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Research Article

ENDOGENOUS INTOXICATION SYNDROME AND ACUTE KIDNEY INJURY OF CHILDREN WITH PNEUMOCOCCAL PNEUMONIA

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ABSTRACT

Endogenous toxins are protein molecules whose content in the blood is determined by the destruction of cells. Not being normal components of blood plasma, they are subject to elimination from the bloodstream. Due to the accumulation of endogenous toxic substances, endogenous intoxication is a frequent complication of many acute and chronic diseases of the respiratory system. The present study revealed a significant increase in the markers of tubular lesion in children with pneumococcal pneumonia, even against the background of an uncomplicated course of the disease, which reflects the renal link of endotoxicosis syndrome.

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KEYWORDS

Endogenous intoxication, kidneys, acute kidney injury, pneumococcal pneumonia, children.

INTRODUCTION

In acute inflammatory processes, proteins of the acute phase of inflammation, binding proteolytic enzymes, increase in plasma. It is considered that the main substrate of autoaggression and dysfunction of the protease and antiprotease systems in endogenous intoxication syndrome is the products of incomplete decomposition of blood and tissues, represented mainly by medium-molecular peptides (MMP) or medium-mass molecules (MMM) with a molecular weight of 300-5000 Daltons (Da). Endogenous toxins are protein molecules whose content in the blood is determined by the destruction of cells. Not being normal components of blood plasma, they are subject to elimination from the bloodstream. Currently, it is known that up to 95% of medium-weight molecules are removed mainly by glomerular filtration. Inactivation, cleavage and destruction of the bulk of MMM occurs inside the proximal tubular apparatus of the kidneys. The accumulation of MMM in the blood serum in a number of diseases with normal glomerular filtration is noted due to their enhanced formation. In chronic renal failure, one of the reasons is the insufficiency of their complete catabolism.

Due to the accumulation of endogenous toxic substances, endogenous intoxication (EI) is a frequent complication of many acute and chronic diseases of the respiratory system. There is some discrepancy among specialists regarding the definition of the main links in the pathogenesis of endogenous intoxication syndrome.

Bacterial toxins and endotoxins circulating in the blood of patients with pneumococcal pneumonia damage cell membranes, disrupting the functional state of organs and systems. One of the most sensitive organs to toxic effects is the kidney. Endogenous and bacterial intoxication causes acute kidney damage. Various markers are used to diagnose acute kidney injury: glomerular dysfunction is determined by an increase in the plasma concentration of substances that are completely filtered in the glomeruli and not reabsorbed in the tubules – creatinine (undergoes minor reabsorption, the degree of which increases with renal failure) and cystacin, and violation of tubular function – by definition in urine 1) enzymes released when damage to tubular cells – ALT, AST and glutathione transferase isoforms; 2) low–molecular proteins that are completely metabolized in the cells of the renal tubules – cystacin and MMP; 3) specific proteins produced by the cells of the tubules when they are damaged - lipocalin; 4) structural and functional proteins of the epithelium of the tubules.

In this study, it was found that in children with pneumococcal pneumonia, the level of all the studied substances in the urine was significantly increased compared to the control group of healthy children ($p<0.001$ for the concentration of lipocalin, cystacin, α-glutathione transferase, MMP and alt and $p<0.01$ for π-glutathione transferase and ast; Table 1). The separation of children depending on the presence of complications revealed a significantly higher concentration of markers of acute kidney injury in children with a complicated course of the disease ($p<0.001$ for all markers).

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Table 1

Markers of acute renal injury in children with pneumococcal pneumonia, depending on the presence of complications and the control group

Indicators	all patients (n=200)	impl+ (n=102) impl- (n=98)	healthy (n=40)	impl+ - heal-	impl+- heal	impl- - heal
Lipocalin, ng/ml	0,87±0,02	1,03±0,03 0,70±0,02	0,64±0,03	P<0,001	P<0,001	ND
Cystatin, mcg/ml	1,03±0,04	1,47±0,05 0,58±0,01	0,32±0,01	P<0,001	P<0,001	P<0,001
Alpha glutathione transferase, ng/ml	196,76±4,19	226,75±5,90 165,55±4,00	154,60±5,28	P<0,001	P<0,001	ND
Pyglutathione transferase, mcg/ml	5,48±0,22	6,91±0,30 3,99±0,24	4,15±0,37	P<0,001	P<0,001	ND
MMP 254, US L. Ed	0,34±0,01	0,45±0,01 0,23±0,01	0,18±0,01	P<0,001	P<0,001	P<0,001
MMP 280, usl.ed	0,37±0,01	0,48±0,01 0,25±0,01	0,22±0,01	P<0,001	P<0,001	P<0,01
Urine ALT, units/l	1,47±0,06	1,89±0,09 1,03±0,05	1,06±0,05	P<0,001	P<0,001	ND
Urine AST, units/l	1,30±0,05	1,65±0,08 0,94±0,05	0,97±0,08	P<0,001	P<0,001	ND

Then, a comparison was made of the indicators recorded in the control group with patients with pneumonia, depending on the presence of complications. It was revealed that in patients with uncomplicated course of the disease, the levels of lipocalin, α- and π-glutathione transferases, alanine and aspartate transferases in the urine did not differ from those characteristic of healthy children. The concentration of proteins, which are normally completely filtered in glomeruli, and then catabolized in tubules and the resulting amino acids are completely reabsorbed – cystacin and MMP, was significantly increased in patients with uncomplicated pneumococcal pneumonia compared with healthy children ($p<0.001$ for cystacin and MMP 254 and $p<0.01$ for MMP 280), which indicates acute kidney damage even against the background of uncomplicated pneumonia.

Also, during the study, the distribution of patients by age groups was undertaken. It was revealed that the concentration of lipocalin in the urine of healthy children under the age of 1 year and 1-2 years remains stable, and then significantly increases systematically

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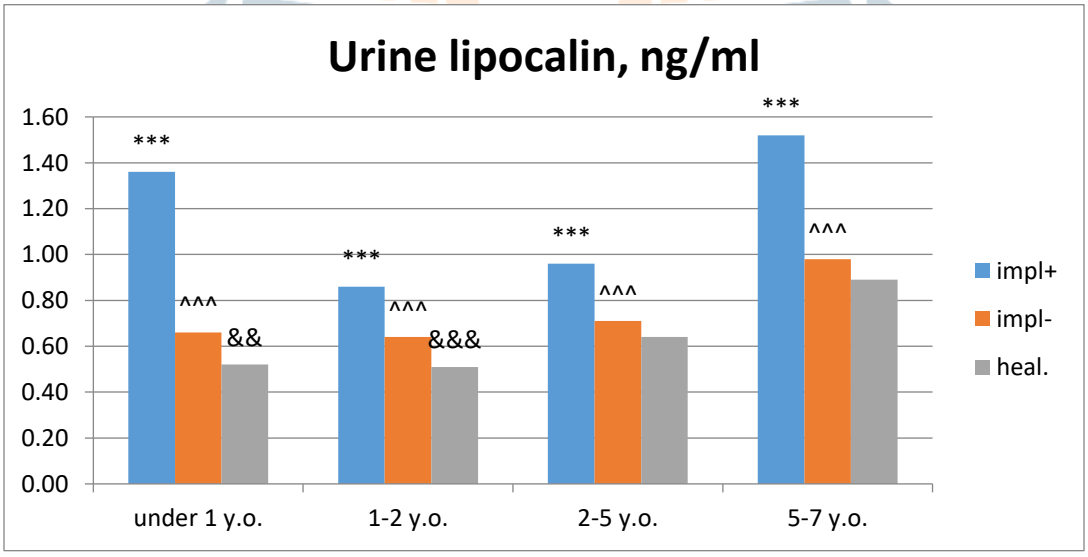
(p<0.01 reliability of the difference between groups up to 1 year and 2-5 years and p<0.001 reliability of the difference in other comparisons, Figure 6.1). In children with uncomplicated pneumonia in the first two years of life, the concentration of urine lipocalin, reflecting the involvement of renal parenchyma in systemic inflammation, was consistently high and significantly (p<0.01 for children under 1 year and p<0.001 for children 1-2 years) exceeded the concentration in the urine of healthy children. In children older than 2 years (in age groups 2-5 and 5-7 years) on the background of uncomplicated pneumonia, the concentration of lipocalin was comparable to that in the control group. At the same time, as in the control group, the concentration of lipocalin in children with uncomplicated pneumonia increased with age, reaching a significant difference in children 5-7 years old compared with the younger age group (p<0.001 the reliability of the difference between the 5-7 years old group and the three younger groups). Complicated course of pneumococcal pneumonia in all age groups was associated with significantly higher levels of lipocalin compared to both healthy children and patients with uncomplicated course of the disease (p<0.001 for both comparisons in all age groups). However, the age dynamics of the indicator was paradoxical: in children from 1 year to 5-7 years, the concentration of lipocalin gradually significantly increased (ND by 2-5 years and reliably by 5-7 years – p<0.001 when comparing the older age group with both averages). While in the youngest group, the concentration of lipocalin was higher than in the middle groups (p<0.001 when compared with both middle groups) and was comparable with the older age group.

The described dynamics of the concentration of urine lipocalin indicates that children under 1 year old are the most vulnerable to acute kidney injury against the background of pneumococcal pneumonia.

Figure 1

The concentration of lipocalin in the urine of healthy children and patients with pneumococcal pneumonia, depending on age and the presence of complications



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Note: the significance of the difference between clinical groups: * - between groups of Impl+ and Impl-, ^ - between groups of Impl+ and healthy children, & - between groups of Impl- and healthy children; two signs - p<0.01, three signs - p<0.001.

Table of reliability of intergroup indicators to Fig. 1 (the values of the Student's T criterion and the reliability of the difference are indicated, taking into account the Bonferroni correction).

Clinical groups	under 1 / 1-2	under 1/2-5	under 1/5-7	1-2 / 2-5	1-2 / 5-7	2-5 / 5-7
Impl+ (n=102)	3,33E-07***	3,41E-06***	0,041468	0,033481	7,37E-10***	6,03E-09***
Impl- (n=98)	0,550627	0,150158	2,01E-06***	0,034676	3,4E-07***	9,03E-06***
Heal. (n=40)	0,684584	0,000168**	1,33E-09***	7,15E-05***	8,71E-10***	6,86E-07***

Note: * differences by age categories within clinical groups are two signs - p<0.01, three signs – p<0.001.

Cystacin is a protein inhibitor of cysteine proteases secreted by all cells containing nuclei, its biological role is to protect genetic material from genotoxic and apoptotic agents. Cystacin, being a protein with a low molecular weight, is completely filtered in the glomeruli of the kidneys and then completely metabolized by the epithelial cells of the tubules, without undergoing reabsorption. Normally, it is detected in urine in trace concentrations. In glomerular pathology, its amount in blood plasma increases, reflecting a decrease in the glomerular filtration rate. Tubular pathology is characterized by a violation of the processes of catabolism in the cells of the tubules, as a result of which the concentration of cystacin in the urine increases. As the present study showed, in healthy children, the concentration of cystacin in the urine practically did not depend on the age of the child (Fig.6.2). In children with uncomplicated pneumonia, the concentration of urine cystacin was significantly increased, also with slight age fluctuations, which reflects the hidden processes of tubular damage, even with uncomplicated course of the disease. Against the background of complicated pneumonia, the concentration of cystacin in urine was significantly increased and progressively increased with increasing age of sick children (p<0.001 reliability of the difference in the concentration of urine cystacin between all age categories). To determine the pathogenesis of this phenomenon, a parallel study of the concentration of cystacin in blood and urine is required in the future, since the probable explanation may be a predominant violation of tubular function against the background of pneumococcal pneumonia in older children and a combination of glomerular and tubular dysfunction at a younger age due to immaturity of protective and compensatory mechanisms.

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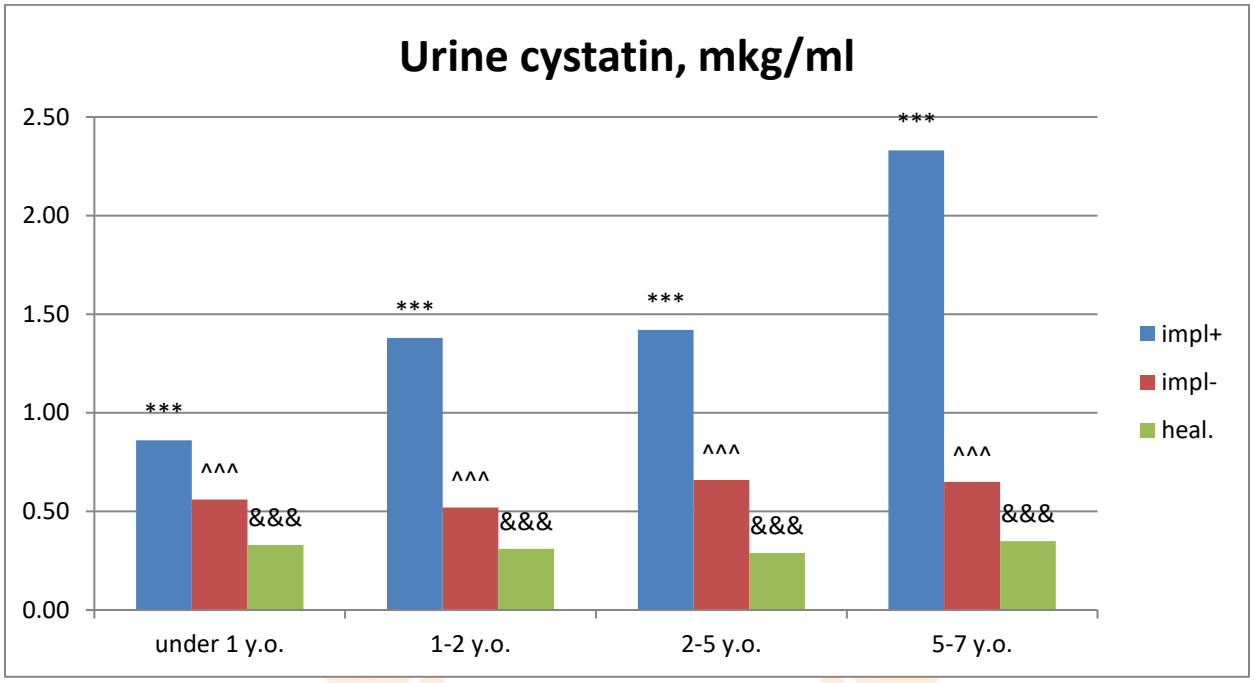
Figure 2

The concentration of cystatin C in the urine of healthy children and patients with pneumococcal pneumonia, depending on age and the presence of complications



Note: the significance of the difference between clinical groups: * - between groups of impl+ and impl-, ^ - between groups of impl+ and healthy children, & - between groups of impl- and healthy children; three signs - p<0.001.

Table of reliability of intergroup indicators to Fig. 2 (the values of the Student's T criterion and the reliability of the difference are indicated, taking into account the Bonferroni correction).

Clinical groups	under 1/1-2	under 1/2-5	under 1/5-7	1-2 / 2-5	1-2 / 5-7	2-5 / 5-7
Impl+ (n=102)	2,35E-12***	2,65E-12***	2,1E-13***	0,504065	2,47E-11***	1,27E-10***
Impl- (n=98)	0,210028	0,006315*	0,014522	1,26E-05***	0,000134**	0,754676

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Heal. (n=40)	0,290857	0,034722	0,268386	0,268386	0,034722	0,001982*

Note: * differences by age categories within clinical groups one sign - p<0.05, two signs - p<0.01, three signs – p<0.001.

Other markers of renal damage, the concentration of which in the urine is associated with a violation of their metabolism by epithelial cells of the renal tubules, are medium molecular peptides. MMP are degradation products of various proteins with a molecular weight of 300-5000Da that occur during proteolysis. These peptides lose their spatial and structural conformation and acquire the properties of endogenous toxins and free radicals. 95% of MMP are filtered in the renal glomeruli, then catabolized by epithelial tubule cells to amino acid residues, which are completely reabsorbed into the bloodstream. In this study, it was found that in all age categories, the concentration of MMP 254 and 280 was significantly higher in patients with pneumococcal pneumonia, especially against the background of complications (p<0.05 reliability of the difference in the concentration of SMP 280 in healthy children under 1 year and patients with uncomplicated course of the disease; p<0.001 the significance of the difference in all other age categories between healthy children, patients with uncomplicated and complicated course of the disease in the aspect of MMP 254 and 280, Fig.6.3, 6.4). The dynamics within the clinical groups by age demonstrated that, both in healthy children and against the background of pneumonia, the highest concentration of MMP was observed in children under 1 year and 5-7 years old. We believe that in children under one year old, the kidneys are the most vulnerable in terms of toxic effects. The mechanism of damage is a violation of hemorheology against the background of pronounced inflammatory reactions and activation of the coagulation cascade. In children older than 1 year, due to more advanced protective and aotioxidant mechanisms, damage to the tubules is less pronounced, however, by 4-7 years, there is excessive activation of cellular and humoral immunity, a restructuring of the immune status from suppressor to helper, and a tendency to hyperergic and autoimmune reactions, which may explain the addition of direct immune damage to the epithelium of the tubules with a violation of their function.

Also, markers of kidney damage are enzymes released from the epithelial cells of the tubules when they are damaged, in particular alanine- and aspartame-aminotransferase and glutathione transferase (alpha – from the epithelium of the proximal, pi – from the epithelium of the distal tubules). For these indicators, the age dynamics described above for SMP is also characteristic (Fig.6.5, 6.6, 6.7, 6.8): the highest concentrations were found in children under 1 year and 5-7 years, while maintaining intergroup patterns in all age periods (the maximum concentration in children with complicated pneumonia, the minimum – in healthy peers). The explanation can also be the immaturity of protective mechanisms and a special vulnerability with a tendency to generalize inflammation in young children and activation of hyperergic mechanisms by 4-7 years.

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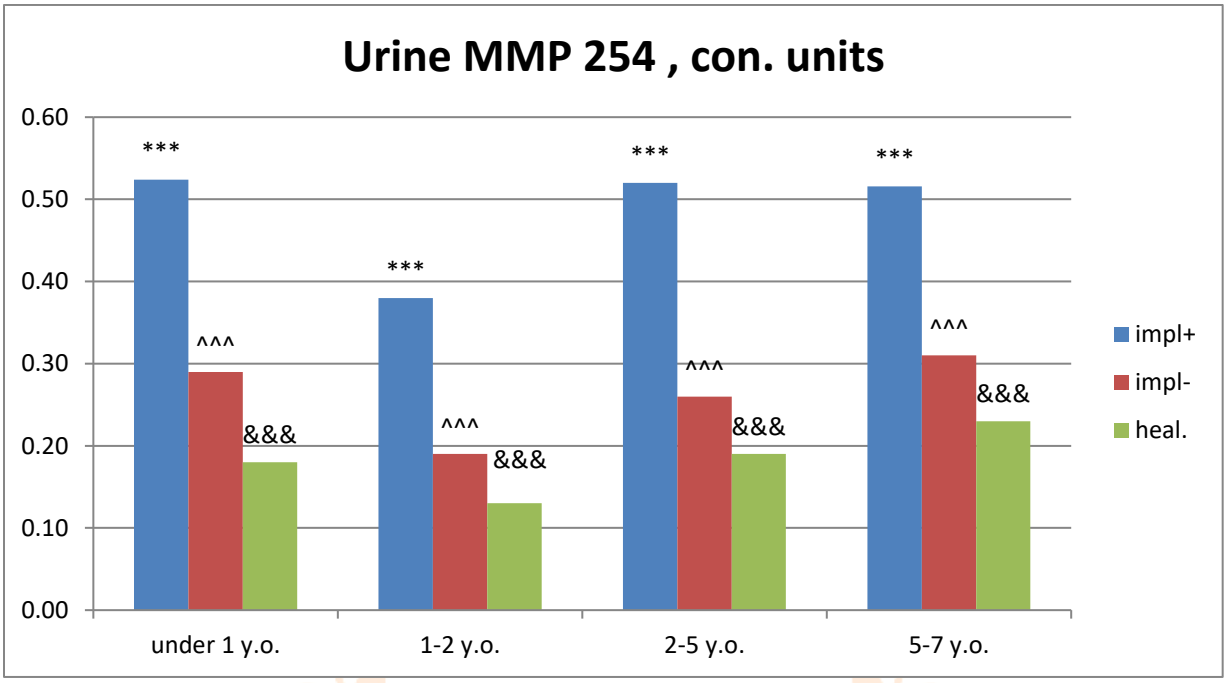
Figure 3

The concentration of MMP 254 in the urine of healthy children and patients with pneumococcal pneumonia, depending on age and the presence of complications



Note: the significance of the difference between clinical groups: * - between groups of impl+ and impl-, ^ - between groups of impl+ and healthy children, & - between groups of impl- and healthy children; three signs - p<0.001.

Table of reliability of intergroup indicators to Fig. 3 (the values of the Student's T criterion and the reliability of the difference are indicated, taking into account the Bonferroni correction).

Clinical groups	under 1/1-2	under 1/2-5	under 1/5-7	1-2 / 2-5	1-2 / 5-7	2-5 / 5-7
Impl.+ (n=102)	1E-06***	0,863603	0,762102	5,66E-09***	1,31E-05***	0,871375
Impl.- (n=98)	1,78E-07***	0,030427	0,223785	1,09E-07***	7,61E-08***	0,00343*
Heal. (n=40)	2,64E-05***	0,325275	0,000631**	4,99E-07***	2E-08***	0,002428*

Note: * differences by age categories within clinical groups one sign - p<0.05, two signs - p<0.01, three signs – p<0.001.

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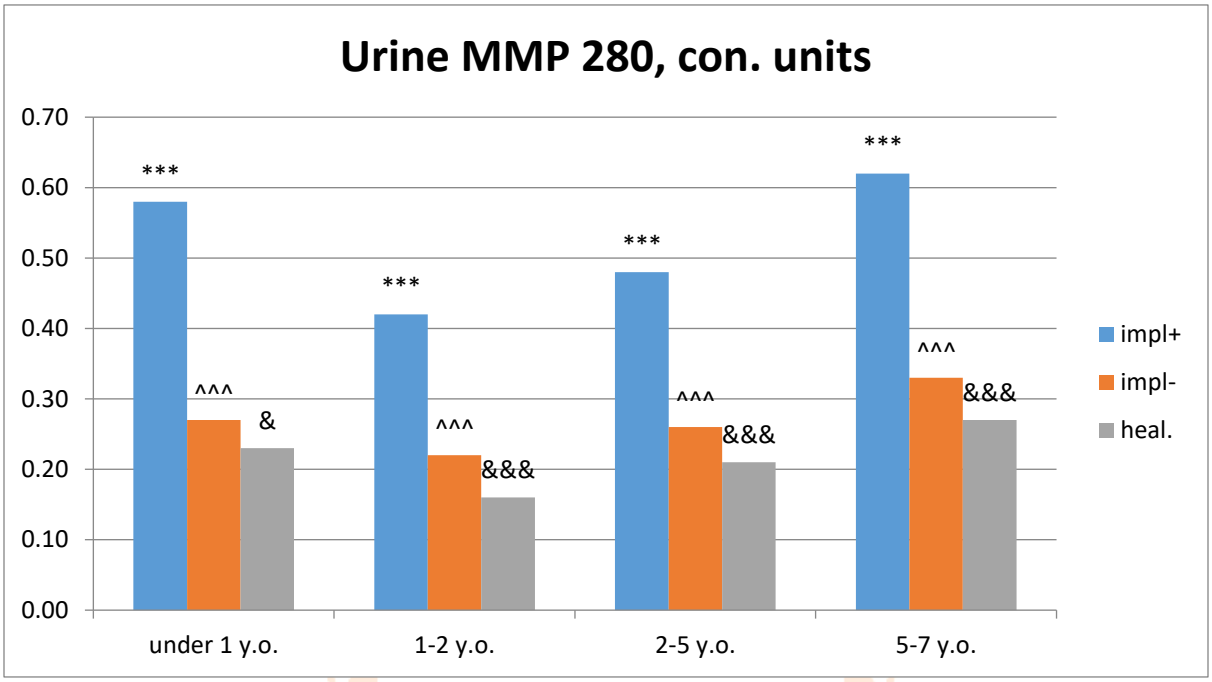
Figure 4

The concentration of MMP 280 in the urine of healthy children and patients with pneumococcal pneumonia, depending on age and the presence of complications



Note: the significance of the difference between clinical groups: * - between groups of impl+ and imp-, ^ - between groups of impl+ and healthy children, & - between groups of impl- and healthy children; one sign - p<0.05, three signs - p<0.001.

Table of reliability of intergroup indicators to Fig. 4 (the values of the Student's T criterion and the reliability of the difference are indicated, taking into account the Bonferroni correction).

Clinical groups	under 1/1-2	under 1/2-5	under 1/5-7	1-2 / 2-5	1-2 / 5-7	2-5 / 5-7
Impl+ (n=102)	1,11E-07***	0,000117***	0,164022	0,00275*	8,69E-08***	2,12E-05***
Impl- (n=98)	0,00102**	0,461296	0,000585**	0,002948*	1,05E-08***	3,31E-05***
Heal (n=40)	6,45E-06***	0,08982	0,004407*	3,61E-05***	4,62E-09***	2,13E-05***

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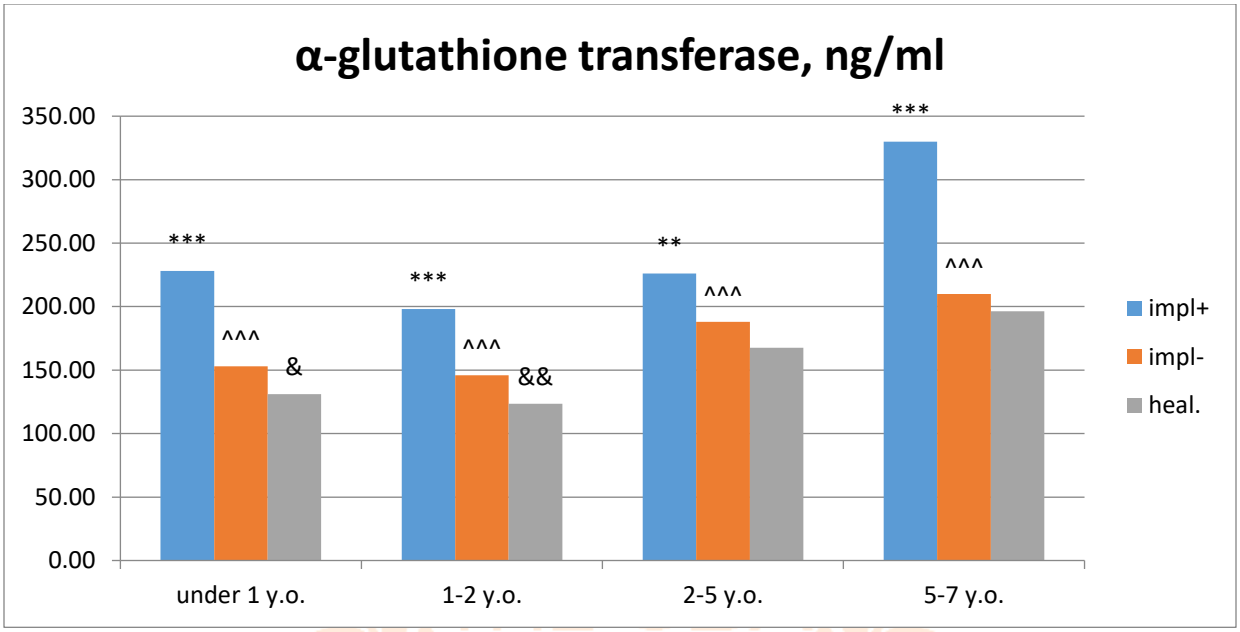
Note: * differences by age categories within clinical groups one sign - p<0.05, two signs - p<0.01, three signs – p<0.001.

Figure 5

The concentration of alpha-glutathione-S-aminotransferase in the urine of healthy children and patients with pneumococcal pneumonia, depending on age and the presence of complications.



Note: the significance of the difference between clinical groups: * - between groups of impl+ and impl-, ^ - between groups of impl+ and healthy children, & - between groups of impl- and healthy children; one sign - p<0.05, two signs - p<0.01, three signs - p<0.001.

Table of reliability of intergroup indicators to Fig. 5 (the values of the Student's T criterion and the reliability of the difference are indicated, taking into account the Bonferroni correction).

Clinical groups	under 1/1-2	under 1/2-5	under 1/5-7	1-2 / 2-5	1-2 / 5-7	2-5 / 5-7
Impl+ (n=102)	0,003573*	0,841604	2,51E-06***	0,003768*	4,76E-08***	1,39E-06***
Impl- (n=98)	0,295135	0,000344**	3,14E-06***	1,15E-05***	1,65E-07***	0,037102
Heal (n=40)	0,263321	4,11E-05***	8,43E-08***	3,4E-06***	1,36E-08***	0,001379**

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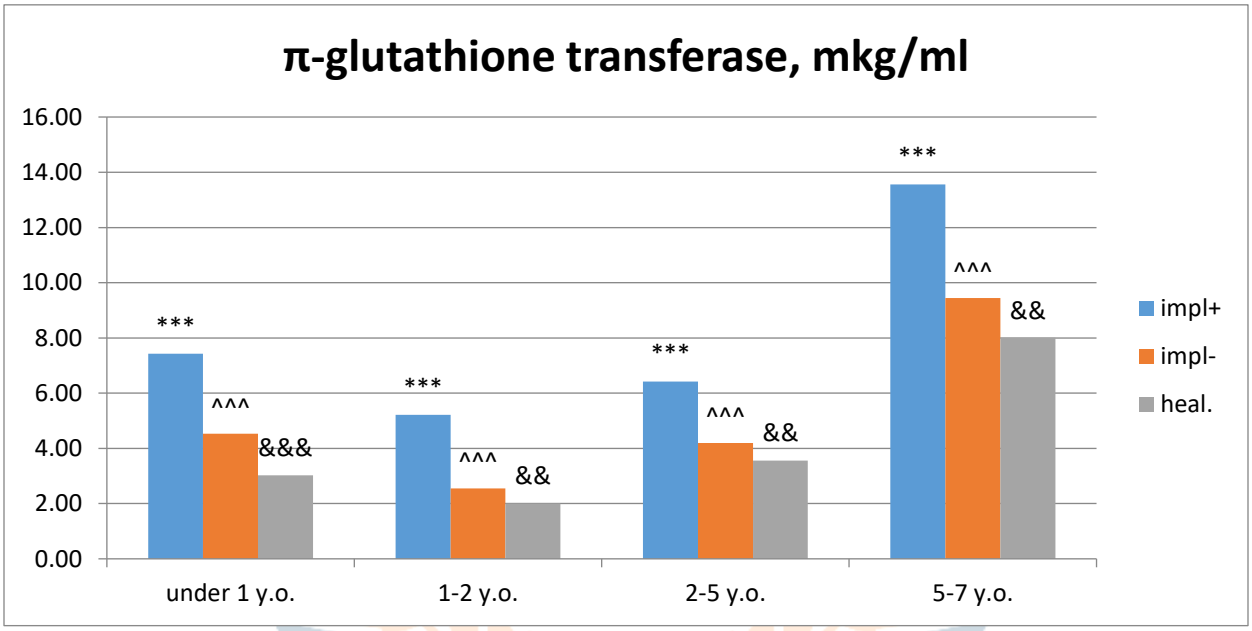
Note: * differences by age categories within clinical groups one sign - p<0.05, two signs - p<0.01, three signs – p<0.001.

Figure 6

The concentration of pi-glutathione-S-aminotransferase in the urine of healthy children and patients with pneumococcal pneumonia, depending on age and the presence of complications.



Note: the significance of the difference between clinical groups: * - between groups of imp+ and impl-, ^ - between groups of impl+ and healthy children, & - between groups of impl- and healthy children; two signs - p<0.01, three signs - p<0.001.

Table of reliability of intergroup indicators to Fig. 6 (the values of the Student's T criterion and the reliability of the difference are indicated, taking into account the Bonferroni correction)

Clinical groups	under 1/1-2	under 1/2-5	under1 /5-7	1-2 / 2-5	1-2 / 5-7	2-5 / 5-7
Impl+ (n=102)	1,65E-06***	0,014492	7,76E-12***	0,000724**	6,65E-14***	6,33E-15***
Impl- (n=98)	3,86E-09***	0,118237	1,97E-10***	9,47E-12***	2,67E-12***	2,47E-11***

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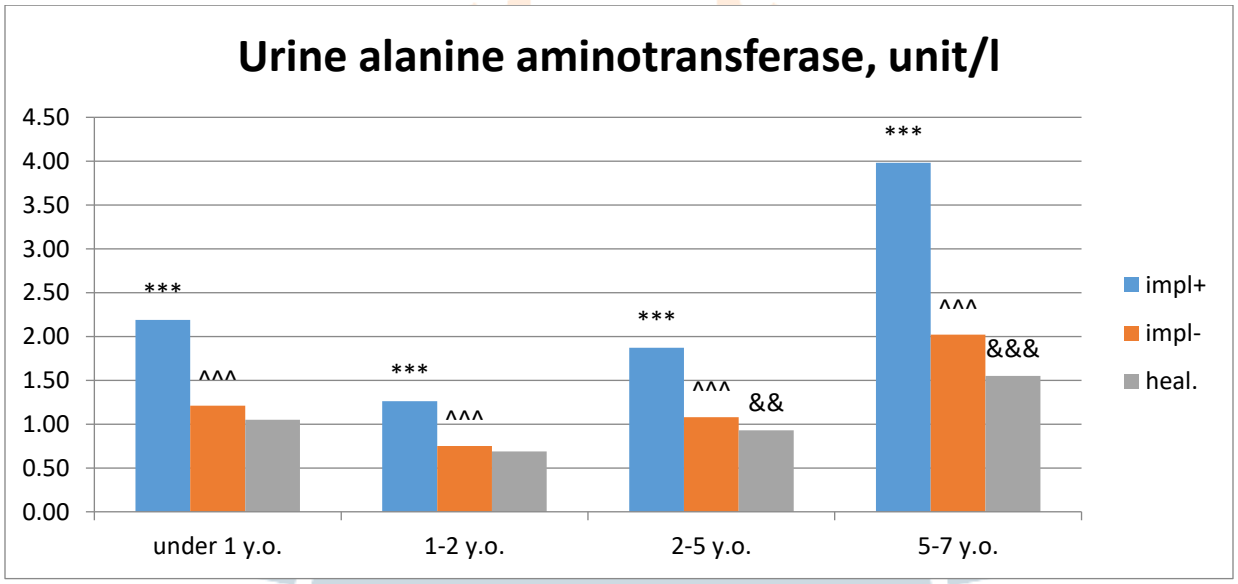
Heal. (n=40)	3,29E-07***	0,002491*	3,07E-13***	5,92E-09***	1,22E-14***	4,09E-12***

Note: the significance of the difference between clinical groups: * - between groups of impl+ and impl-, ^ - between groups of impl+ and healthy children, & - between groups of impl- and healthy children; two signs - p<0.01, three signs - p<0.001.

Table of reliability of intergroup indicators to Fig. 6 (the values of the Student's T criterion and the reliability of the difference are indicated, taking into account the Bonferroni correction).



Note: the significance of the difference between clinical groups: * - between groups of impl+ and impl-, ^ - between groups of impl+ and healthy children, & - between groups of impl- and healthy children; two signs - p<0.01, three signs - p<0.001.

Table of reliability of intergroup indicators to Fig. 7 (the values of the Student's T criterion and the reliability of the difference are indicated, taking into account the Bonferroni correction).

Clinical groups	under 1/1-2	under 1/2-5	under 1/5-7	1-2 / 2-5	1-2 / 5-7	2-5 / 5-7
Impl+ (n=102)	1,19E-07***	0,005816*	2,6E-11***	2,32E-12***	6,54E-14***	1,4E-12***

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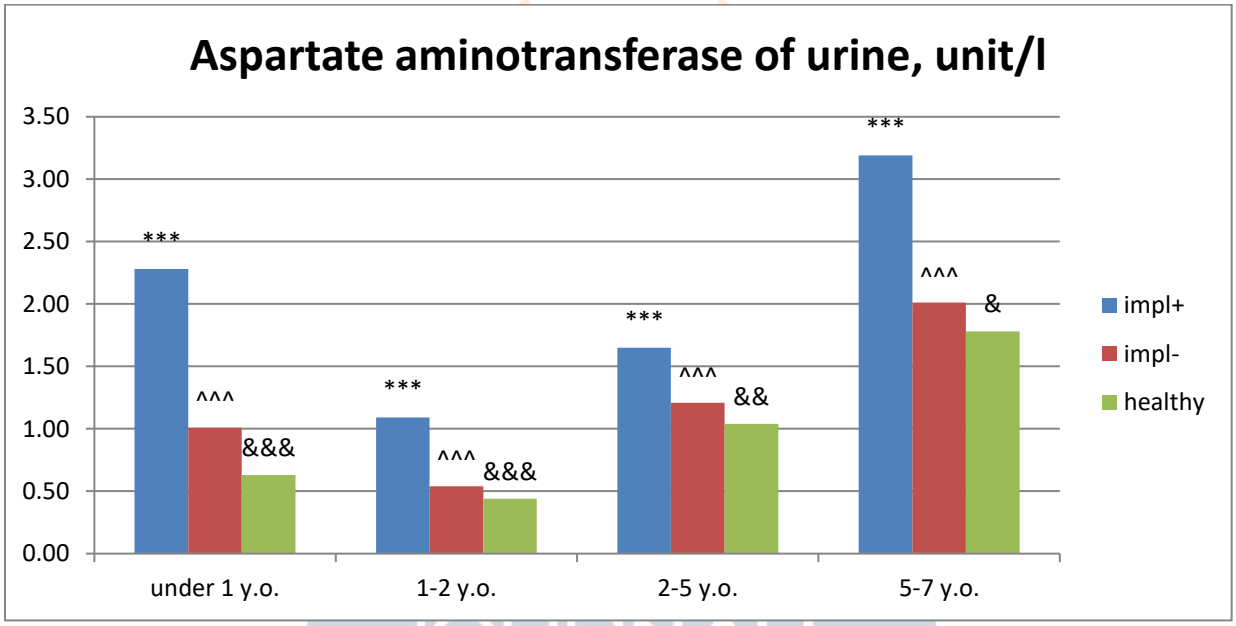
Impl- (n=98)	2,02E-05***	0,069901	2,23E-08***	1,42E-10***	1,16E-11***	2,73E-10***
Heal (n=40)	2,32E-08***	0,015229	1,45E-07***	7,48E-06***	8,47E-12***	6,12E-09***

Note: * differences by age categories within clinical groups one sign - p<0.05, three signs – p<0.001.

Figure 8

The concentration of aspartate aminotransferase in the urine of healthy children and patients with pneumococcal pneumonia, depending on age and the presence of complications



Note: the significance of the difference between clinical groups: * - between groups of impl+ and impl-, ^ - between groups of impl+ and healthy children, & - between groups of impl- and healthy children; one sign - p<0.05, two signs - p<0.01, three signs - p<0.001.

Table of reliability of intergroup indicators to Fig. 8 (the values of the Student's T criterion and the reliability of the difference are indicated, taking into account the Bonferroni correction).

Clinical groups	under 1/1-2	under 1/2-5	under 1/5-7	1-2 / 2-5	1-2 / 5-7	2-5 / 5-7
Impl+ (n=102)	8,95E-11***	1,7E-07***	1,11E-06***	9,25E-13***	1,33E-11***	3,32E-10***

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VOLUME 05 ISSUE 01 Pages: 01-15
SJIF IMPACT FACTOR (2020: 5. 286) (2021: 5. 64) (2022: 6. 319)
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Impl- (n=98)	8,37E-08***	0,00053**	3,86E-10***	3,24E-18***	2,59E-11***	2,81E-09***
Heal (n=40)	2,23E-06***	4,19E-09***	1,67E-13***	2,02E-12***	6,39E-15***	8,06E-10***

Note: * differences by age categories within clinical groups are two signs - p<0.01, three signs – p<0.001.

Thus, the present study revealed a significant increase in the markers of tubular lesion in children with pneumococcal pneumonia, even against the background of an uncomplicated course of the disease, which reflects the renal link of endotoxicosis syndrome. Against the background of complicated pneumonia, urinary excretion of markers of tubular pathology is even more pronounced. The distribution of children by age demonstrated a greater vulnerability of the kidneys to pneumococcal infection in children under 1 year old, as well as an increase in the degree of damage in children 5-7 years old, which is probably due to age-related features of the formation of immunity (insufficiency of the suppressor link, hyperergic reaction). Moreover, if an increase in cystacin and MMP indicates functional disorders of the tubule epithelium (violation of catabolism of micro and medium molecular proteins and reabsorption of amino acids), and lipocalin indicates the reaction of cells to damage, then an increase in the isoforms of glutathione transferase and transaminases indicates structural damage to cells.

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