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Mortality Risk and Etiologic Spectrum of Community-acquired Pneumonia in Hospitalized Adult Patients

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We undersign, certificate that we do not have any financial or personal relationships that might bias the content of this work

ABSTRACT

Background: *The etiology of community-acquired pneumonia (CAP) is specific to each region, as proved by numerous studies conducted so far. Knowledge of these data is essential in developing guidelines for antibiotic prescription. Assessment of severity of CAP patients is crucial in determining the risk of mortality and the site of care. Unusual bacterial etiologies may increase the risk of mortality.*

Objective: *First outcome was the identification of pathogens in CAP patients requiring hospitalization and secondary to determine factors that correlate with increased risk of mortality.*

Material and methods: *A prospective study of patients over 18 years of age hospitalized with CAP from whom pathological products were taken (mainly sputum) for bacteriological analysis (microscopy and culture).*

Results: *120 patients were evaluated over a period of three years (2008-2010); we could identify a bacterial etiology in 33 cases (27.5%). The most commonly isolated were* S. pneumoniae *(11 cases),* H. influenzae *(9 cases) and Gram-negative enteric bacilli (12 cases). The mortality rate was 9.2%, significantly higher in the age group over 65 years and in patients with hypoxemia, impaired consciousness and high CURB 65 score, but the only independent factor for the mortality risk prediction was the presence of confusion on admission.*

Conclusions: S. pneumoniae, H. infuenzae *and enteric Gram negative bacilli remain the most frequent cause of CAP in hospitalized patients in Romania and the first line of antibiotic treatment should be targeted. The only independent risk factor for mortality risk was the presence of disorders of consciousness on admission.*

Keywords: communiy- acquired pneumonia, etiology, microbiology

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INTRODUCTION

CAP is a common disease, prospective population studies showing an annual incidence of 5-11 cases per 1000 adult population (1). The incidence of CAP that requires hospitalization varies from country to country ranging between 1.1 per 1000 adult population in Canada and 2.6 per 1000 in Spain, being influenced by multiple factors, including the health system organization (1). Severe cases requiring hospitalization in intensive care unit (ICU) represent 5-10% of all cases (1). Mortality in CAP patients is different depending on the site of care, being less than 1% for cases treated in an outpatient section, between 8 to 14% for hospitalized patients and ranging up to 50% of those admitted in ICU (1).

In Romania, according to data supplied by the School of Public Health, Management and Training in the Field of Health, about 6.2% of all illnesses requiring hospitalization in 2009 were respiratory infections, among which 3.5% lower respiratory infections (2).

The etiology of CAP assumes a regional variation, as proved by numerous studies conducted so far. These studies documented significant differences according to geographical area of study, evaluated population and complexity of microbiological testing (3-5). Knowledge of these data is crucial in developing recommendations for empirical antibiotic choice. Most of prospective studies conducted have shown that the etiologic agents could be established only in 50% of cases, even using more complex methods of microbiological investigation (6). In normal clinical conditions by routine microbiological investigations (microscopy and bacteriological culture) etiologic agent is identified in 20-25% of cases (7). Additional tests (identification of bacterial antigens, serology or genetic testing) have limited application in the etiologic diagnosis of pneumonia, many of them inaccessible, others providing information retrospectively. No study has shown that the initial microbiological investigations affect the outcome in CAP (8). However, most clinicians agree that it is useful in a guided therapy, especially in severe cases. Even if a germ is isolated, it cannot be ruled out from mixed infections (with more germs) and it is not recommended to change the antibiotic with another with narrower spectrum. Mixed infections were present in some studies in a proportion ranging between 5 and 38% (9). Therefore, bacteriological tests are not influencing the first choice of antibiotic, but are useful in adjusting the antibiotic therapy in clinical non-responsive forms. Decision regarding the most appropriate site of care is the first and the most important decision in the overall management of CAP and is assessed according to the severity of illness at presentation. Various severity scoring systems and predictive models have been developed in an attempt to help the clinician to identify CAP patients with a poor prognosis in an early stage. One of the best validated scores and easy to use in clinical practice is CURB-65 score (recommended by British Thoracic Society) (10,11).

In Romania there is no available information on CAP etiologies; current treatment recommendations are using the data provided by studies conducted in other countries. For this reason we considered important to provide a prospective study to identify the causative germs in hospitalized patients with CAP and the predictive factors for a specific etiology. We also analyzed the risk factors for mortality in patients with CAP in order to guide the clinician decision regarding the site of care. ❑

MATERIAL AND METHODS

We prospectively enrolled consecutive patients diagnosed with CAP requiring hospitalization from January 2008 to October 2010. The diagnosis of CAP was suspected on clinical signs and confirmed by radiologic examination. Clinical suspicion for an acute onset (within 7 days) included at least one of the following symptoms: fever, cough, sputum, chest pain and impaired general status. The diagnosis was confirmed by the presence of new infiltrates on the chest X-ray. Initial antibiotic therapy was recommended according to the ERS guidelines. Exclusion criteria were: patients who developed pneumonia during hospitalization or patients readmitted after a recent hospitalization (less than 14 days), patients with severe immunosuppressant (chemotherapy and severe neutropenia below 1000 mm^3, systemic corticosteroids, known HIV infections, immunosuppressant secondary to organ transplantation) and patients in end stage of chronic diseases or patients with post-obstructive pneumonia in lung cancer. All patients were

assessed at first presentation according to a standardized data sheet. The following parameters were recorded: age, sex, alcohol habits, defined comorbidity conditions, respiratory frequency, systolic and diastolic arterial blood pressure, presence of confusion (disorientation in regard to the person, place or time that is not known to be pre-existing), pulse oximeter oxygen saturation, chest radiography (number of lobes affected, interstitial opacities and pleural effusion) and laboratory parameters (leukocyte count, serum urea and creatinine).

For each patient a CURB-65 score of severity was assessed (following the model recommended by the British Thoracic Society), according to the following parameters: confusion, nitrogen retention (urea more than 7 mmol/l), polypnea (respiratory rate ≥ 30/min), hypotension (systolic blood pressure ≤ 90mmHg or diastolic blood pressure ≤ 60mmHg) and age over 65. One point has been counted for any of these parameters when it was present (minimum score 0, maximum score 5).

When general conditions permitted a valid sputum collection was performed in each patient. The correct technique was detailed by a qualified medical staff in order to obtain a specimen through the depth of the tracheal-bronchial tree. As much as possible the specimen was collected before the first dose of antibiotic was administered and transported to the laboratory within one hour. Only specimens who fulfilled the following criteria were processed and inoculated on culture medium: less than 10 epithelial cells and above 25 PMN per low-power field (total magnification of 100x). Other specimens were examined, in selected cases: pleural fluids and bronchoalveolar lavages (in patients with mechanical ventilation). For all patients who were not receiving antibiotic prior to presentation a blood culture was recommended.

The bacteriological examination consisted of Gram stain smears and cultures (using exclusively aerobic media), identification of isolated germ based on morphological appearance and biochemical tests. The bacteriologic investigation did not involve the use of bacterial antigens testing methods, neither serological nor molecular tests. For this reason it could not determine the role of atypical germs or viruses in the etiology of CAP.

Statistical analysis was expressed as mean values ± standard deviation. Continuous variables were compared using t test method and those nonparametric using chi-square test, taking $p < 0.05$ as the level of statistical significance. The mortality risk was assessed by unvaried and multivariate analysis using the Stepwise logistic regression, the results being expressed as the OR, 95% CI and p values, taking $p < 0.05$ as the level of statistical significance. ❑

RESULTS

120 patients were analyzed: 82 men (representing 68.3%) and 38 women (representing 31.7%), mean age 60.46 ± 14.48 (range 27-97). In 75 cases the aspect of consolidation on the chest X-ray involved one single lobe, in 18 patients more than one lobe and in 3 cases an interstitial pattern was present. Fifty-one patients (42.5%) had no comorbidity, but 69 of them had at least one. The most dominant comorbidity were cardiovascular diseases, which were recorded in 34 patients, representing 28.3% of all patients, other 17 patients having at least one other co morbidity: COPD in 28 patients (23.3%), diabetes mellitus in 7 patients, chronic liver diseases in 5 patients, bronchiectasis in 3 patients, asthma in 2 patients, diffuse interstitial fibrosis in 2 patients, chronic renal failure, respectively seizures or Parkinson disease in other 3 patients. Alcohol abuse was present in 23 patients (19.2%). A high number of patients received antibiotic before the presentation: 47 patients, representing 39.2%. As previous studies have shown before, patient age plays a decisive role in determining the severity of the CAP. So, we divided patients into two groups: less than 65 years (69 patients) and more than or equal to 65 years (51 patients). Nineteen cases, representing 15.8% were admitted in the ICU.

Table 1 displays the demographic and clinical data of patients aged <65 years and ≥ 65 yrs. No significant differences were found between the subgroups regarding sex and smoking status, but elderly patients revealed a higher rate of co morbidities, particularly cardiovascular diseases. On clinical examination, elderly patients showed a higher incidence of confusion. Regarding the laboratory parameters, major differences were observed including elevated levels of blood urea nitrogen in elderly patients, with no differences regarding the radiological involvement. Severity assessments

	<65 years	≥ 65 years	p
Number of patients	69	51	0.100
Man/ Woman	50/19	32/19	0.175
Smokers	46	27	0.091
Cardiovascular diseases	8	26	< 0.001
Other comorbidities	23	29	0.008
Hipoxemia	19	22	0.057
Hypotension	7	7	0.373
Leucocytosis	41	31	0.442
Confusion	3	12	0.002
Nitrogen retention	12	18	0.022
Radiology (unilobal// multilobal/interstitial)	53/13/3	38/12/1	0.660
CURB 65 score 0/1/2/3/4/5	41/18/8/2/0/0	0/19/13/13/6/0	< 0.001

TABLE 1. Differences between the two age groups

	Isolation with AB/ without AB	Absence of isolation with AB/ without AB	p
No of pathogens	13/22	34/51	0.468
S. pneumoniae	2/9	45/64	0.119
H. influenzae	1/8	46/65	0.070
S. aureus	2/2	45/71	0.512
G negative Bacilli	8/5	39/68	0.075

TABLE 2. Correlation of germ isolation with antibiotic (AB) treatment prior to collection

Number of strains	39	
S. pneumoniae	11	28.3%
H. influenzae	9	23.1%
S. aureus	4	10.2%
M. catarrhalis	1	2.7%
Gram negative Bacilli	12	30.5%
H. parainfluenzae	2	5.1%
P. aeuruginosa	4	10.2%
Klebsiella	4	10.2%
Enterobacter	1	2.7%
E. Coli	1	2.7%
Sptreptococcus pyogenes	2	5.1%
Anaerobic germs suspected	4	

TABLE 3. Pathogens isolated in CAP patients

	< 65 years	>65 years	p
Isolated strains/no of patients	17/69	18/51	0.143
S. pneumoniae	6	5	0.539
H. influenzae	5	4	0.584
S. aureus	1	3	0.205
Gram negative Bacilli	6	7	0.279

TABLE 4. Distribution of germs according to the age group

revealed, as expected, lower scores of CURB-65 in younger patients.

A valid sputum specimen was obtained in 68 patients (56.7%). Other pathological products were obtained using invasive methods: bronchoalveolar lavage fluid in 8 patients and pleural fluid in 8 patients. Only three blood cultures were performed, one of them being positive.

There was no significant statistical difference between the two groups regarding the ability to obtain a valid sputum sample (30 of 51 vs. 38 of 69 cases, p 0.412). From a total of 68 valid sputum specimens, at least one pathogen was isolated in 31 cases (representing 45.6% of all collected sputum specimens). The probability for the pathogen isolation was not correlated by age and severity CURB-65 score evaluation. However, the rate of germ isolation was higher in patients presenting comorbidity compared to those without any comorbidity: 26 of 69 cases vs. 9 of 51 cases ($p<0.05$). Not even the absence of a previous antibiotic treatment did influence the possibility of isolating the germ; as table 2 shows, from the group of 47 patients previously treated with antibiotics, a pathogen was identified in 13 patients comparing with 22 cases from those 73 patients who did not take antibiotics before presentation (p 0.468).

Overall, the etiology of CAP was determined in 33 patients, representing a rate of 27.5%. In four patients the presence of an anaerobic germ was suspected, based on clinical evaluation and Gram-stained smear, but no confirmation could be obtained in culture because only media for aerobic germs were used. As table 3 displays, the most common isolated pathogens were *S. pneumoniae* (in 11 cases) and *H. influenza* (in 9 cases). Gram-negative enteric bacilli were also isolated in 12 patients. A mixed etiology was identified in six patients (representing 18.2% of all patients with a documented etiology), two different bacterial species being isolated.

There were no statistically significant differences between the two age groups and preferential isolation of any pathogen, as it is shown in table 4. No significant differences were noted regarding the impact of smoking, presence of co morbidities or CURB-65 score on the identification of a specific bacterial strain. (Table 5 and 6).

In our study, 11 patients died, which corresponds to a mortality of 9.2%. Risk factors as-

	Smoker	p	comorbidities	p	COPD	p
Factor present/absent	73/47		69/51		28/92	
Patients with isolated germs	22/13	0.468	26/9	0.013	9/26	0.430
S.pneumoniae	9/2	0.119	8/3	0.229	3/8	0.497
H. influenzae	8/1	0.070	6/3	0.416	1/8	0.332
S. aureus	3/1	0.488	4/0	0.105	2/2	0.232
G negative Bacilli	5/8	0.075	9/4	0.275	4/9	0.357

TABLE 5. Factors correlation with a specific pathogen isolation

CURB 65 score	0	1	2	3	4	p
No. patients	41	37	21	15	6	
No patient with germ isolated	7	14	4	7	3	0.067
S.pneumoniae	2	4	1	3	1	0.401
H. influenzae	3	5	0	0	1	0.233
S. aureus	0	2	1	1	0	0.598
G negative Bacilli	3	3	2	3	2	0.258

TABLE 6. Correlation of germs isolation with CURB 65 score

	OR	CI 95%	p
Age ≥ 65 years	4.093	1.028-16.292	0.046
Comorbidities	3.675	0.758-17.805	0.106
Cardiovascular diseases	2.298	0.652-8.107	0.196
Alcohol abuse	1.669	0.406-6.854	0.477
Hipoxemia	6.141	1.532-24.617	0.010
confusion	38.852	8.396-179.777	< 0.001
Radiological features	0.4221	0.160-1.112	0.081
CURB 65 score	0.351	0.196-0.629	< 0.001
Change of antibiotic	2.769	0.651-11.779	0.168
Isolation of a pathogen	3.308	0.938-11.668	0.063
S. pneumoniae isolation	4.734	1.046-21.419	0.440
H. influenzae isolation	0.834	1.262-11.146	0.834
S. aureus isolation	3.533	0.336-37.204	0.293
Gram negative bacilli isolation	1.980	0.379-10.350	0.418

TABLE 7. Univariate analysis of factors predictive for risk of mortality

	OR	CI 95%	p
Age > 65 years	2.765	0.206-37.050	0.443
Confusion	63.328	4.663-859.970	0.002
Hipoxemia	7.800	0.985-63.289	0.052
CURB 65 score	1.660	0.383-7.188	0.498

TABLE 8. Multivariate analysis factors for risk of mortality

sociated with mortality were first assessed in the whole study group. As shown in table 7, the CURB 65 score, age, confusion and respiratory failure at presentation were associated with a poor outcome. No effect on mortality risk could be related to any of all germs isolated. Moreover, change of antibiotic therapy due to treatment failure was not a significant risk factor for mortality. Table 8 displays the results of logistic regression analysis of the variables included in the multivariate model to describe independent prognostic factors. The presence of confusion at presentation remained the only significant risk factor for death.

The most common antibiotic prescribed was amoxicillin-clavulanic acid (used in 78 patients, representing 65%), either alone (in 48 cases) or associated to quinolones (14 cases), Clarithromycin (8 cases), metronidazole alone (4 cases) or metronidazole and ciprofloxacin (4 cases). Clarithromycin alone was used in 4 cases and added to moxifloxacin in 3 cases. The

bacteriological examination with sensitivity testing was crucial in pathogen directed antibiotic treatment in 9 cases (3 staphylococcal infections and 6 with Gram-negative bacilli). ❑

DISCUSSIONS

CAP is a common cause of hospital admission, the antibiotic treatment being based primarily on the assessment of the most likely etiology, supplied by the clinical and paraclinical examinations. Because the etiology is not easily established using bacteriological investigations and their information is received late by the clinician, the choice of the antibiotic should take place into account the local epidemiological information on the etiology and bacterial resistance. In our study we only used the bacteriological investigation (Gram stain and culture) to identify the etiology and thus it could be indicated the etiology of a total of 27.5% of patients. These dates are comparable with those of previous similar studies (6,7), but the values are much lower than those provided by the studies using other methods of microbiological identification, where the identification could be possible in more than 50% of cases (12). The values obtained by such studies are primarily due to the ability to identify the atypical agents (*Mycoplasma pneumonia* and *Chlamydia pneumonia*) through the serological tests and the ability to determine the involvement of viruses in the etiology of such infections (13,14). A limit of our study is the low valorization of the blood culture as a possibility of bacterial isolation, knowing that this method could identify up to 18% of cases and in particular the presence of *S. pneumonia* and *H. influenza* (15). In this study only two blood cultures were taken, one of them being positive with the *P. aeruginosa* isolation. In our published article the antibiotic therapy administered prior to the specimen collection did not affect the chance of the bacterial isolation, neither the age nor the smoking habit or the severity class CURVE 65. However, the probability of germ isolation was higher in patients with co morbidities compared to those without co morbidities: 26 of 69 vs. 9 of 51 cases ($p<0.05$). It should be noted that the presence of smoking and COPD were reported in 60.8% and 23.2% of patients analyzed, a rate much higher than the general population, demonstrating that they are risk factors for the development of pneumonia. The most commonly isolated pathogens were *S. pneumonia* (28.3%) and *H. influenza* (23.1%), constituting 51.4% of isolated germs, these data being similar with other studies which have been published until now (1,3-5). However, we found a higher proportion of Gram negative bacilli (30.5% of the isolates strains) and in particular *P. aeruginosa* (4 cases). We found no correlation between Gram negative bacilli isolation and the presence of co morbidities or smoking habit, as expected. Six cases of mixed infections (representing 18.2% of the patients with an identified etiology) were reported, in five cases being present S. pneumonia and one of the following bacteria: *H. influenza, S. pyogenes, S. aureus*. Anaerobic infections were suspected in 4 cases, in which the clinical context suggested a gastric content aspiration. Gram smears strongly oriented towards the etiology of anaerobic infections, but no confirmation was possible in the lack of anaerobic cultures.

Isolation of a specific germ was not correlated with any of the following factors: age group, severity CURB 65 score on admission, comorbidity, smoking and alcoholism. The mortality rate was 9.2%, a value similar to those reported in other studies including hospitalized CAP patients (16). In our study a high proportion of patients, 78 of total cases, had a mild severity score on admission (not requiring hospitalization after being assessed), criteria for hospitalization was based on social context. Hence, the mortality rate is much higher in the group of patient with real indication for admission (remaining 42 patients) with an estimation of 23.8%. There was no link established between the risk of mortality and the isolation of a specific germ. The multivariate analysis showed that the presence of altered mental status at presentation remained the only significant risk factor for death. The presence of COPD has not proved to be a risk factor for mortality as other studies showed. Neither the age, nor the severity determined by CURB 65 score have not been assessed as independent risk factors of mortality, as reported in other series. ❑

CONCLUSION

This study is one of the first published series analyzing the etiology of CAP in our country. The results confirm that S. pneumonia and

H. influenza are the main pathogens isolated in the course of CAP requiring hospitalization (51.4% of germs isolated). Unlike other reported studies we found a significantly higher incidence of Gram-negative enteric bacilli. Despite the efforts of correct sampling of pathological products, isolation of the pathogen was low. The mortality rate was 9.2%, the only independent factor predicting the risk of mortality being the presence of confusion on admission.

The limits of the study are related to the performance of a small number of blood cultures that could have increased the rate of isolation and to the lack of serological investigations for the identification of the atypical agents. This is essential for updating the local guidelines of management of community acquired pneumonia.

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