiotics to evaluate the bacterial inoculum at the sampling site. When interpreting quantitative bacteriology at the bedside, the clinician should weigh a number of factors that can modify bronchial and alveolar bacterial burden: presumed stage of bronchopneumonia, administration of antibiotics, technique of distal sampling, natural host antibacterial defenses, duration of mechanical ventilation, and presence of acute lung injury. The microbiologic complexity of ventilator-associated bronchopneumonia does not support the concept of a standard threshold for the diagnosis of nosocomial pneumonia. Avoiding any dogmatic approach, the intensivist should remember that human ventilator-associated bronchopneumonia is a complex and rapidly changing entity.

Fàbregas et al. \(^1\) found that 92% of their patients had histologic evidence of lung infection. Three autopsy studies performed in critically ill patients also found a high incidence of ventilator-associated bronchopneumonia: 53%, \(^2\) 67%, \(^3\) and 47%. \(^4\) It has been demonstrated that the incidence of lung infection in patients whose lungs are ventilated is significantly greater in nonsurvivors: Among 251 surgical critically ill patients studied over a 16-month period, lung infection was present in 57% of survivors and 61% of nonsurvivors. \(^5\) As suggested 10 years ago, pneumonia is associated with greater incidence of multiple organ failure and death in patients with acute respiratory distress syndrome. \(^6\) In autopsy studies of critically ill patients dying after a prolonged period of mechanical ventilation, disseminated bronchopneumonia is a consistent finding. \(^7\) Unlike liver, spleen, kidney, heart, or brain, the lungs appear particularly susceptible to nosocomial infection. Besides accumulating knowledge on the potential role of inflammatory mediators in the pathophysiology of sepsis and sepsis-like syndromes, intensivists should keep in mind that, as long as their patients’ lungs remain massively infected, it will be difficult to substantially reduce the incidence of septic shock and multiorgan failure in intensive care units.

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