Infection with SARS-CoV-2 among children with asthma: A GAN Survey (short title)

Clinical manifestations and outcomes of infection with SARS-CoV-2 among children with asthma: evidence from 14 Global Asthma Network centres in 10 countries (long title)

Chen-Yuan Chiang DrPhilos[1], Philippa Ellwood MPH[2], Eamon Ellwood DipTch[2], Luis García-Marcos PhD[3], Refiloe Masekela MD, PhD [4], Innes Asher MBChB[2], Héctor Badellino MD, PhD [5], Alberto Bercedo Sanz MD, PhD [6], Konstantinos Douros MD, MSc, PhD[7], Asma El Sony PhD[8], Carlos González Diaz PhD[9], Carmen Luna-Paredes PhD[10], Ana Moreno-Salvador MD[11], Luis F. Pérez-Martini MD[12], Nelson Rosário MD, PhD [13], Andrei Shpakou MD, PhD [14], Shairbek Sulaimanov MD, PhD [15], Marziyeh Tavakol MD[16], José Valverde Molina MD, PhD[17], Abdullah A Yousef MD[18], Neil Pearce PhD[19] AND The GAN COVID Study Group[20]

1. International Union Against Tuberculosis and Lung Disease, Paris, France; and Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University; and Division of Pulmonary Medicine, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University111 Hsin-Long Road, Section 3, Taipei, 116, Taiwan
2. Department of Paediatrics: Child and Youth Health, Faculty of Medical and Health Sciences, Private Bag 92019, University of Auckland, Auckland, New Zealand
3. Pediatric Allergy and Pulmonology Units, Virgen de la Arrixaca University Children's Hospital, University of Murcia and IMIB Bioresearch Institute, Murcia; and ARADyAL Allergy Network, Edificio Departamental-Laib, Avenida Buenavista s/n, 30120 El Palmar, 30394 Murcia Spain
4. Department of Paediatrics and Child Health, Nelson R Mandela School of Clinical Medicine, College of Health Sciences, University of KwaZulu Natal, Durban, South Africa
5. UCES University, and Clínica Regional del Este, Pediatric Respiratory Medicine Department, Corrientes 245- (2400), San Francisco (CBA) Argentina
6. Cantabrian Health Service, Valdecilla Research Institute (IDIVAL), Dobra Health Center, Torrelavega, Cantabria, Spain
7. National and Kapodistrian University of Athens, School of Medicine, 3rd Department of Pediatrics, "Attikon" University Hospital, Rimini 1 124 62, Athens, Greece
8. Epidemiological Laboratory (Epi-Lab) for Public Health, Research and Development, Khartoum, Sudan
9. Department of Pediatrics, University of the Basque Country. UPV/EHU, Basurto University Hospital. Avda Montevideo, 18, 48930 Bilbao, Vizcaya, Spain
10. Sección de Neumología y Alergia Infantil, Hospital Doce de Octubre. Madrid. Spain
11. Pediatric Allergy Unit, Virgen de la Arrixaca University Children's Hospital, University of Murcia
12. Asociación Guatemalteca de Neumología y Cirugía de Tórax, 6 Avenida 3-22 zona 10, Edificio Centro Médico 2. Séptimo Nivel. Oficina 710, Guatemala, Ciudad, cp 01010, Guatemala.
13. Federal University of Parana, Hospital de Clinicas, Rua General Carneiro 181 14 andar, 80060-900 Curitiba, Parana, Brasil

14. Department of Theory of Physical Culture and Sport Medicine, Yanka Kupala State University of Grodno, 22 Ozheshko str. 230023, Grodno, Belarus
15. Kyrgyz-Russian Slavic University, Kiyevskaya, 44, Bishkek city, 720000 Kyrgyzstan
16. Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran
17. Department of Pediatrics, Hospital General Universitario Santa Lucia, C/Mezquita s/n -Paraje Los Arcos- Santa Lucia, 30200, Cartagena, Murcia, Spain
18. Consultant Pediatric Pulmonologist; College of Medicine, Imam Abdulrahman bin, Faisal University and Department of Pediatrics, King Fahd Hospital of the University Alkhobar 31952, Kingdom of Saudi Arabia
19. Department of Medical Statistics, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom
20. Members of the GAN COVID study group are listed at the end of the report

Corresponding author: Professor Chen-Yuan Chiang, Senior Consultant, International Union Against Tuberculosis and Lung Disease, Paris, France; and Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University; and Division of Pulmonary Medicine, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University111 Hsin-Long Road, Section 3, Taipei, 116, Taiwan.
Email: cychiang@tmu.edu.tw

Abstract

Background

Clinical presentations and outcomes of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among children with asthma have not been investigated previously.

Methods

The Global Asthma Network (GAN) developed a questionnaire and conducted a global survey among GAN centres on infection with SARS-CoV-2 among children with asthma. Clinical manifestations and outcomes of COVID-19, exacerbation of asthma and hospitalization associated with SARS-CoV-2 infection were analyzed.

Results

Fourteen GAN centres from 10 countries provided data on 169 asthmatic children infected with SARS-CoV-2. COVID-19 was asymptomatic in 58 (34.3%), mild in 93 (55.0%), moderate in 14 (8.3%) and severe/critical in 4 (2.4%). Thirty-eight (22.5%) patients had exacerbation of asthma and 21 (12.4%) were hospitalized for a median of 7 days (interquartile range 3-16). One adolescent died. Those who used inhaled bronchodilators were significantly more likely to be symptomatic (adjusted odds ratio (adjOR) 3.78, 95% CI 1.66-8.61), have moderate or more severe COVID-19 (adjOR 8.15, 95% CI 2.22-30.0), and to be hospitalized (adjOR 6.75, 95% CI 1.65-27.65) compared to those who did not. Children who used inhaled corticosteroids (ICS) did not differ from those who did not use ICS with regards to being symptomatic, severity of COVID-19, asthma exacerbation and hospitalization.

Conclusions

In general, asthmatic children did not have high morbidity of COVID-19, but a small proportion had severe/critical disease. Use of ICS was safe and should be continued in children with asthma during the pandemic of COVID-19.

Word count: 240 (maximum 250)

Introduction

Severe acute respiratory syndrome (SARS) caused by a novel corona virus (SARS-CoV-1) has mainly caused symptomatic infections in adults. Children appear to be less susceptible to SARS-CoV-1, and have a better prognosis on follow-up.[1-3] During the 2003 outbreak of SARS, there appeared to be a low rate of asthma exacerbations among children with asthma in Singapore, likely due to a reduced incidence of acute respiratory infection.[4] The non-SARS coronaviruses were the second most important cause of the common cold after rhinoviruses, causing exacerbations of asthma among children aged 5 years or older.[5,6] It has been hypothesized that SARS-CoV-1 may be less likely to induce asthma attacks in children.[4]

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is predominant in adults.[7,8] Children and adolescents have lower susceptibility to SARS-CoV-2,[9] are less likely to have severe COVID-19, and have a lower case-fatality rate than adults.[7,10] Although clinical presentations and outcomes of COVID-19 in children have been reported, information on SARS-CoV-2 and childhood asthma is limited.[8,11,12] Previous studies on the association between asthma and COVID-19 did not report consistent findings.[13-15] Some studies reported that asthma was not a risk factor for hospitalization in patients with COVID-19,[16-18] others reported that asthma was associated with increased risk of intubation and mortality.[19,20] Studies reported that during the pandemic of COVID-19, children with asthma experienced fewer upper respiratory tract infections, emergency visits, asthma attacks, and hospitalizations due to asthma, probably due to public health interventions leading to reduced exposure to asthma triggers.[21] Whether there is increased morbidity of COVID-19 and whether treatment with inhaled corticosteroids (ICS) modifies COVID-19 morbidity among children with asthma remains unknown.[15] Furthermore, it is unclear whether SARS-CoV-2, like non-SARS coronaviruses, is associated with exacerbations of asthma.

To improve understanding of COVID-19 and childhood asthma, the Global Asthma Network (GAN) Steering Group conducted a global survey among its worldwide network on clinical manifestations and outcomes of infection with SARS-CoV-2 among children with asthma. Given the limited numbers of asthmatic children infected with SARS-CoV-2, international collaboration would yield a larger number of children[14] and GAN is well placed to meet the challenge.[22,23]

Methods

The study population were asthmatic children infected with SARS-CoV-2 confirmed by reverse transcription polymerase chain reaction (RT-PCR) tests. Detection of antibodies to SARS-CoV-2 may not indicate acute infection.[24] Therefore, serologic assays were not used to confirm acute infection with SARS-CoV-2. A structured questionnaire was developed to collect data on: 1) patient characteristics and comorbidity; 2) medicines used to control asthma in past 3 months before a positive test of SARS-CoV-2; 3) clinical manifestations of infection with SARS-CoV-2; 4) change of asthma medicines associated with SARS-CoV-2 infection; and 5) treatment and outcome of COVID-19 (supplement 1).

Information about the survey of childhood asthma and COVID-19 was sent to 336 GAN collaborators in 137 countries in September 2020 to solicit an expression of interest (EOI) for inclusion. Those not in clinical practice were advised to invite a clinical colleague to collaborate with them. A total of 48 GAN centres from 33 countries replied positively to the EOI, and the questionnaire was sent to those collaborators on 2nd November 2020. Data collection was closed on 28th April 2021.

The sampling frame included asthmatic children who have been tested in contact examinations, in a clinical practice, or in a hospital of the participating centres. All asthmatic children who tested positive for SARS-CoV-2 were included, regardless of symptoms.

The GAN Global Centre, Auckland, New Zealand coordinated the study. Key personnel at the GAN Global Centre were the same as ISAAC Phase I and Phase III.[25,26] The GAN Global Centre communicated with GAN centres, and the questionnaire was developed into a web-based data entry platform which was placed on the GAN website for direct data entry by GAN centres.

Definitions

The structured questionnaire provided definitions of tachypnea,[6] tachycardia,[6] and severity of COVID-19[9](Supplement 1). Children were defined as those aged ≤18 years. Exacerbation of asthma was determined by the relevant clinician taking care of the patients. Change of asthma medicines included new prescriptions, increased dosage and increased frequency of inhaled short acting beta-agonist (SABA), inhaled long acting beta-agonist (LABA), ICS, corticosteroid and bronchodilator in a combined inhaler (combined inhaler), and leukotriene receptor antagonist (LTRA).

Data analysis

Stata version 15 (Stata Corp LP, College Station, Texas) was used for statistical analyses. Clinical manifestations, management and outcomes of COVID-19, medicines used for asthma management and change of asthma medicines associated with SARS-CoV-2 infection were analyzed. Factors associated with being symptomatic, severity of COVID-19, exacerbation of asthma, change of asthma medicines, and hospitalization were assessed. Because the number of patients treated with LABA was relatively small, LABA and SABA were combined as inhaled bronchodilator in the analysis. Asthma medicine administered as needed and daily were combined as use of each asthma medicine. Change of asthma medicines, including new prescription, increased dosage, and increased frequency were combined as change of each asthma medicine. Categorical data were compared by using the Pearson $\chi 2$ test. Logistic regression models were constructed to assess factors associated with being symptomatic, severity of COVID-19 (asymptomatic/mild vs moderate/severe), exacerbation of asthma, change of asthma medicines, and hospitalization to obtain odds ratio (OR) and 95% confidence interval. All analyses were adjusted for age and sex as these were considered a priori to be potential confounders. We initially conducted 'univariable' analyses assessing each variable in turn (adjusted for age and sex). We then ran a 'full' model, with each factor being adjusted for age, sex, and all other variables that were considered. We then checked the standard errors for each variable estimate to check whether there

were problems of collinearity.[27,28] We found that there were problems of collinearity when different asthma medications (use of bronchodilators, use of ICS, use of combined inhaler, and use of LTRA) were entered into the model at the same time. We therefore ran separate models for each asthma medication, adjusted for age, sex, exposure to COVID-19 cases, comorbidity, and severity of COVID-19.

Ethics

Before starting the study, all participating centres were required to attain approval from their ethics committee.

Results

Fourteen GAN centres from 10 countries (Argentina, Belarus, Brazil, Greece, Guatemala, Iran, Kyrgyzstan, the Kingdom of Saudi Arabia, Spain, and Sudan) provided data on a total of 177 asthmatic children infected with SARS-CoV-2. Of the 177 cases, 169 were diagnosed by RT-PCR, six by antibody test, and two by antigen test. We retained 169 asthmatic children whose infection was confirmed by RT-PCR tests in the analysis. Of the 169 children, 110 (65.1%) were male, 128 (75.7%) aged 5-13.9 years, 121 (71.6%) had known exposure to COVID-19 cases in the family, and 29 (17.2%) had comorbidities other than asthma (Table 1, Supplement Table 1).

Of the 169 children, 111 (65.7%) were symptomatic and 76 (45.0%) had body temperature >37.5 ^{0}C. Common symptoms included cough (43.8%), headache (42.0%), rhinorrhoea (34.9%), fatigue (34.3%), and smell reduction (25.4%) (Supplement Table 1).

Thirty-eight (22.5%) patients had exacerbations of asthma associated with SARS-CoV-2 infection; 53 (31.4%) had a change of asthma medicines, including new prescription or increased dosage or increased frequency of inhaled SABA in 41 (24.3%), inhaled LABA in 5 (3.0%), ICS in 22 (13.0%), combined inhaler in 15 (8.9%), and LTRA in 6 (3.6%) (Table 2).

COVID-19 was asymptomatic in 58 (34.3%), mild in 93 (55.0%), moderate in 14 (8.3%) and severe/critical in 4 (2.4%). 21 (12.4%) patients had been hospitalized for a median of seven days (interquarter range 3-16). One (0.6%) received remdesivir; 11 (6.5%) received systemic steroids; 13 (7.7%) received oral steriods. One (0.6%) patient aged 16 died on the 6th day of hospitalization. Ten (5.9%) patients had sequelae, including persisted respiratory sympoms (n=4), decline of lung function (n=5) and hair loss and weight loss (n=1).

Adolescents aged 14 years or older were significantly more likely to be symptomatic than children aged under 10 years (adjusted odds ratio (adjOR) 10.49, 95% confidence interval (CI) 2.21-49.77) (Supplement Table 2). Those with known exposure outside family to COVID-19 cases were significantly less likely to be symptomatic than those who had no documented exposure to COVID-19 cases (adjOR 0.12, 95% CI 0.03-0.55). Use of inhaled bronchodilators (adjOR 3.31, 95% CI

1.48-7.38) was significantly associated with being symptomatic, but use of ICSs or use of a combined inhaler were not.

Use of inhaled bronchodilators (adjOR 7.22, 95% CI 1.86-28.08) and co-morbidities (adjOR 4.43, 95% CI 1.45-13.53) were significantly associated with moderate or more severe COVID-19 (Table 3). Use of ICSs, use of a combined inhaler, and use of LTRA were significantly associated with moderate or more severe COVID-19.

Those who had moderate or more severe COVID-19 were significantly more likely to have exacerbation of asthma as compared to those who were asymptomatic or had mild COVID-19 (adjOR 5.98, 95% CI 2.00-17.86) (Table 4). Use of ICS and other asthma medicines were not associated with asthma exacerbation.

Those with known exposure outside family to COVID-19 cases were significantly less likely to have a change of asthma medicines than those without documented exposure to COVID-19 cases (adjOR 0.11, 95% CI 0.02-0.56) (Supplement Table 3). Those who had moderate or more severe COVID-19 were significantly more likely to have a change of asthma medicines as compared to those who were asymptomatic or had mild COVID-19 (adjOR 5.26, 95% CI 1.65-16.77). Patients who used inhaled bronchodilators were significantly more likely to have a change of asthma medicines as compared to those who did not (adjOR 3.45, 95% CI 1.59-7.49). Use of ICSs, use of a combined inhaler, and use of LTRA were not significantly associated with a change of asthma medicine.

Patients with comorbidity were significantly more likely to be hospitalized as compared to patients without (adjOR 4.54, 95% CI 1.13-18.29) (Supplement Table 4). Those who had moderate or more severe COVID-19 were significantly more likely to be hospitalized as compared to those who were asymptomatic or mild COVID-19 (adjOR 51.64, 95% CI 11.36-234.80). Patients who used inhaled bronchodilators were significantly more likely to be hospitalized as compared to those who did not (adjOR 5.54, 95% CI 1.15-26.77). Use of ICS, use of a combined inhaler an duse of LTRA were not associated with hospitalization.

Discussion

To our knowledge, this is the first study presenting clinical manifestations and outcome of infection with SARS-CoV-2 in a large number of children with asthma. We found that about 90% of asthmatic children were asymptomatic or had mild COVID-19. However, a substantial proportion of children had exacerbations of asthma and a considerable proportion had a change of asthma medicines associated with infection with SARS-CoV-2.

The proportions of COVID-19 cases who were asymptomatic among children varies between previously published studies; the estimates include 12.9% by Dong et al,[29] 15.8% by Lu et al,[30] 21% by Parri et al,[8] and 28% by Qiu et al,[11]; these proportions are generally higher than that observed in adults.[31] About 35% of our study population were asymptomatic, in part because a high proportion of children had known exposure to COVID-19 cases and those who were found to be infected during contact examinations, regardless of symptoms, were included. The proportions of symptomatic cases increased with age, and adolescents were less likely to be

asymptomatic than younger children. A higher proportion of those who used inhaled bronchodilators were symptomatic, likely because their asthma was more severe than those who did not. Of note is that those who used ICS or a combined inhaler were not more likely to be symptomatic than those who did not.

Severity of COVID-19 among children varied between studies. Dong et al reported that among 728 children with confirmed COVID-19, 43.1% had mild disease, 40.9% moderate disease, 2.9% had severe/critical illness.[29] Lu et al reported that of the 171 pediatric COVID-19 cases, 19.3% had mild COVID-19, and 64.9% had moderate COVID-19.[30] Parri et al reported that among 100 pediatric COVID-19 cases, 58% had mild disease, 19% had moderate disease and 2% had severe/critical illness.[8] Garazzino et al reported that of the 168 laboratory-confirmed COVID-19 cases, 15.5% had pneumonia.[32] Zachariah et al reported that among 50 children infected with SARS-CoV-2, 18% were severe cases requiring mechanical ventilation. Tagarro et al reported that among 41 pediatric COVID-19 cases, 10% required oxygen support beyond nasal prongs.[33] In our study, a substantial proportion of patients did not have radiographic examinations, thus we may underestimate the proportion of cases with pneumonia. However, compared with previous reports on COVID-19 in children, our study revealed that asthmatic children did not appear to have a higher frequency of severe COVID-19, consistent with the finding of Zachariah et al that the proportion of patients with asthma was not significantly different between severe and non-severe cases.[12] Studies reported that patients with chronic respiratory disease were significantly under-represented among hospitalized COVID-19 cases.[13] Our findings suggest that this was likely because the majority of patients with asthma had mild COVID-19.

In our study, a substantial proportion of asthmatic children had exacerbations of asthma and a considerable proportion had a change of asthma medicines associated with infection with SARS-CoV-2. However, the severity of COVID-19 was significantly associated with exacerbation of asthma, and a change of asthma medicines. Whether symptoms leading to change of asthma medicines were caused by COVID-19 or due to exacerbation of asthma was less clear. Schultze et al report that in adults, compared with those prescribed SABAs only, people with asthma who were prescribed high-dose ICS were at an increased risk of death (1·55 [1·10–2·18]), whereas those given a low or medium dose were not.[34] Our study revealed that the use of ICS was not associated with asthma exacerbation or a change of asthma medicines in children. Ramakrishnan et al hypothesised that the use of ICS may be protective against severe COVID-19, and reported that in a randomised controlled trial early administration of inhaled budesonide reduced the need of urgent medical care and reduced time to recovery after early COVID-19.[35] Izquierdo et al reported that the use of ICS was lower in adults with asthma who required hospitalisation due to COVID-19, as compared to non-hospitalised patients.[36] Halpin et al conducted a systematic review on ICS and COVID-19 and found no report on prior ICS use in patients with SARS or COVID-19 infection.[37] Our study appears to be the first to report that the use of ICS was not associated with severity of COVID-19, exacerbations of asthma, a change of asthma medicines and hospitalization in children infected with SARS-CoV-2; this clearly supports the recommendation of continuation of the use of ICS among patients with asthma.[37] Given that those who used ICS may have more severe asthma than those did not use, whether our findings imply that ICS is protective against COVID-19 in children require further investigation.

In our study, adolescents were more likely to be symptomatic with SARS-CoV-2 infection as compared to younger children. Furthermore, one adolescent who was a diabetic patient died. It has been reported that teenagers infected with SARS-CoV-1, similar to adults, may develop severe illness.[1]

Our study has several strengths. We enrolled a relatively large number of children with asthma infected with SARS-CoV-2 from many countries, thus were able to assess factors associated with clinical manifestations and outcome of COVID-19. The limitation of our study is that we did not specify duration of follow-up of SARS-CoV-2 infection. Although a few patients have reported sequelae after acute SARS-CoV-2 infection, we were not able to clearly investigate long COVID.[38]

In conclusion, asthmatic children did not have a high frequency of severe COVID-19. SARS-CoV-2 infection was associated with asthma exacerbations, but the overlap of symptoms between COVID-19 and asthma makes it difficult to disentangle the relative contributions of COVID-19 and asthma. The use of inhaled bronchodilators was associated with being symptomatic, having more severe COVID-19, having a change of asthma medicines and being hospitalized, but the use of ICS was not, confirming that ICS is safe to be used by children with asthma during the pandemic of COVID-19.

Word count: 2640 (maximum 2700)
Tables: 4 (maximum 5)

The GAN COVID Study Group

Global Asthma Network Steering Group: MI Asher, Department of Paediatrics: Child and Youth Health, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand; K Bissell, School of Population Health, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand; C-Y Chiang, International Union Against Tuberculosis and Lung Disease, Paris, France; and Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University; and Division of Pulmonary Medicine, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University111 Hsin-Long Road, Section 3, Taipei, 116, Taiwan; A El Sony, Epidemiological Laboratory for Public Health and Research, Khartoum 3 Block3-Building 11, Khartoum, Sudan; P Ellwood, Department of Paediatrics: Child and Youth Health, Faculty of Medical and Health Sciences, Private Bag 92019, University of Auckland, Auckland, New Zealand; L García-Marcos, Pediatric Allergy and Pulmonology Units, Virgen de la Arrixaca University Children‘s Hospital, University of Murcia and IMIB Bioresearch Institute, Murcia; and ARADyAL Allergy Network, Edificio Departamental-Laib, Avenida Buenavista s/n, 30120 El Palmar, 30394 Murcia Spain; GB Marks, Respiratory & Environmental Epidemiology, University of New South Wales, Goulburn St, Sydney 2085, Sydney, Australia; K Mortimer, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, United Kingdom; N Pearce, Department of Medical Statistics, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom; DP Strachan, Population Health Research Institute, St George’s, University of London, Cranmer Terrace, London SW17 0RE, United Kingdom.

AND the Associates of the GAN COVID PIs
Argentina, San Francisco; Alvaro Teijeiro MD, PhD. Respiratory Center-Pediatric Hospital-Córdoba-Argentina

Belarus, **Grodno;** Raisa Khokha MD, PhD. Grodno State Medical University, 80 Gorkogo str. 230015, Grodno, Belarus

Brazil, **Curitiba;** Debora Carla Chong-Silva MD, PhD and Cristine Secco Rosario MD; Federal University of Parana, Hospital de Clinicas, Rua General Carneiro 181 14 andar, 80060-900 Curitiba, Parana, Brasil

Greece, Athens; Ourania Magkoni MD. National and Kapodistrian University of Athens, School of Medicine, 3rd Department of Pediatrics, "Attikon" University Hospital, Rimini 1 124 62, Athens, Greece

Guatemala; Luisa F. Martínez-Valdeavellano MD. Asociación Guatemalteca de Neumología y Cirugía de Tórax,6 Avenida 3-22 zona 10, Edificio Centro Médico 2. Séptimo Nivel. Oficina 710, Guatemala, Ciudad, cp 01010, Guatemala

Iran, Karaj; Farimah Fayyaz, and Hoda Jafari, Student Research Committee, Alborz University of Medical Sciences, Karaj, Iran

Kingdom of Saudi Arabia, **Alkhobar;** Suzan A AlKhater MD. Associate Professor of Pediatrics, Consultant of Allergy & Clinical Immunology. College of Medicine , Imam Abdulrahman bin Faisal University, and Department of Pediatrics, King Fahd Hospital of University, Al-Khobar 31952, Saudi Arabia

Krygysztan, **Jalalabat;** Sulaimanova Aruuke MD. Kyrgyz-Russian Slavic University, Kiyevskaya, 44, Bishkek city, 720000 Kyrgyzstan

Spain, Bilbao; Joseba Rementeria MD and Andres González PhD. Departament of Pediatrics, University of the Basque Country. PV/EHU, Basurto University Hospital. Avda Montevideo, 18, 48930 Bilbao, Vizcaya, Spain

Spain, **Cantabria;** Ana María Rubio Alvarez, MD. Cantabrian Health Service, Valdecilla Research Institute (IDIVAL), Dobra Health Center, Torrelavega, Cantabria, Spain

Spain, **Madrid;** MS Albi Rodríguez PhD. Sección de Neumología y Alergia Infantil, Hospital Doce de Octubre. Madrid. Spain

Spain, **Mar Menor;** Carolina Díaz-García, MD, PhD. Pediatric Allergy and Pulmonology Units, Hospital General Universitario Santa Lucia, C/Mezquita s/n - Paraje Los Arcos- Santa Lucia, 30200 Cartagena, Murcia, Spain

Sudan, **Khartoum;** Mohamed Mustafa Osman Fadul, BSc. Epidemiological Laboratory (Epi-Lab) for Public Health, Research and Development, Khartoum, Sudan

References (maximum 40)

1. Leung C-w, Kwan Y-w, Ko P-w, et al. Severe Acute Respiratory Syndrome Among Children. Pediatrics 2004;113(6):e535-e543. DOI: 10.1542/peds.113.6.e535.
2. Hon KLE, Leung CW, Cheng WTF, et al. Clinical presentations and outcome of severe acute respiratory syndrome in children. The Lancet 2003;361(9370):1701-1703. DOI: 10.1016/S0140-6736(03)13364-8.
3. Peiris JSM, Lai ST, Poon LLM, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003;361(9366):1319-1325. DOI: https://doi.org/10.1016/S0140-6736(03)13077-2.
4. Van Bever HP, Chng SY, Goh DY. Childhood severe acute respiratory syndrome, coronavirus infections and asthma. Pediatric Allergy and Immunology 2004;15(3):206-209. DOI: 10.1111/j.1399-3038.2004.00137.x.
5. Vabret A, Mourez T, Gouarin S, Petitjean J, Freymuth F. An Outbreak of Coronavirus OC43 Respiratory Infection in Normandy, France. Clinical Infectious Diseases 2003;36(8):985-989. DOI: 10.1086/374222.
6. Johnston SL, Pattemore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. BMJ 1995;310(6989):1225-1229. DOI: 10.1136/bmj.310.6989.1225.
7. Guan W-j, Ni Z-y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New Engl J Med 2020. DOI: 10.1056/NEJMoa2002032.
8. Parri N, Lenge M, Buonsenso D. Children with Covid-19 in Pediatric Emergency Departments in Italy. N Engl J Med 2020;383(2):187-190. DOI: 10.1056/NEJMc2007617.
9. Viner RM, Mytton OT, Bonell C, et al. Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared With Adults: A Systematic Review and Meta-analysis. JAMA Pediatrics 2020. DOI: 10.1001/jamapediatrics.2020.4573.
10. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 2020;323(20):2052-2059. DOI: 10.1001/jama.2020.6775.
11. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis 2020;20(6):689-696. DOI: 10.1016/S1473-3099(20)30198-5.
12. Zachariah P, Johnson CL, Halabi KC, et al. Epidemiology, Clinical Features, and Disease Severity in Patients With Coronavirus Disease 2019 (COVID-19) in a Children's Hospital in New York City, New York. JAMA Pediatrics 2020:e202430-e202430. DOI: 10.1001/jamapediatrics.2020.2430.
13. Morais-Almeida M, Pité H, Aguiar R, Ansotegui I, Bousquet J. Asthma and the Coronavirus Disease 2019 Pandemic: A Literature Review. Int Arch Allergy Immunol 2020;181(9):680-688. DOI: 10.1159/000509057.
14. Castro-Rodriguez JA, Forno E. Asthma and COVID-19 in children: A systematic review and call for data. Pediatr Pulm 2020;55(9):2412-2418. DOI: https://doi.org/10.1002/ppul.24909.
15. Abrams EM, Sinha I, Fernandes RM, Hawcutt DB. Pediatric asthma and COVID-19: The known, the unknown, and the controversial. Pediatr Pulm 2020;55(12):3573-3578. DOI: https://doi.org/10.1002/ppul.25117.

16. Beken B, Ozturk GK, Aygun FD, Aydogmus C, Akar HH. Asthma and allergic diseases are not risk factors for hospitalization in children with coronavirus disease 2019. Ann Allergy Asthma Immunol 2021;126(5):569-575. DOI: 10.1016/j.anai.2021.01.018.
17. Chhiba KD, Patel GB, Vu THT, et al. Prevalence and characterization of asthma in hospitalized and nonhospitalized patients with COVID-19. J Allergy Clin Immunol 2020;146(2):307-314.e4. DOI: 10.1016/j.jaci.2020.06.010.
18. Liu S, Cao Y, Du T, Zhi Y. Prevalence of Comorbid Asthma and Related Outcomes in COVID-19: A Systematic Review and Meta-Analysis. J Allergy Clin Immunol Pract 2021;9(2):693-701. DOI: https://doi.org/10.1016/j.jaip.2020.11.054.
19. Rosenthal JA, Awan SF, Fintzi J, Keswani A, Ein D. Asthma is associated with increased risk of intubation but not hospitalization or death in coronavirus disease 2019. Ann Allergy Asthma Immunol 2021;126(1):93-95. (In eng). DOI: 10.1016/j.anai.2020.10.002.
20. Williamson E, Walker AJ, Bhaskaran K, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. medRxiv 2020:2020.05.06.20092999. DOI: 10.1101/2020.05.06.20092999.
21. Papadopoulos NG, Mathioudakis AG, Custovic A, et al. Childhood asthma outcomes during the COVID-19 pandemic: Findings from the PeARL multinational cohort. Allergy 2021;n/a(n/a). DOI: https://doi.org/10.1111/all.14787.
22. Ellwood P, Asher MI, Billo NE, et al. The Global Asthma Network rationale and methods for Phase I global surveillance: prevalence, severity, management and risk factors. Eur Respir J 2017;49(1):1601605. DOI: 10.1183/13993003.01605-2016.
23. Ellwood PE, E.; Rutter, C.; Perez-Fernandez, V.; Morales, E.; García-Marcos, L.; Pearce, N.; Asher, MI.; Strachan, D.; on behalf of the GAN Phase I Study Group. Global Asthma Network Phase I Surveillance: Geographical Coverage and Response Rates. J Clin Med 2020.
24. Younes N, Al-Sadeq DW, AL-Jighefee HY, S.; Al-Jamal, O.; Daas, H.I.; Yassine, H.M.; Nasrallah, G.K. Challenges in Laboratory Diagnosis of the Novel Coronavirus SARS-CoV-2. Viruses 2020;12, 582.
25. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet 1998;351(9111):1225-1232. DOI: https://doi.org/10.1016/S0140-6736(97)07302-9.
26. Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006;368(9537):733-743. DOI: https://doi.org/10.1016/S0140-6736(06)69283-0.
27. Greenland S, Pearce N. Statistical foundations for model-based adjustments. Annu Rev Public Health 2015;36:89-108. (In eng). DOI: 10.1146/annurev-publhealth-031914-122559.
28. Greenland S, Daniel R, Pearce N. Outcome modelling strategies in epidemiology: traditional methods and basic alternatives. Intern J Epidemiol 2016;45(2):565-575. DOI: 10.1093/ije/dyw040.

29. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics 2020;145(6):e20200702. DOI: 10.1542/peds.2020-0702.
30. Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. N Engl J Med 2020. DOI: 10.1056/NEJMc2005073.
31. Guan W-j, Liang W-h, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020;55(5):2000547. DOI: 10.1183/13993003.00547-2020.
32. Garazzino S, Montagnani C, Donà D, et al. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020. Eurosurveillance 2020;25(18):2000600. DOI: doi:https://doi.org/10.2807/1560-7917.ES.2020.25.18.2000600.
33. Tagarro A, Epalza C, Santos M, et al. Screening and Severity of Coronavirus Disease 2019 (COVID-19) in Children in Madrid, Spain. JAMA Pediatrics 2020. DOI: 10.1001/jamapediatrics.2020.1346.
34. Schultze A, Walker AJ, MacKenna B, et al. Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform. Lancet Respir Med 2020;8(11):1106-1120. DOI: 10.1016/S2213-2600(20)30415-X.
35. Ramakrishnan S, Nicolau DV, Jr., Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. Lancet Respir Med 2021. DOI: 10.1016/S2213-2600(21)00160-0.
36. Izquierdo JL, Almonacid C, González Y, et al. The impact of COVID-19 on patients with asthma. European Respiratory Journal 2021;57(3):2003142. DOI: 10.1183/13993003.03142-2020.
37. Halpin DMG, Singh D, Hadfield RM. Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective. Eur Respir J 2020;55(5):2001009. DOI: 10.1183/13993003.01009-2020.
38. Buonsenso D, Munblit D, De Rose C, et al. Preliminary evidence on long COVID in children. Acta Paediatr;n/a(n/a). DOI: https://doi.org/10.1111/apa.15870.

Table 1 Characteristics of 169 asthmatic children infected with SARS-CoV-2

	Number	Percentage
Total	169	100
Location of case identification		
A clinical practice of the participant	18	10.7
A hospital or other medical facility	130	76.9
Household contact examination	15	8.9
School-based contact examination	3	1.8
Others*	3	1.8
Specimen used for testing		
Nasopharyngeal swab	101	59.8
Oral swab	9	5.3
Both Nasopharyngeal and oral swab	59	34.9
Laboratory tests		
In-house RT-PCR	97	57.4
Roche Cobas SARS-CoV-2	29	17.2
Cepheid Xpert Xpress SARS-CoV-2	14	8.3
Abbott ID NOW COVID-19	18	10.7
Others†	11	6.5
Exposure to COVID-19 patients		
Exposure in family	121	71.6
Other known exposure**	26	15.4
Unknown exposure	22	13.0
Sex		
Boy	110	65.1
Girl	59	34.9
Age at infection (years)		
<5	17	10.1
5 - 9.9	68	40.2
10 – 13.9	60	35.5
≥ 14	24	14.2
Asthma medicines used in past 3 months		
Short acting β- agonists (SABA)	67	39.7
As needed	61	36.1
Everyday	6	3.6
Long acting β- agonists (LABA)	3	1.8
As needed	0	0.0
Everyday	3	1.8
Inhaled corticosteroid (ICS)	59	34.9
As needed	4	2.4
Everyday	55	32.5
ICS and LABA combined inhaler	37	21.9
As needed	3	1.8
Everyday	34	20.1
Either ICS or combined inhaler	96	56.8
As needed	7	4.1
Everyday	89	52.7
Leukotriene receptor antagonist	20	11.8
As needed	1	0.6
Everyday	19	11.2

* extended family, 1; community contact examination, 1; telemedicine, 1.
† TaqPath COVID-19 CE-IVD, 5; Procleix SARS-CoV-2 Assay, 5; Biomol one-step COVID-19, 1.
** School, 12; relatives, 5; pleasure activities, 5; friend, 1; soccer camp, 1; homeschool teacher, 1; martial arts academy, 1.

Table 2. Change of asthma medicines, severity, treatment and outcomes of COVID-19 in 169 asthmatic children infected with SARS-CoV-2

	Number	Percentage
Total	169	100
Treatment change	53	31.4
Short acting β- agonists (SABA)	41	24.3
New prescription	12	7.1
Increased dosage	6	3.6
Increased frequency	24*	14.2
Long acting β- agonists (LABA)	5	3.0
New prescription	2	1.2
Increased dosage	0	0
Increased frequency	3	1.8
Inhaled corticosteroid (ICS)	22	13.0
New prescription	12†	7.1
Increased dosage	8	4.7
Increased frequency	2	1.2
Combination ICS and LABA	15	8.9
New prescription	5	2.9
Increased dosage	7	4.1
Increased frequency	3	1.8
Leukotriene receptor antagonist	6	3.6
New prescription	6	3.6
Increased dosage	0	0
Increased frequency	0	0
Severity of COVID-19		
Asymptomatic	58	34.3
Mild	93	55.0
Moderate	14	8.3
Severe/Critical	4	2.4
Treatment		
Hydroxychloroquine	3	1.8
Immune globulin	0	0
Interferon alfa	3	1.8
Lopinavir–ritonavir	0	0
Macrolides	26	15.4
Oseltamivir	2	1.2
Oxygen inhalation	21	12.4
Remdesivir	1	0.6
Steroids, oral	13	7.7
Steroids, systemic	11	6.5
CPAP/BiPAP**	2	1.2
Intubation ventilation	1	0.6
Outcome of COVID-19		
Recovered, no sequelae	158	93.5
Recovered, with sequelae	10	5.9
Died	1	0.6

* one patient had both increased dosage and increased frequency

† one patient was prescribed budesonide nebulization

** CPAP, continuous positive airways pressure; BiPAP, bilevel positive airways pressure.

Table 3. Factors associated with moderate/severe/critical COVID-19

	Total N=	Moderate/severe /critical N (%)	Univariable** OR(95% CI)	Multivariable‡ adjOR(95% CI)
Total	169	18 (10.7)		
Age at infection (years)				
<5	17	3(17.7)	reference	reference
5 - 9.9	68	3(4.4)	0.21(0.04-1.17)	0.27(0.05-1.59)
10 – 13.9	60	7(11.7)	0.61(0.14-2.67)	0.65(0.13-3.08)
≥ 14	24	5(20.8)	1.22(0.25-5.99)	1.34(0.25-7.25)
Sex				
Female	59	6(10.2)	reference	reference
Male	110	12(10.9)	1.14(0.40-3.28)	0.85(0.27-2.65)
Exposure to COVID-19 cases				
Unknown	22	3(13.6)	reference	reference
Family	121	13(10.7)	0.75(0.19-3.04)	0.95(0.22-4.09)
Other exposure	26	2(7.7)	0.45(0.06-3.16)	0.51(0.07-3.84)
Comorbidity				
No	140	10(7.1)	reference	reference
Yes	29	8(27.6)	4.40(1.46-13.25)	4.43(1.45-13.53)
Use of bronchodilator*†				
No	102	3(2.9)	reference	reference
Yes	67	15(22.4)	7.93(2.15-29.27)	7.22(1.86-28.08)
Use of inhaled corticosteroid†				
No	110	14(12.7)	reference	reference
Yes	59	4(6.8)	0.50(0.15-1.70)	0.45(0.12-1.70)
Use of combined inhaler†				
No	132	14(10.6)	reference	reference
Yes	37	4(10.8)	1.20(0.34-4.21)	0.74(0.19-2.91)
Use of Leukotriene receptor antagonist†				
No	149	16(10.7)	reference	reference
Yes	20	2(10.0)	1.09(0.22-5.40)	0.93(0.17-5.19)

*Short acting beta agonist or Long acting beta agonist
† daily or as needed
** adjusted for age and sex

Table 4. Factors associated with asthma exacerbation with SARS-CoV-2 infection

	Total N=	Exacerbation N (%)	Univariable** OR(95% CI)	Multivariable‡ adjOR(95% CI)
Total	169	38 (22.5)		
Age at infection (years)				
<5	17	5(29.4)	reference	reference
5 - 9.9	68	12(17.7)	0.52(0.16-1.77)	0.70(0.18-2.71)
10 – 13.9	60	14(23.3)	0.74(0.22-2.48)	0.80(0.21-3.01)
≥ 14	24	7(29.2)	1.00(0.25-3.91)	1.01(0.22-4.60)
Sex				
Female	59	15(25.4)	reference	reference
Male	110	23(20.9)	0.79(0.37-1.67)	0.73(0.32-1.65)
Exposure to COVID-19 cases				
Unknown	22	7(31.8)	reference	reference
Family	121	28(23.1)	0.67(0.24-1.84)	0.72(0.25-2.10)
Other exposure	26	3(11.5)	0.27(0.06-1.23)	0.29(0.06-1.44)
Comorbidity				
No	140	28(20.0)	reference	reference
Yes	29	10(34.5)	2.12 (0.85-5.25)	1.51(0.55-4.12)
Severity of COVID-19				
Mild	151	27(17.9)	reference	reference
Moderate or more	18	11(61.1)	7.21(2.56-20.32)	5.98(2.00-17.86)
Use of bronchodilator*†				
No	102	14(13.7)	reference	reference
Yes	67	24(35.8)	3.41(1.57-7.46)	2.29(0.98-5.33)
Use of inhaled corticosteroid†				
No	110	23(20.9)	reference	reference
Yes	59	15(25.4)	1.35 (0.62-2.96)	1.63(0.70-3.79)
Use of combined inhaler†				
No	132	26(19.7)	reference	reference
Yes	37	12(32.4)	2.34 (0.99-5.53)	2.30(0.90-5.86)
Use of Leukotriene receptor antagonist†				
No	149	31(20.8)	reference	reference
Yes	20	7(35.0)	2.15 (0.77-5.98)	2.10(0.69-6.44)

*Short acting beta agonist or Long acting beta agonist

† daily or as needed

**adjusted for age and sex

‡ adjusted for age, sex, exposure to COVID-19 cases, comorbidity and severity of COVID-19.