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Clinical value of the inflammatory markers for predicting the severity of community-acquired pneumonia in children

Olena Koloskova[1], **Tetiana Bilous**[1], **Lorina Ivanova**[1], **Olena Korotun**[1], **Roman Tkachuk**[1], **Tetiana Shchudrova**[1]✉, **Mariana Hrytsiuk**[1], **Volodymyr Bilous**[2], **Fedir Herman**[3]

[1]Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", Chernivtsi, Ukraine
[2]Yuriy Fedkovych Chernivtsi National University, Chernivtsi, Ukraine
[3]Chernivtsi State Policlinic #5, Chernivtsi, Ukraine

✉**Corresponding author**
Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", Teatralna sq., 2, 58002, Chernivtsi,
Ukraine;
Email: tshchudrova@gmail.com

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ABSTRACT

The research aimed to study the association of clinical course and inflammatory markers with the risk of severe community-acquired pneumonia in children and to define the diagnostic and prognostic significance of individual markers. A new modified prognostic scale, which includes clinical, laboratory and instrumental indicators, was used for the retrospective analysis and risk stratification of the severe pneumonia course in children. The study involved 70 pediatric patients with community-acquired pneumonia divided into two clinical groups – patients with the low (group I) and moderate (group II) risk of severe pneumonia. A complex examination of patients included the study of the leukogram, serum ceruloplasmin levels, and cellular composition of spontaneous and induced sputum, as well as analysis of the extent and duration of antibacterial therapy. It was found, that in comparison to the group I, in patients from the group II clinical signs of disease and laboratory markers of inflammation remained longer, which required extended and more aggressive antibacterial therapy. It was shown, that the use of the modified prognostic scale is beneficial for optimization predicting severity and management of community-acquired pneumonia in children.

Keywords: pediatric pneumonia, scoring scale, inflammatory markers

1. INTRODUCTION

Respiratory diseases are the most common childhood illnesses and occupy a leading place in the attendance of the family doctor and pediatric departments (Self et al., 2013; Neuman and Keren, 2013). The prevalence of respiratory diseases in children in Ukraine is significantly high (939.67 per 1000 people in 2017) and tends to increase over the past ten years (Antypkin et al., 2016). There is a tendency towards a decrease in the mortality rate from respiratory diseases; however, pneumonia still ranks third in the structure of infant mortality in Ukraine (Bourgeois et al., 2014; Wardlaw et al., 2006). Although pneumonia in children is a common nosology, there is a lack in the validated pediatric models for predicting the severity of community-acquired pneumonia and choosing the optimal treatment approach (Black et al., 2010; Bradley et al., 2011). The WHO has developed a system for the integrated management of childhood disease, which suggests classifying pneumonia in patients into pneumonia, severe pneumonia and very severe pneumonia based on clinical criteria such as tachypnea, dyspnea and other signs of respiratory failure (WHO, 2005). This system aims to optimize the detection of children who may require antibacterial therapy or hospitalization. However, there are many cases of doctors' non-compliance with these recommendations due to attempts to reduce the use of broad-spectrum antibiotics and avoid hospitalization of patients with a low risk of mortality, especially in countries with the scarce capacity for quality of outpatient care (Dean et al., 2015; Chalmers and Rutherford, 2012).

Based on the criteria of the WHO and the recommendations of the Society of Pediatric Infectious Diseases and the Society of Infectious Diseases of America, the PIDS/IDSA criteria for the assessment of the severity of pneumonia were established (Cooper-Sood et al., 2019). According to this guideline, pneumonia in children is classified as "severe" if it meets one and more major or two and more minor PIDS/IDSA criteria. A similar principle was followed by the authors regarding the modification of the PIRO scale for children, which assesses the risk of severe organ dysfunction etc. in adults. However, the PIRO scale includes only clinical signs of the severity of pneumonia without laboratory criteria (Araya et al., 2016; Rello et al., 2009). Several studies considered the use of various acute-phase reactants such as cytokines, C-reactive protein, erythrocyte sedimentation rate, and white blood cells for differentiating the etiology and/or severity of pneumonia (Don et al., 2009; Michelowet al., 2007).

The objective of the research was to study the association of clinical course and inflammatory markers with the risk of severe community-acquired pneumonia in children and to define the diagnostic and prognostic significance of individual markers.

2. MATERIAL AND METHODS

The study was conducted at the Pulmonology and Allergology Department of the Municipal Medical Establishment "Chernivtsi Regional Children's Clinical Hospital" (Ukraine) in 2014-2018. Seventy children with community-acquired pneumonia (M – 38; F – 32; mean age 8.6±0.57 years) were examined by the method of "trial-control" in parallel groups using a simple random sample. Informed consent was obtained from parents of all research participants. Some data were extracted from patients' clinical records. Diagnosis and management of children with pneumonia were performed following the national guideline "Pediatric Pulmonology" (2005).

To obtain sputum, a procedure was performed to induce its discharge by inhalation of serial hypertonic solutions of sodium chloride according to the method of Pavord and Pizzichini (Pavord et al., 1997). An appropriate protocol was used to study the

cytological composition of sputum (Saraiva-Romanholo et al., 2003). Ceruloplasmin level was measured in blood serum and sputum supernatant to determine the activity and type of inflammation (Kamyshnikov, 2016). Biochemical studies were carried out in the accredited laboratory of the Chernivtsi Regional Children's Clinical Hospital (certificate N 000096).

In the present study, a new prognostic scale, designed by authors (Koloskova et al., 2020), was used for the retrospective analysis and risk stratification of the severe pneumonia course in children. The modified complex scale includesa set of clinical, laboratory and instrumental indicators used to assess the risk of severe pneumonia in children (Fig. 1). Presence of each of the indicators was rated at 1 point. Further, the patients were stratified by the risk of severe pneumonia as follows: low risk (0-3 points), moderate risk (4-7 points), high risk (8-10 points), and very high risk (11 and more points).

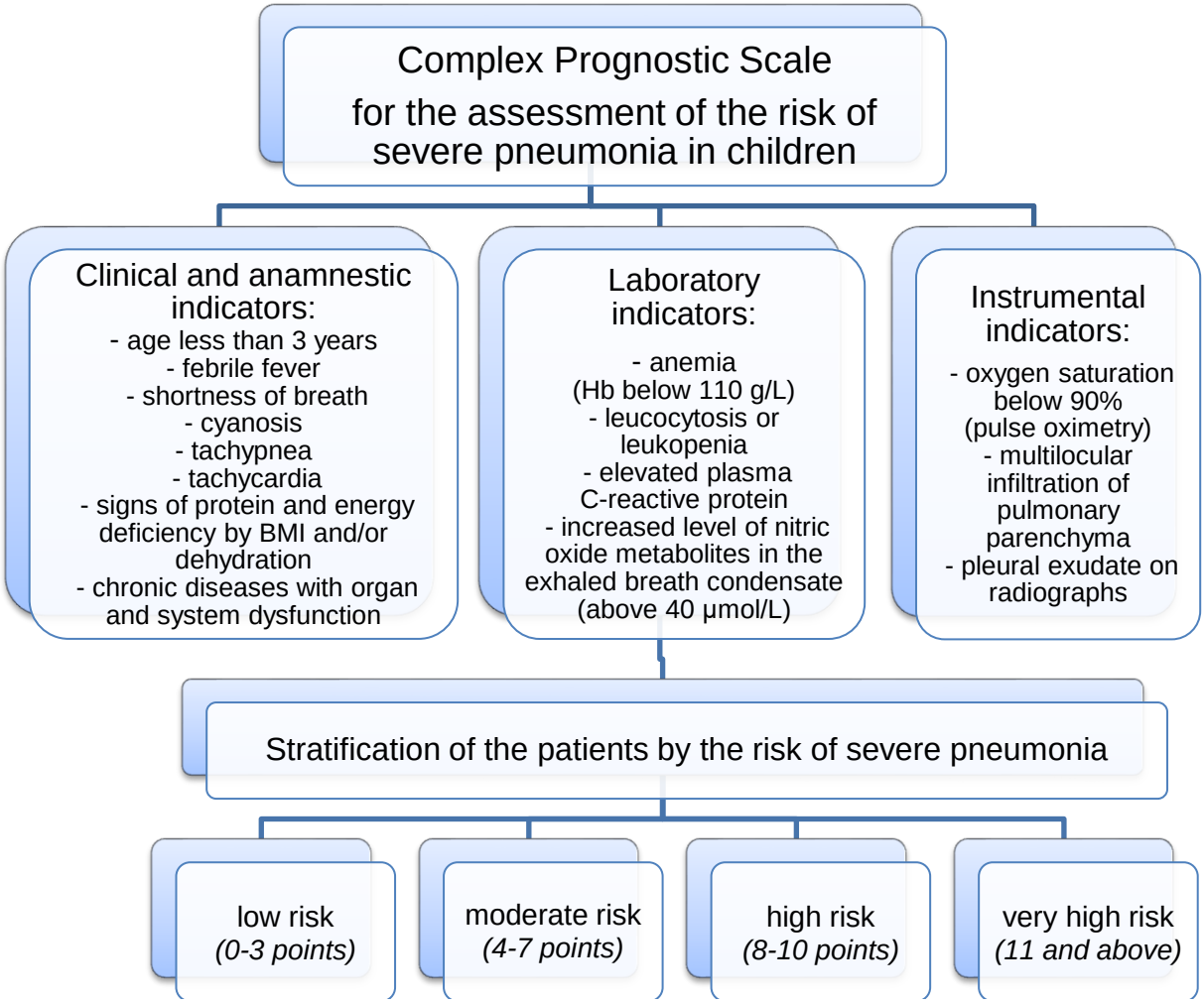

Figure 1 The complex prognostic scale to assess the risk of severe pneumonia in children

The statistical analysis of the obtained results was performed using the Statistica 6.0 software (StatSoft Inc., USA). In all cases, a 95% confidence interval was determined (95% CI). $P<0.05$ was accepted as statistically significant.

3. RESULTS

According to patients' clinical records, 74.3% were diagnosed with moderate pneumonia, and 25.7% of patients had severe pneumonia. A complication in the form of pleuritis was found in 1.4% of patients, signs of respiratory failure – in 94.4% of patients. According to the results of the radiological examination, 47.1% of patients had focal pneumonia, 40% had segmental pneumonia, 8.6% – lobar pneumonia, and only 4.3% – interstitial pneumonia. Majority of children had right-sided pneumonia (60%), 31.4% – left-sided and 8.6% – bilateral pneumonia. The modified complex prognostic scale was used to for the retrospective stratification of 70 patients with pneumonia (Fig. 2). Two clinical comparison groups were formed: clinical group I – 42 children with

the low risk of severe pneumonia (0-3 points), clinical group II – 28 children with the moderate risk of severe pneumonia (4-7 points).

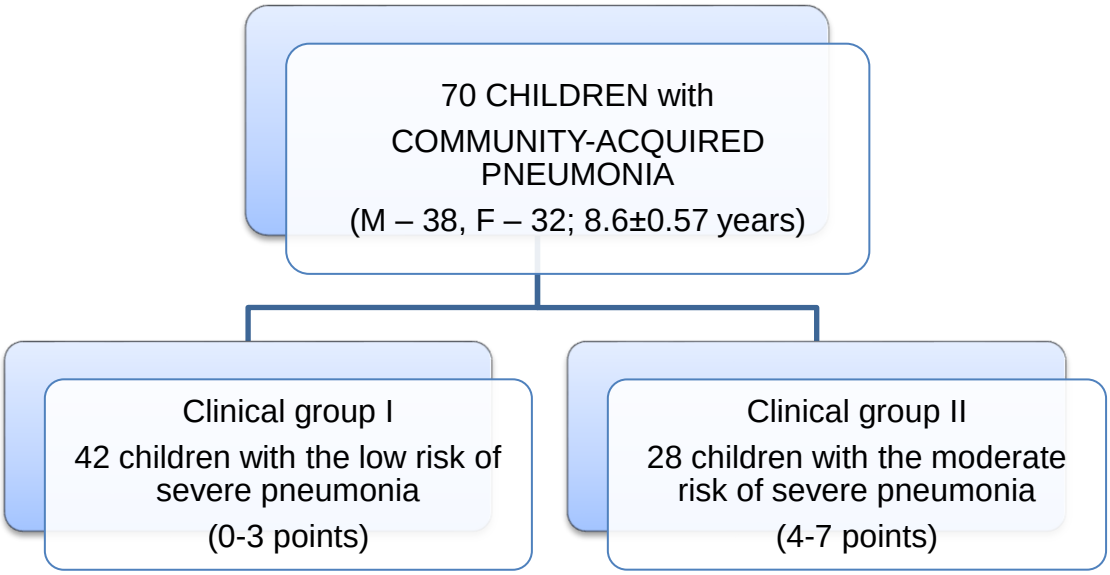

Figure 2 Distribution of patients into clinical groups based on the assessment the risk of severe pneumonia

According to an amnesis of patients, 28.6% of children from the group I and 17.9% of children from group II had the history of acute bronchitis (p>0.05), and community-acquired pneumonia (11.9% vs 10.7%, respectively, p>0.05). During the year before the current hospitalization, acute respiratory diseases were observed in 4.8% of patients from the clinical group I and occurred three times more often in patients from clinical group II (14.3%, p>0.05). It was shown that a history of frequent respiratory diseases increased the risk of a relatively severe course of community-acquired pneumonia as follows: an odds ratio – 3.3 (95% CI: 1.13-9.69), relative risk – 1.6, absolute risk – 27.5%. The actual disease started with signs of acute respiratory infection in 50% of children from the clinical group I and 71.4% of patients from the clinical group II (p>0.05), 71.4% of children from the group I and 78.6% from group II had a fever (p>0.05).

In patients from the clinical group I, a concomitant pathology, which could influence the doctor's decision to start antibacterial therapy, was acute sinusitis (4.8%) and acute otitis (2.4%). In children from the clinical group II, comorbidity was represented by type I diabetes mellitus (3.6%), urinary tract infection (3.6%), bronchiectasis (3.6%), and acute carditis (3.6%). Further, we analysed the dynamics of clinical symptoms during the hospital stay in patients from the clinical comparison groups. On the day 7 of hospital stay fever was found in 10.7% of patients from the clinical group II vs none in the group I (p>0.05), tachypnea (3.6% in the group II vs none in the group I, p>0.05), cough (28.6% in the group II vs 19% in the group I, p>0.05), and local pathological signs on auscultation(in 26.2% of patients from the group II vs 4.8% in the group I, p<0.05).

At the same time, a decrease in the absolute risk of fever on the day 5 in patients from the clinical groupI compared to patients from group II was 22.2%, and the minimum number of patients who need to be treated (NNT) to obtain a positive effect was 4.5. A reduction in the absolute risk of decreased breath sounds on auscultation on the day 7 in patients from the clinical group I compared to patients from group II was 22.8%, a decrease inthe relative risk was 24.1%, and the minimum NNT to obtain a positive effect was 4.4. Thus, the identified patterns emphasize the need to consider the prognosis of the pneumonia course using the modified scale to optimize the management of patients.

4. DISCUSSION

One of the key markers to take into account whether to start antibacterial therapy in children with pneumonia is a white blood cells (WBC) count. According to the literature, some authors suggest differentiating viral from bacterial pneumonia based on the revealed leukopenia or leukocytosis, and granulocytes count. For this reason and according to (Rosias et al., 2004; Korppi, 2004), inflammatory markers such as leukocytosis/leukopenia and plasma level of C-reactive protein were included in the modified prognostic scale of the risk of severe pneumonia. Leukogram data of patients are represented in Table 1.

Table 1 Leukogram of patients from the clinical observation groups

Clinical group	Total WBC(×10^3/μL)	Leukogram(%)				
		Eosinophils	Neutrophils		Lymphocytes	Monocytes
			Band	Segmented		
Group I	8.0±0.50	3.5±0.58	10.6±1.04	43.6±2.83	38.4±3.11	4.1±0.46
Group II	11.5±1.33	2.6±0.40	15.5±2.17	44.1±3.11	34.5±3.99	2.6±0.29
Pt	<0.05	>0.05	<0.05	>0.05	>0.05	<0.05

Leukogram of patients from the clinical group II showed a more significant increase in band neutrophils number with a left shift compared to the clinical group I, where monocyte pool significantly prevailed. An increase in total WBC and immature neutrophils count in blood of patients reflected the bacterial origin of the inflammation and increased risk of severe pneumonia with an odds ratio of 2.8 (95% CI: 1.51-5.08), the relative risk of 1.6 (95% CI: 1.06-2.41), the attributable risk – 24.8%.

The difference in the total WBC count in the blood of children from clinical comparison groups was used as a parameter for the stratification of patients; however, leukocytosis partially remained in patients from both groups. At the end of the hospital treatment, the total WBC count of more than 9.0×103/μL was found in 10% of patients from group I and in 16% of children from group II (p>0.05). At the same time, the Krebs index (the ratio between neutrophils and lymphocytes) averaged 2.4±0.34 in the group I vs 5.0±0.56 in the group II (p<0.05) at the beginning, and 1.0±0.10 vs 1.2±0.18 (p>0.05) at the end of hospital stay, which indicated a more severe inflammation in patients from the group II (Fig. 3).

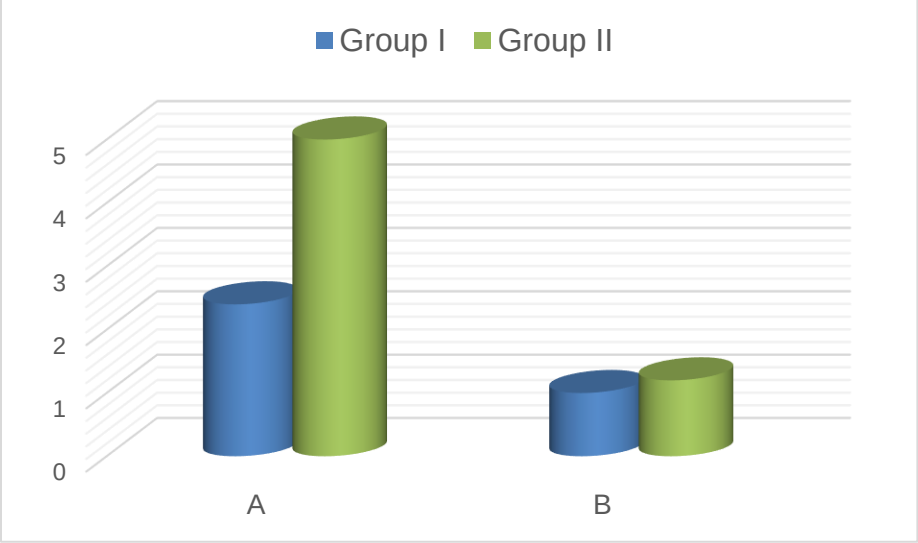

Figure 3 Krebs index in the blood of patients from clinical groups at the beginning (A) and the end (B) of hospital stay

Additionally, more intense inflammatory response and a higher risk of severe pneumonia in patients from group II compared to the group I was confirmed by indicators of neutrophil-mediated phagocytosis. The average phagocytic activity of neutrophils in the group I was 78.8±1.24%, in the group II – 83.2±2.18% (p>0.05), and the phagocytic index was 8.2±0.54 vs 10.2±0.82 (p<0.05), respectively. Ceruloplasmin is one of the acute-phase inflammatory reactants and can be used as a diagnostic and prognostic tool in children with pneumonia. In children from the clinical group II serum ceruloplasmin reached significantly higher levels both at the beginning and the end of hospital stay (p<0.05) (Fig. 4). The odds ratio of severe pneumonia at the ceruloplasmin levels of more than 140 mg/L reached 4.5, the relative risk of 1.9, the absolute risk of 35% at a credibility ratio of 1.6.

For the complex examination of patients with different risk of severe pneumonia, we used several non-invasive procedures to determine their diagnostic and prognostic significance. Cytological examination allowed studying the cellular composition of spontaneous and induced sputum in children from the clinical comparison groups (Table 2).

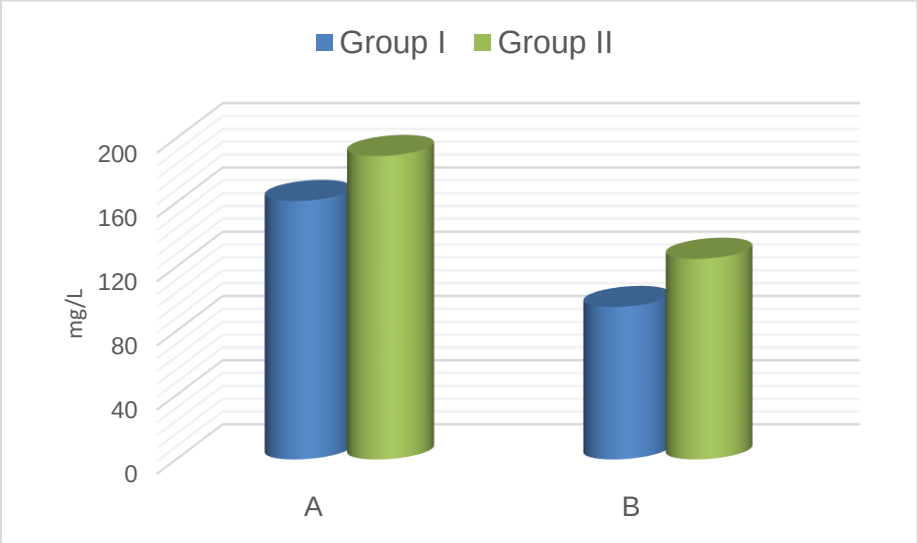

Figure 4 Serum ceruloplasmin levels in patients from clinical groups at the beginning (A) and the end (B) of hospital stay

Table 2 Cellular composition of sputum in children from the clinical comparison groups

Clinical group	Cellular composition, %				
	Eosinophils	Neutrophils	Lymphocytes	Macrophages	Epitheliocytes
Group I	6.4±1.30	63.2±6.44	6.9±2.88	17.8±3.10	16.5±5.13
Group II	0.7±0.42	54.5±5.27	6.0±1.63	9.8±2.17	17.8±10.02
Pt	<0.05	>0.05	>0.05	<0.05	>0.05

The eosinophilic type of inflammation was confirmed in the presence of 3% or more eosinophilic leukocytes in the sputum while the non-eosinophilic type of bronchial inflammation was diagnosed in the absolute absence or the relative content of less than 3% of eosinophils in the cytogram of cell sediment. According to results, along with relatively higher viability of sputum cells (68.5% vs 59%, p>0.05), a higher relative content of eosinophils and macrophages was found in the sputum of children from the clinical group I compared to the group II of patients with a higher risk of severe pneumonia. It was found that content of eosinophils in the sputum of more than 3% and macrophages of more than 10% is associated with a lower risk of severe pneumonia: the odds ratio of 6.7, the relative risk of 1.5, the attributive risk of 30.9% at a credibility ratio of 6.1. It was also found that the Krebs index was slightly higher in the sputum of patients from the II group (10.7±3.7 vs 7.5±2.6, p>0.05), indicating higher activity of inflammation in patients with a moderate risk of severe pneumonia. Thus, in patients with a moderate risk of severe pneumonia compared to children with low risk, clinical signs of disease and laboratory markers of inflammation remained longer.

Antibacterial therapy was started before admission to hospital in 59.5% patients from the group I and 46.4% patients from group II, p>0.05). An early start of antibacterial drugs in children with pneumonia increased the chances of mild pneumonia course: the odds ratio – 1.7 (95% CI: 0.97-2.97), the relative risk of 1.3 (95% CI: 1.00-1.70), the attributive risk 13.2%. All children with pneumonia received antibacterial therapy during the hospital treatment, although the extent and duration of treatment was different (Fig. 5). Oral antibiotics were used in 2.4% of cases in the clinical group I and in 3.6% of cases in the group II (p>0.05); parenteral antibiotics were used in 16.7% and 17.9% of cases, respectively (p>0.05), and their combination – in 80.9% and 78.5% of patients, respectively (p>0.05). The gradual tactic of antibacterial therapy with the initial course of parenteral antibiotics and subsequent transition to oral drugs was used in 57.1% of children from the clinical group I and 42.8% of patients from group II (p>0.05), while the simultaneous administration of parenteral and oral drugs – in 9.6% and 3.6% of cases, respectively (p>0.05).

It was found that initial empiric antibacterial therapy with penicillins or macrolides associated with a relatively mild pneumonia course compared to therapy with cephalosporins: the relative risk of 1.5, the odds ratio of 2.3 (95% CI: 1.24-4.11) at a credibility ratio of 1.7. The duration of oral antibacterial therapy in children with a low risk of severe pneumonia averaged 6.1 days vs 7.0 days in children from group II (p>0.05). Patients from the clinical group I compared to patients from group II more often received parenteral aminoglycosides (mostly amikacin) and less often – a combination of cephalosporins (ceftriaxone) with aminoglycosides. The average duration of parenteral antibacterial therapy in the clinical group I was 8.1 days vs 9.3 days in patients from group II (p>0.05). Parenteral administration of antibiotics for 9 days or longer indicated a high risk of severe pneumonia: the relative risk of 1.6, odds

ratio – 2.8 (95% CI: 0.99-7.75) at a credibility ratio of 1.4.Thus, patients from the clinical group II required extended and more aggressive antibacterial therapy.

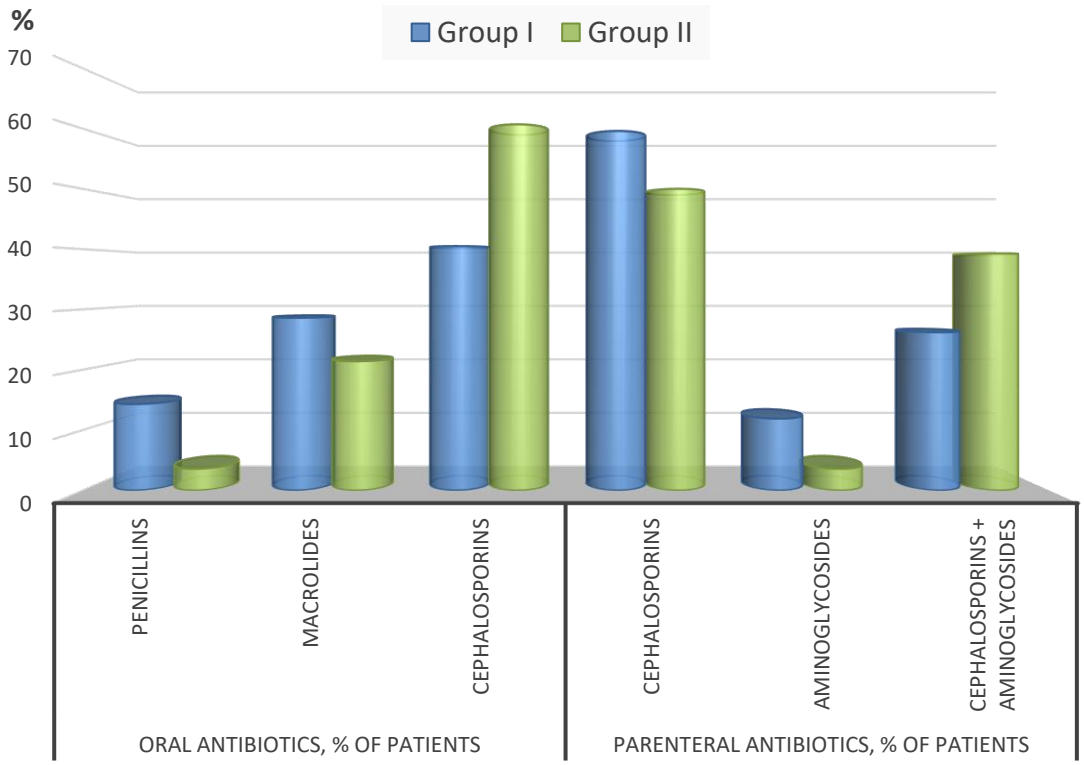

Figure 5 Antibacterial therapy of children with community-acquired pneumonia

5. CONCLUSION

The obtained results show the diagnostic and prognostic significance of individual inflammatory markers and practicability of their use in combination with clinical, instrumental and laboratory findings. Use of modified prognostic scale is beneficial for optimization predicting severity and management of community-acquired pneumonia in children.

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Author Contributions

All authors contributed to the research and/or preparation of the manuscript.

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Conflict of Interest

The authors declare no conflict of interests.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study.

Ethical approval

The study was approved by the Medical Ethics Committee of the Higher State Educational Establishment of Ukraine "Bukovinian State Medical University".

Data and materials availability

All data associated with this study are present in the paper.

Peer-review

External peer-review was done through double-blind method.

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