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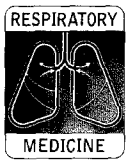

Original Articles

Aetiology of pneumonia following isolated closed head injury

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Patients undergoing mechanical ventilation (MV) after an isolated closed head injury (ICHI) have often been found to develop hospital-acquired pneumonia (HAP) well before subjects who require MV for different reasons. In a prospective study of patients receiving MV after an ICHI, 38 subjects (out of 65 with clinically suspected HAP) had a bacteriological diagnosis established on the basis of correspondence between cultures made from bronchoalveolar lavage and protected specimen brush (with quantitative thresholds of 10^4 and 10^3 cfu ml^{-1}, respectively). Patients were separated according to the time of onset of HAP, with 20 subjects who developed HAP within 4 days of the start of MV (early onset pneumonia, EOP) and 18 subjects who developed HAP after the fourth day (late onset pneumonia, LOP). In those who had LOP, an expected spectrum of organisms was found, with Gram-negatives (especially *Pseudomonas* sp.) accounting for the majority of isolates. However, in EOP cases, Gram-positive bacteria (especially *Staphylococcus* sp. and *Streptococcus pneumoniae*) were found to largely predominate ($P=0{\cdot}0000026$). This confirms the high incidence of staphylococcal pneumonia in neurosurgery patients, and also provides evidence that the vast majority of such staphylococcal pneumonia are EOP. Unlike most previous reports, the microbiological findings from the present study suggest that a cut-off point of 4 days successfully distinguishes between EOP and LOP. Since these two clinical entities differ significantly in terms of pathogenesis and aetiology, preventive measures and therapeutical protocols have to be tailored accordingly.

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Introduction

Hospital-acquired pneumonia (HAP) are among the most frequent complications of mechanical ventilation (MV) (1,2). Most of the current knowledge on pathogenesis of pneumonia in intensive care units (ICUs) has been drawn from studies carried out on patients suffering from a wide spectrum of primary diseases, with pre-existing, severe, chronic underlying clinical conditions in most cases.

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The recognized pathophysiological pattern entails airway colonization (mostly by Gram-negative rods) usually occurring within 48–72 h following intubation, with subsequent development of clinical disease 3–7 days thereafter (3,4). In this process, the oropharynx becomes colonized by Gram-negative aerobic bacteria, and it is suggested that aspiration of such organisms, which occurs around the cuff of endotracheal tubes (5), may eventually lead to acute bacterial pneumonia. According to this pattern, pneumonia in MV patients usually require several days to become clinically recognizable. In recent years, however, a subset of patients developing HAP within a significantly shorter time has been identified (6,7). This chronological difference suggests that while, in the former, some

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minimum time is necessary to allow oropharynx colonization to occur, in the latter, such a step is probably bypassed and pneumonitis is caused by aspiration of organisms commonly resident in the oropharynx (7,8). The latter pattern of HAP development in ICUs is particularly frequent in patients who had an isolated closed head injury (ICHI) (9), in whom a rather different microbial aetiology has also been documented. As compared with the general group of patients developing HAP following MV, these patients have been found to develop higher rates of HAP due to *Staphylococcus* sp.; a usual component of the commensal oropharyngeal flora (10–13).

On the basis of such differences, these two HAP forms have been termed 'early onset pneumonia' (EOP) and 'late onset pneumonia' (LOP), respectively. This separation implies two different aetiological patterns, and it is aimed to distinguish between two different empirical therapeutic strategies to be adopted in each case. However, it is not yet clear which is the best chronological threshold which separates EOP from LOP on an aetiological basis (14).

With the purpose of investigating a possible relationship between the chronology of onset and the aetiology of HAP, a prospective study was carried out on neurosurgical patients who underwent MV following an ICHI and developed HAP.

Patients, Materials and Methods

The study was carried out in the 25-bed ICU of the Institute of Neurosurgery of the University of Verona, which serves as both a reference centre and a first-line hospital. In addition to permanent members of the neurosurgical staff, specialists in infectious diseases and respiratory endoscopy are involved in patients' care on a daily basis as consultants.

A total number of 158 adults who underwent MV following an ICHI were admitted to the neurosurgical ICU in the period January–December 1993. From this series, patients under 15 years of age and those with chest or abdominal injuries or immobilizing skeletal disorders were excluded, as well as those who showed evidence of pulmonary infiltrates on the emergency room chest X-ray, and those with a known prior history of respiratory dysfunction.

All patients were endotracheally intubated either by oral or nasal endotracheal tube. Standard neurosurgical intensive care protocols were always adopted (15). No antibiotic regimen for prophylaxis of HAP or selective gastrointestinal decontamination was administered.

DIAGNOSIS OF PNEUMONIA

Diagnosis of HAP was established when new persistent infiltrates on chest X-ray were detected in the presence of fever (>38·5°C), leucocytosis (white blood cells $>12{\cdot}000\,\mu l^{-1}$) and purulent sputum.

Early onset pneumonia was diagnosed when these signs became recognizable within 4 days following institution of MV, while the diagnosis of LOP was established when signs of pulmonary infection were seen from the fifth day onwards, as done previously by others (6,7). According to prior reports, the present authors chose to investigate all the HAP cases which took place within 10 days of institution of MV, since cases occurring later are usually rare (7,9,16).

Bronchoscopy

In all patients with suspected HAP, bronchoscopy was performed within the first 12 h following the development of the first signs of pulmonary infection.

In order to avoid increased intracranial pressure or disturbances of ventilation, adequate sedation (morphine or propofol) and curarization (pancuronium bromide) were performed before undertaking the procedure.

The fibre bronchoscope (Olympus BF P10) was inserted into the endotracheal tube by means of a connector ensuring an air-tight seal. Secretions were cleared out (when present), and the bronchoscope was moved down to the orifice corresponding to the segment which was determined to be involved on the basis of the chest X-ray findings. The diagnostic manoeuvre based on protected specimen brush (PSB) (Microbiology Specimen Brush n. 1650, Microvasive Inc., Milford MA, U.S.A.) was performed according to a described standardized technique (17,18).

Following the brushing procedure, the bronchoscope was wedged in the same subsegmental bronchus, and bronchoalveolar lavage (BAL)

was carried out. Five separate 20 ml aliquots of saline non-bacteriostatic solution were serially instilled and collected. The first aliquot was discarded (19–21).

Specimen Processing

The brush was aseptically extracted and then cut into a sterile tube containing 1·0 ml of Ringer's lactate solution. After vigorous vortexing, 0·1 ml of the original suspension as well as 0·1 ml aliquots of serial dilutions (0·1, 0·01, 0·001) were inoculated into blood, chocolate and McConkey agars at 37°C.

Samples taken by BAL were homogenized by repeated aspiration with a conventional Pasteur's pipette. Serial 10-fold dilutions were made up in sterile saline solution, and 0·1 ml of each dilution were plated on the same agar culture media employed in PSB processing.

Growth in culture was evaluated 24 and 48 h following inoculation, and negative plates were discarded after no less than 6 days. Positive cultures were then processed for bacterial identification according to standard biochemical laboratory methods, and for quantitative measurement by counting the colony-forming units (cfu) per millilitre of Ringer's solution and BAL fluid for each identified species.

In accordance to previously described standards, quantitative thresholds of 10^3 and 10^4 cfu ml^{-1} for PSB and BAL, respectively, were adopted for differentiation between colonization and true infection (22). Bacterial isolates were definitely considered to be of aetiologic significance when present in both types of specimen (PSB and BAL) at a concentration equal to or greater than the described threshold values.

STATISTICS

The Fisher's exact test (23) was employed in the analysis of microbiological findings recorded in patients who developed an EOP and those who had LOP. A significance level of 0·05 was always adopted.

Results

HOSPITAL-ACQUIRED PNEUMONIA

Sixty-five of 158 patients (41·1%) had a clinical diagnosis of HAP. Of these patients, 38 had a microbiologically proven HAP as determined by quantitative cultures of PSB and BAL. In an additional 27 patients, the microbiological findings did not meet the defined diagnostic criteria, in spite of clinical evidence of HAP (EOP in 17 cases and LOP in 10 cases); these subjects were not included in the study. On the basis of the required correspondence between BAL and PSB, and according to the defined quantitative thresholds, a microbiological diagnosis was thus established in 58·5% of pneumonia suspected cases.

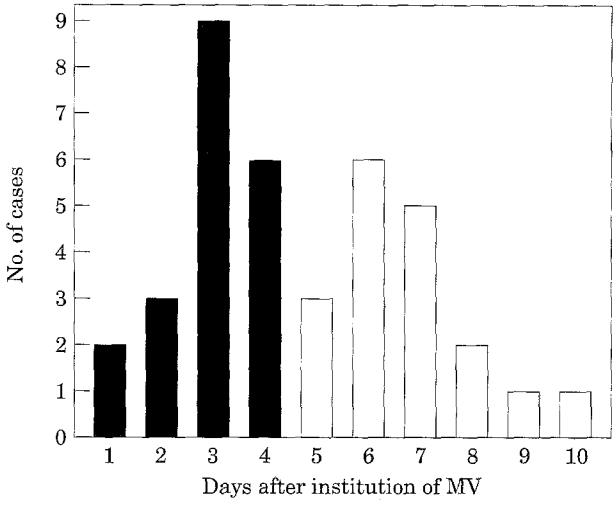

FIG. 1. Chronology of clinical onset of microbiologically documented bacterial pneumonia in 38 patients who underwent mechanical ventilation (MV) after an isolated closed head injury. Solid bars, early onset pneumonia; open bars, late onset pneumonia.

Of the 38 patients who met the inclusion criteria, 20 developed HAP within 4 days of intubation (EOP), while 18 did so after 4 days (LOP). The chronology of onset of pneumonia in the patients investigated is shown in Fig. 1. In three EOP cases and four LOP cases, a single pathogen was isolated, while in the remnants, a polimicrobial aetiology was documented.

In the EOP group, the mean age was 43·5 years (range 16–69 years) with 13 males and seven females, while in the LOP group, the mean age was 46 years (18–72 years) with 12 males and six females.

MICROBIOLOGY

Bacteria isolated from the 38 patients investigated are represented in Table 1 according to the

TABLE 1. Bacteria isolated from 38 patients who underwent mechanical ventilation (MV) following an isolated closed head injury are represented according to the time of onset of acute pneumonia

	EOP	LOP
Staphylococcus aureus	16	7
Staphylococcus epidermidis	4	1
Streptococcus pneumoniae	8	–
Pseudomonas aeruginosa	4	12
Xanthomonas maltophilia	1	5
Haemophilus sp.	1	–
Klebsiella sp.	5	3
Escherichia coli	–	5
Enterobacter sp.	–	1
Proteus sp.	–	6
Serratia sp.	–	4

EOP, early onset pneumonia, within the 4th day of MV; LOP, late onset pneumonia, at least 4 days after MV.

separation between subjects who had EOP and those with LOP.

The distribution of Gram-positive and Gram-negative isolates between the two groups is represented in Table 2 and Fig. 2. Gram-positive organisms were found to be significantly more frequent in the EOP group, while Gram-negative organisms were significantly predominant in subjects who developed LOP (Yates corrected $P=0{\cdot}0000026$).

Organisms belonging to the *Staphylococcus* sp. and *Pseudomonas* sp. (including *Xanthomonas maltophilia*) were found to be significantly more frequent in the EOP group (Yates corrected $P=0{\cdot}0031$) and in the LOP group (Yates corrected $P=0{\cdot}015$), respectively. Isolates of *Staphylococcus* sp. were grown from 85% of patients with EOP and from 38·9% of LOP cases (Yates corrected $P=0{\cdot}0091$), while *Pseudomonas aeruginosa* and *X. maltophilia* were found in 25 and 77·8% of EOP and LOP cases, respectively (Yates corrected $P=0{\cdot}0034$).

Discussion

Patients who undergo an ICHI represent a subset of the wide group of subjects who may develop an HAP after institution of MV. As opposed to the majority of subjects requiring MV, those who had an ICHI were generally healthy and ran a normal life until the traumatic event occurred. This implies that none of the identified risk factors which are known to predispose to oropharyngeal colonization with

TABLE 2. Microbiological findings observed in patients who developed early onset pneumonia (EOP) and late onset pneumonia (LOP) after an isolated closed head injury and institution of mechanical ventilation

	EOP		LOP
All isolates			
Gram+	28 (71·8%)	$P=0{\cdot}0000026$	8 (18·2%)
Gram −	11 (28·2%)		36 (81·8%)
Predominant species			
Staphylococcus sp.	20	$P=0{\cdot}0031$	8
Pseudomonas aeruginosa + *Xanthomonas maltophilia*	5	$P=0{\cdot}015$	17
Frequency in patients			
Staphylococcus sp.	17/20 (85%)	$P=0{\cdot}0091$	7/18 (38·9%)
Pseudomonas aeruginosa + *Xanthomonas maltophilia*	5/20 (25%)	$P=0{\cdot}0034$	14/18 (77·8%)

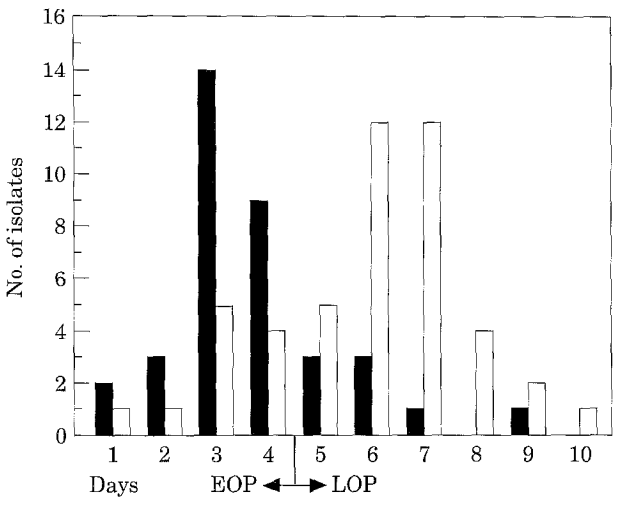

FIG. 2. Bacteria isolated from 38 patients who developed pneumonia after an isolated closed head injury; Gram-positive (solid bars) and Gram-negative (open bars) organisms are represented according to the day of bronchoscopic sampling (bronchoalveolar lavage and protected specimen brush following the institution of mechanical ventilation. EOP, early onset pneumonia; LOP, late onset pneumonia.

nosocomial pathogens can be considered as possible pre-existing conditions favouring the development of pneumonia.

It has been found that HAP following MV is mostly attributable to Gram-positive organisms if the disease develops in the first days of MV, while Gram-negative pathogens predominate if pneumonia occurs at a later time (24,25). This is in agreement with the hypothesis that the recently defined EOP in patients receiving MV is primarily due to aspiration of the resident original oropharyngeal flora, while LOP follows a prior colonization process from endogenous or exogenous sources (7,16). Such distinction between different pathogenetic mechanisms has to be considered when patients who had an ICHI are concerned. The latter undergo a sudden impairment of airway reflexes, including delay in glottic closure, absence of cough reflex and loss of spontaneous breathing activity in deep coma, which favours the aspiration of an otherwise commensal flora from nasal cavities and oropharynx (mostly formed by Gram-positive organisms).

In the present study, 38 patients who required MV after an ICHI were selected from a series of 65 subjects with suspected HAP on the basis of strictly defined diagnostic microbiological criteria. Correspondence between PSB and BAL bacteriological findings (above recognized quantitative thresholds) was found in 58·5% of cases of suspected pneumonia; a value close to that reported in prior studies (26).

The selected 38 patients were separated into two groups depending on the time of onset of pneumonia (within or after the 4th day). While those who had acute bacterial pneumonia diagnosed after the 4th day (LOP) were mostly affected by Gram-negative organisms — as expected on the basis of current knowledge on the aetiology of HAP — in the patients who developed pneumonia within 4 days (EOP) of MV, Gram-positive bacteria were by far the most common causative organisms. The latter represented 71·8% of the isolates grown from patients with EOP, while in the LOP group, Gram-negative organisms account for 81·8% of all isolates. Among Gram-positive bacteria, *Staphylococcus* sp. was isolated from 85% of EOP cases (and from 38·9% of LOP cases; $P=0{\cdot}0091$), while organisms belonging to *Pseudomonas* sp. (including *X. maltophilia*) were grown from 77·8% of LOP cases (and from 25% of EOP cases; $P=0{\cdot}0034$).

The present study results confirm the high frequency of staphylococcal pneumonia in neurosurgical patients requiring MV (10–13,27). Moreover, these data, unlike prior studies (not addressed to evaluate any chronological relationship between aetiology and time of onset of pneumonia), provide evidence that the vast majority of staphylococcal pneumonia in this setting are EOP. These findings are in agreement with the proposed pathogenetic pattern of EOP, such as that the sudden aspiration of the resident oropharyngeal flora is the central event leading to pulmonary infection (7,16). This pathogenetic hypothesis also supports the fact that all *S. pneumoniae* isolates were grown from patients with EOP (Table 1). Since *S. pneumoniae* is a component of the oropharyngeal flora of at least 5% of healthy adults (28) and has no role as a nosocomial pathogen, its concentration among subjects who developed EOP confirms that aspiration of the resident orophyaryngeal flora is the most likely mechanism accounting for such an early development of pneumonia after institution of MV.

These results are also of interest for the ongoing debate on the definition of the chronological threshold separating EOP from LOP (14). On the basis of the microbiological characterization, the cut-off point of 4 days adopted here seems to separate these two HAP forms properly. Most authors consider those pneumonia which develop 48 h after hospital admission as nosocomial (1,2,13,29), but in the present series, the cut-off point of 48 h would have been inadequate, as the majority of Gram-positive pneumonia were observed 3 and 4 days following the institution of MV (Fig. 2). As a consequence, these cases should have been classified as true nosocomial pneumonia (LOP) and consequently considered (erroneously) to be of Gram-negative aetiology. On an empirical treatment basis, the latter would have been an aetiological mistake, with possible consequences in terms of therapeutic failure. The cut-off point of 48 h is probably adequate for different clinical settings, in which a variety of conditions may have led to oropharyngeal colonization (usually by Gram-negative bacteria) well before the institution of MV. However, in the medical context investigated here, no prior illnesses were present before the acute cerebral injury occurred, and therefore there were no reasons justifying the adoption of the same cut-off point which is used in the more general setting of ICUs.

The high frequency of staphylococcal pneumonia in neurosurgery patients has led some authors (27–30) to recommend antimicrobial protocols, including drugs active against *Staphylococcus* sp., regardless of the time of onset of HAP. On the basis of the present results, the authors believe that such therapeutical strategy has to be strictly adopted in cases of HAP developing in the first 4 days following institution of MV (when the vast majority of staphylococcal pneumonia are observed), while the HAP cases taking place later than the 4th day have the same features of the usual forms of staphylococcal pneumonia encountered in ICUs (mostly due to Gram-negative organisms) and therefore should be approached accordingly.

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