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PhD THESIS
SUMMARY

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PROCALCITONIN DYNAMICS IN THE MANAGEMENT OF LOWER RESPIRATORY TRACT INFECTIONS ÎN CHILDREN

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INTRODUCTION

Procalcinonin (PCT) is a new generation biological marker that has proven superiority in the diagnosis of bacterial infections.

Numerous studies mention its role in the diagnosis of bacterial infections and, at the same time, the contribution it has in establishing therapeutic managemnt.

Because excessive and inappropriate prescription of antibiotic treatment is an important problem associated with health care by increasing the risk of bacterial resistance, it is very important to identify diagnostic tools that could contribute to the etiological disgnosis of an infection.

In the pediatric patients, even in the presence of a well-documented etiology and a favorable clinical evolution, the decision of the pediatrician regarding the duration of antibiotic therapy and the duration of hospitalization is difficult to make.

Increased microbial resistance and, consequently, the severity of infections require an assessment of the risk of infection and the need to establish treatment in accordance with the etiology. The goal is not only ideal, but also mandatory, and to achieve this, biomarkers could come to the aid in order to differentiate an infection of viral etiology from one of bacterial etiology.

Currently, numerous clinical studies have demonstrated the utility of procalcitonin in sepsis diagnosis and assessing the risk of infection.

The determination of procalcitonin was also studied in the pathology of the respiratory system, as a marker that was useful in therapeutic management, taking into account its dynamics and the clinical condition of patients.

Procalcitonin is not a biological marker that replaces the doctor's medical thinking and clinical intuition in assessing the patient's general condition, but if used in a well-established algorithm, it provides additional information and may be useful to the physician in making rational clinical decisions for the diagnostic and therapeutic management of each patient.

As with any laboratory analysis, knowledge of the efficacy and potential limitations of procalcitonin is conditional on its effective and safe use in medical practice.

PART I

1. PROCALCITONIN METABOLISM

1.1. DEFINITION

Procalcitonin (PCT) is the precursor peptide or prehormone calcitonin (CT), being expressed by the CALC-1 gene on chromosome 11.

It is produced in many tissues in response to bacterial infection by direct stimulation of proinflammatory cytokines (TNF-α, IL-6, IL-1β) [140].

1.2. STRUCTURE OF PROCALCITONIN

Procalcitonin was first identified in 1975 by Leonard J. Deftos and Bernard A. Roos in the United States, San Diego, Department of Endocrinology [46].

Procalcitonin is a peptide consisting of 116 amino acids, with a molecular weight of 14.5 kDa [15]. Procalcitonin is enzymatically cleaved into low molecular weight peptides.

1.3. NORMAL VALUES

In healthy people, procalcitonin is produced almost entirely in thyroid C cells and is converted to calcitonin before procalcitonin enters the systemic circulation. Very low serum procalcitonin values below 0.02 ng / ml were detected in healthy people [193].

Normal baseline values of procalcitonin (PCT) are similar in both adults and children (after the first 72 hours after birth), being below 0.15 ng / mL [121].

Procalcitonin limit of detection is 0.05 ng / mL [103].

1.4. PATHOLOGICAL VALUES

In bacterial infections, a way to produce procalcitonin in an alternative way in many non-thyroid tissues, respectively in the lungs, brain, spleen, pancreas, colon or adipocytes, by direct stimulation of cytokines [126,140,193].

Some parenchymal tissues do not have the necessary pathway to convert procalcitonin to calcitonin, thus allowing the passage of procalcitonin into the systemic circulation, with the direct consequence of increasing its serum level [193].

The increase in serum procalcitonin levels has been shown to be induced by certain triggers, such as bacteria, lipopolysaccharides or proinflammatory cytokines [88].

A slightly elevated serum procalcitonin (PCT) level, between 0.15-2 ng / mL, can be found in the following pathological situations: [141]

- localized bacterial infection, from mild to moderate;
- in case of systemic inflammatory response (infectious);
- in the last stage of renal failure, untreated.

Elevated serum procalcitonin (PCT) levels above 2 ng / ml may be found in the following pathological conditions: [141]

- bacteremia;
- severe form of a localized bacterial infection (lower respiratory tract infection, meningo-cerebral infections, acute peritonitis);
- pielonephritis, an elevated procalcitonin level more than 0.5 ng / mL may suggest a localized infection of the renal parenchyma;
- in newborns, after 72 hours, a procalcitonin level more than 1 ng / mL at birth, 100 ng / mL or more at 24 hours and 50 ng / mL or more at 48 hours suggests the presence of an infection severe bacterial [7,112].

There are certain pathological conditions that are not accompanied by an increase in serum procalcitonin levels:

- viral etiology infections (hepatitis B virus hepatitis B, HIV virus infection, cytomegalovirus infection - CMV, Epstein Barr virus infection - EBV, etc .;
- meningitis of viral etiology;
- chronic inflammatory diseases;
- allergic reactions;
- type I-IV hypersensitivity reactions;
- autoimmune diseases or immune-mediated inflammation;
- localized infections - abscess, empyema [141].

1.5. HOMEOSTASIS OF PROCALCITONINEI

The data published in literature states that procalcitonin is converted to calcitonin, and under physiological conditions is not released into the circulation, explaining the low value in healthy people [8].

Procalcitonin production is induced in response to bacterial toxins and alternatively, by direct stimulation of proinflammatory cytokines, especially interleukin 1β (IL-1β), tumor necrosis factor (TNF-α) and interleukin 6 (IL-6) [176].

Procalcitonin production is decreased by the intervention of proinflammatory cytokines released in viral infections, such as interferon-γ (IFN-γ).

The selective cellular mechanism makes procalcitonin a tool for diagnosing infections of bacterial etiology, compared to other known inflammatory markers, such as C-reactive protein [176].

Procalcitonin becomes detectable 3-4 hours after the triggering event reaching a maximum level after 12-24 hours [129]. In the absence of a persistent stimulus it is eliminated.

The half-life of procalcitonin is 24-35 hours, which is why it is a useful biological parameter for dynamic monitoring [122].

C-reactive protein (PCR) becomes detectable within 4-6 hours after the onset of the infectious event, reaching a peak after 36 hours [191].

2. THE VALUE OF PROCALCITONIN IN LOWER RESPIRATORY TRACT INFECTIONS ÎN CHILDREN

2.1. ACUTE ACQUIRED PNEUMONIA

Determining the serum level of procalcitonin has aroused particular interest because it has been shown to be more useful than PCR, leukocyte count or IL-6 in differentiating viral pneumonia from bacterial pneumonia [71,93,97,98,137,199].

It is assumed that serum levels of procalcitonin may indicate the severity of bacterial pneumonia [90]. There are studies that have shown a direct proportional relationship between increased severity of infection and increased serum procalcitonin [100,139].

Procalcitonin, along with lung ultrasound, has been shown to contribute to the accuracy of the diagnosis of bacterial pneumonia and thus to reducing the prescription of antibiotic treatment, exposure to ionizing radiation and reduce the costs [169].

PART II

3. BACKGROUND

More than ever, some aspects of the diagnostic and treatment protocol have a negative impact on the evolution of pediatric patients with lower respiratory tract infections.

Despite improvements in diagnostic and treatment guidelines by the British Thoracic Society and the American Society of Infectious Diseases, many questions remain:

- since the objective clinical exam becomes more and more subjective, and the radiological interpretation may differ from specialist to specialist, which are still the ideal “tools” for diagnosis?

- with the aim of reducing the percentage of 'false' positive or 'false' negative patients, which is the most effective chain of use of the ideal diagnostic tools?

- what changes can be made to the treatment guidelines so that the percentage of 30-85% of "uselessness" of antibiotic therapy decreases and, with it, the period of hospitalization?

The idea of a possible research started precisely from the "dilemma" of diagnosis and the "abuse" of antibiotics.

The use of procalcitonin in the protocol for the diagnosis and treatment of lower respiratory tract infections remains controversial. Some studies exclude its usefulness, but others (and more and more in recent years) give it more and more importance:

- procalcitonin has a specificity, sensitivity, positive predictive value and negative predictive value higher than the number of leukocytes, C-reactive protein, interleukin-6 in differentiating bacterial from viral pneumonia; the latest data from the literature provide a percentage of 65-70%;

- the reference value in differentiating bacterial from viral pneumonia differs from author to author (0.25 ng / mL; 0.5 ng / mL or 1 ng / mL);

- the hypothesis that elevated procalcitonin levels are associated with severe forms of pneumonia is certain, although the degree of growth may be different depending on the microbial agent involved;

- the promptness with which the level of procalcitonin decreases (once the maximum level is reached), by 50% daily, has an impact on the need for antibiotics which can be reduced by 25-50%;

- a procalcitonin value of less than 0.25 ng / mL may be considered an indicator of discontinuation of antibiotic therapy.

The arguments in the literature are extremely attractive and generous, convincingly motivating the topic of this research.

4. WORKING HYPOTHESIS AND RESEARCH OBJECTIVES

4.1. RESEARCH MOTIVATION

I chose to approach this topic because the pathology we encounter most frequently among the pediatric population is represented by respiratory pathology.

Pneumonia, an acute infection of the lower respiratory tract, can be found at any age and is the leading cause of morbidity and mortality in children worldwide.

The estimated annual incidence of acute pneumonia worldwide is 150-160 million cases in children under 5 years of age. In 2017, the World Health Organization reported a number of 808,694 deaths caused by pneumonia, all occurring under the age of 5 years.

The diagnosis of pneumonia can be established based on well-known clinical criteria. Even if imaging is the gold standard of diagnosis, the etiological classification is difficult to achieve.

In recent years, more and more studies have aimed to use old and new generation inflammatory markers as diagnostic tools.

The need to institute antibiotic treatment as early as possible in bacterial pneumonia and to avoid prescribing antibiotic therapy in viral pneumonia is another reason why we chose this study.

With the help of a rigorous anamnesis, objective clinical examination, chest x-ray and biological parameters, I propose as an objective of the thesis to demonstrate the superiority of procalcitonin in differentiating bacterial pneumonia from viral pneumonia.

Given the already known data that make procalcitonin a marker of interest in the diagnosis of bacterial infection, I want to compare the dynamics of procalcitonin in pneumonia with the dynamics of leukocyte, erythrocyte and platelet indices, the usual biochemical parameters and, last but not least, C-reactive protein.

4.2. RESEARCH OBJECTIVES

4.2.1. Main objectives

The main objective of the thesis was to demonstrate the value of procalcitonin in the management of childhood pneumonia, respectively the role of procalcitonin in improving stages of diagnosis and treatment, with the immediate consequence of reducing the antibiotherapy and also the hospitalization. The following methods were used:

- transverse dynamics of procalcitonin, between study groups
- longitudinal dynamics of procalcitonin, between study stages
- establishing a level of correlation between procalcitonin and other study parameters, proving the superiority of procalcitonin over them.

4.2.2. Secondary objectives

The secondary objectives aimed at outlining the profile of the pediatric patient with bacterial pneumonia and viral pneumonia, respectively, foundations for compiling a procalcitonin utilization score. In fact, both the patient's profile and the procalcitonin use score are, in the end, the most important personal contributions of the thesis.

The study underlying the research is prospective, observational, conducted in the Pediatric Clinic Sibiu, between October 2016 and December 2018, having as subjects pediatric patients hospitalized with clinical suspicion of acute pneumonia.

4.3. MATERIAL AND METHODS

The general study underlying the research is prospective, observational, conducted in the Pediatric Clinic Sibiu, between October 2016 and December 2018, having as subjects pediatric patients hospitalized with clinical suspicion of acute pneumonia.

It consists of 3 studies.

First study (study no. I), the most extensive, is intended for the comparative analysis of the results of the study parameters, by using the mean, percentiles, percentages, Fisher test and odds ratio. It follows the following aspects from the thesis objectives: transversal dynamics (between study groups) of study parameters, including procalcitonin, respectively longitudinal dynamics (between study stages) of study parameters, including procalcitonin, in the evolution of bacterial or viral pneumonia.

Second study (study no. II) has as methodology the use of percentages in order to analyze the longitudinal dynamics of the study parameters (initiated in first study) and compare them with data from the literature. It meets the main objective of the thesis and overlaps with the last two stages of the study design, exposed in the first study: control I (72 hours after admission) and control 2 (at the time of discharge). The results will highlight either compliance or deviations (in the sense of decreasing or increasing, partially - only at control I or continuously - control I and II) from the evolutionary trend of a bacterial or viral pneumonia.

Third study (study no. III), establishing a level of correlation, is intended to evaluate how procalcitonin relates to other study parameters in the evolution of bacterial or viral pneumonia. It meets the main objective of the thesis, in order to prove the superiority of procalcitonin over other study parameters. For the same purpose, a level of correlation of the following most important inflammatory markers was established: leukocyte count, C-reactive protein, platelet count. The correlation index used is rated from very strong to negligible, positive or negative, with or without statistical significance.

4.4. RESULTS AND DISCUSSIONS

4.4.1. Study no. I consists in the comparative analysis of the results of the study parameters

Age is the most important demographic parameter. The most of the patients with bacterial pneumonia were registered in the age group of 1-5 years (35 patients), and most patients with viral pneumonia in the age group under 1 year (59 patients). Consequently, the mean age was also higher in the group of patients with bacterial pneumonia. Comparative analysis of age groups provided additional evidence to support the correlation of etiology with age, the statistical calculation stating that the frequency of bacterial etiology increases with age, while the statistical significance decreases with age ($p = 0.004$, in the age group below 1 year, respectively $p = 0.53$, in the age group 1-5 years, for viral etiology and $p = 0.001$, in the age group 5-15 years, respectively $p = 0.11$, in the age group over 15 years , for bacterial etiology).

Both general anamnestic parameters used resulted in statistically significant results. Thus, early **exposure to smoking** (from infant age) becomes significant for patients with viral pneumonia (OR = 0.2957, 95% CI: 0.1301-0.6722; $p = 0.0024$), as is the h**istory positive for previous hospitalizations** was significantly more present among patients with bacterial pneumonia (OR = 4.125, 95% CI: 1,939-8,775, $p = 0.0001154$).

According to the literature, **fever** is described as one of the most important criteria in addressing an infectious pathology and, as expected, was significantly more present in patients with bacterial pneumonia ($p = 0.019$), and the average was higher in patients with bacterial pneumonia ($38,8^0C$) compared to those with viral pneumonia ($38,1^0C$). The comparative analysis of the duration of fever from onset to hospitalization revealed valuable results in the practical approach, respectively the duration of one day is characteristic of viral pneumonia ($p = 0.0000001$), and the duration of 3 ($p = 0.043$) or 5 days ($p = 0.01$) characteristic of bacterial pneumonia.

Clinical parameters, specific to lower respiratory pathology, respectively **respiratory rate, heart rate, oxygen saturation**, did not bring significant statistical evidence (one exception, for polypnea, in viral pneumonia, in the age group 4-6 years, $p = 0.048$) . On the contrary, some results were even contradictory: starting from the hypothesis that fever induces

polypnea and tachycardia, it is difficult to interpret why the results revealed higher values of respiratory and heart rate in patients with viral pneumonia.

Together with the physical examination of the lungs, the three parameters allowed the classification of patients in **grades of cardio-respiratory failure**, and the comparative analysis provided evidence, this time, statistically significant:

- mild cardio-respiratory failure, significantly more common in viral pneumonia ($p = 0.0013$)

- moderate cardio-respiratory failure, significantly more common in bacterial pneumonia ($p = 0.0024$)

- severe cardio-respiratory failure, significantly more common in viral pneumonia ($p = 0.015$).

Laboratory parameters were addressed depending on the frequency (mandatory investigations) and novelty (old and new generation markers) of use in practice.

Leukocyte indices (leukocytes count, percentage of neutrophils and percentage of lymphocytes), mandatory investigation and old generation inflammatory markers were analyzed according to the absolute value, the differentiated values by age groups and according to the time of performance. at the onset of pneumonia).

The comparative analysis of the absolute values of the **leukocytes count** located at the 25th, 50th and 75th percentiles were consistent with the undisputed data from the medical practice:

- leukocytosis, with a reference value higher than 16.18 x 103 / mmc (average of the whole group), is extremely significant in patients with bacterial pneumonia ($p = 0.00001$);

- hyperleukocytosis, with a reference value higher than 19.87 x 103 / mmc (75th percentile of the whole group), is extremely significant in patients with bacterial pneumonia ($p = 0.0006$);

- leukopenia, with a reference value of less than 11.14 x 103 / mmc (25th percentile of the whole group), is extremely significant in patients with viral pneumonia ($p <0.0000001$).

The significant tendency to leukocytosis in patients with bacterial pneumonia is maintained only in the age group 0-1 year ($p = 0.02$) and only for the first day of illness ($p = 0.013$), while the tendency to leukopenia in patients with pneumonia viral is maintained in all age groups ($p = 0.006$, in the age group 0-1 years, $p = 0.034$, in the age group 1-5 years, $p = 0.017$, in the age group 5-15 years), without differences between sick days ($p> 0.5$).

The comparative analysis of the **percentage of neutrophils** located at the 25th, 50th and 75th percentiles was also consistent with the undisputed data from medical practice:

- neutrophilia, with a reference value higher than 59.63% (average of the whole group) is significant in patients with bacterial pneumonia (p = 0.0012);

- hyperneutrophilia, with a reference value higher than 75.2% (75th percentile of the whole group) is extremely significant in patients with bacterial pneumonia (p = 0.0005);

- neutropenia, with a reference value of less than 45.7% (25th percentile of the whole group), is extremely significant in patients with viral pneumonia (p = 0.00004).

The significant tendency to neutrophilia in patients with bacterial pneumonia is maintained, as is the number of leukocytes, only in the 0-1 year age group (p = 0.01), while the tendency to neutropenia in patients with viral pneumonia is maintained. maintains in the age group 0-1 years (p = 0.01) and the age group 1-5 years (p = 0.001), the statistical calculation losing its significance in the age group 5-15 years (p = 0.4). Unlike the number of leukocytes, there is no statistical significance between days of illness (p> 0.5).

The comparative analysis of the **percentage of lymphocytes** located at the 25th, 50th and 75th percentiles was also consistent with the data from medical practice, being a mirror image of the results of the percentage of neutrophils:

- mild lymphocytosis, with a reference value higher than 28.56% (average of the whole group), is significantly more frequent in the group of patients with viral pneumonia (p = 0.003);

- hyperlymphocytosis, with a reference value higher than 39.2% (75th percentile of the whole group), is significantly more frequent in group B (p = 0.006);

- lymphopenia, with a reference value of less than 15.3% (25th percentile of the whole group), is significantly more frequent in group A (p = 0.001).

However, the significant trend of lymphopenia in patients with bacterial pneumonia (p = 0.03) or lymphocytosis in patients with viral pneumonia (p = 0.003) is found only in the age group 1-5 years. The first day of illness is the only day of statistical significance, with patients with viral pneumonia prone to lymphopenia.

The mean and percentiles of leukocyte indices maintain a uniform tendency to increase or decrease according to the data in the literature, but the reporting to age groups and sick days is uneven: the significance decreases as we progress in age groups and sick days.

The comparative analysis of **erythrocyte indices**, respectively hemoglobin, hematocrit, mean erythrocyte volume and erythrocyte distribution did not show any statistical

significance between the study groups, the expected result, according to data from the literature.

The comparative analysis of **platelet indices** (platelet count, mean platelet volume and platelet count) did not reveal any statistical significance between the study groups, a surprising result, given the data in the literature. The decrease in mean platelet volume (below 8.2 fl), with a proven prognostic value in viral infection, was statistically significant only in bacterial pneumonia.

Biochemical parameters, such as **TGO, TGP, urea, creatinine, glycemia**, which are part of the protocol of any condition, did not show special relationships with the infectious process itself, as, incidentally, the literature has not proven.

C-reactive protein and **procalcitonin** are two of the most important markers of inflammation, which is why they were analyzed at the end of each subchapter, with significance of intermediate conclusion.

Consistent with the data in the literature, the average absolute values of **C-reactive protein** in patients with bacterial pneumonia is much higher than those with viral pneumonia (108.4 mg / L compared to 36.65 mg / L). In the same context come the results of the comparative analysis, with statistical significance for slightly increased values (5-9 mg / L) in viral pneumonia ($p = 0.000007$) and extremely high values (over 100 mg / L) in bacterial pneumonia ($p = 0.000004$). In patients with bacterial pneumonia, C-reactive protein proved to be a marker with rapid and progressive growth in the first two days of disease, with the highest statistical significance on the first day ($p = 0.0003$ compared to 0.03) and with the highest and significant value the next day (over 100 mg / L compared to 67.1 mg / L). In patients with viral pneumonia, C-reactive protein was shown to have a slight and steady increase, both in value (less than 6 mg / L) and in significance level ($p = 0.016$ and 0.02, respectively) in the first two days of illness. In other words, compared to the anticipated rhythm, bacterial pneumonia is characterized by a rapid increase in C-reactive protein ($p = 0.001$), and viral pneumonia by a slower growth ($p = 0.001$).

As an **intermediary conclusion**, C-reactive protein has been shown to be a rapid and progressive marker in bacterial pneumonia and a slower but steady marker in viral pneumonia.

The data from the study prove the rapid growth of **procalcitonin** from day one, but the longitudinal dynamics is variable; moreover, the data in the literature do not provide more information related to this aspect;

- the comparative analysis showed that slightly / moderately elevated and moderately / severely elevated values are significantly more common on the first day of onset (p = 0.003 and p = 0.02, respectively), while extremely elevated values are significantly more common in next day (p = 0.03); the results are as expected, because procalcitonin increases rapidly in the first 24 hours and intensely in the next 24 hours;
- although C-reactive protein showed the same rapid growth rate as procalcitonin, the analysis reported only on disease days, not between batches (A and B) showed statistical significance only for day 2 and only for moderate / moderate values. severely increased (p = 0.01); by comparison, procalcitonin showed significance for extremely high values (p = 0.04);
- comparative analysis between procalcitonin and C-reactive protein and sick days, respectively, showed that procalcitonin values have a significantly faster rate of growth, from the first day, to moderately / severely elevated values (p = 0.03). comparison with C-reactive protein; the values of the C-reactive protein from the next day are significantly more frequently slightly / moderately increased (p = 0.04), while those of procalcitonin are extremely high (p = 0.02).

As an intermediary conclusion, both C-reactive protein and procalcitonin are fast-growing markers; C-reactive protein has shown superiority in bacterial pneumonia over viral pneumonia, while procalcitonin has shown superiority over C-reactive protein in both rapidity (first day significance) and intensity (significance for extreme values, raised the next day).

Among the therapeutic parameters were used:

- **days of oxygen therapy**, the comparative analysis showed statistical significance only in patients with viral pneumonia and who did not need additional oxygen (p = 0.011)

- **systemic corticosteroid therapy**, administered in a statistically insignificant proportion in the study groups (p = 0.34)

- **antibiotic therapy**, the most important parameter, was administered in the same proportion in both study groups (p = 0.18), a situation that interferes negatively over the main objective of the thesis

- as expected monotherapy was significantly more common in patients with viral pneumonia (p = 0.00008), and the combination of two (p = 0.0001) and three (p = 0.02) antibiotics significantly more common in patients with bacterial pneumonia;

- the most frequently used was Cefuroxime alone ($p = 0.058$) and in combination with Gentamicin ($p = 0.29$), both situations being statistically insignificant;
- when C-reactive protein levels were slightly elevated, patients with viral pneumonia were initiated with either monotherapy or combinations of two antibiotics, both of which were statistically significant ($p < 0.0000001$ and $p = 0.0003$, respectively);
- when procalcitonin and C-reactive protein levels were moderately / severely elevated, patients with bacterial pneumonia received either monotherapy or combinations of two antibiotics, both decisions being statistically significant ($p < 0.001$ and $p = 0.012$, respectively).
- when C-reactive protein or procalcitonin values showed an extreme increase, the combination of two antibiotics was significantly the most common decision ($p = 0.0001$).
- as an intermediate conclusion, the decision of antibiotherapy, class and regimen, differs significantly within the groups, depending on the values of C-reactive protein and procalcitonin, but insignificant between groups.

The evolutive parameters were derived from the investigations performed during control 1 and 2.

The evolution of the laboratory parameters was as follows:

- **leukocyte indices** decrease early, but normalization occurs differently:
  - a late, over 6 days, for the leukocytes count,
  - a late, over 7 days, for the percentage of neutrophils
  - an early, in 3 days, and only in patients with viral pneumonia and initial hyperlymphocytosis, for the percentage of lymphocytes ($p = 0.04$).
- **erythrocyte indices** normalize much later, after 12 days
- among **platelet indices**, the number of platelets normalizes late, after 12 days; thrombocytocrit increases early and significantly ($p = 0.04$), in patients with viral pneumonia, at a reference value of more than 0.41%; in contrast, the mean platelet volume decreases early, significantly ($p = 0.04$) and persistently (at any time of evolution, after the initial stage), in patients with bacterial pneumonia, at a reference value below 10 fl.

According to the literature, procalcitonin and C-reactive protein decreased continuously throughout the hospitalization period.

In viral pneumonia, the slight increase in C-reactive protein is sustainable (p = 0.04), but the moderate increase is "ephemeral", with early normalization (p = 0.007).

In bacterial pneumonia, the severe increase in C-reactive protein is sustainable (p = 0.005), found in control 1.

The normalization of mild (p <0.0000001), moderate (p = 0.02) and severe (p = 0.0002) values of procalcitonin is early and long-lasting. Instead, the extremely severe values normalize later, and without statistical significance (p = 0.68).

Control 1, by re-evaluating procalcitonin and C-reactive protein, is an indicator of appreciation of antibiotic therapy initiated at admission.

The **days of antibiotic therapy** was significantly longer (over 12 days) in patients with bacterial pneumonia (p = 0.044).

Anticipation of C-reactive protein and procalcitonin values could reduce monotherapy by 43.47% (p = 0.00004) in bacterial pneumonia and by 70.96% (p = 0.0001) in viral pneumonia. The decrease is also allowed in the combination of two antibiotics, respectively by 31.42%, in bacterial pneumonia (p = 0.00002) and by 15% in viral pneumonia (p = 0.0001)

At control 1, the most frequent and extremely significant situations (p <0.0000001) were those in which the therapeutic scheme from hospitalization was continued, in the conditions of decrease (bacterial pneumonia) or not of C-reactive protein values (viral pneumonia).

Control 2, at the time of discharge, by re-evaluation of C-reactive protein and procalcitonin, is an indicator of the continuation or discontinuation of antibiotic therapy initiated at admission or modified during control 1.

Comparative analysis was statistically significant for discontinuation of antibiotic therapy one day before discharge in patients with viral pneumonia (p = 0.03),

The **days of hospitalization** is another important parameter of study, in turn deriving from the secondary objective of the thesis. The comparative analysis revealed statistical significance for a longer hospital stay of patients with bacterial pneumonia, at a reference value of more than 12 days (p = 0.013).

The anticipated length of hospitalization was derived from the anticipated length of antibiotic therapy and remains in line with the actual length of hospitalization, ie significantly longer for patients with bacterial pneumonia, but at a reference value greater than 11 days (p = 0.016). With the anticipated decrease in antibiotic therapy, the average length of hospitalization could decrease to 10.59 days in patients with bacterial pneumonia and to 8.61

days in patients with viral pneumonia; the number of days of hospitalization could decrease by 155 days in bacterial pneumonia and by 92 days in viral pneumonia.

Study no. I revealed results that overlap with data from the literature (of demographic, clinical parameters - the grade of acute cardio-respiratory failure, laboratory, such as leukocyte indices, C-reactive prorein, evolution - duration of antibiotic therapy and length of hospitalization), but also contributed original data, such as:

- exposure to smoking and previous hospitalizations, with prognostic significance for the etiology of pneumonia
- the prognostic value of the average platelet volume
- expected value of C-reactive protein and procalcitonin
- expected duration of antibiotic therapy
- expected length of hospital stay.

All these data were constituted in intermediate elements for the objectives of the study, being used in outlining the profile of the patient with bacterial pneumonia, respectively of the patient with viral pneumonia.

4.4.2. Study no. II consists in the longitudinal dynamics of the study parameters, by using the percentages and comparing them with the data from the literature.

The dynamics of the study parameters was analyzed as a percentage by comparing the trend in the study with that known in the literature. The results showed either compliance with the trend or deviations (in the sense of decreasing, increasing, partial or continuous) from normal. The dynamics was analyzed for each study group, longitudinally, between the study stages.

The best reproductions of normalization in bacterial pneumonia showed C-reactive protein (42.6%), procalcitonin (30.8%) and the percentage of neutrophils (25.31%), and the lowest average erythrocyte volume (7.69 %), mean platelet volume (2.7%) and erythrocyte distribution (2.5%).

The best reproductions of normality in viral pneumonia showed C-reactive protein (18.9%), leukocyte count (9.09%) and thrombocytocrit (3.5%), and the lowest hemoglobin (2.2%), erythrocyte distribution (2.2%), platelet count (2.2%) and mean erythrocyte volume (1.1%).

As an **intermediary conclusion**, C-reactive protein and procalcitonin are again noted for the accuracy of the values in dynamics.

4.4.3. Study no. III consists of the correlation between procalcitonin and the other study parameters, using the Pearson correlation index.

It is intended to evaluate how procalcitonin relates to other study parameters. The correlation index used is rated from very strong to negligible, positive or negative, with or without statistical significance.

Procalcitonin has shown very strong / strong relationships, of direct proportionality and statistically significant with:

- age at admission ($r = 0.9096$, $p < 0.000001$)
- fever, hospitalization ($r = 0.865$, $p < 0.000001$)
- respiratory rate, at admission ($r = 0.853$, $p < 0.000001$)
- C-reactive protein, at hospitalization, onset of 1 day ($r = 0.767$, $p = 0.00007$)
- C-reactive protein, at hospitalization, onset of 4 days ($r = 0.866$, $p = 0.005$)
- oxygen demand, in days ($r = 0.853$, $p < 0.00001$)
- antibiotic therapy, at admission ($r = 0.855$, $p < 0.00001$)
- duration of antibiotic therapy, in days, after the value of procalcitonin from control 1 ($r = 0.716$, $p < 0.00001$)

Intermediary conclusions:

- a strong relationship of procalcitonin with parameters such as age, fever, respiratory rate, oxygen therapy and antibiotic therapy, at the time of initiation, is proven in the literature;
- if "conditions" such as the day of illness or the time of evolution are interposed (control 1 or 2), the procalcitonin relationship increases in intensity: with C-reactive protein, if the onset of the disease is one day or with the duration of antibiotic therapy, if taken into account procalcitonin value at control 1
- are particular situations, frequently encountered in medical practice, as well
    - the poor relationship between procalcitonin and C-reactive protein resulting from control 1 and 2 is explained as follows:
        - although both showed rapid growth rates (including, depending on the anticipated value), procalcitonin is significantly faster (slightly elevated procalcitonin values equivalent to slightly / moderately elevated C-reactive protein, at admission, become equal in intensity to control 1);

- procalcitonin has shown a continuous decrease over the course of evolution, while C-reactive protein
  - inverse proportional relationship between procalcitonin and C-reactive protein, evolving at control 2, explained by the fact that C-reactive protein values tend to increase from one control to another, while procalcitonin values are more accurate (decreasing continuously , during evolution, when it is favorable)
  - the fact that the relationship of procalcitonin with the duration of antibiotic therapy is stronger at control 1 than at control 2 and negative at control 2 proves that the duration of antibiotic therapy is prolonged despite the normalization of procalcitonin values
  - the hypothesis of prolonged antibiotic therapy partially supports the negative relationship between procalcitonin and length of hospital stay.
- any other correlation with parameters other than procalcitonin showed only weak, very weak or negligible relationships.

The recommendations also include the most important data related to the **superiority of procalcitonin** in the management of pneumonia in children. Thus, in differentiating bacterial pneumonia from viral pneumonia, the role of procalcitonin was highlighted from the beginning, from the study design, by eliminating false positive and negative patients. By anticipating procalcitonin (and C-reactive protein) values, the anticipated antibiotic regimen (with reduced monotherapy and the combination of two or three antibiotics) was designed with repercussions during antibiotic therapy and hospitalization.

The study parameters with the most significant results were included in the **profile of the patient** with bacterial pneumonia, respectively with viral pneumonia, the original contribution of the thesis. The parameters used in the profiles of patients with bacterial and viral pneumonia are well argued, both by the results of the study and by comparison with data from the literature.

Tabel 1: Profile of the patient with bacterial pneumonia, respectively patient with viral pneumonia

PARAMETERS	PROFILE OF PATIENT WITH BACTERIAL PNEUMONIA	PROFILE OF PATIENT WITH VIRAL PNEUMONIA
Age	5-15 years old	0-1 years old
Smoke exposure	NO	YES
Previous hospitalizations	YES	NO
Fever	Hypertermia	Subfebrile
Duration of fever	3-5 days	One day
Respiratory rate	< 40 breaths/minute	> 40 breaths/ minut
Respiratory failure	Moderate	Mild/ severe
Leukocyte count	> 16000/ mmc	< 11000/ mmc
Neutrophils percentage	> 75%	< 45%
Lymphocytes percentage	< 15%	> 40 %
MPV	8,2 fl at admission, <10 fl in any moment of evolution	
C reactive protein	> 67 mg/L in first day, >100 mg/L in second day	< 6 mg/L in first 2 days
Procalcitonin	10 ng/mL in second day	Negative
Normalization of leukocyte indices	> 6 days	> 6 zile (limfocytes in 3 days)
Normalization of PCR	After 3 days values mild and moderate/severe highly and after 7 days values extremely highly	After 7 days
Normalization of PCT	After 3 days values mild and moderate/severe highly and after 7 days values extremely highly	-

Once established, and being part of the secondary objectives of the study, the profile will be an important step in achieving the main objective, in anticipation of the most important original contribution: **PROCALCITONIN USE SCORE** IN BACTERIAL PNEUMONIA IN CHILDREN.

The procalcitonin use score resulted from the study data, according to the results and the comparative analysis used, from the data provided by the profile of the patient with bacterial pneumonia. The score is applied to the remaining eligible patients after completing the two eligibility stages (clinical-biological stage, with a minimum score of 1 and a maximum of 12,

respectively the confirmation stage by the value of C-reactive protein, with a minimum score of 1 and maximum 2). The minimum utilization score for procalcitonin will be 7 (with one criterion met for C-reactive protein) or 3 (with two criteria met for C-reactive protein). The diagnosis of bacterial pneumonia can be established with a minimum score of 6 + 1 + 1 (6 points from stage 1 of eligibility and 1 point from the criteria for C-reactive protein and procalcitonin) or 1 + 2 + 1 (1 point from stage 1 of eligibility, 2 points from the criteria for C-reactive protein and 1 point from the criteria for procalcitonin).

The procalcitonin use score can be used in medical practice as an alternative to situations where, during evolution, the diagnosis of bacterial pneumonia becomes uncertain or "threatened" by false positivity or negativity. Until the widespread use of real-time pulmonary ultrasonography and multiplex PCR tests, procalcitonin may be the best effective management option in bacterial pneumonia in children.

The procalcitonin use score is applied to patients who remain eligible after confirmation of C-reactive protein:

Minimun score:

- **7 (6 + 1)**
  - where 6 is the eligibility score for stage I of eligibility, and 1 is a criteria for C-reactive protein

or

- **3 (1 + 2)**
  - where 1 is the minimum eligibility score for stage I of eligibility, and 2, the criteria met for C-reactive protein

Finally, the diagnosis of bacterial pneumonia is established with a minimum score of:

- ✓ **6 + 1 + 1** (6, points from stage I eligibility; 1, criteria for C-reactive protein; 1, criteria for procalcitonin)
- ✓ **1 + 2 + 1** (1, point of eligibility stage I; 2, criteria for C-reactive protein; 1, criteria for procalcitonin)

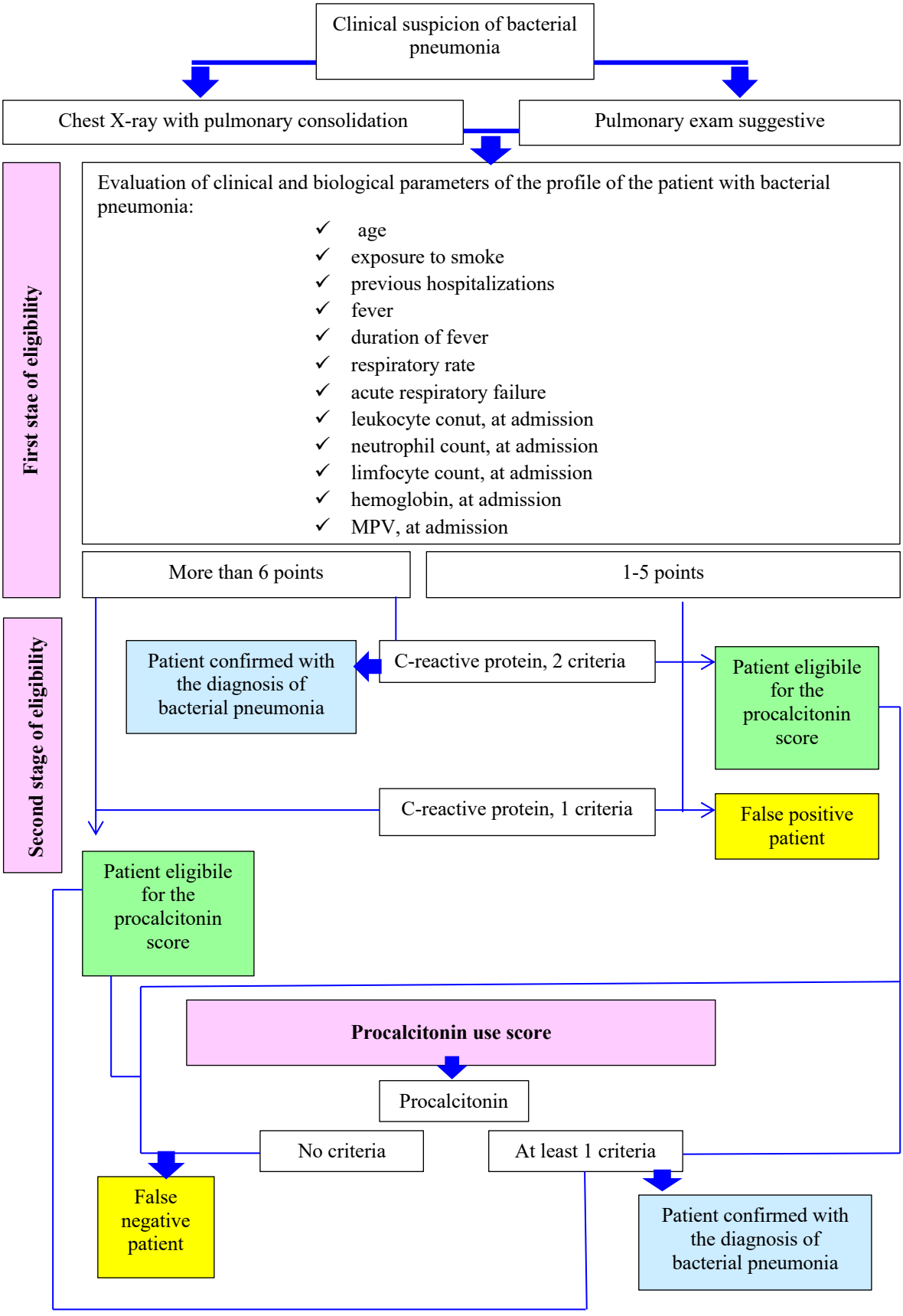

Figure 1: Procalcitonin use score

CONCLUSIONS

1. The differentiation of bacterial pneumonia from viral pneumonia was made on the basis of numerous parameters (demographic, general anamnestic and related to current pathology, clinical, laboratory, therapeutic and evolutionary). Chest X-ray was the only criteria for separating the groups subjected to the analysis of the study.
2. Bacterial pneumonia is more common in the age group of 5-15 years ($p = 0.001$), and viral pneumonia in the age group 0-1 years ($p = 0.004$).
3. Early exposure to smoking is a risk factor for viral pneumonia, and patients with bacterial pneumonia have a rich history of acute pathology, including respiratory ($p = 0.127$).
4. One-day fever is assimilated to viral pneumonia ($p = 0.0000001$), and a prolonged duration of 3 days ($p = 0.043$) and 5 days ($p = 0.01$) of bacterial pneumonia.
5. Mild ($p = 0.0013$) and severe ($p = 0.015$) forms of respiratory failure are attributed to viral pneumonia and moderate ($p = 0.0024$) to bacterial pneumonia.
6. Leukocytosis ($p = 0.00001$), neutrophilia ($p = 0.0012$) and lymphopenia ($p = 0.001$), have been demonstrated in most patients with bacterial pneumonia, as well as leukopenia ($p < 0.0000001$), neutropenia ($p = 0.00004$) and lymphocytosis ($p = 0.003$) in patients with viral pneumonia with individualized reference values.
7. Erythrocyte and platelet indices did not contribute to the biological picture of pneumonia, regardless of etiology, except for the average platelet volume, the values of which provide information for bacterial etiology ($p = 0.034$): an initial value of less than 8 , 2 fl and / or a value less than 10 fl, at any time during evolution.
8. Usual biochemical parameters other than C-reactive protein do not provide additional information.
9. C-reactive protein demonstrated superior values and a rapid increase (from day one, $p = 0.0003$) in bacterial versus viral pneumonia. Mild ($p = 0.000007$) and extremely high ($p = 0.000004$) values in bacterial pneumonia are the most statistically significant.
10. In bacterial pneumonia, procalcitonin increases rapidly, on the first day, to moderately/severely increased values ($p = 0.02$) and intensely, on the second day,

to extremely high values (p = 0.03).Prin comparaţie, în pneumonia bacteriană, procalcitonina este mai rapidă (p = 0,03) şi mai intensă (p = 0,04) decât proteina C reactivă.

11. Patients with viral pneumonia require oxygen therapy more frequently and for a longer period of time (p = 0.011).
12. The administration of antibiotics in monotherapy was significantly more common in patients with viral pneumonia (p = 0.00008), and the combination of two and three antibiotics significantly more common in patients with bacterial pneumonia (p = 0.0001, p = 0, 02).
13. For both groups the most frequently used was Cefuroxime, either alone or in combination with Gentamicin, without the difference being statistically significant.
14. The decision of monotherapy (p = 0.0000004) or combination of two antibiotics (p = 0.003) was made in similar proportions in viral pneumonia when C-reactive protein levels were slightly elevated and in bacterial pneumonia when protein values C-reactive and procalcitonin were moderately / severely elevated or extremely elevated (p = 0.03) - monotherapy, respectively a combination of two antibiotics (p = 0.001).
15. In bacterial pneumonia the leukocyte indices decrease early and normalize relatively late (over 6 days), but in viral pneumonia the lymphocytes normalize early (3 days, p = 0.04).
16. Normalization of procalcitonia values is early (except for extremely high values), long-lasting and continuous. Normalization of C-reactive protein values is early (except for extremely high values), but duration and continuity are lower than procalcitonin.
17. Significantly, for most patients with bacterial pneumonia the treatment regimen initiated at hospitalization was maintained despite the decrease in C-reactive protein and procalcitonin (p = 0.0000001).
18. Significantly, for most patients with viral pneumonia, the treatment regimen initiated at hospitalization was maintained in the conditions in which the C-reactive protein remained unchanged (p = 0.0000001).
19. Statistically significant was the decision to discontinue antibiotic therapy one day before discharge in patients with viral pneumonia (p = 0.03).

20. Expected C-reactive protein and procalcitonin values could significantly reduce the antibiotic prescription and, consequently, the length of hospital stay.
21. The longitudinal dynamics of the studied parameters is observed in various proportions in bacterial and viral pneumonias.
22. Procalcitonin correlates strongly, negatively or positively, and statistically significant with age, hospitalization fever, respiratory rate, C-reactive protein, oxygen requirements, need for antibiotic therapy, and duration of antibiotic therapy.
23. Procalcitonin has shown, compared to other parameters, including C-reactive protein, a well-defined dynamic in the evolution of bacterial pneumonia: early, rapid, intense and continuous increase and decrease. The dynamics of procalcitonia can significantly and positively change the duration of antibiotic therapy and, implicitly, the lenght of hospitalization.

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