Gaceta Médica Boliviana
ISSN: 1012-2966
ISSN: 2227-3662
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Universidad Mayor de San Simón
Bolivia

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Gaceta Médica Boliviana, vol. 43, no. 1, 2020
Universidad Mayor de San Simón, Bolivia
Available in: https://www.redalyc.org/articulo.oa?id=445674690024
DOI: https://doi.org/10.47993/gmb.v43i1.20

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Artículos de Revisión

COVID-19, a look from pediatrics

Covid-19, una mirada desde la pediatría

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Gaceta Médica Boliviana, vol. 43, no. 1, 2020

Universidad Mayor de San Simón, Bolivia

Received: 16 April 2020
Accepted: 16 May 2020

DOI: https://doi.org/10.47993/gmb.v43i1.20

Redalyc: https://www.redalyc.org/articulo.oa?id=445674690024

Abstract: COVID-19 was predominantly more prevalent among adults over 15 years of age in the early stages of the outbreak and the proportion of confirmed cases among children was relatively lower. However, due to the increasing global spread of SARS-CoV-2, we have new challenges for the prevention and control of the COVID-19 epidemic among children. Since prevention measures (face masks) cannot be used in the youngest children, the non-specific clinical presentation, difficulties in diagnosis, poor patient-physician and family communication have contributed to the challenge of developing measures to protect this population, as well as health care personnel managing paediatric cases. At the same time, children with comorbidities are vulnerable to SARS-CoV-2 infection. The present review attempts to show this disease from a paediatric point of view, to provide guidance on diagnosis and management.

Keywords: coronavirus, Covid-19, pediatrics, pandemic, SARS-CoV-2.

Resumen: El COVID-19 fue predominantemente más prevalente entre adultos mayores de 15 años en las primeras etapas del brote y la proporción de casos confirmados entre niños fue relativamente menor. Sin embargo, debido a la creciente propagación mundial del SARS-CoV-2, tenemos nuevos desafíos para la prevención y el control de la epidemia de COVID-19 entre los niños. Ya que en los más pequeños no se pueden emplear medidas de prevención (barbijos), la clínica inespecífica que presentan, las dificultades para el diagnóstico, la deficiente comunicación entre médico-paciente y familiar que han contribuido al desafío de desarrollar medidas para proteger a esta población, al igual que al personal de salud que manejan casos pediátricos. Al mismo tiempo, los niños con comorbilidades, s on vulnerables a la infección por SARS-CoV-2. La presente revisión intenta mostrar esta enfermedad desde el punto de vista pediátrico, para orientar en su diagnóstico y manejo.

Palabras clave: coronavirus, Covid-19, pediatría, pandemia, SARS-CoV-2.

Coronaviruses are a large family of RNA viruses (39 species) affecting mammals and birds and capable of causing illness in humans ranging from the common cold (10%) to severe disease. To date, 6 viruses have been recognised as causative agents of a range of respiratory tract infections, including HCoV229E, HCoV-OC43, HCoV-NL63, HCoV-HKU [1], SARS-CoV (severe acute respiratory syndrome) and MERS-CoV (Middle East Respiratory Syndrome). SARS-CoV was described in 2003 in a single epidemic in China, which caused more than 700 deaths with 20-30% requiring mechanical ventilation and with a case fatality of 10%, especially high in patients with comorbidities. MERS-CoV was first detected in 2012 causing a similar clinical situation, but with a higher case fatality (36%). This infection is not extinct and sporadic cases persist. Both are zoonoses transmitted to humans, the former via bats and the latter via dromedaries.

In December 2019, a new type of coronavirus infection appeared in Wuhan (Hubei province), China, and has spread rapidly. To date, the disease epidemic caused by this virus has spread to all parts of China and in approximately 197 countries. On 10 January 2020, the genome of the virus isolated from a patient?s lower respiratory tract was sequenced and confirmed to be a new type of coronavirus. Two days later, the World Health Organization (WHO) named this pathogen ? new coronavirus 2019 (2019-nCoV)?. On 20 January 2020, the National Health Commission of the People?s Republic of China (PRC) formally incorporated the disease caused by the virus, known as COVID-19. It adopted measures for the prevention and control of Class A infectious diseases. On 7 February 2020, the National Health Commission of the PRC named the latest type of coronavirus-infected pneumonia as ? New coronavirus pneumonia?. On 11 February 2020, the Coronavirus Study Group of the International Virus Classification Commission named the new coronavirus as ?Severe Acute Respiratory Syndrome due to coronavirus 2 (SARS-CoV-2)?. On the same day, WHO named the disease caused by the new coronavirus as coronavirus disease-2019 (COVID-19). After assessment, on 12 March 2020, WHO announced that COVID-19 had reached pandemic status.

Current research has determined that SARSCoV-2 belongs to a new type of coronavirus family, namely the genus ?. Its genetic characteristics are clearly different from those of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). SARS-CoV-2 is more than 85% similar to bat CoV (batSL-CoVZC45).

The Wuhan Institute of Virology also obtained evidence that SARS-CoV-2 originated in bats and confirmed that SARS-CoV-2, similar to SARS-CoV, enters cells by binding to angiotensin-converting enzyme 2 (ACE-2) [2] . Subsequently, the South China Agricultural University (Guangdong, China) targeted pangolins as a possible intermediate host for SARS-CoV-2. A study by Matthew et al. reported that SARS-CoV-2 and recombinant Malaysian pangolin coronavirus share 98% of their amino acids and 89% of their nucleotides. Zhou et al. used cryo-electron microscopy to analyse the full-length structure of the SARS-CoV-2 receptor, i.e. ACE-2, for the first time, which will be useful in the development of inhibitors to block viral entry into cells.

On 21 February 2020, Jorerg et al. proposed that active SARSCoV-2 can produce transformations depending on the viral genetic structure, in order to understand and predict virus development and disease trends. On 3 March 2020, Tang et al. described the genome evolution of 103 new coronaviruses and found that SARS-CoV-2 has evolved into two subtypes, L and S, and the virus strain now has 149 more mutation points than in the early stages of the Wuhan outbreak, which is why it is speculated to be more infectious and capable of spreading.

Literature review

Covid-19 in the paediatric age

The retrospective study by DONG et al. is probably the first study to show the epidemiological characteristics and transmission dynamics of childhood COVID-19.

It shows that most of these children are exposed to family members and other children with COVID-19, clearly indicating easy person-to-person transmission. Evidence supporting such a transmission pathway has been corroborated in adult patients. As of 8 February 2020, of the 2,143 paediatric patients included in this study, only one child died and most cases were mild, with far fewer severe and critical cases (5.9%) than in adult patients (18.5%) [14].

The reason why most cases of COVID-19 in children are less severe than in adults is puzzling. This may be related to both exposure and host factors.

Children are generally at home and may have relatively fewer opportunities for exposure to the pathogen and/or sick patients. On the other hand, in relation to the angiotensin-converting enzyme 2 (ACE2) cellular receptor for SARS CoV-2, it is speculated that children are less sensitive to SARS CoV-2 because of maturity and function, e.g. the binding capacity of ACE2 in children may be lower than in adults.

Another alternative is that children often experience respiratory infections (e.g., RSV) in winter and may have higher levels of antibodies to viruses than adults. In addition, children?s immune systems are still developing and may respond to pathogens differently than adults. However, the results of the study by Down Yo et al. found a higher proportion of severe cases at younger ages: 10.6% in children under 1 year; 7.3% from 1 to 5 years; 4.2% from 6 to 10 years; 4.1% from 11 to 15 years and 3.0% by 15 years. Suggesting that young children, especially infants, are more vulnerable to SARS CoV-2 infection.

The mechanisms for the difference in clinical manifestations between children and adults are still unclear. The same study showed that the temporal distribution of COVID-19 cases in children in the early stage of the epidemic, between December 2019 and early February 2020, there was a trend of rapidly increasing cases in paediatric age, but since early February 2020, the number of COVID-19 cases in children has decreased. This could indicate that the disease control measures implemented such as social isolation and quarantine have been effective.

Something that should be stressed is that this same study showed that the child, being asymptomatic or having non-specific signs or symptoms, is an entity that facilitates person-to-person transmission, in addition to the fact that prevention measures such as the use of masks cannot be applied, especially in children under 1 year of age, adding to the fact that children can eliminate the virus via the faecal route up to 2 weeks after having tested negative for the presence of the virus in the respiratory tract, which makes the child, especially the infant, a spreader of the disease.

On 2 February 2020, the People?s Republic of China39 issued an advisory on ?doing a good job in preventing and controlling outbreaks of pneumonia in children and pregnant women with new coronavirus infection?, which clearly states that children are susceptible to SARSCoV-2. However, severe COVID-19 in children is rare. To date, the largest review of children with COVID-19 by Dong et al, which included 2,143 children in China, only 112 children (5.6%) had severe disease (defined as hypoxia) and 13 children (0.6%) developed respiratory failure, multi-organ failure or ARDS.

The latest research corroborates that children are not only susceptible to SARS-CoV-2, but are also important sources of spread. On the other hand, non-specific clinical features, difficulties in diagnosis, poor patient-physician and family communication have contributed to the serious challenge of protecting, diagnosing and treating this population, as well as health care workers managing paediatric cases.

The increasing global spread of SARS-CoV-2 poses new challenges for the prevention and control of COVID-19 among children. Considering also that children with comorbidities, such as congenital heart, lung and respiratory tract diseases and malnutrition among others, are vulnerable to SARS-CoV-2 complications; more specifically, they are ?prone to severe disease ?14.

Epidemiological and clinical features in paediatrics

Based on Dong et al. on 2,135 children, paediatric cases are defined as:

Suspected cases

High-risk child with two of the following conditions:

- Fever or respiratory symptoms or digestive symptoms (e.g. vomiting, nausea and diarrhoea) or fatigue.
- Laboratory test: normal or decreased white blood cell count or low lymphocytes or increased C-reactive protein level.
- Abnormal chest X-ray images.

For a child at medium or low risk, similar diagnostic criteria were applied after excluding influenza and other common respiratory infections.

Suspected cases that met any of the following criteria were defined as:

Confirmed cases

If any of the following criteria are met:

- Real-time polymerase chain reaction (RT-PCR) positive for SARS CoV-2 in nasal and/or throat swabs or blood samples.
- Genetic sequencing of respiratory tract or blood samples highly homologous with SARS CoV-2.

Severity of COVID-19

Based on the recommendations of Calvo et al. (Table 1) of the Spanish Association of Paediatrics, severity is defined in clinical syndromes integrating the official WHO criteria for standardised management. We mention however that the diagnostic criteria for severity proposed by Dong et al. include a first phase of asymptomatic infection without any

symptoms or clinical signs, normal chest X-ray, with positive PCR for SARS CoV 2.

Management of COVID-19 in pediatrics

Home care and general measures

The following are recommendations based on the basic and general guidelines that the WHO has issued regarding the management of suspected cases, mildly infected SARS CoV-2 positive patients and contacts:

1. Place the patient in a single, well-ventilated room who should always be kept with mouth covers.
2. Limit the number of caregivers; ideally, assign a caregiver who is in good health and free of risk diseases. Do not allow visitors.
3. The other inhabitants of the household should be placed in a separate room; if this is not possible (infants), they should maintain a minimum distance of one metre from the sick person (e.g. sleep in separate beds).
4. Limit patient movement and minimise shared spaces (e.g. kitchen, bathroom), ensuring in any case that they are well ventilated (e.g. by leaving windows open).
5. The caregiver should wear a tight-fitting medical mask when in the same room as the patient. The mask should not be touched or handled while it is worn. If it becomes wet or soiled with secretions, it should be changed immediately. Discard the mask after use and wash hands thoroughly after removal.
6. Apply hand hygiene measures after any contact with the sick person or their immediate environment, as well as before and after preparing food, before eating, after using the toilet and whenever soiling of the hands is evident. If there is no visible dirt on the hands, alcohol-based lotions can also be used. When visible soiling is present, hands should be washed with soap and water. Before recommending alcohol-based lotions for household use, the potential risks (e.g. accidental ingestion, fire, etc.) should be considered
7. For drying hands after washing with soap and water, it is preferable to use disposable paper towels. If these are not available, a cloth towel should be used exclusively for this purpose and changed when wet.
8. Respiratory hygiene measures should be followed by all persons at all times, especially those who are ill. Respiratory hygiene means covering the mouth and nose when coughing or sneezing, using medical or cloth masks, tissues or the elbow, and washing hands afterwards.
9. Discard materials used to cover mouth and nose or wash them properly (e.g. wash tissues with soap and water or detergent).
10. Avoid direct contact with body fluids, especially oral and respiratory secretions, and faeces. Use disposable gloves when in contact with mouth and nose and when handling faeces,

urine and waste. Apply hand hygiene before and after removing gloves.

11. Gloves, handkerchiefs, masks and all waste generated by the sick person or care of the sick person should be placed in a bagged container in the sick person?s room until it is disposed of with the general household waste.
12. Avoid other forms of exposure to sick people or contaminated objects in your immediate environment (e.g. do not share toothbrushes, cigarettes, cutlery, plates, drinks, towels, sponges, sheets, etc.). Dishes and cutlery should be washed with soap and water or detergent after each use, but do not throw them away.
13. Clean and disinfect surfaces that have been in contact with the patient, such as the bedside table, bed frame and other furniture in the room, with chlorine household disinfectant (1% chlorine bleach and 99% water) on a daily basis.
14. Clean and disinfect bathroom and toilet surfaces at least once a day with a household disinfectant composed of a diluted bleach solution (1% bleach and 99% water).
15. Wash clothes, sheets, towels, etc. of sick persons with liquid soap and water, or machine wash at 60°-90°C with ordinary detergent, and allow to dry thoroughly. Contaminated linen should be placed in a bag until laundering. Do not shake soiled clothing and avoid direct contact of skin and clothing with contaminated materials.
16. Wear disposable gloves and protective clothing (e.g. plastic aprons) when cleaning and handling surfaces, clothing or linen soiled with body fluids. Apply hand hygiene before and after removing gloves.
17. Persons with symptoms should remain at home until the clinical picture resolves or laboratory tests normalise (two negative RT-PCRs within at least 24 hours of each other).

Uncomplicated infection [1].

1. Observe general protective measures (WHO). Fit the patient (if possible) and family members with surgical masks. Ideally maintain 2 m (minimum 1 m separation) from other patients or other family members at all times.
2. be placed in the waiting rooms of health care facilities, including information adapted to paediatric patients to warn and provide both children old enough to cooperate and their caregivers with the necessary instructions on hand washing and respiratory hygiene (including elbow protection when coughing or sneezing).

   It is recommended that visual information (posters, leaflets etc.) be placed in the waiting rooms of health care facilities, including information adapted to paediatric patients to warn and provide both children old enough to cooperate and their

caregivers with the necessary instructions on hand washing and respiratory hygiene (including elbow protection when coughing or sneezing).

Children, especially younger children, have certain characteristics that make it difficult to control infections and that can facilitate contagion:

- They do not control secretions and excretions: drooling, lack of sphincter control.
- Inability to adopt personal hygiene measures.
- Difficulty keeping the mask over the nose and mouth.
- Children under one year of age should not wear it.
- Difficulty in controlling their movements and remaining still in a certain place, which makes it impossible to control contacts properly.
- Children tend to share toys and objects and interact with each other.
- The age and idiosyncrasies of pediatric patients make the figure of the caregiver essential. Hygiene measures and isolation of the patient involve all those responsible for the patient?s care.
- The possible higher frequency of asymptomatic infections and gastrointestinal manifestations in children.
- Possible transmission before the onset of symptoms

3. In pediatric waiting rooms, there should be no materials such as toys, books or other utensils that can be shared by children and where it cannot be ensured that the recommended standards of cleanliness and hygiene of materials are met.
4. Children under one year of age, who are unable to wear a mask, should be kept in cars, car seats or baby restraints and away from other patients.
5. In patients over one year of age who cannot tolerate the use of a mask, they should be kept at least two metres away from the rest of the patients.
6. It would be a measure to consider, if reasonable restraint is impossible and in certain particularly susceptible clinical scenarios or settings, that medically stable patients may choose to wait in a personal vehicle or outside the health care facility, where they can be contacted by mobile phone when it is their turn to be assessed.
7. In general, any patient who comes to the clinic with symptoms of COVID-19 infection will be offered a surgical mask. In children under 1 year of age who cannot wear a mask, they shall be kept in the infant restraint systems or, failing that, in the arms of their caregivers, who shall put on the mask. In children over one year of age, if it is not possible to place the mask, they should be next to their caregivers, who will ensure that they do not interact with other patients within two metres

8. Children must always be accompanied by an adult, parents, relatives or caregivers responsible for the minor and will be offered a hydro-alcoholic hand hygiene gel solution, both to the accompanying person and the child, explaining that it must not be ingested or come into contact with the eyes. The accompanying person must wear a mask.
9. Healthcare personnel shall be notified and the patient shall be escorted to the designated area until attended to in order to avoid contact with other persons. If the designated area is a room, the door shall be closed and only staff essential for the care and attention of the patient shall have access.
10. Once there, the healthcare staff will complete the anamnesis to verify that the patient meets the COVID-19 criteria.
11. Personnel attending the patient should follow the recommended preventive measures (contact and respiratory), using personal protective equipment (PPE) FPP2 FPP3 mask, gloves, impermeable gown and protective goggles, for the exploration and taking of the clinical history or sampling procedures.
12. Administration of usual antipyretics when necessary (paracetamol).
13. If the patient presents fever, a chest X-ray (CXR) and blood tests to rule out bacterial superinfection are recommended: blood count, blood culture, C-reactive protein (CRP), procalcitonin (PCT), transaminases, ions and coagulation.
14. Depending on the epidemiological situation and family conditions, admission or home monitoring will be decided, with clear instructions on what to do in the event of worsening.

Mild lower respiratory tract infection

- General measures as above.
- Isolated admission and monitoring of all patients is recommended.
- Non-invasive monitoring of constants including SatO? with oximetry for adequate supply while maintaining saturation >94% as far as possible.
- Chest X-ray, blood tests (haemogram, PCR, PCT, blood culture, biochemistry with transaminases, ions, coagulation and blood gases) and peripheral line cannulation.
- Bronchodilators may be used when the examination suggests it (wheezing), preferably with a spacer chamber and MDI device.
- Usual analgesics (paracetamol or ibuprofen).

Consideration should be given to the possibility of the child?s father or mother being admitted with the patient. It is recommended that only one person, always the same person, who should comply at all times with the isolation measures (mask, gown, gloves and goggles). It may also be

the case that the parents and the child are infected and could be admitted together.

Severe lower respiratory tract infection.

Consider the possible clinical, analytical and radiological evolution of COVID 19 in children from a mild to a severe form:

1. Conservative fluid management, as aggressive management may worsen oxygenation (usual serum therapy at 2/3 of baseline requirements). Hypotonic fluids are not recommended (no starches or jellies in case of resuscitation).
2. Oxygen therapy to maintain SatO2>92%.
3. If there is suspicion of bacterial superinfection (leukocytosis and elevated CRP or PCT), start antibiotic therapy with amoxicillin-clavulanic acid.
4. Avoid or limit aerosol-generating measures.

Admission criteria.

- Signs of mild to moderate respiratory distress requiring treatment with oxygen therapy.Signs of mild to moderate respiratory distress requiring treatment with oxygen therapy.
- Child under one year of age with fever, respiratory symptoms, gastrointestinal symptoms and general condition, or social risk, who was in contact with a suspected or probable case.
- Older than 1 year: Chest pain, dehydration, not feeding, sensory disturbances, patient in risk group, vulnerable cohabitants.

Pharmacological treatment

Glucocorticoids.

The use of glucocorticoids in cases of COVID-19 pneumonia is not recommended by the WHO or CDC [15, 16]. The use of glucocorticoids has to be well justified, especially in patients with exacerbated underlying diseases such as asthma or other chronic pulmonary pathologies that require it. The available data from studies of other viruses are contradictory. Despite this, some scientific societies have defined situations in which corticosteroid treatment can be used to alleviate the uncontrolled inflammatory response caused by the virus, although there is no unanimity in their proposals [17]. Previous studies in patients with MRSA, MERS and even influenza have shown no beneficial effect and even delayed clearance of the virus. Their use may be considered in cases of ARDS, septic shock, encephalitis, hemophagocytic syndrome and when there is frank bronchospasm with wheezing.

Nonsteroidal anti-inflammatory drugs.

The use of NSAIDs in early disease has been the subject of much controversy. Some authors have shown an association between ibuprofen use and a marked increase in disease severity in young patients. However, these studies are only observational and do not cover large population groups, so it is difficult to draw conclusions. WHO recommends continued use of NSAIDs if required, especially for patients with chronic use of NSAIDs for other pathologies. Given the uncertainty, we propose

the use of paracetamol as a first-line antipyretic or analgesic drug in paediatrics.

Antibiotics

The use of antibiotics is important in those patients arriving at the emergency department or hospitalised without a well-defined aetiological diagnosis.

Recall that up to 45% of paediatric patients with COVID-19 usually present with mild to very severe pneumonia [11].

Most of these patients will not have an accurate diagnosis until a few hours or days after hospitalisation or outpatient management, so it is essential to protocolise the use of antibiotics in paediatrics. On the other hand, it is not yet clear whether COVID-19 infection can lead to bacterial infection as with influenza or other respiratory viruses.

Azithromycin: is a good option as initial treatment while the diagnosis is being ruled out. Azithromycin has good action against germs causing community-acquired pneumonia such as pneumococcus and other atypical pathogens (Mycoplasma, Chlamydia or Legionella), especially in children over 5 years of age.

Concerns about adverse effects on cardiac rhythm have been subject to controversy by some experts. Q-T segment prolongation is a very common pathology in adults but less frequent in paediatrics22. Azithromycin is well known for potential toxicity at this level, so caution should be exercised in patients with a history of arrhythmias or underlying cardiac pathology.

Ceftriaxone: a third generation cephalosporin with excellent action on bacterial pathogens causing pneumonia. It should be taken as first line in empirical treatment of community-acquired pneumonia until bacterial infection is ruled out.

Vancomycin: is an excellent choice for methicillin-resistant staphylococcal infection and multiple strains of penicillin-resistant pneumococci. Its use should be reserved when the diagnostic suspicion of MRSA is very high. Vancomycin can be very toxic to the kidney, especially when used in conjunction with other nephrotoxic drugs or there is nephropathy with decreased renal function23. The latter has been associated with COVID-19 infection, so vancomycin use should be very cautious and well monitored.

Clindamycin: amoxicillin plus clavulanic acid at known paediatric doses are other important alternatives for outpatient or in-hospital management of community-acquired pneumonia until the diagnosis is clarified.

Drugs under investigation

Multiple drugs with antiviral effect against COVID-19 are currently under investigation. Most of these agents have proven their efficacy in vitro and the experience in patients relies on small case series mostly in adults with promising results but with low reliability to date.

Clinical experience in paediatrics is practically non-existent, so the role of these agents in the management of COVID-19 is still uncertain and lacks evidence, and their use should not be extrapolated to all

cases. In the absence of an efficient and well-studied pharmacological treatment for COVID-19, the use of these drugs may be justified and considered according to the clinical need of each patient. Chloroquine and hydroxychloroquine: Both drugs have been shown to efficiently inhibit COVID-19 in vitro, although hydroxychloroquine appears to have a more potent effect [24].

Clinical trials in patients infected with COVID-19 are scarce and its efficacy is still unknown. But given the lack of effective drug treatment, hydroxychloroquine [25] is a reasonable treatment for hospitalised patients with severe disease or at risk of severe disease.

A randomised trial of patients with pneumonia without hypoxia reported clinical improvement and less progression to severe disease in the group using hydroxychloroquine [25]. In another study of 36 patients with COVID-19, Gautret et al. found that the use of hydroxychloroquine (200mg 3 times daily for 10 days) was associated with undetectable levels of virus in the nasopharynx at day 6 compared to non-specific treatment. In this study, the combined use of hydroxychloroquine plus azithromycin appears to be associated with a more rapid decline in viral RNA levels [26].

Contrary to previous studies, Chen et al, demonstrated no difference between hydroxychloroquine and non-specific treatment in 30 adults with COVID-19 [27]. In this study the dose was 400mg/day for 5 days.

The use of chloroquine is included in the treatment guidelines of the National Health Commission in China due to clinical reports of reduced disease progression and duration of symptoms [28]. The FDA has also authorised the use of hydroxychloroquine in adolescents and adults as part of treatment or recruitment for clinical trials [29]. The recommended dose is hydroxychloroquine 800mg on day 1, followed by 400mg/day. Chloroquine at a dose of 1 gram on day 1, followed by 500mg/day, both for 4-7 days, depending on clinical response.

Remdesivir: Several randomised trials are currently underway to evaluate the efficacy of remdesivir in moderate to severe cases of COVID-19. This antiviral is a nucleotide analogue that has demonstrated activity against COVID-19, and other types of coronaviruses such as SARS and MERS [30]. Clinical trials have not yet been published but its use could potentially include adults, children and pregnant women [31]. It could be the best potential drug for the treatment of COVID-19. It is an antiviral developed for Ebola. Animal experiments have shown that compared to the control group, remdesivir can effectively reduce virus titre in MERS-CoV-infected mice as well as ameliorate lung tissue damage. Its effect is better than that of the group treated with lopinavir/ ritonavir combined with IFN. The drug has completed the Phase III clinical trial for the treatment of Ebola virus infection, and pharmacokinetic and safety data are relatively complete. However, the efficacy and safety of remdesivir in patients with COVID-19 infection have yet to be confirmed. This drug is not available in the US but has been used in at least one case with good results. The proposed doses for the paediatric population are: ? 40 kg body weight: same as adults: loading

dose on day 1 of 200 mg/iv followed by a maintenance dose of 100 mg/iv daily from day 2 to day 10. < 40 kg body weight: loading dose on day 1 of 5 mg/kg iv followed by a maintenance dose of 2.5 mg/kg iv daily from day 2 to day 9.

Favipiravir: This is an RNA polymerase inhibitor that is available in some Asian countries for the treatment of influenza. It is now also beginning to be evaluated in coronavirus infection. In a study of patients with mild to moderate COVID-19 infection, favipiravir was associated with more rapid viral negativisation and more frequent radiographic improvement compared to lopinavir plus ritonavir [32]. However, other therapies were used in both groups, which could lead to confounding and confounding of the results.

Lopinavir-ritonavir: These drugs were not shown to have any significant beneficial effect in COVID-19 [33] infections. Despite having in vitro activity against several coronaviruses, it showed no clinical difference vs. routine care treatment in a randomised study of 199 patients with severe COVID-19 [34] disease.

Inmunoglobulins: Intravenous immunoglobulins have been used in severe cases, but their indication and efficacy need to be evaluated. The recommended doses are: 1 g/kg/day, 2 days, or 400 mg/kg/day, 5 days.

IFN-alfa:inhaled has been recommended in combination with lopinavir/ ritonavir as antiviral therapy in adults and a clinical trial has been initiated to test its efficacy. IFN-alpha is a broad-spectrum antiviral used to treat HBV. It has been used with good results in children with bronchiolitis, pneumonia and also in cases of SARS-CoV showing excellent viral load inhibition. Recent studies have shown a reduction in the infection rate of influenza virus, respiratory syncytial virus, adenovirus and SARS-CoV. Its use in COVID-19 cases also showed good preliminary results in in vitro, animal models and case series. Therefore, the expert consensus recommends the use of interferon if available at the following doses: 100,000-200,000 IU/kg and 200,000-400,000 IU/kg in mild or severe cases respectively in nebulised form twice daily for five to seven days [35].

Convalescent plasma therapy:a procedure tried during other pandemics and now being used by a group of physicians to treat people at risk of dying from COVID-19, but with a lack of experience in children.

Considerations in the pediatric critically ill patient with COVID-19.

Although since the onset of the pandemic and the data provided by case reports and statistics from both China and the US indicate that the involvement, signs and symptoms of the large percentage of patients in the paediatric age group are mild and with a low case fatality rate compared to the adult and older adult population, those patients with a chronic underlying condition (especially lung disease) are more likely to present with a more severe condition requiring hospitalisation. Similar to the adult population, those patients with a chronic underlying condition (especially pulmonary) are more likely to present with a more severe

condition requiring hospitalisation. A lower percentage (0.5 -2%) may require intensive care [36, 37].

The cause of why the severity of the disease in children is less severe is still unknown, including the clinical presentation and behaviour of pro-inflammatory markers that make this entity much more heterogeneous. Many theories have been postulated, including that children have higher expression of ACE2 receptors on pneumocytes, their presence apparently protecting against lung damage [36].

When the patient requires intensive care, planning and protocols must be created for various scenarios (intubation, mechanical ventilation care, general patient care, cardiac arrest, medication protocols, etc.), in addition to the preparation of the entire unit team.

Severity criteria and admission to the intensive care unit

While the general clinical presentation is mild to moderate, there are conditions that must be evaluated (Table 1) and met by the patient for admission to the pediatric intensive care unit (PICU) and among these we have [38]:

Uncomplicated infection	Patients with uncomplicated viral upper respiratory tract infection may present with nonspecific symptoms, such as fever, cough, sore throat, nasal congestion, malaise, headache, muscle pain or general malaise. There are no signs of dehydration, sepsis or respiratory distress.
Mild lower tract infection[a]	Tos, dificultad respiratoria + polipnea (en respiraciones/min): < 2 meses, ≥ 60; 2-11 meses, ≥ 50; 1-5 años, ≥ 40 y sin signos de neumonía severa. Saturación sin aporte de oxígeno > 92%. Pueden o no tener fiebre.
Severe lower tract infection[b]	Cough or respiratory distress and at least one of the following: central cyanosis or SatO2 < 92% (< 90% in preterm infants); severe respiratory distress (e.g., wheezing, very severe chest retraction); inability or difficulty feeding, lethargy or loss of consciousness or seizures. Other signs may be present such as: chest retractions, polypnea (in breaths/min): ≥ 70 in children under 1 year; ≥ 50 in children over 1 year. Arterial blood gases: PaO2 < 60 mmHg, PaCO2 > 50 mmHg. Diagnosis is clinical; chest imaging can exclude complications (atelectasis, infiltrates, effusion).
Other manifestations associated with severe disease	Coagulation disorders (prolonged prothrombin time and elevated D-dimer), myocardial damage (increased myocardial enzymes, ST-T changes in the electrocardiogram, cardiomegaly and heart failure), gastrointestinal dysfunction, elevated liver enzymes and rhabdomyolysis.
Acute Respiratory Distress Syndrome (ARDS)	Onset: new or worsening of symptoms in the previous 10 days, Chest X-ray, CT or ECHO: new infiltrate(s) compatible with acute pulmonary parenchymal involvement. Pulmonary edema origin: respiratory failure in the absence of other etiology such as heart failure or volume overload. Oxygenation (OI = oxygenation index and OSI = oxygenation index using SpO2): • VNI bilevel or CPAP ≥ 5 cmH2O through a full face mask: PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤ 264. • Mild ARDS (invasive ventilation): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5. • Moderate ARDS (invasive ventilation): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3. • Severe ARDS (invasive ventilation): OI ≥ 16 or OSI ≥ 12.3.
Sepsis[c]	Suspected or proven infection and ≥ 2 SIRS criteria, of which one must be abnormal temperature or abnormal white blood cell count.
Septic shock.	Any hypotension (SBP < 5th percentile or > 2 SD below normal for age) or 2-3 of the following: Altered mental status; tachycardia or bradycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); slow capillary refill (> 2 s) or warm vasodilation with preserved pulses; tachypnea; mottled skin or petechial or purpuric rash; increased lactate, oliguria, hyperthermia or hypothermia.

DE: standard deviation; FC: Heart Rate; SIRS: systemic inflammatory response syndrome; VNI: noninvasive ventilation; PAS: systolic blood pressure.
[a] Equivalent to WHO mild pneumonia.
[b] Equivalent to WHO severe pneumonia.
[c] Goldstein B, et al.

Table 1
Clinical syndromes associated with COVID-19

General measures to consider

Depending on the characteristics of the unit and institutional policies, patient visits are restricted, avoiding unnecessary transfers and, if considered, having an established protocol with the respective steps and recommendations in order to minimise contamination.

Ventilatory management

- **Non-invasive ventilation and high-flow nasal cannula.**

  Although children may present with mild to moderate bronchiolitis-like symptoms, the use of non-invasive ventilation ((VNI) and/or high-flow nasal cannula (CNAF) may be rational alternatives; however, recommendations regarding their use in patients with COVID-19 restrict their use due to the risk of particle aerosolisation if the appropriate interfaces are not in place or the environments do not have a negative pressure system. Another point to consider is the capacity of the centres to have this equipment and the experience of handling it. If the use of some of these measures is considered, if there is no improvement

within one hour (SatO2 92-97% with FiO2 < 40% with CNAF), early intubation should be considered [39].

- **Intubation and mechanical ventilation**

  Severe cases may require mechanical ventilation, for which the recommendations issued by critical care and anaesthesia societies are [40, 41]:

  - Minimise Minimise the number of personnel performing the procedure, and ensure that they have the appropriate personal protective equipment (PPE). In relation to this point, PPE should consist of biosafety overalls, waterproof gown, protective goggles and/or face mask, N95 or higher mask, sterile gloves.
  - Implement a closed communication circuit between team members.
  - The procedure should be delegated to more experienced staff (anaesthesiologist, emergency physician, therapist).
  - The use of video laryngoscopy is ideal, if the equipment and skills are available.
  - Offer pre-oxygenation with a high-flow, non-rebreathing mask, avoid positive pressure ventilation with a self-inflating bag and mask, and if this is done, have two professionals, one to make a tight seal on the mask and the other to perform the PPV (two-handed technique). Be sure to place a high efficiency HME filter between the mask and the bag.
  - Have a rapid intubation sequence protocol with medication including a neuromuscular blocker (NMB), sedation (ketamine or benzodiazepine) plus analgesia (opioid) or propofol. Always assess the patient?s haemodynamic status if there are signs of shock.
  - Use endotracheal tubes (ETT) with balloon guides and early inflation of the tube once the airway is secured.
  - Once the patient is intubated, connect to the ventilator circuit which should be connected to a closed suction system to minimise unnecessary disconnections.
  - If bronchodilator medication is required, it is recommended to avoid nebulisations and to use metered dose inhalers (MDI or puff) through a spacer connected between the TET and the filter.
  - In case of patient mobilisation and planned disconnection of the ventilator, clamp the TET and always wear full PPE.

- **Invasive mechanical ventilation (VMI)** [42, 43]

  Strategies aim at protective ventilation (paediatric ARDS recommendations (PALICC)):

  - Low tidal volumes (4-8 ml/kg)

- Optimal PEEP for alveolar recruitment with target PaO2 /FiO2 > 150
- Moderate to severe ARDS PEEP between 10 - 15 cm H2O.
- Mild ARDS PEEP < 10 cm H2O.
- Plateau pressure ? 30 cm H2O.
- Driving pressure < 15 cm H2 O.
- Permissive hypercapnia
- FiO2 starts at 100% and progressively decrease to maintain below 60% with SatO2 > 92% or PaO2 ? 60 mmHg.
- Other strategies to consider, depending on the institution?s experience, availability of human and technological resources:
- Ventilation in a prone position for 12 to 16 hours.
- In refractory hypoxaemia despite optimisation of mechanical ventilation, rescue treatments and prone decubitus, ECMO is suggested.
- Intubated patients require deep sedation, often associated with the use of CNBs. Closely assess the patient?s haemodynamic stability which may be compromised or exacerbated by the use of IMV (cardiopulmonary interactions).

- **Ventilation in prone position for 12 to 16 hours.**

  In refractory hypoxemia despite optimization of mechanical ventilation, rescue treatments and prone decubitus, the use of ECMO is suggested.

  Intubated patients require deep sedation, often associated with the use of BNM. Closely assess the hemodynamic stability of the patient, which may be compromised or exacerbated by the use of IMV (cardiopulmonary interactions).

- **Concerning the assembly of the mechanical ventilator** [44]

  - Fit high efficiency filters in both inspiratory and expiratory loops.
  - If using circuits without water traps, use a high efficiency HME filter between the Y-connection and the ETT. Note that in infants the use of passive humidifiers may cause increased dead space and may clog the ETT with secretions or mucus plugs, in these cases consider circuits with water traps connected to active humidifiers (cascade).
  - Reiterate the importance of placing a closed ETT suction circuit.
  - Haemodynamic support [41, 45].
  - Vascular access is essential for both drug administration (central venous catheter) and haemodynamic monitoring (arterial line).

- Assess vital signs (invasive blood pressure, heart rate, peripheral perfusion, diuresis and neurological status), analytical markers (lactate, central venous saturation or SvO2).
- In case of shock and in the initial phase of resuscitation, perform expansion with isotonic crystalloid solutions (10-20 ml/kg boluses) guided by clinical response, avoiding volume overload or very positive water balances.
- In hypotensive patients use noradrenaline/adrenaline as first line. If cardiac dysfunction is suspected, consider dobutamine. In hypotension refractory to vasopressors consider vasopressin (if available).
- Target MAP > 60 mmHg.
- The use of colloids, dextran or gelatine in initial resuscitation is not recommended.
- The use of corticosteroids (hydrocortisone), which is still controversial, is recommended in case of vasoactive refractory shock or suspected adrenal insufficiency.

- **Cardiac arrest** [46, 47]

  One of the most challenging scenarios for healthcare providers is the patient presenting with cardiac arrest who is a suspected or confirmed case of COVID-19. International consensus on advanced resuscitation establishes the following recommendations and modifications to the paediatric advanced resuscitation algorithm (Figure 1)

- **Reduce supplier exposure:**

  First is the safety of the personnel assisting during cardiopulmonary resuscitation (CPR) who must be provided with appropriate and complete PPE.

  Limit the number of personnel to be involved during resuscitation.

  IOT should be carried out by the most experienced personnel.

  Prioritise oxygenation and ventilation strategies with the lowest risk of aerosolization:

  - Use high-efficiency particulate air (HEPA) filters if available -Intubate early with balloon TET and connect to mechanical ventilation (if available)
  - Stop compressions when intubation is performed.
  - Consider use of video laryngoscopy if available.
  - Before intubation, use bag-mask device with HEPA filter and airtight seal.
  - Passive oxygenation with a non-rebreathing mask can be considered as an alternative to bag-mask oxygenation.
  - If intubation is delayed, consider the use of a supraglottic device (laryngeal mask).
  - Minimise disconnections from the closed circuit.

- Defibrillable rhythms should be treated promptly for return of spontaneous circulation.
- Identify reversible causes (Identify Hs and Ts according to PALS guidelines recommendations).

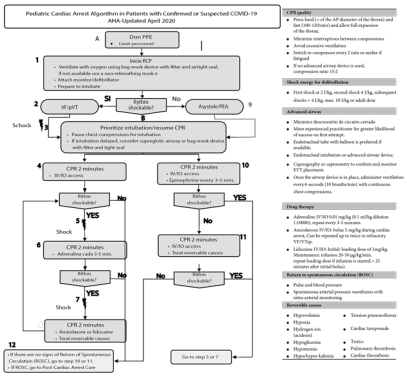

Figure 1:
CPR Algorithm in pediatric patients with COVID-19

Discussion

So far the available evidence is too weak to recommend whether or not treatment with a specific drug, the studies presented for the present review will probably change until the time of publication, within the evidence reviewed, we can conclude.

1. Consider administering hydroxychloroquine ± lopinavir/ritonavir if risk factors or clinical worsening. Lopinavir/ritonavir should only be considered early. Efficacy is currently questionable.
2. Empirical antibiotic therapy if bacterial co-infection or superinfection is suspected. Use of antibiotics as empirical treatment in cases of COVID-19 pneumonia while the diagnosis is being confirmed or bacterial infection is being ruled out. Use antibiotics when there is clinical or laboratory suspicion of bacterial infection.
3. In severe cases, apply for compassionate use of remdesivir and start lopinavir/ritonavir + hydroxychloroquine +/- interferon B1b s.c. Once approval for use of remdesivir has been received, continue antiviral treatment with remdesivir + hydroxychloroquine only. Evaluate the use of Tocilizumab according to evolution.
4. The management of the paediatric critically ill patient should be under the utmost safety measures for the health care personnel. At the same time, management should be performed by personnel experienced in the management of ARDS patients.

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Conflict of interest declaration

The authors declare that there is no conflict of interest.

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