

Current situation's analysis of the problem in intensive care of complicated community-acquired pneumonias in children.



Yuliia Horodkova¹  ORCID <https://orcid.org/0000-0001-5954-7682>

¹ Department of Children Diseases, Zaporizhzhia State Medical University, Zaporizhzhia, Ukraine

ADDRESS FOR
CORRESPONDENCE:

Yuliia Horodkova, MD

Maiakovskiy Avenu, 24a, Ap. 138,
Zaporizhzhia 69035, Ukraine;

e-mail: gorodkovaju@gmail.com

ABSTRACT

INTRODUCTION: The leading place in the nosological structure of pathology in the lower respiratory tract is pneumonia. Community-acquired pneumonia (CAP) remains one of the most common causes of childhood morbidity and accounts for about 16% of all deaths in children under 5 years old. The article presents a review of publications of recent years using the databases PubMed, Scopus, Web of Science, Google Scholar regarding the current possibilities of intensive care of complicated community-acquired pneumonia (CCAP), problems of using extracorporeal detoxication methods (ECDM), the choice of starting antibacterial therapy and microbiological monitoring and the problem of determining the severity of endogenous intoxication syndrome in children with CCAP.

PURPOSE: To analyze the relevance of intensive therapy in children with complicated community-acquired pneumonia, to consider current therapeutic interventions and the need to use extracorporeal detoxication methods in complex treatment based on the analysis of scientific literature data.

CONCLUSIONS: The epidemiology of community-acquired pneumonia is currently characterized by an increasing trend in morbidity and mortality worldwide. Plasmapheresis is not first-line therapy, because antibacterial drug (ABD), conservative detoxication, respiratory support are the mainstay of treatment like for other infections, but in case of CCAP the course of basic therapy is often not enough and then there is a need for ECDM. Identification of causative microorganisms in children with CCAP remains a constant problem. In most cases, therapy is prescribed empirically and knowledge of local epidemiology, the structure of ABD resistance is an important platform for improving antibacterial therapy. The optimal therapeutic approach for CCAP remains open to research.

KEY WORDS: plasmapheresis, pneumonia, child, intensive care units.

INTRODUCTION

The leading place in the nosological structure of pathology in the lower respiratory tract is pneumonia. Community-acquired pneumonia (CAP) remains one of the most common causes of childhood morbidity and accounts for about 16% of all deaths in children under 5 years old [1, 2]. The incidence of complicated pneumonia in children has been increasing over the last two decades, including the leading bacterial pathogens of which are pneumococcus and methicillin-resistant *Staphylococcus aureus* strains (MRSA) [3-5, 7]. It should be borne in mind that currently the evidence base on therapy in pediatrics, including antibacterial therapy (ABT) is clearly insufficient, which is associated with ethical and deontological issues. It is important to keep in mind that the effectiveness of etiotropic therapy for pneumonia is fundamentally dependent on the sensitivity of pathogens to antibacterial drugs (ABD), which has significant regional features [6, 7].

The main links in the pathogenesis of complicated pneumonia, which cause the severity of the course and poor prognosis, are hypoxia and endotoxemia. Endogenous intoxication syndrome arises from the depletion of natural detoxification systems, so extracorporeal detoxification methods [8, 9] should be effective. Despite active research into endogenous intoxication syndrome, many issues remain unresolved. In particular, determination of probable variants of clinical course of endotoxemia and their early diagnosis, development of reasoned criteria of effectiveness of detoxification treatment measures [10]. Issues of severity, use of extracorporeal detoxification methods (ECDM), choice of ABD have not been sufficiently studied.

The goal of the work: to analyze the relevance of intensive therapy in children with complicated community-acquired pneumonia, to consider current therapeutic interventions and the need to use extracorporeal detoxification methods in complex treatment based on the analysis of scientific literature data.

MODERN POSSIBILITIES OF INTENSIVE THERAPY IN CHILDREN WITH COMPLICATED COMMUNITY-ACQUIRED PNEUMONIA

Treatment of pneumonia should be comprehensive and include: action on the causative agent of the disease; elimination of inflammation and intoxication; renewal of the drainage function of the

bronchopulmonary apparatus; normalization of immunobiological reactivity; special methods and remedies for complications of pneumonia [7].

Complex treatment of complicated pneumonia at the present stage involves, in addition to antibiotic therapy, the fight against respiratory failure and toxic complications. Acute respiratory failure (ARF) of the parenchymatous type is a serious problem and is often the cause of patients' death. Different methods of respiratory support are used to treat ARF, and in severe cases, it is fully controlled mechanical ventilation (MVL) with aggressive regimens (high airway pressure, oxygen fraction over 60%, inhalation/exhalation ratio $\geq 1/1$). Pressure support can be performed either through endotracheal intubation or through a non-invasive interface such as a high-flow nasal cannula (HFNC). There is no clear opinion regarding ventilation regimens: although a series of cases describe the benefits of ventilation by airway pressure - airway pressure release ventilation (APRV) as a primary ventilation strategy in children with acute respiratory distress syndrome, the use of this regimen has been associated with a higher mortality rate compared to conventional protective volume regimens (low-tidal volume ventilation LoTV) [15]. Recent decades have seen the progressive use of Constant Positive Airway Pressure (CPAP) and non-invasive ventilation (NIV) as the first ventilation line for the treatment of respiratory failure. Although the useful role of CPAP is supported by two randomized controlled trials, the effectiveness of the NIV has not yet been demonstrated. In particular, the ability of the NIV to prevent endotracheal intubation varies significantly according to analysis in the range of 20-76% [11]. The intensity and aggressiveness of respiratory support depends on the severity of lung injury and the degree of hypoxemia. The number of side effects of respiratory support is more pronounced with more aggressive MVL methods. In connection with this, a wide range of ancillary non-respiratory methods for the treatment of parenchymatous ARF, such as positional therapy [14], are used today in conjunction with MVL.

The most aggressive method of kinetic therapy is the patient's return to the abdomen - prone-position. The effectiveness of mechanical ventilation in the prone-position is that under the action of gravity after the rotation of the patient on the abdomen is redistribution of areas of high density from the lower lungs, where the atelectasis and more pronounced ventilation-perfusion disorders, to the upper. Transpulmonary pressure in these lung areas becomes higher than the pressure of opening the alveoli in these areas, which increases the volume of the functional parenchyma of the lungs and improves pulmonary gas exchange [15, 2]. Patients suffering from CAP with oxygen saturation $\leq 92\%$ when breathing in atmospheric air, need to enter additional

oxygen through the nasal cannulas, masks, or other high-flow device to deliver oxygen, to maintain oxygen saturation > 92% [10, 16]. The flow of oxygen should be 2 l/min, its concentration depends on the method of inhalation: when using nasal cannulas - 30-35%, nasal catheter - 35-40%, nasopharyngeal catheter - 45-60%. The introduction of a nasogastric tube may cause respiratory distress and should therefore be avoided in severely ill children, and especially in children with small nasal passages. If its use cannot be avoided, the smallest tube should be inserted into the smallest nostril. Only moistened and heated oxygen should be used [10].

Most children with severe respiratory failure require extracorporeal membrane oxygenation (ECMO) within 7-10 days. However, some may require a longer ECMO (> 14 days) [14]. Both primary and secondary hyperventilation, which is associated with significant deviations of the acid-base equilibrium, greatly increases the loss of water with respiration. Thus, if the minute volume of breathing increases five to six times, compared to normal, the daily loss of water with the lungs in the infant may exceed 100 ml/kg [10]. Particular attention should be paid to the balance of fluid and analgesia. Surgical treatment is often required (puncture, drainage of the pleural cavity with / without intra pleural fibrinolysis, thoracoscopy) [4, 6]. Used devices for bronchoalveolar lavage and regular fibrobronchoscopy [17]. When carrying out the rehabilitation of the pleural cavity use solutions of antiseptics. One of the remedies for the correction of immunodeficiency is fresh frozen plasma (FFP) derived from the blood of healthy donors containing the basic spectrum of biologically active substances present in the blood: immunoglobulins, lysocyme, components of complement, albumin, electrolytes, etc. FFP has strong opsonizing and detoxifying properties, antiviral and antibacterial activity. For correction of anti-endotoxin immunity in children with purulent-septic diseases, FFP with a high level of anti-endotoxin antibodies was used [14, 24, 25]. A clear positive effect is in the case of staphylococcal pneumonia the use of antistaphylococcal immunoglobulin [4].

Corticosteroids can be useful in the combination of CAP with bronchial obstruction, there is uncertainty in the use of glucocorticoids in patients with CAP [1]. Although glucocorticoids have not been shown to be associated with a reduction in 28-day and 3-month mortality through a retrospective observational study, a randomized controlled trial demonstrated that methylprednisolone compared with placebo reduced the incidence of treatment failure [18]. Given the findings of the above studies, there is an excessive inflammatory

response leading to treatment failure and mortality in CAP [2], and the fact that steroids inhibit the expression of many cytokines involved in the inflammatory response associated with pneumonia, glucocorticoids may play a significant role in management of patients with CAP [11, 19-21], however, corticosteroids suppresses the protective functions of the immune system.

THE PROBLEM OF USING EXTRACORPOREAL DETOXICATION METHODS

Given the enormous role of endotoxin in the pathophysiology of the infectious process, the lack of clinical benefit of anti-endotoxin and anti-kinin therapy, the interest of scientists has shifted to extracorporeal treatments that reduce the level of mediators of the septic process in the systemic circulation [24].

Data on clinical applications of blood purification methods in children are limited. From a review by Bottari G. et al. (2019), for blood purification in children with hyperinflammatory syndromes, it is known that with the exception of three randomized controlled trials (RCTs) for plasmapheresis (PP), there are no RCTs, but only observational studies or case reports of other blood purification methods have been identified. High volume hemofiltration (HVHF) in two non-randomized trials did not significantly reduce 28-day mortality in children. PP has not been associated with a reduction in mortality in pediatric patients with septic shock, but the small number of enrolled patients is an important limitation. The use of polymyxin B and other adsorption columns in children with septic shock and hyperinflammatory syndrome is increasing, but the results are still limited by the observational nature of the studies. Given the low level of data available, no conclusions can be drawn as to the effectiveness and safety of blood purification in children. Further studies with more clinically reliable data are needed to determine the effects of different methods of extracorporeal detoxication (ECMD) in this pediatric population [22, 23]. Summarizing the results of adult studies shows that the use of extracorporeal detoxication methods (including hemoperfusion, plasma exchange, hemofiltration in combination with hemoperfusion) is associated with fewer deaths in patients with severe sepsis (35.7% vs. 50.1%) [24, 25].

In the 2016 International Recommendations for the Management of Sepsis and Septic Shock in Adults, the authors no make recommendations regarding the use of blood-purification methods in relation to the lack of evidence base both to confirm the possibility of using them and to justify the inappropriate use of

such contradictions that exist and it need further research [26]. Removal of anti-inflammatory factors have been reported when using non-selective plasma exchange methods. According to representatives of the American Association of Apheresis, from the point of view of the evidence of PP in MODS belongs to the third group of diseases, when the effect of the method is not confirmed, but it can be used on separate indications. Inclusion of patients with early septic shock with high doses of vasopressors was possible and PP was safe [22-25].

According to other data, high-volume plasmapheresis is a fast and effective means of influencing homeostasis, using high-volume PP for 3-4 hours, that leads to normalization of impaired metabolism, compensation of detoxication reserves of the organism, contributes to the reduction of manifestations of the inflammatory response syndrome, endotoxicosis and reduce the likelihood of the development of multiple organ disorders. At the height of severe toxicity in pneumonia, a number of clinics have successfully used hemosorption and plasmapheresis to promote the removal of bacterial toxins and autotoxic substances from the patient's blood [15, 22]. Successful use of discrete plasmapheresis as a method of nonspecific detoxication therapy in a 6-year-old child with Ray syndrome and ventilator-associated pneumonia has been reported. Decreased length of newborns' stay with the syndrome of endogenous intoxication in the intensive care unit, as well as decreased stay at MVL and decrease in mortality rates when used in complex treatment of PP [17, 22]. Also reported about the patient, a 3-year-old boy who had respiratory, renal, coagulation, hepatic, neurological dysfunction associated with methicillin-resistant staphylococcus and after 5 sessions of PP the patient has fully recovered. Children (1 year old) are advised to use discrete plasmapheresis in cases of significant endogenous toxicosis due to a generalized inflammatory response. It should be noted that discrete plasmapheresis in patients with this pathology was a more effective tool, and its implementation began as early as the first day after admission, especially in children with the toxic form of acute hematogenous osteomyelitis. Also, plasma metabolism in children has proven to be useful as complementary therapy in intensive care settings, especially for non-renal indications [8, 9, 25].

At the height of severe toxicity in pneumonia, a number of clinics have successfully used plasmapheresis, resistance to drug therapy is an indication for this type of efferent therapy. In children for the effective elimination of endotoxicosis a necessary component for the purpose of complex treatment of

purulent-septic diseases was the use of discrete plasmapheresis [17]. PP in children with MODS due to sepsis requiring extracorporeal life support appears to be associated with significant recovery of organ failure and reduced need for vasoactive and/or inotropic agents that may have the potential to improve survival. In addition, earlier initiation of PP compared to later in the inpatient course was associated with better organ function improvement and less need for vasoactive and/or inotropic agents. These findings support the need for larger, prospective studies to determine the indications, clinical benefits, and safety of PP use in pediatric patients with sepsis [9, 23]. Studies indicate that in specialized centers therapeutic plasma exchange can be performed relatively safely in critically ill children, in isolation or in combination with continuous renal replacement therapy and extracorporeal membrane oxygenation. The result in children requiring therapeutic plasma exchange is excellent, but survival decreases depending on the number of organs with insufficiency [17, 24]. Retrospective cohort analysis in patients with TAMOF (multiple organ failure associated with thrombocytopenia) in three different ICUs, comparing those who received PP on standard therapy with those who did not receive PP and received only standard therapy, a positive relationship was found between PP use and improved survival, confirming the potential of this therapy in children with TAMOF [27]. Equally important is the change in the content of blood cells on the background of plasmapheresis, it is believed that the plasma is partially removed with the elements: platelets, leukocytes, erythrocytes, although at the same time therapeutic plasmapheresis is used in the case of TAMOF syndrome [27]. In severe sepsis and septic shock, inflammatory and anti-inflammatory reactions develop simultaneously, so it is likely that when using non-selective methods of removal of harmful molecules, such as plasma exchange, some molecules and some beneficial effects of the molecule can be removed, but the theoretical justification for PP is justified (of course, important) elimination of circulating harmful molecules [17, 25]. The exchange of septic with healthy plasma may also replace consumed protective factors that are important for maintaining microcirculatory blood flow (eg, ADAMTS13) and counterbalancing vascular leakage (eg, angiopoietin-1) [9, 22, 23].

THE PROBLEM OF THE CHOICE OF STARTING ANTIBACTERIAL THERAPY

Essential conditions for reliable eradication of microorganisms in the treatment of pneumonia are compliance with the following rules of antibiotic therapy:

1. the choice of starting antibiotic according to the principles of probable etiology, the nature of the pathological process, the general condition of the patient, the child's age [7];
2. timely evaluation of the effectiveness of starting antibiotic therapy: 24-48 hours after the start of treatment;
3. duration of antibiotic therapy: in the presence of a positive effect of starting therapy, the duration of the course of mild pneumonia does not exceed 7-10 days, but in cases of severe or complicated course of the disease can be more than 14 days [7];
4. routes of administration of antibiotics: ABD in children with CAP treated in an outpatient setting, can be administered orally; parenteral administration of antibiotics should be used in the treatment of pneumonia in children when the child is unable to swallow oral antibiotics (eg through vomiting) or his condition is too severe [7, 10]. Use of inhaled ABD is reported.

Experts from the British Thoracic Society (BTS) believe that all children with clear clinically diagnosed community-acquired pneumonia should receive antibiotics, both in bacterial and viral etiology, since they cannot be clearly distinguished from each other [7, 10]. However, experts from the American Society for Pediatric Infectious Diseases (PIDS) and the American Society of Infectious Diseases Specialists (IDSA) believe that no antibacterial therapy is needed for preschool children with community-acquired pneumonia because viral pathogens are responsible for a large number of clinical diseases [7]. According to PIDS and IDSA guidelines, empirical therapy for typical community-acquired pneumonia in pediatric intensive care units (significant pneumococcal resistance, complicated pneumonia) includes Ceftriaxone (50-100 mg/kg per day in 2 doses) or ceftriaxone/sulbactam (50-70 mg/kg per day ceftriaxone 1-2 doses), additional vancomycin (40-60 mg/kg per day for 3-4 doses) or clindamycin (40 mg/kg per day for 3-4 doses) for suspected MRSA. Alternative: levofloxacin (16-20 mg/kg / day twice a day for children from 6 months to 5 years and 8-10 mg/kg/day once to children 5-16 years intravenous; maximum daily dose 750 mg). In the treatment of atypical pneumonia - Azithromycin (in addition to β -lactam antibiotics, if the diagnosis is in doubt). Alternatives: clarithromycin or erythromycin, doxycycline for children > 7 years; levofloxacin for children who have reached puberty or who do not tolerate macrolides [7, 10]. According to other sources, the use of macrolides both individually and in combination with other ABDs is not supported by reliable evidence [1], including the need for antimycoplasmic antibacterial therapy is rarely reported [7, 10]. Thus, combination antibacterial therapy

is indicated in the absence of the effect of starting treatment, severe and complicated forms of pneumonia. Antibiotics for combination therapy should be administered in such dosing regimens that create therapeutic concentrations [3, 7].

Evaluation of the effectiveness of antibacterial therapy. Full effect: lower body temperature less than 37.5°C after 24-48 hours. with uncomplicated and 3-4 days with complicated pneumonia on the background of improving the general condition and appetite, reducing shortness of breath. X-ray changes do not increase or decrease. Partial effect: maintaining febrile body temperature after the aforementioned periods while reducing the degree of toxicity, shortness of breath, improving appetite and lack of negative radiological dynamics. It is usually seen in destructive pneumonia and/or metapneumonic pleurisy. No antibiotic replacement is required. No effect: retention of fever with worsening of the general condition and/or growth of pathological changes in the lungs or pleural cavity. The absence of the effect requires the replacement of the antibiotic [7]. Time to evaluate the effect of antibacterial therapy on other literature: may be after 24, 36, 48 and 72 hours of treatment. Treatment should be overestimated if fever persists 48 hours after initiation of treatment, increased respiratory function, or if the child has distress or agitation [10]. It is noted that in complicated pneumonia with necrosis, there is usually no adequate response to ABB, which is considered appropriate, so wide-spectrum ABD is recomposed [4].

ENDOGENOUS INTOXICATION SYNDROME IN COMMUNITY-ACQUIRED PNEUMONIA: THE PROBLEM OF THE SEVERITY'S DETERMINING

Despite extensive research on endogenous intoxication syndrome, many issues remain unresolved. In particular, determination of probable variants of clinical course of endotoxiosis and their early diagnosis, development of reasoned criteria for the effectiveness of detoxication treatment measures. The main difficulties in predicting and treating endogenous intoxication are primarily related to the lack of available, pathogenetically sound criteria for assessing the severity of its clinical course. Indeed, establishing the very fact of the presence of a toxic agent in an organism is not sufficient to explain the diversity of clinical manifestations of endotoxiosis and to determine the directions and strategies of treatment appropriate to a particular clinical situation [7, 10]. Today it is advisable to introduce into the laboratory diagnosis of

community-acquired pneumonia in young children reliable tests that will allow objectively assess the activity of the inflammatory process, in accordance with the severity of the patient's condition and to plan the therapeutic tactics of the disease. Traditionally, the activity of the inflammatory process in pneumonia is evaluated by determining the number of leukocytes, the level of body temperature, the possible use of C-reactive protein as a marker of severity and complications of CAP [20]. Research data show that procalcitonin is a universal biochemical marker of the acute phase of inflammation. Known data about the fact that the role of the hemogram for the diagnosis of pneumonia is not as significant as is commonly believed, the clinical features are of higher diagnostic value. The value of interleukin 1 (IL1, pg/ml), tumor necrosis factor α (TNF α), interferon γ (IFN γ), interleukin 17 (IL17), vascular endothelial growth factor (VEGF), MSR1 chemokine in predicting the development of complications in CAP and many other markers are investigated [10, 21, 22].

The global assessment of clinical severity and risk factors is crucial. The criteria for severe disease in a child under 2 years old includes: oxygen saturation $<92\%$, cyanosis; respiratory rate >70 breaths/min; significant tachycardia relative to fever level (deficiency of tachycardia varies with age and temperature [10]); duration of capillary filling >2 s; shortness of breath; intermittent apnea, distant wheezing; refusal of feeding; chronic diseases (eg congenital heart disease, chronic prematurity, chronic respiratory tract diseases leading to infection such as cystic fibrosis, bronchiectasis, lack of immunity). The features of severe disease in older children (2 years and older) include: oxygen saturation $<92\%$, cyanosis; respiratory rate >50 breaths/min; significant tachycardia for fever levels (deficiency of tachycardia varies with age and temperature); duration of capillary filling >2 s; shortness of breath; remote wheezing; signs of dehydration; chronic diseases (eg congenital heart disease, chronic prematurity, chronic respiratory tract diseases leading to infection such as cystic fibrosis, bronchiectasis, lack of immunity) [10].

There are two main scenarios when a child is likely to need admission to the intensive care unit: when the pneumonia is so severe that the child develops severe respiratory failure requiring supportive ventilation; and pneumonia complicated by septicemia. Main features that indicate the need for a transfer to ICU: non-compliance with oxygen saturation $>92\%$ with fractional inhalation oxygen >0.6 ; shock; increased respiratory rate and pulse with clinical signs of severe respiratory distress syndrome and exhaustion, with or without hypertension of arterial carbon dioxide; periodic apnea or irregular breathing [10].

CONCLUSIONS

The epidemiology of community-acquired pneumonia is currently characterized by an increasing trend in morbidity and mortality worldwide. Plasmapheresis is not first-line therapy, because ABD, conservative detoxication, respiratory support are the mainstay of treatment like for other infections, but in case of CCAP the course of basic therapy is often not enough and then there is a need for ECMD. Identification of causative microorganisms in children with CCAP remains a constant problem. In most cases, therapy is prescribed empirically and knowledge of local epidemiology, the structure of ABD resistance is an important platform for improving antibacterial therapy. The optimal therapeutic approach for CCAP remains open to research.

Disclosure statement

The authors did not report any potential conflict of interest.

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