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# STROKE-ASSOCIATED PNEUMONIA AND ACUTE STROKE: FREQUENCY, PROGNOSTIC VALUE AND IMPACT OF COMORBIDITIES

***Key words:*** *ischemic stroke, pneumonia, comorbidity, prognosis.*

***Abstract. The aim of research*** *was to evaluate the frequency of nosocomial pneumonia and other hospital-acquired complications after acute ischemic stroke, to assess the impact of somatic comorbidity on pneumonia occurrence, and to determine the relation of pneumonia to 28-day stroke case fatality.* ***Methods****. We performed a prospective study among 207 patients hospitalized for acute ischemic stroke. Stroke severity was evaluated with National Institutes of Health Stroke Scale. Somatic comorbidity was analyzed and graded with Modified Charlson Comorbidity Index. Post-stroke complications were diagnosed using standardized criteria.* ***Results****. Mean score of the admission stroke severity in all patients was 12.3±0.4. Of all strokes, 87.4% developed against a background3 2 of preexisting somatic pathology. Low comorbidity was recorded in 101 patients (48.8%), moderate – in 58 (28.0%), high – in 48 (23.2%); mean Charlson index score was 1.8±0.07. During admission, one or more medical complications occurred in 61 patients (29.5%). The frequency of pneumonia was 19.3% (40 cases): 27.8% in patients with fatal stroke vs. 8.7% in stroke survivors (*$p<0.01$*). The highest was the frequency of pneumonia in patients with high comorbidity (37.5%) compared to those with low (11.9%) or moderate index scores (17.2%). The further analysis showed positive correlation between the increase of Charlson comorbidity index and pneumonia occurrence (*$r_{pb}=0,389$*). Nosocomial pneumonia was related to 28 days case fatality in ischemic stroke (*$\phi=0,241$*) and this complication significantly increased the probability of death in acute period – OR=3.94 (95% CI 1.59-9.76).* ***Conclusions****. Nosocomial pneumonia is a life-threatening complication that affects almost every 5$^{th}$ patient with acute ischemic stroke. The occurrence of stroke-associated pneumonia positively correlates with the higher level of preexisting somatic comorbidity. Development of pneumonia after acute ischemic stroke is an adverse prognostic factor, which increases the probability of 28-days case fatality by 3.9-fold.*

## Introduction

Patients with acute stroke are at high risk of experiencing a wide range of complications, some of which can be life threatening. These new or exacerbated medical problems may hamper rehabilitation efforts, prevent optimal recovery, prolong the hospital stay, and ultimately worsen stroke outcome [2]. Neurological complications arise due to direct damaging of the brain and its arachnoid membranes. Together with the initial stroke severity they become the main contributors to the early case fatality rate after acute stroke, while the likelihood of death in 30-days period is commonly related to the patient's age and somatic complications of stroke, as well as to preexisting comorbidity [12].

Several previous studies have suggested that the estimated frequency of extracerebral poststroke complications ranges from 27.6 to 59%, which may be due to different inclusion and diagnostic criteria [2, 7]. The commonest among them are nosocomial chest and urinary tract infections that affect on the average 1/3 of stroke patients [1]. The other complications include thromboembolism such as deep vein thrombosis and pulmonary embolism, trophic disorders (pressure sores), gastrointestinal hemorrhage, episodes of cardiac failure, kidney failure etc. [2, 9].

The probability of complications is directly proportional to the severity of stroke and is the major cause of fatal cases in the 2nd and 3rd weeks of disease [15]. Somatic complications have a

significant impact on the long-term prognosis of stroke as they increase the risk of 4-years case fatality by 48.3%. They present potential barriers to optimal recovery and rehabilitation, intensify neuronal damage and neurological deficit; increase the risk of stroke recurrence [2].

Nosocomial pneumonia is a common somatic complication after acute stroke [7, 9]. It accounts for approximately 10% of stroke-related deaths during the hospital stay and increases mortality rate by three-fold [6]. The frequency of pneumonia during inpatient rehabilitation varies between the studies, but estimates have been reported to range between 8.2 and 21.4% [1, 6, 10, 15] with the maximum of 50% in severe stroke [11]. Peak of the disease is observed on the first week after stroke onset [1, 9] with the fatality rate up to 20-50% [7, 13]. Contributory factors for pneumonia in acute stroke include dysphagia, the use of mechanical ventilation [7], impaired pharyngeal and cough reflex, aspiration, dehydration, immobility and expiratory muscle weakness [1].

It has been shown that pneumonia is associated with an increase of early case fatality rate in ischemic stroke by 3-fold, and late case fatality by 2.5-fold. It also deepens the severity of functional deficit and slows the recovery of neurological functions [7]. In another study a 5.1-fold increase of 90-days stroke fatality and strong correlation of nosocomial pneumonia with the extent of patient disability and dependence was reported [1]. Early development of pneumonia after ischemic stroke is associated with the older age of patient, higher baseline stroke severity score, impairment of consciousness, central paresis of facial nerve [3], speech disorders (dysarthria or no speech due to aphasia), cognitive decline and general severity of poststroke disability [13].

Somatic comorbidities are also found to have an impact on complications after stroke. Thus chronic obstructive pulmonary disease (COPD) leads to a 5.3-fold increase of frequency of nosocomial pneumonia [13]. The risk of this complication after ischemic stroke is elevated by the preexisting atrial fibrillation and congestive heart failure, and at the same time it is substantially decreased in patients with dementia [10]. The other investigators point out diabetes mellitus as a prognostic factor for pneumonia [1].

Despite the seriousness of pneumonia as a stroke complication this disease is potentially preventable and treatable if recognized in time, that sustantially improve the consequences of the disease. The first step towards effective prevention is obtaining accurate data about the incidence of different medical conditions that follow acute stroke. Although many studies have reported frequencies of poststroke complications, particularly pneumonia, the results vary significantly due to methodological bias. Getting reliable information is impossible without a clearly defined cohort of patients, prospective design of the study, standardized definitions of complications and follow-up of all patients for a prolonged period of time.

The second step is identifying clinical factors that are independently related to the occurrence of a medical complication which is essential for appropriate preventive measures and management. Third, knowledge of onset and course of typical complications following acute stroke is mandatory to determine the duration of close monitoring and acute care.

**The aim of research**

To evaluate the frequency of nosocomial pneumonia and other hospital-acquired complications after acute ischemic stroke, to assess the impact of somatic comorbidity on pneumonia occurrence, and to determine the relation of pneumonia to 28-day stroke case fatality.

**Methods**

We performed a prospective study among hospitalized patients admitted to the neurology department and intensive care unit of Chernivtsi municipal clinical hospital No3. We examined 207 patients within 5 days of stroke onset with the consecutive follow-up until the 28-s day of the disease. Mean (SD) age of patients was 69.4±11.5 years. 46.4% were men (96 patients) and 53.6% women (111 patients).

Patients were examined within 24 hours after hospitalization. Stroke was diagnosed according to WHO criteria [14]. Ischemic stroke subtype was defined on the basis of clinical analysis and neuroimaging data (in 102 patients). In fatal cases the diagnosis was verified by autopsy results.

Stroke severity was evaluated with National Institutes of Health Stroke Scale, NIHSS (T. Brott et al., 1989), which is a simple, reliable and validated scale whereby higher scores indicate more severe stroke. Somatic comorbidity was analyzed after consultation of the specialists, studying patients' medical documentation and history. For qualitative assessment of comorbidity we used Charlson Comorbidity Index (M.E. Charlson et al., 1987) modified for the stroke outcome studies [5]. The Charlson index provides an approach to classifying comorbid diseases. It consists of a weighted count of 17 serious medical conditions that was originally developed to predict 1-year mortality among hospitalized patients but since has been widely used in health services research. According to the modified

Charlson index all patients were divided into three groups for analysis: 0 or 1 – low comorbidity, 2 – moderate and ≥3 – high comorbidity.

During prospective follow-up we recorded the occurrence of extracerebral complications, particularly nosocomial pneumonia. Stroke-associated pneumonia was diagnosed using standardized Mann criteria [3]. Subjects were required to have 3 or more of the following characteristics: fever (≥38°C), productive cough with purulent sputum, abnormal respiratory examination (tachypnea ≥22/min, tachycardia, inspiratory crackle, bronchial breathing), abnormal chest radiographic findings, arterial hypoxemia ($PO_2$ ≤70 mm Hg or $SpO_2$ ≤94%), and isolation of a relevant pathogen (positive Gram's stain and culture). Among the other complications we recorded urinary tract infection, pressure sores, thromboembolism, and acute heart failure.

During 28-day period after stroke onset 115 deaths were registered (56 men and 59 women). For the further analysis all stroke cases were grouped into two categories: fatal and non-fatal strokes (115 and 92 cases respectively).

All patients received basic treatment and after stroke subtype verification – differential therapy according to the existing standards. This precluded the influence of medication on the sample assessment.

Statistical analysis was performed with an open access software package OpenOffice.org Calc (version 2.0.4), Sun Microsystems Inc. and Microsoft® Excel. $x^2$ tests were used to compare categorical variables; Student's *t* tests and median 2-sample tests were used for continuous variables. The degree of relationship between two dichotomous (binary) variables was computed with mean square contingency coefficient (φ correlation coefficient). The correlation between two variables when one is dichotomous and the other is continuous was calculated with point biserial correlation coefficient ($r_{pb}$). All tests were 2 tailed, and probability values <0.05 were considered significant. The probability of the outcome or the strength of association between two binary data values was analyzed with odds ratio (OR) and its confidence intervals (CI) with p=0.05.

**Results**

After a complete neurological examination the admission stroke severity in 29 patients (14.0%) was given NIHSS score of 1-4, which meant minor stroke. Neurological deficit in more than a half of patients (51.7%) was moderate – NIHSS 5-14. Moderate/severe stroke (NIHSS 15-20) was found in 46 (22.2%) and severe stroke (NIHSS 21-40) was diagnosed in 25 (12.1%) patients. Mean score of all ischemic stroke patients was 12.3±0.4.

In 87.4% of patients, ischemic stroke developed against a background of preexisting somatic pathology. According to the Charlson index components the frequencies of the comorbidities were the following: history of myocardial infarction or unstable angina – 33 patients (15.9%), congestive heart failure – 144 (69.6%), diabetes (uncomplicated) – 34 (16.4%), diabetes (complicated) – 15 (7.2%), chronic pulmonary disease – 39 (18.8%), peripheral vascular disease – 12 (5.8%), peptic ulcer disease – 11 (5.3%), rheumatologic disease – 10 (4.8%), dementia – 7 (3.4%), chronic renal failure – 6 (2.9%), mild liver disease – 7 (3.4%), moderate to severe liver disease – 4 (1.9%), any malignancy (non-metastatic, excluding full remission ≥5 years) – 5 (2.4%), leucosis – 1 patient (0.5%).

Baseline modified Charlson index scores ranged from 0 to 9 with a mean of 1.8±0.07. Low comorbidity was registered in 101 (48.8%) patients, moderate – in 58 (28.0%) and high – in 48 (23.2%).

A total of 61 patients (29.5%) experienced at least 1 prespecified complication during their stay in hospital. Hospital-acquired pneumonia appeared to be the most common somatic complication; it was diagnosed clinically and/or confirmed by autopsy in 40 cases. The overall frequency of pneumonia was 19.3%. 62.5% of pneumonia cases were registered within 7 days of stroke onset. The other complications included: urinary tract infection – 8.7%, pressure sores – 5.8%, thromboembolism – 3.9%, and acute heart failure – 2.9%.

Of all stroke patients diagnosed with pneumonia 32 died within 28 days of stroke onset. The overall frequency of nosocomial pneumonia in patients with fatal stroke compared to stroke survivors was 27.8% vs. 8.7% ($p$<0.01).

We have analyzed the level of preexisting somatic comorbidity in the cohort of patients with pneumonia. The results are presented in Table.

The data from the Table show that the frequency of nosocomial pneumonia was significantly higher in patients with Charlson index ≥3, compared to those with low or moderate level of comorbidity.

After the assessment of connection between the level of the preexisting somatic comorbidity and stroke-associated pneumonia we have found that the increase of Charlson comorbidity index is significantly related to pneumonia occurrence with the moderate strength of relation – $r_{pb}$=0,389.

Association of pneumonia with comorbidity is an issue of special interest because it expands the capability of preventive measures. Pneumonia after stroke may be caused either by aspiration or hypostasis [11]. Aspiration after stroke is a consequence of bulbar disorder as a sign of focal

**Table**

**Frequencies of pneumonia in stroke patients with different levels of comorbidity**

| Charlson comorbidity index | Frequency of pneumonia in ischemic stroke | |
|---|---|---|
| | Number of cases | % |
| - low (0-1), n=101 | 12 | 11.9±3.2 |
| - moderate (2), n=58 | 10 | 17.2±4.8 |
| - high (≥3), n=48 | 18 | 37.5±7.1*,** |

**Note.** * – *p*-value <0.05 when compared to low comorbidity; ** – *p*-value <0.05 when compared to moderate comorbidity

lesion or central inhibition of laryngeal cough reflex, as well as the reflex that provides the spasm of glottis in patients with severe impairment of consciousness [7]. Besides, extensive lesion of the brain with pronounced cerebral and focal signs is accompanied by the impairment of non-specific immune protection mechanisms including local and humoral immunity, which facilitates chest infection [11]. Taking into consideration the correlations of Charlson index with the level of consciousness and neurological severity of stroke, which were reported in our previous studies [4], it becomes possible that patients with high comorbidity are inclined to the occurrence of aspiration pneumonia. On the other hand, severe somatic comorbidity essentially restricts adequate rehabilitation [8] that increases the frequency of hypostatic pneumonia. In any case, prevention, early detection and proper management of pneumonia during the acute stage of ischemic stroke could essentially improve short-term prognosis after stroke.

Because our goal was to determine the impact of pneumonia on stroke outcome, we have studied the association of this complication with fatal stroke. The analysis with the mean square contingency coefficient has confirmed that the occurrence of pneumonia is directly positively related to 28 days case fatality in ischemic stroke – $\varphi$=0,241. This relation is weak by strength however statistically significant. Computation of OR coefficient has shown that pneumonia increases the probability of death by almost 4-fold – OR=3.94 (95% CI 1.59-9.76). This result adds to the evidence that nosocomial pneumonia is a threatening medical condition, which substantially influences stroke mortality.

**Conclusions**

1. Nosocomial pneumonia is a life-threatening complication that affects almost every 5th patient with acute ischemic stroke.

2. The occurrence of stroke-associated pneumonia positively correlates with the higher level of preexisting somatic comorbidity.

3. Pneumonia after acute ischemic stroke is an adverse prognostic factor, which increases the probability of 28-days case fatality by 3.9-fold.

**Perspectives of the future research**

The further research should be aimed at studying the impact of separate comorbidities on the risk of post-stroke complications, particularly chest infection. Definition of new baseline factors that predict occurrence of any complication will assist in the early screening and monitoring of patients as well as in decreasing stroke mortality.

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## НОЗОКОМІАЛЬНА ПНЕВМОНІЯ ТА ГОСТРИЙ ІНСУЛЬТ: ЧАСТОТА ВИНИКНЕННЯ, ПРОГНОСТИЧНЕ ЗНАЧЕННЯ ТА ВПЛИВ СУПУТНЬОЇ СОМАТИЧНОЇ ПАТОЛОГІЇ

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**Резюме.** Вивчено частоту розвитку нозокоміальної пневмонії та інших внутрішньогоспітальних екстрацеребральних ускладнень у 207 пацієнтів із гострим ішемічним інсультом. Визначено поширеність фонової соматичної патології та проведено її якісну оцінку з використанням модифікованого індексу коморбідності Чарлсона. Встановлено, що частота розвитку інсульт-асоційованої пневмонії суттєво вища в хворих із високим рівнем супутньої соматичної патології, ніж у пацієнтів із низькою або помірною коморбідністю. Зростання індексу достовірно позитивно корелює з розвитком цього ускладнення з помірною силою зв'язку – $r_{pb}$=0,389. Виникнення пневмонії має достовірний кореляційний зв'язок із 28-денною летальністю при ішемічному інсульті – $\varphi$=0,241. Визначення асоціації пневмонії з летальністю за допомогою показника відношення шансів показало, що розвиток ускладнення підвищує ризик фатального наслідку ішемічного інсульту в 3,94 разу (95% ДІ 1,59-9,76). Такий результат підтверджує, що нозокоміальна пневмонія є загрозливим ускладненням, яке суттєво впливає на смертність від інсульту. Профілактика, рання діагностика та ефективне лікування пневмонії у гострій стадії ішемічного інсульту може значно покращити ранній прогноз захворювання.

**Ключові слова**: ішемічний інсульт, пневмонія, коморбідність, прогноз.

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## НОЗОКОМИАЛЬНАЯ ПНЕВМОНИЯ И ОСТРЫЙ ИНСУЛЬТ: ЧАСТОТА ВОЗНИКНОВЕНИЯ, ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ И ВЛИЯНИЕ СОПУТСТВУЮЩЕЙ СОМАТИЧЕСКОЙ ПАТОЛОГИИ

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**Резюме.** Изучена частота развития нозокомиальной пневмонии и других внутригоспитальных экстрацеребральных осложнений у 207 пациентов с острым ишемическим инсультом. Исследована распространенность фоновой соматической патологии и проведена ее качественная оценка с использованием модифицированного индекса коморбидности Чарлсона. Установлено, что частота развития инсульт-ассоциированной пневмонии существенно выше у больных с высоким уровнем сопутствующей соматической патологии, чем у пациентов с низкой либо умеренной коморбидностью. Увеличение индекса достоверно положительно коррелирует с развитием этого осложнения с умеренной силой связи – $r_{pb}$=0,389. Присоединение пневмонии показывает достоверную корреляционную связь с 28-дневной летальностью при ишемическом инсульте – $\varphi$=0,241. Определение ассоциации пневмонии с летальностью при помощи показателя отношения шансов показало, что развитие осложнения повышает риск фатального исхода ишемического инсульта в 3,94 раза (95% ДИ 1,59-9,76). Такой результат подтверждает, что нозокомиальная пневмония является угрожающим осложнением, которое существенно влияет на смертность от инсульта. Профилактика, ранняя диагностика и эффективное лечение пневмонии в острой стадии ишемического инсульта может значительно улучшить ранний прогноз заболевания.

**Ключевые слова**: ишемический инсульт, пневмония, коморбидность, прогноз.

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