DOI: https://doi.org/10.2298/SARH250806001V
UDC: 616.248-053.4

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Clinical characteristics of status asthmaticus in preschool children

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SUMMARY

Introduction/Objective Asthma is the most common chronic disease in children. Status asthmaticus is a severe exacerbation of asthma that can lead to hypoxemia and respiratory failure. Diagnosing asthma in preschool-aged children is often challenging as wheezing episodes at this age are most often caused by viral infections.

The objective was to assess this issue in our population and improve clinical practice for diagnosing and treating status asthmaticus in preschool children.

Methods A retrospective study included 200 children aged up to five years who were hospitalized with status asthmaticus during January 2019 – December 2023.

Data on patients, diagnostic procedures, therapy, and clinical course were analyzed.

Results The largest proportion of patients was aged one year (31.5%), and males predominated (60.5%). The patients were most commonly hospitalized during the fall months, with an average length of hospital stay of 6.4 days. Allergy was confirmed in 50% of the children. Family history of atopy was present in 56% of the children. Previously diagnosed asthma was present in 13.5% of the children. At discharge, asthma preventive therapy was introduced in 91.5% of the children. All the children had a favorable outcome and were discharged from the hospital.

Conclusion Status asthmaticus most commonly occurs in children in the first year of life, often presenting as the initial manifestation of asthma. More than half of the children had a family history of atopy and confirmed allergies. Timely treatment according to current protocols is crucial for a good outcome.

Keywords: asthma; children; exacerbation; allergy

INTRODUCTION

Asthma is the most common chronic disease in the pediatric population, with a prevalence of approximately 14% among children worldwide, and the prevalence is on the rise [1]. Defining asthma in preschool-aged children is challenging, as the underlying pathophysiology in this age group is not well established, primarily due to the lack of available objective pulmonary function tests [2].

A variety of risk factors may be associated with the development of asthma, including a positive personal or family history of atopy, a family history of asthma, exposure to secondhand smoke, air pollution, or premature birth [3]. The development of asthma is an interaction between genetic and environmental variables, many of which are not fully understood or identified [4].

The clinical presentation typically manifests as a triad of symptoms: cough, difficulty breathing, and wheezing [5]. The three most common phenotypes of preschool wheezing, categorized by the timing of onset, are as follows: a) transient early wheezing, which occurs before the age of three and resolves by the age of six, without any impairment of lung function; b) late-onset wheezing, which appears after the age of three, persists into childhood, and is associated with atopy. Some studies also suggest a connection with reduced lung function and bronchial hyperreactivity; c) persistent wheezing, which begins at an early age (before three years of age) and is associated with high levels of IgE, atopy, reduced lung function, and early sensitization to allergens [6].

Asthma exacerbation is an episode of worsening of the disease characterized by progressive deterioration of symptoms such as difficulty breathing, coughing, wheezing, and a decline in lung function compared to the child's usual status. It requires the use of additional treatment and changes to the existing therapy [7]. A severe asthma exacerbation that does not improve with bronchodilator use and can lead to hypoxemia, hypercapnia, and secondary respiratory failure is referred to as status asthmaticus [7, 8]. All patients with asthma are at risk of developing this condition. Even children with mild and intermittent asthma can experience serious exacerbations that require admission to intensive care units. If not recognized and treated appropriately, status asthmaticus can lead to acute respiratory failure and even death. This serious and potentially life-threatening condition remains one of the leading causes of emergency department visits [8, 9]. Rapid clinical evaluation of patients is necessary to ensure an appropriate therapeutic approach in

Received • Примљено: August 6, 2025
Accepted • Прихваћено: December 19, 2025
Online first: January 13, 2026

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Table 1. Allergy testing results

Parameter	Positive results (%)	Negative results (%)	Test was not performed (%)
IgE values	18	20.5	61.5
Skin-prick test	18.5	14	67.5
Eosinophils in nasal secretions	15	11	74

IgE – immunoglobulin E

managing status asthmaticus [9]. Viral respiratory infections are the primary cause of asthma exacerbations across all age groups [4].

Diagnosing asthma in children aged five years and younger, particularly those under the age of two, can be challenging, as episodic respiratory symptoms such as wheezing and coughing are common in this age group and are often not related to asthma but rather a result of viral respiratory infections [5]. The diagnosis of asthma in young children with recurrent wheezing episodes is more likely if they exhibit: wheezing or coughing that occurs during exercise, crying, laughing, or in the absence of obvious respiratory infections; a history of other allergic diseases (such as eczema or allergic rhinitis); sensitization to allergens; a positive family history of atopy; clinical improvement during 2–3 months of treatment with low doses of inhaled corticosteroids (ICS); and deterioration after discontinuation of therapy [5].

In a study involving children aged 2–5 years, the combination of wheezing, increased daytime cough, and nighttime use of β2-agonists was a strong predictor for developing status asthmaticus the following day. This combination of three symptoms predicted 70% of exacerbations [10].

Children with recurrent wheezing episodes and suspicion of asthma use a disproportionately large number of medications, most commonly bronchodilators and corticosteroids, as the diagnosis, as previously mentioned, is not easily established in preschool-aged children [11]. According to the 2024 Global Initiative for Asthma recommendations, asthma treatment in children aged up to five years should be implemented stepwise. Management of exacerbations in primary care or an acute care facility should include inhaled short-acting β2-agonist (SABA) every 20 minutes for the first hour, systemic corticosteroids and oxygen. Transfer to the hospital is recommended if there is no response to inhaled SABA within 1–2 hours; if the child is unable to speak or drink, has a respiratory rate > 40 breaths/min. or is cyanotic; if resources are lacking in the home; or if oxygen saturation is < 92% on room air. Additional options in the first hour of treatment could be the use of ipratropium bromide and nebulized isotonic magnesium sulfate [5].

When discussing second-line treatments for status asthmaticus, the use of intravenous magnesium sulfate is becoming increasingly common in children with asthma. This medication is generally safe with few side effects. It should be used if there is a poor response to first-line therapy and is not recommended for mild to moderate forms of asthma [12].

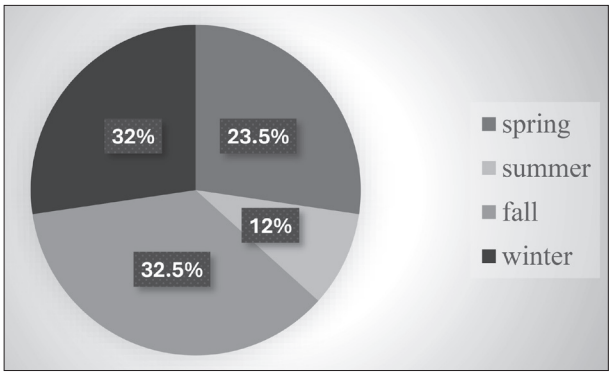

Figure 1. Distribution of hospitalized children by season

A review of the literature reveals a lack of studies focusing on status asthmaticus, the most severe and potentially life-threatening form of asthma exacerbation, and in our population, there are still no studies addressing this clinical entity. All of the above are reasons for conducting our research, which would contribute to understanding this significant health issue in the pediatric population.

METHODS

The study was a retrospective analysis of 200 children aged up to five years who were hospitalized at the Department of Pulmonary Diseases, Pediatric Clinic, Institute for Child and Youth Health Care over five years (January 2019 – December 2023) with status asthmaticus. Data concerning the patients were collected and analyzed from medical records: age, gender, anamnestic data regarding the current illness (type and duration of symptoms), asthma and atopy information (previous number of wheezing episodes, existing asthma diagnosis, use of asthma preventive therapy, presence of eczema, allergic rhinitis, or conjunctivitis, allergies to medications or food, family history of atopy). Allergy test results (total IgE, specific IgE, prick tests, eosinophils in nasal secretions) and acute-phase inflammatory markers upon admission, as well as data on the hospital course (length of hospitalization, duration of oxygen therapy, frequency of inhaled bronchodilator use upon admission, duration of systemic corticosteroid therapy, use of other therapeutic modalities and asthma preventive therapy at discharge) were analyzed.

For statistical data processing, IBM SPSS Statistics, Version 21.0 (IBM Corp., Armonk, NY, USA) was used. Numerical characteristics are presented as arithmetic means and ranges (minimum and maximum), while categorical characteristics are expressed in percentages. The results are presented in Table 1 and Figure 1.

Ethics: The authors declare that the article was written in accordance with ethical standards of the Serbian Archives of Medicine as well as the ethical standards of institutions for each author involved. Before the start of the study, approval was granted by the Ethics Committee of the Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia (No.: 17/56-23).

RESULTS

Patient characteristics

In the studied sample of 200 preschool-aged children hospitalized due to status asthmaticus, there were 121 male children (60.5%) and 79 female children (39.5%).

The largest number of patients were aged one year – 63 children (31.5%). There were 20 children (10%) under one year of age, 41 children (20.5%) aged two years, 38 children (19%) aged three years, 22 children (11%) aged four years, and 16 children (8%) aged five years.

Month of hospitalization and number of hospital days

Figure 1 shows the distribution of patients by seasons. The winter months are classified as December, January, and February; the spring months are March, April, and May; the summer months are June, July, and August; while the fall months include September, October, and November. The highest number of patients was hospitalized in the fall months, while the lowest number was in the summer months.

The minimum number of hospital days was 2, while the maximum number was 22 days. The average number of hospital days was 6.4 days.

Symptoms and therapy administered prior to hospitalization

The minimum duration of symptoms prior to hospitalization for status asthmaticus was 1 day, while the maximum duration was 21 days. The average duration of symptoms was 3.5 days.

Regarding the therapy administered prior to hospitalization in the studied sample of 200 children, 155 children (77.5%) received SABA inhalations, while 45 children (22.5%) did not receive inhalations prior to hospitalization. Systemic corticosteroids were administered to 100 children (50%), while 100 children (50%) did not receive this therapy.

Previous wheezing episodes, asthma, personal and family history of atopy

In the studied sample of 200 children, 152 children (76%) had a history of previous wheezing episodes, while 48 children (24%) did not. Among the 152 children with previous wheezing episodes, 71 children (47%) experienced 1–3 wheezing episodes, 79 children (51.7%) had more than three, and data on the number of wheezing episodes were not available for two children (1.3%).

A previously diagnosed asthma was present in 27 children (13.5%), while 173 children (86.5%) had not been diagnosed with asthma prior to hospitalization. Asthma maintenance therapy was administered to 37 children (18.5%), while 163 children (81.5%) did not receive asthma maintenance therapy. The minimum duration of asthma maintenance therapy prior to hospitalization was 15 days, while the maximum duration was 450 days (15 months). The average duration of asthma maintenance therapy prior to hospitalization was 145 days.

Eczema was reported in 45 children (22.5%), while 155 children (77.5%) had not had eczema. Allergic rhinitis was present in 44 children (22%), while 156 children (78%) had not previously had allergic rhinitis. Allergic conjunctivitis was reported in 7 children (3.5%), while 193 children (96.5%) had not experienced allergic conjunctivitis.

Five children (2.5%) had a drug allergy, while 195 children (97.5%) had not reported a drug allergy. Food allergies were reported in 17 children (8.5%), while 183 children (91.5%) did not have food allergies.

A positive family history of atopy and asthma was present in 112 children (56%), while 88 children (44%) did not have a family history of atopy.

Clinical characteristics at admission

In the studied sample of 200 children hospitalized due to status asthmaticus, 123 children (61.5%) had oxyhemoglobin saturation at admission < 95%. Wheezing was present in all 200 children (100%) upon lung auscultation, while 107 children (53.5%) had both wheezing and crackles.

Diagnosis

Regarding specific IgE, it was positive in 36 children (18%), negative in 41 children (20.5%), and was not tested in 123 children (61.5%). Of the 36 children (18%) with positive specific IgE results, 13 (36%) had positive results for food allergens, while 23 (64%) had positive results for inhalant allergens.

In 37 children (18.5%), the skin prick test was positive: nine children (24.3%) were positive for food allergens, 22 (59.5%) for inhalant allergens, and six (16.2%) for both. In 28 children (14%), the test was negative, while in 135 children (67.5%) the skin prick test was not performed.

In 30 children (15%), the value of eosinophils in nasal secretions was elevated, 22 children (11%) had non-elevated values, whereas in 148 children (74%), the value of eosinophils in nasal secretions was not assessed. The allergy testing results are presented in Table 1.

Of the 200 children, allergy was confirmed in 100 children (50%) by any of the methods mentioned above (elevated total IgE and/or positive specific IgE and/or positive prick test and/or positive eosinophils in nasal secretions).

When analyzing C-reactive protein (CRP) levels in children upon hospital admission, CRP values were < 5 mg/L in 83 children (41.5 %), 5–20 mg/L in 86 children (43 %), 20–100 mg/L in 29 children (14.5 %), and > 100 mg/L in 2 children (1%).

Therapy

In the studied sample of 200 children hospitalized due to status asthmaticus, 136 children (68%) needed oxygen

treatment, while 64 children (32%) did not require oxygen therapy. Among the 136 children who required oxygen, the minimum duration of this therapy was one day, the maximum was nine days, and the average duration was 2.3 days.

Antibiotic therapy during hospitalization was administered to 136 children (68%), while 64 children (32%) were not treated with antibiotics. All patients received SABA. Inhalations were initially performed every 20 minutes for 68 children (34%), every hour for 100 children (50%), and every two hours for 32 children (16%). Inhaled magnesium sulfate ($MgSO_4$) was administered to 105 children (52.5%), while 95 children (47.5%) did not require $MgSO_4$ therapy.

Seven children (3.5%) received aminophylline, while 193 children (96.5%) did not receive aminophylline during hospitalization.

All children received systemic corticosteroids during hospitalization, with a minimum duration of one day, a maximum of 10 days, and an average duration of four days. Upon discharge, 17 children (8.5%) did not receive asthma maintenance therapy, while it was introduced for 183 children (91.5%). Among them, 121 children (66.1%) received ICS, and 62 children (33.9%) received both ICS and montelukast.

DISCUSSION

Patient characteristics

The prevalence of asthma ranges from just 1% in some countries to as high as 18%, with over 339 million people affected by this disease worldwide. This prevalence varies between genders and across different age groups. In children, asthma is more common in boys, while in adulthood, women show higher prevalence and severity of the disease. Factors contributing to gender differences in asthma prevalence and severity include sex hormones, genetics, environmental factors, and varying responses to treatment [13].

In a study conducted by Bollinger et al. [14], which included 222 children aged 3–12 years experiencing acute asthma exacerbations, a higher percentage of boys (64.8%) was observed. In the study conducted by Bisgaard et al. [15], where parents of children aged 1–5 years with respiratory symptoms resembling asthma were contacted by phone, 55.8% were boys. Similar data have been reported in other studies [16]. These trends are also confirmed in our study, which showed that 60.5% of children hospitalized due to status asthmaticus were boys, while 39.5% were girls.

Seasonality of hospitalization

The influence of seasonality on the frequency of asthma exacerbations is well-documented. The highest rate of asthma worsening in children occurs during the fall, which is thought to be related to viral infections and exposure to allergens when children return to school [17, 18]. A study by Bloom et al. [19] found that wheezing episodes were least common in August (4.1%) and most frequent in late fall and early winter (30.6%). In our study, the lowest number of patients was hospitalized during the summer (12%), while the highest number was hospitalized in the fall (32.5%), which aligns with the literature.

Symptoms and pre-hospitalization therapy

Upper respiratory symptoms often precede asthma exacerbations, highlighting the significant role of viral infections of the upper airways in triggering exacerbations in many children [5]. Most children in our study exhibited mildly elevated CRP levels (84.5% had CRP values up to 20 mg/L). Considering slightly elevated levels of acute-phase reactants, we believe that most of these patients had viral infections. Severe asthma exacerbation that does not improve with bronchodilator use is termed status asthmaticus [7]. Children exhibiting symptoms of severe exacerbation that do not regress within 1–2 hours despite repeated use of inhaled SABA require hospitalization [5]. In our research, 155 children (77.5%) received SABA prior to hospitalization, while 100 children (50%) were given systemic corticosteroids before admission.

The fact that slightly over 20% of children did not receive inhalation therapy in an outpatient setting, which is essential for those with severe asthma exacerbations, indicates the need for improvement in primary health-care to ensure timely recognition and initiation of treatment for status asthmaticus.

Previous wheezing episodes, asthma, personal and family history of atopy

Recurrent wheezing is common in preschool children, often associated with respiratory tract infections, which occur 6–8 times a year at this age. Given this, it can be challenging to determine when wheezing is a result of a respiratory infection and when it is a symptom of asthma in childhood. In a study involving children aged 12–59 months with recurrent moderate to severe wheezing episodes, 71% had at least four episodes of wheezing [20]. In our study, 76% of children had previous episodes of wheezing, and 51.7% had experienced more than three wheezing episodes.

There is no gold standard for accurately diagnosing asthma in preschool-aged children. Diagnosis is based on the presence of symptoms, evidence of airflow limitation, and response to therapy. In this age group, asthma diagnoses can sometimes be made too liberally or too conservatively, leading to significant issues in both cases. Additionally, routine lung function tests are not conducted in children under five years of age, further complicating asthma diagnosis in this age group. The response to therapy in preschool children is a useful clinical parameter for diagnosis and is recommended in numerous studies [3]. Status asthmaticus is more commonly seen in children who do not have a diagnosed asthma condition and therefore do not receive asthma therapy. This is supported by studies conducted by Bollinger et al. [14], where only

20.1% of children evaluated for acute exacerbations had a diagnosis of asthma, and by Bisgaard et al. [15], where 20% of surveyed children aged 1–5 with respiratory symptoms resembling asthma had a confirmed asthma diagnosis. The results of our study align with these findings, as only 13.5% of children had a prior asthma diagnosis, and 18.5% received preventive asthma therapy (primarily ICS) before hospitalization.

Risk factors for asthma development

It is well known that risk factors for the development of asthma include a positive personal or family history of eczema, allergic rhinitis, or nasal polyps. Epidemiological studies indicate that 15–40% of patients with allergic rhinitis also have asthma, while 76–80% of asthma patients have allergic rhinitis [21]. In a study conducted by Bollinger and colleagues, 40.5% of children evaluated for acute asthma exacerbations had allergic rhinitis, 57.7% had eczema, and 27.3% had food allergies [14]. In our study, 22% of children had allergic rhinitis, 22.5% had eczema, 8.5% exhibited food allergies, and 2.5% had drug allergies. Family history of atopy was positive in more than half of the children (56%).

Clinical characteristics on admission

Status asthmaticus can be accompanied by hypoxemia, hypercapnia, and secondary respiratory failure. In pediatric acute asthma exacerbations, the percentage of oxyhemoglobin saturation is one of the most significant factors influencing the decision to admit a child to the hospital or continue treatment at home [8]. In this study, among the sample of 200 children, 123 (61.5%) had oxyhemoglobin saturation levels of less than 95% upon admission.

Wheezing is a common clinical finding in patients with acute asthma exacerbations, resulting from turbulent airflow through narrowed airways. Diminished breath sounds, due to limited airflow, typically indicate severe bronchial obstruction. Wheezing is predominantly expiratory and is usually symmetric. Asymmetric distribution suggests the presence of atelectasis, pneumothorax, or foreign body obstruction in the airway [22]. In this study, as expected, wheezing was present in all children (100%) during lung auscultation.

Atopy assessment

Asthma is a heterogeneous disease with several underlying phenotypes. Childhood asthma, unlike adult asthma, is typically characterized by personal and family histories of atopy, along with positive markers for type 2 allergic reactions, such as elevated total or specific IgE and eosinophilia in the airways. This type of asthma responds well to treatment with ICS. Allergy testing (skin prick tests, measurement of specific IgE levels) is not routinely required for the diagnosis of asthma, but it is recommended in numerous clinical guidelines [3, 23]. Most preschool children with asthma enter remission or show significant improvement by school age [4]. In a study conducted by Bollinger and colleagues, which included 222 children aged 3–12 years who were examined in outpatient settings for acute asthma exacerbation, 82.6% of the children had positive results for various inhalant allergens [14]. In our study, we assessed atopic status through the following diagnostics: skin prick test, total IgE, specific IgE for inhalant and food allergens, and eosinophils in nasal secretions. This diagnostic workup was not performed on all patients, but only on those with personal and family histories indicating asthma. Elevated IgE levels were found in 48.7% of patients, specific IgE was positive in 18% (primarily for inhalant allergens), while 18.5% of children had a positive prick test (mainly for food allergens). Additionally, 15% of children had positive eosinophil levels in nasal secretions. In total, 50% of the tested children had at least one positive finding indicating an allergy.

Therapy

Episodes of wheezing should initially be treated with SABA, regardless of whether asthma has been diagnosed. However, this treatment may be ineffective in children under one year of age with bronchiolitis. Therefore, the response to the administered therapy should be evaluated before continuing it. If the response is incomplete or absent, it is necessary to reconsider the diagnosis and differential diagnoses [5]. The cornerstone of treatment for status asthmaticus is the administration of SABA (primarily salbutamol) at short intervals, along with systemic corticosteroids and oxygen therapy. In cases of poor response to the administered therapy, other therapeutic options, especially inhaled or intravenous magnesium sulfate, should be considered [5]. In our study, therapy was conducted according to current protocols. All patients were treated with systemic corticosteroids and SABA most commonly initiated for 20 minutes. Children with severe asthma exacerbations often experience a mismatch between pulmonary ventilation and perfusion due to airway obstruction and atelectasis, which causes hypoxemia. In such cases, the administration of oxygen is indicated to maintain oxygen saturation above 92% [22, 5]. In a study conducted by Donath et al. [23], which included children aged 1–5 years hospitalized due to asthma, 56.1% of the children received oxygen therapy. In our study, the percentage was slightly higher, at 68%.

Earlier, aminophylline was considered the first-line treatment during status asthmaticus in children, but today intravenous magnesium sulfate is recommended rather than aminophylline due to reduced side effects and comparable efficacy [12]. Nebulized isotonic magnesium sulfate can be used as an adjunctive therapy in the first hour of treatment for children aged two years or older with acute severe asthma (SaO_2 < 92%), especially if symptoms have persisted for less than six hours [5]. In our study, inhaled $MgSO_4$ was administered to 105 children (52.5%), and no child received intravenous $MgSO_4$. Seven children (3.5%) with severe clinical presentations were treated with aminophylline.

If a patient's symptoms suggest asthma, and episodes of wheezing are frequent or severe, while other alternative diagnoses have been excluded, it is recommended to start treatment with low-dose ICS as a trial therapy. The response to treatment should be assessed before deciding whether to continue therapy. The goal of asthma treatment in young children is to achieve good symptom control and maintain normal activity levels, while reducing the risk of asthma exacerbations, inadequate lung development, and adverse drug effects [5]. In this study, at discharge, 17 children (8.5%) did not receive asthma preventive therapy, while it was initiated in 183 children (91.5%); 121 (66.1%) received ICS, and 62 (33.9%) received both ICS and montelukast.

CONCLUSION

Status asthmaticus most commonly occurred in children during their early years, with a higher prevalence in boys and a significant number of cases presenting as the first manifestation of asthma. As expected, the highest incidence was noted in the fall months. More than half of the children had a family history of atopy and confirmed allergies. A significant percentage of children did not receive bronchodilator inhalations and systemic corticosteroid therapy on an outpatient basis, indicating a need for improvements in primary health-care to ensure timely recognition and initiation of treatment for status asthmaticus.

Conflict of interest: None declared.

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САЖЕТАК

Увод/Циљ Астма је најчешће хронично обољење у педијатријском узрасту. Астматски статус је тешка егзацербација астме која може довести до хипоксемије и респираторне инсуфицијенције. Постављање дијагнозе астме у предшколском узрасту често је изазовно, с обзиром на то да су епизоде визинга у овом узрасту углавном узроковане вирусним инфекцијама.

Методе Ретроспективна студија обухватила је 200 деце, узраста до пет година, која су била хоспитализована због астматског статуса у периоду од јануара 2019. до децембра 2023. године. Анализирани су подаци о пацијентима, дијагностичким поступцима, терапији и клиничком току болести.

Резултати Највећи број болесника био је узраста од годину дана (31,5%), уз предоминацију мушког пола (60,5%). Болесници су најчешће хоспитализовани током јесењих месеци, а просечно трајање хоспитализације износило је 6,4 дана. Алергија је потврђена код 50% деце. Атопију у породици имало је 56% деце. Претходно дијагностиковану астму имало је 13,5% деце. На отпусту је код 91,5% деце уведена превентивна терапија за астму. Сва деца су имала повољан исход лечења и отпуштена су из болнице.

Закључак Астматски статус најчешће се јавља код деце у првим годинама живота, при чему је код великог броја деце то прва манифестација астме. Више од половине деце има атопију у породици и потврђену алергију. За повољан исход кључно је да терапија буде започета на време и у складу са важећим протоколима.

Кључне речи: астма; деца; егзацербација; алергија