

Nosocomial pneumonia in critically ill comatose patients: need for a differential therapeutic approach

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Nosocomial pneumonia in critically ill comatose patients: need for a differential therapeutic approach. J. Rello, V. Ausina, M. Ricart, C. Puzo, A. Net, G. Prats.

ABSTRACT: The purpose of this prospective clinical study was to determine the incidence, bacteriology and outcome of lower respiratory tract infections developed among 208 consecutive, critically ill comatose patients, hospitalized in a university hospital, medical-surgical intensive care unit, over a three year period.

Nosocomial pneumonia developed in 53 (25%) patients after a mean of 8.1 days (range 3-31 days). Furthermore, there were five superinfections, raising the mean incidence to 28%. One patient developed secondary bacteraemia, and another two had septic shock. Fifteen (28%) patients from the pneumonia group died, and six of these deaths were considered to be directly related to nosocomial pneumonia. Identification of the causative agent, using the protected specimen brush technique, was possible in 42 episodes; in 10 (24%) of these cases more than one microorganism was isolated. Gram-positive cocci represented 53% of isolates, and *Staphylococcus aureus* accounted for 78% of all Gram-positive cocci, being the most frequent microorganism in this population.

In conclusion, nosocomial pneumonia is a common complication of critically ill comatose patients. Its characteristic aetiological spectrum in this population should affect antibiotic prescription. Consequently, we suggest including antimicrobial drugs which are active against *S. aureus* in the empirical regimen until aetiological diagnosis is established.

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Nosocomial pneumonia (NP) is a common complication in hospitalized patients, particularly those cared for in intensive care units (ICU). This population is heterogeneous and it is conceivable that different patient populations would have different incidence, risks and bacteriology that might affect the management. Although patients in coma represent only a small proportion of the hospital population, it often comprises critically ill patients with disproportionately high rates of mortality. Nosocomial pneumonia in patients with coma is not an uncommon finding and may be caused by "community" endogenous flora or by microorganisms acquired during hospitalization. Information about their epidemiology would be of great interest and might affect the therapeutic regimen chosen. Several factors account for the high risk, including abnormal swallowing, depressed gag reflexes [1], bronchoaspiration, and the debilitated general state of these patients [2]. The problem is particularly serious in those patients who require endotracheal intubation [3-7] and several strategies for prevention, such as selective decontamination of the digestive tract, are currently recommended or are being investigated. Since NP is common in this setting and is associated

with high fatality, the precise identification of causative agents and the early and accurate administration of antibiotic therapy are important clinical goals [8-10].

The present study was undertaken to prospectively assess the incidence, causative agents and outcome of NP in patients in coma, who were hospitalized in a medical-surgical ICU.

Patients and methods

Population study

This study was conducted over a 3 yr period, in a 16 bed medical-surgical ICU, at a 1,000 bed teaching hospital, which serves both as a referral centre and a first-line hospital. All critically ill patients in coma admitted to the ICU were included. Diagnosis on admission, prior antibiotic therapy, the duration of mechanical ventilation prior to NP development, the presence of a prior surgical procedure or trauma, any episode of gastric content bronchoaspiration,

tracheostomy, and the presence of chronic obstructive pulmonary disease (COPD) were recorded. Chest X-rays and white blood cell (WBC) counts were performed daily. All patients had a nasogastric tube in place if they were receiving mechanical ventilation and all received antacids and/or ranitidine to obtain a gastric pH ≥ 4 . No regimen for NP prophylaxis or selective decontamination of the digestive tract was administered.

The patients' clinical progress was observed until ICU discharge or death. Subsequent bouts of pneumonia after discharge from the ICU were not studied. Patients who developed septic shock were recorded. If the episode of NP was considered to be the primary cause of death, and any other potential cause of death could be identified while the infection was still active, the mortality was categorized as directly related.

Definitions

Nosocomial pneumonia is defined as any lower respiratory tract infection developed from the third day postadmission [11]; any infection developed earlier than this was considered as community-acquired [12]. The criteria for clinical diagnosis of pneumonia were: presence of a new and persistent lung infiltration on chest X-ray, excluding those of noninfectious origin [13]; plus two of the following items: a) fever $\geq 38^\circ\text{C}$; b) leucocytosis $\geq 10,000$ WBC $\cdot\text{mm}^{-3}$, c) purulent respiratory secretions. Superinfection was defined as recurrence of fever, leucocytosis, and increasing symptoms and signs of infection after definitive clinical and radiographic improvement of a prior pneumonia [14]. Coma was defined as a score lower than nine on Glasgow coma scale [15], over 24 h.

Microbiology

Fibreoptic bronchoscopic examination was performed in each patient suspected of having pneumonia within the first 12 h after the development of a new pulmonary infiltrate, excepting weekends. The telescoping plugged catheter (TPC) technique was used to obtain uncontaminated lower airway secretions for bacterial cultures [16]. A telescoping canula brush with a distal polyethyleneglycol occlusion (Model BWF/10/70/90; Meditech Inc., Watertown, MA, USA) was inserted through the inner suction channel of the bronchoscope (Model BF 10; Olympus Corp. of America, New Hyde Park, NY, USA). This protected brush was advanced to a wedged peripheral position, after dislodging the distal catheter plug, to obtain lower airway secretions for microbial cultures. Empirical intravenous antibiotic therapy was started immediately after TPC performance, or within 6 h if the procedure could not be done. When culture results became available, the antimicrobial regimen was adjusted for the identified organisms by sensitivity testing. Blood, urine and samples from other sites were collected for bacterial culture in all patients.

Bacteriological processing

Specimens were sent to the laboratory immediately after collection. The brush was advanced and aseptically cut into a sterile tube containing 1 ml of sterile saline solution. The vial was then agitated vigorously for at least 60 s to thoroughly suspend all material from the brush. Two serial hundred fold dilutions were made, and 0.1 ml aliquots of the original suspension and each dilution were inoculated on agar plates for aerobic and anaerobic culture: one agar plate with selective buffered charcoal-yeast extract medium for isolation of *Legionella* species was included [17]. Bacterial counts $\geq 1,000$ cfu $\cdot\text{ml}^{-1}$ were the cut-off point to diagnose causative agents, according to the standards adopted in previous studies [18]. Bacterial identification and susceptibility testing were performed by standard methods [19].

Statistical analysis

Proportions were compared using the chi-squared test with Yates' correction or the Fisher's exact test when necessary [20].

Results

Two hundred and eight consecutive patients in coma were hospitalized in our ICU during the study period. The aetiology of coma was heterogeneous and the main causes are shown in table 1.

Table 1. - Aetiology of coma among 208 patients studied

| Aetiology of coma | Patients | |
|------------------------|----------|----|
| | n | % |
| Trauma | 80 | 38 |
| Stroke | 38 | 18 |
| Sedation | 28 | 13 |
| Anoxic encephalopathy | 13 | 6 |
| Overdose | 9 | 4 |
| Intracranial infection | 9 | 4 |
| Intracranial neoplasia | 8 | 4 |
| Miscellaneous | 23 | 11 |

Fifty three patients underwent neurosurgical procedures. In total, 93 (45%) were surgical patients. Most patients (166 out of 208, 80%) were ventilated for more than 2 days, 42 of them through a tracheostomy. In our study population, only 13 (6%) patients were diagnosed as COPD. We recorded an episode of large volume bronchoaspiration of gastric contents in 13 other patients and 7 of them developed NP.

Nosocomial pneumonia developed in 53 (25%) patients (52 of whom were mechanically ventilated) after a mean of 8.1 days (3–31 days) in ICU. Furthermore, there were 5 superinfections raising the mean incidence to 28%. Of these, 22 had received antibiotics before the onset of NP and 36 had not. The most frequently prescribed agents were cephalosporins in combination with another antibiotic (n=9), or imipenem used alone (n=8). Isolation of *Pseudomonas aeruginosa*, Enterobacteriaceae and enterococci occurred almost exclusively in infected patients who had received previous antibiotics. Risk for NP was statistically greater ($p < 0.01$) among patients with trauma antecedent (28 of 80) compared with patients with coma from other aetiologies (25 of 128). One patient developed secondary bacteraemia and another two had septic shock. Fifteen (28%) patients from the pneumonia group and 38 (24%) of those without pneumonia died during ICU admission; deaths in the pneumonia group were considered to be directly related to NP in six cases. The mean length of stay in ICU for pneumonia survivors was 29.6 days compared with 13.9 days for patients without pneumonia ($p < 0.05$).

Table 2. – Summary of causative agents

| Microorganisms | n | %* |
|--------------------------------------|----|----|
| Gram-positive cocci | | |
| <i>Staphylococcus aureus</i> | 22 | 41 |
| <i>Streptococcus pneumoniae</i> | 4 | 7 |
| Enterococci | 2 | 4 |
| Aerobic Gram-negative bacilli | | |
| <i>Pseudomonas aeruginosa</i> | 10 | 19 |
| <i>Haemophilus influenzae</i> | 10 | 19 |
| <i>Proteus mirabilis</i> | 2 | 4 |
| <i>Citrobacter freundii</i> | 1 | 2 |
| <i>Escherichia coli</i> | 1 | 2 |
| Anaerobes | | |
| <i>Bacteroides fragilis</i> | 1 | 2 |

*: Percentage of organisms isolated.

A total of 53 microorganisms were cultured from protected brush specimens (PBS), in significant (more than 1,000 cfu·ml⁻¹) concentrations in 42 episodes (table 2). In 10 episodes, more than one bacterial species was isolated from PSB cultures; two organisms in nine episodes and three in one case. Of these isolates, 53% were gram-positive organisms, 45% were aerobic gram-negative bacteria and 2% were anaerobes. *Staphylococcus aureus* was the most frequent microorganism isolated, accounting for 78% of all gram-positive cocci and for 41% of the total organisms isolated. The staphylococci found were all penicillinase producing but sensitive to all other antibiotics tested. The most frequent gram-negative bacilli were *P. aeruginosa* (19%) and *Haemophilus influenzae* (19%).

Discussion

We found a 28% mean incidence of NP in our study population, a similar rate to that found in former studies of NP in unselected populations of patients admitted to ICUs [3, 21] or requiring mechanical ventilation [6, 7, 22]. Indeed, the high incidence of mechanical ventilation contributes to an explanation of this high incidence rate. Furthermore, we use ranitidine or antacids as stress ulcer prophylaxis, which in several studies have been associated with increased rate of pneumonia [23].

In 42 out of 58 episodes of NP, we were able to determine the causative microbiological agents. Polymicrobial associations of microorganisms were responsible for 24% of episodes. Previous studies [3, 4, 6, 7] in mechanically-ventilated patients, using similar diagnostic techniques, also found similar percentages. The organisms reported to be responsible for NP vary greatly from one study to another, but Gram-negative bacilli were the organisms most frequently isolated in the literature [22, 24–27] with a range of 40–87%, while Gram-positive cocci were responsible for less than 20% of cases [24]. The present study demonstrates that Gram-positive cocci are important pathogens in this population. This finding differs from the data in other patients with NP. Indeed, *S. aureus* was the main organism responsible for this high incidence of Gram-positive cocci in our population. Recently, the development of methicillin-aminoglycoside-resistant *S. aureus* (MARSA) has been reported [28–30], most commonly in tertiary and teaching institutions. These organisms are also capable of causing widespread outbreaks of serious infection and colonization. However, we did not identify MARSA strains in this study. The uncommon isolation of *S. aureus* in the remaining critically ill population in our ICU [5, 31] and the unlikelihood of cross-infection indicate that the high frequency of staphylococcal pneumonia does not reflect epidemic spread in our ICU. A prolonged use of selective decontamination of the digestive tract and oropharynx may lead to the selection and emergent colonization by Gram-positive cocci [32], but this element could not be argued because we did not use these regimens in our ICU.

The pathogenesis of most cases of NP initially involves the aspiration of secretions from the colonized oropharynx or gastrointestinal tract and subsequently the inability of the host pulmonary defences to contain this microbial inoculum [1]. The ability of microorganisms to adhere to oropharyngeal epithelial cells appears to be pivotal to successful colonization [23]. Host factors, types of bacteria colonizing the pharynx or stomach, levels of gastric pH, use of antibiotics and duration of hospitalization may alter colonization and adherence of microorganisms. A high incidence of *S. aureus* pneumonia in neurosurgical patients [33, 34], as well as in head-trauma victims [35] receiving mechanical ventilation has been described previously. Recently, we prospectively

studied 161 multiple trauma patients [31] and found that *S. aureus* [56%] was the predominant pathogen isolated in those patients who were in coma, while in patients with Glasgow coma score above 8, aerobic Gram-negative bacilli were responsible for the majority of cases. In another study [36], univariate and multivariate statistical analyses were performed to determine the influence of some clinical and epidemiological variables on the risk of developing staphylococcal pneumonia, in a population of 50 critically ill patients with NP and an established aetiological diagnosis. In the univariate analysis, the variables significantly associated with *S. aureus* NP were: age below 25 yrs, non-use of corticosteroids, antecedent of trauma and coma. A step-forward logistical regression analysis, however, defined only coma as significantly influencing the risk of developing *S. aureus* NP. Further studies are needed to clarify why patients in coma are at high risk to airway colonization and pulmonary infection by *S. aureus*.

The importance of an adequate antimicrobial treatment on the outcome of NP has been reported previously [3, 7] and should be emphasized, since NP is associated with a high mortality rate [3, 4]. However, aerobic Gram-negative bacilli were relatively uncommon causes of pneumonia on this highly selected population despite the fact that empirical broad-spectrum combination antibiotic therapy is so often directed at this subgroup. On the other hand, *S. aureus* is largely insensitive to the antimicrobial drugs usually selected for empirical treatment of NP. Our results suggest that antimicrobial drugs active against *S. aureus* should be included in the empirical antimicrobial regimen for treating NP in critically ill comatose patients, and this strategy may be useful to improve prognosis. Further studies investigating the efficacy of different interventions, such as the use of mupirocin, should be performed in order to reduce colonization by *S. aureus* and subsequent pneumonia in this population.

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