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# Prognosis and risk factors of early onset pneumonia in ventilated patients with Guillain–Barré syndrome

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**Abstract** *Objective:* Invasive mechanical ventilation is required in 30% of patients with Guillain–Barré syndrome (GBS) and is associated with pneumonia and increased mortality. Our objective was to determine the incidence, characteristics, outcomes, and risk factors of pneumonia in GBS patients receiving mechanical ventilation. *Design and setting:* Study of a prospective database in an intensive care unit of a university hospital. *Patients:* The study included 81 patients who required intubation for GBS. Neurological findings, vital capacity, and signs of respiratory distress were recorded at admission and at intubation. A score predicting the risk of intubation (0–4) was calculated for each patient. Pneumonia was diagnosed based on predefined criteria and retrospectively confirmed by two observers. Early-onset pneumonia was defined as pneumonia diagnosed within 5 days after intubation. *Measurements and results:* Mean vital capacity was $57 \pm 22\%$ of predicted at admission and $33 \pm 11\%$ at intubation. Pneumonia developed in 63 patients (78%), including 48 with early-onset pneumonia. Bacteria were consistent with aspiration. Of the 63 patients with pneumonia 11 (18%) had septic shock, 6 (10%) had acute respiratory distress syndrome, and 9 (14%) died. In the univariate analysis milder weakness, a lower risk of intubation (score $< 2$), and time from admission to intubation longer than 2 days were associated with early-onset pneumonia. Time from admission to intubation was the only independent predictor in the multivariate logistic regression model. *Conclusions:* Early-onset pneumonia is a common and severe complication that is related to aspiration in patients with GBS. Delaying intubation may increase the risk of early-onset pneumonia.

**Keywords** Aspiration · Mechanical ventilation · Intubation · Early-onset pneumonia · Guillain–Barré syndrome

## Introduction

Guillain–Barré syndrome (GBS) is the most common cause of acute neuromuscular paralysis in industrialized countries, with an incidence ranging from 0.4 to 4 per 100,000 population [1]. The most severe complication of GBS is respiratory failure, which occurs in 20–30% of patients [2, 3, 4]. Respiratory muscle weakness leads to hypoventilation, impaired coughing, secretion retention, and atelectasis. Bulbar dysfunction often contributes to respiratory failure by causing aspiration, which has been documented in about half of all mechanically ventilated patients with GBS [5]. The risk of pneumonia increases with the severity of muscle weakness, being highest in ventilated patients and chiefly related to aspiration [4, 6]. Pneumonia is associated with increased mortality [7]. Therefore decreasing the occurrence of pneumonia would be expected to im-

prove survival in mechanically ventilated patients with GBS.

In an effort to develop strategies for preventing pneumonia we designed a study to identify risk factors for early-onset pneumonia that are amenable to therapeutic intervention in patients receiving mechanical ventilation (MV) for GBS. Preliminary results of this work have been presented elsewhere [8].

## Material and methods

### Patients

Patients were enrolled if they both fulfilled standard criteria for GBS [9] and required MV for more than 5 days. The decision to intubate was at the discretion of the attending physicians, who were aware of current recommendations to intubate patients who have either one major criterion (signs of respiratory distress consisting of paradoxical breathing and/or use of accessory muscles, $PaCO_2$ higher than 48 Torr or 6.4 kPa, $PaO_2$ less than 56 Torr or 7.5 kPa on room air, and vital capacity (VC) under 30% of predicted, about 15 ml/kg of body weight) or two minor criteria (bulbar dysfunction, impaired coughing, and atelectasis) [6, 10]. Exclusion criteria were age below 18 years, pregnancy, other cause of peripheral neuropathy, intubation before ICU admission, and MV for less than 5 days. All data were recorded prospectively.

Of the 360 patients admitted to our ICU for GBS between January 1996 and December 2002, 98 patients (27%) required MV (Fig. 1) including 12 who were started on MV before ICU admission and one who was found to have another neuropathy. This left 85 patients, of whom

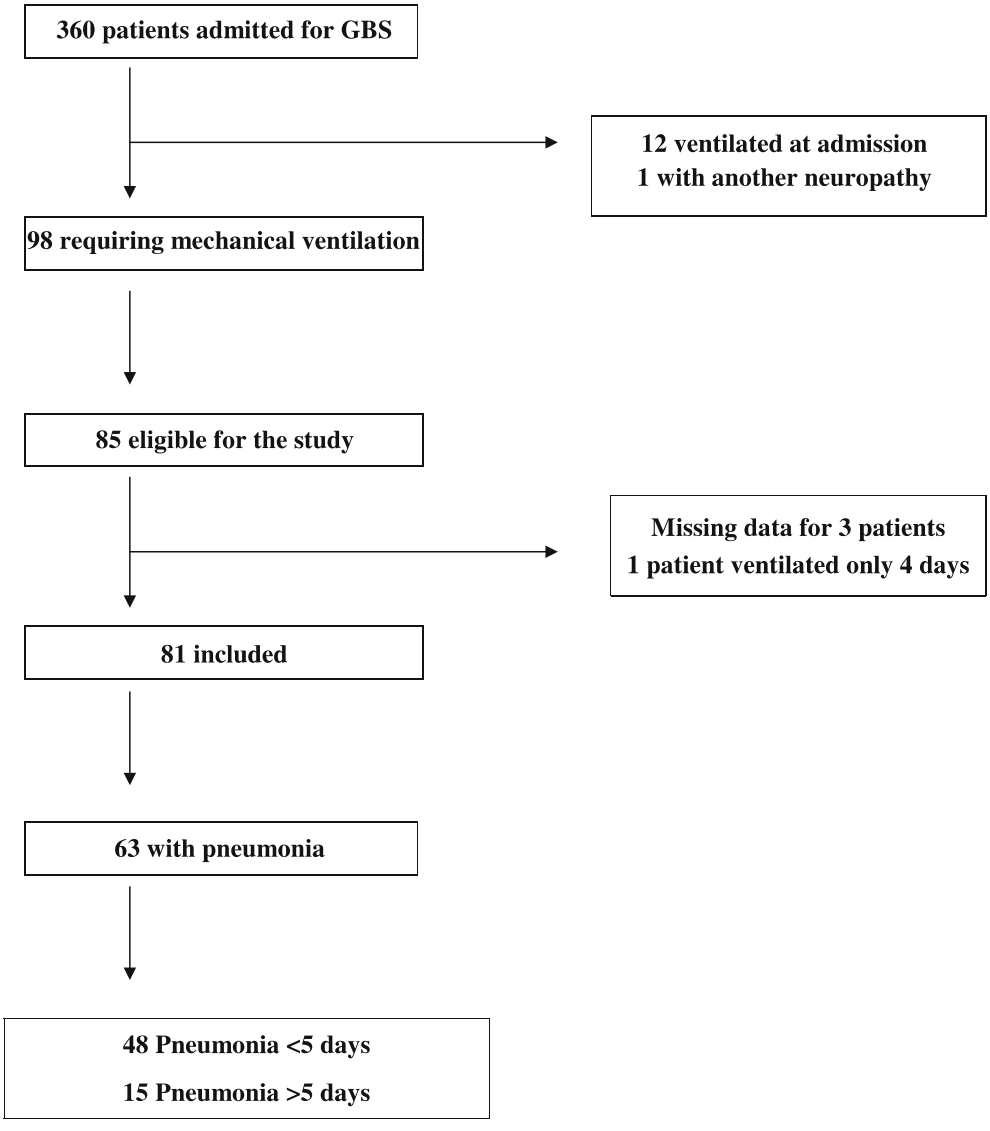


**Fig. 1** Distribution of patients who received mechanical ventilation for Guillain–Barré syndrome

three could not be evaluated, and one was ventilated for only 4 days. Thus 81 patients were included in the study (51 men, 30 women; mean age 54 ± 20 years). Patient characteristics at admission and at intubation are presented in Table 1. Median time from neurological symptom onset to ICU admission was 4 days (first quartile 3; third quartile 7). Mean Simplified Acute Physiology Score (SAPS) II was 24 ± 13 at admission. At admission impaired swallowing was noted in 34 (42%) patients and an inability to lift the head in 36 (44%). Mean Medical Research Council (MRC) sumscore was 28 ± 14 at admission and 23 ± 14 at intubation; corresponding mean VC values were 57 ± 22% and 33 ± 11.0%. Median time from admission to intubation was 3 days (2–5). Treatment for

**Table 1** Characteristics of the population and factors associated with early-onset pneumonia (within 5 days after initiation of mechanical ventilation) (*RR* relative risk, *SAPS II* Simplified Acute Physiology Score II, *VC* vital capacity, *MRC* sumscore, Medical Research Council sumscore, *IVIg* intravenous immunoglobulins, *PE* plasma exchange)

| | *n* | Pneumonia within 5 days | RR (95% CI) | *p* |
|---|---|---|---|---|
| Total | 81 | 48 (59%) | | |
| Age (years) | | | | |
| < 45 | 25 (31%) | 13 (52%) | 1 | |
| 45–64 | 29 (36%) | 19 (66%) | 1.26 (0.75–1.64) | 0.32 |
| ≥ 65 | 27 (33%) | 16 (59%) | 1.14 (0.63–1.56) | 0.60 |
| SAPS II | | | | |
| ≥ 30 | 23 (28%) | 13 (57%) | 1 | |
| < 30 | 58 (72%) | 35 (60%) | 1.07 (0.64–1.42) | 0.75 |
| MRC sumscore at admission | | | | |
| < 20 | 22 (32%) | 8 (36%) | 1 | |
| ≥ 20 | 46 (68%) | 30 (65%) | 1.79 (1.08–2.32) | 0.028 |
| Time from first signs to admission (days) | | | | |
| < 4 | 30 (38%) | 17 (57%) | 1 | |
| 4–6 | 23 (29%) | 13 (57%) | 1.00 (0.53–1.40) | 0.99 |
| ≥ 7 | 27 (34%) | 17 (63%) | 1.11 (0.65–1.47) | 0.63 |
| Swallowing difficulties at admission | | | | |
| No | 47 (58%) | 29 (62%) | 1 | |
| Yes | 34 (42%) | 19 (56%) | 0.91 (0.55–1.23) | 0.60 |
| Facial palsy at admission | | | | |
| No | 57 (71%) | 33 (58%) | 1 | |
| Yes | 23 (29%) | 14 (61%) | 1.05 (0.63–1.39) | 0.81 |
| Able to lift head | | | | |
| No | 36 (44%) | 17 (47%) | 1 | |
| Yes | 45 (56%) | 31 (69%) | 1.46 (1.00–1.79) | 0.051 |
| VC at admission (% of predicted) | | | | |
| ≥ 60% | 36 (47%) | 25 (69%) | 1 | |
| < 60% | 40 (53%) | 21 (53%) | 0.76 (0.43–1.06) | 0.14 |
| Time from admission to ventilation (days) | | | | |
| ≤ 2 | 38 (47%) | 15 (40%) | 1 | |
| > 2 | 43 (53%) | 33 (77%) | 1.94 (1.41–2.27) | 0.0009 |
| MRC sumscore at intubation | | | | |
| < 16 | 20 (29%) | 8 (40%) | 1 | |
| 16 to 30 | 24 (35%) | 16 (67%) | 1.67 (0.92–2.18) | 0.081 |
| > 30 | 24 (35%) | 14 (58%) | 1.46 (0.74–2.06) | 0.23 |
| VC at intubation (% of predicted) | | | | |
| ≥ 30% | 44 (61%) | 23 (52%) | 1 | |
| < 30% | 28 (39%) | 19 (68%) | 1.30 (0.84–1.63) | 0.19 |
| Intubation score | | | | |
| 3–4 | 29 (36%) | 12 (41%) | 1 | |
| 0–2 | 52 (64%) | 36 (69%) | 1.67 (1.13–2.06) | 0.016 |
| Treatment before ventilation | | | | |
| None | 48 (60%) | 30 (63%) | 1 | |
| IVIg | 4 (5%) | 2 (50%) | 0.80 (1.18–1.42) | 0.62 |
| PE | 28 (35%) | 15 (54%) | 0.86 (0.50–1.20) | 0.42 |

**Table 2** Criteria used for intubation in patients with and without pneumonia (all differences nonsignificant)

| Criteria | Total (*n* = 81) | Pneumonia (*n* = 63) | No pneumonia (*n* = 18) |
|---|---|---|---|
| Hypoxemia (< 56 Torr, 7.5 kPa) | 5 (6%) | 3 (5%) | 2 (11%) |
| Hypercarbia (> 48 Torr, 6.4 kPa) | 19 (23%) | 15 (24%) | 4 (22%) |
| Inability to clear airway | 39 (48%) | 31 (49%) | 8 (39%) |
| Mean vital capacity (% predicted) | 33 ± 11% | 32 ± 11% | 36 ± 11% |
| Presence of signs of respiratory distress | 36 (44%) | 31 (46%) | 5 (28%) |

GBS was started before intubation in 32 patients (40%). At least one major criterion for intubation was present in 55 patients (68%), including 34 (42%) with signs of respiratory distress. Criteria for intubation are reported in Table 2.

### Measurements

The following data were recorded at ICU admission: age, sex, SAPS II [11], time from motor weakness onset to ICU admission, MRC sumscore [12, 13], inability to raise the head, bulbar dysfunction, and facial palsy. Cerebrospinal fluid (CSF) analysis, liver enzyme (aspartate aminotransferase and alanine aminotransferase) assays, and standard electrophysiological testing within 2 days of admission were recommended. Neurological status and VC (percentage of predicted value) were assessed daily from admission to MV initiation. Time from ICU admission to MV initiation was recorded. At the time of the study we determined a risk-of-intubation score (0–4) based on features known to predict intubation: (a) time from GBS onset to ICU admission less than 7 days, (b) inability to raise the head, (d) VC less than 60% of predicted, and (d) bulbar dysfunction [14, 15].

### Definition of pneumonia in ventilated patients

Pneumonia was defined as a clinical suspicion with a new or worsening infiltrate on chest radiography and at least two of the following [16]: (a) temperature higher than 38.3 °C, (b) purulent tracheal secretions, and (c) white blood cell count higher than 12,000/mm$^3$ or lower than 4,000/mm$^3$. Bronchoalveolar lavage or protected specimen catheter samples were subjected to microbiological studies, which were considered positive if the number of colony-forming units (CFUs) was greater than $10^4$/ml. Pneumonia was classified as early-onset pneumonia when diagnosed within the first 5 days of MV and as late-onset pneumonia otherwise. Ventilator-associated pneumonia (VAP) was pneumonia starting at least 48 h after MV initiation [17, 18]. Antimicrobial therapy was at the discretion of the attending physician. Clinical, laboratory, radiological, and therapeutic data were reviewed retrospectively by two investigators (D.O. and B.C.).

### Follow-up

The following variables were recorded in the database: worst $PaO_2/FIO_2$ ratio, MV duration, and specific treatments for GBS (plasma exchange and intravenous immunoglobulins) with their time of initiation. We determined the proportions of patients who experienced the following events during their ICU stay: pneumonia, acute respiratory distress syndrome [19], septic shock [20], and tracheotomy. Mortality on day 28 after ICU admission was recorded.

### Statistical analyses

Variables are reported as numbers and percentages or means $\pm$ SD. For the statistical analysis continuous variables were categorized according to recognized cutoff values if available and approximate tertiles if not. Associations between potential risk factors and early-onset pneumonia were tested using logistic regression models. From the estimated odds ratios 95% confidence intervals (95% CIs), approximate relative risks with their 95% CIs were derived using the method of Zhang and Yu [21]. Multiple logistic regression with backward stepwise variable selection was used to identify the variables independently associated with early-onset pneumonia. Variables yielding $p$ values smaller than 0.20 in the marginal analysis were entered into the multivariate model. Variables with $p$ values larger than 0.05 were eliminated, whereas previously deleted variables were reentered into the final model at this 0.05 cutoff value. Model validity was examined using the Cessie and Van Houwelingen [22] goodness-of-fit test. Because plasma exchange adversely affects the clinical status of patients with infections, we tested the association between plasma exchange and pneumonia. Plasma exchange was handled as a time-dependent covariate in a Cox model. In this analysis all observations were censored after 5 days. The cumulative incidence of pneumonia during follow-up was estimated using the conventional method [23]. All tests were two-sided, and $p$ values of 0.05 or lower were considered significant. The R statistical package (The R Development Core Team, Vienna, Austria) was used for all statistical tests.

## Results

### Characteristics of pneumonia

Pneumonia developed in 63 (78%) patients, including 48 (76%) with early-onset pneumonia and 15 (24%) with late-onset pneumonia. Three patients experienced more than one episode of pneumonia. Pneumonia was polymicrobial in 31 (49%), including 21 (43%) with early-onset and 10 (67%) with late-onset pneumonia. The predominant organisms in patients with early-onset pneumonia were *Haemophilus influenzae* (23%), methicillin-susceptible *Staphylococcus aureus* (22%), *Streptococcus pneumoniae* (16%), and α-hemolytic streptococci (15%). In late-onset pneumonia the main organisms were *Pseudomonas aeruginosa* (20.6%), methicillin-susceptible *S. aureus* (17.6%), *Haemophilus influenzae* (14.7%), methicillin-resistant *S. aureus* (11.8%), and enterobacteria (11.8%; Fig. 2).

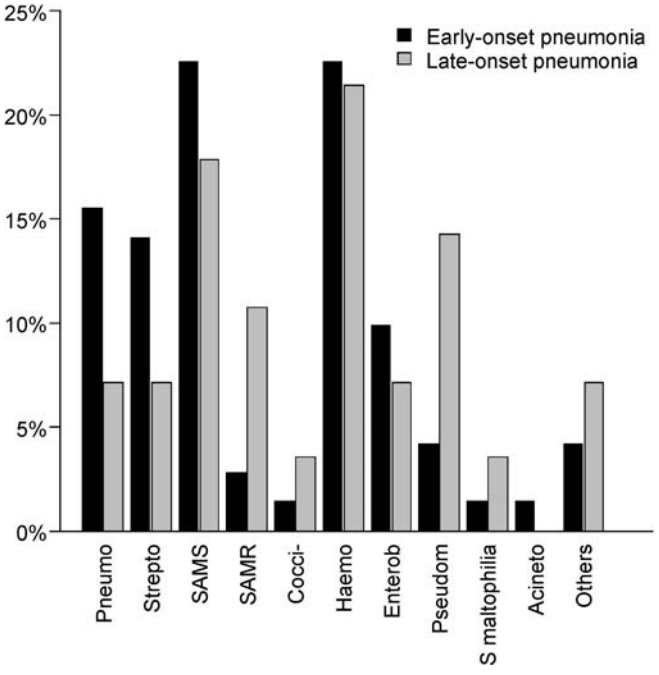


**Fig. 2** Organisms recovered in patients with early- and late-onset pneumonia. The numbers are percentages of total organisms in the study population. (*Pneumo Streptococcus pneumoniae*; *strepto* α-haemolytic streptococci; *MSSA* methicillin-susceptible *Staphylococcus aureus*; *MRSA* methicillin-resistant *S. aureus*; *haemo Haemophilus influenzae*; *enterob* Enterobacteria; *pseudom Pseudomonas aeruginosa*; *acineto Acinetobacter baumanii*, *S. maltophilia Stenotrophomonas maltophilia*; *other Corynebacterium*, *Enterococcus*, anaerobic organisms, and Gram-negative cocci)

Antibiotics were selected empirically based on onset characteristics then adjusted according to microbiological test results. The empirical regimen proved adequate in 48 (76%) cases. Septic shock developed in 11 (18%) patients and acute respiratory distress syndrome in 6 (10%) patients. Of the 81 patients 9 (14%) died. All the patients who died experienced pneumonia. Tracheostomy was required in 11 patients. No complications or deaths occurred in the group without pneumonia.

## Risk factors for pneumonia

In the univariate analysis an admission MRC sumscore greater than 20, a risk-of-intubation score lower than 2, and a time from ICU admission to MV initiation longer than 2 days were associated with early-onset pneumonia (Table 1). A trend was noted between an inability to lift the head and the occurrence of early-onset pneumonia. Factors that were not associated with pneumonia included

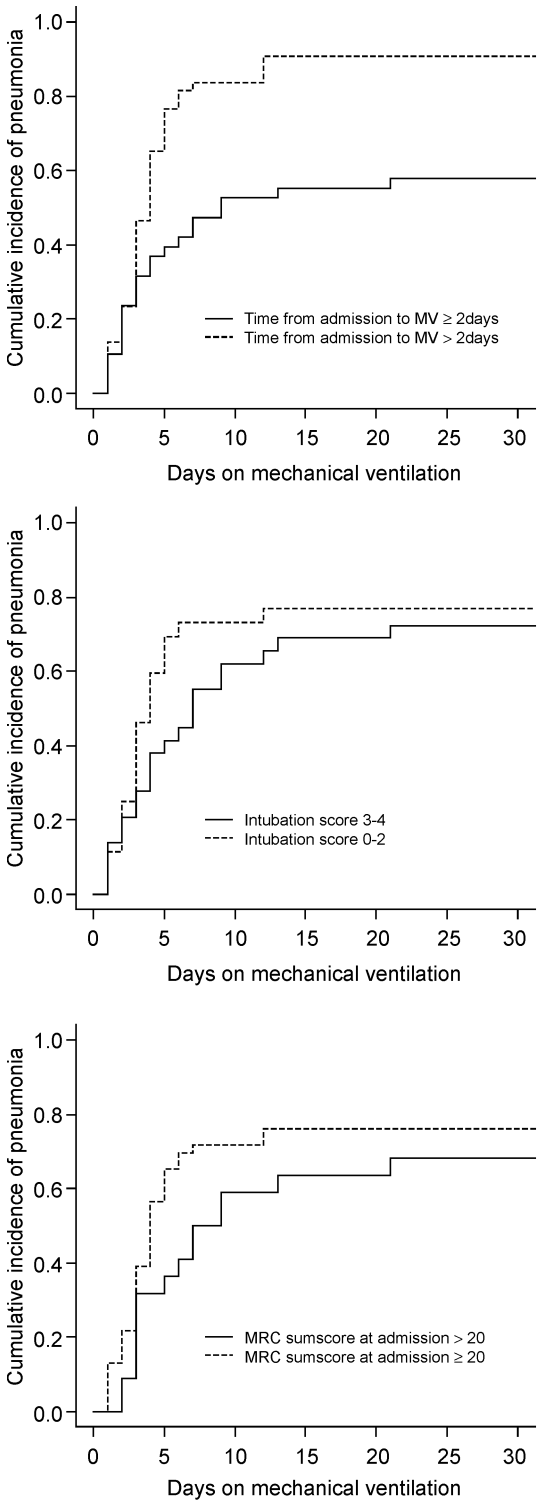


**Fig. 3** Cumulative incidence of pneumonia during the first 30 days on mechanical ventilation for Guillain–Barré syndrome

the time from GBS onset to ICU admission, bulbar involvement, VC, and type of treatment used before intubation. Figure 3 shows the cumulative incidence of pneumonia during the first 30 days of MV according to predictors identified in the univariate analyses. In the multiple logistic regression model only the time from ICU admission to intubation independently predicted early-onset pneumonia. Plasma exchange was not associated with the risk of early-onset pneumonia (hazards ratio, 0.87; 95% CI, 0.48–1.59; $p = 0.65$).

## Discussion

Early-onset pneumonia occurred in more than three-quarters of our patients receiving MV because of GBS. Similarly, pneumonia occurred in 53–83% of patients receiving MV for GBS in earlier studies, none of whom sought to identify risk factors for pneumonia. In our study a longer time from ICU from admission to intubation was the only factor independently associated with early-onset pneumonia.

Henderson et al. [24] reported that MV patients with GBS were at high risk for nosocomial pneumonia, which was the leading cause of death [25]. However, late-onset pneumonia was far more common than early-onset pneumonia in their study [24]. Whether this lower rate of early-onset pneumonia was related to earlier intubation cannot be determined, as the time from ICU admission to intubation was not reported. Furthermore, pneumonia rates were assessed retrospectively in a cohort of patients admitted to the ICU between 1976 and 1996 [25]. The epidemiology, causative organisms, and outcomes of VAP probably underwent major changes over the two decades of the study. Since 1996, which was the start date for our study, new multiresistant micro-organisms have emerged, and new treatment guidelines have been issued [26, 27, 28]. Furthermore, specific treatments for GBS have changed in recent years.

Because early-onset pneumonia is related chiefly to aspiration [29] and constitutes a common source of morbidity and mortality in patients with acute neurological disease, we considered all episodes of early-onset pneumonia, even those occurring within the first 48 h of MV initiation. The microbiological profile seen in our patients with early-onset pneumonia was consistent with aspiration and similar to that found in patients with pneumonia during a coma [30]. Multiresistant bacteria may be identified in patients with early-onset pneumonia [31]. Upper-airway colonization has been demonstrated to be an independent risk factor for VAP [32] and for early-onset pneumonia in patients with critical neurological conditions [33, 34]. In patients who are conscious but unable to cough and to protect their airways, a pattern seen in GBS, underestimation of bulbar dysfunction severity may lead to delayed intubation and therefore to an increased risk of aspiration [35]. Aspiration may occur at any time but is particularly common during sleep. Feeding via a nasogastric tube without oral intake does not prevent salivary aspiration. Impaired coughing may lead to accumulation of airway secretions, atelectasis, and pneumonia, particularly when bulbar function is compromised [36]. Impairment of coughing and swallowing is difficult to assess objectively in everyday practice. No guidelines for assessing bulbar function or coughing in patients with GBS are available, to our knowledge. Cough augmentation has been shown to decrease respiratory morbidity in patients with chronic neuromuscular disorders, but whether the same is true in GBS has not been determined [37]. These data suggest that delaying intubation may increase the risk of pneumonia by increasing the opportunities for aspiration.

Aspiration may occur during intubation [38]. We recorded neither the duration of the intubation procedure nor the sedative and neuromuscular-blocking drugs used for intubation. However, guidelines have been established in our ICU to standardize the intubation procedure [39]. Although patient position during the days preceding intubation and before the occurrence of pneumonia was not recorded, we usually keep patients with GBS in the semirecumbent position to decrease the risk of aspiration [40]. The severity and neurological pattern of GBS did not differ between our study and previous studies [14]. The clinical, laboratory, and electrophysiological features of GBS in our patients were consistent with those reported previously in Western countries [41, 42], indicating that our population was representative of ICU patients with GBS.

Our study suggests that determining the best time for intubation and MV initiation may be crucial in patients with GBS. Two recent studies sought to identify factors predicting a need for MV. Bulbar dysfunction and a VC less than 20 ml/kg predicted MV in one of these studies [14]. In the other, which was conducted by our group, ICU admission within 7 days after GBS onset, inability to lift the head, and a VC less than 60% of predicted were independent predictors of respiratory deterioration [15]. MV was required in over 80% of patients who had these three factors at ICU admission. Interestingly, in our study the pneumonia risk was higher in patients with a low intubation score and a high MRC sumscore, indicating less severe GBS at ICU admission. Presumably, respiratory, and neurological monitoring was less stringent in these patients with milder impairments at admission. Furthermore, published criteria for intubation [6, 43] reflect impending respiratory arrest and may lead to excessively late intubation in patients with GBS, who need MV not only because of respiratory failure, but also for airway protection [44].

The high rate of pneumonia in our study indicates a need for considering the possibility that pneumonia was overdiagnosed. Atelectasis may be very difficult to distinguish from pneumonia, especially in patients

with neuromuscular disorders. However, the diagnosis of pneumonia in our study relied on established criteria and was confirmed retrospectively by two investigators. Furthermore, the incidence of pneumonia in our patients was similar to that in earlier studies [4], and the detailed protocol for nosocomial-infection assessment and antibiotic therapy that is used in our ICU is conducive to optimal diagnosis of pneumonia. The rate of early-onset pneumonia in our patients was consistent with that in critically ill patients with coma [34]. In addition, the overall incidence of pneumonia in our ICU, assessed using the same criteria as in our study, is 25.7% (cumulative incidence 21/1000 days of MV, personal data), which is consistent with reports from other ICUs [45, 46], suggesting that the pneumonia rate was not overestimated. The micro-organisms identified in our GBS patients with pneumonia were similar to those reported in other ICU populations, most notably patients with early-onset pneumonia complicating acute neurological disease [29], suggesting that the bronchial specimens were correctly sampled and examined [47].

The high rate of pneumonia in our patients with GBS was probably related to underestimation of the risk of aspiration, rather than to inappropriate evaluation of established criteria for intubation, i.e., of the risk of respiratory failure. A longer time to intubation was independently associated with an increased risk of early-onset pneumonia. This finding indicates a need for separately evaluating the risk of aspiration and the risk of respiratory failure. Further studies are needed to identify GBS patients at high risk for aspiration among those who will progress to MV. The results of these studies may lead to strategies for decreasing the rate of pneumonia and therefore improving the prognosis of GBS. We believe that a simple and reliable test for assessing bulbar dysfunction and cough impairment is needed. It would be of considerable interest to determine whether earlier intubation reduces the incidence of pneumonia. Furthermore, a short course of antibiotic therapy following intubation or oral decontamination to prevent aspiration of contaminated oropharyngeal secretions deserves to be evaluated in GBS [30]. Although early tracheostomy is not usually performed in GBS patients except those at risk for prolonged ventilation [48] recent findings suggest that early tracheostomy may prevent pneumonia, decrease ICU length of stay, and decrease mortality [49]. Finally, as previously suggested [14], the high rate of pneumonia in patients receiving MV for GBS invites skepticism about the appropriateness of noninvasive MV in patients with GBS, even those without overt evidence of bulbar dysfunction.

In conclusion, in patients who are receiving MV for GBS, early-onset pneumonia is a common and serious event that is related chiefly to aspiration and independently related to delayed intubation. Delaying intubation in patients at risk for progression to respiratory failure may be unwise. The impact of early respiratory intervention and MV on the incidence of pneumonia needs to be assessed in this population.

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