International Journal of Scientific Research and Engineering Development-– Volume 4 Issue 6, Nov-Dec 2021

Available at www.ijsred.com

RESEARCH ARTICLE OPEN ACCESS

# COVID-19 AND SEVERITY IN CHILDREN

Chalida Vijittunukool*

*Satit Prasarnmit International Programme, Khlong Toei Nuea, Watthana, Bangkok 10110

Email: chalidaanny@gmail.com

----------**********----------

## Abstract:

COVID-19 ongoing global pandemic is caused by the recent discovery of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first initiated in Wuhan, China. SARS-CoV-2 is an RNA, enveloped, a zoonotic virus with S-protein making a crown-like shape which is used attached to angiotensin-converting enzyme-2 (ACE-2) receptor as an entry pathway into the host cell. However, the case mortality rate is low in children compared to adults as children often have milder COVID-19 symptoms compared to adults still, neonates and young children have higher severity than older children.

*Keywords* **—Angiotensin-converting enzyme-2 (ACE-2)COVID-19, SARS-CoV-2, COVID-19**

----------**********----------

## I. INTRODUCTION

Youngsters are less susceptible to SARS-CoV-2 infection than adults(1, 2). Children from 10 to 14 years old, on the other hand, are more vulnerable (48% susceptibility compare to 20 years or older). While adolescents have similar susceptibility to adults (1, 2). Nevertheless, some studies suggest that children may have similar infection rates as adults because children have a lower perceived case rate for COVID-19 since children are often asymptomatic or too mildly infected to draw medical attention (3). Another factor can also be that children are less commonly exposed to the main sources of transmission such as animals, outdoor activities and international travels (4, 5). Lastly, adults are the key source of transmission to most children which suggests that the majority of children have been infected by the second or third generation of the virus (6). The latter generation of SARS- and MERS-CoV have been regarded as having diminished pathogenicity causing children to have a milder illness (7). Children often have milder COVID-19 symptoms compared to adults and interestingly, a meta-analysis concludes that almost a quarter of children that have COVID-19 develop gastrointestinal symptoms, for example, diarrhoea, vomit and abdominal pain (8). However, some children experience higher severity of symptoms (9). This revew aims to explore the underlying rationales involved the severity of COVID-19 in children.

## II.DEVELOPMENTAL CHANGES IN IMMUNITY

The antigen-naïve immature immune systems in infants and age-linked correspondtive immunodeficiency/malfunction in the aged influences these individuals toward Acute lower respiratory infections such as Respiratory Syncytial Virus and seasonal influenza (10, 11). Nevertheless, in most cases, children still manage better than the elderly.

The predominant innate immune response to infectious stimuli in infants and the lesser noticeable adaptive immune response (12). An investigation of Latin American children 6-9, 22-26 and 48-60 months, younger children had a stronger innate response to Toll-like receptor (TLR) stimulation, as younger children have higher

  

secretion of TNF-alpha and cytokines (IL -6, IL -8, IL -10.) (13). The rate of naive CD4+ T cells deteriorated with age, whereas memory T cells rose (12-14). Additionally, Children possess greater percentages regarding total lymphocytes and an absolute cells count of B and T cells along with natural killer cells (15). The more severe COVID-19 infection in younger children could be on account of an inadequate adaptive immune system response (16). Furthermore, maternalistic antibodies found in newborns and infants are doubly active toward emerging viruses such as SARS-CoV-2 (16).

The aged are predisposed to a higher rate, as well as the severity of acute lower respiratory infections because of age-linked immune system senescence (15). Infection with the Respiratory Syncytial Virus causes extended viral replication and a delay in the progression of cytokine levels in older cotton rats compared to younger rats (17). In the elderly, various irregularities in immunity have been noted, such as a decrease in dendritic cells and their functions, a decline in TLR induction, upregulated pro-inflammatory cytokines, diminished macrophage, as well as neutrophil function, decreased NK cell activity, reduced proliferation and abundance of γδ-T cells (18, 19).

These variables cause an overly pro-inflammatory response against infections including a prolonged, as well as an absent conversion of innate to adaptive immunity (20, 21). Surviving SARS patients exhibited a gene expression pattern that suggested the emergence of an adaptive immune response, whereas the dead had chronically high levels of proinflammatory cytokines coded by the interferon stimulated genes (22).

Antibodies that are not neutralising can bind to viruses, allowing them to penetrate granulocytic and macrophages cells more efficiently, this is known as antibody dependent enhancement (ADE) (23-26). Viruses coated with antibodies can therefore replicate with higher efficiently, resulting in increased viral loads in children with COVID-19 (27-29). In comparison to adults, children that have COVID-19 had less neutralising antibody levels with lower ADE. Greater amount of Non-neutralising cross-reactive HCoVs antibodies may contribute to older adults' heightened vulnerability to acute COVID-19.The involvement of cross-reactive T cells in SARS-CoV-2 infection, on the other hand, is uncertain (30-32). It was proposed that preexisting T cells with lower avidity, frequently found in more significant amounts in the aged, T-cell responses against SARS-CoV-2 infection may be hampered. The T cell response to the spike protein is less strong in children with COVID-19 (33-35).

## III. DIFFERENCES IN THE ENDOTHELIUM AND CLOTTING FUNCTIONS

SARS-CoV-2 can cause vasculitis by infecting endothelial cells (36, 37). Coagulation pathways are activated in response to endothelial damage, resulting in the formation of microthrombi, as well as angiogenesis, and both of these pathogenic processes are associated with COVID-19-induced thrombotic complications such as heart attacks and strokes (38). This may also explain why patients with endothelium-related diseases, such as diabetes and hypertension, are more likely to develop severe COVID-19 (39).

Children's endothelium is less 'predamaged' than adults', and their coagulation system is also different, making them less prone to abnormal clotting. Notably, the age distribution of severe COVID-19 (and the increased risk in men) is similar to thrombotic diseases such as deep vein thrombosis. While stories of children presenting with a more severe version of Kawasaki disease ('paediatric inflammatory, multisystem syndrome temporally associated with SARS-CoV-2 [PIMS-TS]' in Europe; also known as Multisystem Inflammatory Syndrome in Children [MIS-C] in the USA) may also seem to support the concept that vascular function plays a vital role in the pathogenesis of COVID-19 (40, 41). The reports should be taken with a grain of salt because children have different physiologies from adults and different vulnerabilities to cardiovascular complications than adults. There are some differences between acute COVID-19 and the pathogenesis of PIMS-TS (42). PIMS-TS usually manifests 4–6 weeks after infection (42). As a result,

  

PIMS-TS is associated with a different type of hyper-inflammation than COVID-19, characterised by higher IL-7 and IL-8 and lower levels of effector $CD4^+$ T cells (43). Another intriguing finding is that children and young adults who have chilblain-like skin lesions and are positive for COVID-19 are at an increased risk of developing viral endothelial invasion, vasculitis, or thrombotic vasculopathy (44).

## IV. EFFECTS OF ACE2 EXPRESSION

ACE2 is a renin-angiotensin system counter-regulatory enzyme that converts angiotensin-2 to form Ang-(1-7) (45). The activity of ACE2 maintains equilibrium between angiotensin-2 (fibrosis, inflammation, proliferation and vasoconstriction, ) and Ang(1-7) (anti-fibrosis, anti-apoptotic, anti-proliferation and vasodilation) in a healthy condition (46). Following the pneumocyte invasion, SARS-CoV-2 lower the expression of ACE2, thereby reducing angiotensin-2 conversion. Increased angiotensin-2 elevates permeability and inflammation of pulmonary vascular, exacerbating lung damage (47). Angiotensin-2 in COVID -19 patients concentrations were reported to be elevated compared with healthful adults. Angiotensin-2 concentration also correlates positively along SARS-CoV-2 viral load ,as well as severity of lung damage significantly, most likely due to ACE2 downregulation (48). Elevated angiotensin-2 concentration that was observed in pneumonia caused by a respiratory syncytial viruses (RSV), as well as avian influenza virus (49). ACE2 concentrations decline with age, as well as comorbidities such as diabetes or hypertension, which may explain poorer prognosis and lung damage of patients with SARS-CoV-2 (50). A substantial drop in angiotensin-2 levels, as well as a rise in Ang-(1-7) and surfactant protein-4 levels were reported in the second stage clinical trials with recombinant ACE -2 infusion in individuals with acute respiratory distress syndrome (ARDS). The high activity of ACE2 observed in youngsters may serve as a protecting mechanism against COVID -19 in children resulting in a milder illness in contrast to older individuals because ireased blood levels of ACE2 may act as a virus neutraliser and defend upon lung injury by inactivating angiotensin II circualtion(51). Human ACE2 protects the lungs during influenza infection in mice (52). Additionally, plasma ACE2 concentration are inversely associated with BMI (body mass index),as well as oestrogen concentration, suggesting a link between male sex or obesity and COVID-19 severity. Because ACE2 is also a major receptor for entry of SARS-CoV-2, the notion of ACE2 potential usefulness in COVID-19 lung damage is debatable. Several human cells, including heart, kidney, gut, testis, placenta, lungs, central nervous system, nasopharyngeal epithelial cells, blood vessels and liver contain ACE2 (53). While genetic variants encoding ACE2 have been Associate with an increase in the risk of severe COVID-19 (68), though it remains unknown whether the circulating level of ACE2 correlates with COVID-19 severity. Studies show that ACE2 knockout mice demonstrated more severe lung damage during RSV and avian influenza virus infections, but showed lower viral load, injury scores and inflammatory cell infiltration compared to wild-type rats during SARS-CoV-1 infections (54). There were no differences in ACE -2, ACE and ACE -2 from ACE activity in acute respiratory distress syndrome (ARDS) patients of all ages (2, 55).

It was suggested that children's ACE2 receptors have a reduced affinity for SARS-CoV-2 and are distributed differently across the body, resulting as more challenging for the SARS-CoV-2 virus to enter the host cells. Nonetheless, ACE2 has not been demonstrated to affect COVID-19 symptoms. Additionally, the abundance of ACE2 receptors diminishes in the age range with the highest susceptivity to COVID-19, the elderly.

In contradiction, ACE2 is overexpressed in individuals consuming angiotensin receptor blockers for arterial hypertension or angiotensin-converting enzyme, enhancing their vulnerability to COVID-19 of higher severity. 62 63 However, the intricacy of the ACE2-angiotensin system's regulation, which is important for immune regulation (ARDS), contributes to the debate. ACE2 helps protect against SARS-CoV-2 and influenza correlated lungs damaged in animal

  

studies.64 65. ACE2 down-regulation in expression when SARS-CoV-2 enters the cell via ACE2 receptor, impairing its anti-inflammatory effects, as well as ability to convert angiotensin (1–7) from angiotensin II. In COVID-19, an angiotensin II's overabundance may lead to organ damage.Angiotensin II levels in the blood are considerably higher in individuals with SARS-CoV-2 infection and are positively correlated to viral load, as well as lung injury. 67 This discovery is consistent with the findings that organ damage occurs in Mellitus diabetic individuals have low ACE2 expression, most probably because of glycosylation (56).

SARS-CoV-2 infection of cells is also aided by transmembrane serine protease 2 (TMPRSS2), which cleaves the SARS-CoV-2's spike proteins, in addition to the ACE2 receptor (57, 58). In the lungs' and nasal epithelial cells, TMPRSS2 expression rise by age, similar to ACE2 (56). Two subsequent investigations, however, disputed these conclusions (57, 58).

Base on the existing information, it is hard to determine which impact of ACE2 is more influential for SARS-CoV-2 viral infection, specifically, its protecting role against inflammation mediated lung damage or enhancement of lung damage by facilitating viral invasion. Because young infants are more severely affected by COVID19 than older kids, it's necessary to verify if ACE2 facilitated cell infection is to blame (58). Studies to determine angiotensin 2 levels in the blood and children with COVID-19's lower respiratory tract ACE2 activities are needed (56, 59).

## V. EFFECTS OF LUNG DEVELOPMENT

With increasing age, lungs' regenerative potential moderately decreases (60). Younger mice (2–3 months) and older (16–18 months) mice were used in a study about lungs infection. It has been shown that in older mice, influenza viral infection resulted in worse alveolar damage, delayed regeneration of alveolar type II cells, as well as pro-SPC positive bronchial epithelial cells (59). As a whole, the better regenerative capacity in children could justify the milder and faster recuperation in children with COVID-19 as opposed to adults patients (61). Available data indicate that children may have greater involvement with the upper airway than with the lower airway (62). This may be due to the fact that children have higher resistance in the upper respiratory tract, and so aerosol particles are more prone to deposit in the tracheobronchial trees than in the alveoli (63). It might result in more bronchitis like infections, as well as fewer pneumonia-like illnesses in SARS-CoV-2 infected children. It would be gainful to study if the location of the respiratory's epithelium has a difference in SARS-CoV-2 affinity along with age (64).

## VI. MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C)

MIS-C appears as a comparatively uncommon COVID -19 complication in children, occurring around 1 percent in children infected SARS-CoV-2 (65, 66). MIS-C appears to resemble but differs from incomplete Kawasaki disease (KD) in that most MIS-C cases occurred among healthy teenagers as well as adolescents, particularly Hispanic and black children, as opposed to common KD (67, 68). MIS-C varies from acute COVID19 epidemiology, which usually occurs in youngsters with underlying health complications. The peak of COVID -19 cases in different regions and the increase in MIS-C cases were few weeks apart in most studies (69). For example, in London this 3 - 4 weeks delay is compatible with the acquired immunity timing suggesting that MIS-C is an after complication of SARS-CoV-2 viral infection instead of an acute infection in certain children (70, 71).

## VII. IMMUNE DYSREGULATION

Despite these resemblances to macrophage activation syndrome (MAS), cytokine release syndrome, and Kawasaki disease (KD) (72). MIS-C seems to be immunophenotypically distinct from KD and MAS (73). SARS-CoV-2 causes an aberrant immunological response, although the specific pathways are unclear. Patients with critical MIS-C symptoms have enduring immunoglobulin G (IgG) antibodies of enhanced capacity to stimulate monocytes, enduring cytopenias

  

(especially T-cell lymphopenia), as well as more elevated activation of $CD8^+$ T cells, which differ from acute COVID -19 infection, according to preliminary research (74). The certainty of these findings is limited due to the small number of participants in these studies (75). The majority of children showed positive serology but negative polymerase chain reaction (PCR) to SARS-CoV-2, supporting the notion that MIS-C is linked to immunological dysregulation after the infection has ceased (76, 77). Nonetheless, certain children are tested positive PCR. In the earlier case reports, 783 children received PCR and serology tests, 34 percent had positive on serology and PCR, 60 percent were positive serology but negative PCR, and 5 percent had the two tests negative (78, 79).

## CONCLUSIONS

There are several possible explanations for children's relatively mild illness. Apart from their decreased outdoor activity, children possess several characteristics that make them immune to SARS-CoV-2. The pediatric population possesses a more robust respiratory system and a distinct receptor expression pattern in the lower respiratory tract. Additionally, we believe that a combination of immune system characteristics, which includes a somewhat less robust adaptive immune system alongside an initial vigorous innate immune response, a constitutionally more elevated lymphocyte count, a trained immunity including cross-reactive neutralizing antibodies, an absence of aging deterioration, the immune system-respiratory tract interaction, a different ACE2 expression, different in endothelium and clotting function may protect the pediatric population. While these data suggest that COVID-19 is far less prevalent and less severe in the pediatric population than in the older population, children have been reported to have severe infections this might be due to genetic, underlying conditions, and blood types. Other than this some children develop extreme complications after SARS-CoV-2 infection such as MIS-C in rare cases. It is unclear how frequently MIS-C develops after a mildly or even asymptomatic SARS-CoV-2 infection. However, additional research remains essential to determine other probable reasons for milder SARS-CoV-2 infection in children.

## REFERENCES

1. Delahoy MJ, Ujamaa D, Whitaker M, O'Halloran A, Anglin O, Burns E, et al. Hospitalizations associated with COVID-19 among children and adolescents—COVID-NET, 14 states, March 1, 2020–August 14, 2021. Morbidity and Mortality Weekly Report. 2021;70(36):1255.
2. Kompaniyets L, Agathis NT, Nelson JM, Preston LE, Ko JY, Belay B, et al. Underlying Medical Conditions Associated With Severe COVID-19 Illness Among Children. JAMA Netw Open. 2021;4(6):e2111182.
3. Ludvigsson JF. Systematic review of COVID‐19 in children shows milder cases and a better prognosis than adults. Acta paediatrica. 2020;109(6):1088-95.
4. Dhochak N, Singhal T, Kabra SK, Lodha R. Pathophysiology of COVID-19: why children fare better than adults? Indian journal of pediatrics. 2020:1.
5. Duarte-Salles T, Vizcaya D, Pistillo A, Casajust P, Sena AG, Lai LYH, et al. Thirty-Day Outcomes of Children and Adolescents With COVID-19: An International Experience. Pediatrics. 2021;148(3).
6. Cruz AT, Zeichner SL. COVID-19 in children: initial characterization of the pediatric disease. Pediatrics. 2020;145(6).
7. Sinha IP, Harwood R, Semple MG, Hawcutt DB, Thursfield R, Narayan O, et al. COVID-19 infection in children. The Lancet Respiratory Medicine. 2020;8(5):446-7.
8. Wu H, Zhu H, Yuan C, Yao C, Luo W, Shen X, et al. Clinical and immune features of hospitalized pediatric patients with coronavirus disease 2019 (COVID-19) in Wuhan, China. JAMA network open. 2020;3(6):e2010895-e.
9. Ghosh R, Dubey MJ, Chatterjee S, Dubey S. Impact of COVID-19 on children: special focus on the psychosocial aspect. Minerva Pediatrica. 2020;72(3):226-35.
10. Ludvigsson JF. Children are unlikely to be the main drivers of the COVID‐19 pandemic–a systematic review. Acta Paediatrica. 2020;109(8):1525-30.
11. Tahaghoghi-Hajghorbani S, Zafari P, Masoumi E, Rajabinejad M, Jafari-Shakib R, Hasani B, et al. The role of dysregulated immune responses in COVID-19 pathogenesis. Virus research. 2020:198197.
12. Schwartz DA, Dhaliwal A. Infections in pregnancy with Covid-19 and other respiratory RNA virus diseases are rarely, if ever, transmitted to the fetus: Experiences with coronaviruses, parainfluenza, metapneumovirus respiratory syncytial virus, and influenza. Archives of pathology & laboratory medicine. 2020;144(8):920-8.
13. Opek MW, Yeshayahu Y, Glatman-Freedman A, Kaufman Z, Sorek N, Brosh-Nissimov T. Delayed respiratory syncytial virus epidemic in children after relaxation of COVID-19 physical distancing measures, Ashdod, Israel, 2021. Eurosurveillance. 2021;26(29):2100706.
14. Williams TC, Sinha I, Barr IG, Zambon M. Transmission of paediatric respiratory syncytial virus and influenza in the wake of the COVID-19 pandemic. Eurosurveillance. 2021;26(29):2100186.
15. Kuitunen I, Artama M, Mäkelä L, Backman K, Heiskanen-Kosma T, Renko M. Effect of social distancing due to the COVID-19 pandemic on the incidence of viral respiratory tract infections in children in Finland during early 2020. The Pediatric infectious disease journal. 2020;39(12):e423-e7.
16. Brandão SCS, Ramos JdOX, Dompieri LT, Godoi ETAM, Figueiredo JL, Sarinho ESC, et al. Is Toll-like receptor 4 involved in the severity of COVID-19 pathology in patients with cardiometabolic comorbidities? Cytokine & Growth Factor Reviews. 2021;58:102-10.
17. Ahmadpoor P, Rostaing L. Why the immune system fails to mount an adaptive immune response to a Covid‐19 infection. Transplant International. 2020;33(7):824-5.
18. Gankovskaya LV, Zinina EV, Gankovskii VA, Semushkin AR. Changes in the expression of Toll-like receptors, cytokines and chemokines in the cells of the mucous membrane of the oropharynx in children with COVID-19. Immunologiya. 2021:222-31.

  

19. Esposito S, Zona S, Vergine G, Fantini M, Marchetti F, Stella M, et al. How to manage children if a second wave of COVID-19 occurs. Int J Tuberc Lung Dis. 2020;24:1116-8.
20. Manik M, Singh RK. Role of Toll‐like receptors in modulation of cytokine storm signaling in SARS‐CoV‐2‐induced COVID‐19. Journal of Medical Virology. 2021.
21. Jia R, Wang X, Liu P, Liang X, Ge Y, Tian H, et al. Mild cytokine elevation, moderate CD4+ T cell response and abundant antibody production in children with COVID-19. Virologica Sinica. 2020;35(6):734-43.
22. Ruggiero A, Attinà G, Chiaretti A. Additional hypotheses about why COVID‐19 is milder in children than adults. Acta Paediatrica (Oslo, Norway: 1992). 2020.
23. Cusenza F, Davino G, D'alvano T, Argentiero A, Fainardi V, Pisi G, et al. Silence of the lambs: the immunological and molecular mechanisms of COVID-19 in children in comparison with adults. Microorganisms. 2021;9(2):330.
24. Ricke DO. Two Different Antibody-Dependent Enhancement (ADE) Risks for SARS-CoV-2 Antibodies. Frontiers in immunology. 2021;12:443.
25. Negro F. Is antibody-dependent enhancement playing a role in COVID-19 pathogenesis? Swiss Medical Weekly. 2020;150(1516).
26. Ulrich H, Pillat MM, Tárnok A. Dengue fever, COVID‐19 (SARS‐CoV‐2), and antibody‐dependent enhancement (ADE): a perspective. Cytometry Part A. 2020;97(7):662-7.
27. Alrubayyi A. NK cells in COVID-19: protectors or opponents? Nature Reviews Immunology. 2020;20(9):520-.
28. van Eeden C, Khan L, Osman MS, Cohen Tervaert JW. Natural killer cell dysfunction and its role in COVID-19. International Journal of Molecular Sciences. 2020;21(17):6351.
29. Arvin AM, Fink K, Schmid MA, Cathcart A, Spreafico R, Havenar-Daughton C, et al. A perspective on potential antibody-dependent enhancement of SARS-CoV-2. Nature. 2020;584(7821):353-63.
30. De Biasi S, Meschiari M, Gibellini L, Bellinazzi C, Borella R, Fidanza L, et al. Marked T cell activation, senescence, exhaustion and skewing towards TH17 in patients with COVID-19 pneumonia. Nature communications. 2020;11(1):1-17.
31. de Candia P, Prattichizzo F, Garavelli S, Matarese G. T cells: warriors of SARS-CoV-2 infection. Trends in Immunology. 2020.
32. Fierz W, Walz B. Antibody dependent enhancement due to original antigenic sin and the development of SARS. Frontiers in immunology. 2020;11:1120.
33. Suratannon N, Dik WA, Chatchatee P, van Hagen PM. COVID-19 in children: Heterogeneity within the disease and hypothetical pathogenesis. Asian Pacific journal of allergy and immunology. 2020;38(3):170-7.
34. Anbarasu A, Ramaiah S, Livingstone P. Vaccine repurposing approach for preventing COVID 19: can MMR vaccines reduce morbidity and mortality? Human vaccines & immunotherapeutics. 2020;16(9):2217-8.
35. Peron JPS, Nakaya H. Susceptibility of the elderly to SARS-CoV-2 infection: ACE-2 overexpression, shedding, and antibody-dependent enhancement (ADE). Clinics. 2020;75.
36. Rothan HA, Byrareddy SN. The potential threat of multisystem inflammatory syndrome in children during the COVID‐19 pandemic. Pediatric Allergy and Immunology. 2021;32(1):17-22.
37. Conway EM, Pryzdial ELG. Is the COVID‐19 thrombotic catastrophe complement‐connected? Journal of Thrombosis and Haemostasis. 2020;18(11):2812-22.
38. Mitchell WB. Thromboinflammation in COVID-19 acute lung injury. Paediatric Respiratory Reviews. 2020;35:20-4.
39. Wang J, Zand MS. The potential for antibody-dependent enhancement of SARS-CoV-2 infection: Translational implications for vaccine development. Journal of Clinical and Translational Science. 2021;5(1).
40. Gavriilaki E, Eftychidis I, Papassotiriou I. Update on endothelial dysfunction in COVID-19: severe disease, long COVID-19 and pediatric characteristics. Journal of Laboratory Medicine. 2021.
41. Seitz R, Gürtler L, Schramm W. Thromboinflammation in COVID‐19: Can α2‐macroglobulin help to control the fire? Journal of Thrombosis and Haemostasis. 2021;19(2):351-4.
42. Perico L, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nature Reviews Nephrology. 2021;17(1):46-64.
43. O'Sullivan JM, Mc Gonagle D, Ward SE, Preston RJS, O'Donnell JS. Endothelial cells orchestrate COVID-19 coagulopathy. The Lancet Haematology. 2020;7(8):e553-e5.
44. Patel AB, Verma A. Nasal ACE2 levels and COVID-19 in children. Jama. 2020;323(23):2386-7.
45. Zhang Z, Guo L, Huang L, Zhang C, Luo R, Zeng L, et al. Distinct disease severity between children and older adults with COVID-19: Impacts of ACE2 expression, distribution, and lung progenitor cells. Clin infect dis. 2021.
46. Kolberg ES. ACE2, COVID19 and serum ACE as a possible biomarker to predict severity of disease. Journal of Clinical Virology. 2020;126:104350.
47. Dioguardi M, Cazzolla AP, Arena C, Sovereto D, Caloro GA, Dioguardi A, et al. Innate immunity in children and the role of ACE2 expression in SARS-CoV-2 infection. Pediatric reports. 2021;13(3):363-82.
48. Felsenstein S, Hedrich CM. COVID-19 in children and young people. The Lancet Rheumatology. 2020;2(9):e514-e6.
49. Ciaglia E, Vecchione C, Puca AA. COVID-19 infection and circulating ACE2 levels: protective role in women and children. Frontiers in pediatrics. 2020;8:206.
50. Steinman JB, Lum FM, Ho PP-K, Kaminski N, Steinman L. Reduced development of COVID-19 in children reveals molecular checkpoints gating pathogenesis illuminating potential therapeutics. Proceedings of the National Academy of Sciences. 2020;117(40):24620-6.
51. Hou Y, Zhao J, Martin W, Kallianpur A, Chung MK, Jehi L, et al. New insights into genetic susceptibility of COVID-19: an ACE2 and TMPRSS2 polymorphism analysis. BMC medicine. 2020;18(1):1-8.
52. Wambier CG, Goren A, Vaño‐Galván S, Ramos PM, Ossimetha A, Nau G, et al. Androgen sensitivity gateway to COVID‐19 disease severity. Drug development research. 2020;81(7):771-6.
53. Fu Q, Zheng X, Zhou Y, Tang L, Chen Z, Ni S. Re-recognizing bromhexine hydrochloride: pharmaceutical properties and its possible role in treating pediatric COVID-19. European Journal of Clinical Pharmacology. 2021;77(2):261-3.
54. Tao Y, Yang R, Wen C, Fan J, Ma J, He Q, et al. Preliminary analyses of scRNA sequencing and immunohistochemistry of children's lung tissues indicate the expression of SARS‐CoV‐2 entry‐related genes may not be the key reason for the milder syndromes of COVID‐19 in children. Clinical and translational medicine. 2021;11(5).
55. Chatziparasidis G, Kantar A. COVID-19 in Children with Asthma. Lung. 2021:1-6.
56. Singh T, Heston SM, Langel SN, Blasi M, Hurst JH, Fouda GG, et al. Lessons from COVID-19 in children: key hypotheses to guide preventative and therapeutic strategies. Clinical Infectious Diseases. 2020;71(8):2006-13.
57. Zipeto D, Palmeira JdF, Argañaraz GA, Argañaraz ER. ACE2/ADAM17/TMPRSS2 interplay may be the main risk factor for COVID-19. Frontiers in immunology. 2020;11:2642.
58. Cheng J, Zhou J, Fu S, Fu J, Zhou B, Chen H, et al. Prostate adenocarcinoma and COVID‐19: The possible impacts of TMPRSS2 expressions in susceptibility to SARS‐CoV‐2. Journal of Cellular and Molecular Medicine. 2021;25(8):4157-65.
59. Kloc M, Ghobrial RM, Kuchar E, Lewicki S, Kubiak JZ. Development of child immunity in the context of COVID-19 pandemic. Clinical Immunology. 2020;217:108510.
60. Safadi MAP. The intriguing features of COVID-19 in children and its impact on the pandemic☆. SciELO Brasil; 2020.
61. Wang Y, Zhu F, Wang C, Wu J, Liu J, Chen X, et al. Children hospitalized with severe COVID-19 in Wuhan. The Pediatric infectious disease journal. 2020;39(7):e91-e4.
62. Lingappan K, Karmouty-Quintana H, Davies J, Akkanti B, Harting MT. Understanding the age divide in COVID-19: why are children overwhelmingly spared? American Journal of Physiology-Lung Cellular and Molecular Physiology. 2020;319(1):L39-L44.
63. Blumfield E, Levin TL. COVID-19 in pediatric patients: a case series from the Bronx, NY. Pediatric radiology. 2020;50(10):1369-74.
64. Pagliaro P. Is macrophages heterogeneity important in determining COVID-19 lethality? Medical hypotheses. 2020;143:110073.

  

65. Greene AG, Saleh M, Roseman E, Sinert R. Toxic shock-like syndrome and COVID-19: Multisystem inflammatory syndrome in children (MIS-C). The American journal of emergency medicine. 2020;38(11):2492-e5.
66. Rostad BS, Shah JH, Rostad CA, Jaggi P, Richer EJ, Linam LE, et al. Chest radiograph features of multisystem inflammatory syndrome in children (MIS-C) compared to pediatric COVID-19. Pediatric radiology. 2021;51(2):231-8.
67. Shah K, Upadhyaya M, Kandre Y, Pandya A, Saraf V, Saxena D, et al. Epidemiological, Clinical and Biomarker Profile of Pediatric Patients Infected with COVID-19. QJM. 2021.
68. Yasuhara J, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID‐19 in children: a systematic review. Pediatric pulmonology. 2020;55(10):2565-75.
69. Bowen A, Miller AD, Zambrano LD, Wu MJ, Oster ME, Godfred-Cato S, et al. Demographic and Clinical Factors Associated With Death Among Persons <21 Years Old With Multisystem Inflammatory Syndrome in Children-United States, February 2020-March 2021. Open Forum Infect Dis. 2021;8(8):ofab388.
70. Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. Jama. 2021;325(11):1074-87.
71. Hennon TR, Penque MD, Abdul-Aziz R, Alibrahim OS, McGreevy MB, Prout AJ, et al. COVID-19 associated multisystem inflammatory syndrome in children (MIS-C) guidelines; a Western New York approach. Progress in pediatric cardiology. 2020.
72. Frenkel LD, Gomez F, Bellanti JA, editors. COVID-19 in children: Pathogenesis and current status2021.
73. Osman MS, van Eeden C, Tervaert JWC. Fatal COVID-19 infections: Is NK cell dysfunction a link with autoimmune HLH? Autoimmunity reviews. 2020;19(7):102561.
74. Costagliola G, Spada E, Consolini R. Age‐related differences in the immune response could contribute to determine the spectrum of severity of COVID‐19. Immunity, inflammation and disease. 2021.
75. Dolinger MT, Person H, Smith R, Jarchin L, Pittman N, Dubinsky MC, et al. Pediatric Crohn's disease and multisystem inflammatory syndrome in children (MIS-C) and COVID-19 treated with infliximab. Journal of pediatric gastroenterology and nutrition. 2020.
76. Ebina-Shibuya R, Namkoong H, Shibuya Y, Horita N. Multisystem inflammatory syndrome in children (MIS-C) with COVID-19: insights from simultaneous familial Kawasaki disease cases. International Journal of Infectious Diseases. 2020;97:371-3.
77. Wahlster L, Weichert-Leahey N, Trissal M, Grace RF, Sankaran VG. COVID-19 presenting with autoimmune hemolytic anemia in the setting of underlying immune dysregulation. Pediatric blood & cancer. 2020;67(9):e28382.
78. Larenas-Linnemann D, Luna-Pech J, Navarrete-Rodríguez EM, Rodríguez-Pérez N, Arias-Cruz A, Blandón-Vijil MV, et al. Cutaneous Manifestations Related to COVID-19 Immune Dysregulation in the Pediatric Age Group. Current Allergy and Asthma Reports. 2021;21(2):1-19.
79. Tanner T, Wahezi DM. Hyperinflammation and the utility of immunomodulatory medications in children with COVID-19. Paediatric respiratory reviews. 2020.

  