EMERGING PNEUMONIA IN CHILDREN

EDITED BY: Hong - Ren Yu, Jong-Hau Hsu, Mario Barreto and Ting Fan Leung
PUBLISHED IN: Frontiers in Pediatrics

frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88974-151-9
DOI 10.3389/978-2-88974-151-9

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

EMERGING PNEUMONIA IN CHILDREN

Topic Editors:
Hong - Ren Yu, Kaohsiung Chang Gung Memorial Hospital, Taiwan
Jong-Hau Hsu, Kaohsiung Medical University, Taiwan
Mario Barreto, Sapienza University of Rome, Italy
Ting Fan Leung, The Chinese University of Hong Kong, China

Citation: Yu, H.-R., Hsu, J.-H., Barreto, M., Leung, T. F., eds. (2022). Emerging Pneumonia in Children. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-88974-151-9

Table of Contents

frontiers in Pediatrics

EDITORIAL
published: 08 December 2021
doi: 10.3389/fped.2021.813034

Editorial: Emerging Pneumonia in Children

Hong-Ren Yu[1,2] *and Jong-Hau Hsu*[3,4]*

[1] Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [2] Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan, [3] Department of Pediatrics, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, [4] Department of Pediatrics, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

Keywords: pneumonia, pediatric, pathogen, pathophysiology, treatment

Editorial on the Research Topic

Emerging Pneumonia in Children

Given the development and progress of antimicrobial therapy, effective vaccines for pneumonia, and related guidelines management in the past several decades, pneumonia persists as a leading cause of death in children younger than 5 years in developing countries and accounts for ∼20% of childhood deaths. Although advanced imaging modalities including chest sonography, computed tomography, and magnetic resonance imaging are promising for more accurate and timely diagnosis, their roles in clinical management need further investigation. Even though there are various specific or sensitive laboratory tests for upper respiratory tract samples or sputum, which can reveal nucleic acid from potential pathogens in children, it is, unfortunately, difficult to attribute the cause due to limitations in our ability to distinguish between the colonized organisms or pathogens in the upper respiratory tract. In addition, the emergence of other novel pathogens such as Covid-19 presents further issues. Thus, better diagnostic and therapeutic strategies are essential for children, and diagnostic and therapeutic guidelines also need to be updated with new evidence.

Due to the importance of emerging pneumonia, this special volume of Frontiers in Pediatrics invited contributions that highlight recent developments in this field. The main aim of this Research Topic is to consider the available data on pathogenesis, pathogens, imaging modalities, treatment, and the prevention of pneumonia in children. This special volume comprises ten articles.

FACE PROTECTION FOR CHILDREN IN HEALTHCARE SETTINGS (Vlacha and Feketea)

The COVID-19 pandemic has had a huge impact on countries around the world. It is important to reduce the spread of the virus in medical institutions between patients and medical staff. The first study in this volume provides evidence from the real world, showing the effects of state government mandates for face mask use in public. More than 200,000 COVID-19 cases were estimated to be avoided. The findings suggest that requiring face mask use in public could help in mitigating the spread of COVID-19. The CDC recommends that pediatric patients receive enhanced barrier prevention measures including face masks after entering the outpatient setting. However, due to the special characteristics of young children, the implementation of safety measures in outpatient pediatric centers can sometimes be extremely challenging. Based on personal experience, Vlacha and Feketea recommend the use of face shields for children who refuse to wear masks. Young children seem to tolerate face shields better than masks. Face protection equipment can ensure

OPEN ACCESS

Edited and reviewed by:
Anne B. Chang,
Charles Darwin University, Australia

***Correspondence:**
Jong-Hau Hsu
jhh936@yahoo.com.tw

Specialty section:
This article was submitted to Pediatric Pulmonology, a section of the journal Frontiers in Pediatrics

Received: *11 November 2021*
Accepted: *16 November 2021*
Published: *08 December 2021*

Citation:
Yu H-R and Hsu J-H (2021) Editorial: Emerging Pneumonia in Children. Front. Pediatr. 9:813034. doi: 10.3389/fped.2021.813034

social distance, avoid the risk of suffocation and eliminate children's facial touching behavior. More evidence is expected to support the beneficial effect of face shields for children.

HIGHER HOSPITALIZATION RATE FOR LOWER AIRWAY INFECTION IN TRANSFUSION-NAÏVE THALASSEMIA CHILDREN (Vlacha and Feketea)

Thalassemia is common among people of Italian, Greek, Middle Eastern, South Asian, and African descent. In China, the prevalence of α-thalassemia, β-thalassemia, and α + β-thalassemia were estimated at 7.88, 2.21, and 0.48%, respectively. Non-transfusion-dependent thalassemia patients can be at risk of ineffective erythropoiesis, peripheral hemolysis, and iron overload that contributes to a number of clinical morbidities. However, few articles discuss the infection susceptibility of non-transfusion-dependent thalassemia patients. Tsai et al. conducted a nationwide population-based retrospective cohort study using the Taiwan National Health Insurance Research Database. After confounding factors were adjusted, the hospitalization rate and incidence rate of bronchitis/bronchiolitis and pneumonia for transfusion-naïve thalassemia children were found to be higher than those for non-thalassemia controls. However, the exact pathologic mechanism needs to be further clarified. Whether the transfusion-naïve thalassemia patients also have a higher risk of other types of infection, such as urinary tract infection and acute gastroenteritis is worth further study. This finding reminds us to pay more attention to lower airway infection of non-transfusion-dependent thalassemia children in clinics.

CLINICAL FEATURES AND TEMPORAL CHANGES OF RT-PCR AND CHEST CT IN COVID-19 PEDIATRIC PATIENTS (Wei et al.)

Viral nucleic acid testing and chest CT have been considered as the main diagnostic methods for patients with suspected COVID-19 pneumonia. In adults, the positive rate of pharyngeal swabs reverses transcription polymerase chain reaction (RT-PCR) and is sometimes lower than that of RT-PCR in certain conditions, and chest CT is considered a more accurate early diagnostic tool. In contrast to adults, children with COVID-19 infection often present mild manifestation. Besides, children are more sensitive to radiation exposure than adults. Thus, a reasonable diagnostic approach for children suspected to have COVID-19 infection should be different from adults. In this study, Wei et al. investigated the clinical features and changes of RT-PCR and chest CT in COVID-19 children. They found that lung involvement in children with COVID-19 is mild, even with 28% of them as normal in CT. They concluded RT-PCR is more reliable than chest CT in the initial diagnosis of pediatric patients with COVID-19. Research from Guo et al. reflects the limitation of chest CT in the diagnosis of COVID-19 children.

NONINVASIVE VENTILATION AND MECHANICAL INSUFFLATOR-EXSUFFLATOR FOR ACUTE RESPIRATORY FAILURE IN CHILDREN WITH NEUROMUSCULAR DISORDERS (Chen and Hsu)

Non-invasive ventilation and secretion clearance strategy is a recent trend for patients of neuromuscular disease with respiratory failure. This strategy has the advantages of convenience, life-quality preservation, and low cost. In this review, Chen and Hsu. describe recent advances in this non-invasive strategy for this particularly vulnerable group of patients who are often threatened by respiratory failure or airway obstruction by inadequate clearance of secretions during respiratory infections.

FEATURES DISCRIMINATING COVID-19 FROM COMMUNITY-ACQUIRED PNEUMONIA IN PEDIATRIC PATIENTS (Guo et al.)

The clinical symptoms of COVID-19 pneumonia in children are similar to other pediatric community-acquired pneumonia but they have a different treatment strategy. It is important to distinguish COVID-19 from other pediatric pneumonias. Guo et al. compared the clinical, laboratory, and radiological results of COVID-19 children collected during the COVID-19 outbreak with other pneumonia patients collected before the COVID-19 outbreak in the same hospital, especially mycoplasma pneumonia. They found that no reliable specific features could discriminate COVID-19 from community-acquired pneumonia in pediatric patients. Even though more COVID-19 cases showed ground-glass opacity on CT scan and elevated level of ALT than other community-acquired pneumonia. A reliable and specific RT-PCR or antigen screening is necessary for quickly and accurately identifying the pathogen.

COVID-19 PNEUMONIA IN CHILDREN: FROM ETIOLOGY TO MANAGEMENT (Parisi et al.)

In this review article, Parisi et al. summarize the characteristics of COVID-19 in children, including pathological mechanisms, clinical manifestation, radiologic findings, and therapeutic strategies. For their unique immune response and ACE2 expression, the clinical manifestation of COVID-19 in pediatric patients is often much less severe than in adults, progression of the disease remains possible and should be intercepted with appropriate treatment. Besides children are important vectors of COVID-19. In this article, Parisi et al. also provided a clear graphic abstract illustrating the virus-host interaction and reasons why children are less affected.

POST-INFECTIOUS BRONCHIOLITIS OBLITERANS: HRCT, DECT, PULMONARY SCINTIGRAPHY IMAGES, AND CLINICAL FOLLOW-UP IN EIGHT CHILDREN (Chen et al.)

Bronchiolitis obliterans (BO) is an uncommon but challenging lung disease for pediatricians. It is characterized by chronic irreversible inflammation and limited treatment strategy, thus it is important to make a timely diagnosis and start treatment promptly. High-resolution CT (HRCT) is a widely used imaging modality for the diagnosis of BO, and scintigraphy is an alternative tool that can functionally evaluate BO. Another choice of imaging modality, dual-energy computed tomography (DECT), has also recently been applied to BO. In this retrospective study, Chen et al. showed that the most common HRCT finding of BO is a mosaic pattern, where matched ventilation/perfusion (V/Q) defect is an essential feature in pulmonary scintigraphy. Furthermore, they found that DECT could reveal various degrees of decreased perfusion, which was compatible with the decreased perfusion on pulmonary scintigraphy.

COVID-19 IN CHILDREN: RESPIRATORY INVOLVEMENT AND SOME DIFFERENCES WITH THE ADULTS (Hernández and Orozco)

In this review, Hernández and Orozco summarize some of the mechanisms and findings that are different between adult and pediatric COVID-19 infections. They also review some important issues about the physiopathology, diagnosis, clinical and paraclinical presentation, severity, treatment, and control of the disease. Immune responses, microbiota effects, ACE2 activity, and more preserved coagulation and endothelial function account for the clinical advantages that contribute to milder presentation in children with COVID-19 infection. CT scan is suggested if there is clinical worsening or suspicion of pulmonary embolism. Pediatric treatment focuses on supportive care as there is less research into vaccines and specific pharmacotherapy. There are still knowledge gaps in pediatric COVID-19 and further research on children is required.

ALL YOU NEED IS EVIDENCE: WHAT WE KNOW ABOUT PNEUMONIA IN CHILDREN WITH NEUROMUSCULAR DISEASES (Cherchi et al.)

Respiratory failure is the most common cause of mortality in patients with neuromuscular diseases (NMD). Respiratory weakness is defined as the inability of the respiratory muscles to generate sufficient levels of pressure and flow to overcome the respiratory load. Alveolar hypoventilation will develop first during sleep and then progress to involve wakefulness. In this review, Cherchi et al. summarize the pathophysiology, issues of inadequate clearance, respiratory interventions, and future therapeutic directions and shed some light on the more comprehensive understanding and management of pneumonia in children with NMD.

EMERGENT PNEUMONIA IN CHILDREN (Perret et al.)

After the outbreak of the COVID-19 pandemic, emerging pneumonia has become an important issue for pediatricians across all fields. In this review, Perret et al. classify emerging pathogens into three categories: 1) true emerging: SARS-CoV-1, SARS-CoV-2, avian influenza, MERS-CoV, and hantavirus; 2) re-emerging, including measles, tuberculosis, and antimicrobial resistant bacteria such as CA-MRSA, Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia, Mycoplasma pneumoniae, and new serotypes of post-vaccine pneumococcal; and 3) old known with new presentations, including rhinovirus, and non-SARS coronavirus. In this article, the epidemiology, forms of presentation, therapy, and prognosis in children are comprehensively described and compared with those in adults.

AUTHOR CONTRIBUTIONS

H-RY and J-HH contributed to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This article was supported in part by a grant CMRPG8K0071 (H-RY) from Chang Gung Memorial Hospital.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Pediatrics

OPINION
published: 11 September 2020
doi: 10.3389/fped.2020.00553

Face Protection for Children in Healthcare Settings

Vasiliki Vlacha[1]* *and Gavriela Feketea*[2,3]

[1] Department of Early Years Learning and Care, University of Ioannina, Ioannina, Greece, [2] School "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania, [3] Department of Pediatrics, Pediatric Allergy Outpatient Clinic, "Karamandaneio" Children's Hospital, Patras, Greece

Keywords: children, COVID-19, face shield, pediatric primary care, personal protective equipment

The healthcare system in several countries is overwhelmed due to the COVID-19 pandemic. The ambulatory care settings carry a substantial patient burden with the risk of potential rise after the ending of the lockdown. The nosocomial transmission of SARS-CoV2 has been well-described (1). It is extremely important to minimize the viral transmission in the healthcare facilities among patients and the healthcare personnel as well (2). However, the implementation of safety measures becomes extremely challenging in ambulatory pediatric centers due to particular characteristics of children.

We would like to propose enhanced barrier precautions for pediatric patients of almost all ages as soon as they enter the ambulatory setting. These would include a face mask for children above 2 years of age and their care givers, according to CDC recommendation (3). Additionally, we also strongly recommend a face shield for children from 1 to 2 years of age. We also propose an alternative facial protective gear using a face shield for children aged between 2 and 5 years as a substitute for a face mask. These recommendations are based on our personal experience that toddlers resist wearing face masks and they tolerate face shields better. In addition, the face shield for children aged 1–2 years offers a face barrier without the risk of suffocation. The goal is to achieve the maximal protection for the pediatric patients of almost all ages and the healthcare workers.

The current suggestions are based on the unique characteristics of the pediatric population compared to adults. Most of the children, particular toddlers, cannot effectively practice social distancing so the use of a facepiece is required even more as a barrier to viral spread. Another marked characteristic is the crying behavior of children especially when they visit a medical setting. The dynamic of the SARS-Cov2 spread during crying has not been yet studied. However, the analysis of the peak expiratory airflow in premature newborns revealed that it was on average 6.6 times higher during crying than the flow during quiet breathing. Moreover, the ventilation during crying increased by 255% in comparison to quiet ventilation (4). Thus, crying probably facilitates the viral spread. Most importantly, the facepiece seems to control the transmission from asymptomatic carriers. It is well-known that the silent spreaders have high prevalence among children (5). Finally, the face protection equipment may eliminate the children's face-touching behavior. This could result in breaking the transmission by self-inoculation. The face shields as mode of protection against influenza virus have been shown to reduce the viral exposure by 96% in an 18-inch distance from a cough simulator (6). A systematic review analysis published by Chu summarizes the importance of social distancing and face/eye protection (7).

There are several limitations to our proposal. During the global shortage of personal protected equipment, the need of child size face masks and face shields would lead to exhaustion of manufacturing. In addition, some children could not tolerate wearing a facepiece even if repeatedly instructed to do so. A third issue could be the parental concern of potential suffocation by the face protectors requiring reassurance from the healthcare providers. We strongly advise the children to be under parental supervision while wearing a face-protective equipment.

OPEN ACCESS

Edited by:
Mario Barreto,
Sapienza University of Rome, Italy

Reviewed by:
Kelechi Benjamin Ugonna,
Sheffield Children's Hospital, United Kingdom
Paolo Bottau,
Azienda Unità Sanitaria Locale (AUSL) Imola, Italy
Maria Elena Liverani,
Azienda Ospedaliera Sant'Andrea, Italy

***Correspondence:**
Vasiliki Vlacha
vasovlaha@gmail.com

Specialty section:
This article was submitted to Pediatric Pulmonology, a section of the journal Frontiers in Pediatrics

Received: *24 May 2020*
Accepted: *30 July 2020*
Published: *11 September 2020*

Citation:
Vlacha V and Feketea G (2020) Face Protection for Children in Healthcare Settings. Front. Pediatr. 8:553. doi: 10.3389/fped.2020.00553

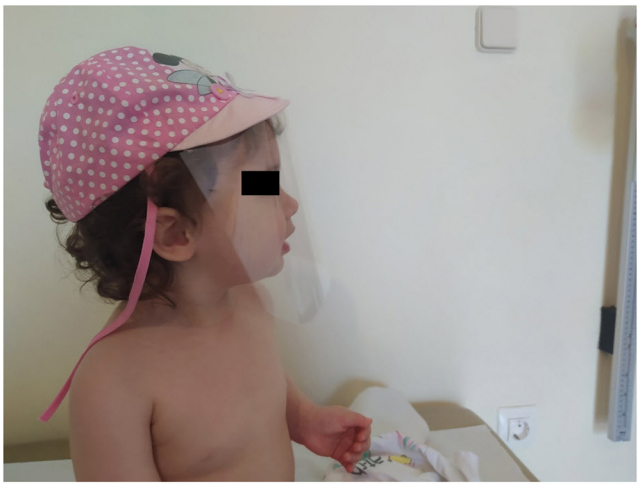

FIGURE 1 | A 19-month-old child wearing a handmade face shield. It is being been published with permission.

Children's face shields are available in the market as sun-protective or anti-dust equipment, and some parents may be familiar with their usage. They come in different sizes according to the child's head circumference or they are adjustable. In **Figure 1**, you can see a handmade face shield made by sewing a transparent plastic sheet on a baby's hat. Written informed consent for publication of the child's figure was obtained from the child's mother.

It is important to apply additional safety measures for COVID-19 transmission, considering the unique children's characteristics, especially after lifting of pandemic restrictions.

AUTHOR CONTRIBUTIONS

VV and GF contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Schwierzeck V, König JC, Kühn J, Mellmann A, Correa-Martínez CL, Omran H, et al. First reported nosocomial outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in a pediatric dialysis unit. *Clin Infect Dis*. (2020). doi: 10.1093/cid/ciaa491. [Epub ahead of print].
2. Adams JG, Walls RM. Supporting the Health Care Workforce During the COVID-19 Global Epidemic. *JAMA*. (2020) 323:1439–40. doi: 10.1001/jama.2020.3972
3. Centers of disease control and prevention. *Interim Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) in Healthcare Settings*. Available online at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html#minimize (accessed May 20, 2020).
4. Javorka K, Tomori Z, Zavarská L. Mechanics of breathing during sneezing and crying in premature newborns. *Eur J Respir Dis*. (1982) 63:442–8.
5. Bai Y, Yao L, Wei T, Tian F, Jin D-Y, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. *JAMA*. (2020) 2020:2565. doi: 10.1001/jama.2020.2565
6. Lindsley WG, Noti JD, Blachere FM, Szalajda JV and Beezhold DH. Efficacy of face shields against cough aerosol droplets from a cough simulator. *J Occup Environ Hyg*. (2014) 11:509–18.
7. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. *The Lancet*. (2020) 395:1973–87. doi: 10.1016/S0140-6736(20)31142-9

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

ORIGINAL RESEARCH
published: 09 October 2020
doi: 10.3389/fped.2020.579512

Clinical Features and Temporal Changes of RT-PCR and Chest CT in COVID-19 Pediatric Patients

Wei Xia[1], *Yu Guo*[1], *Zhiyao Tian*[1], *Yan Luo*[2], *Daoyu Hu*[2], *Jianbo Shao*[1], *Zhen Li*[2]* and *Ihab R. Kamel*[3]

[1] *Department of Imaging Center, Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China,* [2] *Department of Radiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China,* [3] *Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins Hospital, Johns Hopkins Med Institute, Baltimore, MD, United States*

Objective: This work aims to investigate the clinical features and the temporal changes of RT-PCR and CT in COVID-19 pediatric patients.

Methods: The clinical, RT-PCR, and CT features of 114 COVID-19 pediatric in-patients were retrospectively reviewed from January 21 to March 14, 2020. All patients had chest CT on admission and were identified as positive by pharyngeal swab nucleic acid test. The clinical features were analyzed, as well as the features and the temporal changes of RT-PCR and CT.

Results: Fever (62, 54%) and cough (61, 54%) were the most common symptoms. There were 34 (30%) cases of concurrent infections. The most common imaging features on CT were ground-glass opacities (46, 40%) and consolidation (46, 40%). The bilateral lower lobes were the most common pattern of involvement, with 63 cases (55%) involving one to two lobes, and in 32 (28%) cases CT was normal. Throughout the whole duration of COVID-19 in children, the diagnostic positive rate of RT-PCR has been far higher than that of CT (all $P < 0.05$). For RT-PCR follow-up, reliable negative results were obtained only 7 days after the onset of symptoms. Though lung involvement on chest CT progressed rapidly in several cases, lung involvement in children with COVID-19 is mild, with a median value of 2 on CT score.

Conclusions: RT-PCR is more reliable than CT in the initial diagnosis of pediatric patients with COVID-19. On follow-up, reliable negative RT-PCR results are available 7 days after the initial symptoms. The use of CT should be considered for follow-up purposes only if necessary.

Keywords: COVID-19, polymerase chain reaction, computer tomography, child, infection

OPEN ACCESS

Edited by:
Ting Fan Leung, The Chinese University of Hong Kong, China

Reviewed by:
Aleksandar Sovtic, The Institute for Health Protection of Mother and Child Serbia, Serbia
Kelechi Benjamin Ugonna, Sheffield Children's Hospital, United Kingdom

***Correspondence:**
Zhen Li
zhenli@hust.edu.cn

Specialty section:
This article was submitted to Pediatric Pulmonology, a section of the journal Frontiers in Pediatrics

Received: *02 July 2020*
Accepted: *02 September 2020*
Published: *09 October 2020*

Citation:
Xia W, Guo Y, Tian Z, Luo Y, Hu D, Shao J, Li Z and Kamel IR (2020) Clinical Features and Temporal Changes of RT-PCR and Chest CT in COVID-19 Pediatric Patients. Front. Pediatr. 8:579512. doi: 10.3389/fped.2020.579512

INTRODUCTION

Since December 2019, a newly discovered infectious disease named COVID-19, caused by a novel coronavirus (SARS-CoV-2), has wildly spread worldwide. Millions of COVID-19 patients have been confirmed, and thousands of children are also involved in this pandemic all over the world (1–3).

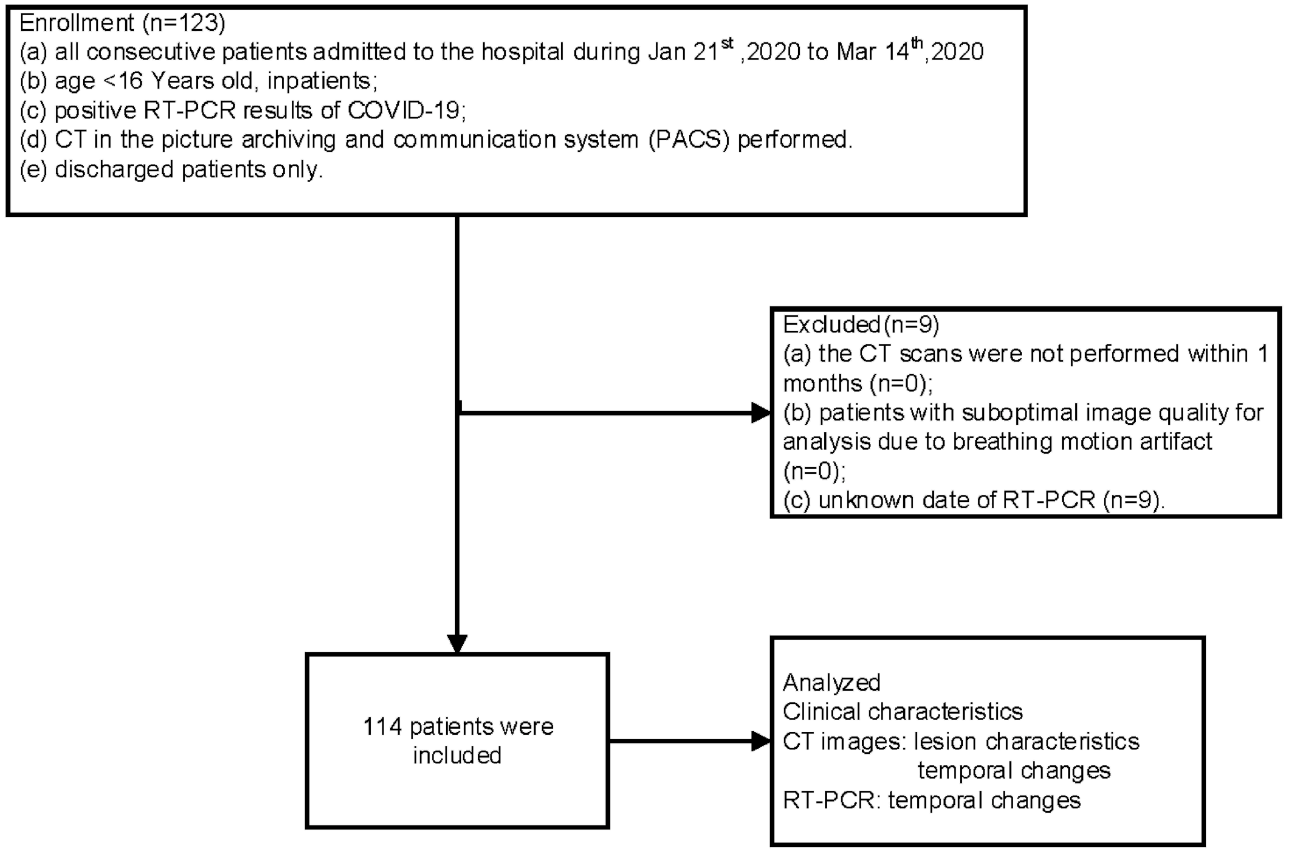

FIGURE 1 | Flow chart of this study.

To date, viral nucleic acid testing and chest CT have been considered as the main diagnostic methods for patients with suspected COVID-19 pneumonia. However, in adults, the positive rate of pharyngeal swabs reverse transcription polymerase chain reaction (RT-PCR) is only 59–61.3% (4, 5). For adults, despite the possibility of false positives, the positive rate of chest CT is significantly higher than that of RT-PCR and is considered a more accurate early diagnostic tool (6–9).

For pediatric patients with suspected COVID-19, studies on chest CT values are limited (2, 10). Some studies have suggested that normal CT or lack of typical features were not uncommon in pediatric patients, especially during the early stage of the disease (11–14). The most common CT feature of pediatric patients was bilateral ground-glass opacities with a ratio of only 32.7% (11). However, the use of CT should be carefully assessed since pediatric patients are sensitive to radiation, and reducing CT scans for children is a top priority.

Compared with adults, the risk of severe or fatal COVID-19 disease is rare, while the majority of them were mild cases requiring only conventional therapy for viral pneumonia (11–13). In clinical practice, every child with fever and signs and symptoms of respiratory infection should be considered to have COVID-19, as during this pandemic healthy carriers or children with unproven COVID-19 can spread the infection to others.

In this pandemic emergency, it is important to optimize limited medical resources, reduce the radiation dose for children, and obtain a rapid and accurate diagnosis. Thus, we performed a longitudinal study to analyze the clinical characteristics, CT manifestations, and RT-PCR changes to explore early diagnosis strategies for pediatric patients.

MATERIALS AND METHODS

Study Design and Participants

The study was performed in accordance with the Declaration of Helsinki principles and good clinical practice. The study protocol was approved by the Institutional Review Board of Wuhan Children's Hospital and Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China). Written informed consent was waived because of the emergence of this infectious disease.

A medical record review was conducted using the institution's database from January 21 to March 14, 2020 in Wuhan Children's Hospital and Tongji Hospital. A prior study including only 20 patients in Wuhan Children's Hospital only described the general clinical and CT features without follow-up and did not include the evaluation of RT-PCR (12).

TABLE 1 | Demographics of the included 114 pediatric patients.

Characteristics	Cases (percentage)
GENDER	
Male	69 (61%)
Female	45 (39%)
AGE	
<6 months	11 (10%)
6 months−6 years	47 (41%)
>6 years	56 (49%)
DURATION FROM SYMPTOM ONSET TO DISCHARGE (DAYS)	
8–14	42 (37%)
15–21	45 (39%)
22–28	15 (13%)
>28	12 (11%)
SYMPTOMS	
Fever	62 (54%)
Cough	61 (54%)
Other symptoms (sore throat, diarrhea, nasal discharge, sneezing, vomiting)	42 (37%)
CONCURRENT INFECTION	
None	80 (70%)
One other pathogen	31 (27%)
Two other pathogens	3 (3%)

Data are presented as cases (percentage), while percentage was calculated by the number of cases/114 cases.

TABLE 2 | CT characteristics of the included 114 pediatric patients.

CT characteristics	Cases (percentage)
NUMBER OF CHEST ct PERFORMED DURING HOSPITAL STAY	
1	33 (29%)
2	64 (56%)
3	14 (12%)
4	3 (3%)
INITIAL CT FINDINGS	
Normal	32 (28%)
Abnormal	82 (72%)
Unilateral lung involvement	46 (40%)
Bilateral lung involvement	36 (32%)
LOBAR INVOLVEMENT	
Right upper lobe	31 (27%)
Right middle lobe	23 (20%)
Right lower lobe	43 (38%)
Left upper lobe	25 (22%)
Left lower lobe	43 (38%)
NUMBER OF LOBES INVOLVED	
1 lobe	33 (29%)
2 lobes	30 (26%)
3 lobes	8 (7%)
4 lobes	5 (4%)
5 lobes	6 (5%)
LESION CHARACTERISTICS	
Ground-glass opacity	46 (40%)
Consolidation	46 (40%)
Nodule	7 (6%)
Thickened interlobular septa	5 (4%)

Data are presented as cases (percentage), while percentage was calculated by the number of cases/114 cases.

The inclusion criteria were (a) age <16 years old, in-patients, (b) positive RT-PCR results of COVID-19, (c) CT in the picture archiving and communication system (PACS) was performed, and (d) discharged patients only.

The exclusion criteria were (a) CT scans performed earlier than 1 month, (b) patients with suboptimal image quality for analysis due to breathing motion artifact, and (c) unknown date of RT-PCR.

The pharyngeal swab samples of all the pediatric patients in our study were collected, and SARS-CoV-2 RNA was detected by RT-PCR. The RT-PCR kits were from Wuhan Huada Biotechnology Co., Ltd., Shanghai Huirui Biotechnology Co., Ltd., or Shanghai BioGerm Medical Biotechnology Co., Ltd. These were approved by China Food and Drug Administration for the detection of SARS-CoV-2 nucleic acid.

The discharge criteria were as follows: (1) normal temperature for at least 3 days, (2) significantly improved respiratory symptoms, and (3) two consecutive SARS-CoV-2 throat swabs with negative RT-PCR results, performed at least 24 h apart. The second result of the two consecutive RT-PCR with negative results was considered as reliable.

Chest CT Protocols

All the CT scans, including repeated CT scans, were performed according to the clinical presentation judged by pediatricians. Non-enhanced chest CT was performed in either of the four CT units (SOMATOM Definition AS128, Siemens; uCT 780, United Imaging; Optima 660, GE; SOMATOM Definition AS+, Siemens) with the following parameters varying according to body weight: 80–120 kV, 50–120 mAs, and slice thickness of 10 mm. The scanning range covered from the lung apex to the diaphragm on axial plane taken under free breathing, with the patients in supine position. If necessary, 0.50 ml/kg body mass of 10% chloral hydrate was taken orally before the examination. Thin-section CT images were reconstructed with 0.625-mm collimation with a standard algorithm and then sent to the PACS for analysis.

Data Collection and Analysis

We reviewed the clinical charts of all the pediatric patients for demographic information, symptoms, date of symptom onset, admission date, discharge date, and dates and results of nucleic acid tests for COVID-19 and other identified concurrent infectious pathogens.

Two radiologists (WX and ZL, with 12 and 18 years of experience, respectively) independently reviewed the chest CT images on PACS; only decisions reached in consensus

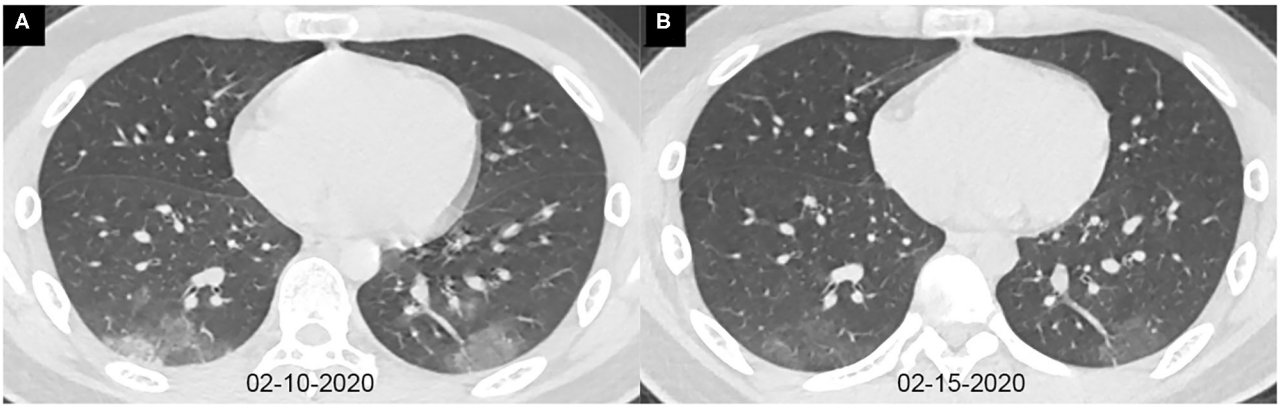

FIGURE 2 | Axial chest CT images of a 13-year-old boy with fever and cough for 10 days. Pharyngeal swab RT-PCR tests were performed on February 4, 5, and 16, 2020, with positive results, and on February 20 and 21, 2020, with negative results. Chest CTs were obtained on February 10 **(A)** and 15 **(B)**. **(A)** The typical ground-glass opacities are shown in the bilateral lower lobes. **(B)** The ground-glass opacities are obviously absorbed.

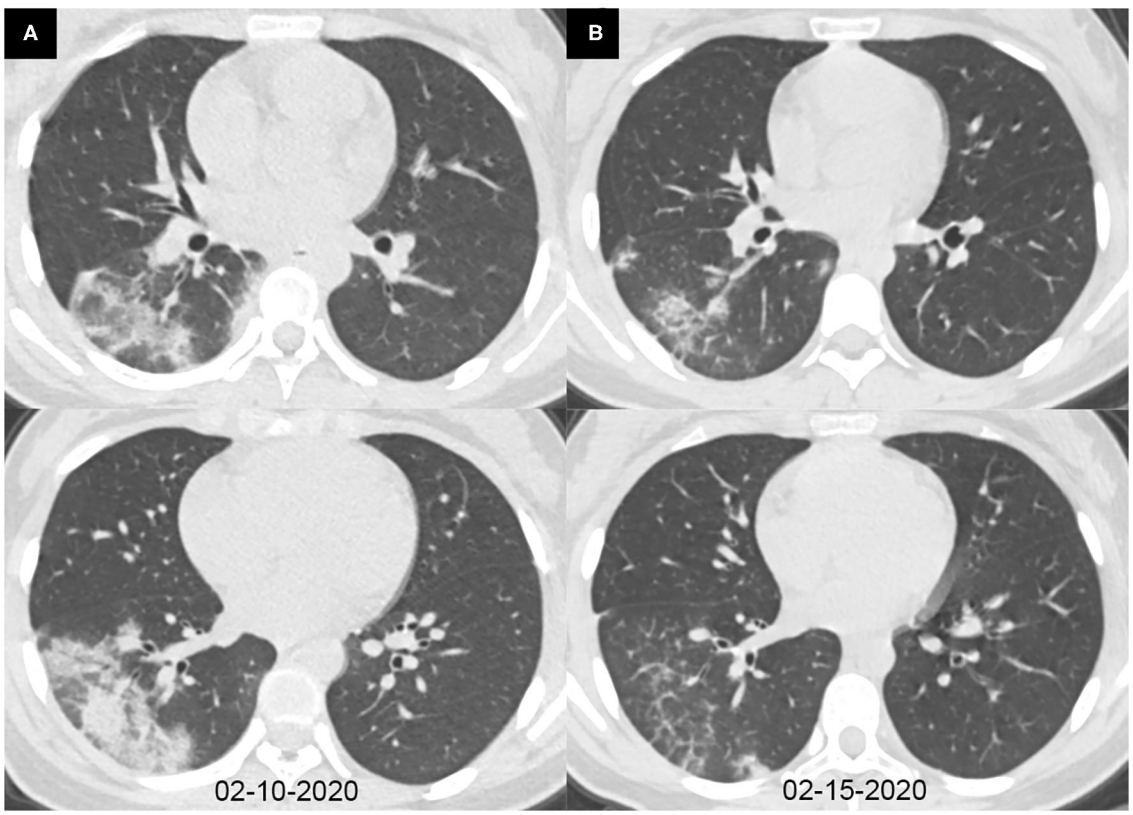

FIGURE 3 | Axial chest CT images of a 14-year-old girl with fever and cough for 6 days. Pharyngeal swab RT-PCR tests were performed on February 9, 2020, with positive results, and on February 6, 13, and 15, 2020, with negative results. Chest CTs were obtained on February 10 **(A)** and 15, 2020 **(B)**. **(A)** Consolidations were seen in the right lower lobe. **(B)** The consolidations were obviously absorbed.

were reported. The initial CT images were stratified into one of two groups: normal or abnormal groups. The CT images in the abnormal group were further assessed for imaging features including (a) unilateral or bilateral distribution, (b) lobes involved, and (c) lesion characteristics. Lesion characteristics were subcategorized into (a) ground-glass

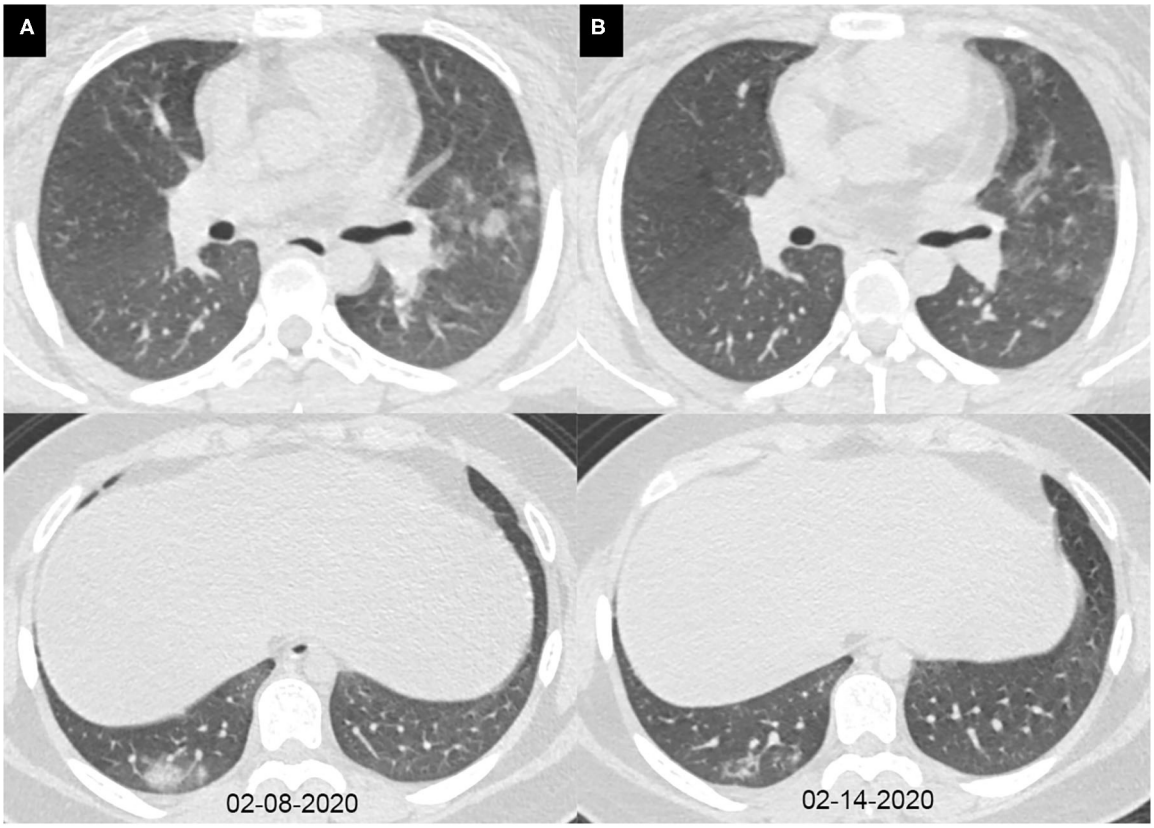

FIGURE 4 | Axial chest CT images of a 15-year-old girl with fever, cough, diarrhea, and headache for 7 days. Pharyngeal swab RT-PCR tests were performed on February 12, 2020, with positive results, and on February 15 and 17, 2020, with negative results. Chest CTs were obtained on February 8 **(A)** and 14, 2020 **(B)**. **(A)** The subpleural consolidations and nodules were seen in the right lower lobe and the left upper lobe. **(B)** The consolidations and nodules were obviously absorbed.

opacity, (b) consolidation, (c) nodule, and (d) thickened interlobular septa.

The involvement of the lung was quantified according to a previously published paper, which had applied it in adults with COVID-19 (15). We divided each lung into the upper zone (above the carina), the middle zone, and the lower zone (below the inferior pulmonary vein). Each zone was scored for percentage of lung involved on a scale of 0–4 (0 for 0% involvement, 1 for <25% involvement, 2 for 25% to <50% involvement, 3 for 50% to <75%, and 4 for more than 75% involvement). The overall CT score of lung involvement was the summation of scores from all six lung zones.

Statistics

Statistical analysis was performed using SPSS 19 (IBM Corporation, NY, USA). The day of onset of symptom was set as day 0. The cumulative percentages of cases diagnosed by RT-PCR and CT as a function of time were plotted separately. Following an initial positive RT-PCR, the cumulative percentages on first negative results and final negative results of follow-up RT-PCR were plotted as well. The CT scores of lung involvement were plotted over time. The cumulative cases diagnosed by RT-PCR and CT at different time points were compared by chi-square test, two-tailed, and $P < 0.05$ was considered as a statistically significant difference, as well as for the comparison of chest CT features between cases with and without co-infection.

RESULTS

Between January 21 and March 14, 2020, the total number of RT-PCR confirmed COVID-19 pediatric discharged patients who have undergone CT was 123. Of those, nine cases with an unknown date of RT-PCR were excluded. The final number of patients included in this cohort was 114. All included patients were residents of Wuhan. The flow chart is shown in **Figure 1**.

Clinical Characteristics

The demographics and the clinical characteristics of all the patients are summarized in **Table 1**. Male (69, 61%) and school-aged children (older than 6 years; 56, 49%) were more susceptible to COVID-19. In most cases, the duration from symptom onset to discharge was <21 days (87, 76%), with an average hospital

TABLE 3 | Comparison on CT findings between 34 patients with co-infection and 80 patients without co-infection.

CT characteristics	34 cases with co-infection (percentage)	80 cases without co-infection (percentage)	*P*-value
NUMBER OF CHEST ct PERFORMED DURING HOSPITAL STAY			
1	9/34 (26%)	24/80 (30%)	0.704
2	19/34 (56%)	45/80 (56%)	0.971
3	6/34 (18%)	8/80 (10%)	0.409
4	0/34 (0%)	3/80 (4%)	0.614
INITIAL CT FINDINGS			
Normal	8/34 (24%)	24/80 (30%)	0.386
Abnormal	26/34 (76%)	56/80 (70%)	0.482
Unilateral lung involvement	12/34(35%)	34/80 (43%)	0.473
Bilateral lung involvement	14/34(41%)	22/80 (27%)	0.151
LOBAR INVOLVEMENT			
Right upper lobe	10/34 (29%)	21/80 (26%)	0.729
Right middle lobe	7/34 (21%)	16/80 (20%)	0.943
Right lower lobe	15/34 (44%)	28/80 (35%)	0.358
Left upper lobe	10/34 (29%)	15/80 (19%)	0.208
Left lower lobe	14/34 (41%)	29/80 (36%)	0.620
NUMBER OF LOBES INVOLVED			
1 lobe	8/34 (24%)	25/80 (31%)	0.406
2 lobes	13/34(38%)	17/80 (21%)	0.060
3 lobes	0/34 (0%)	8/80 (10%)	0.131
4 lobes	3/34 (9%)	2/80 (3%)	0.313
5 lobes	2/34 (6%)	4/80 (5%)	1.000
LESION CHARACTERISTICS			
Ground-glass opacity	14/34 (41%)	32/80 (40%)	0.907
Consolidation	15/34 (44%)	31/80 (39%)	0.593
Nodule	2/34 (6%)	5/80 (6%)	1.000
Thickened interlobular septa	2/34 (6%)	3/80 (4%)	0.993

Data are presented as cases (percentage), while percentage was calculated by the number of cases/34 cases or number of cases/80, respectively. The P-values comparing the differences of CT findings between patients with and without co-infection are from chi-square test. $P < 0.05$ was considered as a statistically significant difference.

stay of 13 days. Fever (62, 54%) and cough (61, 54%) were the most common symptoms. A concurrent infection was found in 34 (30%) cases, with mycoplasma (29, 25%) being the most common concurrent infectious pathogen.

Chest CT Features

The characteristics of chest CT are reported in **Table 2**. During the hospitalization period, 97 (85%) pediatric patients had no more than two chest CTs, while 17 (15%) cases had three or more CT scans, with intervals of 1 to 21 days (average, 8.9 days). Among all the patients, initially normal chest CTs were found in 32 (28%) cases, among whom 24 patients had undergone repeated CT scans. No more than two lobes were involved in 63 (55%) cases. Unilateral lung involvement was found in 46 (40%) cases, and bilateral lung involvement was found in 36 (32%) cases. The bilateral lower lobes were most susceptible to COVID-19, with 43 cases (38%) affected in both the left and the right lower lobes, respectively. Ground-glass opacity (46, 40%) and consolidation (46, 40%) were the most common lesion patterns (see **Figures 2**, **3** for details), while nodules were found in seven (6%) cases (see **Figure 4** for details). A comparison of chest CT features between cases with and without co-infection is shown in **Table 3**.

TABLE 4 | Characteristics of RT-PCR test in 114 pediatric patients.

Characteristics	Cases (percentage)
NUMBER OF RT-PCR TESTS PERFORMED	
3	41 (36%)
4	28 (24%)
5	20 (17%)
6	11 (10%)
7	7 (6%)
8	3 (3%)
9	2 (2%)
10	1 (1%)
12	1 (1%)
DURATION FROM FIRST POSITIVE TO FINAL NEGATIVE RESULT (DAYS)	
≤7	21 (18%)
8–14	59 (52%)
15–21	25 (22%)
22–28	7 (6%)
>28	2 (2%)
TEMPORAL TENDENCY OF ALL THE RESULTS (FROM SYMPTOM ONSET)	
Positive to negative	91 (80%)
Positive to negative to positive to negative	19 (17%)
Negative to positive to negative	4 (3%)

Data are presented as cases (percentage), while percentage was calculated by the number of cases/114 cases.

RT-PCR Characteristics

Detailed information on RT-PCR is displayed in **Table 4**. All the cases have three to 12 times RT-PCR during their hospital stay, and 89 (77%) cases have five or less RT-PCR assays, with intervals of 1–13 days (average, 3.5 days). The duration from the first positive result to the final negative result was within 21 days in 105 (92%) cases. The most common temporal tendency pattern of RT-PCR was positive to negative (91, 80%).

Temporal Changes of Initial Chest CT and RT-PCR

The cumulative percentage of cases identified by RT-PCR and initial chest CT is shown in **Figure 5**. In the first week after the onset of symptoms, the cumulative percentage of RT-PCR and CT both increased rapidly. On the 4th day after the onset of symptoms, 72 (63%) patients had a positive RT-PCR, but only 36 (42%) patients had infiltrates in the chest CT at the same time (χ^2

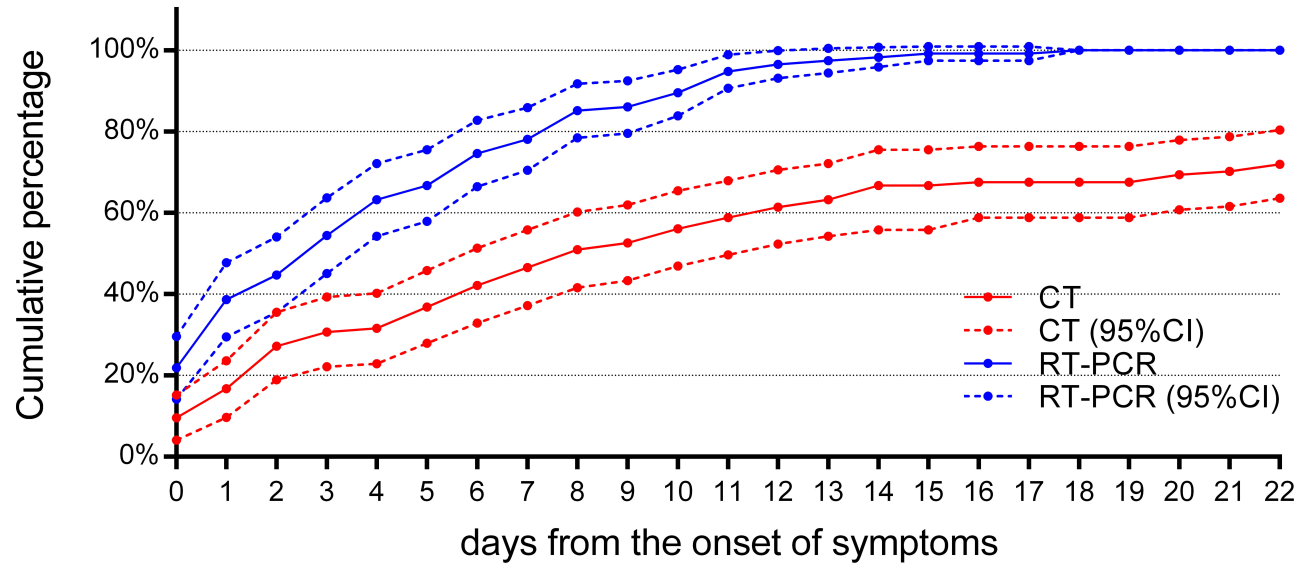

FIGURE 5 | The cumulative percentage of identified cases by RT-PCR and chest CT. Both curves of RT-PCR and CT increased rapidly after the onset of symptoms (n = 114). By the 7th day after the onset of symptoms, 89 (78%) cases have been confirmed by RT-PCR, compared to 53 (46%) cases by chest CT ($P < 0.05$). By day 14 after the onset of symptoms, RT-PCR diagnosed 112 (98%) cases, but chest CT was positive in only 76 (67%) cases ($P < 0.05$). 95% CI, 95% confidence interval.

= 22.8, $P < 0.05$). On the 7th day after the onset of symptoms, RT-PCR confirmed 89 cases (78%) of COVID-19 pneumonia, while chest CT confirmed only 53 cases (46%) ($\chi^2 = 24.2$, $P < 0.05$). By the 14th day of symptom onset, 112 cases (98%) were confirmed by RT-PCR, but only 76 cases (67%) were positive for chest CT ($\chi^2 = 39.3$, $P < 0.05$). At 18 days after the onset of symptoms, the last patient was confirmed by RT-PCR, compared to 77 (68%) identified cases by CT ($\chi^2 = 44{\cdot}2$, $P < 0.05$). As the chest CT of 32 children was normal, the cumulative percentage of cases identified by CT was only 72% (82), compared to 114 (100%) cases identified by RT-PCR ($\chi^2 = 37.2$, $P < 0.05$), by day 22 after the onset of symptoms. Throughout the whole duration of COVID-19 in children, the diagnostic positive rate of RT-PCR has been far higher than that of CT (all $P < 0.05$), as shown in **Table 5**.

At the same time, it was found that, after the first week of symptoms, the rise of cumulative percentage of cases identified by RT-PCR and chest CT became less and reached a plateau after 11 days. Compared with the initial chest CT, the cumulative percentage of cases identified by RT-PCR is more significant.

Temporal Changes of RT-PCR and Chest CT

For treatment response, a review of the follow-up RT-PCR for children indicated that (**Figure 6**) there were no reliable negative RT-PCR results until 7 days after the onset of symptoms; otherwise, it should be false negative. There were 52 (46%) reliable negative RT-PCR result cases on the 14th day, 92 (81%) cases on the 21st day, and 106 (93%) cases on the 28th day, and the latest time for RT-PCR to turn negative was 37 days after the onset of symptoms.

A total of 215 chest CTs were obtained from 114 children with COVID-19. In **Figure 7**, the CT scores on lung involvement were plotted as a function of time. The CT score reached 14 in one case during 0–5 days from the onset of symptoms, but the median values of the CT scores were low before the 11th day from the onset of symptoms, with a median value of 1. The median value of CT score on lung involvement reached a peak at 12–17 days, with a median value of 2. After the 24th day from the onset of symptoms, the median value of CT score fell back to 1.

DISCUSSION

In the current study, the length of hospital stay in most pediatric patients with COVID-19 (average, 13 days) was not significantly different from pneumonia caused by other pathogens (average, 11.2 days) (16). Interestingly, the number of pediatric patients younger than 6 months was significantly less than that in other age groups, which may be related to residual protection from maternal immune factors, such as virus-specific antibodies according to Zeng et al. (17). The number of patients in two other age groups was not significantly different from each other. Similar to results reported in previous studies, according to lung involvement, the majority of cases were mild cases (11, 12, 18). Severe and fatal cases in pediatric patients were very rare. Thus, except for treatment for individuals, early diagnosis to avoid the further spread of the disease was an essential issue under this pandemic circumference.

In the current study, chest CT had similar characteristic manifestations including ground-glass opacities and consolidations with bilateral lower lobes, as was recently published (12, 19). Of all COVID-19-positive children in this study, completely normal chest CT was not uncommon,

infiltrates on chest CT were not severe in most of them, and concurrent infections may lead to ambiguous CT imaging. Similar to previous studies, CT of the chest is often atypical, especially in the early stage, resulting in difficulty in diagnosing or ruling out COVID-19 (20). In addition, in our study, the cumulative percentage of identified cases by chest CT was low throughout the course of COVID-19, compared to RT-PCR. This is totally different from the results of related research in adults. In adults, as an important complementary tool for less-sensitive and time-consuming RT-PCR, chest CT has first been considered as a diagnostic tool for clinically confirmed cases of COVID-19 in China (21, 22). Considering that the clinical manifestations and CT features of most children are mild, CT has limited diagnostic value for children (especially 0–7 days after onset). Therefore, CT of the chest is of limited value in diagnostic algorithm and should be discouraged to reduce the radiation dose to children.

In the current study, throughout the entire course of COVID-19 pneumonia in children, the diagnostic positive rate of CT has been far lower than that of RT-PCR (all $P < 0.05$), and 28% of children have no obvious abnormal signs of CT. However, in adults, previous studies have shown that the positive rate of RT-PCR is only 59–61.3%, while the positive rate of chest CT is 88% (4, 5). These findings suggest that most infected pediatric patients have less lung involvement in the early stages of COVID-19 infection. As some COVID-19 cases confirmed by RT-PCR could have no lesions on chest CT, pathogen identification by RT-PCR has a more important role in the management of an infectious source. RT-PCR may be more reliable than CT in pediatric patients' diagnosis, and repeated RT-PCR every other day is the recommended screening for pediatric patients during the first 7 days.

In addition, the main indicator of children's discharge criteria is to determine the reliable RT-PCR negative examination results. As inappropriate sampling, preservation, and processing may lead to a low virus level, we may inevitably get false negative RT-PCR results in treatment response evaluation. Our research shows that negative RT-PCR results obtained 7 days after the onset of symptoms are reliable. This indicates that, for children whose clinical symptoms have disappeared and who may totally recover, follow-up tests of RT-PCR must be performed at least after day 7 to evaluate the efficacy.

To reduce radiation dose among the pediatric patients included in this study, most cases (85%) had one or two chest CT scans during their hospital stay. In our study, it was found that the median values of CT scores were low before the 11th day from the onset of symptoms, with a median value of 1. The median value of CT score on lung involvement reached a peak at 12–17 days, with a median value of 2. After the 24th day from onset of symptoms, the median value of CT score fell back to 1. Compared to the median CT score of 5 on lung involvement in adults reported in a previous study (15), it indicates that children with COVID-19 pneumonia are relatively mild. As reported, lung involvement peaked on 6–11 days from symptom onset in adults, while the delayed peaking in children may be related to a different immune reaction to the virus (15). In our study, the CT score reached 14 in one case during 0–5 days from the onset of symptoms, which suggested that rapid progression could also be observed in pediatric patients, even if it was rare.

TABLE 5 | Comparison of identified cases by RT-PCR and chest CT over time.

Days from symptom onset (days)	Chest CT	RT-PCR	*P*-value
	Cases (percentage, 95% CI)	Cases (percentage, 95% CI)	
0	11/114 (10%, 4–15%)	25/114 (22%, 14–30%)	0.011
1	19/114 (17%, 10–24%)	44/114 (39%, 30–48%)	<0.001
2	31/114 (27%, 19–36%)	51/114 (45%, 36–54%)	0.006
3	35/114 (31%, 22–39%)	62/114 (54%, 45–64%)	<0.001
4	36/114 (32%, 23–40%)	72/114 (63%, 54–72%)	<0.001
5	42/114 (37%, 28–46%)	76/114 (67%, 58–76%)	<0.001
6	48/114 (42%, 33–51%)	85/114 (75%, 66–83%)	<0.001
7	53/114 (46%, 37–56%)	89/114 (78%, 70–86%)	<0.001
8	58/114 (51%, 42–60%)	97/114 (85%, 78–92%)	<0.001
9	60/114 (53%, 43–62%)	98/114 (86%, 80–92%)	<0.001
10	64/114 (56%, 47–65%)	102/114 (89%, 84–95%)	<0.001
11	67/114 (59%, 50–68%)	108/114 (95%, 91–99%)	<0.001
12	70/114 (61%, 52–71%)	110/114 (96%, 93–100%)	<0.001
13	72/114 (63%, 54–72%)	111/114 (97%, 94–100%)	<0.001
14	76/114 (67%, 58–76%)	112/114 (98%, 96–101%)	<0.001
15	76/114 (67%, 58–76%)	113/114 (99%, 97–101%)	<0.001
16	77/114 (68%, 59–76%)	113/114 (99%, 97–101%)	<0.001
17	77/114 (68%, 59–76%)	113/114 (99%, 97–101%)	<0.001
18	77/114 (68%, 59–76%)	114/114 (100%, 100–100%)	<0.001
19	77/114 (68%, 59–76%)	114/114 (100%, 100–100%)	<0.001
20	79/114 (69%, 61–78%)	114/114 (100%, 100–100%)	<0.001
21	80/114 (70%, 62–79%)	114/114 (100%, 100–100%)	<0.001
22	82/114 (72%, 64–80%)	114/114 (100%, 100–100%)	<0.001

Data are presented as cases (percentage), while percentage was calculated by the number of cases/114 cases. P-values comparing the differences of cumulative diagnosed cases between RT-PCR and CT at different time points are from chi-square test. $P < 0.05$ was considered as a statistically significant difference. 95% CI, 95% confidence interval.

There are several limitations in our study. First, even if the sample was the largest as we know, the overall cases in the two included hospitals were still limited. Second, as a retrospective study, selection bias could not be avoided. Third, during this outbreak period of COVID-19, delay in seeking care (more than 7 days from symptom onset) would influence the diagnosis and the prognosis.

In conclusion, chest CT is not recommended as a primary method for early diagnosis in children with COVID-19, especially to avoid repeated CT scans. While RT-PCR may have a more valuable position, repeated RT-PCR every other day is the recommended screening for pediatric patients during the first 7 days. For treatment response, reliable negative RT-PCR follow-up results, in accordance with discharge criteria, are not available until at least 7 days after the onset of symptoms. CT can be employed as a tool to assess lung involvement only if necessary.

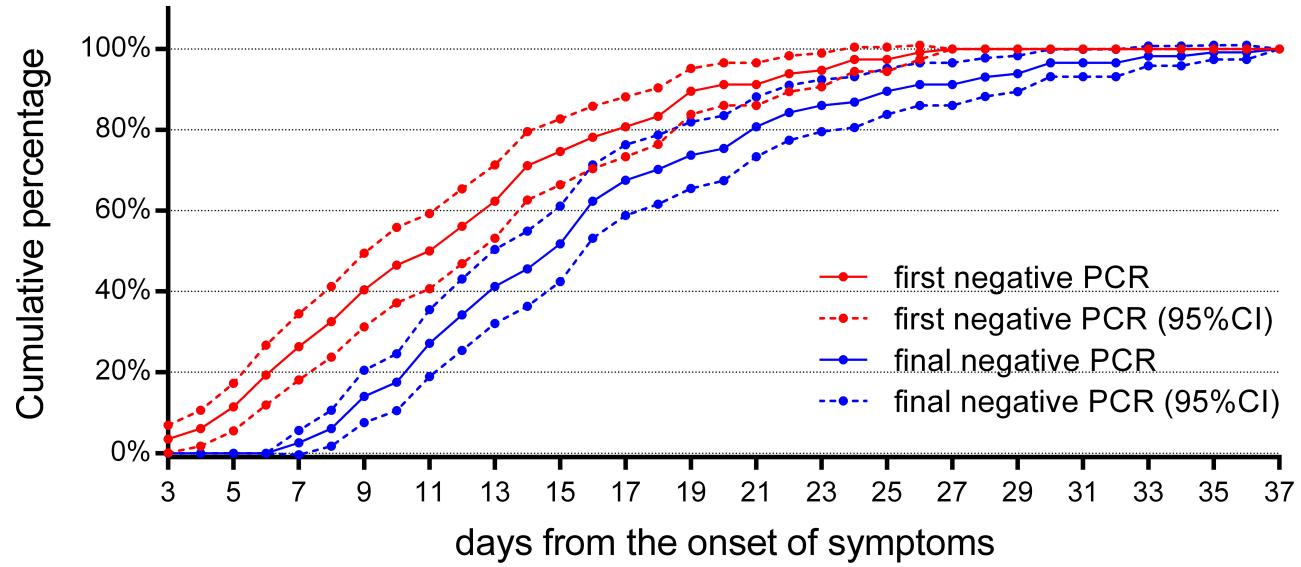

FIGURE 6 | The cumulative percentages of the follow-up RT-PCR. The cumulative percentages of the first and the final negative results of follow-up RT-PCR (n = 114). The first negative RT-PCR results could be obtained as early as 3 days from the onset of symptoms in four cases, but they returned to positive later. A reliable final negative RT-PCR result could not be obtained until 7 days after the onset of symptoms. 95% CI, 95% confidence interval.

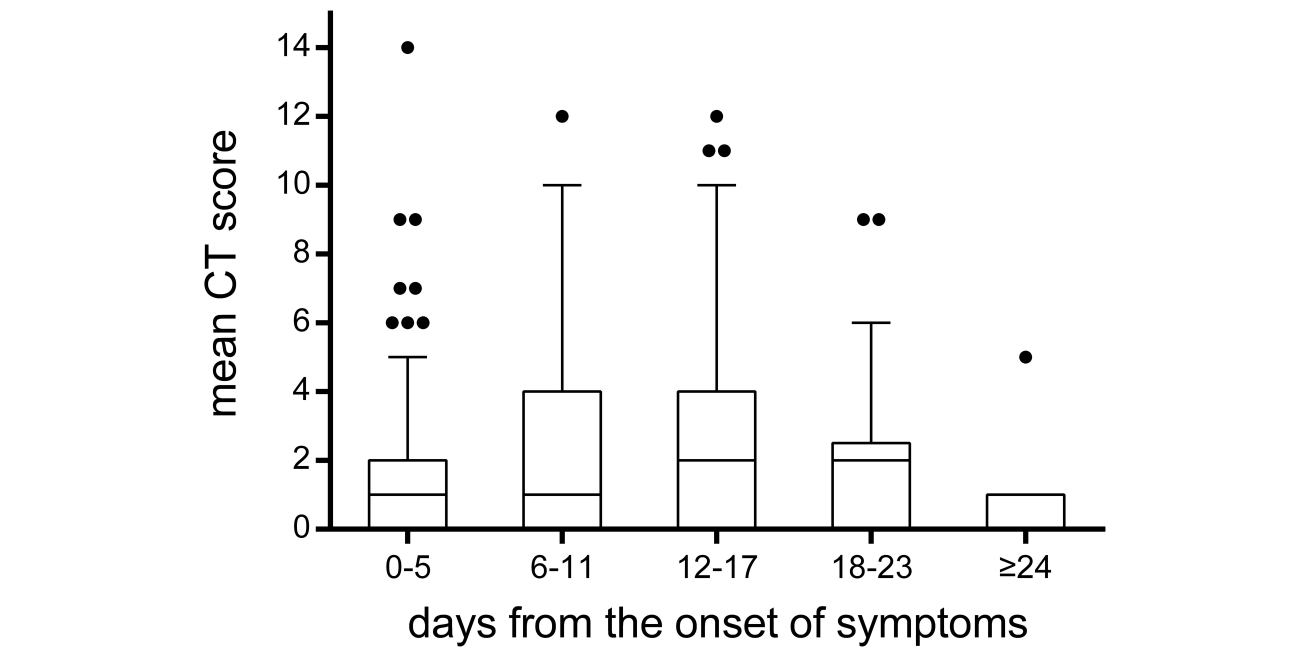

FIGURE 7 | The temporal change of CT scores on lung involvement. The CT scores on lung involvement in all chest CT scans (n = 215). Throughout the whole duration of COVID-19 in children, the median value of CT scores was low, with a median value of 1 or 2. It was worth noting that the CT score reached 14 in one case during 0–5 days from the onset of symptoms. The bounds of the boxes represent the 25th to the 75th percentiles; the line in the middle of the box is plotted as the median. The whiskers and the outliers are drawn according to Tukey method.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Wuhan Children's

Hospital and Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

WX, ZL, and DH conceived and designed the study. YG, YL, and DH contributed to the literature search. WX, YG, and YL collected the data. WX and YG analyzed the data. WX drafted the manuscript. ZL and IK revised the manuscript. WX and ZL had full access to all data in the study and took responsibility for the integrity of data and the accuracy of the data analysis. All authors reviewed and approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported by the National Natural Science Foundation of China (81771801), Hubei Province Health and Family Planning Scientific Research Project (WJ2018H0160), HUST Innovation Project 2020 (2020kfyXGYJ031), and Wuhan Children's Hospital Foundation (2020FE002). The funding organization had no role in study design, data collection, data analysis, and manuscript preparation and publication decision. This work was the responsibility of the authors.

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
2. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032
3. Kandel N, Chungong S, Omaar A, Xing J. Health security capacities in the context of COVID-19 outbreak: an analysis of international health regulations annual report data from 182 countries. *Lancet*. (2020) 395:1047–53. doi: 10.1016/S0140-6736(20)30553-5
4. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 Cases. *Radiology*. (2020) 296:E32–40. doi: 10.1148/radiol.2020200642
5. Yang Y, Yang M, Shen C, Wang F, Yuan J, Li J, et al. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. *medRxiv [Preprint]*. (2020). doi: 10.1101/2020.02.11.20021493
6. Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, et al. Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection. *Radiology*. (2020) 295:200463. doi: 10.1148/radiol.2020200463
7. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, et al. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. *Radiology*. (2020) 296:E115–7. doi: 10.1148/radiol.2020200432
8. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. *Radiology*. (2020) 295:715–21. doi: 10.1148/radiol.2020200370
9. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for typical 2019-nCoV pneumonia: relationship to negative RT-PCR testing. *Radiology*. (2020) 296:E41–5. doi: 10.1148/radiol.2020200343
10. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese center for disease control and prevention. *JAMA*. (2020) 323:1239–42. doi: 10.1001/jama.2020.2648
11. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 infection in children. *N Engl J Med*. (2020) 382:1663–5. doi: 10.1056/NEJMc2005073
12. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: different points from adults. *Pediatr Pulmonol*. (2020) 55:1169–74. doi: 10.1002/ppul.24718
13. Liu W, Zhang Q, Chen J, Xiang R, Song H, Shu S, et al. Detection of covid-19 in children in early january 2020 in Wuhan, China. *N Engl J Med*. (2020) 382:1370–1. doi: 10.1056/NEJMc2003717
14. Yu N, Li W, Kang Q, Xiong Z, Wang S, Lin X, et al. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. *Lancet Infect Dis*. (2020) 20:559–64. doi: 10.1016/S1473-3099(20)30176-6
15. Wang Y, Dong C, Hu Y, Li C, Ren Q, Zhang X, et al. Temporal changes of CT findings in 90 patients with COVID-19 pneumonia: a longitudinal study. *Radiology*. (2020) 296:E55–64. doi: 10.1148/radiol.2020200843
16. Wen ZH, Wei J, Xue HL, Chen YQ, Melnick D, Gonzalez J, et al. Epidemiology, microbiology, and treatment patterns of pediatric patients hospitalized with pneumonia at two hospitals in China: a patient chart review study. *Therap Clin Risk Manag*. (2018) 14:501–10. doi: 10.2147/TCRM.S143266
17. Zeng H, Xu C, Fan J, Tang Y, Deng Q, Zhang W, et al. Antibodies in infants born to mothers with COVID-19 pneumonia. *JAMA*. (2020) 323:1848–9. doi: 10.1001/jama.2020.4861
18. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. (2020) 382:727–33. doi: 10.1056/NEJMoa2001017
19. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). *Radiology*. (2020) 295:202–7. doi: 10.1148/radiol.2020200230
20. Virkki R, Juven T, Rikalainen H, Svedstrom E, Mertsola J, Ruuskanen O. Differentiation of bacterial and viral pneumonia in children. *Thorax*. (2002) 57:438–41. doi: 10.1136/thorax.57.5.438
21. General Office of the National Health Commission of China. *Diagnosis and Treatment Protocol for 2019-nCoV (Fifth Trial Edition)*. (2020). Available online at: http://www.nhc.gov.cn/yzygj/s7653p/202002/d4b895337e19445f8d728fcaf1e3e13a.shtml (accessed June 24, 2020).
22. Yang W, Yan F. Patients with RT-PCR confirmed COVID-19 and normal chest CT. *Radiology*. (2020) 295:E3. doi: 10.1148/radiol.2020200702

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

REVIEW
published: 30 October 2020
doi: 10.3389/fped.2020.593282

Noninvasive Ventilation and Mechanical Insufflator-Exsufflator for Acute Respiratory Failure in Children With Neuromuscular Disorders

Tai-Heng Chen [1,2,3] *and Jong-Hau Hsu* [1,4]*

[1] *Department of Pediatrics, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan,* [2] *Department of Emergency, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan,* [3] *Department of Biological Sciences, University of Southern California, Los Angeles, CA, United States,* [4] *Department of Pediatrics, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*

OPEN ACCESS

Edited by:
Ron Rubenstein, Washington University in St. Louis, United States

Reviewed by:
Oren Kupfer, Children's Hospital Colorado, United States
Ignacio Tapia, Children's Hospital of Philadelphia, United States

***Correspondence:**
Jong-Hau Hsu
jhh936@yahoo.com.tw

Specialty section:
This article was submitted to Pediatric Pulmonology, a section of the journal Frontiers in Pediatrics

Received: *10 August 2020*
Accepted: *12 October 2020*
Published: *30 October 2020*

Citation:
Chen T-H and Hsu J-H (2020) Noninvasive Ventilation and Mechanical Insufflator-Exsufflator for Acute Respiratory Failure in Children With Neuromuscular Disorders. Front. Pediatr. 8:593282. doi: 10.3389/fped.2020.593282

Children with neuromuscular disorder (NMD) usually have pulmonary involvement characterized by weakened respiratory muscles, insufficient coughing, and inability to clear airway secretions. When suffering from community-acquired pneumonia, these patients are more likely to develop acute respiratory failure (ARF). Therefore, recurrent pneumonias leading to acute on chronic respiratory failure accounts for a common cause of mortality in children with NMD. For many years, noninvasive ventilation (NIV) has been regarded as a life-prolonging tool and has been used as the preferred intervention for treating chronic hypoventilation in patients with advanced NMD. However, an increasing number of studies have proposed the utility of NIV as first-line management for acute on chronic respiratory failure in NMD patients. The benefits of NIV support in acute settings include avoiding invasive mechanical ventilation, shorter intensive care unit or hospital stays, facilitation of extubation, and improved overall survival. As the difficulty in clearing respiratory secretions is considered a significant risk factor attributing to NIV failure, combined coughing assistance of mechanical insufflator-exsufflator (MI-E) with NIV has been recommended the treatment of acute neuromuscular respiratory failure. Several recent studies have demonstrated the feasibility and effectiveness of combined NIV and MI-E in treating ARF of children with NMD in acute care settings. However, to date, only one randomized controlled study has investigated the efficacy of NIV in childhood ARF, but subjects with underlying NMD were excluded. It reflects the need for more studies to elaborate evidence-based practice, especially the combined NIV and MI-E use in children with acute neuromuscular respiratory failure. In this article, we will review the feasibility, effectiveness, predictors of outcome, and perspectives of novel applications of combined NIV and MI-E in the treatment of ARF in NMD children.

Keywords: noninvasive ventilation, neuromuscular disorder, acute respiratory failure, mechanically assisted coughing, risk factors

PATHOPHYSIOLOGY UNDERLYING ACUTE RESPIRATORY FAILURE IN CHILDREN WITH NEUROMUSCULAR DISORDER

Neuromuscular disease (NMD) is a heterogeneous group of diseases caused by various defects from multiple sources, including skeletal muscle, motor neurons, peripheral nerves, and neuromuscular junctions (1–4). Most primary NMD is associated with an inherited gene defect and usually onset in childhood with progressive degeneration. Due to weakened either one or all of the main respiratory muscle groups and impaired coughing ability, the respiratory dysfunction represents not only a critical health issue but a frequent unmet medical need of NMD patients (2, 5, 6).

Children with NMD may have progressively developed chronic respiratory failure in the process of disease course. However, episodic attacks of acute respiratory failure (ARF) may further aggravate the already existed respiratory compromises (7). Factors posing a risk of ARF in children with NMD are usually multifactorial and occur simultaneously (8–11). **Table 1** summarizes the risk levels of various NMD potentially affected by the acute respiratory compromise. According to the timing of ARF occurrence, NMD can also be classified into two main categories: (1) early-onset (may as early as in neonatal period) with rapidly progressive NMD with acute episodes of respiratory failure; (2) late-onset and slowly progressive NMD with acute exacerbations of chronic respiratory failure (12, 14).

As shown in **Figure 1**, the pathophysiological mechanism of respiratory muscle groups involved in NMD patients can be summarized into three main components and several predisposing factors (6, 7, 9, 13, 14). First, the weakness of bulbar muscles impedes the protection against the risk of aspiration

TABLE 1 | Risk levels and susceptible age groups of acute respiratory compromises in different neuromuscular disorders.

Primarily affected age group	Risk level of ARF occurrence	Affected NMD
At birth or within the first year of life	Usually inevitable if untreated	Spinal muscular atrophy (SMA) type 1 (if untreated)* Spinal muscular atrophy with respiratory distress (SMARD) Congenital myotonic dystrophy (type 1) Infantile Pompe disease (if untreated)* Some congenital myopathies (e.g., neonatal form of nemaline myopathy, minicore myopathy, and X-linked myotubular myopathy) Some congenital muscular dystrophies (CMD) (e.g., Walker-Warburg syndrome and Muscle–eye–brain disease) Some mitochondrial diseases Some congenital myasthenic syndromes
Infant-to-adult life	Very high risk	Some limb-girdle muscular dystrophy (LGMD), especially with sarcoglycanopathies (LGMD types 2C, 2D, 2E, 2F) and LGMD type 2I Some CMD, especially merosin negative types 1A, 1B, 1C Some myofibrillar myopathies (e.g., hereditary myopathy with early respiratory failure) Early-onset infantile facioscapulohumeral muscular dystrophy (FSHD) Early-onset Charcote-Marie-Tooth disease (CMTD) especially with *GDAP1* mutation Some congenital myopathies (e.g., severe recessive type of central core myopathy)
infant-to-adult life	High risk	Duchenne muscular dystrophy (DMD), usually after second decade SMA type 2 Myotonic dystrophy type 1 (DM1) Late-onset Pompe disease (LOPD) Some CMD (e.g., Ullrich type, and Fukuyama congenital muscular dystrophy) Some LGMD (e.g., calpainopathy) Some congenital myopathies (e.g., centronuclear myopathy) Bethlem myopathy Congenital myasthenic syndromes Some mitochondrial myopathies (e.g., A3243G mutation in the $tRNA^{Leu}$ gene)
	Intermediate risk	Becker muscular dystrophy (BMD) SMA type 3 Inflammatory myopathies (e.g., polymyositis, dermatomyositis) Classical type of FSHD Some types of Charcot–Marie–Tooth disease (e.g., CMTD type 1B and 4) Some congenital myopathies Some mitochondrial myopathies Guillain–Barré syndrome (GBS) Myasthenia gravis (MG)
	Low risk	Oculopharyngeal muscular dystrophy (OPMD) Other types of CMTD Chronic inflammatory demyelinating polyneuropathy (CIDP)

**Novel therapies are currently available (e.g., enzyme replacement, antisense nucleotide, and gene therapy) to be delivered in the neonatal period.*
Data of this table are modified and summarized from references: (11–13).

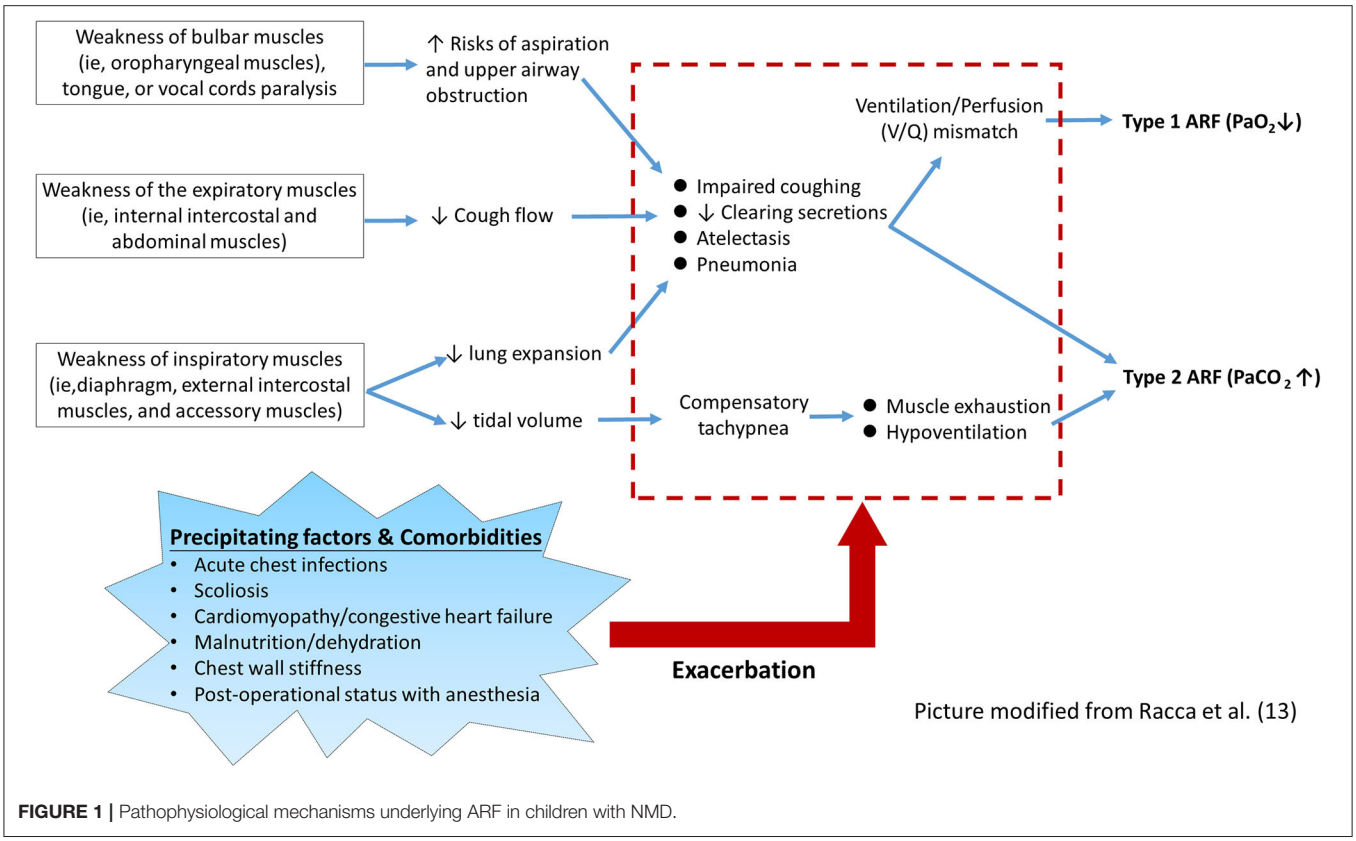

FIGURE 1 | Pathophysiological mechanisms underlying ARF in children with NMD.

of the food or airway secretions, which may lead to frequent atelectasis and pneumonia (14). Additionally, weakness of bulbar muscles and tongue, and paralysis of vocal cords may cause mechanical obstruction of the upper airway, particularly in the supine position, and increase the likelihood of aspiration (9, 14). Second, weakness of the inspiratory muscles leads to reduced lung expansion and impaired coughing ability, which may lead to a ventilation/perfusion mismatch and consequent hypoxemia. Compensatory tachypnea due to small tidal volumes may further increase the mechanical load on already weakened respiratory muscles (6, 7, 13). Third, the weakness of expiratory muscles leads to ineffective coughing and encumbrance of airway secretion, which consequently increases breathing load (14).

On the other hand, other systemic involvements associated with NMD may further aggravate the impairment of lung function, which precipitate the occurrence of ARF (5, 6, 14, 15). In the advanced stage of NMD, progressive scoliosis is common and usually causes reduced chest wall compliance and unequal lung expansion. Patients with certain types of NMD, such as Duchenne muscular dystrophy and Emery-Dreifuss muscular dystrophy, frequently have cardiac involvement that may further worsen the respiratory function (e.g., pulmonary edema related to congestive heart failure) (11, 12). ARF may also occur in the perioperative period of some major surgeries, for example, correction of scoliosis or insertion of percutaneous gastrostomy. Such ARF episodes usually happen after extubation and are associated with bulbar dysfunction, postoperative pain, use of pain medications, or atelectasis caused by mucus plugging (16, 17). Malnutrition and dehydration developing during an acute illness should be aggressively intervened, as unmet caloric and metabolic needs may further aggravate ARF. Thus, each of these comorbidities necessitates multidisciplinary interventions and meticulous monitoring (5, 18–23).

In most cases, the occurrence of ARF in children with NMD is usually initiated by an upper respiratory tract infection, followed by complications of congested airway secretions, mucus plugs, and atelectasis (9, 24, 25). In addition, increased nasal airflow resistance with nasal congestion in the setting of pre-existing upper airway obstruction from bulbar dysfunction also increases respiratory muscle load in the absence of bronchial secretions. Due to community pneumonia, the decreased lung compliance and the increased workload of already weak muscles may further contribute to the onset of ARF (6). Among children with NMD, ARF is the main cause of unscheduled admissions and prolonged stay in the pediatric intensive care unit (ICU) (11, 26). Moreover, complications known to be associated with prolonged ICU stay and conventional invasive mechanical ventilator (IMV) may also contribute to high ICU mortality (27, 28). As a consequence, acute-on-chronic respiratory failure represents the most common cause of morbidity and mortality in children with NMD (9, 29).

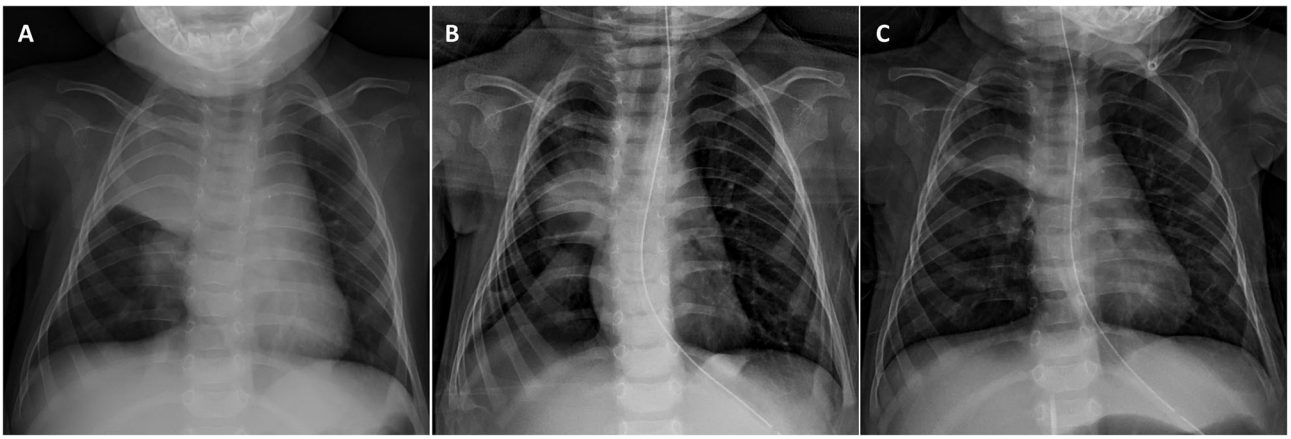

FIGURE 2 | Resolution of right upper lobe opacification in an infant with severe type 1 spinal muscular atrophy (SMA) after combining NIV and MI-E. **(A)** Chest X-ray on admission showing right lung pneumonia with significant atelectasis complicated by copious secretions. **(B)** A significant improvement was found after 2-days treatment, with a resolution of atelectasis. **(C)** A progressive improvement of the pneumonic patch was observed on day 7 when discharged from PICU.

NONINVASIVE VENTILATION IN CHILDHOOD ACUTE NEUROMUSCULAR RESPIRATORY FAILURE

In the past few decades, noninvasive ventilation (NIV) has been regarded as a life-prolonging tool for managing chronic respiratory failure in patients with NMD (6, 11, 21, 30). On the other hand, recent studies and guidelines have also proposed the role of NIV as a first-line intervention for ARF in NMD patients to avoid endotracheal intubation and the use of invasive mechanical ventilation (IMV) (11, 31, 32). Support for alternative use of NIV is based on concerns about the many complications of IMV use in patients with NMD. These include laryngeal edema, subglottic stenosis, barotrauma, and ventilator-associated pneumonia, leading to subsequent tracheotomy and poor quality of life (17, 33–35). Besides, long-term dependence on IMV and prolonged ICU stay are associated with nosocomial infections, aspiration, atelectasis, thromboembolic events, contractures, and bedsores, all of which can lead to high mortality in NMD patients (8). In this regard, emerging evidence supports the alternative NIV administration to manage ARF in patients with NMD (36–38). Indeed, several studies have indicated several potential benefits of NIV in treating ARF of NMD patients, including shortening the ICU and hospital stay, facilitating extubation, and improving the overall survival (16, 39–42).

ROLE OF AGGRESSIVE SECRETION MANAGEMENT IN MANAGING ARF OF NMD CHILDREN

Mucociliary clearance is generally not affected by NMD, except for damage to the ciliary epithelium due to repeat aspiration or acute chest infection (43). Aggressive secretion clearance is crucial for children with NMD to avoid progression to severe respiratory compromises during respiratory infections (44, 45). Also, excessive secretion has been regarded as a major risk factor causing NIV failure in treating ARF of NMD patients (6, 46, 47). Therefore, facilitating secretion clearance and normalizing gas exchange by augmenting cough ability is the mainstay to treat ARF in children with NMD (48).

Although NMD patients rarely achieve sufficient chest and abdomen pressure due to the weakness of the intercostal and abdominal muscles, the coughing can be augmented manually or mechanically. Among various coughing-assist techniques, the mechanical insufflator-exsufflator (MI-E) represents the most powerful tool that can promote the most effective peak flow to expel mucus plugging and resolve atelectasis (7, 49, 50). MI-E can deliver a brief positive inspiratory pressure through a mask, mouthpiece, tracheostomy, or endotracheal tube to fully expand the chest, allowing air to enter the distal end of the mucus plugging, and then applying negative pressure, resulting in expiratory "cough" flow to remove airway secretions (45). A previous study showed that MI-E is superior to manual cough assistance in increasing cough flow in healthy subjects as well as in patients with amyotrophic lateral sclerosis (ALS), regardless of bulbar weakness (51). The additional use of MI-E helps to resolve excessive secretions and eliminate the risk of NIV failure in treating ARF of NMD patients. Therefore, recent evidence suggests that combining NIV and MI-E can be used as the first-line treatment for ARF in children with NMD (14, 44, 45, 47, 50). Our experiences also show that it can effectively treat ARF even for the most severe types of NMD (**Figure 2**).

EFFECTIVENESS OF NIV IN POST-EXTUBATION SUPPORT FOR CHILDREN WITH NMD

After recovering from an acute illness or surgery requiring sedation, a considerable number of NMD patients may not pass the IMV-dependent weaning tests, resulting in a high failure rate

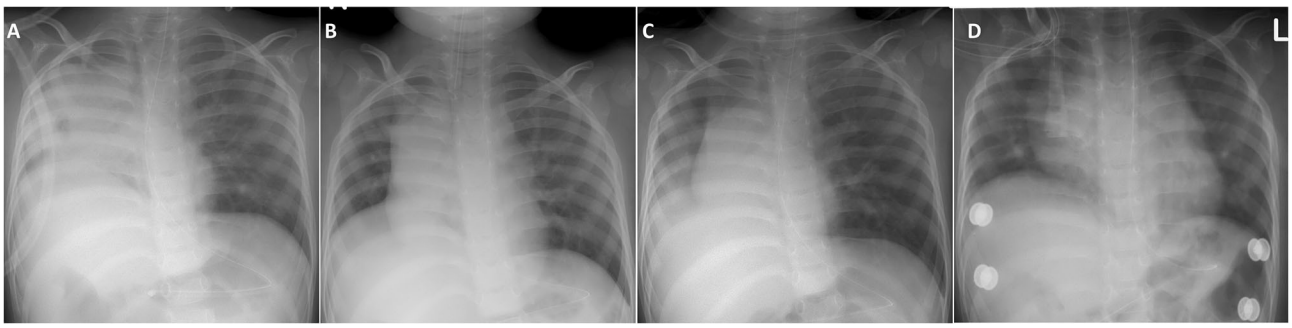

FIGURE 3 | Demonstration of chest X-ray in a toddler with congenital myopathy who immediately received NIV and MI-E for post-extubation respiratory support. **(A)** Previously failed extubation in another hospital was related to frequent right lung atelectasis and mucus plugging developing soon after extubation. **(B)** In our hospital, appropriate expansion of both lungs were noted before extubation. **(C)** Day 2 post-extubation showed mild right lung infiltration without atelectasis. **(D)** Discharge from PICU on day 7 post-extubation showed re-expansion of both lungs.

of extubation (26–28). Post-extubation ARF in NMD patients shares several pathomechanism features with episodic ARF, such as weak respiration drive, airway mucus-plugging due to difficulty in expectorating secretion, mostly categorized as type 2 (hypercapnic) ARF (28). The advent of active NIV support reduces the need for extensive weaning trials before extubation, which requires prolonged pressure support and spontaneous breathing. Some studies have validated that prompt NIV and MI-E use after extubation can significantly eliminate the risk of reintubation in NMD patients (40, 52, 53). There is a general agreement that, if not contraindicated (e.g., uncontrolled airway secretions or severe bulbar dysfunction), patients with chronic NMD should be extubated directly to NIV combined with MI-E (28, 54). The effectiveness of this NIV support is significant in preventing reintubation in young children with NMD (**Figure 3**).

REVIEW OF CLINICAL STUDIES ON NIV FOR THE TREATMENT OF ACUTE-ON-CHRONIC NEUROMUSCULAR RESPIRATORY FAILURE

There are relatively few prospective studies on the management of NMD patients with ARF, which may be because most chronic NMDs are rare diseases, making it difficult to recruit patients. As shown in **Table 2**, evidence that NIV can help avoid intubation of patients with chronic NMD during the ARF episodes comes from 11 non-randomized observational studies of a total of 178 subjects (age range 2 months to 69 years), of which most subjects are known to be under 25 years (36, 37, 39–42, 52, 53, 56, 57). However, in most studies, there are few descriptions of methods to manage airway secretions, and its role in contributing to the success of NIV in treating ARF is not well defined (45). Even though an increasing number of studies have recognized the benefit of combined NIV and MI-E use in the ARF management and facilitation of extubation in adult NMD patients (37, 40, 54), similar studies on the pediatric NMD populations are scarce. In heterogeneous pediatric populations, several risk factors for predicting the failure of NIV treatment fo ARF have been reported (11, 32, 44), but it is still unclear whether similar factors exist in a specific pediatric NMD population.

However, only one randomized controlled study has investigated the efficacy of NIV in treating children with ARF but has excluded children with underlying NMD (31). Two recent studies reported by the same team described the protocol and effectiveness of a combination of NIV with MI-E in treating ARF of children with chronic NMD (52, 57). The pilot study of children encompassing various NMDs has demonstrated the feasibility of this combined noninvasive approach. The following research on a larger cohort of NMD patients further verified its safety and effectiveness. Overall, combining the data of these two studies on 71 NMD patients shows that timely implementation of NIV and MI-E can avoid intubation or reintubation in 75–86% of ARF events, of which 80% are pediatric cases. The PICU and hospital stay of children successfully rescued through NIV/MI-E is shorter than that of children who received intubation. Besides, several predictors of NIV failure were identified, including physical parameters (changes in respiratory rate) and laboratory variables (changes in $PaCO_2$ and pH value of arterial blood gas).

COMBINED NIV AND MI-E IN ARF TREATMENT OF NMD CHILDREN

The interface connects the ventilator tubing to the patient to deliver pressurized gas to the airway during NIV administration. It may take several attempts to find a suitable interface, but this is the key to successfully treating ARF in NMD children with NIV while minimizing air leakage, maximizing patient comfort, and synchronizing with the ventilator (44, 58, 59). However, although interface tolerance is a pivotal factor associated with NIV success, comparative data on the interface of infants and young children is scarce (60).

A transparent interface is highly recommended to ensure correct positioning and enhance patient monitoring (59). The medical team should be well trained to select the most suitable interface individualized for each critically ill child (61). As proof of principle, the smallest interface with the least air leakage should be selected to minimize the dead space. For infants,

TABLE 2 | Noninvasive airway approaches for patients with NMD with acute on chronic respiratory failure.

References	Study Design	Number of NMD patients (age)	NMD diagnosis (n)	ARF types* (n, %)	NIV/interface/ secretion clearance	Success rate and main findings	Predictor of NIV failure	NIV Complications (n)	Limit
Padman et al. (39)	Monocenter retrospective study	11 patients; (range: 4-21 y)	DMD (7), SMA (2), SCI (1), nonspecific myopathy (l)	Type 2 (11, 100%)	BLPAP via nasal mask	• NIV success rate (no intubation): 91 % • Improved RR, $PaCO_2$, serum bicarbonate, and length of hospitalization after NIV use	None identified	No major complications	Hypoxic ARF and significant difficulty handling secretions
Birnkrant et al. (55)	Monocenter retrospective study	8 patients (range 1-18 y)	DMD(5), SMA(3)	Undefined ARF, including 3 post-extubation ARF	BLPAP via nasal interface	• Allowed weaning from an invasive airway: 100% effective in avoiding ETI or facilitating extubation	None identified	NA	Non described
Niranjan and Bach (40)	Monocenter retrospective study	10 patients (median: 17 y; range: 13-21 y) vs. 7 historical controls	DMD (8), SMA (1), SCI (1)	Type 2 (10, 100%), including 6 post-extubation ARF	BLPAP via mouthpiece or nasal interface + MI-E	• NIV success rate (no intubation): 100% • Shorter hospital stay in NIV group than historical control	None identified	NA	Non described
Bach et al. (56)	Monocenter retrospective study	11 children with 28 ARF episodes (median: 6 m; range: 2-11 m)	SMA type 1 (11)	Post-extubation ARF (28, 100%)	BLPAP via nasal interface+ MI-E for post-extubation support	• NIV success rate (no intubation): 82 % • NIV can facilitate extubation for type 1 SMA children even with severe bulbar muscle weakness	None identified	NA	Non described
Vianello et al. (36)	Monocenter prospective case-control study	14 patients (median: 24 y; range: 10-69 y) vs. 14 historical controls	DMD (7), ALS (4), CMD(1), HMSN (1), CM(1)	Type 2 (14, 100%)	E = BLPAP via nasal interface + cricothyroid-mini-tracheostomy; C = IMV via ETI	• NIV success rate (no intubation): 71% (14% mortality rate) vs. 21% of controls (57% mortality rate) • Lower mortality and complications, and shorter ICU stay of NIV group than controls • NIV combined with cricothyroid-mini-tracheostomy for secretion clearance was well tolerated without significant complications	None identified	No major complications	Severe bulbar involvement
Vianello et al. (37)	Monocenter prospective case-control study	11 patients (median: 31 y; range: 16-64 y) vs. 16 historical controls	DMD (4), SMA (3), ALS (2), LGMD(1), FSHD (1)	Type 2 (11, 100%)	E = BLPAP via nasal interface+ MI-E+CPT; C = BLPAP+CPT	• NIV success rate (no intubation): 82 vs. 37% of controls • No serious side effects and well-tolerated in all subjects with MI-E use	None identified	Gastric distension (1), epistaxis (1)	
Servera et al. (41)	Monocenter prospective cohort study	17 patients (48.7±20.9 y)	ALS (11), DMD (4), transverse myelitis (1), nonspecific myopathy (1)	Type 2 ARF (17, 100%)	BLPAP via nasal/oronasal interfaces + MI-E	• NIV success rate (no intubation): 79.2% • Severe bulbar involvement limited NIV effectiveness	Bulbar dysfunction	NA	Severe bulbar involvement NIV/MI-E performed in non-ICU settings

(Continued)

TABLE 2 | Continued

References	Study Design	Number of NMD patients (age)	NMD diagnosis (n)	ARF types* (n, %)	NIV/interface/ secretion clearance	Success rate and main findings	Predictor of NIV failure	NIV Complications (n)	Limit
Piastra et al. (42)	Monocenter prospective observational cohort study	10 children (4.1 ± 4.5 y; range 3 m-12 y)	SMA type 1(2), CMD –Ullrich (1), CM-nemaline CM (1), MG (2), mitochondrial myopathy (1), spinal cord hamartomatosis (1), nonspecific myopathies (2)	Type 2 (5, 50%); Type 1 (2, 20%); mixed/undefined (3, 30%)	BLPAP via facial mask or helmet+ CPT	• NIV success rate (no intubation): 80% • Hypercarbic ARF resolved within 6 h of NIV use • Oxygenation markers improved rapidly after NIV introduction	Airway obstruction	No major complications	Copious tracheal secretion needing frequent suction
Dohna-Schwake et al. (53)	Monocenter retrospective study	15 children (median: 6 y)	SMA (6), DMD (3), Pompe disease (2); CMD (2), myopathy (1), myotonic dystrophy (1)	Undefined ARF, including 2 post-extubation ARF	CPAP via mask	• NIV success rate (no intubation): 87% • Improved HR, RR, blood pH, $PaCO_2$, and SaO_2 after 1-2 h of NIV use in the success group	Low pH at 1–2 h after NIV	midface skin ulcers and gastric distension	3 patients requested "do-not-intubate-status"
Chen et al. (57)	Monocenter prospective observational cohort study	15 children with 16 ARF episodes (mean: 8.1 y; range 3 m- 18 y)	SMA (6), DMD (2), CM (2), MM (2), HMSN (2), LGMD 2I (1)	Type 2 (15, 94%) including 1 post-extubation ARF; Type 1 (1, 6%)	BLPAP via nasal/oronasal or facial mask + MI-E	• NIV success rate (no intubation): 75% • Improved blood pH, and $PaCO_2$ after 12 h of NIV use in the success group	Fewer decrement of RR after 3 h of NIV use	No major complications	
Chen et al. (52)	Monocenter prospective observational cohort study	56 NMD patients (44 children) with 62 ARF episodes; median: 13 y; range: 2 m-39 y)	SMA (32), DMD (14), CM (6), CMD (4), MM (4), HMSN (1), SMARD (1)	Type 2 ARF (53, 85%) including 23 post-extubation failure; Type 1 ARF (9, 15%)	BLPAP via nasal/oronasal or facial mask + MI-E	• NIV success rate (no intubation): 86% • Improved HR, RR, blood pH, and $PaCO_2$ after 4 h of NIV use in the success group • Shorter PICU and hospital stay of success group	RR decreased at 4 h; pH increased, and $PaCO_2$ decreased at 4-8 h after NIV	No major complications	Initial checking blood gases at a later point of 4–8 h after NIV

**Type 1 ARF, Hypoxemic ARF; Type 2 ARF, hypercapnic ARF.*

NMD, neuromuscular disorders; NIV, non-invasive ventilation; ARF, acute respiratory failure; BLPAP, bi-level positive airway pressure; MI-E, Mechanical insufflator-exsufflator; E, experiment; C, control; CPT, chest physical treatments; DMD, Duchenne muscular dystrophy; SMA, spinal muscular atrophy; SCI, spinal cord injury, HMSN, hereditary motor and sensory neuropathy; CMD, congenital Muscular Dystrophy; CM, congenital Myopathy; MG, myasthenia gravis; MM, mitochondrial myopathy; SMARD, spinal muscular atrophy with respiratory distress; LGMD 2I, limb-girdle muscular dystrophy type 2I; NA, Not available.

CPAP, Continuous positive airway pressure.

nasal interface (nasal cannula, nasal prong, or nasal mask) is recommended the interface of first choice (6, 44). Otherwise, choosing the right interface for older children is usually based on available materials and training of an experienced medical team, not on scientific data. Generally, in older children and young adults with ARF, full oronasal face masks are preferable to nasal interfaces because of better tolerance and a better sealing with less air leak (60, 62). Although some studies have shown that the feasibility and effectiveness of helmets in infants and young children, the experience of using helmets as interfaces in children is even rarer (62). It should be kept in mind that there is no single interface suitable for all situations, and the use of these interfaces in NMD children, especially in the critical care setting, requires better evidence support (59).

Recommendations for the initial setting of NIV are mainly based on clinical experience and expert consensus as there are no consistent data on optimal settings. If not contraindicated as the list aforementioned, the initial settings chosen should be disease and device-specific. Importantly, the information regarding the potential contraindications or complications related to NIV administration in the NMD patient population should be addressed (6, 11). Generally, the administration of NIV support should be set low initially to allow patient acclimation and then increase according to the physiologic needs and patient tolerance. According to our protocol specialized for NMD children, bilevel positive airway pressure (BLPAP) with an adequate interface is always effective in rescuing ARF (52, 57). Especially during an acute chest infection, NIV should be used more intensively for these patients. Under adequate approaches of secretion clearance, supplemental oxygen may be added to NIV to maintain appropriate oxygenation. However, if the patient becomes almost whole-day dependent on NIV during an acute event, consider alternating masks to prevent pressure sores and alternate day and night between two ventilators of the same model so as not to run a ventilator continuously for days. The MI-E can be applied either in combination with NIV through a full-face mask or solitarily used in intubated patients via the endotracheal or tracheostomy tube with the cuff inflated. If applicable, supplementary manual augmentation of cough may be applied intermittently, followed by MI-E use.

In addition to noninvasive airway approaches, all other sensible standard measures can be taken during ARF episodes. These approaches include adapting a low threshold to deliver broad-spectrum antibiotics, adequate hydration, and attention to nutritional support. Humidification of the ventilator is often beneficial in reducing sputum viscosity and mobilizing secretions. Therapies of nebulized bronchodilator or systemic steroid may be considered if evidence of asthma or asthmatic bronchitis (10, 60).

From the perspective of chronic respiratory care, proactive use of NIV, and cough assistant MI-E in NMD children has been shown to reduce the rate of hospitalization and ICU admission (63–65). The familiarity of NMD patients with NIV use can help the effectiveness of NIV in the treatment of ARF (60). Several studies have shown that prior training of NIV and MI-E at home can contribute to a higher success rate in acute care settings (14, 52, 66). In this regard, the proactive use of NIV and MI-E in the routine respiratory care of children with chronic NMD may also be beneficial (65).

Besides MI-E, high-frequency chest wall oscillation (HFCWO) has recently been proposed as a potential intervention used to facilitate secretion clearance in NMD patients. HFCWO delivers pressure to the chest wall accompanied by high-frequency vibration, which shows to move secretions from peripheral airways toward more central airways (67). However, the safety and effectiveness of HFCWO have not been well studied in managing ARF of NMD children, and its benefit in acute care settings is unclear (68). There is still a lack of data on the safety and effectiveness of NMD infants and young children known to be more susceptible to consistent and high frequent oscillation waves. Further research on HFCWO in NMD children is needed.

CONTRAINDICATIONS AND COMPLICATIONS OF NIV AND MI-E

The patient selection remains the most critical factor for the success of NIV in treating ARF. The contraindications to the NIV use include hemodynamic instability, severely decreased consciousness level, severe bulbar dysfunction (i.e., absence of gag reflex, or vocal cord paralysis), un-drained pneumothorax, facial deformity or injuries, recent surgery of facial, upper airway, or upper gastrointestinal tract, intolerance to NIV interface, multi-organ failure, life-threatening hypoxemia ($PaO_2 < 60$ mmHg with $FiO_2 > 0.6$), and lack of familiarity of health-care provider with NIV operation (6, 14, 62, 69, 70).

In general, NIV is a safe approach in managing ARF of infants and children with NMD, and the adverse effects described are minor (71). However, similar to any ventilation therapy, there are some adverse reactions and severe complications worthy of understanding. Reducing complications of NIV and MI-E largely depends on the well-trained and experienced staff of a multidisciplinary care team (21, 44, 62, 72). Gastric distension may occasionally occur, which can be ameliorated by nasogastric tube insertion and keeping adequate enteral feeding. Barotrauma may occur, but the risk is extremely low during NIV and much lower than during mechanical ventilation (73). For patients with hypovolemia, NIV should be used with caution, because NIV can cause an additional increase in intrathoracic pressure, which may result in a decrease in venous return (preload) and further deteriorate cardiac output (74).

Agitation may develop, especially during the initial interface placement on a child, but it is not necessary to discontinue NIV for this reason. Pharmacological sedation may be required, especially for children with NMD who receive NIV for the first time (75, 76). Choosing a more comfortable interface and fine-tuning NIV settings can reduce the need for sedatives (62). Other related complications include skin lesions, discomfort, claustrophobia, nasal mucosa trauma, and conjunctivitis, which may be prevented by a sophisticated selection of appropriate interface, alternating interface intermittently, and humidification of the ventilator (59, 60).

CONCLUSIONS

The care of chronically progressive NMD has evolved significantly in the last decade, and many NMD children are now achieving prolonged survival through the advances in novel treatments (e.g., gene and molecular therapies) as well as respiratory care. However, there is still no consensus on the timing and limitations of NIV use in the treatment of ARF in children with NMD. Therefore, the administration protocol must be integrated with individualized clinical judgment. NMD usually includes various diseases of different severity, and the pathomechanism of ARF may vary with the type of NMD. Thus, it is unclear whether certain types of NMD may be more sensitive to NIV treatment for ARF. The variety and complexity of specific problems presented by different NMD necessitate separate remarks on the early recognition and adequate management of ARF in children with NMD. More future researches designed specifically for the pediatric NMD population are still needed, and several issues remain to be clarified.

AUTHOR CONTRIBUTIONS

T-HC and J-HH contributed to conception and design, acquisition of data, revising the manuscript critically for relevant intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

FUNDING

This study was funded by a research grant from Kaohsiung Medical University Hospital, Kaohsiung, Taiwan (KMUH-108-8R47).

REFERENCES

1. Aslan GK, Gurses HN, Issever H, Kiyan E. Effects of respiratory muscle training on pulmonary functions in patients with slowly progressive neuromuscular disease: a randomized controlled trial. *Clin Rehabil.* (2014) 28:573–81. doi: 10.1177/0269215513512215
2. Howard RS. Respiratory failure because of neuromuscular disease. *Curr Opin Neurol.* (2016) 29:592–601. doi: 10.1097/WCO.0000000000000363
3. Boentert M, Wenninger S, Sansone VA. Respiratory involvement in neuromuscular disorders. *Curr Opin Neurol.* (2017) 30:529–37. doi: 10.1097/WCO.0000000000000470
4. Hocker S. Primary acute neuromuscular respiratory failure. *Neurol Clin.* (2017) 35:707–21. doi: 10.1016/j.ncl.2017.06.007
5. Yuan N. Neuromuscular disease and the pulmonologist. *Curr Opin Pediatr.* (2012) 24:336–43. doi: 10.1097/MOP.0b013e3283531bb0
6. Panitch HB. Respiratory implications of pediatric neuromuscular disease. *Respir Care.* (2017) 62:826–48. doi: 10.4187/respcare.05250
7. Benditt JO, Boitano LJ. Pulmonary issues in patients with chronic neuromuscular disease. *Am J Respir Crit Care Med.* (2013) 187:1046–55. doi: 10.1164/rccm.201210-1804CI
8. Mehta S. Neuromuscular disease causing acute respiratory failure. *Respir Care.* (2006) 51:1016–21; discussion 21–3.
9. Panitch HB. The pathophysiology of respiratory impairment in pediatric neuromuscular diseases. *Pediatrics.* (2009) 123 Suppl 4:S215–8. doi: 10.1542/peds.2008-2952C
10. Voulgaris A, Antoniadou M, Agrafiotis M, Steiropoulos P. Respiratory involvement in patients with neuromuscular diseases: a Narrative review. *Pulm Med.* (2019) 2019:2734054. doi: 10.1155/2019/2734054
11. Hull J, Aniapravan R, Chan E, Chatwin M, Forton J, Gallagher J, et al. British thoracic society guideline for respiratory management of children with neuromuscular weakness. *Thorax.* (2012) 67 Suppl 1:i1–40. doi: 10.1136/thoraxjnl-2012-201964
12. Shahrizaila N, Kinnear WJ, Wills AJ. Respiratory involvement in inherited primary muscle conditions. *J Neurol Neurosurg Psychiatry.* (2006) 77:1108–15. doi: 10.1136/jnnp.2005.078881
13. Rezania K, Goldenberg FD, White S. Neuromuscular disorders and acute respiratory failure: diagnosis and management. *Neurol Clin.* (2012) 30:161–85, viii. doi: 10.1016/j.ncl.2011.09.010
14. Racca F, Del Sorbo L, Mongini T, Vianello A, Ranieri VM. Respiratory management of acute respiratory failure in neuromuscular diseases. *Minerva Anestesiol.* (2010) 76:51–62.
15. Hill NS. Neuromuscular disease in respiratory and critical care medicine. *Respir Care.* (2006) 51:1065–71.
16. Khirani S, Bersanini C, Aubertin G, Bachy M, Vialle R, Fauroux B. Noninvasive positive pressure ventilation to facilitate the post-operative respiratory outcome of spine surgery in neuromuscular children. *Eur Spine J.* (2014) 23 Suppl 4:S406–11. doi: 10.1007/s00586-014-3335-6
17. Bach JR, Goncalves MR, Hon A, Ishikawa Y, De Vito EL, Prado F, et al. Changing trends in the management of end-stage neuromuscular respiratory muscle failure: recommendations of an international consensus. *Am J Phys Med Rehabil.* (2013) 92:267–77. doi: 10.1097/PHM.0b013e31826edcf1
18. Wang CH, Bonnemann CG, Rutkowski A, Sejersen T, Bellini J, Battista V, et al. Consensus statement on standard of care for congenital muscular dystrophies. *J Child Neurol.* (2010) 25:1559–81. doi: 10.1177/0883073810381924
19. Wang CH, Dowling JJ, North K, Schroth MK, Sejersen T, Shapiro F, et al. Consensus statement on standard of care for congenital myopathies. *J Child Neurol.* (2012) 27:363–82. doi: 10.1177/0883073812436605
20. Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, et al. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol.* (2007) 22:1027–49. doi: 10.1177/0883073807305788
21. Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, et al. Diagnosis and management of spinal muscular atrophy: part 2: pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscul Disord.* (2018) 28:197–207. doi: 10.1016/j.nmd.2017.11.004
22. Schroth MK. Special considerations in the respiratory management of spinal muscular atrophy. *Pediatrics.* (2009) 123 Suppl 4:S245–9. doi: 10.1542/peds.2008-2952K
23. Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, et al. Diagnosis and management of duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. *Lancet Neurol.* (2010) 9:177–89. doi: 10.1016/S1474-4422(09)70272-8
24. Poponick JM, Jacobs I, Supinski G, DiMarco AF. Effect of upper respiratory tract infection in patients with neuromuscular disease. *Am J Respir Crit Care Med.* (1997) 156(2 Pt 1):659–64. doi: 10.1164/ajrccm.156.2.9611029
25. Katz SL, Gaboury I, Keilty K, Banwell B, Vajsar J, Anderson P, et al. Nocturnal hypoventilation: predictors and outcomes in childhood progressive neuromuscular disease. *Arch Dis Child.* (2010) 95:998–1003. doi: 10.1136/adc.2010.182709
26. Yates K, Festa M, Gillis J, Waters K, North K. Outcome of children with neuromuscular disease admitted to paediatric intensive care. *Arch Dis Child.* (2004) 89:170–5. doi: 10.1136/adc.2002.019562
27. Cabrera Serrano M, Rabinstein AA. Causes and outcomes of acute neuromuscular respiratory failure. *Arch Neurol.* (2010) 67:1089–94. doi: 10.1001/archneurol.2010.207
28. Vianello A, Arcaro G, Braccioni F, Gallan F, Marchi MR, Chizio S, et al. Prevention of extubation failure in high-risk patients with neuromuscular disease. *J Crit Care.* (2011) 26:517–24. doi: 10.1016/j.jcrc.2010.12.008
29. Katz S, Selvadurai H, Keilty K, Mitchell M, MacLusky I. Outcome of noninvasive positive pressure ventilation in paediatric neuromuscular disease. *Arch Dis Child.* (2004) 89:121–4. doi: 10.1136/adc.2002.018655

30. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, et al. Diagnosis and management of spinal muscular atrophy: part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord.* (2018) 28:103–15. doi: 10.1016/j.nmd.2017.11.005
31. Yanez LJ, Yunge M, Emilfork M, Lapadula M, Alcantara A, Fernandez C, et al. A prospective, randomized, controlled trial of noninvasive ventilation in pediatric acute respiratory failure. *Pediatr Crit Care Med.* (2008) 9:484–9. doi: 10.1097/PCC.0b013e318184989f
32. Najaf-Zadeh A, Leclerc F. Noninvasive positive pressure ventilation for acute respiratory failure in children: a concise review. *Ann Intensive Care.* (2011) 1:15. doi: 10.1186/2110-5820-1-15
33. Stauffer JL, Olson DE, Petty TL. Complications and consequences of endotracheal intubation and tracheotomy. A prospective study of 150 critically ill adult patients. *Am J Med.* (1981) 70:65–76. doi: 10.1016/0002-9343(81)90413-7
34. Konrad F, Schreiber T, Brecht-Kraus D, Georgieff M. Mucociliary transport in iCU patients. *Chest.* (1994) 105:237–41. doi: 10.1378/chest.105.1.237
35. Rivera R, Tibballs J. Complications of endotracheal intubation and mechanical ventilation in infants and children. *Crit Care Med.* (1992) 20:193–9. doi: 10.1097/00003246-199202000-00008
36. Vianello A, Bevilacqua M, Arcaro G, Gallan F, Serra E. Noninvasive ventilatory approach to treatment of acute respiratory failure in neuromuscular disorders. A comparison with endotracheal intubation. *Intensive Care Med.* (2000) 26:384–90. doi: 10.1007/s001340051171
37. Vianello A, Corrado A, Arcaro G, Gallan F, Ori C, Minuzzo M, et al. Mechanical insufflation-exsufflation improves outcomes for neuromuscular disease patients with respiratory tract infections. *Am J Phys Med Rehabil.* (2005) 84:83–8; discussion 9–91. doi: 10.1097/01.PHM.0000151941.97266.96
38. Rabinstein A, Wijdicks EF. BiPAP in acute respiratory failure due to myasthenic crisis may prevent intubation. *Neurology.* (2002) 59:1647–9. doi: 10.1212/01.WNL.0000033797.79530.16
39. Padman R, Lawless S, Von Nessen S. Use of BiPAP by nasal mask in the treatment of respiratory insufficiency in pediatric patients: preliminary investigation. *Pediatr Pulmonol.* (1994) 17:119–23. doi: 10.1002/ppul.1950170208
40. Niranjan V, Bach JR. Noninvasive management of pediatric neuromuscular ventilatory failure. *Crit Care Med.* (1998) 26:2061–5. doi: 10.1097/00003246-199812000-00042
41. Servera E, Sancho J, Zafra MJ, Catala A, Vergara P, Marin J. Alternatives to endotracheal intubation for patients with neuromuscular diseases. *Am J Phys Med Rehabil.* (2005) 84:851–7. doi: 10.1097/01.phm.0000184097.17189.93
42. Piastra M, Antonelli M, Caresta E, Chiaretti A, Polidori G, Conti G. Noninvasive ventilation in childhood acute neuromuscular respiratory failure: a pilot study. *Respiration.* (2006) 73:791–8. doi: 10.1159/000090777
43. Panitch HB. Airway clearance in children with neuromuscular weakness. *Curr Opin Pediatr.* (2006) 18:277–81. doi: 10.1097/01.mop.0000193297.40388.19
44. Demaret P, Mulder A, Loeckx I, Trippaerts M, Lebrun F. Noninvasive ventilation is useful in paediatric intensive care units if children are appropriately selected and carefully monitored. *Acta Paediatr.* (2015) 104:861–71. doi: 10.1111/apa.13057
45. Chatwin M, Toussaint M, Goncalves MR, Sheers N, Mellies U, Gonzales-Bermejo J, et al. Airway clearance techniques in neuromuscular disorders: a state of the art review. *Respir Med.* (2018) 136:98–110. doi: 10.1016/j.rmed.2018.01.012
46. Tzeng AC, Bach JR. Prevention of pulmonary morbidity for patients with neuromuscular disease. *Chest.* (2000) 118:1390–6. doi: 10.1378/chest.118.5.1390
47. Rabinstein AA. Noninvasive ventilation for neuromuscular respiratory failure: when to use and when to avoid. *Curr Opin Crit Care.* (2016) 22:94–9. doi: 10.1097/MCC.0000000000000284
48. Panitch HB. Respiratory issues in the management of children with neuromuscular disease. *Respir Care.* (2006) 51:885–93; discussion 94–5.
49. Auger C, Hernando V, Galmiche H. Use of mechanical insufflation-Exsufflation devices for airway clearance in subjects with neuromuscular disease. *Respir Care.* (2017) 62:236–45. doi: 10.4187/respcare.04877
50. Morrow B, Zampoli M, van Aswegen H, Argent A. Mechanical insufflation-exsufflation for people with neuromuscular disorders. *Cochrane Database Syst Rev.* (2013) 12:CD010044. doi: 10.1002/14651858.CD010044.pub2
51. Mustfa N, Aiello M, Lyall RA, Nikoletou D, Olivieri D, Leigh PN, et al. Cough augmentation in amyotrophic lateral sclerosis. *Neurology.* (2003) 61:1285–7. doi: 10.1212/01.WNL.0000092018.56823.02
52. Chen TH, Liang WC, Chen IC, Liu YC, Hsu JH, Jong YJ. Combined noninvasive ventilation and mechanical insufflator-exsufflator for acute respiratory failure in patients with neuromuscular disease: effectiveness and outcome predictors. *Ther Adv Respir Dis.* (2019) 13:28. doi: 10.1177/1753466619875928
53. Dohna-Schwake C, Stehling F, Tschiedel E, Wallot M, Mellies U. Noninvasive ventilation on a pediatric intensive care unit: feasibility, efficacy, and predictors of success. *Pediatr Pulmonol.* (2011) 46:1114–20. doi: 10.1002/ppul.21482
54. Bach JR, Goncalves MR, Hamdani I, Winck JC. Extubation of patients with neuromuscular weakness: a new management paradigm. *Chest.* (2010) 137:1033–9. doi: 10.1378/chest.09-2144
55. Birnkrant DJ, Pope JF, Eiben RM. Pediatric noninvasive nasal ventilation. *J Child Neurol.* (1997) 12:231–6. doi: 10.1177/088307389701200401
56. Bach JR, Niranjan V, Weaver B. Spinal muscular atrophy type 1: a noninvasive respiratory management approach. *Chest.* (2000) 117:1100–5. doi: 10.1378/chest.117.4.1100
57. Chen TH, Hsu JH, Wu JR, Dai ZK, Chen IC, Liang WC, et al. Combined noninvasive ventilation and mechanical in-exsufflator in the treatment of pediatric acute neuromuscular respiratory failure. *Pediatr Pulmonol.* (2014) 49:589–96. doi: 10.1002/ppul.22827
58. Keenan SP, Sinuff T, Burns KE, Muscedere J, Kutsogiannis J, Mehta S, et al. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. *CMAJ.* (2011) 183:E195–214. doi: 10.1503/cmaj.100071
59. Pavone M, Verrillo E, Caldarelli V, Ullmann N, Cutrera R. Noninvasive positive pressure ventilation in children. *Early Hum Dev.* (2013) 89 Suppl 3:S25–31. doi: 10.1016/j.earlhumdev.2013.07.019
60. Simonds AK. Ventilator support in children with neuromuscular disorders. In: Sterni LM, Carroll JL, editors. *Caring for the Ventilator Dependent Child: A Clinical Guide*. New York, NY: Springer. (2016). p. 283–98. doi: 10.1007/978-1-4939-3749-3_14
61. Fauroux B, Lavis JF, Nicot F, Picard A, Boelle PY, Clement A, et al. Facial side effects during noninvasive positive pressure ventilation in children. *Intensive Care Med.* (2005) 31:965–9. doi: 10.1007/s00134-005-2669-2
62. Viscusi CD, Pacheco GS. Pediatric emergency noninvasive ventilation. *Emerg Med Clin North Am.* (2018) 36:387–400. doi: 10.1016/j.emc.2017.12.007
63. Young HK, Lowe A, Fitzgerald DA, Seton C, Waters KA, Kenny E, et al. Outcome of noninvasive ventilation in children with neuromuscular disease. *Neurology.* (2007) 68:198–201. doi: 10.1212/01.wnl.0000251299.54608.13
64. Simonds AK. Respiratory support for the severely handicapped child with neuromuscular disease: ethics and practicality. *Semin Respir Crit Care Med.* (2007) 28:342–54. doi: 10.1055/s-2007-981655
65. Lemoine TJ, Swoboda KJ, Bratton SL, Holubkov R, Mundorff M, Srivastava R. Spinal muscular atrophy type 1: are proactive respiratory interventions associated with longer survival? *Pediatr Crit Care Med.* (2012) 13:e161–5. doi: 10.1097/PCC.0b013e3182388ad1
66. Sancho J, Servera E, Diaz J, Marin J. Efficacy of mechanical insufflation-exsufflation in medically stable patients with amyotrophic lateral sclerosis. *Chest.* (2004) 125:1400–5. doi: 10.1378/chest.125.4.1400
67. Lechtzin N, Wolfe LF, Frick KD. The impact of high-Frequency chest wall oscillation on healthcare use in patients with neuromuscular diseases. *Ann Am Thorac Soc.* (2016) 13:904–9. doi: 10.1513/AnnalsATS.201509-597OC
68. Yuan N, Kane P, Shelton K, Matel J, Becker BC, Moss RB. Safety, tolerability, and efficacy of high-frequency chest wall oscillation in pediatric patients with cerebral palsy and neuromuscular diseases: an exploratory randomized controlled trial. *J Child Neurol.* (2010) 25:815–21. doi: 10.1177/0883073809350223
69. Racca F, Vianello A, Mongini T, Ruggeri P, Versaci A, Vita GL, et al. Practical approach to respiratory emergencies in neurological diseases. *Neurol Sci.* (2020) 41:497–508. doi: 10.1007/s10072-019-04163-0
70. Chen TH, Hsu JH, Jong YJ. Noninvasive airway approaches for acute neuromuscular respiratory failure in emergency departments. *Pediatr Pulmonol.* (2017) 52:E55–E7. doi: 10.1002/ppul.23693

71. Calderini E, Chidini G, Pelosi P. What are the current indications for noninvasive ventilation in children? *Curr Opin Anaesthesiol.* (2010) 23:368–74. doi: 10.1097/ACO.0b013e3283 39507b
72. Gay PC. Complications of noninvasive ventilation in acute care. *Respir Care.* (2009) 54:246–57; discussion 57–8.
73. Modi HN, Suh SW, Hong JY, Cho JW, Park JH, Yang JH. Treatment and complications in flaccid neuromuscular scoliosis (Duchenne muscular dystrophy and spinal muscular atrophy) with posterior-only pedicle screw instrumentation. *Eur Spine J.* (2010) 19:384–93. doi: 10.1007/s00586-009-1198-z
74. Carron M, Freo U, BaHammam AS, Dellweg D, Guarracino F, Cosentini R, et al. Complications of noninvasive ventilation techniques: a comprehensive qualitative review of randomized trials. *Br J Anaesth.* (2013) 110:896–914. doi: 10.1093/bja/aet070
75. Abadesso C, Nunes P, Silvestre C, Matias E, Loureiro H, Almeida H. Noninvasive ventilation in acute respiratory failure in children. *Pediatr Rep.* (2012) 4:e16. doi: 10.4081/pr.2012.e16
76. Wolfler A, Calderini E, Iannella E, Conti G, Biban P, Dolcini A, et al. Evolution of noninvasive mechanical ventilation use: a Cohort study among Italian PICUs. *Pediatr Crit Care Med.* (2015) 16:418–27. doi: 10.1097/PCC.0000000000000387

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

ORIGINAL RESEARCH
published: 05 November 2020
doi: 10.3389/fped.2020.602083

Features Discriminating COVID-19 From Community-Acquired Pneumonia in Pediatric Patients

*Yu Guo, Wei Xia, Xuehua Peng and Jianbo Shao**

Department of Imaging Center, Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Purpose: To discuss the different characteristics of clinical, laboratory and chest computed tomography (CT) between coronavirus disease 2019 (COVID-19) and community-acquired pneumonia (CAP) in pediatric patients.

Methods: We retrospectively retrieved data of inpatients with COVID-19 from January 21st to March 14th, 2020, and CAP from November 1st, 2019 to December 31st, 2019 in Wuhan Children's Hospital. We divided CAP into mycoplasma pneumonia and other viral pneumonia. We analyzed clinical and radiological features from those patients, and compared the differences among COVID-19, mycoplasma pneumonia and other viral pneumonia.

Results: Eighty COVID-19 inpatients from January 21st to March 14th, 2020, as well as 95 inpatients with mycoplasma pneumonia and 50 inpatients with other viral pneumonia from November 1st, 2019 to December 31st, 2019 were included in our study. All patients were confirmed with RT-PCR. The clinical symptoms were similar in the three groups. Except fever and cough, diarrhea (6/80, 7.5%), tachypnea (2/80, 2.5%), and fatigue (6/80, 7.5%) were less common in COVID-19 patients. Compared to mycoplasma pneumonia and other viral pneumonia inpatients, COVID-19 patients present remarkably increased alanine aminotransferase (69/80, 86.3%). The typical CT feature of COVID-19 is ground-glass opacity, and it was more common in COVID-19 patients (32/80, 40%).

Conclusion: The COVID-19 shared similar onsets with CAP. Even though the ground-glass opacity and elevated level of ALT were frequent in COVID-19, the better way for treatment and management of this disease is quickly and accurately identifying the pathogen.

Keywords: COVID-19, children, computed tomography, Community-Acquired Pneumonia (CAP), respiratory infection

OPEN ACCESS

Edited by:
Hong Ren Yu,
Chang Gung Memorial Hospital, Taiwan

Reviewed by:
Jong-Hau Hsu,
Kaohsiung Medical University, Taiwan
Yusei Ohshima,
University of Fukui, Japan

****Correspondence:***
Jianbo Shao
xzhuge27@163.com

Specialty section:
This article was submitted to Pediatric Pulmonology, a section of the journal Frontiers in Pediatrics

Received: *02 September 2020*
Accepted: *15 October 2020*
Published: *05 November 2020*

Citation:
Guo Y, Xia W, Peng X and Shao J (2020) Features Discriminating COVID-19 From Community-Acquired Pneumonia in Pediatric Patients. Front. Pediatr. 8:602083. doi: 10.3389/fped.2020.602083

INTRODUCTION

In late December 2019, the pneumonia caused by a novel coronavirus (SARS-Cov-2) was identified in Wuhan Hubei province, China (1). The world health organization named the disease caused by SARS-Cov-2 coronavirus disease 2019 (COVID-19) (2). By September 1st, 2020, 90,383 confirmed cases of COVID-19 in China, and 25,118,689 cases in 216 countries (3). Person-to-person transmission of SARS-CoV-2 occurs through close contact with infected person, mainly

via respiratory droplets and after touching contaminated objects (4). And the infections showed familiar aggregation, pediatric patients infected by SARS-CoV-2 appeared later than adult (5, 6). At present, defining the clinical characteristics of the disease in large cohorts of patients is an urgent need. While plenty of data are available for adult patients with COVID-19, limited reports were available for pediatric patients infected with SARS-CoV-2 (5–7).

Pneumonia is the most common cause of illness in children (8). Community-acquired pneumonia accounts for a large part of pediatric pneumonia. Many pathogens, including bacteria, viruses and other microorganisms, are associated with pneumonia. And viral pneumonia and mycoplasma pneumonia in children are common during autumn and winter (9). So it is very hard time for public health and doctors in this outbreak.

Mycoplasma pneumoniae (MP) is one of most important etiologic agents causing community-acquired pneumonia (CAP) in children (10, 11). The common pathogens of pediatric viral pneumonia include respiratory syncytial virus, influenza A/B virus and so on (11–13). The clinical symptoms of COVID-19 are similar to the other pediatric pneumonias, but there were effective treatments for pneumonia caused by these pathogens already (11). So it is important to distinguish COVID-19 from other pediatric pneumonias.

The aim of this study was to compare clinical, laboratory and radiological results of COVID-19 patients collected during the COVID-19 outbreak with other pneumonia patients collected before COVID-19 outbreak in the same hospital. If early discriminating features are recognized, they may facilitate the diagnosis of COVID-19 and timely control the transmission of COVID-19, since the overall detection rate for SARS-CoV-2 RNA by PCR assays is currently only 60% in the 1st week of illness. It would be important to find the differences in distinguishing SARS from other respiratory illnesses.

METHODS

Patients

For comparative study, we extracted data of 109 COVID-19 inpatients from January 21st to March 14th, 2020 and 166 non-COVID-19 inpatients from November 1st, 2019 to December 31st, 2019, before this outbreak, at Wuhan Children's Hospital. Among 109 COVID-19 inpatients, 26 patients had COVID-19 co-infection with mycoplasma pneumoniae, three patients had COVID-19 co-infection with other viruses. Among 166 non-COVID-19 inpatients, 50 patients infected by other virus (influenza A virus, influenza B virus, respiratory syncytial virus, parainfluenza virus and adenovirus) and 95 patients infected by mycoplasma pneumoniae, 18 patients had mycoplasma pneumoniae co-infection with other viruses, three patients infected with multi-viruses. Excluded all co-infected patients, 80 COVID-19 patients, 50 patients infected by only one type of virus and 95 patients infected by mycoplasma pneumoniae were included in our study. We defined patients infected with mycoplasma pneumoniae as mycoplasma pneumonia patients, and defined patients infected with only one type of virus as other viral pneumonia patients.

Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography; RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCT, procalcitonin; ALT, alanine aminotransferase.

Inclusion and Exclusion Criteria

Patients were included in the study if they met the following criteria: (a) presented to the emergency department and required hospitalization; (b) had a respiratory illness, as defined by the presence of lower respiratory symptoms (cough, sputum production, shortness of breath); (c) performed a chest CT scan; and (d) had positive etiological confirmation and identified a single pathogen infection. Patients without established etiologies or co-infected were excluded.

Identification of Pathogens

According to the guideline of laboratory detection for COVID-19 (14), we collected throat swabs or/and sputa from suspected patients to detect the pathogen by RT-PCR. Serological assays were performed to detect mycoplasma pneumoniae by detecting IgM and Respiratory Virus Identification Kit (D3 Ultra TM DFA, Diagnostic Hybrids) was used to detect and identify influenza A virus, influenza B virus, respiratory syncytial virus, parainfluenza virus, adenovirus.

Data Collection

We reviewed clinical chart, laboratory findings and chest CTs for all COVID-19 and non-COVID-19 patients. The admission data of these patients were from Nov 1st to Dec 31st, 2019 and January 21st to March 14th, 2020. For all patients, non-contrast chest CT studies were performed on SMATON Definiton AS128 unit (Siemens, Siemens medical system, Germany). All the images were reviewed by two experienced pediatric radiologists.

Statistical Analysis

Demographic, clinical, laboratory and radiological features were analyzed using Chi-square test or Fisher's exact test for categorical variables. Continuous variables were expressed as mean ± SD and compared with the Mann-Whitney *U*-test. Data were analyzed using SPSS version 25. All analyses were two tailed and a p-value of <0.05 was considered statistically significant.

RESULT

We reported a comparative analysis on 80 pneumonia patients with SARS-CoV-2 infection, 95 pneumonia patient with mycoplasma pneumoniae infection and 50 pneumonia patient with other virus infection. Other viral pneumonia patients consisted of 35 patients infected with respiratory syncytial virus, one patient infected with influenza A, six patients infected with influenza B, six patients infected with parainfluenza virus and two patients infected with adenovirus. All patients are identified as a single pathogen infection (**Figure 1**).

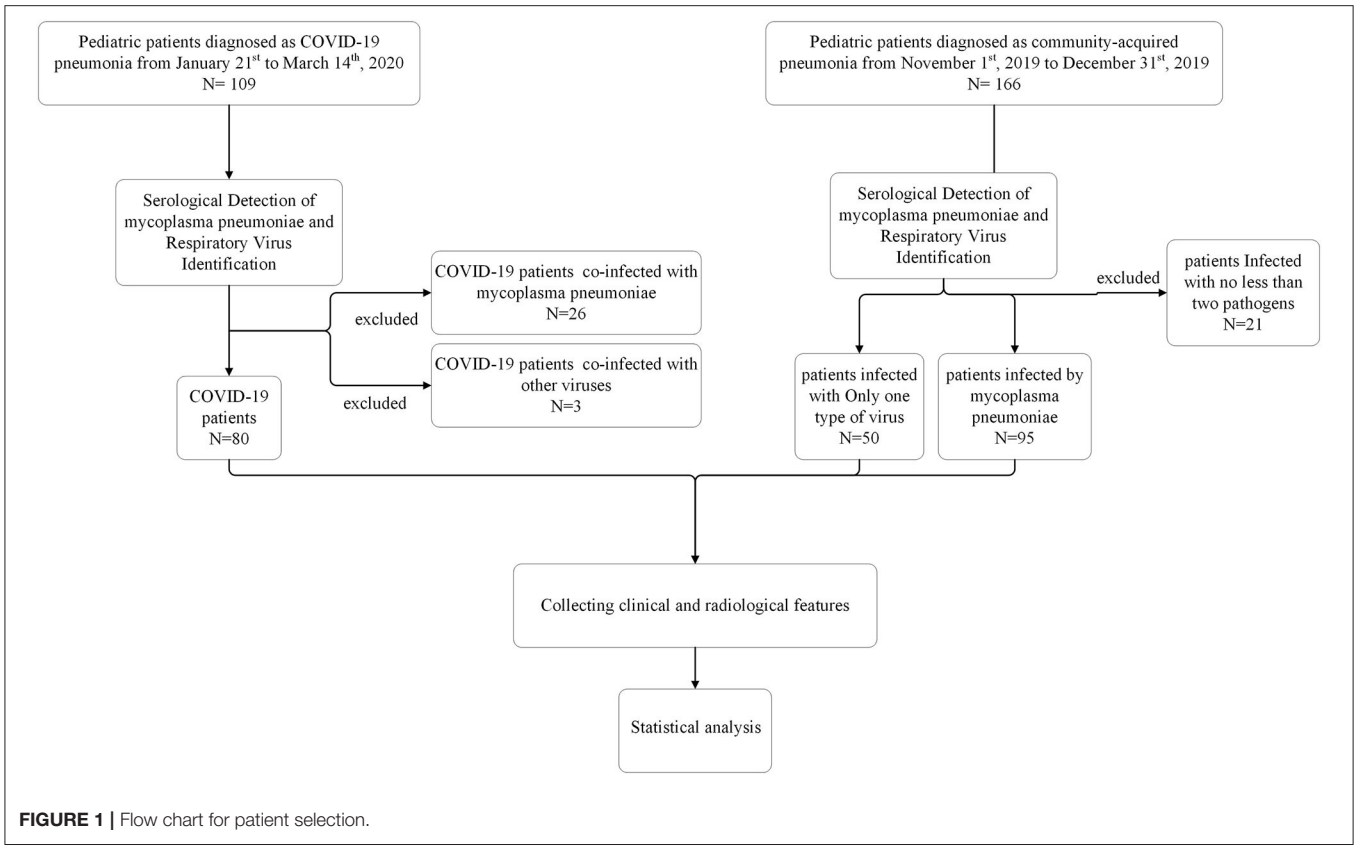

FIGURE 1 | Flow chart for patient selection.

Clinical Features of Cases

The demographic characteristics of pediatric COVID-19 patients and non-COVID-19 patients were displayed in **Table 1**. In this study, patient ages ranged 18 days to 15 years old, the mean age was 5.99 ± 4.77 in COVID-19 patients, 5.03 ± 3.26 in mycoplasma pneumoniae patients and 1.03 ± 1.38 in other viral pneumonia patients. COVID-19 patients and mycoplasma pneumonia patients were mainly distributed in the group of over 6 years old (48.8 and 48.4%), while other viral pneumonia patients were concentrated in the group of under 1 year old (68%), and the proportion of population in the COVID-19 patients and other viral pneumonia patients is significantly different between the group under 1 year old ($p < 0.0001$) and the group over 6 years old ($p < 0.0001$). Twenty eight (35%) were female in COVID-19 patients, 59 (62.1%) in mycoplasma pneumoniae patients, and 14 (28%) in other viral pneumonia patients. On admission, the most common symptoms were fever and cough in all patients, COVID-19 (38/80 [47.5%] and 39/80 [48.4%]), mycoplasma pneumoniae (77/95 [81.1%] and 83/95 [87.4%]), other viral pneumonia (25/50 [50%] and 48/50 [96%]). Less common symptoms in COVID-19 patients were diarrhea (6/80, 7.5%), tachypnea (2/80, 2.5%) and fatigue (6/80, 7.5%). These symptoms were less common in mycoplasma pneumoniae patients too, but proportion of tachypnea in other viral pneumonia patients (30/50, 60%) was higher than other groups. In comparison, no significant differences were observed between COVID-19 and mycoplasma pneumoniae patients on these symptoms, but there were significant differences between COVID-19 and other viral pneumonia patients in age distribution of onset and some symptoms.

TABLE 1 | The Clinical features of pediatric patients.

Characteristic	COVID-19 *N* = 80	Mycoplasma *N* = 95	Other virus *N* = 50	p^a	p^b
Sex					
Boy	52 (65%)	36 (37.9%)	36 (72%)	NULL	NULL
Girl	28 (35%)	59 (62.1%)	14 (28%)	NULL	NULL
Age					
<1 y	18 (22.5%)	9 (9.5%)	34 (68%)	0.017	<0.0001
1–3 y	12 (15%)	14 (14.7%)	9 (18%)	0.961	0.651
3–6 y	11 (13.8%)	26 (27.4%)	6 (12%)	0.028	0.773
>6 y	39 (48.8%)	46 (48.2%)	1 (2%)	0.965	<0.0001
Symptom					
Fever	38 (47.5%)	77 (81.1%)	25 (50%)	<0.0001	0.781
Cough	39 (48.8%)	83 (87.4%)	48 (96%)	<0.0001	<0.0001
Diarrhea	6 (7.5%)	2 (2.1%)	6 (12%)	0.089	0.388
Tachypnea	2 (2.5%)	12 (12.6%)	30 (60%)	0.014	<0.0001
Fatigue	6 (7.5%)	7 (7.4%)	12 (24%)	0.974	0.008

[a] *Group COVID-19 vs. Group mycoplasma pneumonia.*
[b] *Group COVID-19 vs. Group other viral pneumonia.*
NULL, not appropriate for statistical analysis.

Laboratory Findings of the Patients

Table 2 shows findings of laboratory examinations related to immunological responses and cardiac, liver damage. There were significant differences between COVID-19 patients and mycoplasma pneumonia patients in many laboratory findings except for procalcitonin (PCT) and Creatine kinase-MB (CK-MB). WBC count of most COVID-19 patients (7.67 ± 3.08, $*10^9$/L) were less than mycoplasma pneumonia patients (11.58 ± 6.78, $*10^9$/L) ($p < 0.0001$). The level of C-reaction protein (CRP) in mycoplasma pneumonia patients (1.22 ± 7.16) was higher than COVID-19 patients (4.21 ± 8.97) ($p < 0.0001$). While lymphocytes and alanine aminotransferase (ALT) in COVID-19 patients were higher than mycoplasma pneumonia patients. The laboratory characteristics of COVID-19 patients are similar to those of other viral pneumonia patients. It was worth noting that the level of CRP in COVID-19 patients (4.21 ± 8.97) was lower than other viral pneumonia patients (9.85 ± 16.77) ($p = 0.032$). And ALT of COVID-19 patients was highest in three group. As the reference range were different for WBC, lymph in different age groups, we had to categorize them as elevated, normal or decreased one according to the reference values (15–17). We represented it in **Supplementary Table**. The laboratory findings of COVID-19 pneumonia and other viral pneumonia were similar, except decreased ratio of lymphocytes ($p < 0.0001$), elevated PCT ($p < 0.0001$) and elevated ALT ($p < 0.0001$). There were significant differences between COVID-19 patients and mycoplasma pneumonia patients in many laboratory findings except for CK-MB. WBC count of most COVID-19 patients were in normal range (66/80, 82.5%), while that was not common in mycoplasma pneumonia patients (45/95, 47.4%) ($p < 0.0001$). Decreased ratio of lymphocytes in mycoplasma pneumonia patients (79/95, 83.2%) was more common than COVID-19 (14/80, 17.5%) ($p < 0.0001$), and elevated levels of CRP in mycoplasma pneumonia patients (66/95, 69.5%) was also more common than COVID-19 (20/80, 25%) ($p < 0.0001$). Comparison of three groups, elevated ALT (69/80, 86.3%) ($p < 0.0001$) was more common in COVID-19 than non-COVID-19. This reminded us that COVID-19 patients would suffer liver injury, even though most COVID-19 patients presented with mild symptoms. According to our findings, it was easy to distinguish COVID-19 and mycoplasma pneumonia in laboratory examinations, while laboratory findings of COVID-19 were similar to other viral pneumonia. It was noteworthy that the level of ALT in most COVID-19 patients were abnormal (69/80, 86.3%), and we should pay more attention to liver function in treatment.

TABLE 2 | Laboratory features of pediatric patients.

	COVID-19 $N = 80$	Mycoplasma $N = 95$	Other virus $N = 50$	p^a	p^b
WBC, $*10^9$/L	7.67 ± 3.08	11.58 ± 6.78	8.63 ± 3.04	<0.0001	0.085
LYM%	48.37 ± 12.13	28.71 ± 16.50	46.96 ± 18.44	<0.0001	0.669
CRP, mg/L	4.21 ± 8.97	19.40 ± 33.72	9.85 ± 16.77	<0.0001	0.032
PCT, mg/L	0.10 ± 0.14	1.22 ± 7.16	0.37 ± 1.11	0.131	0.089
ALT, U/L	45.66 ± 19.37	17.29 ± 19.30	31.44 ± 37.19	<0.0001	0.005
CK-MB, U/L	34.13 ± 29.06	37.78 ± 33.64	45.04 ± 30.07	0.448	0.042

[a] *Group COVID-19 vs. Group mycoplasma pneumonia.*
[b] *Group COVID-19 vs. Group other viral pneumonia.*

The Features of CT Images

CT imaging findings were shown in **Table 3**. Although COVID-19 patients were confirmed by RT-PCR tests, only 56 (70%) COVID-19 cases had definite pneumonia visible on chest CTs, while all patients infected by mycoplasma ($p < 0.0001$) or other virus ($p < 0.0001$) had abnormal on chest CT. There were more patients presented with unilateral pulmonary lesions in COVID-19 (34/80, 42.5%), while there were more inclined to bilateral

TABLE 3 | CT imaging findings in pediatric patients.

Findings / No. (%)	COVID-19 $N = 80$	Mycoplasma $N = 95$	Other virus $N = 50$	p^a	p^b
Pulmonary lesions					
Null	24 (30%)	0 (0%)	0 (0%)	<0.0001	<0.0001
Unilateral pneumonia	34 (42.5%)	45 (47.4%)	14 (28%)	0.519	0.096
Bilateral pneumonia	22 (27.5%)	50 (52.6%)	36 (72%)	0.001	<0.0001
Distribution					
Left upper lobe	16 (20%)	48 (50.5%)	43 (86%)	<0.0001	<0.0001
Left lower lob	29 (36.3%)	56 (58.9%)	46 (92%)	0.003	<0.0001
Right upper lobe	20 (25%)	46 (48.4%)	39 (78%)	0.001	<0.0001
Right middle lobe	16 (20%)	48 (50.5%)	40 (80%)	<0.0001	<0.0001
Right lower lobe	30 (37.5%)	58 (61.1%)	44 (88%)	0.002	<0.0001
Manifestation					
Consolidation	31 (38.8%)	93 (97.9%)	49 (98%)	<0.0001	<0.0001
Cord sign	3 (3.8%)	14 (14.7%)	7 (14%)	0.014	0.033
Ground-glass opacities	32 (40%)	5 (5.3%)	1 (2%)	<0.0001	<0.0001

[a] *Group COVID-19 vs. Group mycoplasma pneumonia.*
[b] *Group COVID-19 vs. Group other viral pneumonia.*

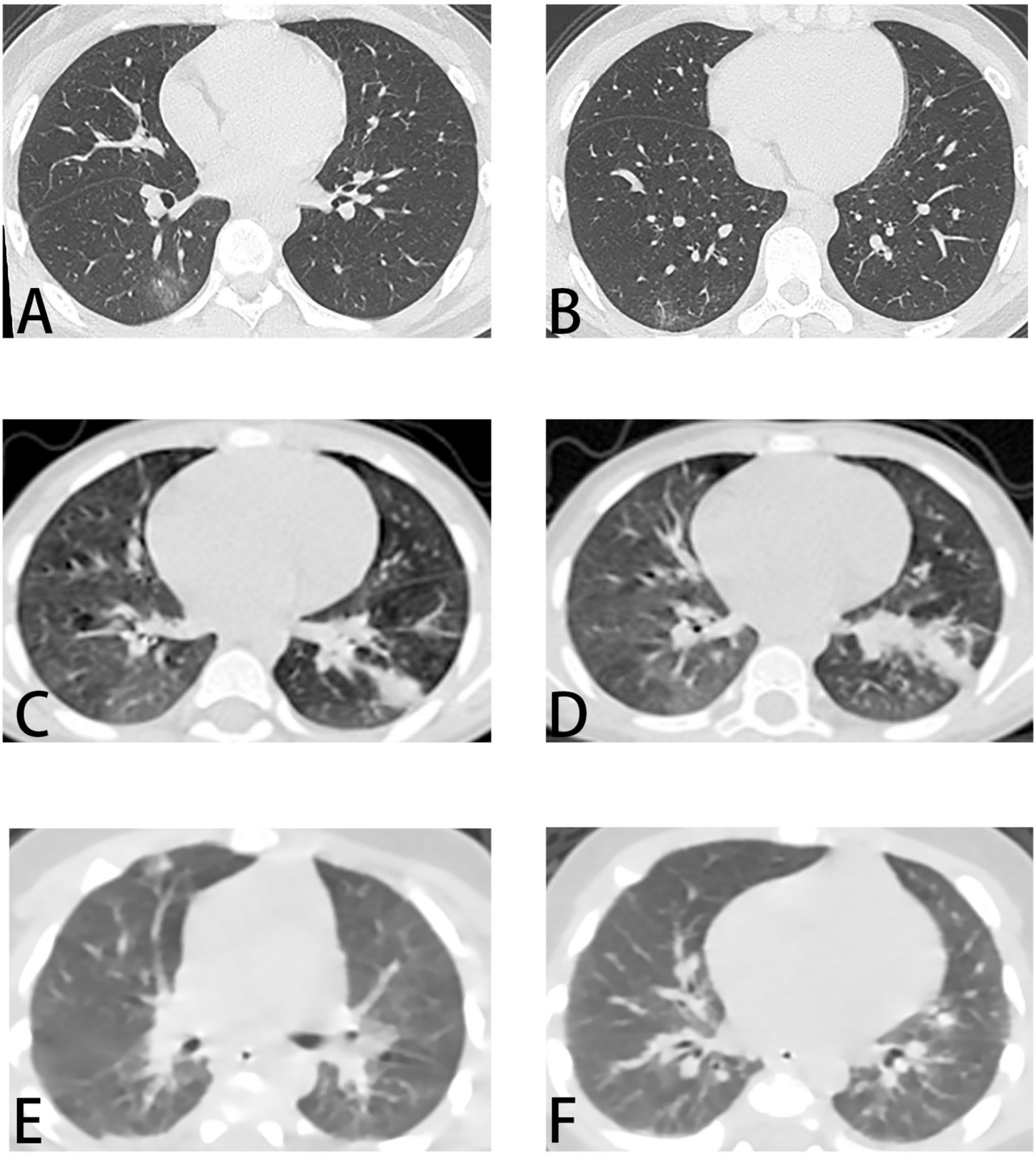

FIGURE 2 | Chest CT images of patients. **(A,B)** COVID-19. Male, 15 years old. On admission, chest CT showed ground-glass opacities in the inferior lobe of the right lung. **(C,D)** Mycoplasma pneumonia. Male, 4 years old. Chest CT showed bilateral lesions with consolidation in inferior lobe of the left lung. **(E,F)** Other viral pneumonia (respiratory syncytial virus). Male, 1 month old. Chest CT showed diffused consolidations in both lungs. CT, computed tomography.

lesions in other viral pneumonia patients (46/50, 92%) ($p < 0.0001$). The lesions were more concentrated in the lower lobes in all patients. The typical feature of COVID-19 is ground-glass opacity (6), and it presented more in COVID-19 patients (32/80, 40%) than mycoplasma pneumonia (5/95, 5.3%) ($p < 0.0001$) and other viral pneumonia patients (1/50, 2%) ($p < 0.0001$). The other typical feature is consolidation (6), while it was more common in mycoplasma pneumonia (93/95, 97.9%) ($p < 0.0001$)

and other viral pneumonia patients (49/50, 98%) ($p < 0.0001$) than COVID-19 patients (31/80, 38.8%). In the three groups, the streaky sign was not as obvious in COVID-19 patients (3/80, 3.8%) as mycoplasma pneumonia (14/95, 14.7%) ($p = 0.014$) and other viral pneumonia patients (7/50, 14%) ($p = 0.033$).

DISCUSSION

Until now, COVID-19 still poses a huge threat to human survival. More and more children are infected all over the world, it is important to understanding the manifestations of COVID-19 in children. Pneumonia is the most common disease in children, understanding the clinical features of COVID-19 in pediatric patients and distinguishing CAP in children are important for diagnosis and effective treatment.

In our study, the prevalence of COVID-19 patients and other viral pneumonia patients is significantly different between the group under 1 year old and the group over 6 years old (**Table 1**). School-age children are more susceptible to COVID-19. Since the outbreak of COVID-19 in the winter vacation, school-age children have their own small social circle, they would be exposed to more potential patients, so the prevalence of COVID-19 in this age group was higher than other viral pneumonia. The clinical symptoms were similar in three groups. Fever and cough were common in cases with COVID-19, mycoplasma pneumonia or other viral pneumonia. As COVID-19 was mostly mild in children, tachypnea (2.5%) and fatigue (7.5%) were less common in COVID-19. The similar symptoms make it hard to distinguish the pathogens, as well as control this epidemic. So it is very important to identify the pathogen.

As the symptoms were similar in COVID-19 and CAP, we analyzed laboratory and radiological features. A striking characteristic of COVID-19 differs from CAP is that it affects the function of liver, as shown by elevated amounts of alanine aminotransferase (86.3%), even though all children with COVID-19 was mild or moderate according to clinical type. Previous reports showed that adult patients with COVID-19 had different degrees of liver function abnormality (18, 19), but it was infrequent in pediatric patients. Elevated level of ALT may be important for subsequent treatment planning.

Because clinical signs and symptoms are poor predictors for pediatric pulmonary infections, and chest radiography is not sensitive enough, chest CT will be helpful with diagnosis. Our study of chest CTs in COVID-19 in children showed the lung lesions were mainly concentrated in the lower lobes, while lesions of mycoplasma pneumonia and other viral pneumonia patients are more diffuse (**Figure 2**, **Table 3**). And the ground-glass opacity (40%) and consolidation (38.8%) were typical manifestations in COVID-19 pediatric patients (6), similar to those in adults (20). And the ground-glass opacity was rare in mycoplasma pneumonia (5.3%) and other viral pneumonia (2%). Even though the ground-glass opacity can be used as a typical sign, there were 24 (30%) COVID-19 patients showed normal on chest CT.

Above all, it is difficult to distinguish COVID-19 and CAP in children from these clinical features. As a high morbidity of COVID-19, and at this time there are no specific vaccines or treatments, establish a method to quickly and accurately identify the pathogen is a reasonable strategy and is likely to be more effective in treatment and management.

Nevertheless, the present study had several limitations. It was conducted at a single center, the applicability of our findings may vary depending upon the relative prevalence of the etiological agent during any particular period. And the non-COVID-19 groups are comprised of relatively severe pneumonia patients. The non-COVID-19 patients with mild pneumonia were excluded. There was a selection bias in the non-COVID-19 group. There were limitations of our study.

In conclusion, the results of this study indicated COVID-19 has similar onsets with mycoplasma pneumonia and other viral pneumonia, while it appears to have a mild or moderate course in pediatric patients. And there was less fever, cough and tachypnea in the COVID-19 patients than CAP patient. Remarkably, liver function damage is more frequent in COVID-19 than CAP patients. On chest CTs, the ground-glass opacity is the typical feature. In this study, we compared COVID-19 and other common pneumonia in pediatric patients, and we suggest to consider the clinical features, laboratory results and CT findings together on pediatric patients with COVID-19. Combining with pathogen identification, reasonable management could be drawn out under this circumstance.

DATA AVAILABILITY STATEMENT

The original contributions generated for this study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This study was approved by the Research Ethics Board of Wuhan Children's Hospital (No. 2020208).

AUTHOR CONTRIBUTIONS

WX and JS designed the study. YG collected patient's data, analyzed data, prepared tables and figures, and wrote the manuscript. JS supervised data collection. JS, WX, and XP reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by Wuhan Children's Hospital Foundation under Grant 2020FE001, 2020FE002, Huazhong University of Science and Technology under Grant 2020kfyXGYJ096, Hubei Province Health and Family Planning Scientific Research project under Grant WJ2018H0160.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2020.602083/full#supplementary-material

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032
2. Guthrie LM, Soma S, Yuan S, Silva A, Zulkifli M, Snavely TC, et al. Elesclomol alleviates Menkes pathology and mortality by escorting Cu to cuproenzymes in mice. *Science*. (2020) 368:620–5. doi: 10.1126/science.aaz8899
3. *WHO Coronavirus Disease (COVID-19) Dashboard* (2020). Available online at: https://covid19.who.int/
4. Sun P, Lu X, Xu C, Sun W, Pan B. Understanding of COVID-19 based on current evidence. *J Med Virol*. (2020) 92:548–51. doi: 10.1002/jmv.25722
5. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *Lancet Infect Dis*. (2020) 20:689–96. doi: 10.1016/S1473-3099(20)30198-5
6. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: different points from adults. *Pediatr Pulmonol*. (2020) 55:1169–74. doi: 10.1002/ppul.24718
7. Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. *JAMA Pediatr*. (2020) 174:882–9. doi: 10.1001/jamapediatrics.2020.1467
8. Dagan R, Bhutta ZA, de Quadros CA, Garau J, Klugman KP, Khuri-Bulos N, et al. The remaining challenge of pneumonia: the leading killer of children. *Pediatr Infect Dis J*. (2011) 30:1–2. doi: 10.1097/INF.0b013e3182005389
9. Campbell H, Nair H. Child pneumonia at a time of epidemiological transition. *Lancet Glob Health*. (2015) 3:e65–6. doi: 10.1016/S2214-109X(14)70308-0
10. Xiao-yan H, Xing-bin W, Rong Z, Zhao-jian Y, Jun-jie T, Bin P, et al. Investigation of Mycoplasma pneumoniae infection in pediatric population from 12,025 cases with respiratory infection. *Diagn Microbiol Infect Dis*. (2013) 75:22–7. doi: 10.1016/j.diagmicrobio.2012.08.027
11. Principi N, Esposito S. Biomarkers in pediatric community-acquired pneumonia. *Int J Mol Sci*. (2017) 18:447. doi: 10.3390/ijms18020447
12. Nye S, Whitley RJ, Kong M. Viral infection in the development and progression of pediatric acute respiratory distress syndrome. *Front Pediatr*. (2016) 4:128. doi: 10.3389/fped.2016.00128
13. Guo W, Wang J, Sheng M, Zhou M, Fang L. Radiological findings in 210 paediatric patients with viral pneumonia: a retrospective case study. *Br J Radiol*. (2012) 85:1385–9. doi: 10.1259/bjr/20276974
14. *Diagnosis and Treatment Protocol for COVID-19* (Seventh Revised Edition). Available online at: http://www.gov.cn/zhengce/zhengceku/2020-03/04/5486705/files/ae61004f930d47598711a0d4cbf874a9.pdf
15. Gao Y, Zou C, Jiang J, Yang J, Tian X. Determination of normal reference ranges for venous blood count among 526 children aging from 1year old to 12 years old in Shanghai. *Guo Ji Jian Yan Yi Xue Za Zhi*. (2015) 16:2332–4. doi: 10.3969/j.issn.1673-4130.2015.16.017
16. Du Y, Wang W, He F, Zhong K, Yuan S, Liu J, et al. Investigation and analysis on pediatric reference intervals of routine chemistry items in China. *Jian Yan Yi Xue*. (2020) 7:676–81. doi: 10.3969/j.issn.1673-8640.2020.07.011
17. Zhong X, Ding J, Zhou J, Yu Z, Sun S, Bao Y, et al. A multicenter study of reference intervals for 15 laboratory parameters in Chinese children. *Zhonghua Er Ke Za Zhi*. (2018) 56:835–45. doi: 10.3760/cma.j.issn.0578-1310.2018.11.009
18. Zhang Y, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: a retrospective analysis of 115 cases from a single centre in Wuhan city, China. *Liver Int*. (2020) 40:2095–103. doi: 10.1111/liv.14455
19. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, et al. Clinical features of COVID-19-related liver damage. *Clin Gastroenterol Hepatol*. (2020) 18:1561–6. doi: 10.1101/2020.02.26.20026971
20. Kong W, Agarwal PP. Chest imaging appearance of COVID-19 infection. *Radiol. Cardiothorac Imaging*. (2020) 2:e200028. doi: 10.1148/ryct.20202 00028

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as no potential conflict of interest.

frontiers in Pediatrics

ORIGINAL RESEARCH
published: 24 November 2020
doi: 10.3389/fped.2020.574014

Higher Hospitalization Rate for Lower Airway Infection in Transfusion-Naïve Thalassemia Children

Ti-An Tsai[1], Chang-Ku Tsai[1], Yao-Hsu Yang[2], Zon-Min Lee[3†], Jiunn-Ming Sheen[1], Yi-Chen Lee[1], Chih-Min Tsai[1], Chih-Cheng Chen[1], Chih-Hao Chang[4], Chen-Kuang Niu[1] and Hong-Ren Yu[1,5†]*

[1] Department of Pediatrics, Chang Gung Memorial Hospital-Kaohsiung Medical Centre, Kaohsiung City, Taiwan, [2] Department of Chinese Medicine, Chiayi Chang Gung, Chiayi City, Taiwan, [3] Department of Pharmacy, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung City, Taiwan, [4] Department of Respiratory Therapy, Chang Gung Memorial Hospital-Kaohsiung Medical Centre, Kaohsiung City, Taiwan, [5] Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan City, Taiwan

OPEN ACCESS

Edited by:
Alan F. Isles,
Children's Health Queensland, Australia

Reviewed by:
Yusei Ohshima,
University of Fukui, Japan
Valentina Coutinho Baldoto Gava Chakr,
Federal University of Rio Grande Do Sul, Brazil

***Correspondence:**
Hong-Ren Yu
yuu2004taiwan@yahoo.com.tw

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Pediatric Pulmonology, a section of the journal Frontiers in Pediatrics

Received: 18 June 2020
Accepted: 02 November 2020
Published: 24 November 2020

Citation:
Tsai T-A, Tsai C-K, Yang Y-H, Lee Z-M, Sheen J-M, Lee Y-C, Tsai C-M, Chen C-C, Chang C-H, Niu C-K and Yu H-R (2020) Higher Hospitalization Rate for Lower Airway Infection in Transfusion-Naïve Thalassemia Children. Front. Pediatr. 8:574014. doi: 10.3389/fped.2020.574014

Few studies have addressed the risk of infection in transfusion-naïve thalassemia patients. We aimed to investigate whether transfusion-naïve thalassemia population has higher hospitalization rates for lower airway infection-related diseases than non-thalassemia population in children. A nationwide population-based retrospective cohort study was conducted using detailed medical records of the Taiwan National Health Insurance Research Database. Transfusion-naïve thalassemia patients were compared with a matched cohort at a ratio of 1:4. Data of the selected patients were adjusted for age, sex, and related comorbidities. We recorded the frequency of admissions or outpatient clinic visits for patients with a diagnosis of pneumonia or acute bronchitis/bronchiolitis. Based on our results, the hospitalization rates and incidence rate ratios of bronchitis/bronchiolitis and pneumonia for transfusion-naïve thalassemia children were all higher than those for non-thalassemia controls. Therefore, we conclude that transfusion-naïve thalassemia children are more likely to experience lower airway infections and have a higher probability of hospitalization for these conditions.

Keywords: thalassemia, transfusion-naïve, pneumonia, bronchitis, children

INTRODUCTION

Thalassemia is a common autosomal-recessive hereditary hemoglobinopathy, mainly characterized by a point mutation on globin gene expression (1). In adults, hemoglobin comprises four protein chains (two α and two β globin chains) that are assembled into a heterotetramer. In α-thalassemia and β-thalassemia, the production of the α and β globin chains is affected, respectively. Thalassemia is commonest among people of Italian, Greek, Middle Eastern, South Asian, and African descent (2). In China, the prevalence of α-thalassemia, β-thalassemia, and α + β-thalassemia were estimated at 7.88, 2.21, and 0.48%, respectively (3). In a previous study, the prevalence of α-thalassemia traits in Taiwan was 3.4% (4).

Clinical manifestations of thalassemia may range from no symptoms to severe lethal complications depending on how many of the four genes for α globin or two genes for β globin are involved. People with thalassemia may have iron overload (owing to the disease itself or frequent blood transfusions), infection, splenomegaly, slowed growth rates, or heart disease. Infection is a major cause of morbidity and mortality in patients with thalassemia major and is assumed to result from splenectomy, blood transfusion, and immunological changes with iron overload (2, 5). Patients with splenectomy are more susceptible to gram-negative microorganisms and pneumococcus than other organisms (6, 7), and patients who receive regular blood transfusions are at a risk of developing transfusion-transmitted infections such as *Toxoplasma gondii*, hepatitis C virus, and hepatitis B virus (8–10).

Unlike thalassemia major, patients with non-transfusion-dependent thalassemia (NTDT) (including those with various phenotypes) do not require lifelong regular transfusion therapy for survival. NTDT patients can be at risk of ineffective erythropoiesis, peripheral hemolysis, and iron overload that contribute to a number of clinical morbidities (11, 12), and these patients with iron overload may have higher risk for severe bacterial infection (13).

Intracellular iron overload has been proven to lead to DNA damage of lymphocytes and immune dysfunction in thalassemia major patients who receive blood transfusions (14). However, whether the immune function in NTDT patients is impaired is still unclear. Some reports suggested the presence of decreased CD4+/CD8+ ratios and increased Treg cells, which might suppress immune activation status, in β-thalassemia major patients, but not in those with β-thalassemia traits, compared to controls (15, 16). Another report stated that reduced CXCR2 expression and neutrophil migration were observed in NTDT patients (17). Therefore, this study aimed to examine whether NTDT children without history of blood transfusion have a higher risk of infection, especially lower respiratory tract infections.

METHODS

Data Source

Nearly the entire Taiwanese population, i.e., over 23 million people, have been enrolled in National Health Insurance since 1995. Details of the medical records of each person are stored in the National Health Insurance Research Database (NHIRD), which was created by the National Health Research Institutes (NHRI). In this retrospective cohort study, we used the Longitudinal Health Insurance Database 2010 (LHID 2010), released by NHRI, as our data source. The LHID 2010 includes one million people randomly selected from the 2010 Registry for Beneficiaries. The database contains detailed medical records of each insurant from 1997 to 2013. Among these one million people, we selected people whose birth year was from 1998 to 2007, so all people we analyzed were children and adolescents. International Classification of Diseases, ninth revision (ICD-9-CM) coding was used for disease identification. The study protocol was approved by the institutional review board of the study hospital.

Sampled Participants

We defined patients as having thalassemia if they were diagnosed with thalassemia (ICD-9-CM: 282.4) once during hospitalization or at least twice when examined at the outpatient department in 1 year. We excluded patients with a history of catastrophic illness certificates, blood transfusion (ICD-9 procedure code 94005C or 990), partial or total splenectomy (ICD-9 procedure code 70001B, 70003B, and 70006B), immunodeficiency (ICD-9-CM: 279) and other hematological disorders, including iron deficiency, and other deficiency anemias (ICD-9-CM: 280∼281), sickle-cell anemia and other hemoglobinopathies, hereditary/acquired hemolytic anemia, aplastic anemia, and chronic disease-related anemia (ICD-9-CM: 282.6∼285.8), myelodysplastic syndrome (ICD-9-CM: 238.7), hyperferritinemia and primary or secondary hemochromatosis (ICD-9-CM: 275.0), and hematological malignancies (ICD-9-CM: 200∼208) diagnosed once during hospitalization or more than once in the outpatient department in 1 year. We also excluded patients for whom information on age or sex was missing. The catastrophic illness certificates in Taiwan include cancer, hematologic abnormality, renal failure with hemodialysis required, generalized autoimmune diseases with life-long treatment required, chronic mental disorders, congenital metabolic disorders, major organs and genes abnormality (e.g., congenital anomalies of heart), massive burns, major organs transplantation, complicated nervous, or musculoskeletal disorders (e.g., cerebral palsy), injury severity scores more than 16, chronic respiratory failure with ventilator required, uncorrected malnutrition status, Myasthenia gravis, spinal cord injuries, occupational diseases, acute stage of cerebrovascular diseases, multiple sclerosis, leprosy, liver cirrhosis with complication, complications related to prematurity, toxic effect of arsenic and its compounds, Creutzfeldt-Jakob disease, and other rare diseases (e.g., cystic fibrosis).

One thalassemia patient was matched with four control patients without thalassemia (1:4 matching) according to birth year, sex with frequency match. The comorbidities included were asthma (ICD-9-CM: 493), diabetes mellitus (DM) (ICD-9-CM: 450), chronic lung disease (ICD-9-CM: 770.7), heart failure (ICD-9-CM: 428), epilepsy (ICD-9-CM: 345), and chronic kidney disease (CKD) (ICD-9-CM: 580∼589), diagnosed once at hospitalization or at least thrice in the outpatient department in 1 year. These medical conditions were proved to be risk factors of pneumonia (18, 19). The propensity score was calculated using the Statistical Analysis System 9.4 program (SAS Institute, Cary, North Carolina, USA).

Outcome and Comorbidities

The patients in this cohort study were followed up from their birthday to death or 2013/12/31. The outcome was defined as having records of lower airway infections such as acute bronchitis/bronchiolitis (ICD-9-CM: 466) and pneumonia (ICD-9-CM: 480∼486), diagnosed at hospitalization or at least thrice in the outpatient department in 1 year. Each incident of

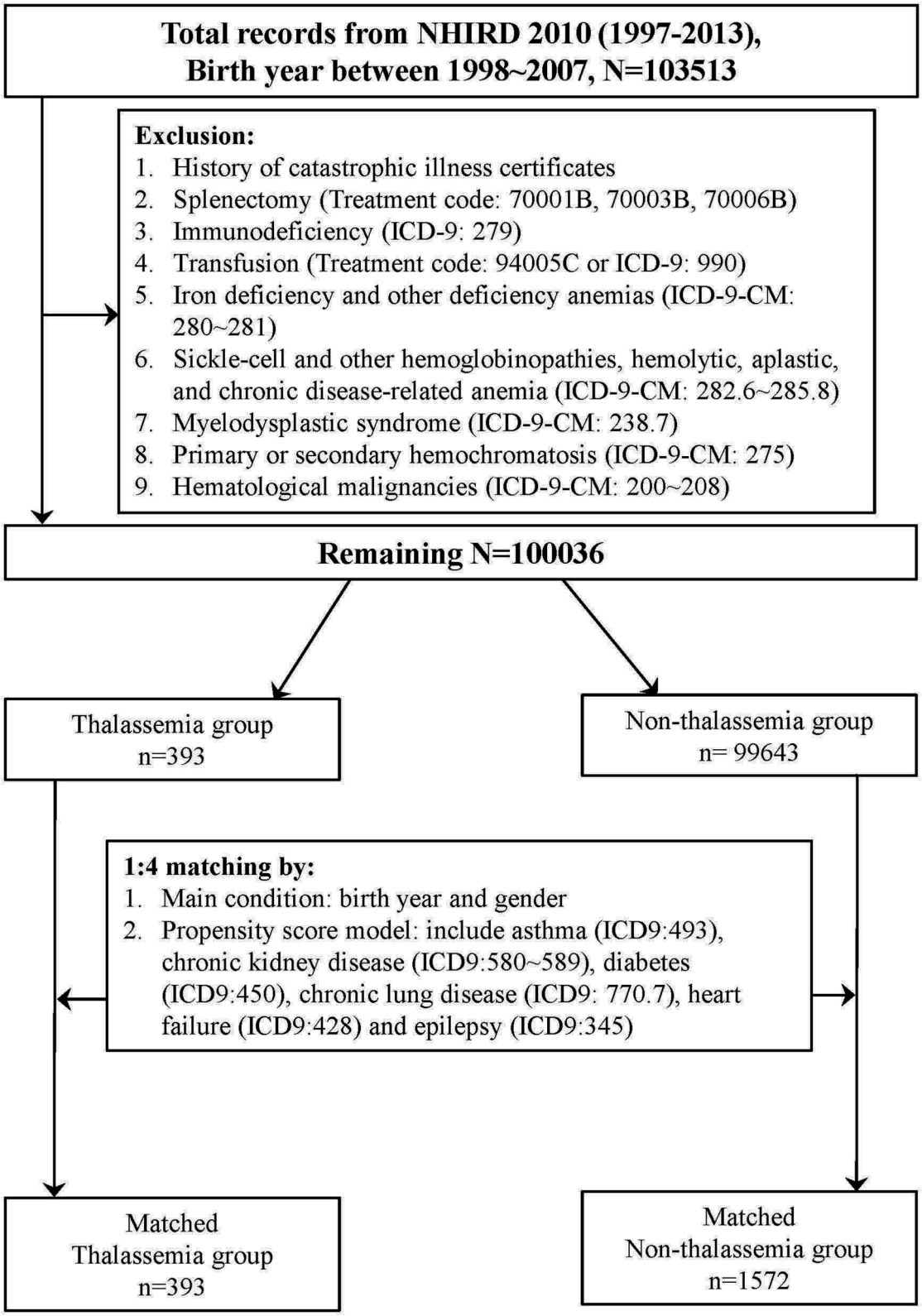

FIGURE 1 | Flow chart of matched cohorts' selection. One million people were randomly selected from the Longitudinal Health Insurance Database 2010 (LHID 2010). After the screening process, 393 persons in the thalassemia group and 1,572 persons in the non-thalassemia group were analyzed.

hospitalization due to lower respiratory tract infection was included for analysis. The effects of baseline comorbidities, which may be related to lower airway infection, were eliminated via the propensity score model.

Statistical Analysis

Differences between the demographic characteristics and comorbidities and the events of hospitalization due to lower airway infections in patients with thalassemia and matched non-thalassemia controls were analyzed using the chi-square test. The incidence rate ratios (IRRs) and 95% confidence intervals (CIs) were estimated using Poisson regression. A $P < 0.05$ in 2-tailed tests was considered statistically significant.

RESULTS

One million people were randomly selected from LHID 2010, and those born between 1998 and 2007 were selected for further analysis. Subjects who matched the inclusion and exclusion criteria were separated into a group with thalassemia and a group with non-thalassemia. Details of these processes are shown in **Figure 1**. Finally, 393 patients were identified in the thalassemia group and 1,572 controls in the non-thalassemia group (the control group), with 1:4 matching according to birth year, sex, and propensity score.

Demographic characteristics and comorbidities in these matched cohorts are shown in **Table 1**. Similar distributions occurred with sex, age, place of residence, income, and comorbidities, including asthma, DM, CKD, chronic lung disease, heart failure, and epilepsy between the thalassemia and non-thalassemia groups because both cohorts were matched for factors. For lower respiratory diseases, the patients in the thalassemia group had a higher prevalence of acute bronchiolitis/bronchitis (92.88% vs. 87.60%, $P = 0.003$) and pneumonia (60.65 vs. 36.96%, $P < 0.001$) than those in the non-thalassemia group.

Thereafter, we focused on events related to hospitalization due to lower respiratory diseases (**Table 2**). The hospitalization rates for acute bronchitis/bronchiolitis (31.55 vs. 13.42%, $P < 0.001$) and pneumonia (49.11 vs. 23.22%, $P < 0.001$) were also higher in the thalassemia group than in the non-thalassemia group. The average number of admissions for inpatients and the average number of hospitalization days each time were also compared, and there was almost no difference between these two groups. **Figures 2**, **3** show the cumulative number of admissions or hospitalization days per person due to acute bronchitis/bronchiolitis and pneumonia across the 17 years, respectively. For both acute bronchitis/bronchiolitis and pneumonia, the cumulative rates for the thalassemia group were obviously higher than for the non-thalassemia group.

The IRR of admissions due to acute bronchitis/bronchiolitis and pneumonia was also analyzed (**Tables 3**, **4**, respectively). Age of the study patients was classified into three groups: preschooler (<6 years); grade schooler (≥6 to <12 years); and teenager (≥12 to < 16 years). In **Tables 3**, **4**, "Age (year old)" implied the age of the patient at the date of admission, and "Times" implied the number of admissions. Person-years (PY) was calculated as:

$$\mathrm{PY} = [\mathrm{deathdateor2013/12/31}] - [\mathrm{birthday}].$$

For acute bronchitis/bronchiolitis, those with transfusion-naïve thalassemia had a higher incidence rate of admission than the non-thalassemia controls, irrespective of sex, age, or whether there was comorbidity or not. The only exception was patients with epilepsy or chronic kidney diseases, but these were not statistically significant because only few data were included for analysis. Comparing the age at admission, grade schoolers (≥6 to <12 years) had higher IRR (IRR 4.48, 95% CI 2.64–7.61) than preschoolers. The IRR of teenagers could not be calculated because no non-thalassemia teenagers were admitted for acute bronchiolitis/bronchitis during our study period. The admissions due to pneumonia showed the same trend. Those

TABLE 1 | Demographic characteristics and comorbidities in matched cohorts.

			THA, $n = 393$ (20%)		Non-THA, $n = 1572$ (80)		
***N* = 1,965**		***N* (%)**	***n***	**%**	***n***	**%**	***P***
Gender	Male	1205	241	61.32	964	61.32	1
	Female	760	152	38.68	608	38.68	
Birth year	1998	175	35	8.91	140	8.91	1
	1999	230	46	11.7	184	11.7	
	2000	255	51	12.98	204	12.98	
	2001	215	43	10.94	172	10.94	
	2002	200	40	10.18	160	10.18	
	2003	150	30	7.63	120	7.63	
	2004	160	32	8.14	128	8.14	
	2005	205	41	10.43	164	10.43	
	2006	175	35	8.91	140	8.91	
	2007	200	40	10.18	160	10.18	
Comorbidity	Yes	760	152	38.68	608	38.68	1
	No	1205	241	61.32	964	61.32	
Asthma	Yes	710	142	36.13	568	36.13	1
	No	1255	251	63.87	1004	63.87	
CKD	Yes	25	5	1.27	20	1.27	1
	No	1940	388	98.73	1552	98.73	
Diabetes	Yes	0					1
	No	1965	393	100	1572	100	
CLD	Yes	0					1
	No	1965	393	100	1572	100	
Heart failure	Yes	0					1
	No	1965	393	100	1572	100	
Epilepsy	Yes	40	8	2.04	32	2.04	1
	No	1925	385	97.96	1540	97.96	
Bronchiolitis	Yes	1742	365	92.88	1377	87.6	0.003
	No	223	28	7.12	195	12.4	
Pneumonia	Yes	817	236	60.05	581	36.96	<0.001
	No	1148	157	39.95	991	63.04	

Chi-square test.

THA, thalassemia; Non-THA, non-thalassemia; CLD, chronic lung disease; CKD, chronic kidney disease.

TABLE 2 | Number of inpatients, number of admissions and hospitalization days for lower airway disease (acute bronchitis/bronchiolitis and pneumonia) from matched cohorts.

		Overall	THA, $n = 393$		Non-THA, $n = 1,572$		P
BRO	Inpatients, *n* (%)	335	124	(31.55)	211	(13.42)	<0.001[a]
	Total admissions	501	208		293		
	Total hospitalization days	2,299	939		1,360		
	Total admissions/Total inpatients	1.50 ± 1.11*	1.68 ± 1.42*		1.39 ± 0.87*		0.0417[b]
	Total days/Total admissions	4.59 ± 2.47*	4.51 ± 2.70*		4.64 ± 2.30*		0.5811[b]
PN	Inpatients, *n* (%)	558	193	(49.11)	365	(23.22)	<0.001[a]
	Total admissions	926	354		572		
	Total hospitalization days	4,301	1,753		2,548		
	Total admissions/Total inpatients	1.66 ± 1.30*	1.83 ± 1.51*		1.57 ± 1.16*		0.0329[b]
	Total days/Total admissions	4.64 ± 2.61*	4.95 ± 2.70*		4.45 ± 2.54*		0.0048[b]

Plus-minus values are mean ± SD.
[a] *T-test.*
[b] *Chi-square test.*
THA, thalassemia; Non-THA, non-thalassemia; BRO, acute bronchitis/bronchiolitis; PN, pneumonia.

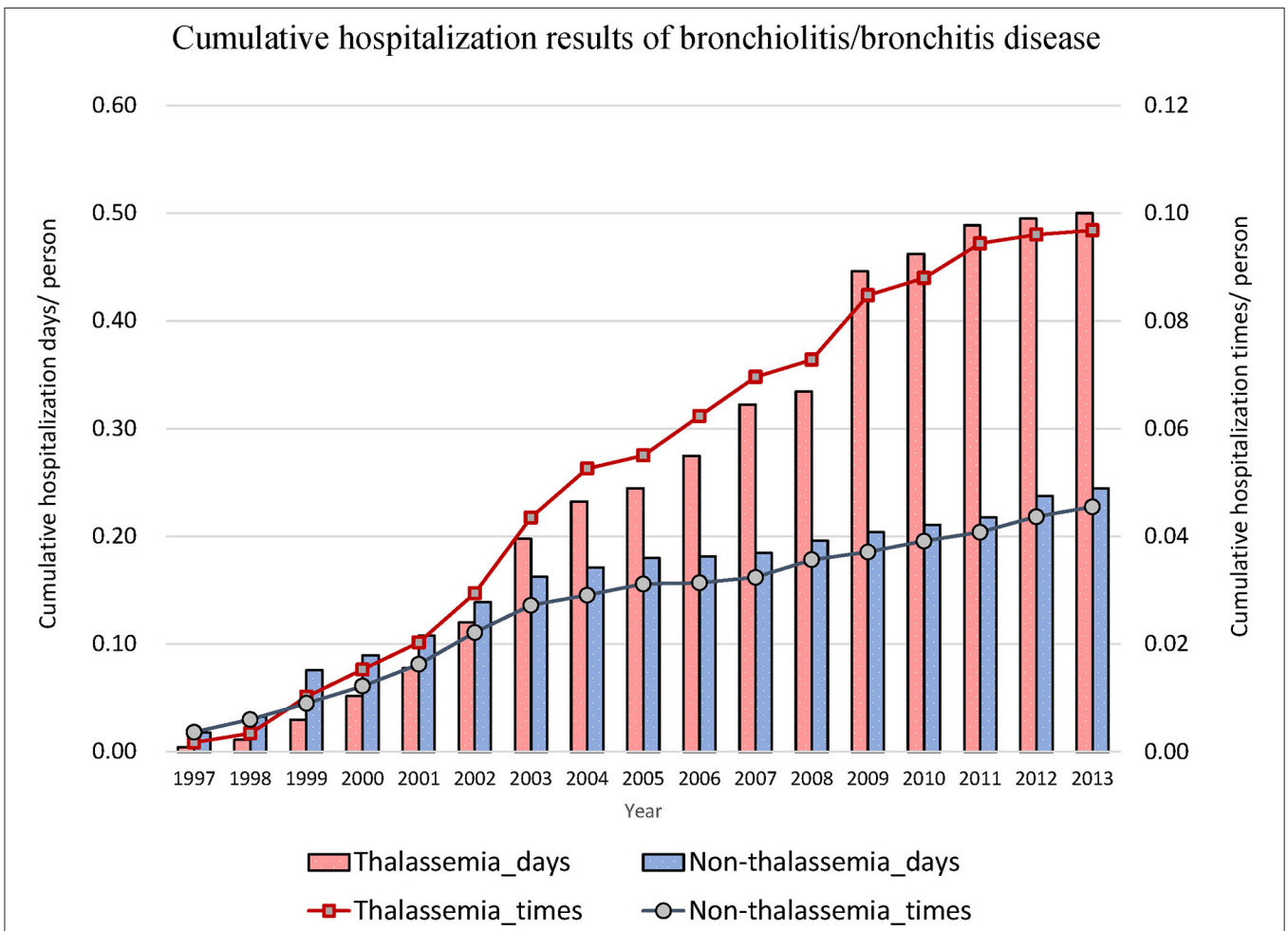

FIGURE 2 | Cumulative number of admissions due to acute bronchitis/bronchiolitis for patients with (dashed line) or without (solid line) thalassemia, and cumulative hospitalization days for patients with (white bar) or without (black bar) thalassemia. The x-axis is the cumulated years from 1997 to 2013, 17 years in total. The cumulative rate for the thalassemia group was higher than that for the non-thalassemia group.

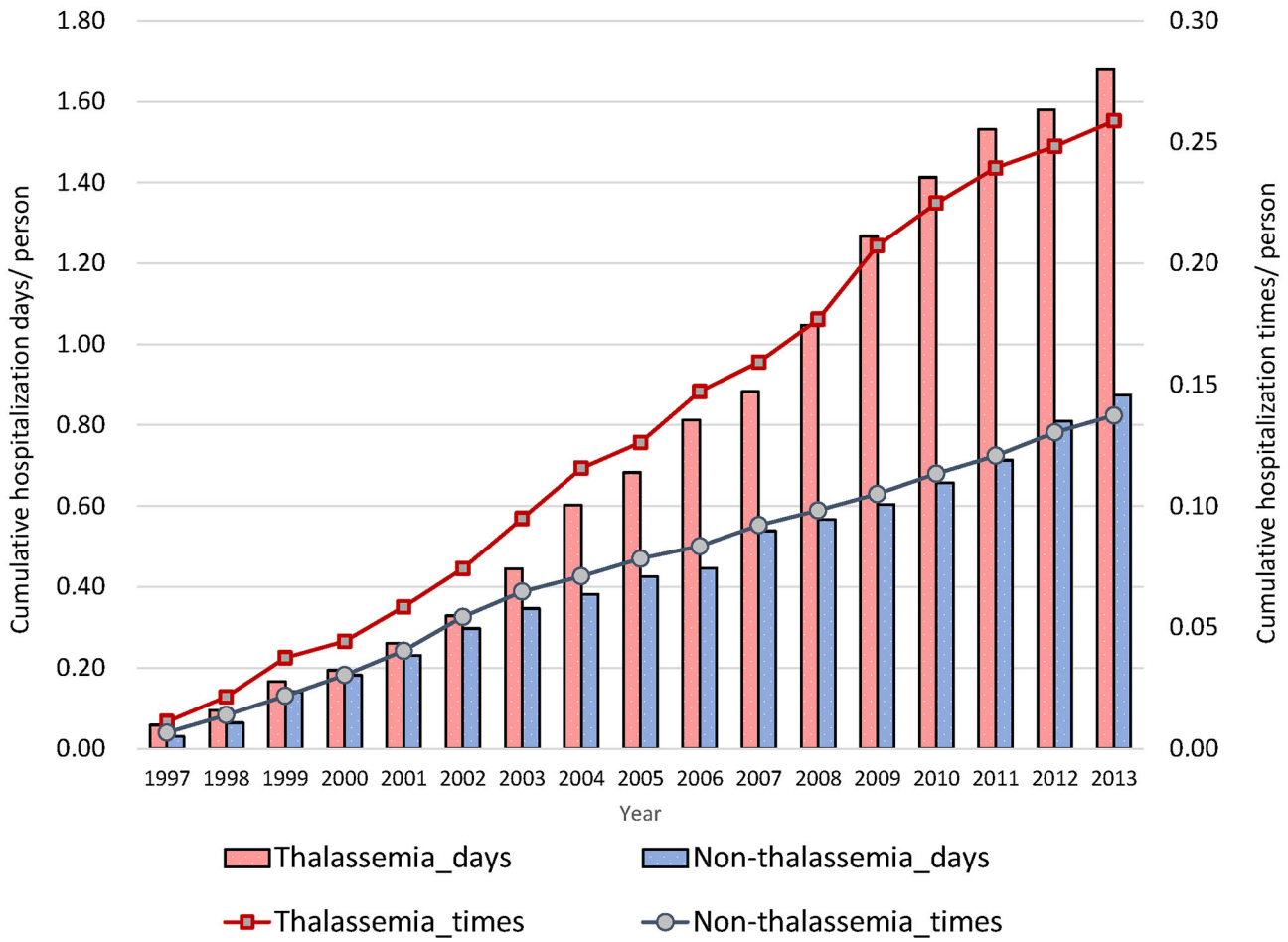

FIGURE 3 | Cumulative number of admissions due to pneumonia for patients with (dashed line) or without (solid line) thalassemia, and cumulative hospitalization days for patients with (white bar) or without (black bar) thalassemia. The x-axis is the cumulated years from 1997 to 2013, 17 years in total. The cumulative rate for the thalassemia group was higher than that for the non-thalassemia group.

with transfusion-naïve thalassemia had higher incidence rates of admissions than non-thalassemia controls, irrespective of sex, age, or presence of comorbidity, except for the patients with chronic lung diseases or epilepsy. The highest IRR according to age of admission was observed in the teenager group (IRR 23.98, 95% CI 2.89–199.22). Most inpatients who were admitted for acute bronchitis/bronchiolitis or pneumonia were aged below 6-year-old.

DISCUSSION

Thalassemia is a common hematologic disorder, and its complications include bone dysmorphism, hemochromatosis, splenomegaly, infection, endocrine disorders, and heart failure. Some of these complications result from long-term, repeated blood transfusions (20). Infection is a major issue for patients with the severe form of thalassemia, and the proposed predisposing factors are anemia, iron overload, splenectomy, transfusion-associated viral infections, and a range of immune abnormalities (2). For thalassemia patients without a history of blood transfusion, although there may be no symptoms of anemia or it may be mild, such as thalassemia minor patients, they also have a higher risk of coronary artery disease, erectile dysfunction, and fractures (21–23). Their hematopoiesis may be less effective, and the abnormal erythrocyte cell membrane structure leads to peripheral hemolysis and subsequent iron overload, which are risk factors for susceptibility to infection (11, 12). However, no strong evidence to this effect has been provided before our study.

The risk of infection for thalassemia major patients has been demonstrated in previous studies; our study, a nationwide, population-based cohort study, revealed that transfusion-naïve thalassemia children are also susceptible to lower respiratory tract infection. This present study showed a higher prevalence of acute bronchitis/bronchiolitis and pneumonia, common diseases related to lower respiratory infection, in the transfusion-naïve thalassemia population compared to the

TABLE 3 | Incidence rate ratio of admissions for acute bronchitis/bronchiolitis.

	THA (n = 393)				Non-THA (n = 1,572)					
	N	**Times**	**PY**	**Rate (per 1,000 PY)[a]**	***N***	**Times**	**PY**	**Rate (per 1000 PY)[a]**	**IRR (95% CI)[†]**	***p***
Overall	124	208	4393.12	47.35 (41.33–54.24)	211	293	17602.2	16.65 (14.84–18.67)	2.84 (2.38–3.4)	***
Female	42	74	1662.83	44.50 (35.43–55.89)	78	100	6670.8	14.99 (12.32–18.24)	2.97 (2.2–4.01)	***
Male	82	134	2730.28	49.08 (41.43–58.13)	133	193	10931.4	17.66 (15.33–20.33)	2.78 (2.23–3.47)	***
Age (y/o) <6	112	176	2358	74.64 (64.39–86.52)	197	267	9432	28.31 (25.11–31.92)	2.64 (2.18–3.19)	***
6≦Age<12	21	29	1692.02	17.14 (11.91–24.66)	20	26	6798.7	3.82 (2.60–5.62)	4.48 (2.64–7.61)	***
12≦Age<16	2	3	343.1	8.74 (2.82–27.11)	0	0	1371.49	0.00		
No comorbidity	56	84	2654.97	31.64 (25.55–39.18)	97	119	10630.7	11.19 (9.35–13.4)	2.83 (2.14–3.74)	***
Comorbidity[b]	68	124	1738.15	71.34 (59.83–85.07)	114	174	6971.46	24.96 (21.51–28.9)	2.86 (2.27–3.6)	***
w/o Asthma	57	85	2774.88	30.63 (24.77–37.89)	103	127	11115	11.43 (9.60–13.6)	2.68 (2.04–3.53)	***
with Asthma	67	123	1618.24	76.01 (63.70–90.70)	108	166	6487.16	25.59 (21.98–29.7)	2.97 (2.35–3.75)	***
w/o CKD	124	208	4328.54	48.05 (41.95–55.05)	206	285	17339.9	16.44 (14.63–18.4)	2.92 (2.45–3.5)	***
with CKD	0	0	64.58	0.00	5	8	262.31	30.50 (15.25–60.9)	0	***
w/o Epilepsy	123	207	4293.28	48.21 (42.07–55.25)	207	287	17198.7	16.69 (14.86–18.7)	2.89 (2.42–3.45)	***
with Epilepsy	1	1	99.84	10.02 (1.41–71.11)	4	6	403.48	14.87 (6.68–33.1)	0.67 (0.08–5.59)	0.715

*[†] Poisson regression, ***p < 0.001.*

[a] Rate, incidence rate, per 1,000 person years.

[b] Individuals with any comorbidity of asthma, epilepsy, and chronic kidney disease.

THA, thalassemia; Non-THA, non-thalassemia; PY, person-year; IRR, incidence rate ratio; CI, confidence interval; w/o, without; CKD, chronic kidney disease.

TABLE 4 | Incidence rate ratio of admissions for pneumonia.

	THA (n = 393)				Non-THA (n = 1,572)					
	N	**Times**	**PY**	**Rate (per 1,000 PY)[a]**	**N**	**Times**	**PY**	**Rate (per 1,000 PY) [a]**	**IRR (95% CI)[†]**	***p***
Overall	193	354	4393.12	80.58 (72.61–89.43)	365	572	17602.2	32.50 (29.94–35.27)	2.48 (2.17–2.83)	***
Female	71	131	1662.83	78.78 (66.38–93.50)	135	198	6670.8	29.68 (25.82–34.12)	2.65 (2.13–3.31)	***
Male	122	223	2730.28	81.68 (71.63–93.13)	230	374	10931.4	34.21 (30.92–37.86)	2.39 (2.02–2.82)	***
Age (y/o) <6	178	305	2358	129.35 (115.62–144.71)	332	490	6432	76.18 (47.55–56.76)	2.49 (2.16–2.87)	***
6≦Age<12	31	43	1692.02	25.41 (18.85–34.27)	60	81	6798.7	11.91 (9.58–14.81)	2.13 (1.47–3.09)	***
12≦Age<16	3	6	343.1	17.49 (7.86–38.93)	1	1	1371.49	0.73 (0.10–5.18)	24 (2.89–199.22)	0.003
No comorbidity	106	161	2654.97	60.64 (51.96–70.77)	154	200	10630.7	18.81 (16.38–21.61)	3.22 (2.62–3.97)	***
Comorbidity[b]	87	193	1738.15	111.04 (96.43–127.86)	211	372	6971.46	53.36 (48.20–59.07)	2.08 (1.75–2.48)	***
w/o Asthma	109	164	2774.88	59.10 (50.71–68.88)	162	214	11115	19.25 (16.84–22.01)	3.07 (2.5–3.76)	***
with Asthma	84	190	1618.24	117.41 (101.85–135.35)	203	258	6487.16	39.77 (49.76–61.21)	2.13 (1.78–2.54)	***
w/o CKD	192	353	4328.54	81.55 (73.47–90.52)	358	553	17339.9	31.89 (29.34–34.66)	2.56 (2.24–2.92)	***
with CKD	1	1	64.58	15.48 (2.18–109.93)	7	19	262.31	72.43 (46.20–113.56)	0.21 (0.03–1.6)	***
w/o Epilepsy	190	351	4293.28	81.76 (73.63–90.77)	356	556	17198.7	32.33 (29.75–35.13)	2.53 (2.21–2.89)	***
with Epilepsy	3	3	99.84	30.05 (9.69–93.17)	9	16	403.48	39.66 (24.29–64.73)	0.76 (0.22–2.6)	0.659

*[†] Poisson regression, ***p < 0.001.*

THA, thalassemia; Non-THA, non-thalassemia; PY, person-year; IRR, incidence rate ratio; CI, confidence interval; w/o, without; CKD, chronic kidney disease.

[a] Rate, incidence rate, per 1,000 person years.

[b] Individuals with any comorbidity of asthma, epilepsy, and chronic kidney disease.

non-thalassemia controls. Previous studies had shown that non-transfusion-dependent thalassemia (NTDT) patients may have altered immune function and increased susceptibility to severe bacterial infections, especially for patients with iron overload or post splenectomy (13, 17). The NTDT patients do not need lifelong regular blood transfusion but occasional blood transfusion may be required for some stressful conditions. Patients who had ever received blood transfusion, splenectomy, or had been diagnosed as having other hematologic disorders were excluded based on the ICD-9-CM codes in this study. Thus, our study group is in a milder status than NTDT. We assume that the thalassemia patients that included are silent carriers and have α- or β- thalassemia minor or α- or β-thalassemia intermedia without a history of blood transfusion.

The effects of confounding factors, i.e., age, sex, and comorbidities of asthma, heart failure, DM, chronic lung disease, epilepsy, and CKD, were adjusted for when matching the thalassemia and control groups. Focusing on those who were

hospitalized with diseases related to lower respiratory infection, the thalassemia group had a higher percentage of admissions for both acute bronchitis/bronchiolitis and pneumonia compared to the control group. However, there was almost no difference between the two groups with respect to average number of admissions and average days of hospitalization of inpatients. It seemed that although transfusion-naïve thalassemia patients had a higher possibility of hospitalization than the non-thalassemia controls, irrespective of sex, age, or presence of comorbidity, the severity of the diseases was similar. In this study, most inpatients were aged below 6 years, which may be because the immune system of preschoolers is relatively immature (24, 25), and to some extent, the criterion of admission maybe loose. Among different age groups, the highest IRR fell into the teenager ($\geq$12 to $<$16 years).

Similar to previous similar studies, this study has several limitations (21–23). First, there are several genotypes of thalassemia, in which the structure of hemoglobin is different. Thus, thalassemia patients have varying hemoglobin and ferritin levels. These data may affect the risk of infection and they could not be obtained from the NHIRD. However, the proportion of thalassemia intermedia is just about 1.5 percent among the NHIRD (26). We had also excluded cases that received blood transfusion and splenectomy, which account for near 50% and 30 of thalassemia intermedia (27). Thus, the effect of thalassemia intermedia in NHIRD is too small and can be neglected. Second, although we used ICD-9 codes to screen out thalassemia patients, some asymptomatic patients were missed because the physicians did not include thalassemia in the diagnostic lists for this population. There might have been some thalassemia patients in the control group. Thus, the hospitalization rate for lower airway infection in the control group may be overestimated. In other words, in real condition, the NHIRD may have higher hospitalization rates for lower airway infection than control. The incidence of pneumococcus disease decreased dramatically after the introduction of pneumococcal vaccine (28). In Taiwan, pneumococcal vaccine has been provided for free since 2015 to all young children (29), which was beyond our study period (1997–2013). The introduction of pneumococcal vaccine should have no influence on our data.

Nowadays, the number of cases of severe thalassemia in Taiwan is decreasing because of the policy of prenatal screening. Most thalassemia patients are silent carriers or have thalassemia minor. Previously the prevention of infections was usually focused on thalassemia patients with history of blood transfusion. The main contribution of our study is the elucidation of the risk of lower airway infection in transfusion-naïve thalassemia patients. It is therefore important to identify the nearly asymptomatic thalassemia populations and educate them regarding the importance of preventing themselves from acquiring airborne or droplet-transmitted infections.

The phenomenon that transfusion-naïve thalassemia patients are susceptible to lower respiratory tract infection was observed in our study, and this observation proved that besides of blood transfusion, there are other mechanisms contributes to higher infection risk, like ineffective erythropoiesis and increased intestinal iron absorption (30), although the exact pathologic mechanism remains unclear. Further studies should be designed to obtain more details on the pathophysiology concerned. In addition, it would be valuable to study whether these transfusion-naïve thalassemia patients have a higher risk of other types of infection, such as urinary tract infection and acute gastroenteritis.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Chang Gung Memorial Hospital-Kaohsiung Medical Center. Written informed consent for participation was not provided by the participants' legal guardians/next of kin because: big data (Taiwan National Health Insurance Research Database).

AUTHOR CONTRIBUTIONS

H-RY, Z-ML, T-AT, and C-KT contributed to design of the work. H-RY, Y-HY, Y-CL, and T-AT contributed to data acquisition. H-RY, C-KT, Y-CL, C-CC, and C-MT performed data analysis and interpretation. H-RY, C-MT, C-HC, and C-KN drafted the manuscript. H-RY, Z-ML, T-AT, C-KT, and C-KN finalized the article. All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work.

FUNDING

This study was supported in part by grants CFRPG8H0251 (H-RY) from Chang Gung Memorial Hospital, Taiwan.

ACKNOWLEDGMENTS

We thank the Biostatistics Center, Kaohsiung Chang Gung Memorial Hospital, for their assistance with the statistics.

REFERENCES

1. Origa R. β-Thalassemia. *Genet Med.* (2017) 19:609–19. doi: 10.1038/gim.2016.173
2. Vento S, Cainelli F, Cesario F. Infections and thalassaemia. *Lancet Infect Dis.* (2006) 6:226–33. doi: 10.1016/S1473-3099(06)70437-6
3. Lai K, Huang G, Su L, He Y. The prevalence of thalassemia in mainland China: evidence from epidemiological surveys. *Sci Rep.* (2017) 7:920. doi: 10.1038/s41598-017-00967-2
4. Lin CK, Lee SH, Wang CC, Jiang ML, Hsu HC. Alpha-thalassemic traits are common in the Taiwanese population: usefulness of a modified hemoglobin H preparation for prevalence studies. *J Lab Clin Med.* (1991) 118:599–603.

5. Bisharat N, Omari H, Lavi I, Raz R. Risk of infection and death among post-splenectomy patients. *J Infect.* (2001) 43:182–6. doi: 10.1053/jinf.2001.0904
6. Holdsworth RJ, Irving AD, Cuschieri A. Postsplenectomy sepsis and its mortality rate: actual versus perceived risks. *Br J Surg.* (1991) 78:1031–8. doi: 10.1002/bjs.1800780904
7. Sakran W, Levin C, Kenes Y, Colodner R, Koren A. Clinical spectrum of serious bacterial infections among splenectomized patients with hemoglobinopathies in Israel: a 37-year follow-up study. *Infection*. (2012) 40:35–9. doi: 10.1007/s15010-011-0178-5
8. Choudhury N, Saraswat S, Naveed M. Serological monitoring of thalassaemia major patients for transfusion associated viral infections. *Indian J Med Res*. (1998) 107:263–8.
9. Hassanshahi G, Arababadi MK, Assar S, Hakimi H, Karimabad MN, Abedinzadeh M, et al. Post-transfusion-transmitted hepatitis C virus infection: a study on thalassemia and hemodialysis patients in southeastern Iran. *Arch Virol*. (2011) 156:1111–5. doi: 10.1007/s00705-011-0950-y
10. Atwa ZT, Abdel Wahed WY. Transfusion transmitted infections in frequently transfused thalassemic children living in Fayoum Governorate, Egypt: Current prevalence and risk factors. *J Infect Public Health.* (2017) 10:870–4. doi: 10.1016/j.jiph.2017.02.012
11. Musallam KM, Rivella S, Vichinsky E, Rachmilewitz EA. Non-transfusion-dependent thalassemias. *Haematologica*. (2013) 98:833–44. doi: 10.3324/haematol.2012.066845
12. Musallam KM, Cappellini MD, Wood JC, Taher AT. Iron overload in non-transfusion-dependent thalassemia: a clinical perspective. *Blood Rev*. (2012) 26(Suppl 1):S16–9. doi: 10.1016/S0268-960X(12)70006-1
13. Teawtrakul N, Jetsrisuparb A, Sirijerachai C, Chansung K, Wanitpongpun C. Severe bacterial infections in patients with non-transfusion-dependent thalassemia: prevalence and clinical risk factors. *Int J Infect Dis IJID Off Publ Int Soc Infect Dis.* (2015) 39:53–6. doi: 10.1016/j.ijid.2015.09.001
14. Hagag AA, Elgamsy MA, El-Asy HM, Gamal RM, Elshahaby WN, Abd Elbar ES. Immune status 'in children with beta thalassemia' in correlation 'with iron overload': single center Egyptian study. *Endocr Metab Immune Disord Drug Targets*. (2016) 16:181–8. doi: 10.2174/1871530317666161107160213
15. Ezer U, Gülderen F, Culha VK, Akgül N, Gürbüz O. Immunological status of thalassemia syndrome. *Pediatr Hematol Oncol.* (2002) 19:51–8. doi: 10.1080/088800102753356194
16. Bozdogan G, Erdem E, Demirel GY, Yildirmak Y. The role of Treg cells and FoxP3 expression in immunity of β-thalassemia major AND β-thalassemia trait patients. Pediatr *Hematol Oncol.* (2010) 27:534–45. doi: 10.3109/08880018.2010.503334
17. Thiengtavor C, Siriworadetkun S, Paiboonsukwong K, Fucharoen S, Pattanapanyasat K, Vadolas J, et al. Increased ferritin levels in non-transfusion-dependent β°-thalassaemia/HbE are associated with reduced CXCR2 expression and neutrophil migration. *Br J Haematol.* (2020) 189:187–98. doi: 10.1111/bjh.16295
18. Pelton SI, Shea KM, Farkouh RA, Strutton DR, Braun S, Jacob C, et al. Rates of pneumonia among children and adults with chronic medical conditions in Germany. *BMC Infect Dis.* (2015) 15:470. doi: 10.1186/s12879-015-1162-y
19. Sterky E, Bennet R, Lindstrand A, Eriksson M, Nilsson A. The impact of pneumococcal conjugate vaccine on community-acquired pneumonia hospitalizations in children with comorbidity. *Eur J Pediatr*. (2017) 176:337. doi: 10.1007/s00431-016-2843-2
20. Taher AT, Weatherall DJ, Cappellini MD. Thalassaemia. *Lancet Lond Engl.* (2018) 391:155–67. doi: 10.1016/S0140-6736(17)31822-6
21. Chen Y-G, Lin C-L, Ho CL, Chen Y-C, Kao C-H. Risk of coronary artery disease in transfusion-naïve thalassemia populations: a nationwide population-based retrospective cohort study. *Eur J Intern Med.* (2015) 26:250–4. doi: 10.1016/j.ejim.2015.02.001
22. Chen Y-G, Lin T-Y, Lin C-L, Dai M-S, Ho C-L, Kao C-H. Risk of erectile dysfunction in transfusion-naive thalassemia men: a nationwide population-based retrospective cohort study. *Medicine.* (2015) 94:e700. doi: 10.1097/MD.0000000000000700
23. Chen Y-G, Lu C-S, Lin T-Y, Lin C-L, Tzeng H-E, Tsai C-H. Risk of fracture in transfusion-naïve thalassemia population: a nationwide population-based retrospective cohort study. *Bone*. (2018) 106:121–5. doi: 10.1016/j.bone.2017.10.016
24. Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. *Proc R Soc B Biol Sci.* (2015) 282:20143085. doi: 10.1098/rspb.2014.3085
25. Georgountzou A, Papadopoulos NG. Postnatal innate immune development: from birth to adulthood. *Front Immunol.* (2017) 8:957. doi: 10.3389/fimmu.2017.00957
26. Ashtiani MTH, Monajemzadeh M, Sina AH, Berenji F, Abdollahi M, Said MG, et al. Prevalence of haemoglobinopathies in 34,030 healthy adults in Tehran, Iran. *J Clin Pathol.* (2009) 62:924–5. doi: 10.1136/jcp.2009.064568
27. Sripichai O, Makarasara W, Munkongdee T, Kumkhaek C, Nuchprayoon I, Chuansumrit A, et al. A scoring system for the classification of beta-thalassemia/Hb E disease severity. *Am J Hematol.* (2008) 83:482–4. doi: 10.1002/ajh.21130
28. Chen C-H, Su L-H, Li H-C, Hsu M-H, Wu T-L, Chen C-L, et al. Evaluation of the impact of 13-valent pneumococcal conjugate vaccine immunization in children by surveillance of culture-confirmed pneumococcal disease: a prospective clinical microbiological study. *Vaccine*. (2019) 37:5147–52. doi: 10.1016/j.vaccine.2019.07.073
29. Wei S-H, Chiang C-S, Chen C-L, Chiu C-H. Pneumococcal disease and use of pneumococcal vaccines in Taiwan. *Clin Exp Vaccine Res.* (2015) 4:121–9. doi: 10.7774/cevr.2015.4.2.121
30. Gardenghi S, Marongiu MF, Ramos P, Guy E, Breda L, Chadburn A, et al. Ineffective erythropoiesis in beta-thalassemia is characterized by increased iron absorption mediated by down-regulation of hepcidin and up-regulation of ferroportin. *Blood*. (2007) 109:5027–35. doi: 10.1182/blood-2006-09-048868

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

REVIEW
published: 14 December 2020
doi: 10.3389/fped.2020.616622

COVID-19 Pneumonia in Children: From Etiology to Management

Giuseppe Fabio Parisi[1], *Cristiana Indolfi*[2], *Fabio Decimo*[2], *Salvatore Leonardi*[1] *and Michele Miraglia del Giudice*[2]*

[1] Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy, [2] Department of Woman, Child and Specialized Surgery, University of Campania "Luigi Vanvitelli", Naples, Italy

COVID-19 is less serious in children than in adults. However, respiratory management dominates the clinical picture of hospitalized COVID-19 even in children. In some case series, deterioration of the clinical picture wherein dyspnea, cyanosis, and the onset of acute respiratory distress syndrome (ARDS) emerged ∼8–10 days after the onset of SARS-CoV-2 infection, which could rapidly progress to multiple organ failure and death. This review aimed to evaluate the characteristics of COVID-19 pneumonia in pediatric populations, beginning from its etiology and pathological mechanisms and closing with its clinical management.

Keywords: COVID-19, children, pneumonia, SARS-CoV2, treatment

OPEN ACCESS

Edited by:
Hong-Ren Yu,
Chang Gung Memorial Hospital, Taiwan

Reviewed by:
Chung-Ming Chen,
Taipei Medical University, Taiwan
HaiLun Sun,
Chung Shan Medical University Hospital, Taiwan

***Correspondence:**
Michele Miraglia del Giudice
michele.miragliadelgiudice@unicampania.it

Specialty section:
This article was submitted to Pediatric Pulmonology, a section of the journal Frontiers in Pediatrics

Received: *12 October 2020*
Accepted: *27 November 2020*
Published: *14 December 2020*

Citation:
Parisi GF, Indolfi C, Decimo F, Leonardi S and Miraglia del Giudice M (2020) COVID-19 Pneumonia in Children: From Etiology to Management. Front. Pediatr. 8:616622. doi: 10.3389/fped.2020.616622

INTRODUCTION

At the close of December 2019, a new coronavirus originating from the Chinese city of Wuhan began to spread rapidly throughout the world (1). At the beginning of 2020, the International Committee on Taxonomy of Viruses denominated this new virus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (2). SARS-CoV-2 is the causative agent of the disease COVID-19, an abbreviation decided by the World Health Organization (WHO). In other words, SARS-CoV-2 is the etiologic agent, while COVID-19 is the disease (3).

The clinical spectrum of COVID-19 is wide, varying from completely asymptomatic forms to those characterized by severe respiratory distress requiring intensive care. SARS-CoV-2 causes acute viral infection of both the upper and lower respiratory tract, with an incubation period varying from 1 to 15 days (average: 3–7 days). The most common symptoms of COVID-19 include fever, cough, sore throat, headache, asthenia, diarrhea, and vomiting (4).

There is ample evidence in the literature that COVID-19 is less serious in children than in adults (5–10). Lu et al. found the main symptoms in 171 children with COVID-19 to be cough (48.5%), pharyngitis (46.2%), fever (41.5%), diarrhea (8.8%), and vomiting (6.4%); only 2.3% of cases experienced desaturation upon hospitalization, while 15.8% of cases were asymptomatic (9). Olfactory and gustatory anomalies characteristic of adult COVID-19 cases are rare in pediatric populations (11, 12).

The underlying cause of the lower incidence and pathogenicity of SARS-CoV-2 infection in children remains unclear at present. Although this lower incidence and morbidity was attributed to a reduced exposure and the presence of risk factors during the initial phase of the pandemic, it is now clear that biological factors that intervene in the pathogenesis of the infection and in the immune response may play a protective role in children against the more aggressive clinical manifestations seen in adults (13).

Respiratory management dominates the clinical picture of hospitalized COVID-19 patients. In some case series, deterioration of the clinical picture wherein dyspnea, cyanosis, and the onset of acute respiratory distress syndrome (ARDS) emerged approximately 8–10 days after the onset of SARS-CoV-2 infection, which could rapidly progress to multiple organ failure and death (14). In a pediatric series of children with COVID-19, 30.8% presented shortness of breath that required oxygen supplementation and 23.1% were transferred to intensive care unit (ICU) for organ dysfunction (15). In another case series of 41 children hospitalized for COVID-19, 11 of these presented lung lesions compatible with a picture of interstitial pneumonia (16). Furthermore, in one of the largest published pediatric series that studied 585 children with SARS-CoV2 infection, 8% required ICU admission and 4% needed mechanical ventilation (17).

Although the clinical picture in pediatric populations is more complex, the severity of infection can be clinically classified as follows: asymptomatic, mild, moderate, severe, or critical (18, 19) (**Table 1**). This classification makes the idea that even pediatric patients can experience severe manifestations of the pathology, which must be addressed as early as possible to limit disease progression.

This review aimed to evaluate the characteristics of COVID-19 pneumonia in pediatric populations, beginning from its etiology and pathological mechanisms and closing with its clinical management.

METHODS

This review used PubMed and Science Direct to locate articles with at least an English abstract using the following keywords: (1) COVID-19 in children; (2) coronavirus in children; (3) COVID-19 pneumonia; (4) SARS-CoV-2 in children; (5) SARS-CoV-2 pneumonia; and (6) COVID-19 imaging. The abstracts of articles were reviewed to determine whether the article was appropriate for the topic. We also reviewed the references contained within the selected articles, and read the full articles that were deemed relevant.

EPIDEMIOLOGY

The SARS-CoV-2 virus is transmitted via droplets and through direct or indirect contact with infected objects (1). The time during which the virus remains active on surfaces remains unclear, but was found to be ∼48–72 h on plastic and steel, and ∼4–8 h on copper and cardboard (20). Cohabitation with symptomatic or asymptomatic patients is the main source of contagion for pediatric populations (21), but given the frequency of paucisymptomatic forms in pediatric populations, children are likely to be a frequent vector of infection for adults and the elderly. The positivity in reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 in the stools of infants and children for several weeks, even after a negative nasopharyngeal swab (22), may indicate the stools could represent an additional means of transmission of the virus.

However, since growth of the virus in fecal culture—and therefore its viability on feces—has not been demonstrated, further research is needed to define a possible fecal–oral route of transmissibility of the virus. Similarly, maternal–fetal transmissibility of the virus has been explored since the beginning of the epidemic. A first report on nine women with COVID-19 in their third trimester of pregnancy confirmed the absence of SARS-CoV-2 in amniotic fluid, cord blood, and breast milk (23). More recently, the maternal–fetal transmission has been confirmed in three infants (transmission rate: 9%) born to a positive mother; one of these infants had onset of respiratory symptoms within 48 h of life (24). However, a larger retrospective cohort analysis involving 101 infants born to 100 SARS-CoV2 positive mothers did not show vertical transmission in any of these (25).

PATHOGENESIS OF LUNG DAMAGE

When SARS-CoV-2 enters the airways of a newly infected person, the viral S protein (spike protein) binds with high affinity to the angiotensin-converting enzyme 2 (ACE2) cellular transmembrane receptor found on the apical membranes of respiratory epithelial cells, mainly type II pneumocytes. Subsequently, the ACE2 receptor and SARS-CoV-2 are transported inside the cell and the S protein is cleaved by the protease TMPRSS2, inducing the release of the viral RNA within the cell and thereby allowing its replication (**Figure 1**). The ACE2 receptor is subsequently cleaved by a tumor necrosis factor alpha converting enzyme (TACE or ADAM17), a metalloprotease that allows the release of the ACE2 ectodomain (defined as soluble ACE2) into the extracellular space. Soluble ACE2 is enzymatically active and appears to be capable of binding with SARS-CoV-2. This led to speculation that administration of recombinant human ACE2 may reduce inflammation secondary to the action of SARS-CoV-2 (26).

The immune response induced by SARS-CoV-2 infection is characterized by two phases: an initial immunoprotective phase and an activation phase of the cytokine storm, which yields a more severe clinical manifestation. In the first phase, a robust adaptive response can control the virus and block inflammatory progression. If the immune system fails to control this phase, cell damage in organs with high concentrations of ACE2, especially pneumocytes, progresses by the release of cytokines and chemokines (IL-6, IL-10, and interferon) and the recruitment of inflammatory cells, which mediate lung damage and progression toward ARDS (27). Xu et al. found evidence of diffuse alveolar damage with desquamation of pneumocytes, hyaline membrane formation, and the presence of fibromyxoid cells with interstitial lymphocyte infiltration during histopathological examination of a patient who died of COVID-19 (28). In fact, clinically speaking, SARS-CoV-2 causes interstitial pneumonia.

One of the possible complications of this "exaggerated" inflammation is Pediatric Inflammatory Multisystem Syndrome (PIMS) or Multisystem Inflammatory Syndrome of Children (MIS-C) which occurs when inflammation becomes generalized.

TABLE 1 | Classification of COVID-19 in children.

Classification	Clinical features
Asymptomatic	Positivity of the RT-PCR buffer to SARS-CoV-2 or positive serology in the absence of any symptoms of illness.
Mild	Symptoms are mild and mainly affect the upper airways (nasal obstruction, sneezing) sometimes associated with fever, cough, and gastrointestinal symptoms.
Moderate	Symptoms are more critical fever and cough (mainly dry) are almost always present and are associated with breathing difficulties. It is characterized radiologically by lung anomalies compatible with interstitial pneumonia.
Severe	It is characterized by the presence of hypoxemia (SpO_2 < 92%) with signs of respiratory distress (tachypnea, groaning, wing flaps, sags), cyanosis, neurological signs and symptoms, refusal to eat, and signs of dehydration.
Critical	Disease progression with onset of respiratory failure requiring mechanical ventilation, signs of shock or multi-organ failure.

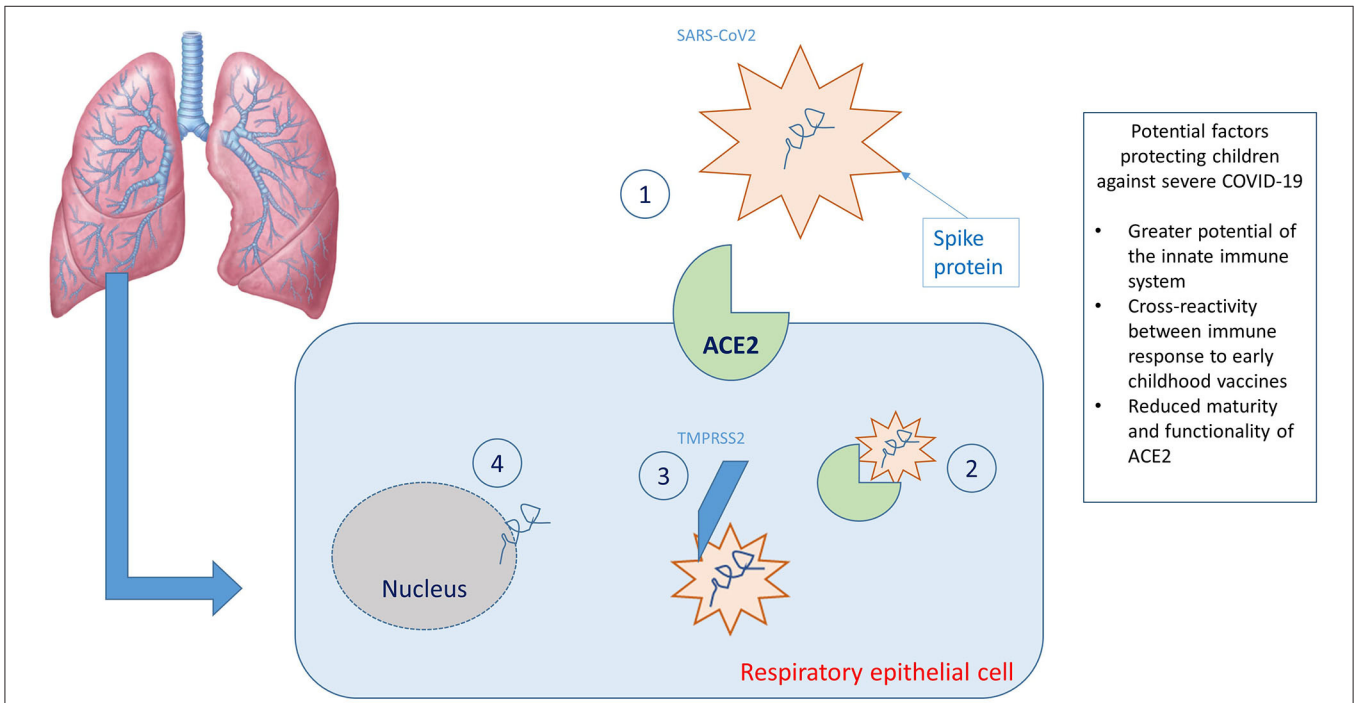

FIGURE 1 | Graphic representation of the virus-host interaction and reasons why children are less affected. (1) Binding between SARS-CoV2 spike protein and ACE2 receptors; (2) transport of the ACE2 receptor/SARS-CoV 2 complex within the cell; (3) cleavage of the spike protein by the protease TMPRSS2; (4) release of viral RNA within the cell.

This would appear to be a post-immunological reaction caused by non-neutralizing IgG antibody and worsened by a cytokine storm that causes generalized inflammation that resembles an atypical Kawasaki's disease or a toxic shock syndrome (29).

Why Are Children Less Affected?

Many explanations have been proposed for the fact that children appear to be less frequently affected and have milder manifestations of COVID-19; however, they remain assumptions given the lack of scientific evidence on the subject.

The immune response of children differs from that of adults, which progressively deteriorates with age such that preschoolers have a repertoire of immune cells 5–10 times larger than that of a 50-year-old, and 20 times larger than that of an 80-year-old. It remains to be seen to what degree this may play a role in mitigating the spread of the virus and in the cytokine signaling cascade triggered by SARS-CoV-2 as they relate to severe outcomes in adulthood (30).

A cross-reactivity between immune response to early childhood vaccines—especially MMR—and response to SARS-CoV-2 has also been proposed. However, no clear evidence has emerged to date to support this proposal, and paucisymptomatic cases are reported even in unvaccinated children. A large pediatric clinical series on 2,143 children reported a 5.9% rate of serious and critical cases—and only one death (31). Shekerdemian et al. reported a mortality rate of 4.2% in a cohort of 48 COVID-19-positive children admitted to the ICU, most of whom had previous comorbidities (disabling genetic diseases in 40% of cases) (32).

A second explanation for the tendency of children be less affected by SARS-CoV-2 relates to the ACE2 receptor which, as previously mentioned, binds the SARS-CoV-2 virus.

In fact, the reduced maturity and functionality of ACE2 and its lower expression in the nasal epithelium in pediatric populations relative to adults could partly explain children's reduced susceptibility to COVID-19 (33, 34). However, studies do not unilaterally support this hypothesis. In fact, some evidence suggests that ACE2 expression in children is neither up- nor downregulated (35, 36). On the other hand, another study found that ACE2 is downregulated once the virus penetrates the cell and replicates, resulting in fewer receptors upon which the virus can act (37). In light of these data, the role of the expression levels of ACE2 in the pathogenesis of COVID-19-induced lung damage remains to be fully elucidated.

CHEST IMAGING

According to the American College of Radiology, pediatric radiologic imaging is recommended for patients with a confirmed diagnosis of COVID-19 with mild symptoms and pre-existing comorbidities, and for children with moderate to severe symptoms. Chest X-ray is the first choice exam; however, its lower sensitivity and specificity mean that pulmonary involvement cannot be excluded in patients with a laboratory-confirmed diagnosis of COVID-19. Unlike in adults, computed tomography (CT), is indicated in children in cases of suspicion of pulmonary embolism and clinical worsening (38).

Chest X-Ray

Pulmonary abnormalities on chest X-ray were found in 46–90% of cases (39, 40). The most common radiologic trends were peribronchial thickening, ground-glass opacities, consolidation, and pleural effusion (39). Lung findings were unilateral in 55% and bilateral in 45% of affected children, without any significant difference between the left and right lung, but with greater involvement of the lower lobes (40). Although these radiological abnormalities typically resolve during recovery from the disease, they have been reported to persist in ∼16% of cases (39).

Chest Computed Tomography (CT)

The radiological anomalies evident on CT are certainly much more characterizing the disease, although these anomalies are less frequent and less specific than those described in adults (41). The most common findings are multifocal and peripherally located ground-glass appearance starting from the lower lobes, accompanied by thickening in the interlobular septa, prominent vascular structures, halo signs, and inverted halo signs. In severe cases, a striking paving appearance and fragmented consolidation are observed (40, 41).

Liu et al. described the radiological characteristics examined by high-resolution (HR)-CT of five children with a confirmed diagnosis of COVID-19, three of whom were asymptomatic. These three patients had unilateral ground glass opacities, whereas only one child had bilaterally distributed opacity, and another had a negative report (42). Some radiological differences between children and adults were highlighted (43). Although the ground glass finding is characteristic and common in both adulthood and childhood, 44% of adult patients also had thickening of the interlobular septum, bronchial texture, a striking paving pattern, and—less frequently—halo signs, pleural or pericardial effusion, and lymphadenopathy (44).

In a group of 98 patients of varying ages (4–88 years) with COVID-19, the majority of lung lesions upon HR-CT were located in the right lower lobe of the lung, possibly due to the thinner and shorter structure of the lower lobe bronchus, especially in the peripheral area of the lung. However, children and adolescents had fewer lung lesions, predominantly unilateral involvement, and smaller clusters than adults, with no signs of air bronchogram (45). Zheng et al. also reported a higher incidence of respiratory impairment in children <3 years of age, with bilateral lung involvement in >70% of children in this age group (46). A report of eight patients aged <15 years admitted to intensive care found abnormalities on CT scans in all cases (six children with bilateral involvement, two with unilateral involvement). Moreover, two of the eight patients that originally had a worse prognosis also had higher expression of IL-6 and IL-10, further corroborating a relationship between the severity of the pulmonary picture and activation of the cytokine cascade (47).

Lung Ultrasound

Several studies report the usefulness of pulmonary ultrasound for the diagnosis and follow-up of COVID-19 pneumonia, given that it is a simple and repeatable investigation that does not expose the child to radiation or sedation. Musolino et al. reported the main ultrasound findings of 10 children with COVID-19 as follows: B lines (70%), pleural irregularities (60%), white lung (10%), and subpleural thickening (10%) (48, 49). According to Allinovi et al., lung ultrasound may support diagnosis and monitoring of COVID-19 pneumonia, as it reveals a typical pattern of diffuse interstitial lung syndrome and correlates with chest CT findings (50).

MANAGEMENT AND TREATMENT OF COVID-19 PNEUMONIA

Given the paucisymptomatic course characteristic of children diagnosed with COVID-19, the majority of cases only require supportive home therapy. Evidently, cases must be isolated, and they require an adequate intake of fluids and calories (51, 52). For the management of fever, paracetamol is recommended. Some authors have proposed a correlation between the use of ibuprofen and a more aggressive course of SARS-CoV-2 infection (53); however, these data were not confirmed. For patients already being treated with topical steroids (e.g., for allergic rhinitis or bronchial asthma), continuation of basic therapy is indicated. In case of need for inhalation treatment with steroids and bronchodilators, the use of pressurized metered-dose inhalers with spacer is recommended over nebulizers, which could increase infectivity due to their aerosolization of particles (54).

Hospitalization is indicated when there is a need to ensure supportive therapy (e.g., pharmacological or respiratory support) or in severe forms of pathology (13, 19, 55). Upon entering the ward, performing laboratory blood testing may prove useful, even though it is often non-specific. In most children it is

TABLE 2 | Summary of most common antivirals for COVID-19 in children.

Antiviral	Route of administration	Pediatric dose	Duration of treatment
Interferon-α*	Inhalation	200,000–400,000 IU/kg in 2 mL of sterile water, twice daily	5–7 days
Lopinavir/Ritonavir	Oral	12 mg/3 mg/kg if weight 7–15 kg, 10 mg/2.5 mg/kg if weight 15–40 kg, 400 mg/100 mg (adult dose) if weight > 40 twice daily	1–2 weeks
Ribavirin	Intravenous	10 mg/kg/dose, 2 or 3 times daily	Max 5 days
Remdesevir	Intravenous	5 mg/kg loading dose, then 2.5 mg/kg once daily	10 days
Hydroxychloroquine sulfate	Intravenous	3–5 mg/kg/day (max dose 400 mg), twice daily	5 days

Most commonly used.

possible to find: (i) a normal or reduced number of white blood cells, accompanied by lymphocytopenia; (ii) normal or slightly increased C-reactive protein and procalcitonin values (in case of excessive upregulation, a bacterial superinfection should be considered); (iii) slightly increased transaminases and lactic dehydrogenases (13, 19, 55).

Patients with chronic diseases should be subjected to greater attention because the presence of comorbidities seems to be associated with a greater risk of fatal evolution (56). In this sense, these patients should be monitored more frequently and subjected to earlier treatments.

General Support

Hospitalized children must have their vitals monitored and have adequate intake of fluids and calories aimed at maintaining a hydro-electrolytic homeostasis. Additionally, bed rest and maintenance of cleared upper airways are recommended (13, 19, 55).

Oxygen Therapy

In case of hypoxia (SpO_2 < 95%) without signs of respiratory distress, the administration of oxygen via nasal cannulae or mask is sufficient, while constant monitoring of vital parameters and attending to changes in the acid-base balance may be indicative of clinical worsening (13, 19, 55).

Ventilatory Support

In case of respiratory distress associated with hypoxemia, simple oxygen administration is insufficient. In these cases, high-flow nasal oxygen (HFNO) or non-invasive ventilation, such as continuous positive airway pressure (CPAP), should be used (13, 19, 55). The utility of HFNO for COVID-19 treatment is the subject of debate given that the incontrovertible benefits afforded by this treatment are countered by the risk of viral particle aerosolisation within the patient's environment, thereby placing the safety of healthcare workers at risk (57). The World Health Organization (WHO) recommends that HFNO be used in single or negative pressure rooms "whenever possible." This means that negative pressure room, while advantageous, are not essential (58). What is certainly essential, however, is the use of personal protective equipment (PPE) when entering patients' rooms (57).

A valid alternative to HFNO is CPAP—preferably helmet CPAP—with positive end-expiration pressure (PEEP) ranging from 5 to 10 cmH_20 (59). In any case, the critically ill child should be transferred to a pediatric intensive care unit and, in the event of non-response to non-invasive ventilation or of onset of pediatric acute respiratory distress syndrome (PARDS), initiation of invasive mechanical ventilation should be considered and, ultimately, extracorporeal membrane oxygenation (ECMO) (19).

Pharmacological Treatment

There is little reliable evidence for the utility of drugs in treating COVID-19 pneumonia in pediatric populations, and any available data to date are based on observations in adult populations. For this reason, pharmacological therapy discouraged in milder COVID-19 forms, while recommended for more severe forms; such decisions should invariably be made on a case-by-case basis (13, 19, 51, 55, 60).

No specific anti-SARS-CoV-2 drug has yet been proven effective. Antiviral drug therapy seems to be effective if initiated before clinical deterioration. The drug most commonly used is interferon-alpha by nebulization, as it has shown effectiveness at reducing viral replication with consequent improvement of symptoms and reduction of the duration of the disease (21). Other possible pharmacological interventions include:

- Lopinavir/Ritonavir: A drug used in the treatment of HIV which appears to be effective in reducing viral replication as long as it is administered in the very early stages of the disease. Common side-effects include diarrhea and nausea, and it is contraindicated in cases of hepatic impairment (61).
- Ribavirin: A drug used in combination with interferon-alpha or Lopnavir/Ritonavir. Hemolytic anemia is a possible side-effect (19, 62).
- Remdesevir: A new-generation antiviral that has a potent antireplicative action against SARS-CoV-2 (63, 64).
- Hydroxychloroquine: A drug that, despite the initial enthusiasm surrounding its use for treatment of COVID-19, has not shown real efficacy according to the most recent scientific evidence (65). **Table 2** summarizes the main antivirals, their formulations, and their respective dosages in pediatric patients.

Other drugs worth mentioning include:

- Antibiotics: Their use is discouraged unless there are signs of bacterial co-infection. The usefulness of macrolides, especially azithromycin, for their anti-inflammatory properties is also questionable (19, 52, 60, 66).
- Corticosteroids: Their routine use is discouraged; however, they should be considered in cases of PARDS, secondary

haemophagocytic lymphoistiocytosis, septic shock, or concomitant asthma. In these cases, the administration of methylpredisolone at a dose of 1–2 mg/kg/day for a maximum of 4–5 days is recommended (19, 52, 60).

- Gamma globulins: Their effectiveness is not clear. They can be attempted in particularly severe forms of COVID-19 and in those with symptoms similar to Kawasaki disease at the dose of 2 g/kg/day for one day, 1 g/kg/day for two days or 400 mg/kg/day for five days (67, 68).
- Tocilizumab: This human anti-IL-6 monoclonal antibody appeared to be effective in the treatment in adults with extensive and bilateral lung involvement (60). However, recently its effectiveness has been greatly diminished to the extent that it appears not effective for preventing intubation or death in moderately ill hospitalized patients with COVID-19 (69). For this reason, it should be used cautiously in children: 12 mg/kg in children weighing <30 kg, 8 mg/kg (max: 800 mg) in children >30 kg, to repeat once after 12 h if no improvement (60, 70).

CONCLUSION

This review summarizes the characteristics of COVID-19 in pediatric populations, with a focus on pulmonary involvement. Although clinical picture of COVID-19 in children is much less severe than in adults, progression of the disease remains possible and must, therefore, be intercepted with appropriate therapy. It should also be emphasized that children, although paucisymptomatic, are important vectors of the disease.

AUTHOR CONTRIBUTIONS

MM developed the original idea and made the final revision. GP wrote the manuscript. CI and FD revised the manuscript and contributed to the English revision and compilation of references. SL made the final analysis and critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. China novel coronavirus investigating and research team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med.* (2020) 382:727–33. doi: 10.1056/NEJMoa2001017
2. *International Committee on Taxonomy Viruses, Naming the 2019 Coronavirus.* (2020). Available online at: https://talk.ictvonline.org/ (accessed October 11, 2020).
3. *World Health Organization, Naming the Coronavirus Disease (COVID-19) and the Virus That Causes It*. (2020). Available online at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it (accessed October 11, 2020).
4. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032
5. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr.* (2020) 109:1088–95. doi: 10.1111/apa.15270
6. Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. *Pediatr Infect Dis J.* (2020) 39:355–68. doi: 10.1097/INF.0000000000002660
7. Ong JS, Tosoni A, Kim YJ, Kissoon N, Murthy S. Coronavirus disease 2019 in critically ill children: a narrative review of the literature. *Pediatr Crit Care Med.* (2020) 21:662–6. doi: 10.1097/PCC.0000000000002376
8. Liguoro I, Pilotto C, Bonanni M, Ferrari ME, Pusiol A, Nocerino A, et al. SARS-COV-2 infection in children and newborns: a systematic review. *Eur J Pediatr.* (2020) 179:1029–46. doi: 10.1007/s00431-020-03684-7
9. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 infection in children. *New Engl J Med.* (2020) 382:1663–5. doi: 10.1056/NEJMc2005073
10. Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. *JAMA Pediatr.* (2020) 174:882–9. doi: 10.1001/jamapediatrics.2020.1467
11. Parisi GF, Brindisi G, Indolfi C, Diaferio L, Marchese G, Ghiglioni DG et al. Upper airway involvement in pediatric COVID-19. *Pediatr Allergy Immunol.* (2020) 31(Suppl 26):85–8. doi: 10.1111/pai.13356
12. Diaferio L, Parisi GF, Brindisi G, Indolfi C, Marchese G, Ghiglioni DG, et al. Cross-sectional survey on impact of paediatric COVID-19 among Italian paediatricians: report from the SIAIP rhino-sinusitis and conjunctivitis committee. *Ital J Pediatr.* (2020) 46:146. doi: 10.1186/s13052-020-00906-4
13. Zardini H, Soltaninejad H, Ferdosian F, Hamidieh AA, Memarpoor-Yazdi M. Coronavirus Disease 2019 (COVID-19) in children: prevalence, diagnosis, clinical symptoms, and treatment. *Int J Gen Med.* (2020) 13:477–82. doi: 10.2147/IJGM.S262098
14. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
15. Cai X, Jiang H, Zhang S, Xia S, Du W, Ma Y, et al. Clinical manifestations and pathogen characteristics in children admitted for suspected COVID-19. *Front Med.* (2020) 1–10. doi: 10.1007/s11684-020-0820-7.[Epub ahead of print].
16. Zhang Y, Xie RM, He YL, Xing LH, Dong L, Zhang JZ, et al. Clinical and imaging features of pediatric COVID-19. *Ital J Pediatr.* (2020) 46:153. doi: 10.1186/s13052-020-00917-1
17. Götzinger F, Santiago-García B, Noguera-Julián A, Lanaspa M, Lancella L, Calò et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health.* (2020) 4:653–61. doi: 10.1016/S2352-4642(20)30177-2
18. Chen ZM, Fu JF, Shu Q, Chen YH, Hua CZ, Li FB, et al. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. *World J Pediatr.* (2020) 16:240–6. doi: 10.1007/s12519-020-00345-5
19. Miao H, Li H, Yao Y, Wu M, Lu C, Wang J, et al. Update on recommendations for the diagnosis and treatment of SARS-CoV-2 infection in children. *Eur J Clin Microbiol Infect Dis.* (2020) 39:2211–23. doi: 10.1007/s10096-020-03973-x
20. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med.* (2020) 382:1564–7. doi: 10.1056/NEJMc2004973
21. Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. *World J Pediatr.* (2020) 16:223–31. doi: 10.1007/s12519-020-00343-7
22. Xu Y, Li X, Zhu B, Liang H, Fang C, Gong Y, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat Med.* (2020) 26:502–5. doi: 10.1038/s41591-020-0817-4
23. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in

nine pregnant women: a retrospective review of medical records. *Lancet*. (2020) 395:809–15. doi: 10.1016/S0140-6736(20)30360-3
24. Zeng L, Xia S, Yuan W, Yan K, Xiao F, Shao J, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. *JAMA Pediatr.* (2020) 174:722–5. doi: 10.1001/jamapediatrics.2020.0878
25. Dumitriu D, Emeruwa UN, Hanft E, Liao GV, Ludwig E, Walzer L, et al. Outcomes of neonates born to mothers with severe acute respiratory syndrome coronavirus 2 infection at a large medical center in New York City. *JAMA Pediatr*. (2020) e204298. doi: 10.1001/jamapediatrics.2020.4298.[Epub ahead of print].
26. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. *Circ Res.* (2020) 126:1456–74. doi: 10.1161/CIRCRESAHA.120.317015
27. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ.* (2020) 27:1451–4. doi: 10.1038/s41418-020-0530-3
28. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med.* (2020) 8:420–2. doi: 10.1016/S2213-2600(20)30076-XQ18
29. Lawrensia S, Henrina J, Wijaya E, Suciadi LP, Saboe A, Cool CJ. Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2: a new challenge amid the pandemic. *SN Compr Clin Med.* (2020) 2:2077–85. doi: 10.1007/s42399-020-00602-8
30. Volpi S, Naviglio S, Tommasini A. Covid-19 e risposta immune. *Med Bambino.* (2020) 39:223–31.
31. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics*. (2020) 145:e20200702. doi: 10.1542/peds.2020-0702
32. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. International COVID-19 PICU Collaborative. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. *JAMA Pediatr.* (2020) 174:1–6. doi: 10.1001/jamapediatrics.2020.1948
33. Cristiani L, Mancino E, Matera L, Nenna R, Pierangeli A, Scagnolari C, et al. Will children reveal their secret? The coronavirus dilemma. *Eur Respir J.* (2020) 55:2000749. doi: 10.1183/13993003.00749-2020
34. Saheb Sharif-Askari N, Saheb Sharif-Askari F, Alabed M, Temsah MH, Al Heialy S, Hamid Q, et al. Airways expression of SARS-CoV-2 receptor, ACE2, and TMPRSS2 is lower in children than adults and increases with smoking and COPD. *Mol Ther Methods Clin Dev.* (2020) 18:1–6. doi: 10.1016/j.omtm.2020.05.013
35. Xie X, Chen J, Wang X, Zhang F, Liu Y. Age- and gender-related difference of ACE2 expression in rat lung. *Life Sci.* (2006) 78:2166–71. doi: 10.1016/j.lfs.2006.09.028
36. Ortiz ME, Thurman A, Pezzulo AA, Leidinger MR, Klesney-Tait JA, Karp PH, et al. Heterogeneous expression of the SARS-Coronavirus-2 receptor ACE2 in the human respiratory tract. *EBioMedicine.* (2020) 60:102976. doi: 10.1016/j.ebiom.2020.102976
37. Skarstein Kolberg E. ACE2, COVID19 and serum ACE as a possible biomarker to predict severity of disease. *J Clin Virol.* (2020) 126:104350. doi: 10.1016/j.jcv.2020.104350
38. Foust AM, McAdam AJ, Chu WC, Garcia-Pena P, Phillips GS, Plut D. Practical guide for pediatric pulmonologists on imaging management of pediatric patients with COVID-19. *Pediatr. Pulmonol.* (2020) 55:2213–24. doi: 10.1002/ppul.24870
39. Oterino Serrano C, Alonso E, Andrés M, Buitrago NM, Pérez Vigara A, Parrón Pajares M, et al. Pediatric chest x-ray in covid-19 infection. *Eur J Radiol.* (2020) 131:109236. doi: 10.1016/j.ejrad.2020.109236
40. Palabiyik F, Kokurcan SO, Hatipoglu N, Cebeci SO, Inci E. Imaging of COVID-19 pneumonia in children. *Br J Radiol.* (2020) 93:20200647. doi: 10.1259/bjr.20200647
41. Duan YN, Zhu YQ, Tang LL, Qin J. CT features of novel coronavirus pneumonia (COVID-19) in children. *Eur Radiol.* (2020) 30:4427–33. doi: 10.1007/s00330-020-06860-3
42. Liu M, Song Z, Xiao K. High-resolution computed tomography manifestations of 5 pediatric patients with 2019 Novel Coronavirus. *J Comp Assist Tomogr.* (2020) 44:311–3. doi: 10.1097/RCT.0000000000001023
43. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: different points from adults. *Pediatr Pulmonol.* (2020) 55:1169–74. doi: 10.1002/ppul.24718
44. Pan Y, Guan H, Zhou S, Wang Y, Li Q, Zhu T, et al. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. *Eur Radiol.* (2020) 30:3306–9. doi: 10.1007/s00330-020-06731-x
45. Chen Z, Fan H, Cai J, Li Y, Wu B, Hou Y, et al. High-resolution computed tomography manifestations of COVID-19 infections in patients of different ages. *Eur J Radiol.* (2020) 126:108972. doi: 10.1016/j.ejrad.2020.108972
46. Zheng F, Liao C, Fan QH, Chen HB, Zhao XG, Xie ZG, et al. Clinical characteristics of children with coronavirus disease 2019 in Hubei, China. *Curr Med Sci.* (2020) 40:275–80. doi: 10.1007/s11596-020-2172-6
47. Sun D, Li H, Lu XX, Xiao H, Ren J, Zhang FR, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World J Pediatr.* (2020) 16:251–9. doi: 10.1007/s12519-020-00354-4
48. Denina M, Scolfaro C, Silvestro E, Pruccoli G, Mignone F, Zoppo M, et al. Lung ultrasound in children with COVID-19. *Pediatrics.* (2020) 146:e20201157. doi: 10.1542/peds.2020-1157
49. Musolino AM, Supino MC, Buonsenso D, Ferro V, Valentini P, Magistrelli A, et al. Lung ultrasound in children with COVID-19: preliminary findings. *Ultrasound Med Biol.* (2020) 46:2094–8. doi: 10.1016/j.ultrasmedbio.2020.04.026
50. Allinovi M, Parise A, Giacalone M, Amerio A, Delsante M, Odone A, et al. Lung ultrasound may support diagnosis and monitoring of COVID-19 pneumonia. *Ultrasound Med Biol.* (2020) 46:2908–17. doi: 10.1016/j.ultrasmedbio.2020.07.018
51. College of Paediatrics and Child Health. *COVID-19: Guidance for Paediatric Services*. (2020). Available online at: https://www.rcpch.ac.uk/resources/covid-19-guidance-paediatric-services (accessed October 1, 2020).
52. Shen KL, Yang YH, Jiang RM, Wang TY, Zhao DC, Jiang Y, et al. Updated diagnosis, treatment and prevention of COVID-19 in children: experts' consensus statement (condensed version of the second edition). *World J Pediatr.* (2020) 16:232–9. doi: 10.1007/s12519-020-00362-4
53. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. (2020) 8:e21. doi: 10.1016/S2213-2600(20)30116-8
54. Cardinale F, Ciprandi G, Barberi S, Bernardini R, Caffarelli C, Calvani M, et al. Consensus statement of the Italian society of pediatric allergy and immunology for the pragmatic management of children and adolescents with allergic or immunological diseases during the COVID-19 pandemic. *Ital J Pediatr.* (2020) 46:84. doi: 10.1186/s13052-020-00843-2
55. Yamamoto L, Santos EHD, Pinto LS, Rocha MC, Kanunfre KA, Vallada MG, et al. SARS-CoV-2 infections with emphasis on pediatric patients: a narrative review. *Rev Inst Med Trop São Paulo.* (2020) 62:e65. doi: 10.1590/s1678-9946202062065
56. Oualha M, Bendavid M, Berteloot L, Corsia A, Lesage F, Vedrenne M, et al. Severe and fatal forms of COVID-19 in children. *Arch Pediatr.* (2020) 27:235–8. doi: 10.1016/j.arcped.2020.05.010
57. Lyons C, Callaghan M. The use of high-flow nasal oxygen in COVID-19. *Anaesthesia.* (2020) 75:843–7. doi: 10.1111/anae.15073
58. World Health Organization. *Clinical Management of Severe Acute Respiratory Infection (SARI) When COVID-19 Disease is Suspected. Interim Guidance*. (2020). Available online at: www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-nfection-when-novel-coronavirus-(ncov)-infection-is-suspected (accessed October 1, 2020).
59. Aliberti S, Radovanovic D, Billi F, Sotgiu G, Costanzo M, Pilocane T, et al. Helmet CPAP treatment in patients with COVID-19 pneumonia: a multicenter, cohort study. *Eur Respir J.* (2020) 56:2001935. doi: 10.1183/13993003.01935-2020
60. Naja M, Wedderburn L, Ciurtin C. COVID-19 infection in children and adolescents. *Br J Hosp Med.* (2020) 81:1–10. doi: 10.12968/hmed.2020.0321
61. Chan JF, Yao Y, Yeung ML, Deng W, Bao L, Jia L, et al. Treatment with Lopinavir/Ritonavir or Interferon-β1b improves outcome of MERS-CoV

infection in a nonhuman primate model of common marmoset. *J Infect Dis.* (2015) 212:1904–13. doi: 10.1093/infdis/jiv392
62. Li H, Wang YM, Xu JY, Cao B. Potential antiviral therapeutics for 2019 Novel Coronavirus. *Zhonghua Jie He He Hu Xi Za Zhi*. (2020) 43:E002. doi: 10.3760/cma.j.issn.1001-0939.2020.0002
63. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. *Cell Res.* (2020) 30:269–71. doi: 10.1038/s41422-020-0282-0
64. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). *Biosci Trends.* (2020) 14:69–71. doi: 10.5582/bst.2020.01020
65. Uddin M, Mustafa F, Rizvi TA, Loney T, Suwaidi HA, Al-Marzouqi AHH, et al. SARS-CoV-2/COVID-19: viral genomics, epidemiology, vaccines, and therapeutic interventions. *Viruses.* (2020) 12:526. doi: 10.3390/v12050526
66. Poddighe D, Aljofan M. Clinical evidences on the antiviral properties of macrolide antibiotics in the COVID-19 era and beyond. *Antivir Chem Chemother.* (2020) 28:2040206620961712. doi: 10.1177/2040206620961712
67. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, et al. COVID-19 and Kawasaki Disease: novel virus and novel case. *Hosp Pediatr.* (2020) 10:537–40. doi: 10.1542/hpeds.2020-0123
68. Akca UK, Kesici S, Ozsurekci Y, Aykan HH, Batu ED, Atalay E, et al. Kawasaki-like disease in children with COVID-19. *Rheumatol Int.* (2020) 40:2105–15. doi: 10.1007/s00296-020-04701-6
69. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of Tocilizumab in patients hospitalized with Covid-19. *N Engl J Med.* (2020) doi: 10.1056/NEJMoa2028836.[Epub ahead of print].
70. Banday AZ, Vignesh P. Use of tocilizumab in multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2. *J Pediatr.* (2020). doi: 10.1016/j.jpeds.2020.09.054. [Epub ahead of print].

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

ORIGINAL RESEARCH
published: 18 December 2020
doi: 10.3389/fped.2020.622065

Post-infectious Bronchiolitis Obliterans: HRCT, DECT, Pulmonary Scintigraphy Images, and Clinical Follow-up in Eight Children

I-Chen Chen[1,2,3], *Jui-Sheng Hsu*[4,5], *Yu-Wen Chen*[6,7], *Yi-Ching Liu*[1], *Yen-Hsien Wu*[1], *Jong-Hau Hsu*[1,2], *Yi-Fang Cheng*[1] *and Zen-Kong Dai*[1,2,3]*

[1] *Department of Pediatrics, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan,* [2] *Department of Pediatrics, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan,* [3] *College of Medicine, Graduate Institute of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan,* [4] *Department of Radiology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan,* [5] *Department of Radiology, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan,* [6] *Department of Nuclear Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan,* [7] *Department of Nuclear Medicine, School of Post-Baccalaureate Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*

OPEN ACCESS

Edited by:
Hong-Ren Yu,
Chang Gung Memorial Hospital, Taiwan

Reviewed by:
Chung-Ming Chen,
Taipei Medical University, Taiwan
Daniel Ng,
Hong Kong Sanatorium and Hospital, Hong Kong

****Correspondence:***
Zen-Kong Dai
zenkong@kmu.edu.tw

Specialty section:
This article was submitted to Pediatric Pulmonology, a section of the journal Frontiers in Pediatrics

Received: *27 October 2020*
Accepted: *30 November 2020*
Published: *18 December 2020*

Citation:
Chen I-C, Hsu J-S, Chen Y-W, Liu Y-C, Wu Y-H, Hsu J-H, Cheng Y-F and Dai Z-K (2020) Post-infectious Bronchiolitis Obliterans: HRCT, DECT, Pulmonary Scintigraphy Images, and Clinical Follow-up in Eight Children. Front. Pediatr. 8:622065. doi: 10.3389/fped.2020.622065

Background: Bronchiolitis obliterans (BO), first mentioned in 1901, is a severe and rare chronic lung disease in children. BO has various etiologies and the most common in children is post-infectious BO (PIBO). High resolution CT (HRCT) is an often-used image tool for the diagnosis of BO, and pulmonary scintigraphy is an alternative tool that can functionally evaluate BO. Recently, dual-energy computed tomography (DECT) have also been applied to BO for its accuracy and safety. Here we described the characteristics of HRCT, pulmonary scintigraphy, DECT, and the clinical profiles of patients with PIBO.

Methods: This is a retrospective and descriptive study. Data were collected from patients diagnosed with PIBO from 2014 to 2019 in the Pediatric Cardiopulmonary Outpatient Clinics of Kaohsiung Medical University Hospital. The diagnosis was based on clinical, chest X-ray, and HRCT findings. Clinical profile, radiological characteristics, and images of pulmonary scintigraphy were documented.

Results: Eight children (4 boys and 4 girls) were diagnosed with PIBO at a mean age of 25.8 months (range 15 to 41 months). Two of our patients developed pulmonary hypertension. The most common HRCT finding is mosaic pattern, where match ventilation/perfusion (V/Q) defects is a general feature in pulmonary scintigraphy. DECT pulmonary blood vasculature images revealed various degrees of decreased perfusion and is compatible with the decreased perfusion on pulmonary scintigraphy.

Conclusion: The therapeutic strategy of PIBO is still lacking of standardization. HRCT and V/Q scans are important image tools in diagnosis and follow-up of BO. DECT may be used in BO patients as it has no additional radiation exposure and add value on functional information of HRCT.

Keywords: perfusion, ventilation, dual-energy CT (DECT), pulmonary scintigraphy, children, high resolution computer tomography, post-infectious bronchiolitis obliterans

INTRODUCTION

Bronchiolitis obliterans (BO) is an uncommon but severe lung disease (1). It is currently diagnosed according to a history of lower respiratory tract insults and persistent symptoms that do not respond well to the administration of systemic corticoids and bronchodilators for 2 weeks (2). Due to the chronic irreversible inflammatory process and limited treatment options for BO, it is important to make an early diagnosis and start treatment as soon as possible.

BO describes obliterative changes in the small airways that commonly occur in a variety of lung diseases, including lower respiratory infection, organ transplantation, connective tissue disease, toxic fume inhalation, chronic hypersensitivity pneumonia, aspiration, drugs and Stevens-Johnson syndrome (SJS) (2). However, post-infectious BO (PIBO) is the most common type in children (2). Histologically, two types of BO have been proposed: constrictive-type BO and proliferative-type BO (3). BO that develops during childhood is mainly the constrictive type, and it is characterized by peribronchiolar fibrosis with different degrees of lumen-narrowing (1). The severity of BO mainly depends on the degree of damage to normal tissue in the respiratory tract. However, due to the heterogeneous or patchy involvement of the disease, a lung biopsy has been reported to be non-diagnostic in up to one-third of patients (4). Moreover, due to concerns over the risk of invasive procedures in children, a lung biopsy is rarely performed in the diagnosis of BO (4). Currently, a confirmatory diagnosis is usually made according to typical clinical presentations, fixed airway obstruction on pulmonary function tests, and radiological findings (5). The most commonly used imaging methods to evaluate BO are conventional chest radiograph (CXR), high-resolution computed tomography (HRCT), and lung ventilation/perfusion (V/Q) scan (4, 6–8).

As the findings of BO on CXR are non-specific, HRCT is the most commonly used imaging tool for BO due to its high sensitivity and specificity, and because it can assess regional heterogeneity as well as the global severity of the lung. The typical findings of BO on HRCT include bronchial wall thickening, centrilobular opacities, central bronchiectasis, atelectasis, mucous plugging, and mosaic lung attenuation due to air trapping (6, 7, 9).

V/Q scans show a distinctive pattern of matched ventilation-perfusion defects and segmental, sub-segmental or lobar distribution in PIBO (10, 11). It provides an objective assessment of the distribution pattern of the lesions, and since they highlight more damaged broncho-pulmonary areas, it may also be considered to be an accurate diagnostic tool for BO (7). Furthermore, the degree of ventilation and perfusion abnormalities evaluated by V/Q scans have been associated with disease severity and may be used to predict the outcomes of patients with PIBO (12).

Dual-energy computed tomography (DECT) was first conceptualized in the 1970's (13–15). It enables the simultaneous evaluation of gray-scale vasculature with color-coded pulmonary blood vasculature (PBV) images, which represents parenchymal perfusion. DECT has been used to evaluate ventilation function after xenon inhalation, and this technique has been shown to provide more regional function information without additional radiation exposure in BO patients (4, 16). Therefore, the aim of this study was to investigate the diagnostic utility of HRCT, pulmonary scintigraphy, and DECT PBV images in our patients with PIBO. Moreover, we also discussed the initial clinical presentations and major treatment options for PIBO.

MATERIALS AND METHODS

This retrospective and descriptive study included patients with a diagnosis of PIBO who were followed up at the Pediatric Cardiopulmonary Outpatient Clinics of Kaohsiung Medical University Hospital and was approved by the Ethics in Research Committee of the institution where was conducted (KMUHIRB-SV(II)-20200063). The medical records of the enrolled children were reviewed retrospectively by Kaohsiung Medical University Hospital staff (KMUH) from January 2014 to December 2019. The diagnosis of PIBO was based on a typical clinical history followed by findings on CXR and thoracic HRCT that concurred with the diagnosis as follows: [1] history of acute and severe bronchiolitis/pneumonia; [2] recurrent cough, wheezing, respiratory distress after an acute event; [3] respiratory symptoms which were severe in disproportion to CXR findings; [4] mosaic pattern, air trapping or other typical patterns in HRCT; and [5] exclusion of other congenital heart diseases, immunodeficiency or V/Q scans and DECT were not available. Demographic information including age, sex, weight, onset of disease, clinical presentations, major treatment and cardiac echography reports were obtained.

HRCT and DECT Pulmonary Blood Volume Fused Images

HRCT and DECT images were generated on a Dual Source CT (Siemens Somatom Definition) in dual energy mode at 140 and 80 kVp with 1-mm collimation. The images were retrieved from the hospital records and were read in a random order by two experienced radiologists. The CT scans were performed while the patients were stable with no acute respiratory tract infections. They were investigated under sedation if uncooperative. Heart rate, respiratory rate, and oxygen saturation levels were monitored continuously.

Pulmonary ^{99m}Tc-Diethylenetriamine Penta-Acetic Acid (DTPA) Radioaerosol Ventilation Scintigraphy

^{99m}Tc-DTPA with an activity of ∼370–900 MBq (10–25 mCi) was first put into a high-pressure oxygen jet nebulizer which produced radioaerosol particles at an oxygen flow rate of ∼10 l/min (11). During inhalation, sealed oxygen masks were placed on the patient's face around the mouth region to minimize leakage of the radioaerosol into the surrounding environment. Anterior, posterior, and both lateral and posterior oblique views were acquired, with 250 Kcounts for each planar image using a gamma camera (Toshiba GCA 602A, LEGP collimator, Japan).

Pulmonary ^{99m}Tc-Macroaggregated Albumin Perfusion Scintigraphy

^{99m}Tc-macroaggregated albumin (0.5–2.0 MBq/kg) was injected intravenously slowly during three to five respiratory cycles while the patients were in a supine position (11). Anterior, posterior, and both lateral and posterior oblique views were acquired with 500 Kcounts using the same gamma camera. Two experienced nuclear medicine physicians independently interpreted the V/Q scans. A matched defect was defined as ventilation and perfusion defects in the same location. A mismatched perfusion defect was defined as a perfusion defect not accompanied by a corresponding ventilation defect, and a mismatched ventilation defect was defined as a ventilation defect without a corresponding perfusion defect.

RESULTS

This retrospective and descriptive study included 10 patients with a diagnosis of PIBO who were followed up at our Pediatric Cardiopulmonary Outpatient Clinics. Of the 10 patients, two were excluded due to congenital heart disease and because a full image study could not be obtained. The remaining eight patients were enrolled in the study (four boys and four girls). The mean age at symptom onset was 25.8 months (range 15–41 months). At the time of diagnosis, most of the patients had cough, tachypnea or dyspnea, and wheezing or crackles on auscultation (**Table 1**).

Three of our patients were serum Mycoplasma pneumoniae IgM positive and recognized as *Mycoplasma pneumoniae* related BO; one was positive rapid antigen tests for influenza and others are unknown etiology. The common initial clinical presentation including dyspnea, cough and fever. Interestingly, one case revealed recurrent pneumomediastinum and wheezing (case 7).

An echocardiogram was requested to rule out heart disease and indirectly evaluated pulmonary arterial pressures in all patients. The max velocity (Vmax) was determining by tricuspid regurgitation, and pulmonary hypertension was recognized while Vmax more than 2.8 m/s (17). Subsequently, six patients had normal systolic pulmonary artery pressure (SPAP), whereas two patients had higher SPAP, with a range from 35 to 46 mmHg of SPAP.

All of the enrolled patients underwent HRCT, DECT, and pulmonary scintigraphy. In the main finding on HRCT, mosaic pattern is the most common feature (7/8) in our patients, followed by atelectasis (5/8). In lung pulmonary scintigraphy, two patients received only pulmonary perfusion scintigraphy, and the others received both ventilation and perfusion scintigraphy. In the 2 cases who only received perfusion scintigraphy, reduced pulmonary perfusion was noted, whereas unilateral or bilateral V/Q matched defects were present in the others. The DECT PBV image shows various degree of decreased perfusion, which is correlated to the decreased perfusion on pulmonary perfusion scan. **Figures 1**, **2** shows CXR, HRCT, perfusion scan, and reduced PBV images on DECT of case 1 and case 8.

Five patients (case 1, 4, 6, 7, 8) underwent spirometry during follow-up, and the others were younger than 7 years or uncooperative. The results showed one was normal (case 6); two

TABLE 1 | Clinical and imaging characteristics of the patients with BO.

Case	Age (mo)	Sex	Etiology	Initial clinical presentation	PH	Major treatment	Main finding on HRCT	V/Q scan	Dual-energy CT
1	41	F	*Mycoplasma pneumoniae*	Dyspnea, cough, fever, and crackle	N	(A)+(B)+(C)+(D)	Bronchiectasis, air-trapping, mosaic pattern, centrilobular nodules, atelectasis	Multiple V/Q match reduction	Decreased perfusion
2	20	M	*Mycoplasma pneumoniae*	Hemoptysis, fever, and dyspnea	Y	(B)+(C)+(D)+sildenafil	Mosaic pattern	Multiple V/Q match reduction	Decreased perfusion
3	17	F	NA	Dyspnea, cough, and crackle	Y	(A)+(B)+(C)+(D)+sildenafil	Mosaic pattern	V/Q match reduction in the left lung	Decreased perfusion
4	27	M	NA	Cough and dyspnea	N	(A)+(B)+(C)	Thickening	Bilateral reduced perfusion	Decreased perfusion
5	15	F	NA	Cough and dyspnea	N	(B)+(C)+(D)	Mosaic pattern, effusion, atelectasis,	Bilateral V/Q matched defect	Decreased perfusion
6	27	F	NA	Cough, dyspnea and wheezing	N	(B)+(C)	Mosaic pattern, thickening, atelectasis	Bilateral V/Q matched reduction	Decreased perfusion
7	26	M	*Mycoplasma pneumoniae*	Pneumomediastinum, dyspnea and wheezing	N	(A)+(B)+(C)+(D)	Mosaic pattern, atelectasis, pneumomediastinum	Bilateral V/Q matched reduction	Decreased perfusion
8	33	M	*Influenza*	Dyspnea on exertion, fever, crackle	N	(A)+(B)+(C)	Mosaic pattern, atelectasis	Decreased right pulmonary perfusion	Decreased perfusion

mo, months; PH, pulmonary hypertension; N/A, Not available; V/Q, ventilation/perfusion; HRCT, high resolution computed tomography. (A) Long term azithromycin for BO; (B) short-acting β-agonist; (C) systemic corticosteroid; (D) montelukast.

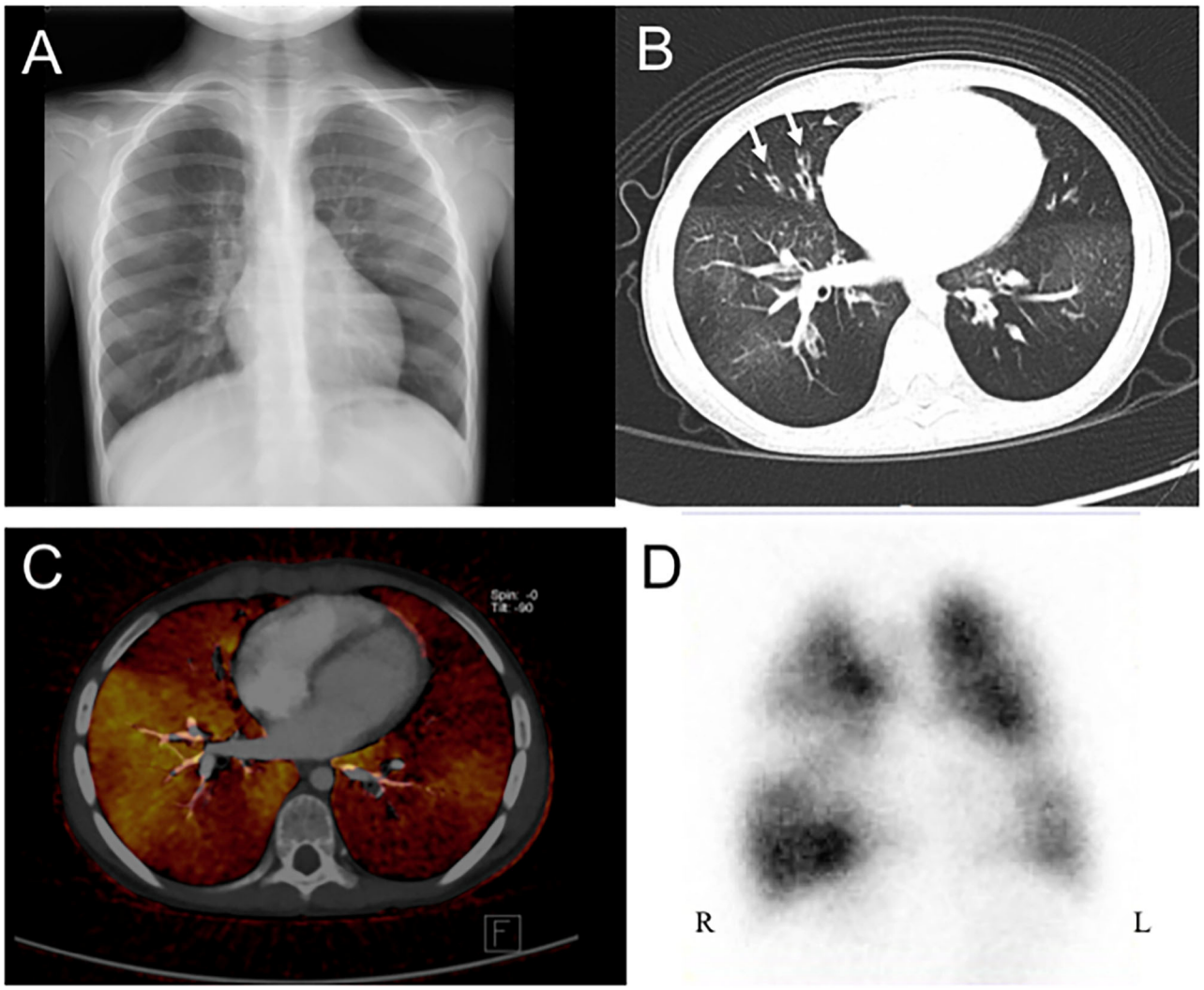

FIGURE 1 | A 4 years old girl diagnosed with post-infectious with initial clinical symptoms of cough and dyspnea. **(A)** Chest X-ray revealed peribronchial thickening and emphysema. **(B)** Axial view of HRCT revealed mosaic pattern and bronchiectasis (arrow). **(C)** Axial view of DECT reveal regional decreased pulmonary blood vasculature, and **(D)** Perfusion scintigraphy showed reduction blood flow in bilateral lungs. HRCT, high resolution computed tomography; DECT, dual energy computer tomography; R, right side; L, left side.

were mixed type pulmonary dysfunction (case 1 and 7); one was airflow obstruction (case 4); and one was restrictive pulmonary dysfunction. Four (case 1, 4, 7, 8) had a decreased end-expiratory flow (MEF25 $<$ 35%).

Treatment varied and was individualized. Systemic or inhaled corticosteroids were administered to all of the patients. The mode of steroid administration was chosen empirically according to the severity of the case. Inhaled bronchodilators (short-acting ß-2) were administered to all of the patients who had exacerbations of the respiratory condition and in those who responded to it clinically. Long-term azithromycin was given to 5 of the patients for immunomodulation. Montelukast was given to five of the patients to control an unstable chronic respiratory status. Moreover, sildenafil was also given to two patients with pulmonary hypertension (PH) secondary to BO and both showed marked improvement of oxygenation and estimated SPAP.

DISCUSSION

Various respiratory viruses or bacteria including adenovirus, respiratory syncytial virus (RSV), *Mycoplasma pneumoniae*, type B *Streptococcus*, *Legionella pneumophilia* and *Bordetella pertussis* have been investigated in relation to the development of PIBO (18–21). Viruses can be identified by polymerase chain reaction, detection of antibodies, rapid antigen test, or virus isolation in acute infections of the respiratory tract. In our study, some of the patients were only referred to our center weeks or months after the acute infection stage, and so it was not possible to verify the pathogens. Three of the 8 patients were *Mycoplasma pneumoniae*

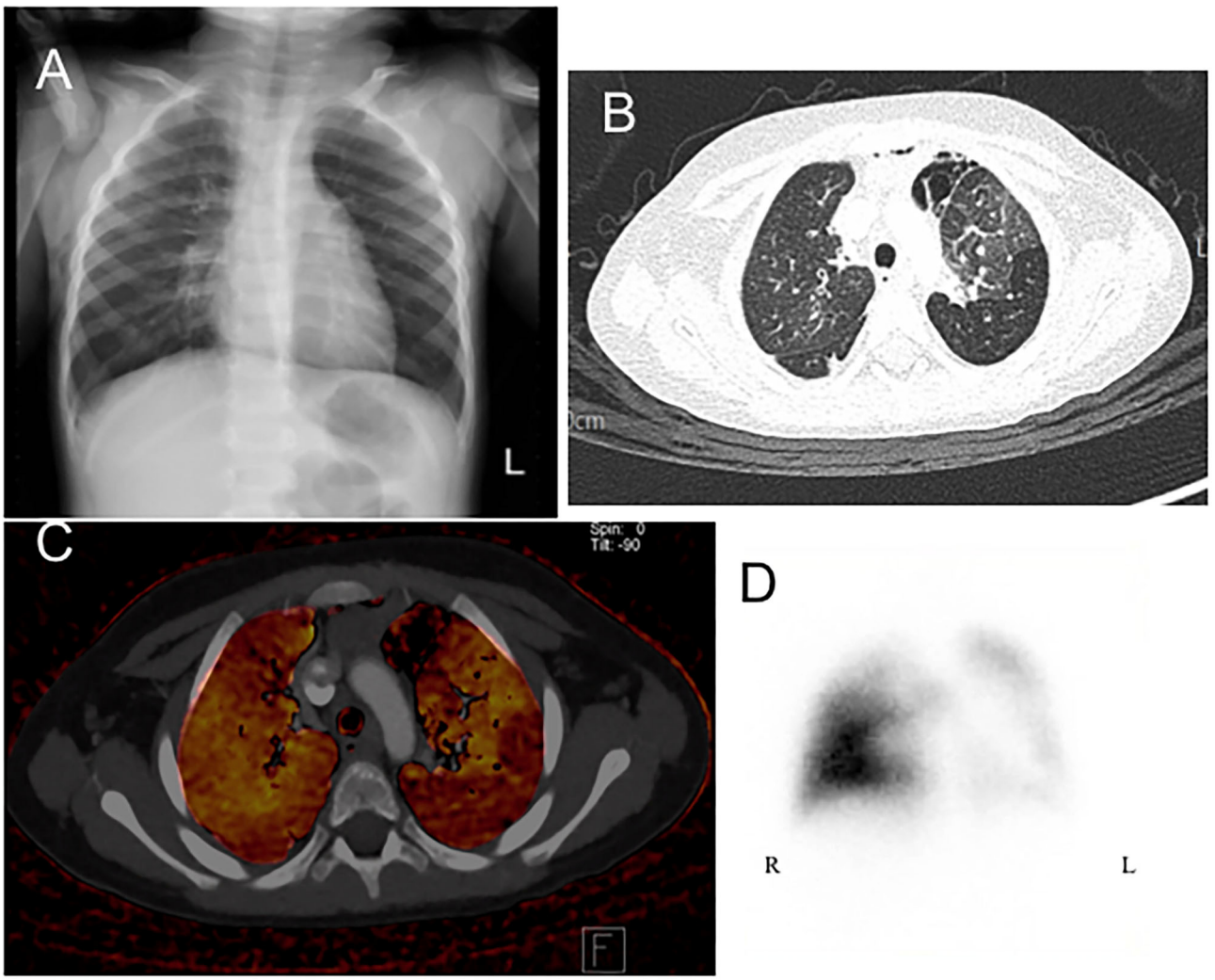

FIGURE 2 | A 2-year-old boy presenting with tachypnea and dyspnea and receiving flexible bronchoscopy, which showed normal tracheobronchial appearance except much whitish sputum. **(A)** Chest X-ray revealed hyperinflation and attenuation of vascular marking in both fields. **(B)** Axial view of HRCT revealed mosaic pattern which are characterized by well-defined border, areas of decreased lung attenuation are associated with decreased pulmonary blood vasculature of DECT image **(C)**. **(D)** Perfusion scintigraphy revealed marked lobar defects in right upper, left lower, and left upper lung fields. HRCT, high resolution computed tomography; DECT, dual energy computer tomography; R, right side; L, left side.

IgM-positive at the initial hospitalization and were diagnosed with *Mycoplasma pneumoniae*-related PIBO.

PIBO is more common in children, especially in those under 1 year old; however, age does not appear to be a risk factor for the development of PIBO (22–24). The common features of BO are tachypnea, wheezing, and hypoxemia persisting for at least 2 months after a causative event (5). In our patients, dyspnea, abnormal breath sounds on auscultation, and cough were the most common symptoms. To the best of our knowledge, only two articles have reported the prevalence of PH in BO. Nathan et al. reported that 42.3% of the lung transplant recipients in their study had an elevated pulmonary pressure (25), and Pate et al. reported that 3 of 4 patients (75%) were diagnosed with PH after the diagnosis of BO at a median of 91 days after hematopoietic stem cell transplantation (26). There was no such study in the aspect of PIBO and our study revealed that two of eight (25%) has PH and start the treatment with sildenafil once the diagnosis was made. Taken together, patients with PIBO should be regularly screened for PH due to its high prevalence. In addition, since hypoxemia presents in both BO and PH, hypoxemia in a patient with BO is typically due to worsening PH, and PH may also contribute to hypoxemia.

Steroid therapy has always been the central of BO treatment (2, 5, 7, 8). However, the side effects of the long-term systemic administration of glucocorticoids and inhaled corticosteroids have caused investigators to search for an alternative treatment for BO. Recently, macrolides have been proven to have anti-inflammatory and immunomodulatory effects, and they have

begun to be used for post-transplantation BO. A comprehensive analysis in 2014 and a large-scale randomized clinical trial in 2015 confirmed that azithromycin can improve the lung function FEV1 and reduce mortality of patients with post-lung transplant BO syndrome (27, 28). The recommendation of macrolides to treat post-transplantation BO is Grade IA and Grade 2C for PIBO (29). A more recent study demonstrated that combination therapy with budesonide, montelukast and azithromycin could improve pulmonary function and respiratory symptoms in children with PIBO who were under 5 years of age compared to unconventional treatment (budesonide for nebulization intermittently, prednisone, montelukast and antibiotics if necessary) (30). In our study, 3 of the patients received azithromycin and montelukast and had clinical improvement.

The obliterative changes in BO include divergent histologic and radiologic findings, the ability to progress to additional compartments of the lung, and different clinical outcomes (31). CXR images are non-specific, and can sometimes be normal or present with air trapping, atelectasis, bronchial thickening, or a more unilateral hyperlucent lung, known as Swyer-James syndrome (22). Similar to other studies on HRCT in BO, we also found that a mosaic pattern/attenuation was the most typical feature, and others included atelectasis, peribronchial thickening, air-trapping, and bronchiectasis (2, 22, 32). The mosaic pattern may be caused by vascular shunt from hypo-ventilated areas to normal or hyper-ventilated areas with decreased perfusion due to vessel constriction caused by regional tissue hypoxia (22). To further understand the distribution of pulmonary blood flow, a V/Q scan can provide functional lung imaging to diagnose BO (33, 34). In accordance with our previous study (11), decreased V/Q-matched defects were the major finding of pulmonary scintigraphy in the patients with BO in the current study.

DECT produces accurate anatomic and functional images by manipulating the differences in the interactions of high- and low-energy photon spectra with the atomic factors of various materials and tissues to accurately discriminate the chemistry of tissues of the body. Xenon ventilation DECT can provide two key insights into lung physiology, i.e., regional perfusion and ventilation, and it has been actively investigated with regards to clinically relevant applications (4, 16, 35). This functional information provided by DECT is supplementary because high-resolution thoracic anatomy is entirely preserved on dual-energy thoracic CT. In addition, virtual non-contrast imaging can omit pre-contrast scanning. In this respect, DECT imaging is at least dose-neutral, which is a critical requirement for pediatric patients (35). To the best of our knowledge, no previous study has compared DECT PBV images to perfusion pulmonary scintigraphy in patients with PIBO. Although we could not perform xenon ventilation CT scans at our facility, the results are the first to show that DECT PBV images and pulmonary perfusion scans are compatible in BO patients. This result could suggest that DECT may be used in BO patients as it has no additional radiation exposure and provides regional pulmonary perfusion information as pulmonary perfusion scan.

CONCLUSION

The therapeutic strategy and diagnostic tools of PIBO are lacking of standardization. HRCT and V/Q scans are important image tools in diagnosis and follow-up of BO, whereas DECT may be used in BO patients as it provides additional information on pulmonary vasculature. We suggested to gather DECT PBV when performing HRCT in patients with BO if available. Better understanding the image presentations and the feasible medication choice of PIBO will lead to better outcome for this lifelong respiratory disease.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by KMUHIRB-SV(II)-20200063. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

I-CC and Z-KD: conceptualization. I-CC, Y-WC, Y-CL, Y-HW, and Z-KD: data collection. J-SH, J-HH, Y-CL, Y-HW, and Y-WC: validation. I-CC, J-HH, and Z-KD: formal analysis. J-SH and Y-WC: investigation. J-SH, Y-WC, and Z-KD: resources. I-CC: writing—original draft preparation. Z-KD: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

FUNDING

This study was supported by grants from the Ministry of Science and Technology, Taiwan (MOST 106-2314-B-037-077-MY3, MOST 109-2314-B-037-076-) and the Kaohsiung Medical University Hospital (KMUH106-6R44, KMUH109-9R46).

REFERENCES

1. Mauad T, Dolhnikoff M, São Paulo Bronchiolitis Obliterans Study G. Histology of childhood bronchiolitis obliterans. *Pediatr Pulmonol.* (2002) 33:466–74. doi: 10.1002/ppul.10097
2. Lino CA, Batista AK, Soares MA, de Freitas AE, Gomes LC, JH MF, et al. Bronchiolitis obliterans: clinical and radiological profile of children followed-up in a reference outpatient clinic. *Rev Paul Pediatr.* (2013) 31:10–6. doi: 10.1590/S0103-05822013000100003
3. Myers JL, Colby TV. Pathologic manifestations of bronchiolitis, constrictive bronchiolitis, cryptogenic organizing pneumonia, and diffuse panbronchiolitis. *Clin Chest Med.* (1993) 14:6 11–22.
4. Goo HW, Yang DH, Hong SJ, Yu J, Kim BJ, Seo JB, et al. Xenon ventilation CT using dual-source and dual-energy technique in children with bronchiolitis obliterans: correlation of xenon and CT density values with pulmonary function test results. *Pediatr Radiol.* (2010) 40:1490–7. doi: 10.1007/s00247-010-1645-3

5. Jerkic SP, Brinkmann F, Calder A, Casey A, Dishop M, Griese M, et al. Postinfectious bronchiolitis obliterans in children: diagnostic workup and therapeutic options: a workshop report. *Can Respir J.* (2020) 2020:5852827. doi: 10.1155/2020/5852827
6. Sabri YY, Ibrahim IMH, Radman AF. Bronchiolitis Obliterans (BO): HRCT findings in 20 patients. *Egypt J Radiol Nuclear Med.* (2014) 45:69–73. doi: 10.1016/j.ejrnm.2013.09.014
7. Fischer GB, Sarria EE, Mattiello R, Mocelin HT, Castro-Rodriguez JA. Post infectious bronchiolitis obliterans in children. *Paediatr Respir Rev.* (2010) 11:233–9. doi: 10.1016/j.prrv.2010.07.005
8. Kavaliunaite E, Aurora P. Diagnosing and managing bronchiolitis obliterans in children. *Expert Rev Respir Med.* (2019) 13:481–8. doi: 10.1080/17476348.2019.1586537
9. Chang AB, Masel JP, Masters B. Post-infectious bronchiolitis obliterans: clinical, radiological and pulmonary function sequelae. *Pediatr Radiol.* (1998) 28:23–9. doi: 10.1007/s002470050286
10. Yuksel H, Yilmaz O, Urk V, Yuksel D, Goktan C, Savas R, et al. Clinical significance of lung perfusion defects in children with post-infectious bronchiolitis obliterans. *Tuberk Toraks.* (2009) 57:376–82.
11. Chen IC, Chen YW, Lin SH, Hsu JH, Wu JR, Dai ZK. Usefulness of combination of pulmonary ventilation and perfusion scintigraphy on the diagnosis of children with unilateral hyperlucent lung. *Nucl Med Commun.* (2011) 32:1052–9. doi: 10.1097/MNM.0b013e32834a6dfd
12. Xie BQ, Wang W, Zhang WQ, Guo XH, Yang MF, Wang L, et al. Ventilation/perfusion scintigraphy in children with post-infectious bronchiolitis obliterans: a pilot study. *PLoS ONE.* (2014) 9:e98381. doi: 10.1371/journal.pone.0098381
13. Chiro GD, Brooks RA, Kessler RM, Johnston GS, Jones AE, Herdt JR, et al. Tissue signatures with dual-energy computed tomography. *Radiology.* (1979) 131:521–3. doi: 10.1148/131.2.521
14. McDavid WD, Waggener RG, Dennis MJ, Sank VJ, Payne WH. Estimation of chemical composition and density from computed tomography carried out at a number of energies. *Invest Radiol.* (1977) 12:189–94. doi: 10.1097/00004424-197703000-00016
15. Millner MR, McDavid WD, Waggener RG, Dennis MJ, Payne WH, Sank VJ. Extraction of information from CT scans at different energies. *Med Phys.* (1979) 6:70–1. doi: 10.1118/1.594555
16. Chae EJ, Seo JB, Goo HW, Kim N, Song KS, Lee SD, et al. Xenon ventilation CT with a dual-energy technique of dual-source CT: initial experience. *Radiology.* (2008) 248:615–24. doi: 10.1148/radiol.2482071482
17. Augustine DX, Coates-Bradshaw LD, Willis J, Harkness A, Ring L, Grapsa J, et al. Echocardiographic assessment of pulmonary hypertension: a guideline protocol from the british society of echocardiography. *Echo Res Pract.* (2018) 5:G11–24. doi: 10.1530/ERP-17-0071
18. Yalcin E, Dogru D, Haliloglu M, Ozcelik U, Kiper N, Gocmen A. Postinfectious bronchiolitis obliterans in children: clinical and radiological profile and prognostic factors. *Respiration.* (2003) 70:371–5. doi: 10.1159/000072900
19. Castro-Rodriguez JA, Daszenies C, Garcia M, Meyer R, Gonzales R. Adenovirus pneumonia in infants and factors for developing bronchiolitis obliterans: a 5-year follow-up. *Pediatr Pulmonol.* (2006) 41:947–53. doi: 10.1002/ppul.20472
20. Colom AJ, Teper AM. [Postinfectious bronchiolitis obliterans]. *Arch Argent Pediatr.* (2009) 107:160–7. doi: 10.1590/S0325-00752009000200011
21. Krasinski K. Severe respiratory syncytial virus infection: clinical features, nosocomial acquisition and outcome. *Pediatr Infect Dis.* (1985) 4:250–7. doi: 10.1097/00006454-198505000-00009
22. Colom AJ, Teper AM. Post-infectious bronchiolitis obliterans. *Pediatr Pulmonol.* (2019) 54:212–9. doi: 10.1002/ppul.24221
23. Colom AJ, Teper AM, Vollmer WM, Diette GB. Risk factors for the development of bronchiolitis obliterans in children with bronchiolitis. *Thorax.* (2006) 61:503–6. doi: 10.1136/thx.2005.044909
24. Zhang L, Irion K, Kozakewich H, Reid L, Camargo JJ, da Silva Porto N, et al. Clinical course of postinfectious bronchiolitis obliterans. *Pediatr Pulmonol.* (2000) 29:341–50. doi: 10.1002/(sici)1099-0496(200005)29:5<341::aid-ppul2>3.0.co;2-4
25. Nathan SD, Shlobin OA, Ahmad S, Barnett SD, Burton NA, Gladwin MT, et al. Pulmonary hypertension in patients with bronchiolitis obliterans syndrome listed for retransplantation. *Am J Transplant.* (2008) 8:1506–11. doi: 10.1111/j.1600-6143.2008.02277.x
26. Pate A, Rotz S, Warren M, Hirsch R, Cash M, Myers KC, et al. Pulmonary hypertension associated with bronchiolitis obliterans after hematopoietic stem cell transplantation. *Bone Marrow Transplant.* (2016) 51:310–2. doi: 10.1038/bmt.2015.248
27. Kingah PL, Muma G, Soubani A. Azithromycin improves lung function in patients with post-lung transplant bronchiolitis obliterans syndrome: a meta-analysis. *Clin Transplant.* (2014) 28:906–10. doi: 10.1111/ctr.12401
28. Corris PA, Ryan VA, Small T, Lordan J, Fisher AJ, Meachery G, et al. A randomised controlled trial of azithromycin therapy in bronchiolitis obliterans syndrome (BOS) post lung transplantation. *Thorax.* (2015) 70:442–50. doi: 10.1136/thoraxjnl-2014-205998
29. Silva Filho LV, Pinto LA, Stein RT. Use of macrolides in lung diseases: recent literature controversies. *J Pediatr.* (2015) 91(6 Suppl. 1):S52–60. doi: 10.1016/j.jped.2015.08.002
30. Chen X, Shu JH, Huang Y, Long Z, Zhou XQ. Therapeutic effect of budesonide, montelukast and azithromycin on post-infectious bronchiolitis obliterans in children. *Exp Ther Med.* (2020) 20:2649–56. doi: 10.3892/etm.2020.8983
31. Jonigk D, Merk M, Hussein K, Maegel L, Theophile K, Muth M, et al. Obliterative airway remodeling: molecular evidence for shared pathways in transplanted and native lungs. *Am J Pathol.* (2011) 178:599–608. doi: 10.1016/j.ajpath.2010.10.032
32. Barker AF, Bergeron A, Rom WN, Hertz MI. Obliterative bronchiolitis. *N Engl J Med.* (2014) 370:1820–8. doi: 10.1056/NEJMra1204664
33. Hasegawa Y, Imaizumi K, Sekido Y, Iinuma Y, Kawabe T, Hashimoto N, et al. Perfusion and ventilation isotope lung scans in constrictive bronchiolitis obliterans. a series of three cases. *Respiration.* (2002) 69:550–5. doi: 10.1159/000066464
34. Nakashima M, Shinya T, Oto T, Okawa T, Takeda Y. Diagnostic value of ventilation/perfusion single-photon emission computed tomography/computed tomography for bronchiolitis obliterans syndrome in patients after lung transplantation. *Nucl Med Commun.* (2019) 40:703–10. doi: 10.1097/MNM.0000000000001021
35. Goo HW. Dual-energy lung perfusion and ventilation CT in children. *Pediatr Radiol.* (2013) 43:298–307. doi: 10.1007/s00247-012-2465-4

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

MINI REVIEW
published: 29 March 2021
doi: 10.3389/fped.2021.622240

COVID-19 in Children: Respiratory Involvement and Some Differences With the Adults

Jenny Libeth Jurado Hernández[1]* *and Iván Francisco Álvarez Orozco*[2]

[1] Department of Pediatric Pulmonology, Fundación Neumológica Colombiana, Bogotá, Colombia, [2] Department of Pediatric Pulmonology, Neumocenter, Valledupar, Colombia

The coronavirus disease 2019 (COVID-19) represents a health problem with multidimensional impacts and heterogeneous respiratory involvement in children, probably due to the interaction between different and complex mechanisms that could explain its variable degrees of severity. Although the majority of reports reveal that children develop less severe cases, the number of patients is increasing with more morbidity. Most serious respiratory manifestations are acute respiratory distress syndrome (ARDS) and pneumonia. By understanding the key aspects that can be used to differentiate between pediatric and adult respiratory compromise by COVID-19, we can improve our knowledge, and thus decrease the negative impact of the disease in the pediatric population. In this mini review, we summarize some of the mechanisms and findings that distinguish between adult and pediatric COVID-19 and respiratory involvement, taking into account some issues related to the physiopathology, diagnosis, clinical and paraclinical presentation, severity, treatment, and control of the disease.

Keywords: SARS-CoV-2, COVID-19, respiratory system, respiratory involvement, pneumonia, ARDS, children

OPEN ACCESS

Edited by:
Mario Barreto,
Sapienza University of Rome, Italy

Reviewed by:
Ozgur Kasapcopur,
Istanbul University-Cerrahpasa, Turkey
Kuldeep Dhama,
Indian Veterinary Research Institute (IVRI), India
Harapan Harapan,
Syiah Kuala University, Indonesia

***Correspondence:**
Jenny Libeth Jurado Hernández
jjurado@neumologica.org

Specialty section:
This article was submitted to Pediatric Pulmonology, a section of the journal Frontiers in Pediatrics

Received: *28 October 2020*
Accepted: *28 January 2021*
Published: *29 March 2021*

Citation:
Jurado Hernández JL and Álvarez Orozco IF (2021) COVID-19 in Children: Respiratory Involvement and Some Differences With the Adults. Front. Pediatr. 9:622240. doi: 10.3389/fped.2021.622240

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is the result of infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1, 2). This coronavirus is characterized by its high level of transmissibility and pathogenicity, resulting in a pandemic, and its multidimensional impact (3–5). SARS-CoV-2 produces heterogeneous respiratory involvement, especially in children (6, 7). Some vascular, immunological, and molecular mechanisms probably explain its variable degrees of severity or atypical presentations compared to adults (8) and, consequently, some differences in diagnosis, severity, treatment, and control of the disease. Currently, pediatric patients with severe manifestations of the disease are increasing (9); pneumonia is the most common respiratory entity, and acute respiratory distress syndrome (ARDS) is the critical form (7).

With the aim of summarizing the mechanisms and findings that can be used to differentiate respiratory involvement between pediatric and adult COVID-19, taking into account issues related to the physiopathology, diagnosis, severity, treatment, and control of the disease, this paper elaborates on the characteristics of the SARS-CoV-2 pathophysiology, clinical and paraclinical presentation, diagnostic and therapeutic approach, and follow-up of COVID-19 in both populations. Using the Scopus and PubMed databases, the keywords SARS-CoV-2, COVID-19, respiratory involvement, respiratory system, pneumonia, and ARDS were searched. This review includes the differences in COVID-19 manifestations between children and adults.

EPIDEMIOLOGICAL ISSUES

COVID-19 occurs in children of all ages (10); however, the pediatric disease represents <5% of total cases (11). In this population, the infection predominates in school children and adolescents (12); the Center of Disease Control and Prevention (CDC) reports 386,329 cases in the United States (13). The percentage of cases is slightly higher in females compared with males (50.5 vs. 49.5%), and the rate of mortality is extremely low in both populations (<0.1%; 62 deaths) with a greater percentage of deaths in males (52.5%) (14). Despite these statistics, global data about morbidity in children may be understated because they have less frequent exposure to some sources of transmission, and the clinical course includes milder respiratory symptoms compared with adults (15–18). These situations may explain why children are less often tested (18, 19). For them, transmission of infection through familial clusters predominates (10).

PATHOPHYSIOLOGY

The **Figure 1** shows the basic structure of SARS-CoV-2 and pathophysiology of COVID-19. SARS-CoV-2 infection causes heterogeneous respiratory involvement ranging from mild to severe respiratory failure. In pediatric and adult patients, this compromise can occur in three phases. In the first phase, the virus binds to epithelial cells of the respiratory tract to commence primary replication; most patients are able to contain the infection in this stage and thus present mild disease. In the second phase, SARS-CoV-2 migrates down the airways and enters alveolar epithelial cells facilitating pulmonary viral replication and localized inflammation (7, 20); most patients need hospitalization due to pneumonia. In the third phase, the rapid replicative process of the virus at the lung level may trigger apoptosis of cells with vascular leakage and the release of pro-inflammatory proteins (5). The simultaneous downregulation of ACE2 expression can alter the renin-angiotensin system with elevation of angiotensin-2, which increases inflammation and vascular permeability, causing pulmonary edema. Patients can develop a strong immune response (21, 22) with subsequent cytokine storm [e.g., release of IL-2, IL-6, IL-7, IL-10, GCSF, IP-10, MCP-1, MIP-1, and TNF-α; (5)] which causes ARDS and respiratory failure (23–25). The proportion of T cells (helper T cells and memory helper T cells) is diminished, and naïve helper T cell levels are elevated in the severe disease (5, 14). To date, pediatric moderate and critical respiratory cases are less frequent than those presented in adults.

Generally, the SARS-CoV-2 viral load is elevated in the first week of clinical presentation, gradually reducing afterward (26). However, after 4–7 days of COVID-19, some patients present a critical evolution concurrent with a decrease in viral load and deterioration of inflammatory parameters. Among the more severe clinical cases, some patients can have a less steep and prolonged decline in the SARS-CoV-2 load (5). Around days 7–10 of symptoms, an elevation in IgG and IgM levels against antigens of the virus appears, and there is a progressive decrease in the viral load (5, 27, 28). The persistence of high viral load and exaggerated inflammatory response in severe lung involvement and multi-organ dysfunction is explained by the combination of virus-mediated cytopathic effects and immunologically mediated injury. Patients can gradually improve, or they do not recover (29).

Mechanisms have been proposed to explain the lower severity of respiratory involvement by COVID-19 in children compared to adults (30). From an immunological standpoint, the function of innate immunity with a predominance of natural killer cells and the previous development of immunological memory against other respiratory infectious processes seem to influence the response capacity against this beta coronavirus, minimizing its clinical impact (5, 31, 32). Likewise, the availability of a greater number of B and T lymphocytes observed in children can prevent an excessive inflammatory response, conferring a less severe course of illness (33), especially in pneumonia (34). In this way, another potential route that can provide clinical benefit is constant immunological training secondary to frequent exposure to early childhood vaccines, including immunization against HiB and pneumococcus (35).

At the vascular level, endothelial function, and coagulation are more preserved in children, reducing the possibility of vasculitic alterations or pulmonary thrombotic phenomena (36).

From a microbiological context, the presence of additional viral infections concomitant to SARS-CoV-2 occurs more frequently in children than in adults and seems to play a protective role by inhibiting the replicative process (37–40). Furthermore, the competitive effect of normal airway microbiota can decrease colonization and growth of the virus (41, 42) and interfere with the appearance or infection severity. Previous infection with other coronaviruses may influence development of cross-protection against the novel coronavirus (43).

In children, exposure to SARS-CoV-2 is usually less frequent and has a lower intensity due to adopted precautionary measures, favoring a milder clinical presentation of COVID-19 (44).

From a molecular perspective, in the pediatric and adolescent population with COVID-19, increased ACE2 activity is observed. This characteristic appears to have a protective function due to its participation in anti-inflammatory signaling (43, 45), leading to less severe disease in children compared to that in the elderly (29). However, Sharif-Askari et al. reported a low expression level of TMPRSS2 and ACE2 in the upper and the lower respiratory tract of children and adolescents in comparison to adults with COPD or who smoked, suggesting the negative impact of some clinical conditions on the severity of COVID-19 in adults (46).

Abbreviations: ACE2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; CDC, Center of Disease Control and Prevention; COPD, chronic obstructive pulmonary disease; GGOs, ground-glass opacities; COVID-19, coronavirus disease 2019; RBD, receptor-binding domains; CT, computerized tomography; CXR, chest x-ray; FDA, Food and Drugs Administration; HDL, lactate dehydrogenase; HiB, *Haemophilus influenzae* B; IgG, immunoglobulin G; IgM, immunoglobulin M; IL-2, interleukin 2; IL-6, interleukin 6; IL-7, interleukin 7; IL-10, interleukin 10; GCSF, granulocyte colony-stimulating factor; IP-10, interferon-inducible protein; MCP-1, monocyte chemoattractant protein-1; MIS-C, multisystem inflammatory syndrome in children; MIP-1, macrophage inflammatory protein 1 alpha; PICU, pediatric intensive care unit; RNA, ribonucleic acid; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane protease serin 2; TNF-α, tumor necrosis factor alpha.

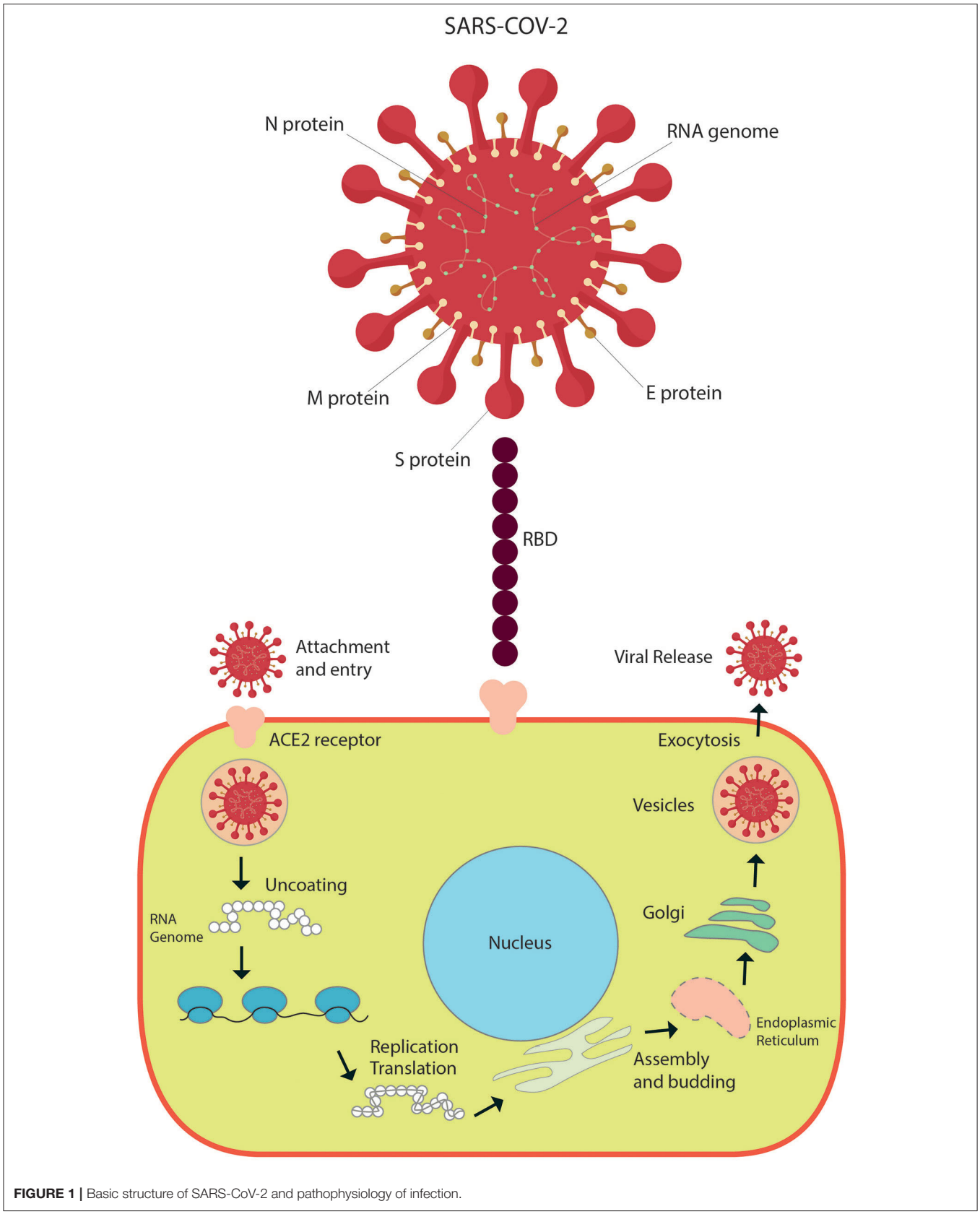

FIGURE 1 | Basic structure of SARS-CoV-2 and pathophysiology of infection.

DIAGNOSIS

The demonstration of SARS-CoV-2 through the reverse transcription polymerase chain reaction (RT-PCR) test confirms diagnosis (15, 19, 28, 47); it is particularly useful in children given their heterogeneity in presentation of COVID-19 (12). In some cases, it is possible to find patients with a high index of suspicion for this viral infection with suggestive symptoms and/or a history of exposure and a negative test result in whom it can be necessary to repeat (48).

Moreover, the serology is available to recognize the population with prior or recent SARS-CoV-2 infection (6). However, this test is not considered the only tool to support diagnosis of acute infection because of the variability in the time for the seroconversion or the detection of antibodies against SARS-CoV-2 (6, 43). The serological assay may be helpful in the case of an individual with a high likelihood of infection whose molecular diagnosis and antigen test show false-negative results (6, 49, 50). Unlike adults, the seroconversion rate can be lower among infected children (51, 52), which suggests a weaker seroconversion in asymptomatic cases and slight forms of COVID-19 (43). Rostad et al. found IgG antibodies to the virus in all children with multisystem inflammatory syndrome in children (MIS-C) and in more than 90% of those with severe or moderate COVID-19 by clinic and inflammatory parameters; however, antibody responses in children with a mild form were not detected (53). With these findings, a prognostic and diagnostic role of antibodies specifically for pediatric COVID-19 is suggested.

CLINICAL PRESENTATION

In about two thirds of pediatric cases of COVID-19, the child had physical contact with a confirmed case (54), and the exposure, different from adults, usually occurred at home (55). In children, most described symptoms are fever (47.5–51.6%) and cough (41.5–47.3%) (7, 10, 18, 21, 22, 36, 56, 57); however, dyspnea (40%) is the most common respiratory signal in more severe presentations, such as pneumonia and ARDS (7, 18). Relative to adults, pediatric cases present other concomitant symptomatology (e.g., fatigue and muscle pain) and more co-morbid conditions even in different systems in a representative proportion (55, 58).

The progression to severe or critical forms is infrequent in pediatric cases (10): 2% are severe cases, and <2% correspond to critical evolutions (7). Some cases are classified as moderate disease due to radiological findings, although the symptoms are few (2, 7, 59). The recovery is faster probably due to lower affectation and a better immune response (60), but complications in the presence of co-morbidities are more likely (10, 61, 62). Although mortality in cases requiring pediatric intensive care units (PICU) is low (12, 63), an increase is being observed.

Götzinger et al. explored various risk factors for admission to intensive care. Age below 1 month, male sex, clinical evolution with lower airway infectious compromise, and a history of co-morbidities showed relevance. They also identified a heterogeneity of previous diseases, including pulmonary entities, cardiac disturbances, malignant diseases, or nervous system disorders. Some patients received antivirals or immunomodulators due to a serious clinical course (64); however, the role of these agents in pediatric COVID-19 is not fully established.

RADIOLOGICAL FINDINGS

The American College of Radiology suggests performing chest x-rays (CXR) in pediatric patients with moderate or severe symptomatology, and in those with antecedents and previous risk factors (18) because they can need hospitalization and greater care (65). Peribronchial cuffing in both lung fields and central and peripheral ground-glass opacities (GGOs) are present in this group. However, these patterns are still non-specific. Another finding is bilateral or unilateral consolidation. Less common presentations include pleural effusion and mediastinal widening. During follow-up, radiological control depends on clinical evolution with rapid resolution of involvement in most of the cases. If patients worsen, a persistence of symptom exacerbation in findings or new consolidations can be observed (66).

Palabiyik et al. observed alterations in CXR in about half of children evaluated for pneumonia, particularly in the lower areas. The most frequent abnormality was unilateral increased density (67). Unlike adults, radiological compromise is less described in children possibly because the cases are mostly mild, the disease goes unnoticed, or it is poorly evaluated (68). Some authors emphasize atypical manifestations in pediatric pneumonia, including unilateral lobar or segmental consolidation, central bilateral or unilateral GGOs, and/or consolidation, single-round consolidation, pleural effusion, or lymphadenopathy (65, 69).

The COVID-19 alterations most recognized on a chest computerized tomography (CT) scan in pediatrics are GGOs and patchy shadowing (7). Although, this imaging study is not recommended for systematic use, it has shown utility mainly in the evaluation of children when the acute clinical course includes hypoxemia or dyspnea, deterioration in clinical or laboratory parameters (for example, a higher D-dimer), or there is a poor response to support therapy (9, 65, 66). Unlike adults, CT indications are more specific, such as in clinical worsening or suspicion of pulmonary embolism (30, 65), because the avoidance of radiation is necessary. Typical features more reported in pneumonia are bilateral, peripheral, and/or sub-pleural GGOs and/or consolidation, especially in the lower lobe—and the "halo" sign. In relation to the indeterminate pattern, the CT scan reveals similar findings to those previously described in CXR and in "crazy paving" signs. Discrete small nodules (tree-in-bud, centrilobular) and lung cavitation can be observed in atypical presentations as well as other alterations mentioned in the radiography. In cases of indeterminate or atypical patterns, it is recommended that additional investigations of differential diagnoses occur according to each case (61, 69).

In comparison to adults, children have a generalized peripheral distribution of lesions (68) and a lower percentage of cases with GGOs, consolidation, crazy paving pattern, pleural

effusion, and bilateral compromise (70). The more pronounced difference between the groups corresponds to a higher frequency of unilateral lesions (30% of cases) and nodules (15%) in children (70, 71); this implies that atypical presentations should be considered more often in pediatrics (67). Also, ∼20% of the pediatric population have normal CT, which reinforces the importance of its performance in selected cases (70).

LABORATORY DATA

Most children with COVID-19 have normal laboratory findings compared with adults; however, a variability in features is recognized (18). In a review that included 655 pediatric patients, 17.1% showed low leucocyte levels, and 13.3% had lymphopenia or neutropenia (18). In other publications that summarize various studies, high levels of ferritin in 26% of children (12), elevation of C-reactive protein in 19%, and procalcitonin in 25–31% have been reported (5, 12). All these alterations present possibly in the context of greater severity secondary to a more inflammatory response. In contrast, a lower presence of marked inflammatory changes and lymphopenia is possible (72). In relation to co-infection, the prevalence of other common respiratory pathogens is high in children; therefore, concomitant evaluation (37) in the peak season for viral respiratory illness is suggested (73).

In a study of 70 adolescents admitted to PICUs, 21 (30%) developed ARDS even in the first 2 weeks of admission with a prolonged hospital stay; most patients had bilateral infiltrates. The platelet counts were significantly lower, and levels of IL-6 were more elevated compared to those without ARDS. Although other markers (lactate, pro-B-type natriuretic peptide) were high, the results did not have statistical relevance (74). The overall mortality was 2.8% (74); however, in adults the percentage of mortality with this condition is higher.

TABLE 1 | Key points in respiratory management of Covid-19 in Children (49, 77).

Oxygen therapy (according to patient's evolution).
- Low flow system: mild hipoxemia.
- High flow system: moderate to severe hipoxemia, with precautions to reduce risk of dispersing contaminating aerosols.

Invasive mechanical ventilation (if respiratory failure, or persistent hipoxemia (Pa02/Fi02 < 200 or Sa/Fi < 264), increased need for oxygen or worsening tachypnea in patient on high-flow nasal cannula).
- Protective mechanical ventilation.
- Initial parameters:
  - ✓ Tidal volume (TV): 4–8 ml/ kg, with monitoring of plateau pressure (if > 30 cm H20, decrease TV).
  - ✓ Respiratory rate: 22–30 bpm (patients from 1 month to 2 years), 18–24 bpm (2–4 years), 14–20 bpm (patients > 8 years).
  - ✓ Inspiration/expiration ratio (I: E ratio):1-2.
  - ✓ End-expiratory pressure (PEEP): titrate according to oxygenation, arterial gases and CXR. Each increase of 2 cm H_20 as required.
- Fraction of inspired O_2 (FiO_2): start at 100% and rapidly reduce to less than 60% in the first 2–6 h.
  - ✓ Alarms: 10% above and below the parameters. Driving pressure < 15 cm H_20 and Plateau pressure < 30 cm H_20.

Prone position (in patients with moderate to severe ARDS who need oxygen therapy or mechanical ventilation).

Glucocorticoids (as adjunctive therapy in select cases).
- Prednisolone 1 mg/kg orally or NG once daily (maximum dose 40 mg).
- Dexamethasone 0.15 mg/kg orally, intravenously (IV), or nasogastrically once daily (maximum dose 6 mg).
- Methylprednisolone 0.8 mg/kg IV once daily (maximum dose 32 mg).
- Hydrocortisone: for patients ≥1 month: 1.3 mg/kg IV every 8 hours (maximum dose 50 mg; maximum total daily dose 150 mg). For neonates: 0.5 mg/kg IV every 12 h for 7 days followed by 0.5 mg/kg IV once daily for 3 days.

Clinic follow-up
- Evaluation of vital signs, symptoms, and signals of respiratory worsening. According to findings, it is recommended the adjustment to care plan.
- Judicious use of empiric antibiotic as indicated for community-acquired or health care-associated pneumonia.
- Special attention to patients with chronic respiratory disease (severe asthma, cystic fibrosis, bronchopulmonary dysplasia, tracheostomy) or other complex uncontrolled conditions due to risk of an inadequate evolution.

TREATMENT

Generally, children with severe and critical presentations of COVID-19 require hospitalization. In addition, patients with non-severe forms and risk of severe disease due to pre-existing conditions can need hospital admission. Pediatric treatment focuses on supportive care by respiratory support with supplemental oxygen and invasive or non-invasive ventilation, fluid and electrolyte support, judicious use of empiric antibiotics as indicated for community-acquired or healthcare-associated pneumonia, systematic clinical follow-up, and laboratory monitoring (75). Unlike adults, anticoagulation seems to be less frequent in children, shown by lower presentation of embolic events. Evaluation of inflammation with C-reactive protein, D-dimer, LDH, ferritin, and IL-6 can be considered two to three times per week or if there is clinical worsening (75, 76). Other laboratory or imaging studies can be required according to each case. Special attention must be given to adequate nutritional support and temperature control. **Table 1** summarizes respiratory management in children (49, 77).

There is no specific treatment for adult and pediatric COVID-19, and pharmacotherapy is controversial (64, 78). Therefore, clinical trials have been developed to investigate the use of antivirals, antimalarials, and adjunct therapies especially in adult patients with severe or non-severe manifestations. Other investigations have evaluated the impact of using different forms of oxygen therapy and prevention measures (79, 80). Few studies have included children. The main limitation in the research on antiviral therapy and other strategies has been the big difference in the number of pediatric and adult events in COVID-19 and asymptomatic infection or with minimal symptoms among children (81).

There are some conditional suggestions for the utilization of antiviral agents in pediatric COVID-19 given the lack of demonstrated efficacy. This therapy should be reserved for children with severe involvement secondary to confirmed disease. Remdesivir, a nucleotide analog prodrug that inhibits viral RNA polymerases (82), has been considered in pediatrics because randomized trials in adults suggest a potential benefit;

however, the use of this agent must be individualized and, preferably, in the context of a clinical trial (75, 77, 81, 83). At this time, remdesivir is approved by the FDA for the treatment of COVID-19 in hospitalized patients aged >12 years and >40 kg in weight (84). Lopinavir/ritonavir is not recommended for routine use in children due to unfavorable pharmacodynamics and the absence of evidence for efficacy (77, 85, 86). Hydroxychloroquine and chloroquine are considered only in clinical trials and in hospitalization (77, 87–90).

As part of adjunctive therapy, low-dose glucocorticoids are suggested for select children with severe or critical disease who cannot participate in a clinical trial: the efficacy is uncertain given children have been underrepresented in the clinical trials (75, 79–81, 90–93). The use of other adjunctive treatment must be discussed case by case according to disease severity and in agreement with multidisciplinary teams as indicated (90). IL-6 inhibitors, interferon-beta 1b, and convalescent plasma from recovered COVID-19 patients are not recommended for routine use because the benefits/risks are uncertain in children (83, 84, 90, 94). Moreover, the clinical potential of other immunomodulators or passive immunization therapies must be elucidated with prospective, randomized, placebo-controlled trials in the pediatric group. Recently, evidence of potential therapeutic options in COVID-19 has been updated; however, it is necessary to develop high-quality trials to improve disease management (95).

Preventive measures to reduce viral spread utilize personal hygiene maintenance, including frequent hand washing, use of a face mask, disinfection of surfaces, social and physical distancing, home isolation, voluntary home quarantine, and operation adjustments in educative centers (77, 96).

Vaccination seems be the most effective method to avoid and control the illness (97, 98). Strategies include recombinant vectors, DNA, mRNA in lipid nanoparticles, protein subunits, inactivated viruses, and live attenuated viruses (7, 97, 99). Recently, the FDA approved the emergency use of two vaccines to prevent SARS-CoV-2 infection in individuals >16 years, generating profound worldwide expectation (100).

CONCLUSIONS

Various mechanisms and findings can be used to differentiate between adult and pediatric COVID-19, especially with respiratory involvement; however, children are less often tested. They have lower seroconversion and less exposure to some sources of transmission, although infection through familial clusters predominates. Adaptive and innate immune responses, previous or concomitant infection with other viruses, microbiota effects, increased ACE2 activity, and more preserved coagulation and endothelial function confer clinical advantages that contribute to the presentation of milder forms of the disease and a better prognosis. Fever and cough are more common manifestations, and dyspnea occurs in the context of pneumonia and ARDS. Co-morbidities can affect evolution. Most children show normal laboratory findings; however, there is certain variability and a lower prevalence of lymphopenia or marked inflammatory parameters. They can present atypical or normal images in a representative proportion of cases. CXR is preferred over CT. A CT scan is performed if there is clinical worsening or suspicion of pulmonary embolism. Pediatric treatment focuses on supportive care as there is less research into vaccines and specific treatments and thus a more conditioned use of pharmacotherapy.

Although there are still knowledge gaps in pediatric COVID-19 discussion, it is necessary to continue comprehensive and specific investigations to mitigate its consequences.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This mini review was financed with own resources.

REFERENCES

1. Coutard B, Valle C, de Lamballerie X, Canard B, Seidah NG, Decroly E. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. *Antiviral Res.* (2020) 176:104742. doi: 10.3389/fped.2021.579922/abstract
2. Min Z, Jun C, Fu F, Shu Q, Hu Y, Chun C, et al. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. *World J Pediatr.* (2020) 16:240–6. doi: 10.1007/s12519-020-00345-5
3. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol.* (2020) 19:141–54. doi: 10.1038/s41579-020-00459-7
4. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol.* (2019) 17:181–92. doi: 10.1038/s41579-018-0118-9
5. Zimmermann P, Curtis N. Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. *Arch Dis Child.* (2020) 1–11. doi: 10.1136/archdischild-2020-320338
6. World Health Organization. *Coronavirus Disease 2019 (COVID-19): Situation Report - 64.* (2020). Available online at: www.who.int (accessed February 25, 2021).
7. de Souza TH, Nadal JA, Nogueira RJN, Pereira RM, Brandão MB. Clinical manifestations of children with COVID-19: A systematic review. *Pediatr Pulmonol.* (2020) 55:1892–9. doi: 10.1002/ppul.24885
8. Kaul D. An overview of coronaviruses including the SARS-2 coronavirus – molecular biology, epidemiology and clinical implications. *Curr Med Res Pract.* (2020) 10:54–64. doi: 10.1016/j.cmrp.2020.04.001
9. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. *Clin Immunol.* (2020) 215:108427. doi: 10.1016/j.clim.2020.108427
10. Ali AS, Al-Hakami AM, Shati AA, Asseri AA, Al-Qahatani SM. Salient conclusive remarks on epidemiology and clinical manifestations of pediatric COVID-19: narrative review. *Front Pediatr.* (2020) 8:584694. doi: 10.3389/fped.2020.584694
11. Meena J, Yadav J, Saini L, Yadav A, Kumar J. Clinical features and outcome of SARS-CoV-2 infection in children: a systematic review and meta- analysis. *Indian Pediatr.* (2020) 57:820–6. doi: 10.1007/s13312-020-1961-0

12. Badal S, Thapa Bajgain K, Badal S, Thapa R, Bajgain BB, Santana MJ. Prevalence, clinical characteristics, and outcomes of pediatric COVID-19: A systematic review and meta-analysis. *J Clin Virol.* (2021) 135:104715. doi: 10.1016/j.jcv.2020.104715
13. Center of Disease Control and Prevention. *CDC COVID Data Tracker* (2020).
14. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis.* (2020) 71:762–8. doi: 10.1093/cid/ciaa248
15. Sanche S, Lin YT, Xu C, Romero-Severson E, Hengartner N, Ke R. High contagiousness and rapid spread of severe acute respiratory syndrome coronavirus 2. *Emerg Infect Dis.* (2020) 26:1470–77. doi: 10.3201/eid2607.200282
16. Robinson J, Freire D. COVID-19 – what does a paediatrician need to know? *Paediatr Respir Rev.* (2020) 35:3–8. doi: 10.1016/j.prrv.2020.05.001
17. Zeng L, Xia S, Yuan W, Yan K, Xiao F, Shao J, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. *JAMA Pediatr.* (2020) 174:722–25. doi: 10.1001/jamapediatrics.2020.0878
18. Liguoro I, Pilotto C, Bonanni M, Ferrari ME, Pusiol A, Nocerino A, et al. SARS-COV-2 infection in children and newborns: a systematic review. *Eur J Pediatr.* (2020) 179:1029–46. doi: 10.1007/s00431-020-03684-7
19. Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. *Pediatr Infect Dis J.* (2020) 39:355–68. doi: 10.1097/INF.0000000000002660
20. Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A, et al. Cell entry mechanisms of SARS-CoV-2. *Proc Natl Acad Sci USA*. (2020) 117:11727–34. doi: 10.1073/pnas.2003138117
21. Teo JTR, Abidin NH, Cheah FC. Severe acute respiratory syndrome-Coronavirus-2 infection: a review of the clinical pathological correlations of Coronavirus disease-19 in children. *Malays J Pathol.* (2020) 42:349–61.
22. Dhama K, Patel SK, Pathak M, Yatoo MI, Tiwari R, Malik YS, et al. An update on SARS-CoV-2/COVID-19 with particular reference to its clinical pathology, pathogenesis, immunopathology and mitigation strategies. *Travel Med Infect Dis.* (2020) 37:101755. doi: 10.1016/j.tmaid.2020.101755
23. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. *Viruses.* (2020) 12:372. doi: 10.3390/v12040372
24. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. *Virol Sin.* (2020) 35:266–71. doi: 10.1007/s12250-020-00207-4
25. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
26. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *Lancet Microbe.* (2020) 2:e13–22. doi: 10.1016/S2666-5247(20)30172-5
27. To KKW, Tsang OTY, Leung WS, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis.* (2020) 20:P565–74. doi: 10.1016/S1473-3099(20)30196-1
28. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature.* (2020) 581:465–9. doi: 10.1038/s41586-020-2196-x
29. Dhochak N, Singhal T, Kabra SK, Lodha R. Pathophysiology of COVID-19: why children fare better than adults. *Indian J Pediatr.* (2020) 87:537–46. doi: 10.1007/s12098-020-03322-y
30. Parisi GF, Indolfi C, Decimo F, Leonardi S, Miraglia del Giudice M. COVID-19 pneumonia in children: from etiology to management. *Front Pediatr.* (2020) 8:616622. doi: 10.3389/fped.2020.616622
31. Lau CM, Adams NM, Geary CD, Weizman O-E, Rapp M, Pritykin Y, et al. Epigenetic control of innate and adaptive immune memory. *Nat Immunol.* (2018) 19:963–72. doi: 10.1038/s41590-018-0176-1
32. Netea MG, Domínguez-Andrés J, Barreiro LB, Chavakis T, Divangahi M, Fuchs E, et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol.* (2020) 20:375–88. doi: 10.1038/s41577-020-0285-6
33. Valiathan R, Ashman M, Asthana D. Effects of ageing on the immune system: infants to elderly. *Scand J Immunol.* (2016) 83:255–66. doi: 10.1111/sji.12413
34. Rahimi B, Vesal A, Edalatifard M. Coronavirus and its effect on the respiratory system: is there any association between pneumonia and immune cells. *J Fam Med Prim care.* (2020) 30:4729–35. doi: 10.4103/jfmpc.jfmpc_763_20
35. Root-Bernstein R. Age and location in severity of COVID-19 pathology: do lactoferrin and pneumococcal vaccination explain low infant mortality and regional differences? *Bioessays.* (2020) 42:e2000076. doi: 10.1002/bies.202000076
36. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* (2020) 323:1061–9. doi: 10.1001/jama.2020.1585
37. Wu Q, Xing Y, Shi L, Li W, Gao Y, Pan S, et al. Coinfection and other clinical characteristics of COVID-19 in children. *Pediatrics.* (2020) 146:e20200961. doi: 10.1542/peds.2020-0961
38. Zimmermann P, Curtis N. COVID-19 in children, pregnancy and neonates: a review of epidemiologic and clinical features. *Pediatr Infect Dis J.* (2020) 39:469–77. doi: 10.1097/INF.0000000000002700
39. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of co-infection between SARS-CoV-2 and other respiratory pathogens. *JAMA.* (2020) 323:2085–6. doi: 10.1001/jama.2020.6266
40. Kumar N, Sharma S, Barua S, Tripathi BN, Rouse BT. Virological and immunological outcomes of coinfections. *Clin Microbiol Rev.* (2018) 31:e00111–17. doi: 10.1128/CMR.00111-17
41. Gonzalez AJ, Ijezie EC, Balemba OB, Miura TA. Attenuation of influenza A virus disease severity by viral coinfection in a mouse model. *J Virol.* (2018) 92:e00881–18. doi: 10.1128/JVI.00881-18
42. Nickbakhsh S, Mair C, Matthews L, Reeve R, Johnson PCD, Thorburn F, et al. Virus-virus interactions impact the population dynamics of influenza and the common cold. *Proc Natl Acad Sci USA.* (2019) 116:27142–50. doi: 10.1073/pnas.1911083116
43. Felsenstein S, Hedrich CM. SARS-CoV-2 infections in children and young people. *Clin Immunol.* (2020) 220:108588. doi: 10.1016/j.clim.2020.108588
44. Dalton CB, Corbett SJ, Katelaris AL. COVID-19: implementing sustainable low cost physical distancing and enhanced hygiene. *Med J Aust.* (2020) 212:443–46.e1. doi: 10.5694/mja2.50602
45. Chen J, Jiang Q, Xia X, Liu K, Yu Z. Individual variation of the SARS-CoV2 receptor ACE2 gene expression and regulation. *Ageing Cell.* (2020) 19:e13168. doi: 10.1111/acel.13168
46. Sharif-askari NS, Sharif-askari FS, Alabed M, Temsah M, Heialy S Al, Hamid Q, et al. Airways Expression of SARS-CoV-2 receptor, ACE2, and TMPRSS2 Is lower in children than adults and increases with smoking and COPD. *Mol Ther Methods Clin Dev.* (2020) 18:1–6. doi: 10.1016/j.omtm.2020.05.013
47. Sankar J, Dhochak N, Kabra SK, Lodha R. COVID-19 in children: clinical approach and management. *Indian J Pediatr.* (2020) 87:433–442. doi: 10.1007/s12098-020-03292-1
48. COVID-19 Treatment Guidelines Panel. *Coronavirus Disease 2019 (COVID-19) Treatment Guidelines*. National Institute of Health (2020).
49. Fernández-Sarmiento J, Acevedo L, Mulett H, Bastidas S, Sarta M, Durán N, et al. Severe SARS-CoV-2 infection in critical care. *Trends Anaesth Crit Care.* (2020) 34:28–37. doi: 10.1016/j.tacc.2020.07.002
50. Yongchen Z, Shen H, Wang X, Shi X, Li Y, Yan J, et al. Different longitudinal patterns of nucleic acid and serology testing results based on disease severity of COVID-19 patients. *Emerg Microbes Infect.* (2020) 9:833–6. doi: 10.1080/22221751.2020.1756699
51. Stringhini S, Wisniak A, Piumatti G, Azman AS, Lauer SA, Baysson H, et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. *Lancet.* (2020) 396:313–9. doi: 10.1016/S0140-6736(20)31304-0
52. Long QX, Liu BZ, Deng HJ, Wu GC, Deng K, Chen YK, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nature Med.* (2020) 26:845–8. doi: 10.1038/s41591-020-0897-1
53. Rostad CA, Chahroudi A, Mantus G, Lapp SA, Teherani M, Macoy L, et al. Quantitative SARS-CoV-2 serology in children with Multisystem

Inflammatory Syndrome (MIS-C). *Pediatrics*. (2020) 146:e2020018242. doi: 10.1542/peds.2020-018242
54. Lok C, Ho T, Oligbu P, Ojubolamo O, Pervaiz M. Clinical characteristics of children with COVID-19. *AIMS Public Heal.* (2020) 7:258–73. doi: 10.3934/publichealth.2020022
55. Pei Y, Liu W, Bilal I, Li F, Xie S. Comparing Chinese children and adults with RT-PCR positive COVID-19: a systematic review. *J Infect Public Health.* (2020) 13:1424–31. doi: 10.1016/j.jiph.2020.06.036
56. Patel NA. Pediatric COVID-19: Systematic review of the literature. *Am J Otolaryngol Head Neck Med Surg.* (2020) 41:102573. doi: 10.1016/j.amjoto.2020.102573
57. Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, et al. Severe Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. *JAMA Pediatr.* (2020) 174:882–9. doi: 10.1001/jamapediatrics.2020.1467
58. Luo H, Liu S, Wang Y, Phillips- PA. Age differences in clinical features and outcomes in patients with COVID-19, Jiangsu, China: a retrospective, multicentre cohort study. *BMJ Open.* (2020) 10:e039887. doi: 10.1136/bmjopen-2020-039887
59. Chinese Medical Association. Recommendations for the diagnosis, prevention and control of the 2019 novel coronavirus infection in children (first interim edition). *Chinese J Pediatr*. (2020) 58:169–74. doi: 10.3760/cma.j.issn.0578-1310.2020.0004
60. Fialkowski A, Gernez Y, Arya P, Weinacht KG, Kinane TB, Yonker LM. Insight into the pediatric and adult dichotomy of COVID-19: Age-related differences in the immune response to SARS - CoV - 2 infection. *Pediatr Pulmonol.* (2020) 55:2556–64. doi: 10.1002/ppul.24981
61. Foust AM, Phillips GS, Chu WC, Daltro P, Das KM, Kilborn T, et al. International expert consensus statement on chest imaging in pediatric COVID-19 patient management: imaging findings, imaging study reporting and imaging study recommendations. *Radiol Cardiothorac Imaging.* (2020) 2:e200214. doi: 10.1148/ryct.2020200214
62. Das BB. Covid-19 and pulmonary hypertension in children: what do we know so far? *Medicina.* (2020) 56:716. doi: 10.3390/medicina56120716
63. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, Mckiernan CA, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to us and Canadian pediatric intensive care units. *JAMA Pediatr.* (2020) 174:868–73. doi: 10.1001/jamapediatrics.2020.1948
64. Götzinger F, Santiago-García B, Noguera-Julián A, Lanaspa M, Lancella L, Calò Carducci FI, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Heal.* (2020) 4:653–61. doi: 10.1016/S2352-4642(20)30177-2
65. Foust A, McAdam A, Chu W, Garcia-Peña P, Phillips G, Plut D, et al. Practical guide for pediatric pulmonologists on imaging management of pediatric patients with COVID-19. *Pediatric Pulmonology.* (2020) 55:2213–24. doi: 10.1002/ppul.24870
66. Oterino C, Alonso E, Andrés M, Buitrago N, Pérez A, Parrón M, et al. Pediatric chest x-ray in covid-19 infection. *Eur J Radiol.* (2020) 131:109236. doi: 10.1016/j.ejrad.2020.109236
67. Palabiyik F, Kokurcan SO, Hatipoglu N, Cebeci SO, Inci E. Imaging of COVID-19 pneumonia in children. *Br J Radiol.* (2020) 93:20200647. doi: 10.1259/bjr.20200647
68. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: different points from adults. *Pediatr Pulmonol.* (2020) 55:1169–74. doi: 10.1002/ppul.24718
69. Simpson S, Kay F, Abbara S, Bhalla S, Chung J, Chung M, et al. Radiological Society of North America expert consensus document on reporting chest CT findings related to COVID-19: endorsed by the society of thoracic radiology, the american college of radiology, and RSNA. *Radiol Cardiothoracic Imaging.* (2020) 2:e200152. doi: 10.1148/ryct.2020200152
70. Azadbakht J, Haghi-aminjan H, Farhood B. Chest CT findings of COVID-19-infected patients, are there differences between pediatric and adult patients? A systematic review. *Egypt J Radiol Nucl Med.* (2020) 51:145. doi 10.1186/s43055-020-00261-8
71. Chen Z, Fan H, Cai J, Li Y, Wu B, Hou Y, et al. High-resolution computed tomography manifestations of COVID-19 infections in patients of different ages. *Eur J Radiol.* (2020) 126:108972. doi: 10.1016/j.ejrad.2020.108972
72. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr.* (2020) 109:1088–95. doi: 10.1111/apa.15270
73. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell.* (2020) 181:281–92.e6. doi: 10.1016/j.cell.2020.02.058
74. Derespina KR, Kaushik S, Plichta A, Conway EE, Bercow A, Choi J, et al. Clinical manifestations and outcomes of critically ill children and adolescents with coronavirus disease 2019 in New York city. *J Pediatr.* (2020) 226:55–63. doi: 10.1016/j.jpeds.2020.07.039
75. Dequin P.-F, Heming N, Meziani F, Plantefève G, Voiriot G. Effect of hydrocortisone on 21-day mortality or respiratory support among critically Ill patients with COVID-19: a randomized clinical trial. *JAMA*. (2020) 324:1298–306. doi: 10.1001/jama.2020.16761
76. Zhou P, Yang X.-L, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* (2020) 579:270–3. doi: 10.1038/s41586-020-2012-7
77. Deville JG, Song E, Ouellette CP. *Coronavirus Disease 2019 (COVID-19): Management in Children*. UpToDate. (2020). Available online at: https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-management-in-children (accessed February 25, 2021).
78. 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. *Clin Infect Dis.* (2020) 71:2006–13. doi: 10.1093/cid/ciaa547
79. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med.* (2021) 384:693–704. doi: 10.1056/NEJMoa2021436
80. REMAP-CAP Investigators. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19 - The REMAP-CAP COVID-19 corticosteroid domain randomized clinical Trial. *JAMA*. (2020) 324:1317–29. doi: 10.1001/jama.2020.17022
81. Tomazini B, Maia I, Cavalcanti A, Berwanger O, Rosa R, Viega V. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19 - the CoDEX randomized clinical trial. *JAMA*. (2020) 324:1307–16. doi: 10.1001/jama.2020.17021
82. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* (2020) 395:565–74.10.1016/S0140-6736(20)30251-8
83. Zhikang Y, Rochwerg B, Mpharm YW, Adhikari N, Murthy S, Lamontagne F, et al. Treatment of patients with nonsevere and severe coronavirus disease 2019: an evidence-based guideline. *CMAJ.* (2020) 192:E536–45. doi: 10.1503/cmaj.200648
84. Piechotta V, Kl C, Sj V, Doree C, Monsef I, Em W, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review (Review). *Cochrane Database Syst Rev.* (2020) 7:CD013600. doi: 10.1002/14651858.CD013600.pub2
85. RECOVERY Collaborative Group. Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. (2020) 396:1345–52. doi: 10.1016/S0140-6736(20)32013-4
86. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe covid-19. *N Engl J Med.* (2020) 382:1787–99. doi: 10.1056/NEJMoa2001282
87. RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med*. (2020) 383:2030–40. doi: 10.1056/NEJMoa2022926
88. Chowdhury S, Rathod J, Gernsheimer J. A rapid systematic review of clinical trials utilizing chloroquine and hydroxychloroquine as a treatment for COVID-19. *Acad Emerg Med.* (2020) 27:493–504. doi: 10.1111/acem.14005
89. Hernandez A V, Roman YM, Pasupuleti V, Barboza JJ, White CM. Hydroxychloroquine or chloroquine for treatment or prophylaxis of COVID-19. *Ann Intern Med.* (2020) 173:287–96. doi: 10.7326/M20-2496
90. Dulek DE, Fuhlbrigge RC, Tribble AC, Connelly JA, Loi MM, El Chebib H, et al. Multidisciplinary guidance regarding the use of immunomodulatory

therapies for acute COVID-19 in pediatric patients. *J Pediatr Infect Dis. Soc.* (2020) 18: piaa098. doi: 10.1093/jpids/piaa098
91. REACT Working Group. Association between administration of systemic corticosteroids and mortality among critically Ill patients with COVID-19: a meta-analysis. *JAMA.* (2020) 324:1330–41. doi: 10.1001/jama.2020.17023
92. World Health Organization. *Corticosteroids for COVID-19. 2020*. Available online at: https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1 (accessed February 25, 2021).
93. Lamontagne F, Agoritsas T, Macdonald H, Leo Y, Diaz J, Agarwal A, et al. A living WHO guideline on drugs for covid-19. *BMJ.* (2020) 370:m3379. doi: 10.1136/bmj.m3379
94. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw F, Lim WS, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis.* (2015) 211:80–90. doi: 10.1093/infdis/jiu396
95. Organización Panamericana de la Salud/Organización Mundial de la Salud (OPS/OMS). *Ongoing Living Update of COVID-19 Therapeutic Options: Summary of Evidence*. (2020). Available online at: https://iris.paho.org/bitstream/handle/10665.2/52719/PAHOIMSEIHCOVID-19200030_eng.pdf?sequence=17&isAllowed=y (accessed January 27, 2021).
96. Ortiz-Prado E, Simbaña-Rivera K, Barreno LG-, Rubio-Neira M, Cevallos-Robalino D, Sanches-Sanmiguel H, et al. Clinical, molecular, and epidemiological characterization of the SARS-CoV-2 virus and the Coronavirus Disease 2019 (COVID-19), a comprehensive literature review. *Diagn Microbiol Infect Dis.* (2020) 98:115094. doi: 10.1016/j.diagmicrobio.2020.115094
97. Rabaan AA, Al-Ahmed SH, Sah R, Tiwari R, Yatoo MI, Patel SK, et al. SARS-CoV-2/COVID-19 and advances in developing potential therapeutics and vaccines to counter this emerging pandemic. *Ann Clin Microbiol Antimicrob.* (2020) 19:1–37. doi: 10.1186/s12941-020-00384-w
98. Korber B, Fischer WM, Gnanakaran S, Labranche CC, Saphire EO, Montefiori DC, et al. Tracking Changes in SARS-CoV-2 Spike: Evidencethat D614G Increases Infectivity of the COVID-19 virus. *Cell.* (2020) 812–27. doi: 10.1016/j.cell.2020.06.043
99. Kaur SP, Gupta V. COVID-19 vaccine: a comprehensive status report. *Virus Res.* (2020) 288:198114. doi: 10.1016/j.virusres.2020.198114
100. Food and Drugs Administration. *Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) of Veklury® (remdesivir)*. (2020). Available online at: https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home (accessed February 25, 2021).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

REVIEW
published: 17 June 2021
doi: 10.3389/fped.2021.676296

Emergent Pneumonia in Children

Cecilia Perret[1], *Nicole Le Corre*[1] *and Jose A. Castro-Rodriguez*[2]*

[1] *Department of Pediatric Infectious Diseases and Immunology, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile,* [2] *Department of Pediatric Pulmonology and Cardiology, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile*

In recent decades there have been multiple pathogens, viruses and bacteria, which have emerged as causal agents of pneumonia affecting adults, albeit less frequently, to children. For the purposes of this article we have classified emerging pathogens as follows: **True emerging,** to pathogens identified for the very first time affecting human population (SARS-CoV-1, SARS-CoV-2, MERS-CoV, avian influenza, and hantavirus); **Re-emerging,** to known pathogens which circulation was controlled once, but they have reappeared (measles, tuberculosis, antimicrobial resistant bacteria such as *CA-MRSA*, *Mycoplasma pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Stenotrophomonas maltophilia,* and new serotypes of post-vaccine pneumococcal); and finally, those that we have called **old known with new presentations**, including common pathogens that, in particular condition, have changed their form of presentation (rhinovirus, and non-SARS coronavirus). We will review for each of them their epidemiology, forms of presentation, therapy, and prognosis in children compared to the adult with the aim of being able to recognize them to establish appropriate therapy, prognostics, and effective control measures.

Keywords: pneumonia - clinical features and management, children, emerging respiratory pathogens, re-emerging respiratory pathogens, COVID - 19

OPEN ACCESS

Edited by:
Ting Fan Leung,
The Chinese University of Hong Kong, China

Reviewed by:
Alfonso J. Rodriguez-Morales,
Fundacion Universitaria Autónoma de las Américas, Colombia
Paolo Bottau,
Local Health Authority of Imola, Italy

***Correspondence:**
Jose A. Castro-Rodriguez
jacastro17@hotmail.com

Specialty section:
This article was submitted to Pediatric Pulmonology, a section of the journal Frontiers in Pediatrics

Received: *05 March 2021*
Accepted: *21 May 2021*
Published: *17 June 2021*

Citation:
Perret C, Le Corre N and Castro-Rodriguez JA (2021) Emergent Pneumonia in Children. Front. Pediatr. 9:676296. doi: 10.3389/fped.2021.676296

INTRODUCTION

Children are not exempt from developing pneumonia from emerging pathogens like adults. The consequences, the likelihood of becoming infected and the prognosis will depend on the pathogen, incidence, and other risk factors. Over the past decades several microbiological agents, including viruses and bacteria that compromise the lower respiratory tract have emerged (**Figure 1**).

For the purposes of this review we have classified emerging pathogens into three categories: **True emerging** pathogens, to pathogens identified for the very first time affecting human population; **Re-emerging,** to known pathogens which circulation was controlled once, but they have reappeared or have developed significant antimicrobial resistance; and finally, those that we have called **old known with new presentations**, including pathogens that have always been present but in which new forms of respiratory involvement have been identified, other than those classically known so far.

In the first category we will discuss emerging new coronaviruses such as SARS-CoV-1, SARS-CoV-2, MERS-CoV, avian influenza and hantavirus (Andes virus). In the group of reemerging we will see the respiratory manifestations in children caused by measles, tuberculosis, bacteria with new developed antimicrobial resistances, new serotypes of post-vaccine pneumococcal; and in the old known with new behavior we will see rhinovirus and coronavirus (HCoV-NL63, HCoV-HKU1).

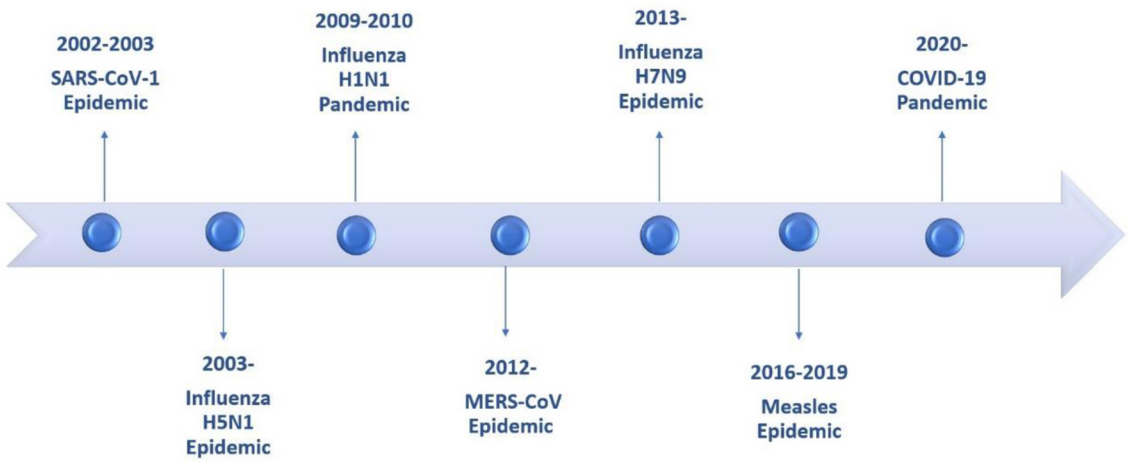

FIGURE 1 | Timeline of epidemics and pandemics involving the lower respiratory tract during the last two decades.

Traditional diagnostic methods, especially for viral respiratory pathogens, do not include many of these new agents so the possibility of identifying the etiology in episodes of low respiratory infections in children reaches 50% (1).

The objective of this review is to bring forward these respiratory pathogens, although with low frequency in children, which are certainly important to recognize to establish prognostics, appropriate therapy, and effective control measures. We do not include in this review certain pathogens, even though they were identified in the last 20 years, nowadays we know their behavior and it is possible to identify them with routine laboratory tests such as human metapneumovirus.

TRUE EMERGING PATHOGENS

Severe Acute Respiratory Syndrome Coronaviruses (SARS-CoV-1, MERS-CoV, SARS-CoV-2)

Coronaviruses are viruses with a single strand of RNA with positive polarity belonging to four genera: alpha, beta, gamma, and delta coronavirus. Human coronaviruses that have traditionally been responsible for the common cold or mild respiratory infections are HCOV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1. In the year 2003, the first coronavirus capable of producing a serious respiratory involvement with high mortality was identified, SARS-CoV-1, causing SARS and later, in the years to come MERS-CoV and recently in 2019 SARS-CoV-2, all belonging to beta coronaviruses and genetically closer to each other than to the traditional human coronaviruses (2), with zoonotic origin, probably bats. These coronaviruses are highly pathogenic and have high mortality when they infect humans (**Figure 2**).

Severe Respiratory Syndrome (SARS)

This syndrome with respiratory failure was identified in 2002 by outbreaks of severe pneumonia in southern China. In February 2003, the World Health Organization (WHO) reported an emerging disease with severe respiratory involvement. Quickly and in collaborative work, the causal agent was identified as a new coronavirus called SARS Coronavirus (3, 4), which was transferred from wild animal species to humans. The virus spread rapidly affecting 32 countries with more than 8,000 cases and 916 deaths between 2003 and 2004 with nearly 10% case fatality rate (CFR). Infection in children during the SARS outbreak was uncommon, ∼6% of cases in the Hong Kong outbreak and less than 5% in China were under the age of 18 and most of them were infected within their household (5). No transmission was documented in schools. Overall mortality was around 15% where older adults and people with associated comorbidity were most at risk of death. In pediatric age, adolescents were the ones who had the highest risk of serious illness (6). The epidemic ended abruptly in July 2003 and just isolated cases were documented in humans until 2004.

Clinical Manifestations

After an incubation period of 5 to 10 days, the most common form of presentation in children was fever, dry cough, and runny nose. It differed from adults in whom the most common form of presentation was fever, cough, and dyspnea, associated with myalgias, headache, and shivers. However, adolescents over the age of 12 developed similar symptoms to adults, more severe lung involvement and hypoxia with oxygen requirement (7). No child had wheezing, lymphadenopathies, or visceromegaly (8). Laboratory tests highlighted the presence of lymphopenia in up to 64% of hospitalized children, with elevation of LDH and CPK. Lymphopenia as well as odynophagia and neutrophilia at admission, were identified as predictive factors of extensive lung involvement and severity (8, 9). Lymphopenia and thrombocytopenia were more common in children >12 years compared to < 12 years who had rather reactive thrombocytosis. Radiological changes in the lungs of hospitalized patients were observed in 55% of children. These changes consisted mainly

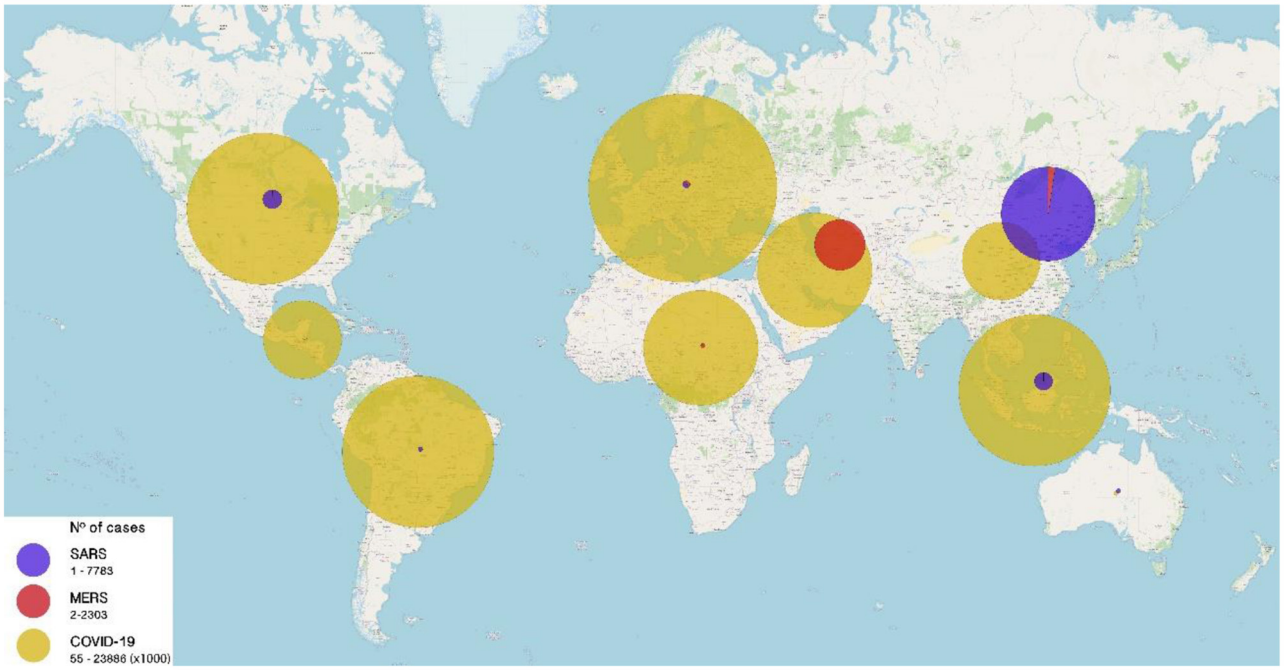

FIGURE 2 | Number of cases of Severe Acute Respiratory Syndrome (SARS) caused by emerging coronaviruses worldwide from 2003 to 2020. SARS (purple), MERS (red), and COVID-19 (yellow) cases until December 21, 2020. Size of circles is proportional to the number of cases (range: 0–23,886,000 cases).

of consolidations (46%) and ground glass opacification (GGO), usually in peripheral locations. Multifocal consolidations were observed in 22%, followed by peribronchial thickening in 14%. Only 1 patient out of a total of 62 had pleural effusion and none showed interstitial pattern (10). In the long term, 34% of children in follow-up had both functional and radiological long-term abnormalities, however, the children were asymptomatic (9).

Diagnosis

SARS diagnosis was made in cohorts of children who met the clinical definition and had epidemiological links, using PCR. Only 48% had positive PCR taken within the first 8 days of symptoms and in 16% the virus was isolated by culture from upper airway samples. The sensitivity of diagnostic methods did not vary depending on the age or severity of the picture. Seroconversion occurred in nearly 100% of children studied within 21 days of onset of symptoms, being as early as 8 days. At 4 to 6 months of follow up most of the children still had positive antibodies although the titles had decreased by more than half (8).

Treatment

Almost all children received ribavirin as part of treatment and 85% of those hospitalized received steroids. Those over the age of 12 were also given methylprednisolone due to the highest frequency of most severe cases in this age group (8).

Prognosis

No deaths were described within the pediatric group with SARS, the risk of serious illness was much lower than in adult patients, except in those over 12 years of age where clinical and radiological manifestations and severity approach adults. In the long term, it is described that a quarter of children had muscle weakness and transient hair loss but with full recovery after a few months (8).

Middle East Respiratory Syndrome (MERS)

MERS-CoV was first isolated from a patient in Saudi Arabia in 2012. Since then and until September 2019, more than 2,500 cases and more than 860 deaths have been identified. The CFR of MERS globally reaches 34.4% (11) and has affected 27 countries, mainly in the Middle East (**Figure 2**). It is thought it has been transmitted from camels to humans. This virus continues to circulate to these days, with low frequency.

The incidence in children is much lower than in adults. During the epidemic, 38 pediatric cases have been reported and 3 deaths have occurred. In the Saudi Arabia's cohort with 1,791 cases, 30 correspond to pediatric cases (1.7%), and most of them were exposed to a household case (12).

Clinical Manifestations

After an incubation period of 5 to 7 days (2–14 days), the most common symptoms in adults are fever, dry cough, myalgias, shivers, arthralgia followed by dyspnoea. Asymptomatic or oligosymptomatic infection is estimated to reach 25–50% of infected individuals. Risk factors for serious illness include age >65, high fever, thrombocytopenia, and lymphopenia as well as the presence of comorbidities such as immunosuppression. In these cases, the risk of mortality is very high (13).

In children the infection is milder than in adults with cough being the predominant symptom (14). In the Saudi Arabia's pediatric cohort, including 30 cases, 3 deaths have occurred: a 9-month-old infant with nephrotic syndrome, a 2-year-old with cystic fibrosis, and a 15-year-old adolescent. The average age of children was 11 years (0–17 years) and 80% of them were over the age of 10. The infection was asymptomatic in 43% (10/23) of patients. Hospitalization reached 50% (12/24) of children. In this cohort the frequency of hospitalization and complications in children was significantly lower than in adults but there was not statistically significant difference in mortality. However, the fatality rate in children is about 8%, much lower than described for adults. In the Thabet's series, that accounts for 14 pediatric cases and 2 deaths, they observed that severe cases of MERS in children had the same presentation as in adults with multiple organ failure and acute renal failure (15). The radiological changes described in the 3 children with the most serious disease, were bilateral diffuse chest infiltrations.

Diagnosis

Like SARS, the diagnosis is based on upper respiratory PCR and later, by the presence of MERS-CoV antibodies (13). The duration of viral excretion in children, especially asymptomatic ones, that could represent an important source for community transmission is unknown (12). Facing a child with low respiratory infection and epidemiological criteria such as travel to the Middle East or contact with someone who has traveled to that area, MERS should be studied as a possible causal agent.

Treatment

Different antiviral therapies have been attempted in adults to treat MERS such as ribavirin, lopinavir-ritonavir, remdesivir, interferon alfa, convalescent plasma but none of them have been studied in randomized clinical trials. The use of corticosteroids does not appear to be indicated in MERS and may even delay viral clearance in critically ill patients (16). None of these therapies have been evaluated in children.

COVID 19

This emerging infection is caused by the latest identified coronavirus, SARS-CoV-2, and it is currently in progress. COVID 19 was decreed pandemic by WHO in March 2020 and since its inception in China at the end of 2019, has affected nearly every country and caused more than 100 million cases worldwide and more than 2.3 million deaths (**Figure 2**). COVID19 has become the most severe pandemic in the last 100 years comparable to Spanish influenza in 1918 (17).

SARS-CoV-2 would apparently have been passed on to humans from its natural reservoir, the bats, but the intermediary species has not been discovered yet. Since the description of the first cases in China in 2019, it has demonstrated its rapid adaptation to human beings, capable of infecting them easily with a high rate of person-to-person transmission. Its incubation period is on average 3 to 5 days with a range between 2 and 14 days. It is transmitted mainly by respiratory droplets and fomites. Aerosol transmission has not been completely ruled out and might play a role in certain situations such as enclosed environments and from severe patients under procedures such as intubation, ventilatory support, airway aspiration, etc.

Although it affects all age groups, children become infected much less frequently than adults and with less severity, corresponding to ∼2% of the total COVID19 cases (18). Most children become infected within their households. Risk factors for a serious infection are age >65 years, presence of comorbidities such as diabetes, chronic kidney failure, hypertension, obesity, immunosuppression. Overall mortality is 2.2% reaching up to 25% mortality in risk groups (17, 19).

In hospitalized adults described in Richardson's series, 14% required intensive care (ICU) management, 12% mechanical ventilation, and 21% died of COVID19 (20). Risk factors for severity were male gender and the presence of comorbidities such as high blood pressure, obesity, and diabetes. The incidence of disease in children is much less common with 0.8 to 1.7% of all patients in different series. The median age in the different series varies between 7 and 11 years. There is no significant difference by sex (21, 22). Initially during the pandemic, it was thought that children did not become seriously ill, however more evidence has accumulated showing that children may require intensive care by ∼2 to 6% (22). The age group at higher risk is infants <1 year, who may have severe disease in about 11% of them, compared to 3% of adolescents (22, 23). However, COVID19 overall mortality in children is very low, <0.1% compared to 34% of fatality in people over 80. The most described comorbidities in children are chronic lung diseases (but not asthma), cardiovascular disease, and immunosuppression.

Clinical Manifestations

Children with COVID19 have mainly fever (70%), which is shorter in duration compared to adults, and dry cough (60%). The presence of dyspnea is less common than in adults. In children, gastrointestinal symptoms are more frequent. Progression to severe illness was observed between 0.5 and 2% and required admission to ICU (21, 22).

The chest X ray in children was abnormal up to 49.1% even some of them being asymptomatic (23). Pulmonary involvement in CT scan described by Simoni et al. in a systematic review, which brought together 166 children, showed mostly bilateral infiltration, between 57 and 75%, and a peripheral distribution between 12.5 and 51.7% (24). The presence of GGO was the most common finding in children with pulmonary involvement, followed by the combination of GGO and consolidation according to different series (24, 25). Predominance of lower lobes and upper lobes has been described according to different series suggesting that in children there is not a clear pattern of pulmonary involvement location. The halo sign was frequently observed in children, between 12.5 and 50%, being a rare presentation in adults (25). Pleural effusion and interstitial involvement are rare findings, as is air bronchogram and interlobular thickening. Alterations in pulmonary CT have been observed in asymptomatic children or with mild manifestations. In newborn abnormal radiological findings were described in 48% but specific lesions were not as frequent as in older children; 4% had GGO, 20%, unilateral patchy infiltration and 12% bilateral involvement (23).

Complications

Children develop a severe lung infection with low frequency unlike adults. However, a complication, formerly known as pediatric inflammatory multisystem syndrome (PIMS) and later on named as Multisystem inflammatory Syndrome in Children (MIS-C), has been described in children who presented with shock and a hyper-inflammatory state like observed in Kawasaki disease and is temporarily associated with SARS-Cov-2 infection. The average age of presentation in a Chilean series including 27 children, was 6 years, 52% male. Fever was the most common symptom and gastrointestinal manifestations such as diarrhea, abdominal pain, and vomiting were present in 63% of cases. Around 67% of children had at least one Kawasaki disease criterion. Alterations in heart function were observed in 31% of children and 60% required ICU management (26). This syndrome tends to be later on the disease's stages. Frequently COVID PCR is negative and specific antibodies are positive in children with this type of complication.

Diagnosis

Diagnosis in the acute phase is made by nasopharyngeal PCR and by serology in the following days 80% of children negativize PCR in the upper respiratory tract between 1 and 15 days of onset of symptoms and 6% persist positive for up to 1 month (27).

Treatment

Treatment in children will depend on the severity of the disease. Only symptoms relief treatment is indicated for mild to moderate cases. In cases of severe respiratory involvement, supportive therapy with oxygen administration and ventilatory support when required is the main pillar. Clinical trials to study different treatments for children have not been done. Remdesivir and dexamethasone can be used in the case of severe respiratory symptoms. Hydroxychloroquine, lopinavir/ritonavir, ribavirin have not shown efficacy in the management of patients with severe COVID19 (27). For systemic hyperinflammatory syndrome, treatment like Kawasaki disease with intravenous immunoglobulin and steroids has been proposed (28).

Avian Influenza

Two are the avian influenza viruses that have caused big outbreaks in humans in the last 15 years: influenza A H5N1 and influenza A H7N9. They share the same natural reservoir, wild and domestic birds, and have a low transmission capacity to humans but with serious lung compromise and high mortality.

The H5N1 avian influenza virus was first identified in birds by the death of geese in 1996 and the cases in humans were described for the first time in Guangdong, China in 1997. This outbreak was controlled with the slaughter of thousands of poultry. It re-emerges again in 2003 and since then, presents in seasonal waves during winter months being the last major wave of circulation in late 2014 and early 2015 (29). To date, 862 cases and 455 deaths with CFR close to 50% have been reported in 16 countries. The last human case diagnosed was in October 2020, in a 1-year-old infant in Laos (30). The H7N9 virus, second in importance in human cases, has a low pathogenicity in birds, first appeared in 2013, in Shanghai and since then 5 waves of human cases have occurred in China, the most intense being in 2017. In the latter wave the appearance of high pathogenic strains were documented. The last documented human case was in March 2019, an 81-year-old man in China. To date it accumulates 1568 laboratory-confirmed human cases and at least 613 deaths, with an overall mortality of 39% (31).

Birds are the main reservoir of influenza A virus. The H5N1 influenza virus emerged as a virus of high pathogenicity, that is, capable of producing great morbidity and mortality among birds, and when infects humans, which do not constitute its natural host, also causes serious lung involvement and high mortality. The H7N9 virus is a low pathogenic virus for birds, therefore it is very difficult to recognize it before cases in humans occur. The way of transmission is mainly from poultry or domestic birds to humans, but human-to-human transmission has also been identified in a much smaller proportion and sustained person to person transmission has not been described so far. The incubation period is longer than seasonal influenza being between 2 and 8 days but can reach up to 17 days. The influenza virus binds by its hemagglutinin molecule to the sialic acid receptor located in the airway epithelium. The human influenza virus has a higher affinity to the sialic acid-α 2,6 galactose receptor. The natural receptor of avian viruses is the sialic acid-α 2,3 galactose molecule found in the bird's airway. In humans, both receptors are present, the upper airway mainly contains the α 2,6 galactose while the lungs have α 2,3 galactose and sialic acid-α 2,6 galactose. Mutations in avian virus hemagglutinin promote the binding of avian virus to human influenza receptors in the airway. The H5N1 virus preferably binds to the α 2,3 galactose receptor, while H7N9 can bind both (32).

H5N1 infections are concentrated in a young population under the age of 40, while cases of H7N9 are grouped in persons over 50 years of age, probably due to the existence of oligosymptomatic or asymptomatic cases in children, which are not reported. There is a male gender predominance in H7N9 infection while in H5N1 there are no differences between sex. Different studies indicate the existence of a larger number of undetected mild cases of H7N9 due to a major proportion of asymptomatic cases. This suggests a more widespread genetic adaptability and higher susceptibility of humans to this virus and therefore with greater potential pandemic risk than H5N1. Influenza H5N1 has a higher frequency of clustered cases and a mortality somewhat higher than H7N9 (33, 34).

Clinical Manifestations

In a study series of 193 children with H5N1 the main symptom was fever. In children under 5 years of age, rhinorrhea was second in frequency after fever followed by vomiting and tachypnea. In older groups, the frequency of myalgia, odynophagia, and headache was higher. Tachypnea was equally common in all groups. Productive cough was more common in adolescents reaching 26%, than in younger children. Mortality was close to 50% and was higher in the adolescent group between 12 and 17 years old (80%) compared to children under 5 years of age whose mortality was 27% (35).

Upon admission to the hospital, which occurs on average on the fifth day of illness, all children showed abnormalities

in chest X-ray. Initial changes were interstitial infiltrates that rapidly progressed to diffuse alveolar infiltrate with segmental distribution and air bronchograms mainly in the lower areas (36). No patients had pleural effusion, pneumothorax, or hilar lymphadenopathy. Patients with severe illness develop diffuse alveolar damage with progression in hours to adult respiratory distress syndrome. The laboratory highlights leukopenia with lymphopenia, thrombocytopenia, and transaminase elevation as a poor prognostic factor.

Clinical manifestations in children with H7N9 avian influenza are little described considering that most of the descriptions come from hospitalized patients. Because children are hospitalized less frequently than adults there is not much information about the clinical manifestation in them. Infection in children is most often mild or asymptomatic. The most common symptoms are high fever, cough followed by expectoration and dyspnea (37). Chest X-ray and CT Scan in several adults show alveolar involvement of GGO or multifocal consolidation, uni or bilateral, which progresses in extension rapidly in the first 2 weeks of onset of symptoms. CT compared to chest X-ray show greater compromise, becoming more sensitive in detecting lung damage (38).

Diagnosis

Diagnosis of avian influenza is made by specific PCR. Diagnostic tests of human influenza are not able to detect zoonotic influenza viruses so clinical suspicion based on clinical manifestation and epidemiology are relevant.

Treatment

The treatment of avian influenza is mainly based on antiviral drugs, neuraminidase inhibitors such as oseltamivir, peramivir, and zanamivir, which should be initiated immediately after clinical suspicion without diagnostic confirmation, given the severity of these infections (39). Oseltamivir is approved for use in children over 2 weeks of age, so it is the treatment of choice in children. However, it has been documented strains resistant to this drug considered the fundamental pillar of treatment (40). The duration of therapy, based on expert opinion, should be longer than for seasonal influenza, 10 days compared to 5 days, considering zoonotic influenza viruses have higher viral loads and longer viral replication. H5N1 and H7N9 viruses are adamantans resistant. Nitazoxanide, an antiviral that blocks the maturation of viral hemagglutinin, has shown *in vitro* to be effective against adamantine- and neuraminidase inhibitors resistant influenza viruses. It has synergistic effect with neuraminidase inhibitors *in vitro* (41). One study showed clinical efficacy in patients treated with 600 mg nitazoxanide twice daily for 5 days, in time to reduce symptomatology and in reducing the viral load of influenza, compared to placebo (42). Further studies are needed to confirm its effectiveness but could be an alternative to resistant strains in children as it is approved to be used over 1 year of age. The use of corticosteroids in patients with severe influenza H7N9 infection showed increased mortality at 30 and 60 days, so its use is not recommended (43).

Hantavirus

Hantavirus infection can be divided into the one that occurs in the Old World and is mainly presented as a hemorrhagic syndrome with renal failure, and the one of the New World whose clinical manifestation is Cardiopulmonary syndrome (HCPS). It is this latest one that we will refer to in this article.

Hantavirus infection was first documented in the United States in 1993 when cases of people with acute respiratory failure and shock appeared. The identified virus was called Sin Nombre virus (SNV). Subsequently, the same clinical entity was recognized in Argentina and Brazil in 1993 and 1994 respectively. Later, Chile diagnosed the first case in 1995 (**Figure 3**). Although hantavirus infection is currently endemic in many countries of the Americas, it is considered an emerging virus, capable of causing severe respiratory involvement, from which we are still learning its clinical course and treatment, and which must be suspected in patients with severe lung compromise associated with cardiogenic shock.

HCPS is produced in the Americas by different types of hantaviruses, in the USA is SNV, Argentina and Chile Andes virus (ANDV), in Brazil Laguna Negra virus or Castelo Do Sonhos virus, among others. The natural reservoir are wild rodents, which are specific to each type of hantaviruses and it is transmitted by inhalation of aerosolized viral particles from rodent feces and urine. Person to person transmission in ANDV has been confirmed and evidence still under investigation suggests possible transmission through breast milk (44–47). Children have the same risk factors of becoming infected as adults such as exposure to contaminated areas by wild rodent fluids. However, for ANDV the presence of a household member with hantavirus infection is also a risk factor given its rare but confirmed person to person transmission of this viral type.

Given the transmission through inhalation of viral particles from the feces or urine of wild rodents, most cases occur in young men during work activities in rural areas and 25% are associated with recreational activities. Other identified risk factors for infection include caring, sexual partner and sleeping with an infected person.

Mortality varies between hantaviruses. SNV, ANDV, Araraquara, and Juquitiba are responsible for the most severe manifestations with case fatality rates ranging from 25 to 40%. Hantaviruses in Panama (Choclo virus) and Paraguay (Laguna Negra) have a lower CFR of 10 and 15% respectively, causing milder infections (48).

In the Chilean series of cases, including 997 cases of ANDV, from the first cases identified in 1995 to 2016, children account for 18.6% of cases and the CFR of this group <15 years is 31%, lower than people of 45 to 59 years who have a CFR of 42.8% (49). Approximately 60 cases are reported on average annually in Chile, with an average incidence of 0.3/100,000 inhabitants in the last 20 years, with most cases concentrated during the summer months (50).

Clinical Manifestations

After an incubation period, which for ANDV virus is between 7 and 39 days with a median of 19 days, and for SNV the maximum incubation period can be up to 17 days, the patient

FIGURE 3 | Numbers of New World Hantaviruses confirmed cases in the Americas. Size of circles is proportional to the number of cases (range 6–2032 cases).

complains of non-specific symptoms such as fever, headache, myalgias, arthralgias. After this prodromal period, the patient develops cardiopulmonary syndrome about 5 days after onset of symptoms, starting with respiratory symptoms such as cough and dyspnea and progressing rapidly to acute non-cardiogenic pulmonary edema caused by increase of capillary leakage associated to cardiogenic shock, which is the main cause of death (48). In cases of human-to-human transmission the incubation period ranges from 12 to 29 days (44–46). The median between onset of symptoms and death is 5 days in the Reyes series (49). In a study of 32 infected Brazilian children showed similar clinical manifestations to adults identifying the two phases, prodromal, with non-specific symptoms and the cardiopulmonary syndrome phase, where cough (46.9%) and dyspnea (59.4%) appears; 59.4%

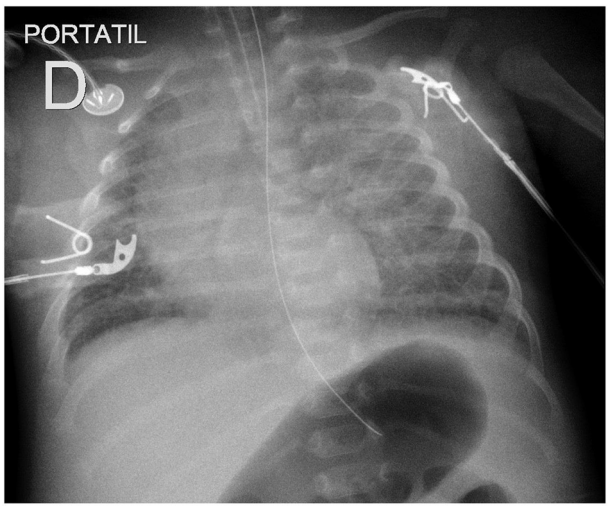

FIGURE 4 | Chest X-ray showing diffuse interstitial and alveolar infiltrates in a newborn with Hantavirus infection.

of these children were hospitalized and the CFR was 34.4%, like was described by Reyes (51). In countries such as Barbados where hantavirus infection is milder, the infection in children can occur as a non-specific febrile syndrome mistaken for arbovirus infections such as dengue (52).

The laboratory findings include thrombocytopenia in 94.7%, hemoconcentration in 63.1%, left shift leukocytosis in 47.3%, and atypical lymphocytes in 26.3% (51).

Typical radiological findings in children include interstitial infiltrate in the initial stage followed by alveolar infiltrate, bilateral, compatible with pulmonary edema. Pleural effusion may also be observed during the cardiorespiratory phase by increasing capillary permeability (**Figure 4**).

Diagnosis

The method of choice is the determination of hantavirus-specific IgM and IgG antibodies, which are present at the time of onset of symptoms of cardiopulmonary syndrome phase. There is a cross-reaction between the different hantaviruses so it is not possible to determine the type by antibodies. The sensitivity of serology decreases during the prodromal period, so a negative result at this stage does not rule out the diagnosis of hantavirus infection.

PCR can detect viremia 5 to 15 days before seroconversion and onset of symptoms of HCPS (44). For this reason, it is the method of choice for the monitoring of close contacts of confirmed cases, to be able to diagnose infection early on, even before symptoms appear, to start early with support measures to infected contacts. It can also be used for the diagnosis of patients in its acute phase due to its higher sensitivity, although its availability is low.

Treatment

The main treatment is the relief of symptoms and the use of support measures in a critically ill patient, such as oxygen therapy, use of vasoactive drugs, different types of ventilatory support including the use of ECMO in the most severe cases.

There is no specific antiviral therapy as *in vitro* efficacy of antivirals such as ribavirin has not been demonstrated *in vivo*. The use of convalescent plasma was shown to decrease CFR significantly, although it did not reach statistical significance (53). This is the standard therapy today in Chile for hospitalized patients with ANDV infection. Corticosteroids are not beneficial and should not be used to treat hantavirus cardiopulmonary syndrome.

Tables 1 and **2** are a summary and show a comparison between these true emerging diseases.

RE-EMERGING PATHOGENS

Measles

Measles is a highly contagious viral infectious disease, with an estimated R0 of 12–18, which could be higher according to recent literature (54). The CFR reaches 5% but can rise to 30% when health service is not accessible or under humanitarian crises (55). Since the global introduction of the measles vaccine in the 1960s, the burden of the disease has decreased considerably worldwide. Despite the vaccine having an excellent efficacy and immunogenicity, some outbreaks continue to be seen around the world. However, during the last few years, these outbreaks have become more frequent, particularly in Africa and some European countries (56, 57). The patients were children and adolescents unvaccinated or with incomplete vaccination. The main risk factor for an outbreak is a low measle vaccination coverage, leaving a larger percentage of the population susceptible to the infection. Lack of vaccination can be due to a low coverage in an entire country, but it also occurs in countries with high vaccination coverage, which have groups of people with no access to healthcare, religious or philosophical beliefs who choose not to vaccinate their children (56–58). These outbreaks are controlled with emergency vaccination campaigns, educational, political, and technical assessments (59). To achieve measles elimination and to obtain herd immunity is essential to reach a 95% of vaccination coverage worldwide (60).

Clinical Manifestations

Measles is transmitted by droplet but also by small aerosolized particles favorizing contagiousness (61). After 7–14 days of incubation, the prodromal period appears characterized by high fever along with conjunctivitis, coryza and cough, which lasts 2–4 days. One or two days later, an oral mucosa involvement is observed with small white lesions at the level of the first molar known as Koplik spots, pathognomonic of measles. Then an erythematous morbilliform exanthema begins on the face and then spreads to the trunk and extremities. Symptoms usually last 7 days, and sometimes a fine scaling follows the rash (55). Measles can complicate with bacterial infection as otitis media or tracheitis, but can compromise any other organ presenting diarrhea, hepatitis, myocarditis, or less frequently central nervous system involvement (subacute sclerosing panencephalitis) (61).

Respiratory compromise, particularly pneumonia, is the most common severe complication and is responsible for hospitalization and death among children with measles (62). Pneumonia can be produced by other viral infections as

TABLE 1 | Comparison of epidemiological, clinical, and radiological features between major emerging pneumonia in children.

Disease	Epidemiology	Clinical features	Radiology
MERS	- Middle East - <2% cases are children - 80% cases are > 10 yo	- Less severe than adults - Main symptom is cough	Bilateral diffuse infiltrations
COVID19	- < 2% cases are children - Median age 7–11 yo - Severe disease more frequent in < 1 yo, respiratory comorbidities and immunosuppresion	- Mild disease - Main symptoms are fever and dry cough - MIS-C is the main complication	- Bilateral infiltration - Bilateral ground-glass opacities and consolidation
Avian influenza			
H5N1	- Present in China, South East Asia - Affects mainly population lesss 40 yo	- Severe disease in children - Main symptoms are fever, rhinorrhea, vomiting, tachypnea - Leukopenia, lymphopenia, thromocytopenia	Diffuse alveolar infiltrate, air bronchograms in lower areas
H7N9	- Present in China - Greater transmission in children compared to H5N1	- High proportion of asymptomatic and mild disease. - Fever, cough	Bilateral ground-glass opacities and consolidation
Hanta cardio pulmonary syndrome (HCPS)	- The Americas - ANDV < 20% cases in children	- Main symptoms are fever, mialgia, cough - Severity varies regarding to type of Hantavirus - Thromocytopenia, hemoconcentration - HCPS is the main complication	- Interstitial infiltrate in the initial stage. - Followed by alveolar infiltrate, bilateral, compatible with pulmonary edema.

TABLE 2 | Comparison of diagnosis, treatment and prognosis between major emerging pneumonia in children.

Disease	Diagnosis	Treatment	Prognosis
MERS	- PCR and serology	- Antivirals - Convalescent plasma - Not steroids	- Less hospitalization - CFR 8% in children with comorbidities
COVID19	- PCR in early stage - Serology after the first week	- Symptoms relief - Supportive therapy - Remdesivir - Dexamethasone MIS-C: - IV Immunoglobuline plus steroids	- 2–6% hospitalization - CFR <0.1%
Avian influeza			
H5N1	- PCR	- Oseltamivir	- Overall CFR 50% - 80% in adolescents - 27% < 5 yo
H7N9	- PCR	- Oseltamivir - Not steroids	- CFR <3%
Hanta cardio pulmonary syndrome (HCPS)	- Hantavirus specific IgM-IgG	- Support measures - Convalescent plasma - Not steroids	- ANDV, Laguna Negra, Castelo dos Sonhos, Sin Nombre CFR 31%

adenovirus or rhinovirus, bacterial secondary infection, or measles alone (63, 64). Early in the course of the illness, after 2–7 days of fever and presence of rash, patients can evolve with dry cough and dyspnea. Young children characteristically present with bronchiolitis. In a recent measles epidemic developed in Italy, 30 (17%) young adults hospitalized with measles presented pneumonia, all of them unvaccinated (64). Five of them developed severe respiratory failure and two died. Having pneumonia was associated with thrombocytopenia and leukopenia. Most frequent findings in chest CT were bilateral lesions as centrilobular nodules and ground-glass opacity.

Treatment

Management of measles pneumonia is based on supportive measure. The role of antibiotics is still controversial. A review suggests, with poor evidence, a benefit of using antibiotics to prevent bacterial superinfection such as pneumonia or otitis media (65). Because cough is often dry, difficult the possibility to obtain bacterial culture and empiric antibiotics frequently are added in severe pneumonia or when secondary bacterial pneumonia is suspected by radiology (62, 64). Regarding vitamin A, there is still lacking evidence to prove it benefice reducing pneumonia associated mortality in children older than 2 years

old, but the WHO recommend it use even in well-nourished children (66, 67). There is not sufficient evidence to support zinc supplementation as it has not demonstrated any effect on clinical outcome of children with measles (68).

Pulmonary Tuberculosis

Tuberculosis (TB) is an infectious disease caused by *Mycobacteria tuberculosis* that has had a major impact on public health along the history of humanity. However, with hygiene improvement, social and economic development, production of appropriate drugs therapies and preventive measures, the incidence of this disease has significantly decreased, particularly in high-income countries (69). On the contrary, in low and middle-income countries, tuberculosis continues to be a leading cause of morbidity and mortality, with 44% of TB cases in South-East Asia, 25% in Sub-Saharan Africa, 18% in Western Pacific, and 8.2% in Eastern Mediterranean (70, 71). In 2019, the WHO estimated that 10 million people were ill with TB, with 1.2 million deaths among HIV-negative individuals and 208.000 among HIV-infected subjects (70). Regarding age distribution, 12% of total cases, and 16% of death from TB were in children under 15 years old, without gender predominance (70).

Few decades ago, tuberculosis re-emerged due to multifactorial causes, increasing its incidence in some countries and slowing its decline in others. The HIV epidemic left this population susceptible to mycobacterial infection, which increased the incidence of TB particularly in Sub-Saharan Africa and South East Asia (70, 72). Tuberculosis is the major cause of morbidity and mortality in HIV infected individuals, being the most common cause of hospital admission in this population (72). On the other hand, the increase in the mobility of population allowed the disease to reappear in places where incidence was low, as in Western Europe (73). Frequently, migrants are exposed to over-crowded facilities, poor hygiene conditions and inadequate access to health care systems increasing their risk of infection and appearance of multidrug resistant TB (MDR-TB). The appearance of these resistant mycobacteria has made the treatment and eradication of the disease difficult. The WHO estimates that 3.3% of new TB cases and 18% of cases already treated were MDR-TB, and the countries with the highest prevalence are India, China, and Russian Federation (70). Among the pediatric population is estimated that 3% of infected children have MDR-TB (74). Finally, the development of new therapies such as anti-TNF, which leave the host highly susceptible to mycobacterial infection, have reflected a reappearance of this infection, particularly in high-income countries (75).

Clinical Manifestations

Tuberculosis infection in children is most frequently asymptomatic. Younger children are at a highest risk to present a symptomatic disease (76). When symptoms occur, they usually begin 1 to 6 months after primary infection but can appear several months after. Non-specific symptoms are often seen such as failure to thrive, and less frequently fever, night sweats or chills. Intrathoracic involvement is the most common manifestation, with enlarged lymphadenopathy or pulmonary lesions (77). Persistent cough, wheezing, or dyspnea can be present and be confused with viral or bacterial pneumonia. Pulmonary involvement varies with age; adolescents can present with typically childhood manifestation but also with a cavitary phenotype as seen in adults (77). Children under 5 years old are at a higher risk to present a disseminated disease with compromise of other organs, such as lymphadenopathies, CNS and osteoarticular, among others.

Radiological findings in pulmonary TB are non-specific, but intrathoracic lymphadenopathy, airway compression, air-space disease, and less often military nodules and cavitation (78). CT is more sensitive to identify lymphadenopathy and parenchymal compromise. Further research should evaluate the role of magnetic resonance imaging and ultrasound for the diagnostic of intrathoracic TB.

Diagnosis

As clinical and radiologic manifestation are poorly specific, pulmonary TB diagnosis in children is challenging. Moreover, children usually have a low bacillary load, which, added to the low sensitivity of diagnostic techniques and the difficulty in sampling, complicates the identification of mycobacteria. A recent meta-analysis demonstrates a lower positivity in smears from children, particularly those younger than 4 years old, compared to adults (79). Mycobacterial culture is the gold-standard for TB diagnosis but is a time-consuming technique and its sensitivity can be as low as 7–40% in children (77).

A recent meta-analysis showed that molecular technique as Xpert MTB/RIF performed in expectorated, induced sputum or gastric lavage has a higher sensitivity compared to microscopy. However, this rapid confirmatory method is still less sensitive than the culture, so a negative test does not rule out the infection (80). To improve the sensitivity of this method, repeated sampling is recommended in the pediatric population (77). Regarding screening tests to evaluate evidence of exposure to mycobacteria, IGRAs have a high specificity, particularly in BCG-vaccinated children, and sensitivity above 90% in children older than 2 years old. Nonetheless, a negative result in a symptomatic child never rules out the infection (81).

Treatment

For the management of pulmonary TB in children, the WHO recommends a regimen of 2 months of three drugs (isoniazid, pyrazinamide, and rifampin) and 4 months of two drugs (isoniazid and rifampin), with exception of extensive pulmonary disease, living in settings with high prevalence of HIV or isoniazid resistance or in HIV-infected children (82). In these scenarios, a regimen of four drugs (isoniazid, pyrazinamide, rifampin, and ethambutol) and two drugs for another 4 months (isoniazid and rifampin) is recommended. When MDR-TB is suspected, it is essential to confirm the diagnosis, with culture and rapid drugs susceptibility testing as molecular tests (Xpert MTB/RIF). Regimens of 4 to 5 drugs (as fluoroquinolones, linezolid, clofazimine, ethambutol, among others) for 9 to 18 months or shorter regimens including an intravenous drug are recommended (74).

Bacteria With New Developed Antimicrobial Resistances

Community-Acquired Methicillin-Resistant Staphylococcus Aureus (CA-MRSA)

Pathophysiology

S. aureus has many virulence factors that help it to instigate colonization, evade host-immune responses, cause tissue injury, and disseminate to other organs. In establishing infection, *S. aureus* expresses surface proteins that mediate adherence and impair local defenses, while later in the infection secreted exotoxins disrupt epithelial barriers and immune cell function responses, thereby facilitating tissue invasion (83).

Although it has long been recognized as an important cause of necrotizing pneumonia (NP), the interest in this pathogen was renewed by recent studies linking strains expressing the virulence factor, Panton-Valentine leukocidin (PVL), with severe forms of this disease in previously healthy children and adults (84–86). In many cases these PVL-producing isolates were also MRSA strains. PVL is a pore-forming exotoxin, which activates and then destroys immune cells, such as neutrophils, potentially releasing damaging proteases into the surrounding tissues (87, 88). Of concern, a multi-center French study (89) involving 50 cases of necrotizing pneumonia caused by PVL-producing strains of *S. aureus* in children and adults aged between 1 month to 78 years, reported a CFR of 56%. Factors associated with mortality were hemoptysis, erythematous rash within 24 h of admission and peripheral blood leukopenia $<3.0 \times 10^6$/L. However, this was a non-comparative study, and it is therefore difficult to infer whether PVL contributed to pathogenicity.

Indeed, whether PVL itself is responsible for the pathological changes seen in NP is controversial. In part, this is because PVL has a strong cell and species specificity, behaving differently in various cell cultures and experimental models. For example, neutrophils from humans and rabbits are very sensitive to the effects of PVL *in vitro*, while those from monkeys and mice are highly resistant (89). Moreover, while a systematic review and meta-analysis found a strong association between PVL producing strains of *S. aureus* and skin and soft tissue infections, no such association was seen for invasive infections, including pneumonia (90). However, this review include only a small study in children from China, which compared cases of methicillin-resistant (MRSA) community acquired pneumonia (CAP) and no significant differences in the proportions of PVL-positive (3/22) and -negative (3/33) strains progressing to NP were found (91). Similarly, linking necrotizing pneumonia with MRSA is also controversial. Many of the observational studies reporting an association between invasive disease and MRSA are from the US, where the PVL-producing USA300 MRSA clone predominates, while in Europe, Australia and elsewhere, there are many different MRSA strains circulating (92). Furthermore, a recent case-control study of 133 French children and adults with PVL-positive strains of *S. aureus* necrotizing pneumonia, found no evidence for increased clinical severity in those with MRSA infections (93). Consequently, there are substantial gaps in our knowledge concerning the pathogenesis of *S. aureus* necrotizing pneumonia and it is likely that other cytotoxins may play an important role. Indeed, attention has been focused recently on other pore-forming toxins including alpha-hemolysin (or α-toxin), with its proposed mechanisms of action including activating the NLRP3 inflammasome, resulting in severe alveolar necrosis, and inducing platelet-neutrophil aggregation, which leads to further tissue destruction (94).

Community-associated MRSA (CA-MRSA) and healthcare-associated MRSA (HA-MRSA) isolates are distinct entities on a molecular level although the terminology is loosely used in the literature. MRSA infections that arise outside the hospital setting are conventionally labelled as "community-acquired" or "community-onset." These can be caused by both the newly emerged CA-MRSA strains as well as HA-MRSA strains that have "escaped" from hospital via colonized patients. Conversely, in areas where the prevalence of CA-MRSA is high, nosocomial infections are increasingly due to CA-MRSA (95).

Infections due to CA-MRSA were first reported in the early 1980s in aboriginal communities living in the Kimberley region of Western Australia (96, 97). The Australian Group on Antimicrobial Resistance in its 2006 *Staphylococcus aureus* Program (98) reported an 87% increase in the number of community-onset *S. aureus* infections due to MRSA in Australia. CA-MRSA clones accounted for 56.7% of all MRSA and 8.8% of all *S. aureus* isolated. Multilocus sequence type 93-MRSA-IV (Queensland strain) was the most frequently isolated CA-MRSA clone. The CA-MRSA as a cause of CAP in children and healthy adults is reported more frequently, mainly in case reports and small case series (99, 100).

Clinical Manifestation

The combined actions of many virulence factors enable *Staphylococcus aureus* to cause disease (101, 102). Depending on these factors and on the immune status of the host, *S. aureus* can cause diseases ranging from superficial skin infections to deep infections such as osteomyelitis, septic shock, and necrotizing pneumonia. Staphylococcal necrotizing pneumonia can affect young, immunocompetent patients (103). This disease, characterized by leukopenia, hemoptysis, and extensive necrosis of the lung tissue, is caused by *S. aureus* strains that produce PVL (104).

Treatment

Recommended therapy for CA-MRSA pneumonia includes vancomycin, linezolid, or clindamycin for 7–21 days. For necrotizing pneumonia, clindamycin with rifampin, vancomycin with rifampin, linezolid with rifampin or vancomycin with clindamycin have been successful in longer duration completing up to 4 weeks of treatment.

Mycoplasma Pneumoniae

M. pneumoniae is a common pathogen that causes CAP in children. The proportion of pneumonia caused by *M. pneumoniae* in different studies ranged from 20 to 40% (105). Increasing numbers of refractory or severe *M. pneumoniae* pneumonia cases have been reported worldwide, especially in Asia (106). Previous studies have shown that refractory *M. pneumoniae* pneumonia is associated with prolonged fever,

high levels of C-reactive protein, airway hypersecretion, and consolidation on chest imaging (107). It has been confirmed that the excessive immune response of the host plays an important role in the development of refractory *M. pneumoniae* pneumonia (108). In this context, corticosteroids have been suggested as an immunomodulator for downregulating the overactive host immune reaction. Previous research confirmed that coinfection with viruses and bacteria led to more severe disease in children with refractory *M. pneumoniae* pneumonia (109). In general, viral coinfection rates in children with *M. pneumoniae* pneumonia ranged from 10 to 30% (110). A recent study done in Shanghai showed 56% coinfection and infection by drug-resistant *M. pneumoniae*. The viral coinfection was more common in patients younger than 3 years old. Adenovirus coinfection and drug-resistant *M. pneumoniae* infection occurred significantly more commonly in patients with refractory *M. pneumoniae* pneumonia (111).

Macrolide-resistant *M. pneumoniae* infection may also play an important role in the occurrence and development of refractory *M. pneumoniae* pneumonia (112). Overuse of macrolides may contribute to macrolide resistance, and thereafter, an increase in macrolide-resistant *M. pneumoniae* pneumonia. Mutations at position 2063 or 2064 domain V in the 23S rRNA gene are related to macrolide resistance (113). Some Chinese series reported a rate of drug-resistant *M. pneumoniae* around 70 to 90%; however, macrolide resistance is less common in the US and European countries, where the macrolide-resistant *M. pneumoniae* prevalence is below 30% (114). Maybe that relatively high mutation rate in China is probably related to excessive exposure to macrolides for respiratory infections in outpatients, especially in children. A study from Japan reported that the macrolide-resistance rate decreased to 59.3% in 2014 and 43.6% in 2015 from the highest macrolide-resistance rate of 81.6% in 2012 (115), may be attributed to the decrease in the use of oral macrolides. In Japan, tosufloxacin was approved for pediatric used in macrolide-resistant M. pneumoniae (MRMP) pneumonia; however minocycline or doxycycline were significantly more effective in achieving defervescence within 24 h and in decreasing numbers of *M. pneumoniae* DNA copies 3 days after initiation (116).

Macrolide-resistant *M. pneumoniae* pneumonia shows persistent fever and/or no radiological regression to macrolide antibiotics and may even progress to severe and complicated pneumonia.

Treatment

In children with drug-resistant *M. pneumoniae* pneumonia, tetracyclines (doxycycline, minocycline) have shown excellent efficacy (117). Because of adverse reactions, tetracyclines are contraindicated in pregnant women and children under 8 years old. However, previous studies showed that short and limited courses of treatment (less than 6 courses, 6 days per course) caused insignificant tooth discoloration in children under 5 years old. Delayed effective antimicrobial treatment is associated with prolonged and/or more severe disease. Thus, the appropriate prescription of antibiotics, as well as the rapid and accurate diagnosis of *M. pneumonia*e pneumonia is important.

Gram-Negative Multiresistant Bacterias

In this article, we will review the main resistant gram negative pathogens causing pneumonia: *Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Stenotrophomonas maltophila*. All of them are responsible mainly for nosocomial pneumonia.

Acinetobacter Baumannii

Acinetobacter baumannii is a major cause of nosocomial pneumonia in certain geographic areas affecting mainly debilitated patients, with prolonged hospitalization and broad-spectrum antimicrobials treatments (118). *A. baumannii* is mainly transmitted via hands of healthcare workers or fomites (119). However, the airborne route also plays an important role in spreading *A. baumannii*. Inappropriate empirical treatment has clearly been associated with increased mortality in *A. baumannii* pneumonia. *A. baumannii* spreads rapidly and possesses an extraordinary capability to develop resistance to almost all antibiotics (120). *A. baumannii* has innate resistance mechanisms against multiple antimicrobials on its core genome. Moreover, this pathogen easily acquires new resistances by diverse mobile elements. These include enzymatic inactivation, alteration of bacterial targets, permeability barriers, or active efflux pumps. Carbapenems may not be considered the treatment of choice in areas with high rates of carbapenem-resistant *A. baumannii*. Nowadays, polymyxins are the antimicrobials with the greatest level of activity *in-vitro*. Colistin is the antimicrobial most widely used although polymyxin B is associated with less renal toxicity. However, lung concentrations of polymyxins are suboptimal in a substantial proportion of patients. Regarding nebulized antibiotics, it seems reasonable to use in patients who are non-responsive to systemic antibiotics or *A. baumannii* isolates with colistin minimum inhibitory concentrations close to the susceptibility breakpoints. Cefiderocol, a novel cephalosporin active against *A. baumannii,* may represent an attractive therapeutic option if ongoing clinical trials confirm preliminary results (118). However, well-designed, randomized controlled trials must be conducted to comprehensively evaluate the effectiveness and safety of nebulized antibiotics for the treatment of *A. baumannii* pneumonia.

Pseudomonas Aeruginosa

Nosocomial pneumonia due to *P. aeruginosa* is associated with considerable morbidity, prolonged hospitalization, increased costs, and mortality. *P. aeruginosa* is one of the few pathogens independently associated with increased mortality among patients with sepsis or pneumonia in the ICU setting (121). The mortality associated with *P. aeruginosa* pneumonia is further increased when inappropriate initial antibiotic therapy is prescribed, usually due to the presence of multidrug-resistant (MDR) pathogens. The overall impact of *P. aeruginosa* pneumonia on clinical outcomes and healthcare costs underscores the importance of this nosocomial infection. In recent study assessing the multinational burden and specific risk factors associated with *P. aeruginosa*-CAP, 3193 patients were enrolled in 54 countries with confirmed diagnosis of CAP who underwent microbiological testing at admission. The prevalence of *P. aeruginosa* and antibiotic-resistant *P.*

aeruginosa-CAP was 4.2 and 2.0%, respectively. The rate of *P. aeruginosa* CAP in patients with prior infection/colonization due to *P. aeruginosa* and at least one of the three independently associated chronic lung diseases (tracheostomy, bronchiectasis and/or very severe chronic obstructive pulmonary disease) was 67%. In contrast, the rate of *P. aeruginosa*-CAP was 2% in patients without prior *P. aeruginosa* infection/colonization and none of the selected chronic lung diseases. The multinational prevalence of *P. aeruginosa*-CAP was low (122). A recent retrospective cohort study in adults showed that almost 31% of patients with *P. aeruginosa* pneumonia were infected with MDR strains. In multivariable analyses, independent predictors of MDR *P. aeruginosa* included age, diabetes mellitus and ICU admission. MDR strains, heart failure, increasing age, mechanical ventilation, and bacteremia were independently associated with in-hospital mortality (123).

Among pediatric patients, this organism is prevalent in pediatric intensive care units (PICU), and its incidence as a nosocomial lung infection has doubled over the last three decades (124). *P. aeruginosa* is intrinsically resistant to several antimicrobial agents, and it can acquire resistance to many others. In recent years, the frequency of multidrug-resistant MDR strains of *P. aeruginosa* is increasing, especially in nosocomial infections and PICU-acquired infections (125), and these infections increase mortality, morbidity, and hospital costs. The mortality of children with *P. aeruginosa* infection ranges from 20 to 50% in Chinese reports (126) and 33 to 61% (127) in other populations.

Among the new antibiotics approved for *P. aeruginosa* are: ceftolozane/tazobactam for extended spectrum β-lactamases (ESBL) *P. aeruginosa* and meropenem/vaborbactam for AmpC β-lactamases *P. aeruginosa* (128).

Stenotrophomonas Maltophilia

Stenotrophomonas maltophilia is a commensal and an emerging pathogen earlier noted in broad-spectrum life-threatening infections among the vulnerable, but more recently as a pathogen in immunocompetent individuals (129). In addition, *S. maltophilia* has emerged as an important pathogen that induces nosocomial infections (130). *S. maltophilia* is a non-fermentative, gram-negative bacilli and causes severe infectious diseases, such as pneumonia, bacteremia, skin and soft-tissue infection, urinary tract infection, and meningitis (131). Recently, the frequency of infection reported worldwide is quite alarming. *S. maltophilia* accounts for about 3.7% ($n = 10{,}000$) in hospital discharges (132). A recovery rate of 3.3% in *S. maltophilia* infections was reported in the US (124). The mortality rate due to *S. maltophilia* infection was 36.6% found in a large study (133) and 25–51% in a multi-center study (134). Pathogenesis is by colonization, rather than infection, which is often accompanied by tissue invasion (135). The most important risk factors for *S. maltophilia* infection in neonates and infants are invasive procedures; previous exposure to antibiotics, such as carbapenem and aminoglycoside; and prolonged hospitalization (136). The duration of hospitalization before the onset of the *Stenotrophomonas* clinical symptoms is an important factor in nosocomial infection. The duration of hospitalization before the onset of *S. maltophilia* bacteremia ranges from 11.5 to 24 days (137, 138). Neonate and infants have low immunity, and often have severe and uncontrollable symptoms after infection. *S. maltophilia* is intrinsically resistant to many antibiotics, including carbapenems and aminoglycosides which are used empirically for nosocomial infection (130). Therefore, early identification and appropriate treatment are important.

Treatment

S.maltophilia is intrinsically resistant to Beta-lactams (penicillins, cepahosporins, aztreonam, and carbapenems) due to chromosomal metallo-beta lactamase and extended-spectrum beta lactamases (ESBLs) production.

Treatment of choice includes trimethoprim-sulfamethoxazole, levofloxacin, minocycline and ceftazidime. Therapy should be guided by *in vitro* susceptibility results.

Other Re-emerging Bacteria

Streptococcus Pneumoniae

WHO reported that pneumonia accounts for 16% of all deaths of children under 5 years old, killing around 1 million children in 2015, with the most common cause of bacterial pneumonia being *S. pneumoniae* (139). *S. pneumoniae* was estimated to be responsible for 341,029 deaths of children younger than 5 years in 195 countries in 2016 (140). Serotype 1 has been predominantly responsible for empyema in a study from UK, although, there is no information about the most frequent serotypes found in pneumonia in this country (141). In a recent review of 197 bacterial and fungal pathogens detected in single case reports and case series, *S. pneumoniae* accounts for 116 (59%) of necrotizing pneumonia (142).

Pneumococci possess multiple virulence factors (143), including its polysaccharide capsule, cell surface proteins, the cell wall, and pneumolysin, a pore-forming toxin (144). Of these, the most important is the polysaccharide capsule, of which there are at least 98 different serotypes, each capable of shielding the organism from the immune system (145). Individual serotypes vary in their capacity to colonize, cause local or invasive disease, and express antibiotic resistance genes (143). Serotypes also vary geographically and change over time, perhaps in response to local ecological competitive pressures from other organisms cohabiting the nasopharyngeal space, as well as selection pressures from antibiotics and PCVs (146).

Vaccines and antibiotics are considered the most effective methods against *S. pneumoniae*. Pneumococcal immunization was powered by WHO to prevent *S. pneumoniae* infections. A reduction in CAP in more than 40% after introduction of pneumococcal conjugate vaccine (PCV7) has been reported (147). Recent data on serotypes identified in bacteremia pneumonia in children from Italy since the introduction of PCV7, found serotypes 1 and 19A to be the most common (148). In children under 2 years, all trials have consistently shown a decrease in radiologically-confirmed pneumonia from 23% in the Philippines using PCV11 (149), to 37% in the Gambia with PCV9 (150), and 23.4% in California with PCV7 (151). This effect is most striking in the first year in these three studies. A Cochrane systematic review found a pooled vaccine efficacy for PCV11 of

27% for reduction of radiographically-confirmed pneumonia in children <2 years and 6% for clinical pneumonia (152).

Before the implementation of PCVs, a few pneumococcal serotypes (mainly serotypes 1, 3, 5, 7F, 14, and 19A) were implicated in proven pneumococcal pneumonia and empyema in children (153). The implementation of PCV7 led to a transient reduction in the frequency of CAP (154), rapidly followed by an increase in CAP with pleural effusion and empyema (155), mainly due to serotypes 1 and 7F, and an increase in frequency of serotype 19A, all non-PC7 serotypes. When PCV13, which included these additional serotypes, replaced PCV7, the frequency of both CAP and empyema greatly decreased worldwide (156).

Serotypes 3 and 19A were most closely associated with pneumococcal necrotizing pneumonia. Serotype 3 has a very thick capsule, which strongly resists opsono-phagocytosis and induces a marked inflammatory response, including an intense neutrophilic infiltration with suppurative necrosis (157). In contrast, serotype 19A strains have greater invasive potential, may have a growth advantage over other pneumococcal serotypes in normally sterile sites, and are often resistant to multiple antibiotics (158).

However, with a recent increase in its frequency due to highly invasive non-PCV13 serotypes in Europe, and in pneumococcal meningitis in France, the serotype replacement has raised concerns about the long-term outcome of PCV13 use beyond 5 years after its implementation (156).

OLD KNOWN WITH NEW PRESENTATIONS

Rhinovirus

Rhinovirus infections are seen worldwide and during all year, with a peak in spring (159). There are 3 species and more than 100 serotypes, so even if the immune response is cross reactive, reinfection is frequent (159). Classically rhinovirus infects the upper respiratory epithelium manifesting as a common cold. Otitis media and rhinosinusitis can also be seen in rhinovirus infection and can be complicated with bacterial coinfection. But, with the development of molecular techniques, it was demonstrated that asymptomatic infection could happen (160). Asymptomatic infection seems to be more frequent in younger children.

Clinical Manifestation

Rhinovirus infection can also compromise lower respiratory tract, as bronchiolitis in younger children. Exacerbation of obstructive symptoms can be observed in asthmatic subjects with rhinovirus infection. However, other factors are involved in the development of wheezing in these children, as the inflammatory response, the virus serotypes, among others (161). Otherwise, community acquired pneumonia are also described in rhinoviral infection. A recent Brazilian study demonstrated that in children hospitalized with radiographically diagnosed pneumonia, 43% presented at least one virus and among them rhinovirus was the most frequently detected (162). Importantly, rhinovirus was associated with mild pneumonia, contrarily to respiratory syncytial virus or influenza infection that were associated with more severe cases. It is not uncommon to find concomitantly a second virus with rhinovirus detection, raising the problem of the role that each virus has in the disease (160).

In the last years, with the increased number of immunocompromised patients and the development of neonatology, rhinovirus has acquired a new pathogenic role producing severe pneumonia and even death in some high-risk patients. Patients with cancer or undergoing hematopoietic stem cell transplant receiving corticosteroids or immunosuppressive drugs are at a high risk of developing severe viral pneumonia with prolonged viral shedding (163). These immunosuppressed patients with rhinovirus infection present variable symptoms and severity, but the disease is associated with high morbidity, reaching a mortality rate close to 10% (164). Another group at high risk of severe pneumonia are preterm infants. Two series of preterm infants with rhinovirus infection showed that the majority had respiratory signs such as cough, apnea, or even respiratory distress, requiring respiratory assistance (165, 166).

Special attention is necessary in hospital settings, as nosocomial outbreaks are described and are associated with increased morbidity in high-risk patients (165, 167).

Treatment

Management of rhinovirus pneumonia is supportive. The use of pegylated interferon-α2A and ribavirin to control viral replication is described only in case report, without systematic studies (168). Prevention of this infection in high-risk patients is crucial to avoid morbidity and mortality in these particular populations.

Coronavirus

Four species of coronavirus exist, but human coronavirus belong only to two of them (alphacoronavirus as HCoV-229E and HCoV-NL63 and betacoronavirus as HCoV-OC43, HCoV-HKU1, SARS-CoV-1, MERS-CoV, and SARS-CoV-2) (160). Even though coronavirus circulates globally and throughout the year, some of them are more detected in winter as HCoV-229E, meanwhile others, such as HCoV-NL63, are transmitted more in early summer (169). As influenza viruses, they have human and animal reservoirs. When animal coronavirus is transmitted to humans, an epidemic or pandemic of a new coronavirus can develop with the potential to produce a severe acute respiratory syndrome, as in the novel SARS-CoV-2 (169).

Clinical Manifestation

As rhinovirus, "non-SARS" coronaviruses cause common cold and upper respiratory infection. However, lower tract infection has also been related with coronavirus infection. In Thailand, a study detected up to 5.9% of coronavirus infection (229E, OC43, N63, and HKU1) in healthy children hospitalized with community-acquired viral pneumonia (170). Interestingly, in 2.1% of asymptomatic children was also identified coronavirus infection. Similar results were observed in a recent study, identifying coronavirus infection in 9% of children hospitalized with respiratory tract infection (73% of which were lower tract infection) and 10% of asymptomatic controls (171). But higher viral load obtained in symptomatic children supports the

role of coronavirus in these respiratory tract infections. Mean hospitalization rate of children younger than 1 year old with low respiratory tract infection and coronavirus detection was 2.8 per 1000 children. Frequently, co-viral detection was identified.

More severe diseases are observed in immunocompromised individuals. A recent study found 2 main risk factors associated with severe low respiratory tract infection: immunocompromised status and viral coinfection (172). Neonatal coronavirus infection has also been associated with increased morbidity, presenting bradycardia and oxygen supplementation (173). These results were observed in a context of nosocomial outbreak, highlighting the importance of prevention and identification of patients at high-risk to develop severe pneumonia.

Treatment

Until now, there is no specific antiviral treatment, only supportive care.

CONCLUSION

Several emerging pathogens have been described in recent years, with SARS-CoV-2 being responsible for the latest pandemic COVID19. Children are affected just like adults, although the frequency, severity and mortality differ from them in many cases, depending on the causal agent.

Vaccination has been an important ally in reducing the risk of re-emergence pathogens such as measles and pneumococcal infections, however low vaccination coverage and the emergence of serotypes not included in vaccines have favored their re-emergence, with children being the most affected age group.

The antimicrobial resistance, mainly due to unregulated or indiscriminate use of antimicrobials, has led to the emergence of pathogens, mainly in hospital settings, capable of causing pneumonia in children with greater severity due to the delayed onset of effective therapy against these pathogens.

Finally, pathogens that have emerged *de novo* affect children apparently in a lower proportion and less severity than in adults, especially those over 60 years old, who are the most seriously compromised. Avian influenza H5N1 and ANDV in the hantavirus group, are however the exception which cause severe infections with high mortality over 20% in children.

Proper use of antimicrobials and childhood vaccination are and will continue to be highly effective strategies in reducing the risk of pneumonia-causing pathogens in children. Similarly, the rapid international response in identifying emerging infections, the ability to diagnose, sequence and characterize these new pathogens with potential pandemic have been able to contain outbreaks in most of them, even though for COVID19 containment hope is placed on vaccines developed in an incredible short period of time to achieve pandemic control.

Being aware to suspect any of the pathogens discussed here in children, depending on their epidemiological conditions and clinical characteristics, will allow a rapid diagnosis and timely treatment, essential conditions to reduce the risk of complications and mortality from these emerging pathogens.

AUTHOR CONTRIBUTIONS

JC-R conceptualized and designed the study. CP and NL collaborated with the study design. CP wrote the first draft. All authors wrote several sections of the paper. All authors read and approved the final manuscript.

REFERENCES

1. Budnik I, Ferrés M, Pardo T, Edwards J, Labarca G, Reyes F, et al. Contribution of molecular biology in the diagnosis of acute respiratory infections. *Rev Chil Enferm Respir.* (2016) 32:224–3. doi: 10.4067/S0717-73482016000400003
2. Chen Z, Boon SS, Wang MH, Chan RWY, Chan PKS. Genomic and evolutionary comparison between SARS-CoV-2 and other human coronaviruses. *J Virol Methods.* (2020) 289:114032. doi: 10.1016/j.jviromet.2020.114032
3. Peiris JS, Lai ST, Poon LL, Guan Y, Yam LY, Lim W, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet.* (2003) 361:1319–25. doi: 10.1016/S0140-6736(03)13077-2
4. Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med.* (2003) 348:1953–66. doi: 10.1056/NEJMoa030781
5. Leung TF, Wong GWK, Hon KLE, Fok TF. Severe acute respiratory syndrome (SARS) in children: epidemiology, presentation and management. *Paediatr Respir Rev.* (2003) 4:334–9. doi: 10.1016/S1526-0542(03)00088-5
6. Zhong NS, Wong GW. Epidemiology of severe acute respiratory syndrome (SARS): adults and children. *Paediatr Respir Rev.* (2004) 5:270–4. doi: 10.1016/j.prrv.2004.07.011
7. Hon KLE, Leung CW, Cheng WTF, Chan PKS, Chu WCW, Kwan YW, et al. Clinical presentations and outcome of severe acute respiratory syndrome in children. *Lancet.* (2003) 361:1701–3. doi: 10.1016/S0140-6736(03)13364-8
8. Leung CW, Kwan YW, Ko PW, Chiu SS, Loung PY, Fong NC, et al. Severe acute respiratory syndrome among children. *Pediatrics.* (2004) 113:e535–43. doi: 10.1542/peds.113.6.e535
9. Li AM, So HK, Chu W, Ng PC, Hon KL, Chiu WK, et al. Radiological and pulmonary function outcomes of children with SARS. *Pediatric Pulmonol.* (2004) 38:427–33. doi: 10.1002/ppul.20078
10. Babyn PS, Chu WC, Tsou IY, Wansaicheong GK, Allen U, Bitnun A, et al. Severe acute respiratory syndrome (SARS): chest radiographic features in children. *Radiol Pediatrician.* (2004) 34:47–58. doi: 10.1007/s00247-003-1081-8
11. WHO reports. *MERS Situation Update*. (2019). Available online at: https://applications.emro.who.int/docs/EMCSR254E.pdf?ua=1 (accessed December 20, 2020).
12. MacIntyre CR, Chen X, Adam DC, Chughtai AA. Epidemiology of paediatric Middle East respiratory syndrome coronavirus and implications for the control of coronavirus virus disease 2019. *J Paediatr Child Health.* (2020) 56:1561–4. doi: 10.1111/jpc.15014
13. Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. *Lancet.* (2015) 386:995–1007. doi: 10.1016/S0140-6736(15)60454-8
14. Memish ZA, Al-Tawfiq JA, Assiri A, AlRabiah FA, Al Hajjar S, Albarrak A, et al. Middle East respiratory syndrome coronavirus disease in children. *Pediatric Infect Dis J.* (2014) 33:904–6. doi: 10.1097/INF.0000000000000325
15. Thabet F, Chehab M, Bafaqih H, Al Mohaimeed S. Middle East respiratory syndrome coronavirus in children. *Saudi Med J.* (2015) 36:484–6. doi: 10.15537/smj.2015.4.10243

16. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med.* (2018) 197:757–67. doi: 10.1164/rccm.201706-1172OC
17. WHO. *COVID-19 Weekly Epidemiological Update*. Available online at: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---8-june-2021
18. CDC COVID-19 Response Team. Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020. *MMWR Morb Mortal Wkly Rep*. (2020) 69:422–6. doi: 10.15585/mmwr.mm6914e4
19. Boban M. Novel coronavirus disease (COVID-19) update on epidemiology, pathogenicity, clinical course and treatments. *Int J Clin Pract*. (2020) 75:e13868. doi: 10.1111/ijcp.13868
20. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. (2020) 323:2052–9. doi: 10.1001/jama.2020.6775
21. Jahangir M, Nawaz M, Nanjiani D, Siddiqui MS. Clinical manifestations and outcomes of COVID-19 in the paediatric population: a systematic review. *Hong Kong Med J.* (2021) 27:35-45. doi: 10.12809/hkmj208646
22. Liguoro I, Pilotto C, Bonanni M, Ferrari ME, Pusiol A, Nocerino A, et al. SARS-COV-2 infection in children and newborns: a systematic review. *Eur J Pediatr.* (2020) 179:1029–46. doi: 10.1007/s00431-020-03684-7
23. Tiruneh FT. Clinical profile of Covid-19 in children, review of existing literatures. *Pediatric Health Med Ther.* (2020) 11:385–92. doi: 10.2147/PHMT.S266063
24. Simoni P, Bazzocchi A, Boitsios G, De Leucio A, Preziosi M, Aparisi Gómez MP. Chest computed tomography (CT) features in children with reverse transcription-polymerase chain reaction (RT-PCR)-confirmed COVID-19: a systematic review. *J Med Imaging Radiat Oncol.* (2020) 64:649–59. doi: 10.1111/1754-9485.13098
25. Katal S, Johnston SK, Johnston JH, Gholamrezanezhad A. Imaging findings of SARS-CoV-2 infection in pediatrics: a systematic review of coronavirus disease 2019 (COVID-19) in 850 patients. *Acad Radiol*. (2020). 27:1608–21. doi: 10.1016/j.acra.2020.07.031
26. Torres JP, Izquierdo G, Acuña M, Pavez D, Reyes F, Fritis A, et al. Multisystem inflammatory syndrome in children (MIS-C): report of the clinical and epidemiological characteristics of cases in Santiago de Chile during the SARS-CoV-2 pandemic. *Int J Infect Dis.* (2020) 100:75–81. doi: 10.1016/j.ijid.2020.08.062
27. Fang F, Chen Y, Zhao D, Liu T, Huang Y, Qiu L, et al. Chinese pediatric society and the editorial committee of the Chinese journal of pediatrics. Recommendations for the diagnosis, prevention, and control of coronavirus disease-19 in children-the Chinese perspectives. *Front. Pediatrician.* (2020) 8:553394. doi: 10.3389/fped.2020.553394
28. Venturini E, Montagnani C, Garazzino S, Dono D, Pierantoni L, Lo Vecchio A, et al. Treatment of children with COVID-19: position paper of the Italian Society of Pediatric Infectious Disease. *Ital J Pediatrician.* (2020) 46:139. doi: 10.1186/s13052-020-00900-w
29. WHO. *Influenza at the Human-Animal Interface Summary and Assessment, From 24 October to 9 December*. (2020). Available online at: *https://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_09_12_2020.pdf?ua=1* L(accessed December 27, 2020).
30. WHO. *Cumulative Number of Confirmed Human Cases for A(H5N1) Reported to WHO, 2003-2020*. Available online at: https://www.who.int/influenza/human_animal_interface/2020_DEC_tableH5N1.pdf?ua=1. (accessed December 24, 2020).
31. WHO. *Influenza at the Human-Animal Interface Summary and assessment, 13 February to 9 April (2019)*. Available online at: *https://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_09_04_2019.pdf?ua=1* (accessed December 24, 2020).
32. Zhou J, Wang D, Gao R, Zhao B, Song J, Qi X, et al. Biological features of novel avian influenza A (H7N9) virus. *Nature.* (2013) 499:500–3. doi: 10.1038/nature12379
33. Qin Y, Horby PW, Tsang TK, Chen E, Gao L, Ou J, et al. Differences in the epidemiology of human cases of avian influenza A(H7N9) and A(H5N1) viruses infection. *Clin Infect Dis.* (2015) 61:563–71. doi: 10.1093/cid/civ345
34. Sha J, Dong W, Liu S, Chen X, Zhao N, Luo M, et al. Differences in the epidemiology of childhood infections with avian influenza A H7N9 and H5N1 viruses. *PLoS ONE.* (2016) 11:e0161925. doi: 10.1371/journal.pone.0161925
35. Oner AF, Dogan N, Gasimov V, Adisasmito W, Coker R, Chan PK, et al. H5N1 avian influenza in children. *Clin Infect Dis.* (2012) 55:26–32. doi: 10.1093/cid/cis295
36. Bay A, Etlik O, Oner AF, Unal O, Arslan H, Bora A, et al. Radiological and clinical course of pneumonia in patients with avian influenza H5N1. *Eur J Radiol.* (2007) 61:245–50. doi: 10.1016/j.ejrad.2006.10.006
37. Gao HN, Lu HZ, Cao B, Du B, Shang H, Gan JH, et al. Clinical findings in 111 cases of influenza A (H7N9) virus infection. *N Engl J Med.* (2013) 368:2277–85. doi: 10.1056/NEJMoa1305584
38. Dai J, Zhou X, Dong D, Liu Y, Gu Q, Zhu B, et al. Human infection with a novel avian-origin influenza A (H7N9) virus: serial chest radiographic and CT findings. *Chin Med J.* (2014) 127:2206–11.
39. Sivanandy P, Zi Xien F, Woon Kit L, Tze Wei Y, Hui En K, Chia Lynn L. A review on current trends in the treatment of human infection with H7N9-avian influenza A. *J Infect Public Health.* (2019) 12:153–8. doi: 10.1016/j.jiph.2018.08.005
40. Marjuki H, Mishin VP, Chesnokov AP, De La Cruz JA, Davis CT, Villanueva JM, et al. Neuraminidase mutations conferring resistance to oseltamivir in influenza A(H7N9) viruses. *J Virol.* (2015) 89:5419–26. doi: 10.1128/JVI.03513-14
41. Belardo G, Cenciarelli O, La Frazia S, Rossignol JF, Santoro MG. Synergistic effect of nitazoxanide with neuraminidase inhibitors against influenza A viruses in vitro. *Antimicrob Agents Chemother.* (2015) 59:1061–9. doi: 10.1128/AAC.03947-14
42. Haffizulla J, Hartman A, Hoppers M, Resnick H, Samudrala S, Ginocchio C, et al. A randomized, double-blind, placebo controlled clinical trial of nitazoxanide in adults and adolescents with acute uncomplicated influenza. *Lancet Infect Dis*. (2014)14:609–18. doi: 10.1016/S1473-3099(14)70717-0
43. Cao B, Gao H, Zhou B, Deng X, Hu C, Deng C, et al. Adjuvant corticosteroid treatment in adults with influenza A (H7N9) viral pneumonia. *Crit Care Med.* (2016) 44:e318–28. doi: 10.1097/CCM.0000000000001616
44. Ferrés M, Vial P, Marco C, Yañez L, Godoy P, Castillo C, et al. Prospective evaluation of household contacts of persons with hantavirus cardiopulmonary syndrome in Chile. *J Infect Dis.* (2007) 195:1563–71. doi: 10.1086/516786
45. Padula P, Edelstein A, Miguel S, López N, Rossi C, Rabinovich R. Hantavirus pulmonary syndrome outbreak in Argentina: molecular evidence for person-to-person transmission of Andes virus. *Virology.* (1998) 241:323–30. doi: 10.1006/viro.1997.8976
46. Martinez-Valdebenito C, Calvo M, Vial C, Mansilla R, Marco C, Palma RE, et al. Person-to-person household and nosocomial transmission of Andes Hantavirus, Southern Chile, 2011. *Emerg Infect Dis.* (2014) 20:1637–44. doi: 10.3201/eid2010.140353
47. Ferrés M, Martínez-Valdebenito C, Angulo J, Henríquez C, Vera-Otárola J, Vergara MJ, et al. Mother-to-child transmission of andes virus through breast milk, Chile. *Emerg Infect Dis.* (2020) 26:1885–8. doi: 10.3201/eid2608.200204
48. Manigold T, Vial P. Human hantavirus infections: epidemiology, clinical features, pathogenesis and immunology. *Swiss Med Wkly.* (2014) 144:w13937. doi: 10.4414/smw.2014.13937
49. Reyes F, Ferrés M. Hantavirus: descripción de dos décadas de endemia y su letalidad. *ARS MEDICA Rev Cienc Méd.* (2018) 43:30–8. doi: 10.11565/arsmed.v44i1.1522
50. Departamento de Epidemiología, Ministerio de Salud de Chile. *Boletín Epidemiológico Trimestral HANTAVIRUS. SE 1 – 52, AÑO*. (2019). Available online at: *http://epi.minsal.cl/wp-content/uploads/2020/02/BET_HANTAVIRUS_2019.pdf* (accessed December 29, 2020). doi: 10.33610/23576189.2021.53
51. Terças-Trettel ACP, Melo AVG, Bonilha SMF, Moraes JM, Oliveira RC, Guterres A, et al. Hantavirus pulmonary syndrome in children: case report and case series from an endemic area of Brazil. *Rev Inst Med Trop Sáo Paulo.* (2019) 61:e65. doi: 10.1590/s1678-9946201961065
52. Kumara A, Krishnamurthya K, Nielsen A. Hantavirus infection among children hospitalized for febrile illness suspected to be dengue in Barbados. *J Infect Public Health.* (2016) 9:81–7. doi: 10.1016/j.jiph.2015.06.004

53. Vial PA, Valdivieso F, Calvo M, Rioseco ML, Riquelme R, Araneda A, et al. A non-randomized multicentre trial of human immune plasma for treatment of hantavirus cardiopulmonary syndrome caused by Andes virus. *Antivir Ther.* (2015) 20:377–86. doi: 10.3851/IMP2875
54. Guerra FM, Bolotin S, Lim G, Heffernan J, Deeks SL, Li Y, et al. The basic reproduction number (R_0) of measles: a systematic review. *Lancet Infect Dis.* (2017) 17:e420–8. doi: 10.1016/S1473-3099(17)30307-9
55. Rota PA, Moss WJ, Takeda M, de Swart RL, Thompson KM, Goodson JL. Measles. *Nat Rev Dis Primers.* (2016) 14:16049. doi: 10.1038/nrdp.2016.49
56. World Health Organization. *New Measles Surveillance Data From WHO*. Geneva (2019). Available online at: *https://www.who.int/immunization/newsroom/new-measles-data-august-2019/en/*
57. O'Connor P, Jankovic D, Muscat M, Ben-Mamou M, Reef S, Papania M, et al. Measles and rubella elimination in the WHO Region for Europe: progress and challenges. *Clin Microbiol Infect.* (2017) 23:504–10. doi: 10.1016/j.cmi.2017.01.003
58. Phadke VK, Bednarczyk RA, Omer SB. Vaccine refusal and measles outbreaks in the US. *JAMA*. (2020) 324:1344–5. doi: 10.1001/jama.2020.14828
59. Lemos DR, Franco AR, de Sá Roriz ML, Carneiro AK, de Oliveira Garcia MH, de Souza FL, et al. Measles epidemic in Brazil in the post-elimination period: coordinated response and containment strategies. *Vaccine.* (2017) 35:1721–8. doi: 10.1016/j.vaccine.2017.02.023
60. Patel MK, Dumolard L, Nedelec Y, Sodha SV, Steulet C, Gacic-Dobo M, et al. Progress toward regional measles elimination — Worldwide, 2000–2018. *MMWR Morb Mortal Wkly. Rep.* (2019) 68:1105–11. doi: 10.15585/mmwr.mm6848a1
61. Misin A, Antonello RM, Di Bella S, Campisciano G, Zanotta N, Giacobbe DR, et al. An overview of a re-emerging disease in children and immunocompromised patients. *Microorganisms.* (2020) 8:276. doi: 10.3390/microorganisms8020276
62. Hester G, Nickel A, LeBlanc J, Carlson R, Spaulding AB, Kalaskar A, et al. Measles hospitalizations at a United States Children's Hospital 2011-2017. *Pediatr Infect Dis J.* (2019) 38:547–52. doi: 10.1097/INF.0000000000002221
63. Haile T, Thach HN, Tuan TA, Nam DH, Dien TM, Sato Y, et al. Adenovirus type 7 pneumonia in children who died from measles-associated pneumonia, Hanoi, Vietnam, 2014. *Emerg Infect Dis.* (2016) 22:687–90. doi: 10.3201/eid2204.151595
64. Lombardo D, Ciampi G, Spicuzza L. Severe and fatal measles-associated pneumonia during an outbreak in Italy: data from the heart of the epidemic. *Adv Respir Med.* (2020) 88:197–203. doi: 10.5603/ARM.2020.0118
65. Kabra SK, Lodha R. Antibiotics for preventing complications in children with measles. *Cochrane Database Syst Rev.* (2013) 2013:CD001477. doi: 10.1002/14651858.CD001477.pub4
66. World Health Organization [Internet]. *Measles Media Factsheet*. Available online at: *http://www.who.int/mediacentre/factsheets/fs286/en/*
67. Huiming Y, Chaomin W, Meng M. Vitamin A for treating measles in children. *Cochrane Database Syst Rev.* (2005) 2005:CD001479. doi: 10.1002/14651858.CD001479.pub2
68. Awotiwon AA, Oduwole O, Sinha A, Okwundu CI. Zinc supplementation for the treatment of measles in children. *Cochrane Database Syst Rev.* (2017) 6:CD011177. doi: 10.1002/14651858.CD011177.pub3
69. Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, et al. Tuberculosis. *Nat Rev Dis Primers.* (2016) 2:16076. doi: 10.1038/nrdp.2016.76
70. *Global Tuberculosis Report 2020*. Geneva: World Health Organization. Licence: CC BY-NC-SA 3.0 IGO (2020).
71. GBD Tuberculosis Collaborators. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. *Lancet Infect Dis.* (2018). 18:261–84. doi: 10.1016/S1473-3099(17)30703-X
72. Ford N, Shubber Z, Meintjes G, Grinsztejn B, Eholie S, Mills EJ, et al. Causes of hospital admission among people living with HIV worldwide: a systematic review and meta-analysis. *Lancet HIV*. (2015) 2:e438–44. doi: 10.1016/S2352-3018(15)00137-X
73. De Lorenzo S, Tiberi S. Tuberculosis a re-emerging disease. *Intern Emerg Med.* (2012) 7(Suppl. 3):S185–7. doi: 10.1007/s11739-012-0822-9
74. Seddon JA, Johnson S, Palmer M, van der Zalm MM, Lopez-Varela E, Hughes J, et al. Multidrug-resistant tuberculosis in children and adolescents: current strategies for prevention and treatment. *Expert Rev Respir Med.* (2021) 15:221–37. doi: 10.1080/17476348.2021.1828069
75. Noguera-Julian A, Calzada-HernÁndez J, Brinkmann F, Basu Roy R, Bilogortseva O, Buettcher M, et al. Tuberculosis disease in children and adolescents on therapy with anti-tumor necrosis factor-alpha agents: a collaborative, multi-centre ptbnet study. *Clin Infect Dis.* (2020) 71:2561–9. doi: 10.1093/cid/ciz1138
76. Perez-Velez CM, Marais BJ. Tuberculosis in children. *N Engl J Med.* (2012) 367:348–61. doi: 10.1056/NEJMra1008049
77. Thomas TA. Tuberculosis in Children. *Pediatr Clin North Am.* (2017) 64:893–909. doi: 10.1016/j.pcl.2017.03.010
78. Pillay T, Andronikou S, Zar HJ. Chest imaging in paediatric pulmonary TB. *Paediatr Respir Rev.* (2020) 36:65–72. doi: 10.1016/j.prrv.2020.10.002
79. Kunkel A, Abel Zur Wiesch P, Nathavitharana RR, Marx FM, Jenkins HE, Cohen T. Smear positivity in paediatric and adult tuberculosis: systematic review and meta-analysis. *BMC Infect Dis.* (2016) 16:282. doi: 10.1186/s12879-016-1617-9
80. Detjen AK, DiNardo AR, Leyden J, Steingart KR, Menzies D, Schiller I, et al. Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: a systematic review and meta-analysis. *Lancet Respir Med.* (2015) 3:451–61. doi: 10.1016/S2213-2600(15)00095-8
81. Kay AW, Islam SM, Wendorf K, Westenhouse J, Barry PM. Interferon-γ release assay performance for tuberculosis in childhood. *Pediatrics.* (2018) 141:e20173918. doi: 10.1542/peds.2017-3918
82. *Guidelines for Treatment of Drug-Susceptible Tuberculosis and Patient Care, 2017 Update*. Geneva: World Health Organization. Licence: CC BY-NC-SA 3.0 IGO (2017).
83. Dayan GH, Mohamed N, Scully IL, Cooper D, Begier E, Eiden J, et al. *Staphylococcus aureus*: the current state of disease, pathophysiology and strategies for prevention. *Expert Rev Vaccines*. (2016). 11:1373–92. doi: 10.1080/14760584.2016.1179583
84. Gillet Y, Issartel B, Vanhems P, Fournet J-C, Lina G, Bes M, et al. Association between *Staphylococcus aureus* strains carrying gene for Panton-valentine leucocidin and highly lethal necrotising pneumonia in young immunocompetent patients. *Lancet*. (2002). 359:753–9. doi: 10.1016/S0140-6736(02)07877-7
85. Chen J, Luo Y, Zhang S, Liang Z, Wang Y, Zhang T, et al. Community acquired necrotizing pneumonia caused by methicillin-resistant *Staphylococcus aureus* producing Panton-valentine leucocidin in a Chinese teenager: case report and literature review. *Int J Infect Dis.* (2014) 26:17–21. doi: 10.1016/j.ijid.2014.02.025
86. Schwartz KL, Nourse C. Panton-valentine leucocidin-associated *Staphylococcus aureus* necrotizing pneumonia in infants: a report of four cases and review of the literature. *Eur J Pediatr.* (2012) 171:711–7. doi: 10.1007/s00431-011-1651-y
87. Löffler B, Niemann S, Ehrhardt C, Horn D, Lanckohr C, Lina G, et al. Pathogenesis of *Staphylococcus aureus* necrotizing pneumonia: the role of PVL and an influenza coinfection. *Expert Rev Anti Infect Ther.* (2013) 11:1041–51. doi: 10.1586/14787210.2013.827891
88. Gillet Y, Vanhems P, Lina G, Bes M, Vandenesch F, Floret D, et al. Factors predicting mortality in necrotizing community-acquired pneumonia caused by *Staphylococcus aureus* containing Panton-valentine leucocidin. *Clin Infect Dis*. (2007). 45:315–21. doi: 10.1086/519263
89. Loffler B, Hussain M, Grundmeler M, Brück M, Holzinger D, Varga G, et al. *Staphylococcus aureus* Panton-Valentine leukocidin is a very potent cytotoxic factor for human neutrophils. *PLoS Pathog.* (2010) 6:e1000715. doi: 10.1371/journal.ppat.1000715
90. Shallcross LJ, Fragaszy E, Johnson AM, Hayward AC. The role of the Panton-valentine leucocidin toxin in staphylococcal disease: a systematic review and meta-analysis. *Lancet Infect Dis*. (2013). 13:43–54. doi: 10.1016/S1473-3099(12)70238-4
91. Geng W, Yang Y, Wu D, Zhang W, Wang C, Shang Y, et al. Community acquired, methicillin-resistant *Staphylococcus aureus* isolated from children with community-onset pneumonia in China. *Pediatr Pulmonol.* (2010). 45:387–94. doi: 10.1002/ppul.21202

92. Chua K, Laurent F, Coombs G, Grayson ML, Howden BP. Not community associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) A clinician's guide to community MRSA – its evolving antimicrobial resistance and implications for therapy. *Clin Infect Dis*. (2011). 52:99–114. doi: 10.1093/cid/ciq067
93. Sicot N, Khanafer N, Meyssonnier V, Dumitrescu O, Tristan A, Bes M, et al. Methicillin resistance is not a predictor of severity in community-acquired *Staphylococcus aureus* necrotizing pneumonia – results of a prospective observational study. *Clin Microbiol Infect*. (2013). 19:E142–8. doi: 10.1111/1469-0691.12022
94. Tong SYC, Davis JS, Eichenberger E, Holland TL, Fowler VG. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. *Clin Microbiol Rev*. (2015). 28:603–61. doi: 10.1128/CMR.00134-14
95. Yang HL, Tambyah PA. Fatal bacteraemic pneumonia due to community-acquired methicillin-resistant *Staphylococcus aureus*. *Singapore Med J*. (2006) 47:1010–1.
96. Nimmo GR, Coombs GW. Community-associated methicillin resistant *Staphylococcus aureus* (MRSA) in Australia. *Int J Antimicrob Agents*. (2008) 31:401–10. doi: 10.1016/j.ijantimicag.2007.08.011
97. Udo EE, Pearman JW, Grubb WB. Genetic analysis of community isolates of methicillin-resistant *Staphylococcus aureus* in Western Australia. *J Hosp Infect*. (1993) 25:97–108. doi: 10.1016/0195-6701(93)90100-E
98. Coombs GW, Nimmo GR, Pearson JC, Christiansen KJ, Bell JM, Collignon PJ, et al. Prevalence of MRSA strains among *Staphylococcus aureus* isolated from outpatients, 2006. *Commun Dis Intell Q Rep*. (2009) 33:10–20.
99. Rubinstein E, Kollef MH, Nathwani D. Pneumonia caused by methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis*. (2008) 46:S378–85. doi: 10.1086/533594
100. Francis JS, Doherty MC, Lopatin U, Johnston CP, Sinha G, Ross T, et al. Severe community on set pneumonia in healthy adults caused by methicillin resistant *Staphylococcus aureus* carrying the panton-valentine leukocidin genes. *Clin Infect Dis*. (2005) 40:100–7. doi: 10.1086/427148
101. Foster TJ, Höök M. Surface protein adhesins of *Staphylococcus aureus*. *Trends Microbiol*. (1998) 6:484–8. doi: 10.1016/S0966-842X(98)01400-0
102. Foster TJ. Immune evasion by staphylococci. *Nat Rev Microbiol*. (2005) 3:948–58. doi: 10.1038/nrmicro1289
103. Hoppe PA, Holzhauer S, Lala B, Bührer C, Gratopp A, Hanitsch LG, et al. Severe infections of Panton-Valentine leukocidin positive *Staphylococcus aureus* in children. *Medicine*. (2019) 98:e17185. doi: 10.1097/MD.0000000000017185
104. Khan A, Wilson B, Gould IM. Current and future treatment options for community-associated MRSA infection. *Expert Opin Pharmacother*. (2018) 19:457–70. doi: 10.1080/14656566.2018.1442826
105. Michelow IC, Olsen K, Lozano J, Rollins NK, Duffy LB, Ziegler T, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. *Pediatrics*. (2004) 113:701–7. doi: 10.1542/peds.113.4.701
106. Sztrymf B, Jacobs F, Fichet J, Hamzaoui O, Prat D, Avenel A, et al. *Mycoplasma*-related pneumonia: a rare cause of acute respiratory distress syndrome (ARDS) and of potential antibiotic resistance. *Rev Mal Respir*. (2013) 30:77–80. doi: 10.1016/j.rmr.2012.06.012
107. Koichi I. Clinical features of severe or fatal *Mycoplasma pneumoniae* pneumonia. *Front Microbiol*. (2016) 7:800. doi: 10.3389/fmicb.2016.00800
108. Yu JL, Song QF, Xie ZW, Jiang WH, Chen JH, Fan HF, et al. An iTRAQ-based quantitative proteomics study of refractory *Mycoplasma pneumoniae* pneumonia patients. *Jpn J Infect Dis*. (2017) 70:571–8. doi: 10.7883/yoken.JJID.2016.355
109. Waites KB, Balish MF, Atkinson TP. New insights into the pathogenesis and detection of *Mycoplasma pneumoniae* infections. *Future Microbiol*. (2008) 3:635–48. doi: 10.2217/17460913.3.6.635
110. Song Q, Xu BP, Shen KL. Effects of bacterial and viral co-infections of *Mycoplasma pneumoniae* pneumonia in children: analysis report from Beijing Children's hospital between 2010 and 2014. *Int J Clin Exp Med*. (2015) 8:15666–74.
111. Zhou Y, Wang J, Chen W, Shen N, Tao Y, Zhao R, et al. Impact of viral coinfection and macrolide-resistant mycoplasma infection in children with refractory *Mycoplasma pneumoniae* pneumonia. *BMC Infect Dis*. (2020) 20:633. doi: 10.1186/s12879-020-05356-1
112. Morozumi M, Takahashi T, Ubukata K. Macrolide-resistant *Mycoplasma pneumoniae:* characteristics of isolates and clinical aspects of community-acquired pneumonia. *J Infect Chemother*. (2010) 16:78–86. doi: 10.1007/s10156-009-0021-4
113. Qu J, Chen S, Bao F, Gu L, Cao B. Molecular characterization and analysis of *Mycoplasma pneumoniae* among patients of all ages with community-acquired pneumonia during an epidemic in China. *Int J Infect Dis*. (2019) 83:26–31. doi: 10.1016/j.ijid.2019.03.028
114. Wu PS, Chang LY, Lin HC, Chi H, Hsieh YC, Huang YC, et al. Epidemiology and clinical manifestations of children with macrolide-resistant *Mycoplasma pneumoniae* pneumonia in Taiwan. *Pediatr Pulmonol*. (2013) 48:904–11. doi: 10.1002/ppul.22706
115. Tanaka T, Oishi T, Miyata I, Wakabayashi S, Kono M, Ono S, et al. Macrolide-resistant *Mycoplasma pneumoniae* infection, Japan, 2008–2015. *Emerg Infect Dis*. (2017) 23:1703–6. doi: 10.3201/eid2310.170106
116. Okada T, Morozumi M, Tajima T, Hasegawa M, Sakata H, Ohnari S, et al. Rapid effectiveness of minocycline or doxycycline against macrolide-resistant *Mycoplasma pneumoniae* infection in a 2011 outbreak among Japanese children. *Clin Infect Dis*. (2012) 55:1642–9. doi: 10.1093/cid/cis784
117. Ishiguro N, Koseki N, Kaiho M, Ariga T, Kikuta H, Togashi T, et al. Therapeutic efficacy of azithromycin, clarithromycin, minocycline and tosufloxacin against macrolide-resistant and macrolide-sensitive *Mycoplasma pneumoniae* pneumonia in pediatric patients. *PLoS ONE*. (2017) 12:e0173635. doi: 10.1371/journal.pone.0173635
118. Amaya-Villar R, Garnacho-Montero J. How should we treat *Acinetobacter* pneumonia? *Curr Opin Crit Care*. (2019) 25:465–72. doi: 10.1097/MCC.0000000000000649
119. Peleg AY, de Breij A, Adams MD, Cerqueira GM, Mocali S, Galardini M, et al. The success of Acinetobacter species; genetic, metabolic and virulence attributes. *PLoS ONE*. (2012) 7:e46984. doi: 10.1371/journal.pone.0046984
120. Garnacho-Montero J, Amaya-Villar R. Multiresistant *Acinetobacter baumannii* infections: epidemiology and management. *Curr Opin Infect Dis*. (2010) 23:332–9. doi: 10.1097/QCO.0b013e32833ae38b
121. El Solh AA, Alhajhusain A. Update on the treatment of *Pseudomonas aeruginosa* pneumonia. *J Antimicrob Chemother*. (2009) 64:229–38. doi: 10.1093/jac/dkp201
122. Restrepo MI, Babu BL, Reyes LF, Chalmers JD, Soni NJ, Sibila O, et al. Burden and risk factors for *Pseudomonas aeruginosa* community-acquired pneumonia: a multinational point prevalence study of hospitalized patients. *Eur Respir J*. (2018) 52:170–90. doi: 10.1183/13993003.01190-2017
123. Micek ST, Wunderink RG, Kollef MH, Chen C, Rello J, Chastre J, et al. An international multicenter retrospective study of *Pseudomonas aeruginosa* nosocomial pneumonia: impact of multidrug resistance. *Crit Care*. (2015) 19:219. doi: 10.1186/s13054-015-0926-5
124. Jones RN. Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *Clin Infect Dis*. (2020) 51(Suppl. 1):S81–7. doi: 10.1086/653053
125. Folgori L, Livadiotti S, Carletti M, Bielicki J, Pontrelli G, Ciofi Degli Atti ML, et al. Epidemiology and clinical outcomes of multidrug-resistant, gram-negative bloodstream infections in a European tertiary pediatric hospital during a 12-month period. *Pediatr Infect Dis J*. (2014) 33:929–32. doi: 10.1097/INF.0000000000000339
126. Zhang Q, Smith JC, Zhu Q, Guo Z, MacDonald NE. A five-year review of *Pseudomonas aeruginosa* bacteremia in children hospitalized at a single center in southern China. *Int J Infect Dis*. (2012) 16:e628–32. doi: 10.1016/j.ijid.2012.03.014
127. Ciofi Degli Atti M, Bernaschi P, Carletti M, Luzzi I, Garcia-Fernandez A, Bertaina A, et al. An outbreak of extremely drug-resistant *Pseudomonas aeruginosa* in a tertiary care pediatric hospital in Italy. *BMC Infect Dis*. (2014) 14:494. doi: 10.1186/1471-2334-14-494
128. Langton Hewer SC, Smyth AR. Antibiotic strategies for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis. *Cochrane Database Syst Rev*. (2014) 11:CD004197. doi: 10.1002/14651858.CD004197.pub4
129. Adegoke AA, Stenstrom, TA, Okoh AI. *Stenotrophomonas maltophilia* as an emerging ubiquitous pathogen: looking beyond contemporary antibiotic therapy. *Front Microbiol*. (2017) 8:2276. doi: 10.3389/fmicb.2017.02276

130. Looney WJ, Narita M, Muhlemann, K. *Stenotrophomonas maltophilia*: an emerging opportunist human pathogen. *Lancet Infect Dis.* (2009) 9:312–23. doi: 10.1016/S1473-3099(09)70083-0
131. Furuichi M, Ito K, Miyairi, I. Characteristics of *Stenotrophomonas maltophilia* bacteremia in children. *Pediatr Int.* (2016) 58:113–8. doi: 10.1111/ped.12745
132. Garcia-Leon G, Ruiz de Alegria Puig C, Garcia de la Fuente C, Martinez-Martinez L, Martinez JL, Sanchez MB. High-level quinolone resistance is associated with the overexpression of smeVWX in *Stenotrophomonas maltophilia* clinical isolates. *Clin Microbiol Infect.* (2015) 21:464–7. doi: 10.1016/j.cmi.2015.01.007
133. Jeon YD, Jeong WY, Kim MH, Jung IY, Ahn MY, Ann HW, et al. Risk factors for mortality in patients with *Stenotrophomonas maltophilia* bacteremia. *Medicine.* (2016) 95:e4375. doi: 10.1097/MD.0000000000004375
134. Ebara H, Hagiya H, Haruki Y, Kondo E, Otsuka, F. Clinical characteristics of *Stenotrophomonas maltophilia* bacteremia: a regional report and a review of a Japanese case series. *Intern Med.* (2017) 56:137–42. doi: 10.2169/internalmedicine.56.6141
135. Juhasz E, Krizsan G, Lengyel G, Grosz G, Pongracz J, Kristof, et al. Infection and colonization by *Stenotrophomonas maltophilia*: antimicrobial susceptibility and clinical background of strains isolated at a tertiary care centre in Hungary. *Ann Clin Microbiol Antimicrob.* (2014) 13:333. doi: 10.1186/s12941-014-0058-9
136. Mutlu M, Yilmaz G, Aslan Y, Bayramoglu, G. Risk factors and clinical characteristics of *Stenotrophomonas maltophilia* infections in neonates. *J Microbiol Immunol Infect.* (2011) 44:467–72. doi: 10.1016/j.jmii.2011.04.014
137. Lai CH, Chi CY, Chen HP, Chen TL, Lai CJ, Fung CP, et al. Clinical characteristics and prognostic factors of patients with *Stenotrophomonas maltophilia* bacteremia. *J Microbiol Immunol Infect.* (2004) 37:350–8.
138. Friedman ND, Korman TM, Fairley CK, Franklin, JC, Spelman DW. Bacteraemia due to *Stenotrophomonas maltophilia*: an analysis of 45 episodes. *J Infect.* (2002) 45:47–53. doi: 10.1053/jinf.2002.0978
139. World Health Organization. *Pneumonia-Key Factors*. Available online at: https//www.who.int/news-room/fact-sheets/details/pneumonia.
140. GBD 2016. Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis*. (2018) 18:1191–210. doi: 10.1016/S1473-3099(18)30310-4
141. Eastham KM, Freeman R, Kearns AM, Eltringham G, Clark J, Leeming J, et al. Clinical features, aetiology and outcome of empyema in children in the north east of England. *Thorax.* (2004) 59:522e5. doi: 10.1136/thx.2003.016105
142. Masters IB, Isles AF, Grimwood K. Necrotizing pneumonia: an emerging problem in children? *Pneumonia.* (2017) 9:11. doi: 10.1186/s41479-017-0035-0
143. Shenoy AT, Orihuela CJ. Anatomical site-specific contributions of pneumococcal virulence determinants. *Pneumonia.* (2016) 8:7. doi: 10.1186/s41479-016-0007-9
144. Cillniz C, Amaro R, Torres A. Pneumococcal vaccination. *Curr Opin Infect Dis.* (2016) 29:187–96. doi: 10.1097/QCO.0000000000000246
145. Jauneikaite E, Tocheva AS, Jefferies JM, Gladstone RA, Faust SN, Christodoulides M, et al. Current methods for capsular typing of *Streptococcus pneumoniae*. *J Microbiol Methods.* (2015) 113:41–9. doi: 10.1016/j.mimet.2015.03.006
146. Linares J, Ardunay C, Pallares R, Fenoll A. Changes in antimicrobial resistance, serotypes and genotypes in *Streptococcus pneumoniae* over a 30-year period. *Clin Microbiol Infect.* (2010) 16:402–10. doi: 10.1111/j.1469-0691.2010.03182.x
147. Falup-Pecurariu O. Lessons learnt after the introduction of the seven valent- pneumococcal conjugate vaccine toward broader spectrum conjugate vaccines. *Biomed J.* (2012) 35:450–6. doi: 10.4103/2319-4170.104409
148. Resti M, Moriondo M, Cortimiglia M, Indolfi G, Canessa C, Becciolini L, et al. Community-acquired bacteremic pneumococcal pneumonia in children: diagnosis and serotyping by real-time polymerase chain reaction using blood samples. *Clin Infect Dis.* (2010) 51:1042e9. doi: 10.1086/656579
149. Lucero MG, Nohynek H, Williams G, Tallo V, Simões EA, Lupisan S, et al. Efficacy of an 11-valent pneumococcal conjugate vaccine against radiologically confirmed pneumonia among children less than 2 years of age in the Philippines: a randomized, double-blind, placebo controlled trial. *Pediatr Infect Dis J.* (2009) 28:455e62. doi: 10.1097/INF.0b013e31819637af
150. Cutts FT, Zaman SM, Enwere G, Jaffar S, Levine OS, Okoko JB, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in the Gambia: randomised, double-blind, placebo-controlled trial. *Lancet.* (2005) 365:1139e46. doi: 10.1016/S0140-6736(05)71876-6
151. Black SB, Shinefield HR, Ling S, Hansen J, Fireman B, Spring D, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. *Pediatr Infect Dis J.* (2002) 21:810e15. doi: 10.1097/00006454-200209000-00005
152. Lucero MG, Dulalia VE, Nillos LT, Williams G, Parreño RA, Nohynek H, et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and x-ray defined pneumonia in children less than two years of age. *Cochrane Database Syst Rev.* (2009) 4:CD004977. doi: 10.1002/14651858.CD004977.pub2
153. Angoulvant F, Levy C, Grimprel E, Varon E, Lorrot M, Biscardi S, et al. Early impact of 13-valent pneumococcal conjugate vaccine on community-acquired pneumonia in children. *Clin Infect Dis.* (2014) 58:918–24. doi: 10.1093/cid/ciu006
154. Byington CL, Korgenski K, Daly J, Ampofo K, Pavia A, Mason EO. Impact of the pneumococcal conjugate vaccine on pneumococcal parapneumonic empyema. *Pediatr Infect Dis J.* (2006) 25:250–4. doi: 10.1097/01.inf.0000202137.37642.ab
155. Grijalva CG, Nuorti JP, Zhu Y, Griffin MR. Increasing incidence of empyema complicating childhood community-acquired pneumonia in the United States. *Clin Infect Dis.* (2010) 50:805–13. doi: 10.1086/650573
156. Alicino C, Paganino C, Orsi A, Astengo M, Trucchi C, Icardi G, et al. The impact of 10-valent and 13-valent pneumococcal conjugate vaccines on hospitalization for pneumonia in children: a systematic review and meta-analysis. *Vaccine.* (2017) 35:5776–85. doi: 10.1016/j.vaccine.2017.09.005
157. Tsai Y-F, Ku Y-H. Necrotizing pneumonia: a rare complication of pneumonia requiring special consideration. *Curr Opin Pulm Med.* (2012) 18:246–52. doi: 10.1097/MCP.0b013e3283521022
158. Hsieh Y-C, Chi H, Chang K-Y, Lai S-H, Mu J-J, Wong K-S, et al. Increase in fitness of *Streptococcus pneumoniae* is associated with the severity of necrotizing pneumonia. *Pediatr Infect Dis J.* (2015) 34:499–505. doi: 10.1097/INF.0000000000000631
159. Jacobs S, Lamson D, St. George K, Walsh T. Human Rhinoviruses. *Clin Microbiol Rev.* (2013) 26:135–62. doi: 10.1128/CMR.00077-12
160. Greenberg SB. Update on human rhinovirus and coronavirus infections. *Semin Respir Crit Care Med.* (2016) 37:555–71. doi: 10.1055/s-0036-1584797
161. Jartti T, Gern JE. Role of viral infections in the development and exacerbation of asthma in children. *J Allergy Clin Immunol.* (2017) 140:895–906. doi: 10.1016/j.jaci.2017.08.003
162. Ferreira HLDS, Costa KLP, Cariolano MS, Oliveira GS, Felipe KKP, Silva ESA, et al. High incidence of rhinovirus infection in children with community-acquired pneumonia from a city in the Brazilian pre-Amazon region. *J Med Virol.* (2019) 91:1751–8. doi: 10.1002/jmv.25524
163. Hijano DR, Maron G, Hayden RT. Respiratory viral infections in patients with cancer or undergoing hematopoietic cell transplant. *Front Microbiol.* (2018) 9:3097. doi: 10.3389/fmicb.2018.03097
164. Fisher BT, Danziger-Isakov L, Sweet LR, Munoz FM, Maron G, Tuomanen E, et al. A multicenter consortium to define the epidemiology and outcomes of inpatient respiratory viral infections in pediatric hematopoietic stem cell transplant recipients. *Pediat Infect Dis J.* (2018) 7:275–82. doi: 10.1093/jpids/pix051
165. Steiner M, Strassl R, Straub J, Böhm J, Popow-Kraupp T, Berger A. Nosocomial rhinovirus infection in preterm infants. *Pediatr Infect Dis J.* (2012) 31:1302–4. doi: 10.1097/INF.0b013e31826ff939
166. van Piggelen RO, van Loon AM, Krediet TG, Verboon-Maciolek MA. Human rhinovirus causes severe infection in preterm infants. *Pediat Infect Dis J.* (2010) 29:364–5. doi: 10.1097/INF.0b013e3181c6e60f
167. Kobayashi H, Shinjoh M, Sudo K, Kato S, Morozumi M, Koinuma G, et al. Nosocomial infection by human bocavirus and human rhinovirus among paediatric patients with respiratory risks. *J Hosp Infect.* (2019) 103:341–48. doi: 10.1016/j.jhin.2019.05.002

168. Walter JM, Wunderink RG. Severe respiratory viral infections: new evidence and changing paradigms. *Infect Dis Clin North Am.* (2017) 31:455–74. doi: 10.1016/j.idc.2017.05.004
169. Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, et al. Epidemiology, genetic recombination, and pathogenesis of Coronaviruses. *Trends Microbiol.* (2016) 24:490–502. doi: 10.1016/j.tim.2016.03.003
170. Dare RK, Fry AM, Chittaganpitch M, Sawanpanyalert P, Olsen SJ, Erdman DD. Human coronavirus infections in rural Thailand: a comprehensive study using real-time reverse-transcription polymerase chain reaction assays. *J Infect Dis.* (2007) 196:1321–8. doi: 10.1086/521308
171. Heimdal I, Moe N, Krokstad S, Christensen A, Skanke LH, Nordbø SA, et al. Human Coronavirus in hospitalized children with respiratory tract infections: a 9-Year population-based study from Norway. *J Infect Dis.* (2019) 219:1198–206. doi: 10.1093/infdis/jiy646
172. Ogimi C, Englund JA, Bradford MC, Qin X, Boeckh M, Waghmare A. Characteristics and outcomes of coronavirus infection in children: the role of viral factors and an immunocompromised state. *J Pediatric Infect Dis Soc.* (2019) 8:21–8. doi: 10.1093/jpids/pix093
173. Gagneur A, Vallet S, Talbot PJ, Legrand-Quillien MC, Picard B, Payan C, et al. Outbreaks of human coronavirus in a pediatric and neonatal intensive care unit. *Eur J Pediatr.* (2008) 167:1427–34. doi: 10.1007/s00431-008-0687-0

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

MINI REVIEW
published: 01 September 2021
doi: 10.3389/fped.2021.625751

All You Need Is Evidence: What We Know About Pneumonia in Children With Neuromuscular Diseases

Claudio Cherchi[1,2]*, *Maria B. Chiarini Testa*[1,2], *Daniele Deriu*[3], *Alessandra Schiavino*[1,2], *Francesca Petreschi*[1,2], *Nicola Ullmann*[1,2], *Maria G. Paglietti*[1,2] *and Renato Cutrera*[1,2]

[1] Pediatric Pulmonology and Respiratory Intermediate Care Unit, Sleep and Long Term Ventilation Unit, Academic Department of Pediatrics (DPUO), Pediatric Hospital "Bambino Gesù" Research Institute, Rome, Italy, [2] Rare Diseases and Medical Genetics Unit, Bambino Gesù Children Hospital (IRCCS), Rome, Italy, [3] Department of Pediatrics, University of Rome Tor Vergata, Rome, Italy

OPEN ACCESS

Edited by:
Jong-Hau Hsu,
Kaohsiung Medical University, Taiwan

Reviewed by:
Antonio Martinez-Gimeno,
Complejo Hospitalario de Toledo, Spain
Kelechi Benjamin Ugonna,
Sheffield Children's Hospital, United Kingdom

***Correspondence:**
Claudio Cherchi
claudio.cherchi@opbg.net

Specialty section:
This article was submitted to Pediatric Pulmonology, a section of the journal Frontiers in Pediatrics

Received: 03 November 2020
Accepted: 04 August 2021
Published: 01 September 2021

Citation:
Cherchi C, Chiarini Testa MB, Deriu D, Schiavino A, Petreschi F, Ullmann N, Paglietti MG and Cutrera R (2021) All You Need Is Evidence: What We Know About Pneumonia in Children With Neuromuscular Diseases. Front. Pediatr. 9:625751. doi: 10.3389/fped.2021.625751

Neuromuscular diseases may involve all major respiratory muscles groups including inspiratory, expiratory, and bulbar muscles. Respiratory complications are the major cause of morbidity and mortality. Pneumonia represents a frequent cause of morbidity in children with neuromuscular disease. The aim of this review is to collect knowledge about pneumonia in children with neuromuscular diseases. Pneumonia usually follows viral respiratory infections of the upper respiratory tract, due to the combination of an increased amount of nasal and oral secretions and an impairment of the cough efficiency and of the clearance of secretions due to the muscle weakness, further compromised by the infection itself. The accumulation of bronchial secretions leads to atelectasis and promote bacterial infection. Moreover, dysfunction of swallowing mechanism exposes these children to the risk of developing aspiration pneumonia. However, etiology of viral and bacterial respiratory infection in these patients is still poorly studied.

Keywords: neuromuscular disease, SMA, duchene muscular dystrophy, pneumonia, atelectasia

INTRODUCTION

Neuromuscular diseases (NMD) may involve most respiratory muscles groups including inspiratory, expiratory, and bulbar. Respiratory complications are the major cause of morbidity and mortality. The natural course of NMD is characterized by ineffective cough and swallowing disorders leading to chronic aspiration, poor secretion clearance, pneumonia and hypercapnic respiratory failure.

Pneumonia represents a frequent cause of morbidity in children with NMD; inhalation, impaired cough and atelectasis are the main risk factors. However, scarce literature investigating on pneumonia in children with NMD is available.

This review is part of the research topic "Emerging Pneumonia in Children" and its aim is to summarize knowledge about pneumonia in children with neuromuscular diseases and to encourage research in this neglected field.

TABLE 1 | Neuromuscular diseases with recurrent pneumonia.

Spinal muscular atrophy type 1
Duchenne muscular dystrophy
SMA with respiratory distress type 1
Facioscapulohumeral muscular dystrophy with infantile onset
Myotonic dystrophy 1 with severe congenital onset
Charcot marie tooth with severe early onset
Pompe disease

RESPIRATORY INVOLVEMENT IN NEUROMUSCULAR DISEASE

NMD are a heterogeneous group of diseases characterized by lesions that may involve motor,neurons, peripheral nerve, neuromuscular junction, or skeletal muscle. They consist of acquired and inherited forms, characterized by very variable age of onset, clinical features, courses and prognoses (1). Most are inherited forms as Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA), congenital muscular dystrophies and myopathies. NMD clinical features range from profound floppiness and respiratory compromising at birth, such as patients affected by SMA type 1, to mild motor impairment and late-onset respiratory problems.

The incidence of respiratory complications varies according to diagnosis, genotype and age (for details, see the British Thoracic Society guideline for respiratory management of children with neuromuscular weakness) (2).

NMD are characterized by a restrictive pattern of spirometry on pulmonary function testing (3). This is caused by the presence of reduced inspiratory muscle strength, thoracic scoliosis and reduced chest wall and pulmonary compliance. Usually, inspiratory and expiratory muscle strength are equally impaired, however in SMA the diaphragm strength may be preserved and expiratory muscle weakness may prevail (4). Progressive neuromuscular weakness can lead to the inability to take deep breaths and to cough effectively (5).

Cough efficacy can be measured by cough peak flow: reduced cough power is defined by values <270 L/min in children, and values <160 L/min are associated with high risk of atelectasis and pneumonia (6).

Respiratory muscle weakness is frequently unrecognized in children and NMD remain undiagnosed until ventilatory is precipitated by aspiration pneumonia or acute respiratory airway infection (7). Acute respiratory failure due to accumulation of lung secretions often represents the first clinical relevant manifestation of these diseases (5). Although the progression of symptoms may be predictable, the timeline will vary, according to the type of NMD and the age of the patient: an infant with SMA type I would be expected to experience serious respiratory impairment, leading to infectious complications within the first year of life, a patient affect by DMD probably would not experience pneumonia before his second decade of life (5). NMDs characterized by recurrent pneumonia are shown in **Table 1**.

PATHOPHYSIOLOGY OF PNEUMONIA IN NEUROMUSCULAR DISEASES

Pneumonia in children with NMD usually follows viral respiratory infections, even if confined to the upper airway (8). Acute upper respiratory infections can cause atelectasis or pneumonia by several mechanisms. It is well-known that viral upper respiratory infections can cause an acute worsening in respiratory muscle strength in the healthy adult population (7). In children affected by NMD the further reduction of an already compromised respiratory muscle strength can cause shortness of breath, decreased vital capacity and acute hypercapnia (2). Moreover, the infections are often associated to an increased production of nasal and oral secretions. Nasopharyngeal secretions also become thicker and purulent, thus weakening an already compromised swallowing mechanism and leading to an higher risk of aspiration of infected upper airway secretions into the lower respiratory tract. The impaired cough mechanism, deriving from the respiratory muscle weakness, makes those secretions more difficult to clear from the lower airways. Children with NMD are particularly prone to develop segmental or lobar atelectasis due to the retention of bronchial secretions. This is particularly evident in the lower lung zones, which may already be compressed by scoliosis or by the heart. They are also at risk for developing widespread, radiographically inapparent micro-atelectasis (8). The appearance of atelectasis exposes these patients to a higher risk of bacterial lung superinfections (9).

Children presenting swallowing disorders, ineffective cough, atelectasis and capacity vital forced (FVC) <50% of predicted value are at high risk of pneumonia and should be trained in protocols that allow successful home treatment of respiratory exacerbations, performed by well-trained parents or healthcare professionals (10, 11).

Risk factors, pathophysiology and treatment of respiratory exacerbations and pneumonia in patients with NMD are shown in **Figure 1**.

Community-Acquired Pneumonia

As specified before, pneumonia in children with NMD usually follows viral respiratory infections (12). Generally, respiratory syncytial virus (RSV) infection predominates in infants, while rhinovirus, influenza and parainfluenza virus infections are common in children and adolescents (2). The risk of serious pulmonary complications associated to RSV infection led the American Academy of Pediatrics to introduce NMDs in the list of diseases requiring RSV immuno-prophylaxis (9). However, scarce literature investigating on microbiologic etiology of both viral and bacterial pneumonia in children with NMD is available (12).

Few data come from a cohort study conducted on 28 children with NMD admitted to PICU (13) which found both viruses (respiratory syncytial virus, rhinovirus, influenza virus) and bacteria (Mycoplasma pneumoniae, Staphylococcus aureus, Haemophilus influenzae) as etiological agents associated to acute respiratory infections, defined by a positive culture from airways within 48 h of admission or signs of upper respiratory tract, respiratory symptoms, fever, and/or leukocytosis (12).

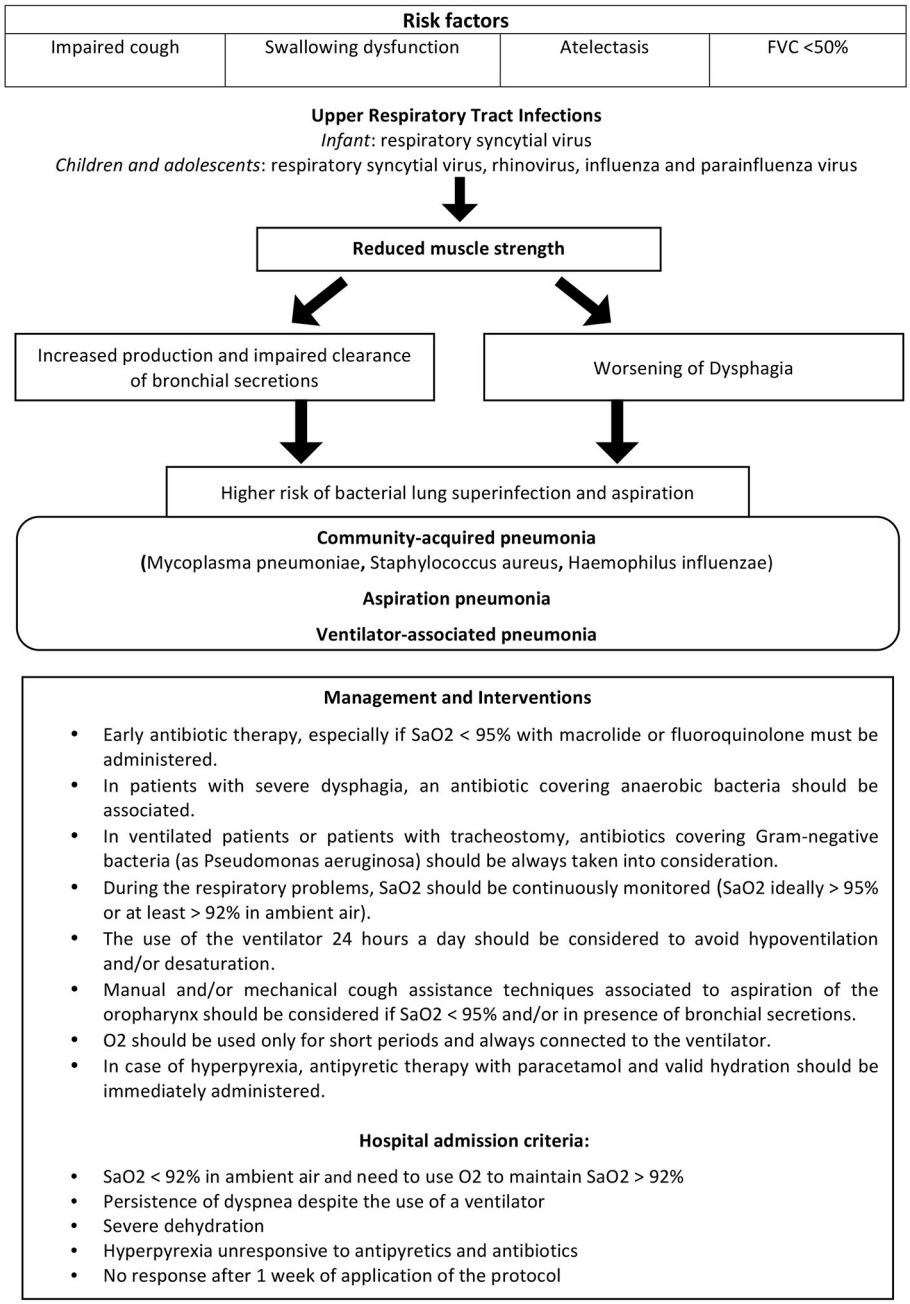

FIGURE 1 | Pathophysiology, clinical management and treatment of respiratory exacerbations/pneumonia in NMD.

Aspiration Pneumonia

Children with NMD show swallowing dysfunction that increases as muscle weakness progresses, and in some conditions such as SMA type 1 and severe forms of nemaline myopathy may present from early infancy (2). Difficulties in swallowing, resulting from loss of control of the larynx and pharynx, associated to ineffective cough predispose to aspiration lung disease (2). Aspirated material includes saliva, mouth organisms and food in children orally fed (2). Gastric contents may be aspirated if gastro-esophageal reflux is present. Aspiration causes inflammation of the lung parenchima and obstruction of the lower airways, leading to worsening restrictive lung disease, Kooi-van Es. et al. (14) demonstrated that the overall prevalence of dysphagia, in a large group of children with NMD was 47.2% (13). Although oral and pharyngeal weakness can increase the risk of aspiration lung disease, aspiration is a relatively rare event and an uncommon cause of respiratory exacerbation (2).

However, for children who cannot safely achieve an adequate oral nutrition, the positioning of a percutaneous gastrostomy should be considered to improve quality of life and reduce respiratory complications.

Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is a common hospital-acquired infection and a source of increased morbidity (15). Between 3 and 19% of all ventilated children are diagnosed with VAP at a reported frequency of 1.1–27.1 per 1,000 ventilator days (16). Due to the high incidence of PICU admissions among children affected by NMD, VAP represent a frequent infective complication and a serious threat. However, literature about this setting of patients is completely lacking.

CLINICAL MANAGEMENT AND TREATMENT OF NMD PEDIATRIC PATIENT WITH RESPIRATORY EXACERBATIONS AND PNEUMONIA

Development of respiratory exacerbations may be a life-threatening event in patients with NMD, deriving from secretion accumulation and further weakening of respiratory muscles, and leading to acute respiratory failure (17). In clinical practice, the management includes early or prophylactic use of antibiotics for respiratory exacerbations, although no studies proving the benefits of this approach are available in literature (2). An antibiotic therapy should be started early, especially when SaO_2 is <95% and the antibiotic coverage must include atypical bacteria (macrolide or fluoroquinolone) (17). In case of suspected inhalation (e.g., in patients presenting with severe dysphagia), a second antibiotic for anaerobic bacteria should be associated (e.g., amoxicillin associated with clavulanic acid) (17). Antibiotics covering Gram-negative bacteria (as Pseudomonas aeruginosa) should be always taken into consideration for ventilated patients or patients with tracheostomy (18). Home management of a respiratory tract infection should comprise a daily or at least every 2–3 days visit of the patient, performed by the specialist or the general practitioner, to prescribe antibiotic therapy and exclude the presence of hospital admission criteria suggested by Racca et al. (17) (shown in **Figure 1**). The general practitioner should maintain telephone contact with a specialist with expertise in home ventilation in order to share the decision-making process (17).

During the infectious exacerbation, the value of SaO_2 should be continuously monitored by pulse oximetry and SaO_2 should be ideally maintained >95% or at least >92% in ambient air.

The use of the ventilator 24 h a day should be considered to avoid hypoventilation and/or SaO_2 < 95%.

When the value of SaO_2 falls below 95%, especially in presence of bronchial secretions the use manual and/or mechanical cough assistance techniques must be considered.

In younger children and in patients with severe dysphagia, the use of a cough machine should always be followed by secretion aspiration in the oropharynx with the aid of a mechanical aspirator.

Oxygen (O_2) therapy can be provided for short periods and the oxygen source must be always connected to the ventilator to prevent hypoxia and hypercapnia. Finally, fever >38.5°C must be treated with paracetamol and a valid hydration protocol should be followed (17).

Finally, during respiratory exacerbations children with NMD are often exposed to chest X-ray which could be reduced if a noninvasive and reliable diagnostic method is identified (17). The use of lung ultrasound should be recommended for early identification of pulmonary atelectasis, in order to reduce frequent ionizing exposition of these fragile patients (19).

DISCUSSION AND FUTURE PERSPECTIVES

Pulmonary complications represent a frequent cause of morbidity and mortality in patients affected by NMD. The pathophysiology of respiratory exacerbations in patients with NMD is deeply understood. Pneumonia usually follows viral respiratory infections of the upper respiratory tract, due to the combination of an increased amount of nasal and oral secretions and an impairment of the cough efficiency and of the clearance of secretions due to the muscle weakness, further compromised by the infection itself. The accumulation of bronchial secretions leads to atelectasis and promote bacterial infection. Moreover, dysfunction of swallowing mechanism exposes these children to the risk of developing aspiration pneumonia.

However, etiology of viral and bacterial respiratory infection in these patients is still poorly studied. No significant data, investigating the etiological agents involved in respiratory infections of children with NMD are available in literature.

A precise characterization of microbial etiology of pneumonia in NMD pediatric patients would be of great help in the antimicrobial strategy definition. Evidence-based empiric antibiotic therapy guidelines for these patients would ameliorate the clinical management of respiratory exacerbations. Wide studies, aimed at identifying the most frequent pathogens involved in community-acquired pneumonia and correlation between etiology and mortality, are necessary to help physicians in their clinical practice. Colonization of the lower respiratory tract, through deep cough-produced sputum culture should also be investigated on large cohorts of children with NMD.

Recently, the possibility of an early diagnosis of NMD, through the introduction of neonatal screening programs, associated to the availability of innovative therapeutic approaches, consisting of Nusinersen for SMA and gene therapy for SMA and DMD, are completely changing the natural history of these diseases (20). Life expectancy of these children drastically improved, exposing them to a higher number of complications. Literature focused on respiratory assistance need to keep up with times.

AUTHOR CONTRIBUTIONS

CC contributed to the research and critical evaluation of the available literature and wrote the first draft of the manuscript. MC, DD, AS, and FP contributed to the research and critical evaluation of the available literature and to writing sections of the manuscript. NU and MP contributed to the research and critical evaluation of the available literature and manuscript. RC contributed to writing the first draft of the manuscript. All authors read and approved the final manuscript.

FUNDING

RC2020 under score genetica Reserch grant Italian ministry of health.

REFERENCES

1. Howard RS. Respiratory failure because of neuromuscular disease. *Curr Opin Neurol.* (2016) 29:592–601. doi: 10.1097/WCO.0000000000000363
2. Hull J, Aniapravan R, Chan E, Chatwin M, Forton J, Gallagher J, et al. British thoracic society guideline for respiratory management of children with neuromuscular weakness. *Thorax.* (2012) 67(Suppl. 1):i1–40. doi: 10.1136/thoraxjnl-2012-201964
3. Simonds AK. Ventilator support in children with neuromuscular disorders. In: Sterni LM, Carroll JL, editors. *Caring for the Ventilator Dependent Child: A Clinical Guide*. New York, NY: Springer (2016). p. 283–98.
4. Abusamra R, Ross Russell R. Management of respiratory disease in children with muscular weakness. *Paediatr Child Health.* (2015) 25:515–21. doi: 10.1016/j.paed.2015.06.011
5. Panitch HB. Respiratory implications of pediatric neuromuscular disease. *Respir Care.* (2017) 62:826–48. doi: 10.4187/respcare.05250
6. Tzeng AC, Bach JR. Prevention of pulmonary morbidity for patients with neuromuscular disease. *Chest.* (2000) 118:1390–6. doi: 10.1378/chest.118.5.1390
7. Mier-Jedrzejowicz A, Brophy C, Green M. Respiratory muscle weakness during upper respiratory tract infections. *Am Rev Respir Dis.* (1988) 138:5–7. doi: 10.1164/ajrccm/138.1.5
8. Schramm CM. Current concepts of respiratory complications of neuromuscular disease in children. *Curr Opin Pediatr.* (2000) 12:203–7. doi: 10.1097/00008480-200006000-00004
9. Panitch HB. Viral respiratory infections in children with technology dependence and neuromuscular disorders. *Pediatr Infect Dis J.* (2004) 23:S222–7. doi: 10.1097/01.inf.0000144670.78558.c7
10. Wang CH, Dowling JJ, North K, Schroth MK, Sejersen T, Shapiro F, et al. Consensus statement on standard of care for congenital myopathies. *J Child Neurol.* (2012) 27:363–82. doi: 10.1177/0883073812436605
11. Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Colvin MK, et al. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. *Lancet Neurol.* (2018). 17:445–55. doi: 10.1016/S1474-4422(18)30026-7
12. Don M. Pneumonia in pediatric acute neuromuscular respiratory failure. *Pediatr Pulmonol.* (2014) 49:825–6. doi: 10.1002/ppul.22961
13. Yates K, Festa M, Gillis J, Waters K, North K. Outcome of children with neuromuscular disease admitted to paediatric intensive care. *Arch Dis Child.* (2004) 89:170–5. doi: 10.1136/adc.2002.019562
14. Kooi-van Es M, Erasmus CE, de Swart BJM, Voet NBM, van der Wees PJ, de Groot IJM, et al. Dysphagia and dysarthria in children with neuromuscular diseases, a prevalence study. *J Neuromuscul Dis.* (2020). 7:287–95. doi: 10.3233/JND-190436
15. Gupta S, Boville BM, Blanton R, et al. A multicentered prospective analysis of diagnosis, risk factors, and outcomes associated with pediatric ventilator-associated pneumonia. *Pediatr Crit Care Med.* (2015) 16:e65e73. doi: 10.1097/PCC.0000000000000338
16. Beardsley AL, Nitu ME, Cox EG, et al. An evaluation of various ventilator-associated infection criteria in a PICU. *Pediatr Crit Care Med.* (2016) 17:7380. doi: 10.1097/PCC.0000000000000569
17. Racca F, Vianello A, Mongini T, Ruggeri P, Versaci A, Vita GL, et al. Practical approach to respiratory emergencies in neurological diseases. *Neurol Sci.* (2020) 41:497–508. doi: 10.1007/s10072-019-04163-0
18. Cutrera R, Chiarini Testa MB, De Luca F, Petreschi F, Pavone M, Petrone A, et al. Complicanze respiratorie in corso di patologie neuromuscolari. *Prospettive Pediatria.* (2007) 37: 115–22.
19. Ullmann N, D'Andrea ML, Gioachin A, Papia B, Testa MBC, Cherchi C, et al. Lung ultrasound: a useful additional tool in clinician's hands to identify pulmonary atelectasis in children with neuromuscular disease. *Pediatr Pulmonol.* (2020) 55:1490–4. doi: 10.1002/ppul.24760
20. Sansone VA, Pirola A, Albamonte E, Pane M, Lizio A, D'Amico A, et al. Respiratory needs in patients with type 1 spinal muscular atrophy treated with nusinersen. *J Pediatr.* (2020) 219:223–8.e4. doi: 10.1016/j.jpeds.2019.12.047

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership