Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Anales de Pediatría 97 (2022) 129.e1–129.e8

analesdepediatría

www.analesdepediatria.org

SPANISH ASSOCIATION OF PAEDIATRICS

Main changes in the ''COVID-19 in paediatrics'' clinical practice guideline☆

Javier González de Dios[a,*], Victoria Martínez Rubio[b], Álvaro Giménez Díaz de Atauri[c], Carlos Ochoa Sangrador[d], Enrique Rodríguez-Salinas Pérez[e], Sergio Flores Villar[f], Jaime Javier Cuervo Valdés[g], en representación del Grupo de Trabajo de Pediatría Basada en la Evidencia de la AEP y AEPap[1]

[a] *Servicio de Pediatría, Hospital General Universitario de Alicante, Instituto de Investigación Sanitaria y Biomédica de Alicante(ISABIAL), Alicante, Spain*
[b] *Centro de Salud Los Fresnos, Torrejón de Ardoz, Madrid, Spain*
[c] *Servicio de Pediatría, Hospital Universitario 12 de Octubre, Madrid, Spain*
[d] *Servicio de Pediatría, Complejo Asistencial de Zamora, Zamora, Spain*
[e] *Centro de Salud Colmenar Viejo Norte, Colmenar Viejo, Madrid, Spain*
[f] *Servicio de Pediatría. Hospital Universitario Mutua Terrasa, Terrasa, Barcelona, Spain*
[g] *Centro de Salud Ciudad Jardín, Badajoz, Spain*

Received 30 May 2022; accepted 21 June 2022
Available online 7 July 2022

KEYWORDS
COVID-19;
Evidence-based medicine;
Paediatrics;
Epidemiology;

Abstract We present a summary of the main modifications to the ''COVID-19 in Paediatrics'' clinical practice guideline made from its initial version, published in 2021, and the version published in 2022. The document was developed following the structured steps of evidence-based medicine and applying the GRADE system to synthesize the evidence, assess its quality and, when appropriate, issue graded recommendations (based on the quality of the evidence, values and preferences, the balance between benefits, risks and costs, equity and feasibility). This update also includes the modifications proposed by external reviewers.

☆ Please cite this article as: González de Dios J, Martínez Rubio V, Giménez Díaz de Atauri A, Ochoa Sangrador C, Rodríguez-Salinas Pérez E, Flores Villar S, et al. Principales modificaciones en la guía de práctica clínica «COVID-19 en pediatría». An Pediatr (Barc). 2022;97:129.

* Corresponding author.
E-mail address: javier.gonzalezdedios@gmail.com (J. González de Dios).

[1] Los miembros del Grupo de Trabajo de Pediatría Basada en la Evidencia de la AEP y de la AEPap que han participado en este documento se presentan en el Anexo 1.

Signs and symptoms;
Diagnosis;
Treatment;
Prevention;
Vaccines;
Update

We summarised the main modifications in the following sections: epidemiology, clinical features, diagnosis, prevention, treatment and vaccines. In relation to the body of knowledge achieved in the first year of the pandemic, the literature published in the second year contributed additional data, but without substantial modifications in many the areas. The main changes took place in the field of vaccine research. This update was completed in December 2021, coinciding with the emergence of infections by the omicron variant, so the document will need to be updated in the future.

PALABRAS CLAVE
COVID-19;
Medicina basada en la evidencia;
Pediatría;
Epidemiología;
Clínica;
Diagnóstico;
Tratamiento;
Prevención;
Vacunas;
Actualización

Principales modificaciones en la guía de práctica clínica «COVID-19 en pediatría»

Resumen Presentamos el resumen de las principales modificaciones surgidas en la guía de práctica clínica ''COVID-19 en Pediatría'' entre su versión inicial publicada en el año 2021 y la publicada en el año 2022. El documento se ha elaborado siguiendo los pasos estructurados de la Medicina basada en la evidencia e incorporando el sistema GRADE para realizar síntesis de la evidencia, con valoración de su calidad y, cuando se consideró apropiado, emitir recomendaciones jerarquizadas (en función de la calidad de la evidencia, los valores y preferencias, el balance entre beneficios, riesgos y costes, la equidad y la factibilidad). En esta actualización se incluyen también los cambios recomendados por los revisores externos.

Se sintetizan las principales modificaciones en los siguientes apartados: epidemiología, clínica, diagnóstico, prevención, tratamiento y vacunas. En el conjunto del conocimiento alcanzado a lo largo del primer año de pandemia, las publicaciones durante el segundo año añaden nuevos datos, sin que en muchas de las áreas se produzcan modificaciones sustanciales. Los principales cambios acaecen en el campo de investigación de las vacunas. Esta actualización finaliza en diciembre de 2021, coincidiendo con el aumento de la infección por ómicron, por lo que será necesario una futura actualización del documento.

Introduction

''The SARS-CoV-2 pandemic has caused drastic changes in our everyday life, in addition to important health care and socioeconomic repercussions.'' This was the opening of an editorial[1] published in *Evidencias en Pediatría* as an introduction to the document titled ''COVID-19 en Pediatría: valoración crítica de la evidencia'' (COVID-19 in paediatrics: critical assessment of the evidence'') developed as a clinical practice guideline using the GRADE methodology, of which the full version was published in GuíaSalud in March 2021[2] and in *Anales de Pediatría* in June 2021.[3] The guideline was also published in the websites of the Asociación Española de Pediatría (AEP, Spanish Association of Pediatrics) and the Asociación Española de Pediatría de Atención Primaria (AEPap, Spanish Association of Primary Care Paediatrics), both societies that support the Working Group of Evidence-Based Paediatrics, whose members were in charge of its development.

Given the continuous and prolific growth of the scientific evidence on the coronavirus disease 2019 (COVID-19) pandemic, that first document already contemplated periodic updates. There is no question that ample knowledge on this disease has been acquired in record time, and therefore updating the paediatric COVID-19 guideline has required a new and exhaustive search of the literature published after the first guideline of March 2021.

The update to the guideline was published in February 2022, approximately a year after the first version. The literature review included documents published from March to November 2021 and followed the methodology described in the original publications.[2,3] The update also includes the modifications proposed by external reviewers of the guideline, following the recommendations of the GuíaSalud.

Updates on epidemiology

Cumulative incidence

Globally, the cumulative incidence of disease (COVID-19) in individuals of any age is of 3512.16 cases per 100 000 inhabitants, and the global cumulative mortality is 68.29 deaths per 100 00 inhabitants.

In Spain, the cumulative incidence of disease in individuals of any age is 12 066.93 cases per 100 000 inhabitants, and the cumulative mortality of 190.11 deaths per 100 000 inhabitants; the case fatality rate is 1.94% and the infection fatality rate is 1.1% (95% confidence interval [CI], 1.0%–1.2%).[4]

Transmission mechanisms

There seem to be virus-related factors (increased transmissibility, previous immune evasion, lower detection by diagnostic tests, pathogenicity) that may promote infection, as evinced by the different SARS-CoV2 variants that have emerged to present.[5] This is obvious in the new omicron variant, which, due to a change in its capsule proteins, can better bind ACE2 receptors, which, in addition to other potential contributing factors, increases infectivity.[6,7]

The incubation period may change depending on the variant: omicron is exhibiting a shorter incubation period compared to previous variants, of 3 days (interquartile range, 3–4) versus 4.3 for the delta variant and 5 for previous non-delta variants.[8]

Risk factors

There are no changes regarding the risk factors predisposing to COVID-19. The patients at highest risk continue to be the elderly, especially those in residential facilities.

As regards the factors associated with case numbers, obesity increases the probability of a positive SARS-CoV-2 test, as confirmed in a literature review with data from the 50 countries with the highest incidence of COVID-19.[9]

New studies have contributed evidence on the association between the incidence of COVID-19 and socioeconomic status: the incidence of infection was greater in families residing in areas with lower household incomes, lower rates of employment and lower rates of health insurance.[10] Unexpectedly, there had been studies that found that smoking could act as a protector against COVID-19, but more recent studies suggest that this association may result from confounding factors.[11]

Updates on clinical presentation

Signs and symptoms

The case series reviewed for the updated guideline were larger and contributed more information on patients managed at the outpatient level and the general population, with little representation of severely ill patients and a high risk of bias.

As regards the clinical manifestations, fever and respiratory symptoms continue to be most prevalent. The frequency of systemic, gastrointestinal and neurologic symptoms varies based on the care setting, while the frequency of cutaneous and mucosal symptoms decreased and cases of multisystemic inflammatory syndrome in children (MIS-C) were only reported in one series. One of the most relevant trends was the higher percentage of asymptomatic patients.[12,13] The seroprevalence study conducted in Spain between April and June 2020 found a proportion of asymptomatic cases of 45%.[14] This implies that the frequencies of all symptoms have declined.

At the individual level, the most frequent symptoms are fever and cough. Upper respiratory tract symptoms, such as sore throat/pharyngitis and rhinorrhoea, continue to be very frequent, while the frequency of dyspnoea/shortness of breath declined considerably compared to the first edition of the guideline. Laryngitis has been described in association with SARS-CoV-2.[15] There have been no changes in the gastrointestinal symptoms (vomiting, diarrhoea and abdominal pain), but they have been reported in fewer series and with lower frequencies. Systemic symptoms have also remained the same (fatigue, changes in appetite), with fatigue being the most frequent. Of all neurologic symptoms (headache, anosmia or dysgeusia), headache continues to be most prevalent. As regards cutaneous or mucosal involvement, there have been reports of urticaria and angioedema secondary to SARS-CoV-2 infection.

Forms of disease

There have been changes in reported forms of disease, such as a more frequent association of certain presentations with specific age groups: more frequent symptoms in children aged less than 5 years, and more frequent pain in adolescents. As regards the predictive value of clinical features, there is evidence of associations that, with the exception of anosmia and ageusia, are very nonspecific.[16] The best combination to predict COVID-19 continues to be the one described in the first version of the guideline, consisting of headache, nausea/vomiting and anosmia/ageusia (positive likelihood ratio, 65.92; 95% CI, 49.48–91.92). As regards risk factors, age less than 6 months is associated with more severe disease (OR, 2.54; 95% CI, 1.08–5.98), as is the presence of underlying chronic disease, chiefly neurologic disorders (OR, 5.16; 95% CI, 2.30–11.60) and obesity (OR, 2.54; 95% CI, 1.08–5.98). The clinical manifestations associated with a less favourable course of disease were diarrhoea (OR, 3.97; 95% CI, 1.80–8.73), other gastrointestinal manifestations (OR, 2.93; 95% CI, 1.19–7.22) and MIS-C (OR, 2.79; 95% CI, 1.84–4.22). The presence of shortness of breath or respiratory distress was associated with a less favourable course of disease, but with a low precision (OR, 8.69 [95% CI, 1.58–47.70] vs OR, 48.29 [95% CI, 10.88–214.33]).[17]

COVID-19 complications: multisystemic inflammatory syndrome in children (MIS-C) and other

The COVID-19 complication that has been addressed most extensively in the literature is MIS-C. There have been no changes in the manifestations most frequently associated with this syndrome, which continue to be fever and gastrointestinal symptoms. The symptoms that are most useful to differentiate MIS-C from severe COVID-19 are the presence of cardiorespiratory or cutaneous/mucosal manifestations in MIS-C, as opposed to respiratory symptoms in isolation.[18] Cardiac involvement, which is probably the greatest concern, develops in slightly more than one third of patients with MIS-C, mainly in the form of left ventricular dysfunction and coronary abnormalities, although in most cases these abnormalities resolve within a few months after discharge.

As regards other complications, there has been significant variability in the reported frequency of severe disease, defined as need of admission to the intensive care unit (ICU), ranging from 1.6% in China or Turkey to 31% in a sample of adolescents in the United States, which could be

attributed to the substantial heterogeneity of the samples. Excluding studies focused specifically on MIS-C, 11% of the total of children admitted to hospital due to COVID-19 (29 studies, 7582 patients) required admission to the ICU. Poor outcomes have been associated with different factors, with variation between studies: age other than 1–14 years (especially infants aged less than 1 month), male sex, underlying disease, MIS-C, acute respiratory distress syndrome, abdominal pain, kidney injury, elevation of C-reactive protein or D-dimer levels and low white blood cell count. Thromboembolic events occur in slightly more than 1% of hospitalised children and are generally associated with known risk factors for this complication.[19] Severe neurologic complications occur in 2.5%–5% of paediatric patients admitted due to COVID-19, most frequently encephalitis, stroke and Guillain-Barré syndrome.[20]

We ought to highlight the larger body of evidence reviewed in the current update on long-COVID symptoms that persist for months after the acute disease, although most of it is based on telephone interviews and therefore carries a high risk of bias. The most frequently described symptoms are fatigue, exercise intolerance and insomnia, and other reported symptoms include cough, headache, difficulty concentrating, other neuropsychiatric symptoms, gastrointestinal symptoms and bone and muscle pain.[21,22]

Perinatal disease

Infants born to mothers with COVID-19 are at higher risk of admission to the ICU and increased morbidity, although there has not been an increase in neonatal mortality. There is evidence of an association between caesarean delivery and the probability of a positive test in neonates born to mothers with COVID-19, but not of an association with exclusive breastfeeding.[23] There were no new data on the clinical manifestations in newborns with a positive result for SARS-CoV-2.

Updates on diagnosis

Microbiological testing

The real-time reverse transcription polymerase chain reaction (RT-PCR) test continues to be the gold standard for diagnosis of infection by SARS-CoV-2. The preferred type of sample continues to be a sample of respiratory secretions, although saliva specimens have exhibited a similar validity, albeit somewhat inferior, to that of nasopharyngeal swab samples (sensitivity, 83.2% [95% CI, 74.7–91.4]; specificity, 99.2% [95% CI, 98.2–99.8]), leading to a weak recommendation in support of the use of saliva specimens in low-prevalence areas.[24,25]

The use of antigen tests in asymptomatic patients has been found to offer a pooled sensitivity of 58.1% (95% CI, 40.2–74.1) and a pooled specificity of 98.9% (95% CI, 93.6–99.8). In asymptomatic individuals with no known positive contacts, the sensitivity is below 40%, based on evidence of low-to-moderate quality. The authors of the guideline concluded that serial antigen tests may be indicated in asymptomatic patients with known exposure to SARS-CoV-2, but that antigen testing is not recommended in asymptomatic individuals with no known exposure due to the low yield of this diagnostic method.[26]

Serologic testing

No new articles of sufficient methodological quality have been published to warrant modification of the previous guidelines. A recent study[27] analysed the sensitivity and specificity of oral fluid assays for IgG antibody measurement, finding a sensitivity of 80% (95% CI, 71–88) and a specificity of 99% (95% CI, 98–100). This assay could be useful to establish seroprevalence, although little is known about antibody kinetics and how they would affect measurements with this kit.

Blood tests

There has not been any relevant new evidence. Available studies are observational, with small samples and of poor methodological quality, which precludes drawing reliable conclusions on this subject.

Imaging tests

There have not been relevant additions to the evidence. A Cochrane review conducted by Islam et al.[28] concluded that imaging tests offer a good sensitivity: 87.9% for computed tomography, 80.6% for the plain chest radiograph and 86.4% for ultrasound; with a moderate specificity of 80%, 71.5% and 54.6%, respectively, as the imaging features are indistinguishable from those of other viral infections.

Updates on prevention

Masks

The observational studies reviewed in the previous guideline found a significant preventive effect in reducing the risk of transmission of viral infections, including SARS-CoV-2, that is more pronounced with N95 or equivalent masks. However, the reviewed randomised clinical trials (RCTs) did not evince this protective effect. The quality of the evidence, assessed with the GRADE method, was poor. There were no studies specifically focused on the paediatric population, although paediatric-age subjects were included in some community-based studies. The current update of the guidelines has included a retrospective cohort study in health care workers (N = 1440) and a large community-based cluster-randomised trial in Bangladesh (N = 342 126 adults).

The results of the retrospective cohort study (Li A et al.)[29] showed, consistent with previous observational studies, that the use of masks reduced the risk of infection by SARS-CoV-2, in both the case of N95 masks (OR, 0.5; 95% CI, 0.28 to 0.90) and the case of surgical masks (OR, 0.45; 95% CI, 0.29 to 0.72).

The results of the cluster-randomised trial (Abaluck J et al.)[30] show a protective effect of masks, and this is the only clinical trial reviewed to date that has found evidence of this effect. Different strategies were implemented in the intervention group (IG) at the village level to promote the

use of surgical and hygiene masks in public areas. Mask use increased significantly in the IG after the intervention compared to the control group (CG) (42% in IG vs 13% in CG). This increase in mask use was associated with a lower symptomatic SARS-CoV-2 seroprevalence in villages subject to the intervention compared to control villages (adjusted prevalence ratio, 0.907; 95% CI, 0.817–0.997) and the effect was greater in individuals aged more than 60 years (adjusted prevalence ratio, 0.65; 95% CI, 0.46–0.85). Since this was a community-level study, it was not possible to assess the impact of mask use at the individual level.

Breastfeeding and vertical transmission

The risk of vertical SARS-CoV-2 transmission from the infected mother is very low, and recent studies have found substantial variability in sample collection, postpartum mother-infant contact and other factors.[31]

As regards the presence of SARS-CoV-2 in breastmilk or transmission through breastfeeding, new studies have corroborated the findings of the previous literature. The authors concluded that breastfeeding is safe and highlighted the passage of maternal antibodies to the infant.[32,33] In addition, since vaccines became available, there have been studies assessing the presence of vaccine-induced antibodies in human milk.[34]

Schools

The first edition of the guideline considered the efficacy of closing schools to reduce the incidence and severity of the COVID-19 pandemic. The updated version has contemplated whether reopening schools and the return to in-person educational activities had a negative impact on the course of the pandemic.

Recently published studies[35–37] have reported that reopening schools, as long as appropriate hygiene and social distancing measures were upheld, did not seem to have a deleterious impact, although most studies acknowledged that the behaviour of new variants of the virus could change this. At the same time, numerous studies highlighted the negative impact of school closures on different aspects of child and adolescent health.[38,39] This evidence, combined with the uncertainty regarding the positive impact of school closures on incidence and mortality, made the recommendation to keep schools open prevail.

Updates on treatment

Chloroquine and hydroxychloroquine

There has not been new evidence contradicting the lack of efficacy of hydroxychloroquine and chloroquine; the partial results of trials currently underway confirm the unfavourable risk-benefit ratio.

Steroid therapy

The final results with more detailed information of 2 preliminary studies and 2 new systematic reviews have been published since the last edition.[40,41] There are no changes to the previous recommendations as we await data from paediatric studies.

Tocilizumab

A systematic review and meta-analysis published by the World Health Organization in July 2022[42] assessed the efficacy of interleukin-6 antagonists (tocilizumab [TCZ] or sarilumab), conducing that TCZ achieves a minimal reduction in mortality and the risk of mechanical ventilation, although without a clear risk-benefit ratio, so that recommendations in favour or against its use in the paediatric population cannot be established at this point.

Convalescent plasma and hyperimmune immunoglobulin

New studies included in a systematic review[43] confirmed that there is no evidence of the efficacy of convalescent plasma or hyperimmune immunoglobulin.

Other treatments

As regards the efficacy of other treatments, the reviewed evidence continues to be indirect and of very poor quality due to methodological limitations or imprecision. Only casirivimab + imdevimab,[44,45] molnupiravir[46] and calcifediol[47] have shown promising results. These treatments should be assessed in paediatric studies before issuing general recommendations on their use in clinical practice. Intravenous remdesivir has only proven effective in outpatients in reducing the risk of admission. The recommendations against the use of other treatments have not changed.

Management of MIS-C

When it comes to MIS-C, there is evidence of very poor quality, on account of the observational design of the studies and the inconsistent results, on the comparison of intravenous immunoglobulin alone or combined with steroid therapy, so that recommendations cannot be made in favour of one or the other approach.[48–50] The evidence in favour of steroid therapy as monotherapy versus intravenous immunoglobulin is also of very low quality. The recommendations on this aspect have changed, as it is now advised to use intravenous immunoglobulin for management of MIS-C, monitoring treatment and resorting to rescue steroid therapy in case of clinical worsening. In a scenario in which access to immunoglobulin is limited, initial treatment with steroids as monotherapy with use of combined therapy for rescue is a possible alternative.

Updates on vaccination

The available evidence on vaccines is constantly changing, and therefore this is the area in which there has been the most changes in the updated clinical practice guideline.

Manufacturing

The current literature review excluded phase 1 and 2 trials and focused in phase 3 and 4 trials, and included additional vaccines, such as the COVID-19 Janssen© vaccine (Janssen Biologics B.V.) and Nuvaxoivid© (Novavax CZ).

Efficacy and effectiveness

The most salient aspect is the publication of studies on the efficacy of RNA vaccines in children and adolescents. A multinational RCT of the Comirnaty© vaccine (Pfizer-BioNTech) has been published that included followup data through 6 months after the second dose of the vaccine and included participants aged 12 or more years.[51] The trial found a vaccine efficacy against symptomatic COVID-19 of 91.1% (95% CI, 88.8–93.0). On the other hand, a phase 3 in adolescents aged 12–15 years[52] found a vaccine efficacy of 100% (95% CI, 75.3–100) in the prevention of laboratory-confirmed symptomatic COVID-19. The results of phases 1, 2 and 3 of another RCT in children aged 5–11 years have also been published,[53] and the authors reported a vaccine efficacy of 90.7% (95% CI, 67.4–98.3) with no cases of severe COVID-19 or MIS-C.

A phase 2/3 RCT[54] in adolescents aged 12–17 years given 2 doses of the Spikevax© vaccine (Moderna Biotech Spain SL) 28 days apart versus placebo was published in June 2021. The trial found a vaccine efficacy of 93.3% (95% CI, 47.9–99.9) 14 days after the second dose in symptomatic cases and of 39.2% (95% CI, −24.7–69.7) in asymptomatic cases.

Another novelty is the evidence regarding vaccination of pregnant women: comparable efficacy as that observed in the general population with no evidence of adverse events in the foetus or the mother.

Immunogenicity

New evidence has been added regarding the duration of immunity, of which there was hardly any in the first edition.

Adverse events

New evidence has been added, for instance regarding arterial and venous thromboembolism and myocarditis/pericarditis.

Vaccination schedule

Updated vaccination schedules for single-manufacturer vaccine schedules and mixed vaccine schedules.

Summary of the update

In this update, there have been modifications particularly in the field of research on vaccination against SARS-CoV-2. Compared to the body of knowledge accrued in the first year of the pandemic, publications in the second year have contributed additional data that have not resulted in substantial modifications in many areas.

The update was completed in December 2021, as infection by the omicron variant was surging. This variant has brought changes as regards transmission, burden of disease, infectiousness and affected age groups. We need to continue studying and analysing publications regarding infection by SARS-CoV-2 to be ready to effectively manage potential new infections.

We recommend a full perusal of the second version of the guideline ''COVID-19 en Pediatría: valoración crítica de la evidencia'', a 386-page document that contains a relevant summary of the quality of the evidence and recommendations in each of its sections (epidemiology, clinical presentation, diagnosis, treatment, prevention and vaccines).[55]

Appendix 1. Members of the Working Group on Evidence-Based Paediatrics of the AEP and AEPap that contributed to this document

Pilar Aizpurua Galdeano, Centro de Salud Ondarreta, San Sebastian.

María Aparicio Rodrigo, Centro de Salud Entrevías, Madrid.

Jaime Javier Cuervo Valdés, Centro de Salud Ciudad Jardín, Badajoz.

Garazi Fraile Astorga, Centro de Salud Portillo, Valladolid.

María Jesús Esparza Olcina, Madrid.

María Mercedes Fernández Rodríguez, Centro de Salud Potes, Madrid.

Paz González Rodríguez, Centro de Salud Barrio del Pilar, Madrid.

Blanca Juanes de Toledo, Centro de Salud Collado Villalba, Madrid.

Victoria Martínez Rubio, Centro de Salud Los Fresnos, Torrejón de Ardoz, Madrid.

Eduardo Ortega Páez, UGC Maracena, Distrito Metropolitano, Granada.

Leo Perdikidis Olivieri, Centro de Salud Juncal. Torrejón de Ardoz, Madrid.

Enrique Rodríguez-Salinas Pérez, Centro de Salud Colmenar Viejo Norte, Madrid.

Juan Ruíz-Canela Cáceres, Seville.

María Salomé Albi Rodríguez, Hospital Universitario 12 de Octubre, Madrid.

Sergio Flores Villar, Hospital Universitario Mutua de Terrassa, Barcelona.

Álvaro Gimeno Díaz de Atauri, Hospital Universitario 12 de Octubre, Madrid.

Javier González de Dios, Hospital General Universitario Dr. Balmis, Alicante.

Rafael Martin Massot, Hospital Regional Universitario de Málaga, Malaga.

Carlos Ochoa Sangrador, Complejo Asistencial de Zamora. Zamora.

Giordano Pérez Gaxiola, Hospital Pediátrico de Sinaloa Dr. Rigoberto Aguilar Pico, Mexico.

Begoña Pérez-Moneo Agapito, Hospital Universitario Infanta Leonor, Madrid.

María José Rivero Martín, Hospital Universitario de Fuenlabrada, Madrid.

References

1. Ochoa Sangrador C, Pérez-Moneo Agapito B, Fernández Rodríguez MM. COVID-19 en Pediatría: investigación, publicaciones y evidencia. Evid Pediatr. 2021;17:14.
2. Grupo de Trabajo de Pediatría Basada en la Evidencia. COVI-19 en Pediatría: valoración crítica de la evidencia. GuíaSalud, marzo 2021 [en línea] [fecha de consulta: 13 abril 2022] Disponible en: https://portal.guiasalud.es/wp-content/uploads/2021/04/gpc_610_covid_pediatria_compl.pdf.
3. González Rodríguez P, Pérez-Moneo Agapito B, Albi Rodríguez MS, Aizpurua Galdeano P, Aparicio Rodrigo M, en representación del Grupo de Trabajo de Pediatría Basada en la Evidencia de la AEP y AEPap. COVID-19 en Pediatría: valoración crítica de la evidencia. An Ped (Barc). 2021;95:207.e1–13.
4. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard [en línea] 2021 [fecha de consulta 25 febrero 2021]. Disponible en: https://covid19.who.int/table.
5. European Centre for Disease Prevention and Control. Rapid increase of a SARS-CoV-2 variant with multiple spike protein mutations observed in the United Kingdom [en línea]. 2020 [fecha de consulta 21 diciembre 2020]. Disponible en: https://www.ecdc.europa.eu/en/publications-data/threat assessment-brief-rapid-increase-sars-cov-2-variant-united-kingdom.
6. Center for Disease Control and Prevention. National Center for Immunization and Respiratory Diseases (NCIRD) D of VD. Science Brief: Omicron (B.1.1.529) Variant [en línea]. CDC. 2021 [fecha de consulta 18 enero 2022]. Disponible en: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicronvariant.html#print.
7. Brandal LT, MacDonald E, Veneti L, Ravlo T, Lange H, Naseer U, et al. Outbreak caused by the SARS-CoV-2 Omicron variant in Norway, November to December 2021. Euro Surveill. 2021;26(50):pii=2101147, http://dx.doi.org/10.2807/1560-7917.ES.2021.26.50.2101147.
8. United Kingdom Health Security Agency. Risk assessment for SARS-CoV_2 variant: Omicron VOC-21NOV-01 (B.1.1.529).London: UK Health Security Agency. [en línea] [fecha de consulta 8 diciembre 2021]. Disponible en: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1038442/3_December-2021-risk-assessment-for-SARS_Omicron_VOC-21NOV01_B.1.1.529.pdf.
9. Morshed MM, Sarkar SK. Common factors of COVID-19 cases and deaths among the most affected 50 countries. Diabetes Metab Syndr. 2021;15:102247.
10. Allan-Blitz L-T, Goldbeck C, Hertlein F, Turner I, Klausner JD. Association of lower socioeconomic status and SARS-CoV-2 positivity in Los Angeles, California. J Prev Med Public Health. 2021;54:161–5.
11. HO KS, Narasimahan B, Sheehan J, Wu L, Fung JY. Controversy over smoking in COVID-19 – A real world experiencial in New York city. J Med Virol. 2021;93:4537–43.
12. Musa OAH, Chivese T, Bansal D, Abdulmajeed J, Ameen O, Islam N, et al. Prevalence and determinants of symptomatic COVID-19 infection among children and adolescents in Qatar: a cross-sectional analysis of 11 445 individuals. Epidemiol Infect. 2021;149:e193.
13. Almuzaini Y, Alsohime F, Subaie S, Temsah M, Alsofayan Y, Alamri F, et al. Clinical profiles associated with SARS-CoV-2 infection and complications from coronavirus disease-2019 in children from a national registry in Saudi Arabia. Ann Thorac Med. 2021;16:280–6.
14. ISARIC Clinical Characterisation. COVID-19 symptoms at hospital admission vary with age and sex: results from the ISARIC prospective multinational observational study. Infection. 2021;49:889–905.
15. Venn A, Schmidt J, Mullan P. Pediatric croup with COVID-19. Am J Emerg Med. 2021;43:287.e1–3.
16. Duque MP, Lucaccioni H, Costa C, Marques R, Antunes D, Hansen L, et al. COVID-19 symptoms: a case–control study, Portugal, March–April 2020. Epidemiol Infect. 2021;149:e54.
17. Shi Q, Wang Z, Liu J, Wang X, Zhou Q, Li Q, et al. Risk factors for poor prognosis in children and adolescents with COVID-19: a systematic review and meta-analysis. EClinicalMedicine. 2021;41:101155.
18. Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, et al. Characteristics and outcomes of US children and qdolescents with Multisystem Inflammatory Syndrome in Children (MIS-C) compared with severe acute COVID-19. JAMA. 2021;325:1074–87.
19. Aguilera-Alonso D, Murias S, Martínez-de-Azagra Garde A, Soriano-Arandes A, Pareja M, Otheo E, et al. Prevalence of thrombotic complications in children with SARS-CoV-2. Arch Dis Child. 2021;106:1129–32.
20. Ray STJ, Abdel-Mannan O, Sa M, Fuller C, Wood GK, Pysden K, et al. Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: a prospective national cohort study. Lancet Child Adolesc Health. 2021;5:631–41.
21. Osmanov IM, Spiridonova E, Bobkova P, Gamirova A, Shikhaleva A, Andreeva M, et al. Risk factors for post-COVID-19 condition in previously hospitalised children using the ISARIC Global follow-up protocol: a prospective cohort study. Eur Respir J. 2022;59:2101341.
22. Say D, Crawford N, McNab S, Wurzel D, Steer A, Tosif S. Post-acute COVID-19 outcomes in children with mild and asymptomatic disease. Lancet Child Adolesc Heal. 2021;5:e22–3.
23. Villar J, Ariff S, Gunier RB, Thiruvengadam R, Rauch S, Kholin A, et al. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: the INTERCOVID multinational cohort study. JAMA Pediatr. 2021;175:1.
24. Trobajo-Sanmartín C, Adelantado M, Navascués A, Guembe MJ, Rodrigo-Rincón I, Castilla J, et al. Self-collection of saliva specimens as a suitable alternative to nasopharyngeal swabs for the diagnosis of SARS-CoV-2 by RT-qPCR. J Clin Med. 2021;10:1–9.
25. Fougère Y, Schwob JM, Miauton A, Hoegger F, Opota O, Jaton K, et al. Performance of RTPCR on saliva specimens compared with nasopharyngeal swabs for the detection of SARS-CoV-2 in children: a prospective comparative clinical trial. Pediatr Infect Dis J. 2021;40:e300–4.
26. Dinnes J, Deeks JJ, Berhane S, Taylor M, Adriano A, Davenport C, et al. Rapid, point-ofcare antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. Cochrane Database Syst Rev. 2021;3:CD01370517.
27. Hoschler K, Ijaz S, Andrews N, Ho S, Dicks S, Jegatheesan K, et al. SARS Antibody testing in children: development of oral fluid assays for IgG measurements. Microbiol Spectr. 2022;10:e00786–21.
28. Islam N, Salameh J-P, Leeflang MM, Hooft L, McGrath TA, van der Pol CB, et al. Thoracic imaging tests for the diagnosis of COVID-19. Cochrane Database Syst Rev. 2020;11:CD013639.
29. Li A, Slezak J, Maldonado AM, Concepcion J, Maier CV, Rieg G. SARS-CoV-2 positivity and mask utilization among health care workers. JAMA Netw Open. 2021;4(6):e2114325.
30. Abaluck J, Kwong LH, Styczynki A, Haque A, Kabir MA, Bates-Jefferys E, et al. Impact of community masking on COVID-19: a cluster-randomized trial in Bangladesh. Science. 2022;375(6577):eabi9069.
31. Musa SS, Bello UM, Zhao S, Abdullahi ZU, Lawan MA, He D. Vertical transmission of SARS-CoV-2: a systematic review of systematic reviews. Viruses. 2021;13:1–20.

32. Shlomai NO, Kasirer Y, Strauss T, Smolkin T, Marom R, Shinwell ES, et al. Neonatal SARS-CoV-2 infections in breastfeeding mothers. Pediatrics. 2021;147:e2020010918.
33. Bäuerl C, Randazzo W, Sánchez G, Selma-Royo M, García Verdevio E, Martínez L, et al. SARS-CoV-2 RNA and antibody detection in breast milk from a prospective multicentre study in Spain. Arch Dis Child Fetal Neonatal Ed. 2022;107:216–21.
34. Romero Ramírez DS, Lara Pérez MM, Carretero Pérez M, Suárez Hernández MI, Martín Pulido S, Pera Villacampa L, et al. SARS-CoV-2 antibodies in breast milk after vaccination. Pediatrics. 2021;148:e2021052286.
35. Villani A, Coltella L, Ranno S, Bianchi di Castelbianco F, Murru PM, Sonnino R, et al. School in Italy: a safe place for children and adolescents. Ital J Pediatr. 2021;47:23.
36. Viner R, Waddington C, Mytton O, Booy R, Ladhani S, Panovska-Griffiths J, et al. Transmission of SARS-CoV-2 by children and young people in households and schools: a meta-analysis of population-based and contact-tracing studies. J Infect. 2022;84:361–82.
37. Walsh S, Chowdhury A, Braithwaite V, Russell S, Birch JM, Ward JL, et al. Do school closures and school reopenings affect community transmission of COVID-19? A systematic review of observational studies. medRxiv. 2021;11:e053371.
38. Loades ME, Chatburn E, Higson-Sweeney N, Reynolds S, Shafran R, Brigden A, et al. Rapid systematic review: the impact of social isolation and loneliness on the mental health of children and adolescents in the context of COVID-19. J Am Acad Child Adolesc Psychiatry. 2020;59:1218–39, e3.
39. Ten Velde G, Lubrecht J, Arayess L, Van Loo C, Hesselink M, Reijnders D, et al. Physical activity behaviour and screen time in Dutch children during the COVID-19 pandemic: Pre-, during-and post-school closures. Pediatr Obes. 2021;16:e12779.
40. Cordeiro LP, Linhares EONN, Nogueira FGO, Moreira-Silva D, Medeiros-Lima DJM. Perspectives on glucocorticoid treatment for COVID-19: a systematic review. Pharmacol Rep PR. 2021;73:728–35.
41. Pulakurthi YS, Pederson JM, Saravu K, Gupta N, Balasubramanian P, Kamrowski S, et al. Corticosteroid therapy for COVID-19: a systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2021;100(20):e2571918.
42. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Shankar-Hari M, Vale CL, Godolphin PJ, Fisher D, Higgins JPT, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID19: a meta-analysis. JAMA. 2021;326:499–518.
43. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19. JAMA. 2020;324:1–11.
44. RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2022;399:665–76.
45. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV antibody combination and outcomes in outpatients with Covid-19. N Engl J Med. 2021;385:e81.
46. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med. 2022;386:509–20.
47. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, López Miranda J, Bouillon R, et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study. J Steroid Biochem Mol Biol. 2020;203:105751.
48. Kaushik A, Gupta S, Sood M, Sharma S, Verma S. A systematic review of multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection. Pediatr Infect Dis J. 2020;39:e340–6.
49. Son MBF, Murray N, Friedman K, Young CC, Newhams MM, Feldstein LR, et al. Multisystem inflammatory syndrome in children - Initial therapy and outcomes. N Engl J Med. 2021;385:23–34.
50. McArdle AJ, Vito O, Patel H, Seaby EG, Shah P, Wilson C, et al. Treatment of multisystem inflammatory syndrome in children. N Engl J Med. 2021;385:11–22.
51. Thomas SJ, Moreira ED, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. N Engl J Med. 2021;385:1761–73.
52. Frenck RW, Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, et al. Safety, mmunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. N Engl J Med. 2021;385:239–50.
53. Walter EB, Talaat KR, Sabharwal C, Gurtman A, Lockhart S, Paulsen GC, et al. Evaluation of the BNT162b2 Covid-19 vaccine in children 5 to 11 years of age. N Engl J Med. 2022;386:35–46.
54. Ali K, Berman G, Zhou H, Deng W, Faughnan V, Coronado-Voges M, et al. Evaluation of mRNA-1273 SARS-CoV-2 vaccine in adolescents. N Engl J Med. 2021;385:2241–51.
55. COVID-19 en Pediatría. Valoración crítica de la evidencia. Febrero 2022. Disponible en AEPED https://www.aeped.es/comite-pediatria-basada-en-evidencia/documentos/covid-19-en-pediatria-valoracion-critica-evidencia y en AEPap https://www.aepap.org/grupos/grupo-de-pediatria-basada-en-la-evidencia/biblioteca/covid-19-en-pediatria-valoracion-critica-de-la-evidencia.