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Review Article

Impact COVID-19 Infection in Childhood Asthma. Review Study

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Abstract

Between December 2019 and first months of 2020 a novel coronavirus called nCoV2019 and SARS-CoV-2 rapidly spreads from city of Wuhan (China) to every country around the world caused Coronavirus Disease 2019 (COVID-19). Children can be affected by COVID-19 and present mild and generally less severe respiratory symptoms than adults. The percentage of pediatric cases is certainly underestimated. Admission of children to Intensive Care Unit (ICU) is rare and prognosis is favorable except very few cases. We aimed to perform a review study analysis about COVID-19 and childhood asthma. An analysis of electronic databases was performed using PubMed, Cochrane library and Embase and searched up to June 2020. The literature review was conducted independently by two reviewers and analyzed 43 published articles. The available information's were limited, with few sources suggesting an underrepresentation and increased risk for severe COVID complications especially in patients with asthma associated with disease severity. The published data of COVID severity infection due to asthma in children are till now extremely rare.

COVID-19 doesn't have a significant impact on childhood asthma and there is no indication to change treatment strategies for asthmatic children. Furthermore, asthmatic children recommended continuing their therapies without making any dose adjustments.

Keywords: *Coronavirus; COVID-19; Pandemic; Asthma; Children*

Introduction

Between December 2019 and first months of 2020 a novel coronavirus called nCoV2019 and SARS-CoV-2 spreads from city of Wuhan (China) to every country around the world caused Coronavirus Disease 2019 (COVID-19). Consequently, the World Health Organization (WHO) declared COVID-19 as pandemic infection on March 11, 2020 [1]. During last months besides the apprehensions raised in asthmatic patients during the flu period there is awareness of COVID-19 infection and its effects on their health [2].

What can patients suffering asthma, both adults and children to protect their health? Are they really at greater risk of infection? If they are infected by the virus, how should behave? These are some of the questions made by scientific community [3]. Many aspects of this new disease are unknown till now [4].

According to epidemiologic data it is clear that high risk patients are elderly immunosuppressed and the chronic patients but it isn't clear even if COVID-19 being major cause for respiratory disease [5].

We aimed to perform a review study analysis about COVID-19 and childhood asthma. An analysis of electronic databases was performed using PubMed, Cochrane library and Embase and searched up to June 2020.

Brief overview on COVID-19 features

Seven species of coronavirus can infect humans such as CoV-229E, CoV-NL63, CoV-OC43, CoV-HKU1, MERS-CoV, SARS-CoV, SARS-CoV-2. Among them SARS-CoV-2 is closely related to SARS-CoV may cause Severe Acute Respiratory Syndrome (SARS) during epidemic outbreak between November 2002 and July 2003 [6].

Phylogenetic analysis revealed SARS-CoV-2 and SARS-CoV share the similar functional receptor on human cells such as Angiotensin-Converting Enzyme 2 (ACE2) and COVID-19 may partly mimic SARS infection. ACE2 expressed on type I and type II alveolar epithelial cells of normal human lung but also on cells of other organs. Men have a higher ACE2 level in their alveolar cells than women and Asians reveals higher level than Caucasian and African American populations [7].

ACE2 protects lungs from Acute Respiratory Distress Syndrome (ARDS) when is decreased due to interaction with virus favors syndrome. Reduction of pulmonary ACE2 activity contributes pathogenesis of lung inflammation, accompanied by the expression of cytokines cooperate with direct effects of viral infection [8].

Damages to alveolar cells trigger systemic reactions lead to death. Accumulating evidence suggests that patients with severe COVID-19 infection might have "cytokine storm" syndrome, as seen in SARS [9,10].

Cytokines are hormonal messengers responsible for many biological effects of immune system such as cell mediated immunity and allergic type responses. T lymphocytes are major source of cytokines and they have antigen specific receptors on their surface to recognize foreign pathogens even in case of autoimmune diseases. There are two main subsets of T lymphocytes, distinguished by the presence of cell surface molecules such as CD4 and CD8. T lymphocytes expressing CD4 are also known as T helper cells (Th). These are the most prolific cytokine producers [10].

This can be further subdivided into Th1 and Th2 and cytokines produce are known as Th1-type cytokines and Th2-type cytokines. Th1-type cytokines tend to produce proinflammatory events responsible for killing intracellular parasites and perpetuating autoimmune responses. Interferon gamma (INF-γ) is the main Th1 cytokine [10].

Excessive proinflammatory responses can lead uncontrolled tissue damage. Th2-type cytokines include interleukins (IL) IL-4, IL-5, and IL-13 are associated with the promotion of IgE and eosinophilic responses in atopic lessons and also IL-10 which reveal an anti-inflammatory response. Th2 responses will counteract the Th1 mediated action. Humans should produce a well-balanced Th1 and Th2 response suited to immune challenge [11].

As have already shown in examinations on SARS victims high levels of proinflammatory cytokines were present in ACE-2 expressing cells infected by SARS- CoV. Plasma cytokine profiles showed Th1 dominated responses with markedly elevated proinflammatory cytokine levels (INF-γ, IL-1β, IL-6, IL-8, IL-12, and Tumor Necrosis Factor-α) associated with the development of ARDS [12].

SARS-CoV-2 is related to SARS-CoV and appears similar mechanisms of action. It is a new disease can present with varying degrees of severity and more research is needed to understand how it really acts and how these pathophysiological mechanisms can be controlled.

Asthma and viral infections

Asthma is one of the most common respiratory diseases. Characterized as chronic inflammatory disease susceptible to triggering factors such as allergens air pollution and viral infections [13]. Even though advances in prevention and management asthma are still

incurable and remains a global healthcare problem [14]. During period from 1990 to 2015 prevalence of asthma has increased by 12.6%. Nowadays there are over than 350 million cases of asthma and estimated that about 400.000 people died from asthma in 2015 [15]. Approximately 8 - 9% of children and adults suffer from asthma in Europe and is estimated that 10% reveal asthma-like symptoms [16].

Viral infections, caused by different families of viruses have been proven to cause asthma exacerbations and cause asthma development [17-19].

A review study in 2018, analyzed the prevalence of viral infection in asthmatic patients. Viruses involved in asthma exacerbations were rhinovirus (42.1%), respiratory syncytial virus (13.6%), herpes simplex virus (12.3%), enterovirus (10.1%), influenza virus (10.0%), coronavirus (8.4%), cytomegalovirus (7.2%), bocavirus (6.9%), parainfluenzavirus (5.6%), metapneumovirus (5.3%) and adenovirus (3.8%). Enterovirus, metapneumovirus, rhinovirus, respiratory syncytial virus were more common in children, whereas adenovirus, bocavirus, coronavirus, influenza virus and parainfluenzavirus were more common in adults [20].

Asthma has long been considered as Th2 cell-mediated disease. Often occurs in patients who reveal atopic reactions, especially genetic tendency to produce immunoglobulin E (IgE) to common allergens by IL-4 mediation. Eosinophils and CD4 cells produce IL-5 are frequently found in the blood and lung lavage fluid of asthma patients. During past years, trials on mouse models showed that many of asthma features were abolished in animals genetically lacking the Th2 cell cytokines IL-4, IL-5, and/or IL-13 [21]. On the other side administration of IL-12 seems to suppress asthma in mice, by producing IFN-γ from Th1 [22].

The Th2 cell-mediated immunity to allergens has dominated over the last 30 years and has pushed forward treatments focused on Th2 cell cytokines [23].

Asthma is complex syndrome with various pathophysiological mechanisms. It has also been found that besides Th2 cells, other innate immune cells like basophils, mast cells and type 2 innate lymphoid cells can produce Th2 cell-associated cytokines in asthma [24]. Asthma is heritable disease and genetics can be considered an important tool to reveal molecular mechanisms. The knowledge of genetic background of asthma has rapidly increased during recent years due to Genome Wide Association Studies (GWAS) of million genetic variants can be tested without a prior hypothesis. Scientists have now identified more than 100 genes/loci associated with asthma [25].

According to literature more studies are crucial for information's on gene variants, gene expression and epigenetics. These studies may reveal unknown pathophysiological mechanisms and functional subtypes of asthma in order to personalize and improve treatment and prevention of the disease [26].

COVID-19 infection: Differences between children and adults

In March 2020 and epidemiological review from China on 2135 pediatric cases (728 confirmed and 1407 suspected) revealed lower frequency of serious (5.2%) or critical (0.6%) cases in children compared to the adult population (18.5%), even if most cases (10.6%) has been reported in infants. Almost 13% of confirmed cases were asymptomatic [27].

Further reports from Wuhan confirm that most pediatric positive cases were asymptomatic (15.8%), indeed, more than half (58.5%) of these children presented with no fever cause underestimation of diagnosed children with COVID-19 infection in the first weeks of disease (only 1% of patients under 10 years old reported on 44,672 cases till February). At the end of March, population under 18 years old in China constituted 2.4% of all reported cases (over 80,000).

In most serious cases dominant symptoms were tachypnea, fever and cough with multiform radiological images from unilateral pneumonia (19%) to "frosted-glass" images (32%) typical of interstitial disease. Plasma increase levels of proinflammatory cytokines (IL-6, IL10, IFN-γ) called "cytokine storm" responsible for lung damage, have already been reported [28].

Cardiovascular, endocrine and digestive system diseases are commonly reported co-morbidities; however, cases of pre-existing chronic respiratory diseases are surprisingly low (< 2% of patients from China) [29].

There is no evidence, till now, asthmatic patients, either children or adults being at risk of developing pneumonia more easily nor prone to hospitalization due to COVID-19 infection [30-32].

According to several studies asthmatic patients has speculated Th2 immune response. This reaction counters the inflammation process induced by COVID-19 such as Th1-mediated "cytokine storm". According to these studies are required to reveal human immune response to inflammation caused by the virus such as COVID-19 [33].

Clinical manifestations of pediatric patients are generally less severe. Children of all ages are susceptible to COVID-19 but no significant gender difference has been found. However, young children, particularly infants, seem more vulnerable to COVID-19 infection and asthmatic patients seem not to be affected more often [34].

There are, however, many urgent questions need to be answered: why does COVID-19 preferentially affect adults? Are there differences in immune response between adults and children to COVID-19? If yes, which ones?

Even during SARS epidemic outbreak of 2003 children appeared to be less susceptible to SARS coronavirus. According to lung samples of SARS adult patients a giant-cell infiltrate composed by cells of monocyte or macrophage lineage fused together. Pronounced increase in macrophages in the alveoli and the interstitium of the lungs has been reported [35].

This infiltrate was different from seen in non-SARS ARDS which comprises activated neutrophils (with increased IL-8 levels) both adults and children [36].

It has been supposed that activated macrophages revealed an important role in severe SARS reaction and maybe lack of activation of macrophages by SARS-CoV causes severe SARS development in children. Although children are vulnerable to non-SARS coronaviruses SARS-CoV used different receptors from other coronaviruses [37].

Macrophages are cells with phagocytic activity be stimulated and activated by bacterial products, neuropeptides, neurohormones, cytokines and other stimuli. Release large amounts of proinflammatory cytokines, nitric oxide, biogenic amines, neuropeptides and hormones [37].

According to "inflamm-aging" theory, macrophage plays as central role not only in the inflammatory response and immunity, but also in stress response. This hypothesis suggests the relation between stress and macrophage activation such as subclinical chronic inflammatory reaction in elderly. This phenomenon is only part of the whole spectrum of immune senescence and indeed macrophage is not the only cell involved in the aging process [38].

Another aspect that has been proved in aging process is the increased plasma levels of IL-6. These levels are low or undetectable in most young people and start to increase in healthy people at about 50 - 60 years of old. Increment of IL-6 plasma levels appears to be unexpectedly present in elderly patients [39].

High levels of IL-6 are found in centenarians even proinflammatory cytokines are similarly increased. These high levels have been referred as the most powerful predictors of morbidity and mortality in elderly [39].

Other researchers noted that cytokine profile associated with COVID-19 resembling to Secondary Haemophagocytic Lymphohistiocytosis (sHLH) an under-recognised hyperinflammatory syndrome characterized by fulminant and fatal hypercytokinaemia with mul-

tiorgan failure. In adults, sHLH is triggered by viral infections. Its features include unremitting fever, cytopenia and hyperferritinaemia. Pulmonary involvement (including ARDS) occurs in approximately 50% of patients [40].

Predictor's fatality according to recent retrospective study of 150 confirmed COVID-19 cases included elevated IL-6 levels, suggesting that mortality caused due to viral hyperinflammation [41]. ACE2 receptors normally decreased throughout life and can easily expose lungs to stress or infections damages [42].

Management of asthma during COVID-19 pandemic

Analyzed data reveal that patients suffering from asthma seem to be at higher risk of COVID-19 infection. However, CIVID-19 infection may worsen disease such as any lung infection worsening the symptoms of asthma. Viral infections can be a strong trigger for exacerbations. Patients must diligently respect all usual precautionary measures (wash hands often, keep a safe distance, limit movement, etc).

According to this is necessary to keep asthma reactions under control reducing disease's exacerbations. This is crucial because it is difficult to distinguish if symptoms such cough, wheezes and other related breathing difficulties caused by asthma or by the virus such as COVID-19 infection and use of systemic steroids must be avoided [43,44].

In fact, has been reported 3 patients with asthma received systemic steroids for a week were subsequently admitted to the ICU with severe respiratory failure requiring invasive mechanical ventilation [45].

Previous studies have shown that systemic steroids can be associated with a higher subsequent viral load caused worse clinical outcomes in previous coronavirus outbreaks (SARS-CoV and MERS-CoV) [46,47].

There are not many case reports or studies but it is advisable to continue the normal treatments underway and contact with clinicians due to check the therapeutic plan or modify it if necessary.

There is only a report with two pediatric patients with a history of allergic rhinitis and atopic dermatitis presented with COVID-19 symptoms both treated with interferon-α inhalation as a nonspecific antiviral therapy. This was trial method recommended in the practice guidance of novel coronavirus pneumonia in China. They get well and admission to ICU was not necessary revealed that allergic diseases and young age may not be aggravating factors of the disease [34,48,49].

The current health crisis may lead some patients to feel sad, confused, frightened or stressed. Anxiety and stress conditions can trigger asthma reactions. In order to manage these emotionally complex is necessary to maintain a healthy lifestyle (proper diet, sleep, exercise, relaxation exercises) feed contacts with family and friends, avoid other triggers such as smoking, alcohol and drugs, stay informed and seek help when is necessary.

Conclusion

Children can be affected by COVID-19 and present with mild and less severe respiratory symptoms. Admission of children to Intensive Care Unit (ICU) is rare and prognosis is almost always favorable except in very few cases.

A more difficult course of disease can be present in infants, as well as in children with pre-existing chronic pathologies. Cardiovascular, endocrine and digestive system diseases are commonly reported co-morbidities (especially hypertension and diabetes) however cases with pre- existing chronic respiratory diseases such as Chronic Obstructive Pulmonary Disease (COPD) and asthma are seems low surprisingly.

Actually, we can say that COVID-19 doesn't have a significant impact on childhood asthma, and there is no indication to radically change treatment strategies for asthmatic children. Furthermore, with regard to asthmatic children it is recommended to continue their therapies without making any dose adjustments. It is better to avoid systemic steroids because it has been shown that may compromise the prognosis of the affected patients.

New data are emerging daily, rapidly updating our understanding of this novel coronavirus and further research is now needed to reveal different aspects of COVID-19.

Declaration of Interest

This article is written without any medical, financial or other external influences.

Bibliography

1. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 (2020).
2. Guo Y., *et al*. "The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak-an update on the status". *Military Medical Research* 13 (2020): 1-11.
3. Eurosurveillance editorial team. Updated rapid risk assessment from ECDC on the outbreak of COVID-19: increased transmission globally". *Eurosurveillance* 25.12 (2020): 2003121.
4. Angel DM., *et al*. "JACI: In Practice Response to COVID-19 Pandemic". *The Journal of Allergy and Clinical Immunology: In Practice* 5 (2020): 1475-1476.
5. Zhang JJ., *et al*. "Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China". *Allergy* 7 (2020): 1730-1741.
6. Center of Disease Control. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases.
7. Zhao Y., *et al*. "Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2". *American Journal of Respiratory and Critical Care Medicine* 202.5 (2020): 756-759.
8. Imai Y., *et al*. "Angiotensin-converting enzyme 2 in acute respiratory distress syndrome". *Cellular and Molecular Life Sciences* 64 (2007): 2006-2012.
9. Hamming I., *et al*. "Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis". *The Journal of Pathology* 203 (2004): 631-637.
10. Huang KJ., *et al*. "An Interferon-g-Related Cytokine Storm in SARS Patients". *Journal of Medical Virology* 75 (2005): 185-194.
11. Berger A. "Science commentary: Th1 and Th2 responses: what are they?" *BMJ* 321 (2000): 424.
12. He L., *et al*. "Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV- infected ACE2 cells in SARS patients: relation to the acute lung injury and pathogenesis of SARS". *The Journal of Pathology* 210 (2006): 288-297.
13. Castillo JR., *et al*. "Asthma exacerbations: pathogenesis, prevention and treatment". *Journal of Allergy and Clinical Immunology: In Practice* 5.4 (2017): 918-927.
14. Masoli M., *et al*. "The global burden of asthma: executive summary of the GINA Dissemination Committee Report". *Allergy* 59 (2004): 469-478.

15. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015". *The Lancet Respiratory Medicine* 5 (2017): 691-706.

16. Selroos O., *et al*. "National and regional asthma programmes in Europe". *The European Respiratory Review* 24 (2015): 474-483.

17. Papadopoulos NG., *et al*. "The role of respiratory viruses in the origin and exacerbations of asthma". *Current Opinion in Allergy and Clinical Immunology* 3 (2003): 39-44.

18. Papadopoulos NG., *et al*. "Viruses and bacteria in acute asthma exacerbations – A GA2LEN-DARE* systematic review". *Allergy* 66 (2011): 458-468.

19. Leino A., *et al*. "Pulmonary function and bronchial reactivity 4 years after the first virus induced wheezing". *Allergy* 74 (2019): 518-526.

20. Zheng XY., *et al*. "Regional, age and respiratory secretion specific prevalence of respiratory viruses associated with asthma exacerbation: a literature review". *Archives of Virology* 163 (2018): 845-853.

21. Brusselle G., *et al*. "Allergen-induced Airway Inflammation and Bronchial Responsiveness in Wild-type and Interleukin-4-deficient Mice". *American Journal of Respiratory Cell and Molecular Biology* 12 (1995): 254-259.

22. Gavett SH., *et al*. "Interleukin 12 Inhibits Antigen-induced Airway Hyperresponsiveness, Inflammation, and Th2 Cytokine Expression in Mice". *Journal of Experimental Medicine* 182 (1995): 1527-1536.

23. Barnes PJ. "Targeting cytokines to treat asthma and chronic obstructive pulmonary disease". *Nature Reviews Immunology* 18 (2018): 454-466.

24. Fahy JV. "Type 2 inflammation in asthma - present in most, absent in many". *Nature Reviews Immunology* 15.1 (2015): 57-65.

25. Pividori M., *et al*. "Shared and distinct genetic risk factors for childhood- onset and adult-onset asthma: genome-wide and transcriptome-wide studies". *The Lancet Respiratory Medicine* 7 (2019): 509-522.

26. Jartti T., *et al*. "Role of viruses in asthma". *Seminars in Immunopathology* 42 (2020): 61-74.

27. Dong Y., *et al*. "Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China". *The Journal of Emergency Medicine* 58.4 (2020): 712-713.

28. Lu X., *et al*. "SARS-CoV-2 Infection in Children". *The New England Journal of Medicine* 382 (2020): 1663-1665.

29. Lupia T., *et al*. "2019 novel coronavirus (2019-nCoV) outbreak: A new challenge". *Journal of Global Antimicrobial Resistance* 21 (2020): 22-27.

30. Huang C., *et al*. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". *Lancet* 15 (2020): 497-506.

31. Ludvigsson JF. "Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults". *Acta Paediatr* 109.6 (2020): 1088-1095.

32. Zheng F., *et al*. "Clinical characteristics of children with coronavirus disease 2019 in Hubei, China". *Current Medical Science* 40 (2020): 275-280.

33. Li X., *et al*. "Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan". *The Journal of Allergy and Clinical Immunology* 146.1 (2020): 110-118.

34. Dong X., *et al*. "Eleven faces of coronavirus disease 2019". *Allergy* 75.7 (2020): 1699-1709.

35. Nicholls JM., *et al*. "Lung pathology of fatal severe acute respiratory syndrome". *Lancet* 361 (2003): 1773-1778.

36. Jorens PG., *et al*. "Interleukin 8 (IL-8) in the bronchoalveolar lavage fluid from patients with the adult respiratory distress syndrome (ARDS) and patients at risk for ARDS". *Cytokine* 4 (1992): 592-597.

37. Van Bever HP., *et al*. "Childhood severe acute respiratory syndrome, coronavirus infections and asthma". *Pediatric Allergy and Immunology* 15 (2004): 206-209.

38. Franceschi C., *et al*. "Inflamm-aging An Evolutionary Perspective on Immunosenescence". *Annals of the New York Academy of Sciences* 908.1 (2000): 244-254.

39. Harris TB., *et al*. "Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly". *The American Journal of Medicine* 106 (1999): 506-512.

40. Mehta P., *et al*. "COVID-19: consider cytokine storm syndromes and immunosuppression". *Lancet* 395 (2020): 1033-1034.

41. Ruan Q., *et al*. "Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China". *Intensive Care Medicine* 46.6 (2020): 1294-1297.

42. Xie X., *et al*. "Age- and gender-related difference of ACE2 expression in rat lung". *Life Sciences* 78.19 (2006): 2166-2171.

43. World Allergy Organization. Allergic patients during COVID-19 pandemic (2020).

44. Niederman MS., *et al*. "Rising to the challenge of the novel SARS-coronavirus-2 (SARS-CoV-2): Advice for pulmonary and critical care and an agenda for research". *American Journal of Respiratory and Critical Care Medicine* 201.9 (2020): 1019-1022.

45. Bhatraju PK., *et al*. "Covid-19 in Critically Ill Patients in the Seattle Region - Case Series". *The New England Journal of Medicine* 382.21 (2020): 2012-2022.

46. Lee N., *et al*. "Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients". *Journal of Clinical Virology* 31 (2004): 304-309.

47. Arabi YM., *et al*. "Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome". *American Journal of Respiratory and Critical Care Medicine* 197 (2018): 757-767.

48. Shaker MS., *et al*. "COVID-19: Pandemic Contingency Planning for the Allergy and Immunology Clinic". *The Journal of Allergy and Clinical Immunology: In Practice* 8.5 (2020): 1477-1488.

49. Bousquet J., *et al*. "Intranasal corticosteroids in allergic rhinitis in COVID-19 infected patients: An ARIA-EAACI statement". *Allergy* (2020).

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