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FEATURES OF BLOOD GAS COMPOSITION AND ACID-BASE BALANCE IN CHILDREN WITH ACUTE RESPIRATORY FAILURE CAUSED BY THE NEW CORONAVIRUS SARS-CoV-2

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A comprehensive examination of 61 children with severe acute respiratory infections made it possible to establish that in patients with a coronavirus infection caused by SARS-CoV2, upon admission to the Department of Anesthesiology and Intensive Care, more pronounced hypoxemia was probably registered more often. It was reflected statistically significant risks of SpO_2 reduction<92 % (odds ratio 3.9), pO_2<41 mm Hg. and ctO_2<14 mL/dL (odds ratio 2.9). Patients with symptoms of COVID-19 had high levels of acid-base disorders, with metabolic and respiratory alkalosis being the most common variants of the disorder. It has been established that there are likely chances of having COVID-19 in hospitalized children in the presence of HCO_3>25 mmol/l (odds ratio – 5.4), Hct >40 (odds ratio – 4.9), TCO_2>30 mmol/l (odds ratio – 3.4).

Key words: respiratory failure, COVID-19, children, blood gas composition

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ОСОБЛИВОСТІ ГАЗОВОГО СКЛАДУ КРОВІ ТА КИСЛОТНО-ЛУЖНОЇ РІВНОВАГИ У ДІТЕЙ ІЗ ГОСТРОЮ ДИХАЛЬНОЮ НЕДОСТАТНІСТЮ, СПРИЧИНЕНОЮ НОВИМ КОРОНАВІРУСОМ SARS-CoV2

Проведене комплексне обстеження 61 дитини з важкими гострими респіраторними інфекціями дозволило встановити, що у пацієнтів, хворих на коронавірусну інфекцію спричинену SARS-CoV2 при поступленні до відділення анестезіології та інтенсивної терапії вірогідно частіше реєстрували виразнішу гіпоксемією, яку відображали статистично достовірні ризики зниження SpO_2<92 % (співвідношення шансів 3,9), pO_2<41 мм рт.ст. та ctO_2<14 мл/дл (співвідношенням шансів 2,9). Пацієнти з симптомами COVID-19 мали високий рівень кислотно-лужних розладів, метаболічний та респіраторний алкалоз були найпоширенішими варіантами порушень. Встановлено, вірогідні шанси наявності COVID-19 у госпіталізованих дітей за наявності HCO_3>25 ммоль/л (співвідношення шансів – 5,4), Hct >40 (співвідношення шансів – 4,9), TCO_2>30 ммоль/л (співвідношення шансів – 3,4).

Ключові слова: дихальна недостатність, COVID-19, діти, газовий склад крові

The work is a fragment of the research project "Modern epidemiological, clinical-paraclinical and diagnostic features of the most common inflammatory diseases of infectious and non-infectious nature in children", state registration No. 0122U002208.

According to the WHO definition, the acute infectious disease caused by the new SARS-CoV-2 coronavirus was named "severe acute respiratory syndrome", which acquired the characteristics of a coronavirus pandemic or COVID-19 [8]. To date, the results of longitudinal observations on a global scale have been accumulated, which showed a sufficiently high susceptibility of the subpopulation of children and adolescents to the new SARS-Co-V-2 coronavirus with a mild or asymptomatic course that is much more frequent than in adults. As a result, according to some researchers, at the beginning of the pandemic, it was believed that children were not susceptible to COVID-19. As a result, the frequency of infection was underestimated due to the low coverage of pediatric patients with SARS-CoV-2 testing [3]. At the same time, convincing evidence has been accumulated that the children's population can play a significant epidemiological role in the spread of infection [4]. Children may also develop severe primary and unique secondary inflammatory complications of infection, including multisystem inflammatory syndrome [9]. In patients with COVID-19, pneumonia is the primary manifestation. It is diagnosed in almost all hospitalized patients and causes a wide range of acid-base changes, and it is also mainly manifested by bilateral ground glass opacities.

The severity of symptoms of COVID-19, as well as the duration of the course of the disease in infected pediatric patients, varies greatly. In particular, according to data [11], the duration of symptoms of the new coronavirus disease ranged from 1 to 36 days, and the release of the virus from various physiological secretions lasted for 2–3 weeks With a generally low frequency of severe infection in children, separate research groups [6] have shown its age distribution. Rare (22 %) neurological disorders in children with a severe course of COVID-19, acute respiratory failure in infected children and other severe clinical syndromes are described.

It is well known that early diagnosis of signs of acute respiratory inconsistency and careful monitoring of patients for timely intervention are of great importance. The initiated non-invasive respiratory support using high-precision nasal cannulae and positive pressure improves gas exchange and reduces the work of breathing in respiratory failure, which allows for achieving rapid recovery and avoiding incubation [15]. In adult patients with acute respiratory distress syndrome caused by COVID-19, non-invasive positive pressure ventilation significantly increases the so-called respiratory index (SpO_2/FiO ratio). In contrast to adults, there is a lack of comparative studies on the characteristics of the course of acute respiratory failure in childhood, which is related or not related to COVID-19 [13].

The purpose of the study was to perform a comparative analysis of the features of arterial blood gas composition and acid-base disorders of respiratory genesis in patients with the new coronavirus disease COVID-19 to improve medical care for children with signs of acute respiratory failure.

Material and methods. To achieve this purpose, a retrospective, single-centre, descriptive study was performed in the conditions of the Infectious Department of Anesthesiology and Intensive Care (IDAIC) of the Chernivtsi Regional Children's Clinical Hospital in 2020–2022. The study included 61 children of various ages who were hospitalized with signs of severe acute respiratory disease and respiratory distress that required oxygen therapy. To identify a viral infection caused by the new SARS-CoV-2 coronavirus, Real-Time Reverse Transcription PCR (RT-PCR) was performed on all patients admitted to the IDAIC [12]. Respiratory support was provided by nasal cannulae and non-invasive positive pressure ventilation, traditionally used in the initial treatment of children with respiratory failure (RF), providing a high level of respiratory support without the side effects of invasive mechanical ventilation [2].

The group-forming feature was the result of the identification of SARS-CoV-2 infection so that the first (I) group was formed by 30 patients with COVID-19 (positive for SARS-CoV-2), who received respiratory support under IDAIC conditions due to acute respiratory failure (mean age – 11.2±0.4 years, the proportion of boys – 43.3 %). At the same time, the second comparison group included the remaining 31 patients in whom the new coronavirus was not detected (negative for SARS-CoV-2). The symptoms of respiratory failure were due to the severe course of acute respiratory diseases of another etiology (mean age – 10.2±0.3 years ($p>0.05$), the share of boys – 41.9 % ($p>0.05$)).

All children underwent standard dynamic monitoring of vital functions, and current guidelines and protocols on respiratory mechanics indicators provided respiratory support. Upon admission to IDAIC, the children were examined for indicators of gas composition and acid-base balance in venous blood using the Medica Easy Gas Stat analyzer (USA). Immediately after taking the material in the conditions of IDAIC, the samples were delivered to the laboratory on Cito for measurements. When analyzing the results of acid-base balance, a comprehensive assessment of balance markers was carried out, taking into account that metabolic acidosis is characterized by an increase in H+, a decrease in blood pH and HCO3, metabolic alkalosis – a reduction in H+, an increase in blood pH and HCO3, respiratory acidosis is characterized by a reduction in blood pH and an increase in the concentration of H+ and HCO3, respiratory alkalosis – an increase in blood pH, a decrease in the concentration of H+ and HCO3 in the blood.

This study was conducted with the informed consent of the parents, by the principles of biomedical ethics and compliance with the main provisions of the Law of Ukraine No. 2801-XII "Basics of the Legislation of Ukraine on Health Care", ICH GSR (1996–2016), Helsinki Declaration of the World Medical Association on Ethical Principles of Scientific Medical Research with Human Participation (1964–2013), Council of Europe Convention on Human Rights and Biomedicine (from 04.04.1997), Order of the Ministry of Health of Ukraine No. 690 from 09.23.2009.

Statistical processing of digital data obtained during the study was carried out using the StatSoft Statistica program package (version 8.0), using the methods of variational statistics and clinical epidemiology. Thus, the average values of a mathematical series were expressed in the form of the average arithmetic value (M) and the standard error of the average value (m). The significance of "P" differences in testing statistical hypotheses was considered at 5 % type I error values ($P < 0.05$).

Using the techniques of "alternative" statistical analysis, the indicators of attributive risk (AR), relative risk (RR), and odds ratio (OR) of a particular event were calculated with the determination of their 95 % confidence intervals (95 % CI).

Results of the study and their discussion. The paper shows that hospitalization of patients of Group I to IDAIC occurred on average on 5.25±0.32 days from the onset of the disease, and representatives of Group II were significantly faster relative to the onset of the disease – on 3.92±0.37 days ($P<0.05$). At the same time, signs of respiratory distress lasted 4.34±0.47 and 3.15±0.22 days in groups I and II, respectively ($P<0.05$). It allowed us to assume that patients of clinical Group II who were not infected with the SARS-CoV-2 virus had a slightly faster rate of increase in the severity of respiratory dysfunction than patients with COVID-19.

However, the assessment of SaO2 parameters upon admission to the hospital showed significantly lower results in patients of group I – 92.6±0.32 % versus 95.2±0.31 % in patients of group II ($p<0.05$). The proportion of patients in whom the SaO2 index <92 % was determined during hospitalization was equal to 33.3 % of cases in the I group, and it was three times smaller in the II group – 11.3 % ($p\varphi<0.05$) of observations. Accordingly, the indicators of the clinical and epidemiological risk of this event in the case of COVID-19 compared to patients of the II group were attributive risk (AR) – 31.7 %, relative risk (RR) – 1.7 (95 % CI: 0.9–3.2) with an odds ratio (OR) of 3.9 (95 % CI: 1.8–8.3).

However, we witnessed the rapid rate of recovery of oxygen saturation of the peripheral blood in patients of group I since the average indicators of oxygen saturation in the blood, according to pulse oximetry data, in the patients of the comparison groups did not have a statistically significant difference during the first 7 days of inpatient treatment.

The analysis of the frequency of individual nosological forms of acute respiratory infection showed that severe pneumonia was registered in 26.0 % of cases in group I patients and 45.0 % of children in group II ($p\varphi<0.05$). However, starting from the 8th day of inpatient treatment, the average SaO2 indicator in patients infected with the SARS-CoV-2 virus was probably lower than in group II, which indicated more pronounced hypoxemia in the latter. Thus, the proportion of patients in whom SaO2<92 % was registered on the 8th day of hospitalization was only 1.9 % in group I, and 10.7 % in group II ($p\varphi<0.05$). The chances of registering SaO2<92 % on the 8th day of inpatient treatment in patients of group II compared to patients of group I were probably higher: AR – 37.3 %, RR – 1.8 (95 % CI: 0.4–8.1), OR – 6.2 (95 % CI: 1.3–29.7). It was probably due to the presence of chronic accompanying pathology in children of group II: congenital heart defects and neurological pathology – 2 cases each, obesity – 1 case, epilepsy – 1 case.

Considering deviations of Intergroup differences in the indicators of blood oxygen saturation, it was considered necessary to conduct a comparative analysis of the indicators of blood gas composition in sick children during their hospitalization in IDAIC (fig.1).

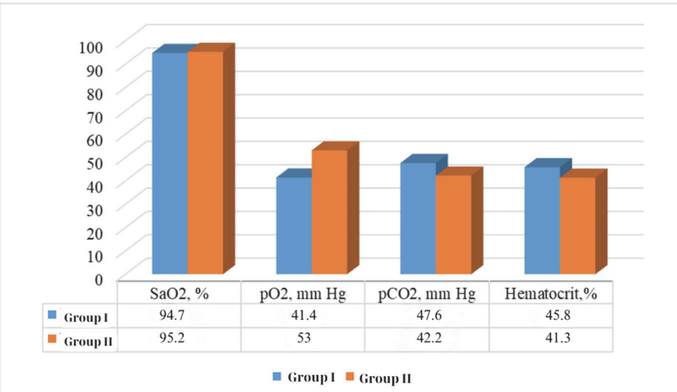

Fig. 1. Parameters of blood oxygen saturation, hematocrit, and arterial blood gas composition in the comparison groups upon admission of children to IDAIC.

The given data illustrate a clear trend towards the predominance of hypoxia, hypercapnia, and blood clotting in children with COVID-19 compared to patients of group II when hospitalized in IDAIC. Thus, when focusing on the reference values of the partial pressure of oxygen in venous blood of 17–41 mm Hg, it was established that children infected with the SARS-CoV-2 virus, hospitalized in IDAIC in a severe condition, had a higher risk of pO2<41 mm Hg, compared to critically ill patients of group II: AR – 26.5 %, RR – 1.8 (95 % CI: 1.4–2.2), OR – 2.9 (95 % CI: 1.6–5.5). At the same time, the average group values of total oxygen content (ctO2), which reflects the sum of its concentrations in plasma and in the hemoglobin-bound state, had no statistically significant differences and were 14.04±1.09 ml/dL and 15.43±0. 74 ml/dL in groups I and II ($P>0.05$). But despite the absence of a reliable difference in average group ctO2 indices, we established a statistically significant risk of a decrease in total oxygen content (ctO2) <14 ml/dL in patients of group I compared to the representatives of group II: AR – 26.2 %, RR – 1.7 (95 % CI: 1.2–2.4), O – 2.9 (95 % CI: 1.6–5.2).

Table 1 shows the indices of a comparative analysis of the acid-base status of venous blood upon admission to the IDAIC of children of the comparison groups.

Table 1

Parameters of the acid-alkaline state of blood in patients of the comparison groups

Parameters	Group I	Group II	p
TCO2, mmol/l	29.4±1.4	25.8±1.8	>0.05
HCO3, mmol/l	28.8±3.3	22.4±1.1	<0.05
BEb, mmol/l	-0.04±0.01	-1.2±0.6	>0.05
Becf, mmol/l	0.15±0.05	-0.6±0.3	>0.05
SBC, mmol/l	22.9±0.6	22.1±0.7	>0.05
% SO2c	68.9±5.3	71.5±4.9	>0.05

As can be seen from the given data, the average group indices of acid-base balance in groups of patients coincided, except for the standard concentration of bicarbonates in venous blood. Based on the fact that the range of 22–29 mmol/l HCO3 is considered normal for venous blood, the amount of HCO3 in patients of group II indicated a deficiency of buffer compounds and the presence of metabolic acidosis, which can be a consequence not only of an increase in acidity in the body but also of excessive loss bicarbonate.

At the same time, in both clinical groups, a symmetrical deficiency of standard bicarbonates of venous blood was observed according to the SBC indicator, the normal values of which are between 38–50 mm Hg. However, a more pronounced difference between the actual and mean values of alkalis in the blood (Becf) in patients of group II, which was 0.75 mmol/l, attracted attention. In the same way, the BEb indicator testified to a more pronounced alkali deficiency in children of group II. In addition, a clear trend towards the predominance of hypoxemic and hypercapnic changes in patients with COVID-19 was established, as demonstrated by the indicators of the percentage of oxygen saturation (%SO2c) and the marker of the total concentration of carbon dioxide in venous blood (TCO2).

Based on the identified patterns, we calculated indicators of the clinical and epidemiological risk of SARS-CoV-2 infection in severely ill children compared to a similar cohort of patients in whom respiratory failure was caused by other etiological factors (Table 2)

Table 2

Parameters of the risk of acid-base disorders in children with COVID-19

Parameters	Risk parameters		
	AR, %	RR (95 % CI)	OR (95 % CI)
Parameters of the risk of acid-base disorders in children of Group I compared to patients of Group II			
ph <7.35	15.6	1.4 (1.1–1.7)	1.8 (1.0–3.3)
HCO3>25 mmol/L	38.7	2.0 (1.2–3.4)	5.4(2.7–10.7)
Hct >40	36.8	2.6(2.1–3.1)	4.9 (2.4–10.1)
pO2<80 mmHg	15.8	1.4 (1.2–1.6)	1.9 (0.8–4.5)
TCO2>30 mmol/L	29.2	1.7 (1.0–2.9)	3.4 (1.7–6.8)
Parameters of the risk of acid-base disorders in children of Group II compared to patients of Group I			
Beb <=-1 mmol/l	24.7	1.7 (1.3–2.2)	2.7 (1.5–4.9)
Becf <=-0.6 mmol/l	17.9	1.4 (1.1–1.9)	2.1 (1.2–3.6)
HCO3<22 mmol/L	37.4	1.9 (1.0–3.5)	5.2 (2.4–11.1)

The mean indices of the respiratory index (RI) in patients of group I was equal to 1.8±0.2 CU, in representatives of group II – 1.2±0.1 CU ($p<0.05$).

The frequency of registration of RI <1.2 CU in patients of group I – 17.6 %, and in patients of group II – 40.0 % ($p\varphi<0.05$) of cases, respectively. Risk indicators for the presence of RI <1.2 CU in patients of Group II compared to representatives of Group I were: AR – 27.3 %, RR – 1.6 (95 % CI: 1.0–2.7) with OR – 3.1 (95 % CI: 1.6–5.9).

Therefore, HCO3>25 mmol/l, Hct>40, and TCO2>30 mmol/l indicate the probable chances of having COVID-19 in severely ill children hospitalized in IDAIC.

At the same time, reliable chances of the absence of SARS-CoV-2 infection in severely ill children in IDAIC conditions based on markers of alkali deficiency in venous blood have been established. Based on this, indices of bicarbonate deficiency in venous blood can act as additional markers of the absence of COVID-19 in severely ill children in IDAIC conditions with sensitivity in the range of 38–66 % and specificity of 57.9–89 %.

The analysis of the acid-alkaline balance made it possible to establish the presence of markers of metabolic acidosis in 15.8 % of children of group I and in 28.6 % of cases ($p\varphi>0.05$) in group II, as well as metabolic alkalosis in 57.9 % and 14.3 % ($p\varphi<0.05$) of observations in groups I and II, respectively. The risk indices for metabolic alkalosis in children with COVID-19 compared to patients of Group II were equal to RR – 2.4 (95 % CI: 1.5–4.0) with OR – 8.2 (95 % CI: 4.1–16.4).

Taking into account methodological approaches to determining acid-alkaline imbalance of respiratory genesis and based on the obtained results, we established that respiratory alkalosis was registered in 47.4 % of group I patients and 23.8 % ($p\varphi<0.05$) of group II patients. The risk indices for respiratory alkalosis in children with severe COVID-19 compared to severe patients of Group II were RR – 1.6 (95 % CI: 1.1–2.4) with OR – 2.9 (95 % CI: 1.6–5.3).

There were no deaths among the studied group. The mean duration of stay in the IDAIC department among patients of Group I was 1.95±0.4 days, for representatives of Group II – 3.05±1.2 days ($p>0.05$).

Thus, we have shown that compared to children with COVID-19, patients not infected with the SARS-CoV-2 virus of the clinical group II had a faster rate of increase in the severity of respiratory failure relative to the onset of the respiratory disease. At the same time, upon admission to IDAIC, children with COVID-19 had a higher risk of decreased blood oxygen saturation (odds ratio was 3.9 (95 % CI: 1.8–8.3)).

Our results are consistent with the work of other researchers [5], who found that about 30 % of critically ill adolescents hospitalized for COVID-19 before the intensive care unit show signs of acute respiratory distress syndrome with higher inflammatory markers expressed by radiographic data. We explained the remaining cases of respiratory dysfunction in the examined patients based on pathomorphological evidence of two main models of the severe course of COVID-19 in children [7]. Therefore, more pronounced hypoxemia in children of group I could be explained by other pathological respiratory and non-respiratory multisystem injuries [10], which require oxygen supplementation. However, the arterial blood gas composition confirmed the predominance of hypoxia (odds ratio – 2.9 (95 % CI: 1.6–5.5)) and hypercapnia in patients with COVID-19 during hospitalization to IDAIC, which is consistent with the data of other authors. They found that 79.7 % of patients with COVID-19 had low arterial partial pressure of oxygen, insufficient blood oxygen saturation, and decreased PO_2/FiO_2 ratio [1].

Analysis of the features of acid-base balance disorders in severely ill children with signs of respiratory failure caused by the SARS-CoV-2 virus and other pathogens allowed us to establish a higher risk of developing metabolic alkalosis (odds ratio – 8.2 (95 % CI: 4.1–16.4) and respiratory alkalosis (odds ratio – 2.9 (95 % CI: 1.6–5.3) in children with COVID-19 relative to the comparison group.

We explained the development of respiratory alkalosis with hyperventilation syndrome and oxygen therapy with excessive losses and a decrease in CO2 production, and the appearance of metabolic alkalosis with iatrogenesis (diuretics, citrates, acetate) and the predominance of dairy products in the diet. As compensation for alkalosis, there is an increase in PaCO2 to buffer alkalinemia, which we determine in patients of group I. It is known that there is an increase in PaCO2 by 0.5 mm Hg. Compensates for a 1 mmol/l increase in HCO3, which is especially important in respiratory pathology since alkalemia contributes to the shift of the oxyhemoglobin dissociation curve to the left, as a result of which the affinity of hemoglobin for oxygen increases, which gets to the tissues less. Therefore, hypercapnic respiratory insufficiency accompanied by hyperventilation with the development of respiratory alkalosis is determined in children severely ill with COVID-19, which has a higher chance than patients with a severe course of other respiratory infections.

Finally, the data of the literature, which shows that patients with metabolic alkalosis have a more extended stay in the intensive care unit, a longer stay on forced ventilation, and a higher mortality rate, should be taken into account. At the same time, an increase in the serum bicarbonate content by 5 mEq/L above the value of 30 mEq/L increases the risk of mortality (OR – 1.21), which does not depend on the cause of alkalinemia [14].

There were no deaths in the studied group. The children were transferred to the appropriate hospital departments and discharged with recovery.

Conclusions

1. Upon admission to IDAIC, children with COVID-19 were characterized by probably more pronounced hypoxemia, which was reflected by statistically significant risks of SpO2 decrease <92 % (odds ratio – 3.9), pO2<41 mm Hg. and ctO2<14 ml/dL (odds ratio – 2.9).

2. Children hospitalized with symptoms of COVID-19 had a high rate of acid-base disorders. Metabolic (57.9 %) and respiratory (47.4 %) alkalosis were the most common variants of such disorders.

It has been established that there are likely chances of having COVID-19 in hospitalized children in the presence of HCO3>25 mmol/l (odds ratio – 5.4), Hct >40 (odds ratio – 4.9), TCO2>30 mmol/l (odds ratio – 3.4).

3. Additional markers that help to refute the coronavirus disease COVID-19 in children with respiratory distress are indices of bicarbonate deficiency in venous blood (Beb <=-1 mmol/l; HCO3<22 mmol/l; Becf <=-0.6 mmol/l) with sensitivity in the range of 38–66 % and specificity from 57.9 to 89 %.

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