Nosocomial Pneumonia After Acute Stroke
Implications for Neurological Intensive Care Medicine

Ruediger Hilker, MD; Carsten Poetter, MD; Nahide Findeisen, MD; Jan Sobesky, MD; Andreas Jacobs, MD; Michael Neveling, MD; Wolf-Dieter Heiss, MD

Background and Purpose—Pneumonia has been estimated to occur in about one third of patients after acute stroke. Only limited data are available on stroke-associated pneumonia (SAP) in specialized neurological intensive care units (NICUs).

Methods—We enrolled 124 patients with acute stroke who were treated at our university hospital NICU in a prospective observational study. Incidence rates and risk factors of SAP and long-term clinical outcome were determined.

Results—SAP incidence was 21% with a spectrum of pathogens, which is comparable to previously published data on general ICU patients. Mechanical ventilation, multiple location, and vertebrobasilar stroke, as well as dysphagia and abnormal chest x-ray findings, were identified as risk factors for the disease. SAP patients showed higher mortality rates than nondiseased subjects (acute, 26.9% versus 8.2%; long-term, 35.3% versus 14.3%) and a significantly poorer long-term clinical outcome (Barthel Index, 50.5±42.4 versus 81.5±27.8; Rankin Scale, 3.5±1.7 versus 2.2±1.6).

Conclusions—Our data underline the considerable epidemiological and prognostic impact of SAP for the treatment of acute stroke patients in a specialized NICU setting. They demonstrate that the occurrence of SAP deteriorates clinical outcome in these patients. Our results allow us to identify high-risk stroke patients at time of NICU admission in whom the use of preventive treatment strategies is most promising. (Stroke. 2003;34:975-981.)

Key Words: intensive care units • pneumonia • stroke

The overall prognosis of patients with acute ischemic brain infarction is crucially dependent on the occurrence of medical complications in the course of the disease that have been found to occur in 59% of stroke patients, leading to death in up to 23% during the hospital stay. Among them, nosocomial infections have been estimated to develop in about one third of patients with acute stroke, most commonly affecting the urinary tract and the lungs. As a result of recent advances in stroke treatment, an increasing number of patients are treated nowadays in specialized wards, eg, stroke units or neurological intensive care units (NICUs). Note that the highest incidence and mortality rates of pneumonia are observed in ICUs, where ~10% to 25% of patients develop the disease. Therefore, these treatment settings imply certain infectious risks that are closely associated with intensive care medicine in general, despite their undoubted benefits for stroke patients. Only limited data are currently available on infection after acute ischemic stroke and incidence rates of nosocomial infections in NICUs. A prospective study investigating the association of pneumonia and acute stroke as the infectious and neurological diseases with highest prevalence rates is still lacking. Therefore, we focused on the coincidence of acute stroke and stroke-associated pneumonia (SAP) in patients treated in an NICU in a university hospital setting.

Subjects and Methods

Study Population
We performed a prospective observational study of consecutive patients with acute stroke who were admitted to the NICU of the Neurology Department at Cologne University Hospital over a 1-year period. The NICU has 9 beds and an annual inpatient count of ~500 patients with 1200 ventilator days per year. The presence of acute stroke was defined in all patients in whom the time interval between symptom onset and NICU treatment was <24 hours and in whom the ischemic brain lesion was clearly visible in cerebral CT or MRI. Data on all acute stroke patients with an NICU stay of at least 24 hours were collected.

Surveillance and Data Collection
A daily surveillance of the study subjects was performed by 4 trained and experienced clinicians (R.H., J.S., M.N., A.J.) from time of admission to 48 hours after NICU discharge. Each patient was followed up by the same observer over the entire study period. One infection control practitioner (C.P.) attended the NICU every 1 to 2 weeks for supervision. Study records were kept on distinct data sheets. On admission, history of lung and heart diseases and general disease severity (Acute Physiology and Chronic Health

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From the Departments of Neurology (R.H., N.T., J.S., A.J., M.N., W.-D.H.) and Hospital Infection Control (C.P.), University Hospital, Cologne, Germany.
Correspondence to Prof Dr Wolf-Dieter Heiss, Department of Neurology, University Hospital, Joseph-Stelzmann-Strasse 9, D-50924 Cologne, Germany. E-mail wdh@pet.mpinn-koeln.mpg.de
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Analysis of variance with posthoc Bonferroni-adjusted contrasts was used on clinical scores (NIHSS, GCS, APACHE II), controlling for possible confounding covariates, was fitted by forward stepwise selection (for inclusion, 5%; for exclusion, 10%) from the 7 categorical variables found to be significant for SAP development at the 5% level in the univariate analysis (Table 1). A repeated-measures analysis of variance with posthoc Bonferroni-adjusted contrasts was used on clinical scores (NIHSS, GCS, APACHE II), with the occurrence of SAP as a between-subjects factor and time (days 1 to 3 after NICU admission) as a within-subjects factor. All probability values are 2 sided, and the level of significance was set at P<0.05.

Results

Evaluation [APACHE II] index, severity of neurological deficit (National Institute of Health Stroke Scale [NIHSS]), and impairment of consciousness (Glasgow Coma Scale [GCS]) were measured on each of the first 3 days after admission. In the same time window, the presence of dysphagia was screened in all study subjects by the study clinicians. In case of swallowing dysfunction, a definitive examination was performed by trained speech-language therapists comprising subtle clinical examination and additional water swallowing or pharyngeal sensation test. Dysphagia was diagnosed if positive clinical signs were accompanied by pathological findings in either additional test. Only dysphagia diagnosed before SAP manifestation was included in the risk factor analysis. The need for mechanical ventilation (MV) was decided in patients with severe impairment of consciousness, respiratory failure (sustained arterial PaO\(_2\) <65 mm Hg, PaCO\(_2\) >50 mm Hg), and severe swallowing dysfunction. Respiration FiO\(_2\) levels were kept below 60% in all cases to avoid oxygen-related damage of lung tissue. Pathological findings in the initial chest x-ray after admission were recorded. Cerebral CT- or MRI-documented ischemic infarctions were classified according to the affected vascular territory. Infarctions in the territory of the middle cerebral artery (MCA) were further subdivided according to the size of the ischemic lesion (I, 0.33%; II, 33% to 66%; III, >66% of the MCA territory affected).

Definition of SAP

SAP was diagnosed by the study clinician team in close collaboration with the infection control practitioner according to Centers for Disease Control and Prevention (CDC) criteria with clinical (lung auscultation and percussion, presence of fever, purulent tracheal secretion), microbiological (tracheal specimens, blood cultures), and chest x-ray findings. The date of onset of the first incident per patient was recorded. Infections occurring within the first 72 hours of NICU treatment were defined as early-onset pneumonia (EOP). All infections in mechanically ventilated patients were assigned as ventilator-associated pneumonia (VAP).

Estimation of Clinical Outcome

By means of a follow-up survey undertaken with a mean time interval of 14.6±3.7 months after NICU discharge, the long-term clinical outcome could be measured in 70 stroke patients (10 with SAP, 60 without SAP; 15 patients died during NICU treatment; 16 died after NICU discharge; 23 patients had no follow-up data). Telephone interviews with the patients or their caregivers were performed, and the Barthel Index and Rankin Scale were used as outcome measures.

Statistical Analysis

Values are expressed as mean±SD. Categorical data were analyzed by χ\(^2\) test or Fisher’s exact test estimating relative risk (RR) factors for SAP development with corresponding 95% confidence intervals (CIs). Subsequently, a multivariable logistic regression model, controlling for possible confounding covariates, was fitted by forward stepwise selection (for inclusion, 5%; for exclusion, 10%) from the 7 categorical variables found to be significant for SAP development at the 5% level in the univariate analysis (Table 1). A repeated-measures analysis of variance with posthoc Bonferroni-adjusted contrasts was used on clinical scores (NIHSS, GCS, APACHE II), with the occurrence of SAP as a between-subjects factor and time (days 1 to 3 after NICU admission) as a within-subjects factor. All probability values are 2 sided, and the level of significance was set at P<0.05. Statistical analyses were performed with SPSS 10.0 for Windows (SPSS Inc).

TABLE 1. SAP Risk Factors and Stroke Location in 124 Patients With and Without SAP Who Have Been Treated in an NICU

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>SAP* (n=26)</th>
<th>Non-SAP* (n=98)</th>
<th>RR</th>
<th>95% CI</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>14 (53.8)</td>
<td>22 (22.4)</td>
<td>4.74</td>
<td>1.80–12.45</td>
<td>0.000</td>
</tr>
<tr>
<td>MV</td>
<td>14 (53.8)</td>
<td>3 (3.1)</td>
<td>7.34</td>
<td>4.13–13.07</td>
<td>0.000</td>
</tr>
<tr>
<td>Abnormal chest x-ray</td>
<td>18 (69.2)</td>
<td>29 (29.6)</td>
<td>4.05</td>
<td>1.83–8.95</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA I (&lt;33%)</td>
<td>3 (11.5)</td>
<td>43 (43.9)</td>
<td>0.22</td>
<td>0.07–0.70</td>
<td>0.002</td>
</tr>
<tr>
<td>MCA II (33–66%)</td>
<td>2 (7.7)</td>
<td>18 (19.4)</td>
<td>0.43</td>
<td>0.11–1.69</td>
<td>0.188</td>
</tr>
<tr>
<td>MCA III (&gt;66%)</td>
<td>8 (30.8)</td>
<td>15 (15.3)</td>
<td>1.95</td>
<td>0.97–3.93</td>
<td>0.071</td>
</tr>
<tr>
<td>ACA</td>
<td>0 (0.0)</td>
<td>2 (2.0)</td>
<td>N/A</td>
<td>N/A</td>
<td>0.460</td>
</tr>
<tr>
<td>PCA</td>
<td>1 (3.8)</td>
<td>7 (7.1)</td>
<td>0.58</td>
<td>0.90–3.75</td>
<td>0.543</td>
</tr>
<tr>
<td>Brain stem</td>
<td>2 (7.7)</td>
<td>6 (6.1)</td>
<td>1.21</td>
<td>0.35–4.23</td>
<td>0.772</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>1 (3.8)</td>
<td>4 (4.1)</td>
<td>0.95</td>
<td>0.16–5.69</td>
<td>0.957</td>
</tr>
<tr>
<td>Multiple hemispheric stroke‡</td>
<td>4 (15.4)</td>
<td>3 (3.1)</td>
<td>3.04</td>
<td>1.44–6.39</td>
<td>0.016</td>
</tr>
<tr>
<td>Multiple vertebrobasilar stroke§</td>
<td>5 (19.2)</td>
<td>0 (0.0)</td>
<td>5.67</td>
<td>3.84–8.35</td>
<td>0.000</td>
</tr>
<tr>
<td>Vertebrobasilar stroke</td>
<td>8 (30.8)</td>
<td>10 (10.2)</td>
<td>3.91</td>
<td>1.36–11.28</td>
<td>0.008</td>
</tr>
</tbody>
</table>

ACA indicates anterior cerebral artery; PCA, posterior cerebral artery.
*Data are expressed as total number (percentage proportion) of all stroke patients in that group.
†Between-group comparison between SAP and non-SAP subjects with χ\(^2\) test or Fisher’s exact test (ACA) (significant values of P<0.05 in bold).
‡More than 1 vascular hemispheric territory (MCA, ACA, PCA) affected by the ischemic lesion.
§Brain stem and cerebellum simultaneously affected by the ischemic lesion.
Acute Ischemic Brain Infarction and Concomitant Diseases

Hemispheric infarction was documented in 106 patients with >1 hemispheric territory affected in 7 of 106 subjects. Eighteen patients suffered from vertebrobasilar stroke with simultaneous lesions in the brain stem and cerebellum in 5 of 18 subjects. There was no overlap between stroke locations; ie, simultaneous acute infarctions in hemispheric and verteobasilar territories were not found. The percentage distribution of infarct sites is presented in Table 1 for the SAP and non-SAP groups.

SAP: Epidemiology, Microbiological Monitoring, and Treatment Response

The overall incidence rate of SAP was 26 of 124 (21%) with a mean latency between NICU admission and disease manifestation of 1.8±1.9 days (range, 0 to 6 days). There was no significant difference between the SAP and non-SAP groups with regard to age and sex. SAP developed in 15 of 26 patients (58%) within the first 48 hours and in 19 of 26 patients within the first 72 hours of NICU treatment (73% fulfilling EOP criteria). From blood and/or tracheal specimens, a single pathogen (Staphylococcus aureus, n=3; Klebsiella oxytoca, n=2; Enterobacter species, n=1; Escherichia coli, n=1) was isolated in 7 of 26 patients, whereas 2 pathogens (Escherichia coli and Candida albicans, n=1; Klebsiella oxytoca and Enterobacter species, n=1; Candida albicans and Candida glabrata; n=1) were found in 3 of 26 cases. With the exception of 1 patient (monoinfection with Klebsiella oxytoca), all positive cultures were found in stroke patients with VAP (pathogen verification in 9 of 14 or 65% of VAP cases). At the time of SAP diagnosis, a clear pulmonary infiltrate in chest x-rays was diagnosed in 7 of 10 cases without cerebral involvement and in 11 of 16 culture-negative patients, whereas only atelectasis was noted in 3 of 10 culture-positive and 5 of 16 culture-negative SAP subjects. However, all patients without definite infiltrate fulfilled the CDC criteria by the presence of fever, pathological findings in clinical lung examination, and purulent tracheal secretion. Immediately after NICU admission, chest x-ray infiltrate was noted in 4 of 26 SAP patients (3 culture negative, 1 culture positive), suggesting prior aspiration. Several days after SAP diagnosis, additional urinary tract infection was found in 4 of 26 SAP patients (2 culture negative, 2 culture positive) and 1 epididymitis in a culture-negative SAP subject.

All SAP patients were treated with intravenous antibiotics, leading to subsequent fever reduction. However, elevated mean serum glucose levels and body temperatures over the first 5 days after SAP manifestation were found despite symptomatic therapeutic interventions (Table 2). Patients with SAP stayed significantly longer in the NICU compared with the non-SAP group (12.3±9.5 versus 6.3±6.0 days; P<0.001, unpaired t test).

Risk Factors for SAP

Results of the univariate SAP risk factor analysis are summarized in Table 1 and Figure 1. Patients with vertebrobasilar stroke had a significantly higher risk of developing SAP than subjects with a hemispheric lesion (RR, 3.9; P=0.05, χ² test). Furthermore, patients with >1 infarcted vascular territory were at higher risk (multiple lesion stroke: vertebrobasilar, RR, 5.7; P<0.001; hemispheric, RR, 3.0; P<0.05, χ² test). In case of small MCA infarction (type I), the risk of SAP was significantly lower compared with other infarction sites (RR, 0.22; P<0.05, χ² test).

MV was needed in 17 patients. The mean length of MV was 9.3±9.4 days. VAP occurred in 14 of 17 patients (82.4%), with a mean latency between endotracheal intubation and VAP occurrence of 1.1±1.8 days. Thus, the need for MV led to a significantly increased RR for pneumonia of 7.3 (P<0.001, χ² test).

TABLE 2. Physiological Parameters Monitored in an NICU in 26 Patients With SAP Over 5 Days From Time of SAP Diagnosis (Day 0)
Dysphagia was present in 36 of 124 patients and was associated with a significantly increased risk for SAP (RR, 4.7; \(P<0.01\), \(\chi^2\) test). Pathological findings in the initial chest x-ray were found in 47 of 124 subjects (51% cardiomegaly, 30% pulmonal congestion, 7% atelectasis, 5% pleural effusion, 4% pulmonal infiltrate, 3% emphysema). They were also related to a significantly increased SAP incidence (RR, 4.1; \(P<0.001\), \(\chi^2\) test). In contrast, this relationship was not detected for the presence of concomitant cardiac and pulmonal diseases and other cerebrovascular risk factors (data not shown).

A multivariable logistic regression analysis with forward stepwise factor selection yielded the following variables as independent risk factors for SAP in acute stroke patients: MV (\(P<0.001\); odds ratio [OR], 35.7; 95% CI, 6.5 to 194.7), abnormal chest x-ray on admission (\(P=0.005\); OR, 7.3; 95% CI, 1.8 to 29.2), and dysphagia (\(P=0.064\); OR, 3.3; 95% CI, 0.9 to 11.7). The logistic regression model reached a 97.4% sensitivity and a lower 45.5% specificity for individual SAP occurrence prediction (cutpoint, 0.5).

**Clinical Scores**

SAP patients scored significantly worse with respect to general disease severity, neurological deficit, and consciousness over the first 3-day period of NICU treatment (APACHE II, \(F=81.8\); NIHSS, \(F=42.6\); GCS, \(F=65.4\); \(P<0.001\) for each subscore). The occurrence of SAP significantly interacted with the time course of all subscores (APACHE II, Wilks-Lambda \(F=8.3\), \(P<0.001\); NIHSS, Wilks-Lambda \(F=8.2\), \(P=0.001\); GCS, Wilks-Lambda \(F=4.9\), \(P<0.001\)), leading to an increase in general disease severity and neurological deficit over time exclusively in the SAP group. Moreover, consciousness deteriorated more in SAP than in non-SAP patients (Figure 2).

**Clinical Outcome**

The overall mortality rate of the study population during the NICU treatment period was 15 of 124 (12.1%) with a significantly higher mortality in the SAP (7 of 26, 26.9%) compared with the non-SAP (8 of 98, 8.2%) group, resulting in an RR of 3.3 to die from acute stroke in the presence of SAP (\(P<0.05\), \(\chi^2\) test). During the poststroke follow-up period, the mortality rate was significantly higher in the SAP group (6 of 17, 35.3%; causes of death: 2 cardiac arrhythmia, 1 heart failure, 1 second pneumonia, 2 unknown) compared with non-SAP subjects (10 of 60, 14.3%; RR, 2.5; 95% CI, 1.0 to 5.9; \(P<0.05\), \(\chi^2\) test; causes of death: 3 pulmonary embolism; 2 second ischemic stroke, 1 cerebral hemorrhage, 1 pharyngeal carcinoma, 1 cardiac arrhythmia, 2 unknown). At time of the follow-up survey, SAP patients had a significantly higher Rankin Scale score (3.5±1.7 versus 2.2 in non-SAP patients; \(P<0.05\), unpaired \(t\) test) and a lower Barthel Index (50.5±42.4 versus 81.5±27.8; \(P<0.05\), unpaired \(t\) test), indicating impaired clinical outcome in pneumonia subjects (Figure 3).

**Discussion**

The overall SAP incidence of 21.4% in our study population is near the upper limit of the 10% to 25% incidence rates found in large multicenter studies on medical and surgical ICU patients.19,20 Thus, NICU-treated patients with acute stroke have to be considered a high-risk group for the development of pneumonia. The criteria of EOP were fulfilled in \(\approx75\%\) of cases, and 58% developed the disease within the first 48 hours of NICU treatment. Therefore, a considerable number of SAP cases are presumably community acquired soon after stroke onset.

The spectrum of pathogens found in our study is in line with previously published data on pneumonia in neurosurgical ICU patients.21 Etiological agents for bacterial pneumonia vary by type of hospital, patient population at risk, diagnostic methods, and the microbial flora in the ICU.6 In general, Gram-negative bacilli have been implicated in 40% to 60%, *Staphylococcus aureus* in 20% to 40%, and anaerobic bacteria in 0% to 35% of cases.5,6 The high frequency of aerobic Gram-negative pathogens found in our SAP population may point to endogenous lung colonization after aspiration of oropharynx secretions. Otherwise, Gram-negative bacteria and *Staphylococcus aureus* may be acquired by exogenous sources such as the hands of hospital personnel.

The mean length of NICU stay was 6 days longer in patients with SAP compared with nondiseased subjects. Furthermore, we found a significantly increased risk of death in SAP patients during both the NICU treatment and the poststroke follow-up period. These data are in line with previous results on pneumonia lethality in general ICUs.22,23
They clearly indicate that the occurrence of SAP is responsible for prolonged ICU stay, excess mortality, and extra treatment costs. Moreover, we found that long-term clinical outcome is impaired in stroke patients who suffered from SAP during their acute illness. This finding may be explained by more extended cerebral infarctions and subsequent more pronounced poststroke deficits in SAP patients. Otherwise, we found elevated mean serum glucose levels and body temperatures after SAP manifestation despite symptomatic therapeutic interventions. Therefore, these SAP-induced dysregulations of body homeostasis might also deteriorate the ability of functionally impaired but morphologically preserved tissue (ischemic penumbra) to recover from ischemia because hyperglycemia, fever, and impaired oxygen supply are known to deteriorate clinical outcome in patients with acute stroke.

We demonstrated that MV is an independent risk factor for SAP in acute stroke patients. Thus, the need for endotracheal intubation is highly predictive of SAP development, which is in agreement with previous findings. Steiner and colleagues found that clinical outcome of ventilated stroke patients is better than previously reported. Several studies have shown that MV exposes ICU patients to a significantly increased risk of ventilator-associated pneumonia. In our study, early-onset VAP developed in ~83% of intubated stroke patients, which is even more frequent than the 70% VAP incidence reported in a previous study on general ICU patients. Hsieh et al found a comparable incidence of early-onset VAP within the first 4 days of MV in comatose patients, particularly those with head injury.

Significantly decreased GCS values at the time of admission in SAP patients, along with the identification of dysphagia as a distinct risk factor, underline the pathophysiological significance of silent aspiration in the absence of sufficient protective reflexes in the development of SAP. Pathological findings in the initial chest x-ray were additionally associated with an increased SAP incidence. We propose that these are early indicators of either aspiration and ongoing SAP or a susceptibility state for the disease, eg, lung congestion in case of cardiac failure. Moreover, the extent and location of the

Figure 2. Comparison of NIHSS (a), GCS (b), and APACHE II scale (c) values obtained during the first treatment days after NICU admission in acute stroke patients with (●) and without (○) SAP. Data are presented as mean (circles) and SD (vertical lines). Repeated-measures analysis of variance revealed significantly worse clinical scores in SAP patients over the entire observation period (each P<0.001) and significant differences between individual time points for NIHSS day 2 versus 3 (P=0.035), GCS day 1 versus 2 and day 1 versus 3 (each P<0.001), and APACHE II scale day 1 versus 2 (P=0.001) and day 1 versus 3 (P=0.005).
ischemic lesion were found to be predictive of the development of SAP because patients with vertebrobasilar and multiple location infarction had a significantly higher risk of acquiring the disease. Both are often associated with impaired consciousness and are believed to have a cumulative effect on the deterioration of swallowing with a high frequency of aspiration. Several studies have shown that swallowing difficulties and aspiration are common within 2 weeks after stroke and are of pathogenetic relevance for the development of pneumonia in these patients. However, it should be noted that dysphagia and aspiration are not limited to vertebrobasilar or bilateral hemispheric stroke but may also be present after unilateral hemispheric infarction.

In conclusion, our data underline the remarkable epidemiological and prognostic impact of SAP on treatment and outcome of acute stroke patients in a specialized NICU setting. The considerably high coincidence rate of acute stroke and pneumonia indicates a close pathophysiological link between the diseases. Furthermore, our findings indicate a high SAP risk in patients with multiple location and vertebrobasilar stroke who also show considerable general disease severity, a need for MV, impaired consciousness, dysphagia, and pathological chest x-ray findings at time of NICU admission. Because case fatality rates of 20% to 50% have been reported in nosocomial pneumonia, intensive care neurologists are urged to make prevention of SAP a treatment priority. We conclude that dedicated standard precautions following the CDC guidelines for pneumonia prevention are minimal requirements for infection control in acute stroke patients treated in the NICU setting.

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References


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