Journal of Asthma and Allergy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Pediatric Asthma Exacerbation in Children with Suspected and Confirmed Coronavirus Disease 2019 (COVID-19): An Observational Study from Saudi Arabia

Ali Alsuheel Asseri

Department of Child Health, College of Medicine, King Khalid University, Abha, Saudi Arabia

Background: Most asthma exacerbations are caused by viral respiratory infections such as rhinovirus, coronaviruses, influenza viruses, and many others. While there have been data about the impact of COVID-19 on adult asthma, much remains unknown about the impact of COVID-19 on childhood asthma.

Methods: This retrospective cohort study included all pediatric patients aged 2 to 12 years who were admitted to Abha Maternity and Children Hospital for acute asthma exacerbation between June 1, 2020, and May 31, 2021, and underwent testing for SARS-CoV-2 using nasopharyngeal real-time polymerase chain reaction.

Results: Sixty children hospitalized with the diagnosis of asthma were included in the study. Out of these patients, 10 (16.7%) were diagnosed with COVID-19. The enrolled patients were between 2 and 12 years, with a median age of five years (interquartile range, 3.8), and 58% were males (35/60). Cough, shortness of breath, and hypoxia were the most common presenting symptoms and signs. Severe asthma was more prevalent among positive COVID-19 compared with negative COVID-19 patients (60 vs 20%; P= 0.016). In addition, chronic asthma for more than five years was more prevalent among positive COVID-19 than negative COVID-19 patients (60 vs 40%, P= 0.305). Fifty-five percent of the enrolled patients had eosinophilic asthma using a 300cells/μL threshold. None of the children required invasive respiratory support (ventilation through an endotracheal tube or tracheostomy), but 12 patients (21.7%) required respiratory support via high-flow nasal cannula. The total days of hospitalization in either PICU or pediatric general ward did not differ between the two groups. All patients were discharged, and there were no reports of serious morbidity or mortality.

Conclusion: Eosinophilic asthma was the most prevalent asthma phenotype in the study group. Furthermore, there was no difference in the presenting symptoms of an asthma flare-up, laboratory indicators, and hospitalization outcomes (critical care admission and hospital stay) between asthmatics with and without a COVID-19 diagnosis.

Keywords: children, COVID-19, SARS-CoV-2, asthma exacerbation

Introduction

A cluster of pneumonia cases with an unknown causative organism was identified in one of China's provinces, Hubei, in the city of Wuhan. Later, the causative organism was identified as a novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes severe respiratory infection in humans.[1–3]

Correspondence: Ali Alsuheel Asseri
Department of Child Health, College of Medicine, King Khalid University, Abha, Saudi Arabia
Tel +966500186013; +966172418589
Email alsoheel11@kku.edu.sa

Received: 29 June 2021
Accepted: 14 September 2021
Published: 23 September 2021

The World Health Organization declared it as a global public health crisis and pandemic in March 2020.[4] According to the COVID-19 dashboard at Johns Hopkins University, it has affected more than 179 million people worldwide as of June 2021.

Most asthma exacerbations are caused by viral respiratory infections such as respiratory syncytial virus, rhinovirus, coronaviruses, influenza viruses, and many others.[5,6] Comparing allergic triggers to the respiratory virus, asthma exacerbation-induced viral infections are usually longer and need intensive therapies.[7,8] It is now well established that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease 2019 (COVID-19) is milder in children than in adults and causes very low morbidity and mortality.[9–15] The data about the association between adult asthmatics and COVID-19 indicated that it could be a risk factor for severe disease, particularly, neutrophilic phenotype.[13,16–19] In addition, several adult studies have suggested that patients with allergic asthma may develop milder COVID-19 disease compared with a non-allergic asthma phenotype.[20] Allergic asthma phenotype is defined as asthma with type 2 driven inflammation characterized endotypically by aeroallergen sensitizations, high total immunoglobulin E level, and high eosinophilic count, which commonly originates in childhood and is associated with other clinical atopic diseases such as allergic rhinitis and eczema.[16,18,19,21] The proposed mechanisms of the allergic asthma protection against COVID-19 disease include lower the angiotensin-converting enzyme (ACE) 2 receptor expression in allergic asthmatics nasal epithelia, eosinophilic-driven reduction of viral load with subsequent attenuation of COVID-19, and downregulation of ACE2 and transmembrane protease serine 2 (TMPRSS2) gene expression using inhaled corticosteroid therapies. Decreased ACE2 and TMPRSS2 in the respiratory epithelium led to the decreased viral attachment to the respiratory epithelium and subsequently alleviated the disease severity.[22] However, much remains unknown about the impact of COVID-19 on childhood asthma.[23]

In children, data on asthma and COVID-19 are scarce. According to a meta-analysis conducted by Castro-Rodriguez and Forno, severe adult asthma is a risk factor for COVID 19 mortality; however, they only found two published studies that included approximately 50 children with chronic lung disease, including asthma.[13] The authors recommended more in-depth research into the relationship between childhood asthma and COVID-19.[13] Many experts, on the other hand, reported that many childhood asthmatics had good asthma control, and their hospitalizations dropped significantly during the COVID-19 pandemic. This could be due to the low infectivity of COVID-19 among asthmatics or a decrease in the other causes of asthma exacerbations (improved air quality, reduced other viral infections).[11,12,17,23] Based on a recently published article that studied the clinical and laboratory characteristics of asthmatic children infected with COVID-19, they found that asthmatic patients represented less than 1% of the studied patients (total cohort 6205; 54 asthmatics and 162 control) with the median age of 10.5 years and male predominance. Cough, shortness of breath, vomiting, and diarrhea were significantly more common in the asthma group than in the control group. Hospitalization was significantly higher in the asthma group, and hospitalization duration was significantly longer in the control group. There were no statistically significant differences between the asthmatic and control groups in terms of needing oxygen treatment and laboratory findings.[24]

The main objectives of this study were to evaluate the impact of COVID-19 infection on childhood asthma in terms of hospital stay and intensive care unit admission and to study the clinical and laboratory characteristics of asthmatics infected with COVID-19.

Methods

Study Population and Setting

This retrospective cohort study included all pediatric patients aged 2 to 12 years admitted to Abha Maternity and Children Hospital for acute asthma exacerbation between June 1, 2020, and May 31, 2021. This hospital is considered a tertiary care and teaching hospital in the southwestern region of Saudi Arabia. Patients with a medical diagnosis of asthma who presented with symptoms consistent with COVID-19 and whose health care provider requested SARS-CoV-2 testing were included in the study. During the hospitalization, a pediatric allergist or pulmonologist who was actively involved in inpatient and outpatient asthma care confirmed the diagnosis of asthma. Exclusion criteria included children with recurrent wheezing episodes under the age of two and those who had coexisting morbidities such as prematurity, cystic fibrosis, sickle cell disease, or any other pulmonary disease. SARS-Cov2 was diagnosed using nasopharyngeal real-time polymerase chain reaction, as recommended by the World Health Organization (WHO) and local health authorities (RT PCR).[4,26]

Study Variables

The data collection sheet consisted of three sections: pre-hospital clinical and demographic variables, emergency room (ER) clinical variables, and current admission clinical and laboratory variables. Pre-hospital clinical and demographic variables include age, gender, age at the first wheezy episode, ED visits and admissions in the last year, food allergies, previously inhaled corticosteroid (ICS) use, asthma severity, baseline eosinophilic counts, total immunoglobulin E level, and previous PICU admissions. The ER clinical variables include initial ER vitals (O2 saturation and temperature) and presenting complaints (cough, fever, runny nose, and wheezing). The last section of the datasheet included whether the patient needed PICU admission, use of high flow nasal cannula, complete blood count (CBC), erythrocyte sedimentation rate (ESR), and the total length of hospital stay (LOS).

Study Variables Definition

Asthma exacerbations were defined according to the Global Initiative for Asthma (GINA) definition, which includes episodes characterized by a progressive increase in symptoms of shortness of breath, cough, wheezing, or chest tightness, representing a change from the patient's usual status sufficient to necessitate a change in treatment.[25]

According to the GINA guidelines, asthma severity was determined based on the frequency of symptoms and the used controller therapies. Patients were classified as having intermittent, mild persistent, moderate persistent, or severe persistent asthma. In addition, upper respiratory tract infection was defined as the presence of acute fever, runny nose, and cough.[25]

Based on their baseline (preadmission) blood eosinophil counts (cells per L, blood), patients were classified as having eosinophilic asthma with blood eosinophil counts >300 eosinophil cells/ μL or non-eosinophilic asthma with blood eosinophil counts < 300 eosinophil cells/ μL.[22]

Statistical Analysis

Stata version 14 was used for statistical analysis (StataCorp, College Station, TX, USA). Data for normally distributed variables were represented as mean and standard deviation, while data for non-normally distributed variables were represented as median with interquartile range. Counts and percentages were used to represent categorical variables. The parametric test (Student's *t*-test) and the non-parametric test Mann–Whitney *U*-test were used to study the differences between normally and non-normally distributed continuous variables, respectively. Fisher exact was used to study the differences between categorical variables. Significant differences were considered at p-values less than 0.05.

Ethical Approval

The study was approved by the Institutional Research Ethics (IRE) board, the College of Medicine's ethical committee, King Khalid University, Abha, Saudi Arabia (approval number ECM#2021-5508). It was carried out according to the Declaration of Helsinki. Patients' informed consents were not needed since this study was a retrospective observational study without any interventions.

Results

Baseline Characteristics of the Study Population

Table 1 summarizes the demographics and the clinical presenting symptoms and signs of the enrolled patients stratified by the covid-19 infection. Sixty children hospitalized with the diagnosis of asthma were included in the study. Out of these patients, 10 (16.7%) were diagnosed with COVID-19. The enrolled patients were between 2–12 years, with a median age of five years (interquartile range, 3.8), and 58% male (35/60). No statistically significant differences were detected between the age and age categories (<3, 3–5, and >5 years) concerning children with COVID-19. Significant variations between the asthmatic with and without COVID-19 were observed based on the previous history of contact with infected individuals (90%, 4%, respectively, p <0.001). The median of the timing of the first wheezy episodes was 12 months (interquartile range, 6–24), and it did not differ significantly between the two groups. The main trigger of asthma exacerbation in the enrolled patients was acute upper respiratory infection 51/60 (85%). There were no significant differences between the two groups of patients for cough, shortness of breath (SOB), runny nose, and fever in terms of the presenting symptoms. All patients had hypoxia (oxygen saturation <92%), and the level did not differ significantly between positive and negative COVID-19 asthmatics. Hemoglobin and erythrocyte sedimentation levels did not differ between the groups.

Severity and Phenotypes of the Study Subjects

Table 2 shows the severity classification and the phenotypes of both asthmatic groups, COVID-19 positive and

Table 1 Characteristics of COVID-19 and Non-COVID-19 Asthmatic

Variables	Total n=60	Asthmatic with COVID-19 n=10 (16.7%)	Asthmatic Without COVID-19 n=50 (83.3%)	*P* value
Age, median (IQR), y	5 (3–8)	6.5 (4.25–8.75)	5 (3–7.75)	0.119
-Toddler (<3y)		0 (0.0%)	11 (22%)	0.183
-Preschool (3–<5y)		3 (30%)	12 (24%)	0.699
-School age (5–12y)		7 (70%)	26 (52%)	0.488
Sex, male, No. (%)	35 (58%)	5 (50%)	30 (60%)	0.727
History of contact with COVID-19, No. (%)	11 (18.3%)	9 (90%)	2 (4%)	<0.001*
Age at first symptoms (months)	12 (6–24)	9 (5.5–20)	12 (6–24)	0.800
Clinical features at presentation, No. (%)				
-Fever	56 (93.3%)	9 (90%)	47 (94%)	0.427
-Cough	60 (100%)	10 (100%)	50 (100%)	–
-Shortness of breath (SOB)	57 (95%)	8 (80%)	49 (98%)	0.308
-Sore throat	52 (86.6%)	9 (90%)	43 (86%)	0.636
-Runny nose	52 (86.7%)	9 (90%)	43 (86%)	0.636
-URTI	51 (85%)	8 (80%)	43 (86%)	0.637
-Temperature, mean –/+SD	37±0.8	37.5 ±0.4	37±0.86	0.014*
-Respiratory Rate, median (IQR)	38 (30–45)	35 (27–38)	39 (30–45)	0.068
-Oxygen saturation, median (IQR)	85% (80–88)	88% (82.5–90)	85% (80–88)	0.149
Hemoglobin (Ref: 11.5–15.5 g/dL), median (IQR)	13(12–13.9)	14(12.9–14.9)	13(11.8–13.8)	0.153
ESR (Ref: 0.0–15 mm/hr), median (IQR)	24(12–41)	28(16–36)	24(11–42)	0.542

Note: *P < 0.05 (significant).

negative. In terms of asthma severity, severe asthma was more prevalent among positive COVID-19 compared with negative COVID-19 patients (60 vs 20%; P= 0.016). Chronic asthmatic children for more than five years were more prevalent among positive COVID-19 than negative COVID-19 patients (60 vs 40%, P= 0.305). No significant differences were found in asthma control indicators, ≥ 1 hospitalization for asthma exacerbation (last year), ER visit the previous year, oral corticosteroid use last year, and prior intubation or PICU admission. Seventy-five percent of the patients had a history of at least one type of atopic disease (allergic rhinitis or eczema or food allergies). Fifty-five percent of the enrolled patients had eosinophilic asthma using a 300 cell/μL threshold. There was no significant difference between the high eosinophil and low eosinophil groups in COVID-19 positive and negative asthmatics (50% vs 56%, P=0.742). COVID-19 infected asthmatics had lower admission eosinophilic and neutrophilic counts than COVID-19 negative asthmatics. The median total IgE level was higher among asthmatic with COVID-19 than in COVID-19 negative asthmatics (864 vs 240; P=0.081).

Therapies and Outcomes

All patients received systemic steroids and bronchodilators following the acute asthma exacerbation treatment guidelines without reporting adverse events. None of the children required invasive respiratory support (ventilation through an endotracheal tube or tracheostomy), but 12 patients (21.7%) required respiratory support via high-flow nasal cannula. The total days of hospitalization in either PICU or pediatric general ward did not differ between the two groups. All patients were discharged, and there were no reports of serious morbidity or mortality (Table 3).

Discussion

The study findings show that hospital stay and critical care admissions do not differ between COVID-19-infected asthmatic children aged 2 to 12 years old and COVID-19-negative asthmatics. Furthermore, children with severe asthma are more vulnerable to COVID-19 infection than children with other severity classifications, intermittent, mild, and moderate. Most of the infected asthmatics had a history of contact with

Table 2 Severity and Phenotypes of COVID-19 and Non-COVID-19 Asthmatic

Variables	Total n=60	Asthmatic (COVID-19 +) n=10 (16.7%)	Asthmatic (COVID-19 −) n=50 (83.3%)	*P* value
Asthma severity, No. (%)				
-Intermittent	21(35%)	1(10%)	20(40%)	0.083
-Mild	11(18.3%)	3(30%)	8(16%)	0.371
-Moderate	12(20%)	0(0%)	12(24%)	0.188
-Severe	16(26.7%)	6(60%)	10(20%)	0.016*
Asthma duration ≥ 5 yrs	26(43.3%)	6(60%)	20(40%)	0.305
≥1 hospitalization for asthma exacerbation (last year)	41(68.3%)	5(50%)	36(72%)	0.263
ER visit last year	59 (98.3%)	9(90%)	49(98%)	0.308
OCS last year (No.)	57 (95%)	9(90%)	47(94%)	0.528
Previous intubation or PICU admission	21(35%)	5(50%)	16(32%)	0.298
Associated atopies for at least one	45(75%)	10 (100%)	36 (72%)	0.097
-Allergic rhinitis	35 (58.3)	8 (80%)	27 (54%)	0.171
-Eczema	40 (66.7%)	6 (60%)	33 (66%)	0.728
-Food allergies	10 (16.7%)	2 (20%)	8 (16%)	0.668
Preadmission eosinophilic counts (cells/μL), median (IQR)	420(275–625)	530(52.5–1100)	420(312.5–570)	0.921
Eosinophilic asthma (Blood Eos ≥ 300/μL)	33 (55%)	5 (50%)	28 (56%)	0.742
Serum IgE (IU/mL), median (IQR)	398(183–249)	864(534–6240)	240(93.5–1486)	0.081
Admission eosinophils counts (cells/μL), median (IQR)	25(10–112.5)	10(0–30)	30(10–130)	0.118
Neutrophils (Ref: 1500–8500 cells/μL), median (IQR)	8120(5287.5–10,957.5)	4810(1707.5–9500)	8465(5922.5–11,032.5)	0.075

Note: *P < 0.05 (significant).

Table 3 Therapies and Outcomes of the Enrolled Patients

Variables	Total n=60	Asthmatic (COVID-19 +) n=10 (16.7%)	Asthmatic (COVID-19 –) n=50 (83.3%)	*P* value
Management, No (%)				
Systemic steroids	60 (100%)	10 (100%)	50(100%)	–
Bronchodilators (SABA)	60 (100%)	10 (100%)	50(100%)	–
Critical care admission and respiratory support, No (%)				
PICU admission	14 (23.3%)	3 (30%)	12 (24%)	0.699
HFNC use	13 (21.7%)	3 (20%)	11 (22%)	0.685
O2 use days, median (IQR)	3 (3–4)	3(1–4)	3(3–4)	0.418
Outcome measures				
-Total hospital stays, median (IQR)	4 (3–5)	4.5 (1.75–6.25)	4 (3–5)	0.738
-Total PICU stays, median (IQR)	2(2–3.25)	5	3(2–3)	0.144
-Discharged, No (%)	60 (100%)	10 (100%)	50 (100%)	–

Abbreviations: SABA, Short-Acting Beta-2 Agonist; PICU, Pediatric Intensive Care Unit; HFNC, High Flow Nasal Cannula; O2, Oxygen; IQR, Interquartile Range.

COVID-19 subjects, which is consistent with previously published reports.[9,10] The most common phenotype among the study cohort is eosinophilic asthma with an average age of more than five years, which could be interpreted by the severity of the underlying asthma disease independent of the COVID-19 diagnosis.

COVID-19 disease in children is well known to be milder than in adults, with less morbidity and mortality and mild presenting respiratory symptoms.[10,14,15] Regardless of subsequent COVID-19 diagnosis in our cohort, the presenting symptoms of asthma exacerbation were similar. Until now, few reports studied the effects of COVID-19 on asthma flare-up among children.[12,13,22,27] However, several adult studies have shown that adult asthmatics, specifically neutrophilic phenotype, had increased mortality and critical care admissions.[28–30]

The association between childhood asthma and COVID-19 disease severity is complex. The question of whether severe childhood asthma worsens COVID-19 disease has yet to be answered. In this study, COVID-19 was common among severe asthmatics. However, the small sample size of this cohort is a significant limiting factor in drawing meaningful conclusions from this finding and should be considered preliminary. This study's high proportion of severe asthmatic children could partly explain the high incidence of severe asthmatics among the COVID-19 group compared with the negative COVID-19 group. Further studies are needed to study whether severe childhood asthma is a risk factor for COVID-19 infection. According to the results of a large multi-national cohort study involving over a thousand childhood asthmatics, asthma did not appear to be a risk factor for severe COVID-19.[11] Nonetheless, most of the patients enrolled were outpatients with mild asthma, and they were compared to healthy controls.[11] In addition, they concluded that in comparison to the previous year, children with asthma experienced fewer upper respiratory tract infections, episodes of pyrexia, emergency visits, hospital admissions, asthma attacks, and hospitalizations due to asthma during the pandemic.[11]

When several asthma severity indicators and phenotypic factors were compared, none were found to be risk factors for COVID-19 diagnosis. Previous PICU admission, preadmission blood eosinophilic counts, and history of ED visits within the previous year are all known predictors of severe asthma exacerbation requiring hospitalization or critical care admission.[20–34] Furthermore, stratifying asthma phenotyping based on baseline blood eosinophilic counts and total IgE levels did not affect hospitalizations or the need for critical care (data not shown). This effect, however, needs to be studied with a large sample size. Several authors have proposed that atopic asthma may be a protective factor against severe COVID-19 disease.[22,35–37]

Lower ACE2 expression in asthmatic children's respiratory tracts is thought to be due to type-2 inflammation cytokines and high blood eosinophil counts. As a result, this could explain low COVID-19 infectivity and absence of complications in the studied children.[23,36,39] However, a well-designed large sample size study is recommended to clearly explore the relationship between eosinophilic asthma phenotype and COVID-19 infections. On the other hand, several other studies have reported a higher risk of severe COVID-19 with increased mortality in patients with low eosinophilic counts.[35–39] In the current study, the admission eosinophilic counts, were low compared to the baseline (pre-hospital admission) eosinophilic count, which was observed mainly in the patients who had received systemic steroids in the ER. It is well known that the inflammatory cell phenotype is modified by corticosteroids use and causes neutrophilia and eosinopenia.[40] Given the high prevalence of severe asthma in this study and using systemic corticosteroids during the acute exacerbation, and this could explain the low admission eosinophilic counts.

When looking for the hospitalization outcomes (critical care admission, need of high flow nasal cannula (HFNC), and hospital stay), there were no differences between the asthmatics with and without COVID-19. Several studies conducted before COVID-19 found that the average length of stay for children with asthma exacerbation ranged between 2–4 days.[33,41–45] Thus, our findings are consistent with the previous research. However, more research is needed to explore the effect of COVID-19 on the patient-centered outcomes of different childhood asthma phenotypes.

This study's limitations included the small sample size, which may have limited the ability of our analysis to detect small differences between the two groups in certain variables. In addition, it was conducted at a single institution, Abha city, so the findings may not apply to children with asthma in other settings. The study also included the children of two years and above, and there may be some overlap with children treated for asthma who had viral-induced wheezing. However, children under the age of four have been included in several previous studies on asthma hospitalizations.[33,42,45–47] Furthermore, the study was conducted in a tertiary and teaching hospital, where the most severe cases are naturally referred. This probably explains the high prevalence of COVID-19 among asthmatic patients (16.7%), especially in cases of severe asthma.

Conclusion

This study shows that eosinophilic asthma is the most prevalent asthma phenotype in the study group. Furthermore, there was no difference in the presenting symptoms of an asthma flare-up, laboratory indicators, and hospitalization outcomes (critical care admission and hospital stay) between asthmatics with and without a COVID-19 diagnosis. However, more research is needed to fully understand the unique and complex relationship between COVID-19 and asthma, particularly childhood asthma.

Acknowledgments

The author is thankful to the Institute of Research and Consulting Studies at King Khalid University, Saudi Arabia, for supporting this research financially through the grant # 4-N-20/21. In addition, the author would like to thank all of the patients and families who contributed to this analysis, as well as all of the front-line healthcare workers and pediatricians at Abha Maternity and Children's Hospital who made this research possible.

Funding

This research was funded by the Institute of Research and Consulting Studies at King Khalid University through grant number # 4-N-20/21.

Disclosure

The author declares no competing interests in this work.

References

1. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med*. 2020;382(13):1199–1207. doi:10.1056/NEJMoa2001316
2. Epidemiology Working Group for NCIP Epidemic Response, Chinese CDC. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) –China. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2020;41:145–151. doi:10.3760/cma.j.issn.0254-6450.2020
3. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet*. 2020;395(10223):470–473. doi:10.1016/S0140-6736(20)30185-9
4. Saudi Center for Disease Control and Prevention. Quick interim guide to COVID-19 surveillance case definitions and disposition; April, 2020. Available from: https://covid19.cdc.gov.sa. Accessed September 16, 2021.
5. Chau-Etchepare F, Hoerger JL, Kuhn BT, et al. Viruses and non-allergen environmental triggers in asthma. *J Investig Med*. 2019;67(7):1029–1041. doi:10.1136/jim-2019-001000
6. James P, Cornish A, Brady K, et al. Is there benefit in identifying asthma triggers during an exacerbation? *Clin Pediatr (Phila)*. 2020;59(2):142–147. doi:10.1177/0009922819887399
7. Busse WW, Lemanske RF Jr, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet*. 2010;376(9743):826–834. doi:10.1016/S0140-6736(10)61380-3
8. Cao L, Lee S, Krings JG, et al. Asthma in patients with suspected and diagnosed coronavirus disease 2019. *Ann Allergy Asthma Immunol*. 2021;126(5):535–541.e2. doi:10.1016/j.anai.2021.02.020
9. Lu X, Zhang L, Du H, et al. SARS-CoV-2 infection in children. *N Engl J Med*. 2020;382(17):1663–1665. doi:10.1056/NEJMc2005073
10. Asseri AA, Alzaydani I, Al-Jarie A, et al. Clinical characteristics and laboratory abnormalities of hospitalized and critically ill children with coronavirus disease 2019: a Retrospective Study from Saudi Arabia. *Int J Gen Med*. 2021;14:1949–1958. doi:10.2147/IJGM.S311831
11. Papadopoulos NG, Mathioudakis AG, Custovic A, et al. Childhood asthma outcomes during the COVID-19 pandemic: findings from the PeARL multi-national cohort. *Allergy*. 2021;76(6):1765–1775. doi:10.1111/all.14787
12. Dosanjh A. COVID 19 and pediatric asthma. *J Asthma Allergy*. 2020;13:647–648. doi:10.2147/JAA.S291796
13. Castro-Rodriguez JA, Forno E. Asthma and COVID-19 in children: a systematic review and call for data. *Pediatr Pulmonol*. 2020;55(9):2412–2418. doi:10.1002/ppul.24909
14. Ali AS, Al-Hakami AM, Shati AA, Asseri AA, Al-Qahatani SM. Salient conclusive remarks on epidemiology and clinical manifestations of pediatric COVID-19: narrative review. *Front Pediatr*. 2020;8:584694. doi:10.3389/fped.2020.584694
15. Zheng F, Liao C, Fan Q-H, et al. Clinical characteristics of children with coronavirus disease 2019 in Hubei, China. *Curr Med Sci*. 2020;40(2):275–280. doi:10.1007/s11596-020-2172-6
16. Lipworth B, Chan R, RuiWen Kuo C. Type 2 asthma inflammation and COVID-19: a double edged sword. *J Allergy Clin Immunol Pract*. 2021;9(3):1163–1165. doi:10.1016/j.jaip.2020.12.033
17. Skevaki C, Karsonova A, Karaulov A, Xie M, Renz H. Asthma-associated risk for COVID-19 development. *J Allergy Clin Immunol*. 2020;146(6):1295–1301. doi:10.1016/j.jaci.2020.09.017
18. Ferastraoaru D, Hudes G, Jerschow E, et al. Eosinophilia in asthma patients is protective against severe COVID-19 illness. *J Allergy Clin Immunol Pract*. 2021;9(3):1152–1162.e3. doi:10.1016/j.jaip.2020.12.045
19. Terry PD, Heidel RE, Dhand R. Asthma in adult patients with COVID-19. prevalence and risk of severe disease. *Am J Respir Crit Care Med*. 2021;203(7):893–905. doi:10.1164/rccm.202008-3266OC
20. Eggert LE, He Z, Collins W, et al. Asthma phenotypes, associated comorbidities, and long-term symptoms in COVID-19 [published online ahead of print, 2021 Jun 3]. *Allergy*. 2021;10(1):1–13. doi:10.1111/all.14972
21. Carr TF, Zeki AA, Kraft M. Eosinophilic and noneosinophilic asthma. *Am J Respir Crit Care Med*. 2018;197(1):22–37. doi:10.1164/rccm.201611-2232PP
22. Chatziparasidis G, Kantar A. COVID-19 in children with asthma. *Lung*. 2021;199(1):7–12. doi:10.1007/s00408-021-00419-9
23. Abrams EM, Sinha I, Fernandes RM, Hawcutt DB. Pediatric asthma and COVID-19: the known, the unknown, and the controversial. *Pediatr Pulmonol*. 2020;55(12):3573–3578. doi:10.1002/ppul.25117
24. Metbulut AP, Mustafaoğlu Ö, Şen G, et al. Evaluation of the clinical and laboratory findings of asthmatic children with SARS-CoV-2 infection [published online ahead of print, 2021 Jun 24]. *Int Arch Allergy Immunol*. 2021:1–8. doi:10.1159/000517153
25. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention (2021 update). Available from: www.ginasthma.org. Accessed May 24, 2021.
26. Saudi MoH protocol for adults patients suspected of confirmed with COVID-19; 2020. Available from: https://www.moh.gov.sa/Ministry/MediaCenter/Publications/Documents/MOH-therapeutic-protocol-for-COVID-19.pdf. Accessed April 26, 2021.
27. Boechat JL, Wandalsen GF, Kuschnir FC, Delgado L. COVID-19 and pediatric asthma: clinical and management challenges. *Int J Environ Res Public Health*. 2021;18(3):1093. doi:10.3390/ijerph18031093

28. Skevaki C, Karsonova A, Karaulov A, et al. SARS-CoV-2 infection and COVID-19 in asthmatics: a complex relationship. *Nat Rev Immunol*. 2021;21(4):202–203. doi:10.1038/s41577-021-00516-z
29. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395 (10223):497–506. doi:10.1016/S0140-6736(20)30183-5
30. Ho KS, Howell D, Rogers L, Narasimhan B, Verma H, Steiger D. The relationship between asthma, eosinophilia, and outcomes in coronavirus disease 2019 infection. *Ann Allergy Asthma Immunol*. 2021;127(1):42–48. doi:10.1016/j.anai.2021.02.021
31. Zeiger RS, Schatz M, Li Q. The association of blood eosinophil counts to future asthma exacerbations in children with persistent asthma. *J Allergy Clin Immunol Pract*. 2015;3(2):283–287.e4. doi:10.1016/j.jaip.2014.10.009
32. Wu AC, Tantisira K, Li L, Schuemann B, Weiss ST, Fuhlbrigge AL; Childhood Asthma Management Program Research Group. Predictors of symptoms are different from predictors of severe exacerbations from asthma in children. *Chest*. 2011;140 (1):100–107. doi:10.1378/chest.10-2794
33. Asseri AA. Predictors of pediatric intensive care unit admissions among children with acute asthma exacerbation. *Middle East J Fam Med*. 2020;18(3):20–26. doi:10.5742/MEWFM.2020.93771
34. Shah SP, Grunwell J, Shih J, Stephenson S, Fitzpatrick AM. Exploring the utility of noninvasive type 2 inflammatory markers for prediction of severe asthma exacerbations in children and adolescents. *J Allergy Clin Immunol Pract*. 2019;7(8):2624–2633.e2. doi:10.1016/j.jaip.2019.04.043
35. Tang HHF, Lang A, Teo SM, et al. Developmental patterns in the nasopharyngeal microbiome during infancy are associated with asthma risk. *J Allergy Clin Immunol*. 2021;147(5):1683–1691. doi:10.1016/j.jaci.2020.10.009
36. Sajuthi SP, DeFord P, Li Y, et al. Type 2 and interferon inflammation regulate SARS-CoV-2 entry factor expression in the airway epithelium. *Nat Commun*. 2020;11(1):5139. doi:10.1038/s41467-020-18781-2
37. Steinman L. A brief history of TH17, the first major revision in the TH1/TH2 hypothesis of T cell–mediated tissue damage. *Nat Med*. 2007;13(2):139–145. doi:10.1038/nm1551
38. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol*. 2020;38(1):1–9. doi:10.12932/AP-200220-0772
39. Hu Z, Hasegawa K, Ma B, Fujiogi M, Camargo CA Jr, Liang L. Association of asthma and its genetic predisposition with the risk of severe COVID-19. *J Allergy Clin Immunol*. 2020;146(2):327–329.e4. doi:10.1016/j.jaci.2020.06.001
40. Cowan DC, Cowan JO, Palmay R, Williamson A, Taylor DR. Effects of steroid therapy on inflammatory cell subtypes in asthma. *Thorax*. 2010;65(5):384–390. doi:10.1136/thx.2009.126722
41. Thaweerujirot C, Daengsuwan T. Comparison between pediatric respiratory assessment measure (PRAM) score and Wood's asthma score to assess acute asthma exacerbation. *Asian Pac J Allergy Immunol*. 2019;37(3):123–129. doi:10.12932/AP-060118-0232
42. Lee DS, Gross E, Hotz A, Rastogi D. Comparison of severity of asthma hospitalization between African American and Hispanic children in the Bronx. *J Asthma*. 2020;57(7):736–742. doi:10.1080/02770903.2019.1609981
43. Munoz FA, Benton LD, Kops SA, Kowalek KA, Seckeler MD. Greater length of stay and hospital charges for severe asthma in children with depression or anxiety. *Pediatr Pulmonol*. 2020;55 (11):2908–2912. doi:10.1002/ppul.25061
44. Drewek R, Mirea L, Rao A, Touresian P, Adelson PD. Asthma treatment and outcomes for children in the emergency department and hospital. *J Asthma*. 2018;55(6):603–608. doi:10.1080/02770903.2017.1355381
45. Rutman L, Atkins RC, Migita R, et al. Modification of an established pediatric asthma pathway improves evidence-based, efficient care. *Pediatrics*. 2016;138(6):e20161248. doi:10.1542/peds.2016-1248
46. Farber HJ, Silveira EA, Vicere DR, Kothari VD, Giardino AP. Oral corticosteroid prescribing for children with asthma in a medicaid managed care program. *Pediatrics*. 2017;139(5):e20164146. doi:10.1542/peds.2016-4146
47. Silber JH, Rosenbaum PR, Calhoun SR, et al. Racial disparities in medicaid asthma hospitalizations. *Pediatrics*. 2017;139(1): e20161221. doi:10.1542/peds.2016-1221