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LIBERTY ASTHMA QUEST Study Design[3]: 1902 patients who were 12 years of age or older with uncontrolled asthma were randomly assigned in a 2:2:1:1 ratio to receive add-on subcutaneous DUPIXENT at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks. The primary end points were the annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in the forced expiratory volume in 1 second (FEV_1) before bronchodilator use in the overall trial population. Secondary end points included the exacerbation rate and FEV_1 in patients with a blood eosinophil count of 300 or more per cubic millimetre. Asthma control and DUPIXENT safety were also assessed.

EOS, eosinophils; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid ; OCS, oral corticosteroid; Q2W, once every 2 weeks; SOC, standard of care.

References: 1. DUPIXENT Summary of Product Characteristics. May 2020. **2.** Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med. 2018;378(26):2475-2485. **3.** Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018;378(26):2486-2496.

Presentation: Dupilumab solution for injection in a pre-filled syringe with needle shield. **Indications:** Atopic Dermatitis (AD): Moderate-to-severe AD in adults and adolescents ≥12 years who are candidates for systemic therapy; severe atopic dermatitis in children 6 to 11 years old who are candidates for systemic therapy. Asthma: In adults and adolescents ≥12 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment. Chronic rhinosinusitis with nasal polyposis (CRSwNP): As an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control(for 300mg) **Dosage & Administration:** Subcutaneous injection. AD adults: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week. AD adolescents(12-17y/o): Body weight <60 kg- initial dose of 400 mg (two 200mg injections), followed by 200 mg every other week. Body weight ≥60 kg- same dosage as adults. Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, e.g. face, neck, intertriginous and genital areas. Consider discontinuing treatment in patients who have shown no response after 16 weeks. AD Children(6-11y/o): Body weight 15Kg~<60 kg- initial dose of 300mg on Day 1 Follow by 300mg on Day 15, then 300mg every 4 weeks. Body weight ≥60 kg- same dosage as adults. * The dose may be increased to 200 mg Q2W in patients with body weight of 15 kg ~ < 60 kg based on physician's assessment. Asthma: Initial dose of 400 mg, followed by 200 mg every other week. For patients with severe asthma and on oral corticosteroids or with severe asthma and co-morbid moderate-to-severe AD or adults with co-morbid severe CRSwNP- initial dose of 600 mg, followed by 300 mg every other week. Patients receiving concomitant oral corticosteroids may reduce steroid dose gradually once clinical improvement with dupilumab has occurred. The need for continued dupilumab therapy should be considered at least annually as determined by a physician. CRSwNP: for adult patients initial dose of 300 mg followed by 300 mg given every other week. Consideration should be given to discontinuing treatment in patients who have shown no response after 24 weeks of treatment for CRSwNP. Some patients with initial partial response may subsequently improve with continued treatment beyond 24 weeks. If a dose is missed, administer it asap and thereafter, resume dosing at the regular scheduled time. **Contraindications:** Hypersensitivity to dupilumab or any of the excipients. **Precautions:** Safety and efficacy in children <6 years or <15kg not been established. Not be used to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Do not discontinue corticosteroids abruptly upon start of dupilumab. Reduction should be gradual and performed under supervision of a physician; it may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. Biomarkers of type 2 inflammation may be suppressed by systemic corticosteroid use. If systemic hypersensitivity reaction occurs, discontinue dupilumab and initiate appropriate therapy. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia. Treat pre-existing helminth infections before initiating dupilumab. If patients become infected while receiving dupilumab and do not respond to anti-helminth treatment, discontinue dupilumab until infection resolves. Patients who develop conjunctivitis and keratitis that does not resolve following standard treatment should undergo ophthalmological examination. AD patients with comorbid asthma should not adjust or stop asthma treatments without consultation with physicians. Carefully monitor patients after discontinuation of dupilumab. Do not give live and live attenuated vaccines concurrently with dupilumab. Patients should be brought up to date with immunisations before starting dupilumab. **Drug Interactions:** Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed. Patients receiving dupilumab may receive concurrent inactivated or non-live vaccinations. **Pregnancy and lactation:** Should be used during pregnancy only if potential benefit justifies potential risk to foetus. Unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. Decision must be made whether to discontinue breast-feeding or dupilumab taking into account benefit of breast feeding for the child and benefit of therapy for the woman. **Undesirable effects:** Most common adverse reactions reported- injection site reactions, conjunctivitis, oral herpes and eosinophilia. Safety profile observed in adolescents consistent with that seen in adults. For other undesirable effects, please refer to the full prescribing information. **Preparation:** 2 x 300mg/2ml in pre-filled syringe with needle shield, 2 x 200mg/1.14ml in pre-filled syringe with needle shield. **Legal Classification:** Part 1, First & Third Schedules Poison **Full prescribing information is available upon request.** API-HK-DUP-22.06

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Contents

Editorial

There are three excellent articles in the issue, including a cross-sectional study to assess the impact of coronavirus disease (COVID-19) infection on pulmonary function tests in children,[1] a case report of high-frequency ventilation in an infant with acute respiratory distress syndrome due to pneumocystis pneumonia,[2] and an overview of the vitamin D deficiency and its impact on respiratory health in the Hong Kong pediatric population.[3]

Lung injuries related to COVID-19 have been widely reported, and there are concerns regarding the assessment of lung injury for discharged patients. Approximately one-third of pediatric patients show ground glass opacities in lung imaging, which correlates with clinical severity. However, there is a lack of pediatric data in Southeast Asia regarding the long-term consequences of COVID-19 infection on lung function. Dr. Archana Kumari conducted a study to evaluate the long-term impact of COVID-19 on lung function in children.[1] The study enrolled 20 children aged 7-18 years, with varying degrees of disease severity, at an average of 8.3 ± 2 months (range 7-14 months) after COVID-19. The results showed that all children had normal respiratory rate, SpO2, and chest auscultation. The mean blood oxygen saturation. Lung function tests, including forced expiratory volume in one second (FEV1), forced expiratory volume in 0.5s, FEV1/forced vital capacity, and peak expiratory flow rate, were all within the normal range, even across different subgroups. Children with mild to moderate infections not exhibited long-term sequelae. This study provided valuable information regarding the long-term effects of COVID-19 infection on lung function in children. They contribute to a better understanding for pediatricians in assessing and managing lung function issues in children after COVID-19 infection. However, due to the small sample size and single-region inclusion, further research is needed to validate and expand upon these results.

The second article reports a case of a 9-month-old infant with Kaposiform hemangioendothelioma and Kasabach-Merritt syndrome who developed acute respiratory distress syndrome suspected caused by *Pneumocystis jirovecii* infection during chemotherapy and prednisolone treatment.[2] The patient received high-frequency oscillatory ventilation (HFOV) due to traditional ventilator failure. On the 28th day of hospitalization, successful extubation was achieved. This report suggests that HFOV may serve as an alternative treatment modality for pediatric patients with severe respiratory failure and excessively high ventilatory settings in the context of *P. jirovecii* infection. HFOV provides a lung-protective strategy by increasing mean airway pressures to maintain oxygenation while minimizing ventilation-induced lung injury. It is important to note that this is a case report, and the conclusions are based on a single patient. Further research is needed to validate the efficacy and safety of this approach.

The third article has reviewed the status of vitamin D deficiency (VDD) in the pediatric population in Hong Kong.[3] VDD is a common phenomenon in the world. The negative impact of VDD on bone health, such as increasing the risk of osteoporosis or osteopenia in adults and rickets in children, is well-known. Emerging evidences support the negative non-skeletal effects of VDD, such as an increased risk of infections, cancer, and autoimmune diseases. Considering the potential impact of VDD on the respiratory system, this review article provides important information on the prevalence of VDD and its impact on respiratory health in the pediatric population in Hong Kong. It highlights the potential benefits of vitamin D supplementation in improving VDD. However, due to limited study quality, further research is still needed to get a more comprehensive understanding of the effects of VDD and the optimal treatment strategies. In clinical practice, assessing individual risk factors for VDD and appropriately supplementing vitamin D may be worth considering.

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Conflicts of interest

There are no conflicts of interest.

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2. High-frequency ventilation in an infant with acute respiratory distress syndrome due to Pneumocystis jirovecii pneumonia: A case report. Pediatr Respirol Crit Care Med 2023;7:57-62.
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Review Article

Vitamin D Deficiency and Its Impact on Respiratory Health in the Hong Kong Pediatric Population: Current Evidence and Future Directions

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Abstract

Vitamin D deficiency (VDD) is a global phenomenon. While well known to negatively influence bone health by increasing the risks of osteoporosis or osteopenia in adults and rickets in children, emerging evidence supports the negative extraskeletal effects of VDD, such as increased risks of infection, cancer, and autoimmune diseases. In view of the potential respiratory impacts of VDD, there is a need to investigate the status quo of VDD in Hong Kong. This review outlines the current prevalence of VDD in the pediatric population of Hong Kong, which is up to 64.7%. It also highlights emerging evidence of its impact on respiratory health (in particular asthma, pneumonia, and COVID-19) and summarizes current guidelines on vitamin D supplementation. Despite limited high-quality studies, evidence seems to suggest that the prevalence of VDD in Hong Kong is in keeping with global trends and that pharmacological treatment by supplementation may be beneficial.

Keywords: Asthma, COVID-19, pediatrics, pneumonia, vitamin D deficiency

Key Messages: Given the potential negative respiratory impacts of vitamin D deficiency (VDD), there is a need to investigate the status of VDD in Hong Kong children, especially in those with respiratory diseases, and to discuss safe and effective interventions to prevent VDD in children during routine health checks.

Introduction

VDD is a worldwide phenomenon.[1] It is well-established to lead to adverse skeletal effects, including rickets and osteopenia/osteoporosis. Further, there has been increasing evidence to suggest that it may play a role in immune modulations of a wide range of conditions, ranging from cancer to infections.[2] A brief literature review was conducted to examine such effects from a respiratory perspective. Further to our query about the adequacy of the detection and treatment of VDD, this text concludes with a discussion of safe treatment options to prevent VDD.

Definitions

Vitamin D

Vitamin D is a fat-soluble vitamin best known for its beneficial effects on bone health and acquisition through sun exposure. It has two major inactive prohormone forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). When activated, they share identical biological functions, potency, and metabolism.[3] Vitamin D2 is the prohormone form added to fortified foods, whereas vitamin D3 is the prohormone form acquired through an animal-based diet or by cutaneous synthesis in reaction to direct dermal exposure to ultraviolet B (UVB) radiation, most commonly from the sun.[2]

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The actions of vitamin D can be categorized into (1) classical and (2) nonclassical actions, depending on the type of target tissues. Classical actions refer to actions on the vitamin D endocrine system and calcium homeostasis, which are comprised of the intestines, bones, and kidneys.[4] Nonclassical actions refer to actions on the immune system, lungs, heart, brain, etc., as evidenced by the presence of the vitamin D receptor in these tissues.[4,5] Hypovitaminosis D may refer to either VDD or insufficiency/inadequacy (VDI) and is a global phenomenon.[1] Classically, it is well proven to cause hypocalcemia, which in turn results in rickets in children and osteomalacia/osteoporosis in adults.[5] Otherwise, hypovitaminosis D is also independently associated with increased risks of cancers, respiratory infections, cardiovascular diseases, autoimmune diseases, and all-cause mortality.[2,6-8]

Reference Range

25-Hydroxy vitamin D (25(OH)D, also known as calcidiol, calcifediol) is the major circulating form of vitamin D. Its serum level is agreed by researchers to be the best biomarker for vitamin D status.[9] Measuring serum 25(OH)D levels allows the categorization of a patient into the states of being VDD, VDI, or vitamin D-sufficient (VDS).[10] Currently, however, there is no international consensus on the cutoff values for VDD or VDI.[11] For the purpose of definition, we will use the higher cutoff points as those adopted by Holick *et al.*,[12] by defining VDS as serum 25(OH)D > 75 nmol/L (or >30 ng/mL) and hypovitaminosis D as serum 25(OH)D < 75 nmol/L (or <30 ng/mL), in which VDI is further defined as serum 25(OH)D of 50–75 nmol/L (or 20–30 ng/mL), and VDD is defined as serum 25(OH)D of <50 nmol/L (or <20 ng/mL). These definitions will be applied across all studies cited herein; different definitions, if used by the cited authors, will be specified where appropriate.

Prevalence of VDI and VDD in Hong Kong

VDD and VDI are highly prevalent worldwide, with reported prevalence rates of VDD (serum 25(OH)D of <50 nmol/L) in the United States, Canada, and Europe to be up to 40% (for children and adolescents, up to 36%),[13,14] subject to variations due to age, ethnicity, and comorbidities that may affect vitamin D metabolism (e.g., liver or renal diseases).[10] In Hong Kong, the prevalence figures are incomplete but generally consistent with trends in global data—the rate of VDD increases with age, with lower rates in younger children and higher rates in early adulthood.[13,14] Prevalence data are summarized by age groups, as follows in Table 1.

For children, Chan *et al.*[11] found that 33.5% of healthy infants at 3 months of age have serum 25(OH)D <50 nmol/L (VDD), and 21.9% have serum 25(OH)D <25 nmol/L (VDD). This finding is consistent with the well-established phenomenon that infants who are exclusively breastfed are prone to VDD or VDI because breast milk does not provide an adequate supply of vitamin D if the mother has VDD or VDI herself due to, for example, poor sun exposure.[16,17]

Table 1: Estimated trend of VDD in Hong Kong, defining VDD as serum 25(OH)D < 50 nmol/L. Asterisk marks data extrapolated from regional data

Age group	Percentage of deficiency (%)
Infants at 3 months	33.5
Children <6 years	10.8*
Children aged 6–11 years	40.3*
Adolescents at 12–16 years	64.7
Young adults aged 18–26 years	72.0
Adults at >26 years	no data

There are no published Hong Kong data for children aged <12 years, but regional data may provide a rough estimation. In particular, for children aged <6 years, a study from Southern China found that 10.8% had serum 25(OH)D <50 nmol/L (VDD).[18] For children aged 6–11 years, a study from Hangzhou, China, found that 40.3% had serum 25(OH)D <50 nmol/L (VDD).[19] A cross-sectional study of children from 6 to 11 years of age from Vietnam also found that 50.4% have serum 25(OH)D <50 nmol/L (VDD).[20] This finding of an increasing prevalence of VDI with age in children corroborates the hypothesis that increased school work and reduced outdoor activities with age might contribute to reduced sun exposure and, thus, VDI/VDD.[15]

For adolescents and young adults, Cheung *et al.*[21] found that 64.7% of Hong Kong adolescents aged 12–16 years have serum 25(OH)D <50 nmol/L (VDD), and 11.4% have serum 25(OH)D <25 nmol/L (VDD), while Wang *et al.*[22] found that 72.0% of Hong Kong young adults aged 18–26 years have serum 25(OH)D <50 nmol/L (VDD), and 6.6% have serum 25(OH)D <25 nmol/L (VDD). There are no published local data for older adults and the elderly.

In short, VDD is likely prevalent in Hong Kong across all age groups, with its prevalence increasing with age. Given that most studies use the lower cutoff range of VDD at serum 25(OH)D <50 nmol/L, the prevalence figures would even be an underestimation if the higher cutoff of serum 25(OH)D <75 nmol/L is adopted.

VDI and VDD as Risk Factors for Respiratory Illnesses

The role and pathophysiology of VDD in bone health is well-established,[23] but research is still ongoing in investigating its role in respiratory health. From a respiratory point of view, in addition to cutaneous synthesis, vitamin D can also be synthesized in the pulmonary alveoli, as

evidenced by the expression of 1-alpha-hydroxylase (an enzyme responsible for synthesizing vitamin D) in the respiratory epithelium and alveolar macrophages.[24] This finding, combined with the immunomodulatory effects of vitamin D, has renewed interest in the research of the impact of VDD/VDI on respiratory health. We present below the evidence for VDD/VDI as a risk factor for respiratory illnesses in the context of three important respiratory conditions in children, namely severe COVID-19, pneumonia, and asthma:

Severe COVID-19

A review has found that vitamin D levels were inversely correlated to not just the number of cases,[25] but also the severity and mortality of cases of COVID-19.[26] Furthermore, VDD was also reported to be a risk factor for the development of acute respiratory distress syndrome,[27] which is associated with mortality resulting from SAR-CoV-2.[28] These clinical findings are corroborated by the role of vitamin D in modulating the action of angiotensin-converting enzyme 2 (ACE2), which is a receptor key to the entry of SARS-CoV-2 into host cells. As a negative modulator of the renin–angiotensin system, vitamin D inhibits renin and increases the activity of ACE2, restoring the ACE/ACE2 balance,[29] which ultimately mitigates the inflammatory and fibrotic effects of angiotensin II.[30] Studies also found that vitamin D decreases levels of the pro-inflammatory IL6, which is responsible for the cytokine storm known to result in fatality from COVID-19.[31]

Pneumonia

A meta-analysis reported serum 25(OH)D < 20 ng/mL (VDI) to be a risk factor of community-acquired pneumonia (CAP) (odds ratio = 1.64, 95% confidence interval [CI]: 1.00, 2.67).[32] There was also an association between serum 25(OH)D < 20 ng/mL (VDI) and the severity[33,34] and poor prognosis[35] of pneumonia, respectively. Another study found that VDI/VDD increases the risk of mortality due to pneumonia (hazard ratio (HR) = 1.91, 95% CI: 1.06, 3.45).[36] These clinical findings are corroborated by research supporting the immunomodulatory, anti-inflammatory, and antimicrobial properties of vitamin D in CAP patients, including but not limited to reducing inflammatory cytokines and chemokines, and promoting monocytic proliferation into macrophages.[10]

Asthma

A meta-analysis found that serum 25(OH)D is significantly lower in asthmatic children than nonasthmatic children,[37] with up to 68.1% of asthmatic children having VDD.[38] Further, serum 25(OH)D was also found to be a stronger predictor of the development of asthma than serum IgE levels and a family history of asthma.[38] In the long run, stunting, a complication of VDD, may cause impaired lung growth and decreased lung function, therefore increasing the risk for asthma.[39] The mechanism behind these clinical findings is multifactorial. Vitamin D inhibits airway smooth muscle proliferation by reducing serum levels of calcitriol, serum, and platelet-derived growth factors, in addition to inflammatory chemokines,[40] Th1-cell activation, Treg activity,[41] and ultimately inflammation in the pathogenesis of asthma. In addition, vitamin D induces the antimicrobial peptide, cathelicidin LL37, which is negatively correlated with bacterial infections as a cause of acute exacerbation of asthma.[42]

In brief, research shows that VDD/VDI is a risk factor for severe COVID-19, pneumonia, and asthma, supporting the notion that VDD/VDI is associated with poor respiratory health.

Safe Treatment of VDI and VDD

The treatment of hypovitaminosis D can be divided into nonpharmacological and pharmacological means.

Nonpharmacological treatment

Nonpharmacological treatment for VDD/VDI is generally considered safe.[13] It can be divided into sun exposure, dietary modification, and food fortification, as illustrated below:

First, adequate sun exposure is an important means of acquiring vitamin D, as cutaneous synthesis is responsible for providing 80%–100% of requirements by the body.[13] This is supported by a UK study which found that repeated low-level sun exposure (defined as 13–17 min, six times per week for 6 weeks, wearing summer clothing exposing ~35% body surface area) can confer a serum 25(OH)D level of >50 nmol/L in light-skinned individuals.[43] Regarding efficacy, it should be noted that sun exposure depends on the time of the day, season of the year, latitude, altitude, and skin complexion, with confounding factors such as the use of sunscreen.[5] In short, low sunlight (e.g., staying indoors, prolonged hospitalization), having a darker complexion (because of poorer penetration by UVB), and the use of sunscreen impair cutaneous synthesis, thus limiting the effect sun exposure on increasing serum 25(OH)D.[3] Further, as UV is a well-established carcinogen for melanomas and nonmelanoma skin cancers, excessive exposure to sunlight of unprotected skin and sunburns are advised against.[5] In sum, adequate and moderate sun exposure is recommended wherever possible, but considering the lifestyle of most urban dwellers, it alone may not be feasible or adequate for achieving VDS.

Where sun exposure is not sufficient, dietary modification may be advised. A wide range of foods, including egg yolk, animal liver, fish, and mushrooms, are considered good sources of vitamin D. A study has found that oily fish contains the highest naturally occurring vitamin D

concentration, followed by irradiated mushrooms, whole eggs, and fortified milk.[44] This is evidenced by a meta-analysis which found that regular fatty fish consumption (defined as five meals of 150 g/week for 4 weeks) resulted in an increase of 6.8 nmol/L in serum 25(OH)D while a choice of lean fish led to an increase of 1.9 nmol/L.[45] For irradiated mushrooms, a study has found that ingestion of mushrooms exposed to UVB irradiation can raise serum 25(OH)D as effectively as supplements containing the same amount of vitamin D2.[46] Regarding efficacy, there may be variation within and between species of oily fish (such as salmon, swordfish, sardines, trout, and tuna), as well as between wild and farmed fish, due to different degrees of supplementation in fish feed.[44] In short, the consumption of foods rich in vitamin D is a potentially effective intervention, but given that they seldom constitute a substantial portion of people's diets, doing so alone may not be sufficient for treating VDD/VDI.

Food fortification is another strategy believed to produce a sustained effect in increasing micronutrient intake more so than supplementation.[47] In the United States, common foods fortified with vitamin D include infant formula, cow's milk, plant-based milk, fruit juices, and breakfast cereal,[48] albeit to varying extents.[44] Research has shown that fortification is positively associated with serum 25(OH)D.[49] A meta-regression has found that fortification results in an increase of serum 25(OH)D by 15.5 nmol/L for the pediatric population aged 1–18 years.[50] Another meta-analysis found that a mean individual intake of 440 IU/day from fortified foods increased 25(OH)D by 19.4 nmol/L.[51] Further, a Finnish study found that following the introduction of a milk fortification policy for 11 years, there is a mean increase of serum 25(OH)D of 20 nmol/L in adult supplement nonusers, with 90% of participants reaching the 50 nmol/L cutoff for sufficiency as defined in the study.[52] Notably, regarding the efficacy of fortification on vitamin D intake, a key factor is whether fortification is policy-based: vitamin D intake is higher in countries with fortification policies (e.g., the United States, Finland, Norway) than those without (e.g., the United Kingdom, the UAE, Ireland, Australia).[49]

Pharmacological treatment

A meta-analysis has found an overall protective effect of supplementation against acute respiratory infections.[53] Not only is supplementation well accepted as a treatment for hypovitaminosis D itself,[3] but it is also shown to significantly increase vitamin D intake and serum 25(OH) D level.[54,55] Rationales and common dosing regimens are described as follows:

Pharmacological treatment of VDD/VDI by oral vitamin D supplementation is indicated in VDD/VDI but not in VDS individuals.[12] Dosing frequency can be daily or in its weekly or monthly equivalents.[56] Forms of vitamin D used as supplementation may be vitamin D2 or D3, but research has shown little difference in the resultant serum 25(OH)D levels at a dose of 1000 IU/day.[57] The oral route is the most common, but the parenteral route may be considered for certain high-risk groups, such as patients with severe malabsorption.[58] The treatment target varies across different guidelines, with some proposing 50 nmol/L (20 ng/mL) (IOM 2011) while others 75 nmol/L (30 ng/mL).[12]

Generally, two types of dosages are pertinent to vitamin D supplementation, namely (1) a therapeutic dose for treating a deficiency, followed by (2) a maintenance dose for keeping the 25(OH)D levels within the range of sufficiency (indefinitely as prophylaxis).[12] The dosages stratified by age groups are listed below. Also included are the tolerable upper intake levels of vitamin D (as either D2 or D3) for the maintenance dose, above which the risk for hypercalcemia begins to increase. However, toxicity is uncommon,[9] and studies found that vitamin D intoxication (with reference to signs of hypercalcemia) was only observed with intake levels of 10,000 IU/day to 30,000 IU/day or higher,[3,16,59,60] with the corresponding serum 25(OH)D levels ranging from 500 to 600 nmol/L or higher. Details of suggested dosing are outlined below:

For infants aged 0-12 months, a therapeutic dose of 2000 IU/day for 6 weeks followed by a maintenance dose of 400–1000 IU/day is recommended. The maintenance upper limit is 1000 IU/day for infants aged 0–6 months and 1500 IU/day for infants aged 6–12 months,[3] which is well within the safe range.[61]

For children and teens aged 1–18 years, a therapeutic dose of 2000 IU/day for 6 weeks, followed by a maintenance dose of 600–1000 IU/day is recommended. The maintenance upper limit is 4000 IU/day.[12] For IBD patients of the same age range, 2000 IU/day as a therapeutic dose is well tolerated.[62]

For adults aged 19 years or above, a therapeutic dose of 6000 IU/day for 8 weeks, followed by a maintenance dose of 1500–2000 IU/day is recommended.[12,26] The maintenance upper limit is 10,000 IU/day.[3] For supplementation during pregnancy, there is insufficient evidence to support a definite conclusion on its use.[63] A randomized controlled trial (RCT) found that a therapeutic dose of vitamin D supplements of at least 4000 IU/day for 12 weeks seems to provide adequate nutritional vitamin D for both the lactating mother and the nursing infant.[16] The vitamin D (and calcium) requirements of pregnant women and lactating mothers are identical to those of nonpregnant adults.[3]

Further, from a respiratory point of view, special considerations may be made with respect to patients with respiratory diseases:

For COVID-19, VDD/VDI should be corrected wherever possible, but supra-physiological supplementation is not

recommended.[3,35] Evidence shows that optimal levels of vitamin D early in the disease course of COVID-19 can prevent progression to severe or critical conditions and reduce mortality.[26] Further, a pilot study found that high-dose calcifediol (25 hydroxyvitamin D, a liver metabolite of cholecalciferol) of at least 0.266 mg/day (equivalent to 10,000 IU of cholecalciferol, assuming equimolar conversion) as a supplement in early stage significantly reduced ICU admission of hospitalized patients.[64] However, its effect in the late stage is less clear.[26]

For pneumonia, VDD/VDI should likewise be corrected where possible, with uncertain evidence to support its use in VDS cases.[3,10] Evidence shows that supplementation as a single high dose for young children aged 1–36 months with VDD reduces the risk of recurrence of pneumonia compared with placebo (HR = 0.71, 95% CI: 0.54, 0.94, $P = 0.02$).[65] A meta-analysis found a protective effect of supplementation against acute respiratory tract infections.[53] Another meta-analysis of 65 RCTs found that daily prophylactic vitamin D supplementation significantly reduced the incidence and event rate of overall respiratory infections despite the high heterogeneity of studies.[66] For asthma, vitamin D3 supplement to inhaled corticosteroids was found to provide no significant effect on the time to develop severe asthma and on asthma morbidity.[40]

Discussion

A problem of definition

Given that hypovitaminosis D is common in both the pediatric and adult population of Hong Kong and increasing evidence for its respiratory implications, it is logical to make the clinical inference that supplementation should be advocated. However, a major hurdle against supplementation is the lack of consensus on the definition of VDD and VDI because without universal cutoffs of VDD and VDI, one does not know whether to supplement and if so, the extent of supplementation. The reason behind the absence of a universal cutoff value is, however, manifold and complex.

Methodologically, there are not just disagreements in cutoff values of serum 25(OH)D for defining VDS; studies may also have been affected by analytical errors, such as interassay and interlaboratory variability.[12] For example, a study has found a misclassification rate of 20% between using chemiluminescence immunoassays versus high-performance liquid chromatography for measuring serum 25(OH)D levels.[67] In addition, findings from studies on the effect of hypovitaminosis D on various diseases are limited to correlation—no evidence has yet emerged to show that hypovitaminosis D has a robust cause-and-effect (or dose–response) relationship with any clinical entity,[3] with the exception of bone health which has been well-researched for decades.[13]

Clinically, the multifactorial etiologies of diseases[3] and a lack of specific symptoms of hypovitaminosis D[68] also contribute to the variability in laboratory results and their interpretations. For example, there were confounding variables (e.g., presence of comorbidities) in studies on the respiratory effects of hypovitaminosis D, which may predispose a subject to a respiratory disease.[3] In the bigger picture, it is also difficult to ascribe a health outcome to the effects of a single micronutrient.[47]

Future directions

Despite the above seemingly fundamental issues, there are still advantages to vitamin D supplementation. Its wide therapeutic window, high intake limit for intoxication, and low cost[12] allow vitamin D supplementation to be valuable as part of the treatment of VDD/VDI individuals who suffer from respiratory illnesses. Disregarding the issue of definition, the case for supplementation may further be strengthened if this field addresses the limitations of studies in the following areas:

In terms of the prevalence of VDD, there is a lack of data in the age groups of children aged <6 years and 6–11 years. This knowledge gap points to a need for further local research on the prevalence of VDD. Although there are international data as well as data from China, they might not be directly translatable to Hong Kong due to differences in their healthcare policies and health systems. This variation in the translatability of results is further complicated by small sample sizes in many studies,[10,11,40] even in age groups for which there exists local data. Specifically, this field would benefit greatly from future cross-sectional studies to confirm the prevalence figures in children aged <6 years and 6–11 years, respectively. More observational studies like that of Guo *et al.*[18] and of large sample sizes of the local population may be valuable to inform clinicians of the true local prevalence of VDD and VDI.

In terms of vitamin D supplementation, there remains a difficulty for the clinician as to which guideline to follow or how much to prescribe when supplementation is considered. There are also various dosing regimens being suggested by studies,[10] and baseline vitamin D data are often not provided.[66] In addition, the duration of maintenance therapy is variable or has not been specified in many studies,[58,69] so more research on treatment durations may be necessary to provide clearer guidance to the prescribing clinician.[70] Most importantly, large-scale RCTs are needed to establish the direct effect of vitamin D supplementation on reducing complications or severity of specific respiratory conditions,[31,33] in order to provide more robust evidence to support supplementation in the context of each clinical entity.

Conclusion

There is evidence that hypovitaminosis D is highly prevalent in the pediatric population of Hong Kong,

which is consistent with global trends. At the same time, the respiratory implications of hypovitaminosis D are highlighted by increasing evidence from studies showing the protective effects of supplementation against acute respiratory infections,[53] as well as basic science studies showing the immunomodulatory effects of vitamin D.[71-73] Considering such strong evidence, vitamin D supplementation in these patients may be beneficial as an adjuvant therapy if it is given to those with VDD/VDI. More translational research is also needed to provide clinicians with clear guidelines on the cutoffs of VDD/VDI, the effect of supplementation on each respiratory disease, accurate dosing regimens, and the duration of vitamin D supplementation.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Cross Sectional Study to Assess the Impact of COVID-19 Infection on Pulmonary Function Tests in Children

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Abstract

Context: Pediatric data on long-term sequalae of Coronavirus disease 2019 (COVID-19) on pulmonary functions (PFT) are lacking from South east Asia. **Aim:** To assess the long-term effect of pediatric COVID-19 disease on PFT. **Study design:** Prospective cohort trial with follow-up of COVID-19 positive children with PFT at Department of Pediatrics, Lok Nayak Hospital, New Delhi, Delhi, India. **Methods:** Pulmonary function test was performed after an average duration of 8.3 ± 2 months (range 7–14) following COVID-19 in 20 children (age 7–18 years) with different disease severity. Findings were recorded and compared among the subgroups. A pre-structured proforma was used for clinical examination and scoring systems. **Statistical analysis:** Categorical data were presented as counts and percentage, and skewed distribution as median/interquartile ranges. Relevant tests of significance were applied for comparison between groups. **Results:** At baseline, fever (80%) and associated cough, headache, myalgia, and fatigue were the most common presenting clinical features (≥50% of cases). Concomitant gastrointestinal disturbances were identified in 10%–30% of cases. On follow-up, respiratory rate, SpO_2, and single breath count along with chest auscultation were normal in all children. Mean saturation on follow-up was 98.5 ± 0.76. The PFT revealed that forced expiratory volume in 1s (FEV1), 0.5s (FEV0.5), FEV1/forced vital capacity, and peak expiratory flow rate remained normal (>80% predicted). This was comparable across subgroups (mild vs. moderate/severe and ground glass opacity, ground glass opacities [GGO] vs. non GGO group; *P* value ≥ 0.05). **Conclusions:** These observations suggest that children with mild/moderate infection may not develop long-term sequelae as evaluated in this study.

Keywords: Coronavirus disease 2019 (COVID-19), follow-up, pediatric patients, pulmonary function test

Key messages: Mild or moderate infection of COVID-19 may not result in long-term sequelae as evaluated by pulmonary function testing (PFT).

Introduction

In light of the widely documented lung injuries related to Coronavirus disease 2019 (COVID-19), concerns have been raised regarding the assessment of lung injury for discharged patients.[1,2] A recent report portrayed that discharged patients with COVID-19 pneumonia still have residual abnormalities in chest computed tomography (CT) scans, with ground-glass opacity as the most common pattern.[3] These were documented to be present even one year after COVID infection.[4] Persistent impairment of PFT and exercise capacity has been known to last for months or even years in the recovered survivors from previous coronavirus pneumonia epidemics (severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome).[5,6]

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Even with the current epidemic waves, PFT in hospitalized adults with COVID-19 was found to be impaired in up to 75.4% of the patients.[7]

However, there was a paucity of data on long-term consequences of COVID-19, especially in pediatric age group. And given the differences in Indian phenotype,

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as compared to western counterparts, contributing to the differences in PFTs,[8,9] there was a requirement of a prospective study from North India. Hence a prospective follow-up study was planned to evaluate the impact of COVID-19 on pediatric lung functions.

Subjects and Methods

Study design and population

This prospective cross-sectional study was conducted between March, 2020 and April 2021, at a tertiary care, referral hospital in North India. Children between 7 and18 years of age who were admitted as an in-patient in the department during this period as confirmed COVID-19 cases, were included in the study. As the study required travel to the hospital for follow-up PFTs, residents of Delhi state who agreed to commute to get spirometry on telephonic conversation were requested to come to undergo spirometry and clinical examination. Any patients with pre-existing (pre-COVID) lung disease, asthma, congenital lung abnormalities, or inability to perform spirometry were excluded from the study.

Collection of clinical data of COVID related hospital admission

The data of children during their respective hospital admissions for COVID, were retrospectively collected from discharge cards, using a pre-structured proforma. Further history was obtained from patients/guardians and included demographic data, underlying comorbidities, symptoms, chest radiograph and therapy details after taking informed written consent. Severity of COVID infection was classified (as mild, moderate, and severe) based on Government of India guidelines.[10] Their treatment details (including immunomodulation, steroids, antibiotics, etc.) were noted including requirement of oxygen therapy was recorded.

Follow-up visit

At the clinical visit, a single investigator filled a pre-formulated questionnaire, from the children and/or their guardians, regarding their persistent symptoms. Fatigue and dyspnea following COVID-19 infection were identified using Dalhousie Dyspnea and Perceived Exertion Scales.[11] Borg CR-10 scale was also utilized to identify exercise tolerance in these children.[12-14]

Pulmonary function testing

Spirometry was performed in an area, which had not been used for COVID care and strict compliance to COVID-19 protocols were followed. Pulmonary function tests were performed by a technician in the pulmonary function laboratory who wore shield, surgical gown and mask at all times. Spirometry was conducted using the spirometer (Spirovit-Sp1 540-10570, Schiller, Switzerland) and the procedure was followed by the American thoracic society (ATS)-European respiratory society guidelines.[15,16] Spirometry was corrected for body temperature, pressure, water vapor saturated (BTPS) which was used to correct for the difference in the volume of air in the lungs (at 37°C) to the volume measured by the spirometer (at room air temperature). Accurate height measurement was ensured. Checklist of factors that the patient should avoid before spirometry were explained telephonically to patients on the date of appointment (Supplementary 2). The patients were coached to inhale maximally and then to BLAST out the air upon exhalation and the following parameters were measured: forced vital capacity (FVC), forced expiratory capacity at the first second of exhalation (FEV1), FEV1/FVC ratio, and peak expiratory flow rate (PEFR). All PFT measurements were expressed as percentages of predicted normal values.

The following respiratory findings were considered as abnormal: An obstructive defect was indicated by a low forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio, less than 85% in patients 5–18 years of age and restrictive pattern was indicated by an FVC less than 80% in patients 5–18 years of age according to ATS guidelines.[15,17]

Ethics

This study was approved by Institutional Ethical Committee vide F.1/IEC/MAMC/(80/08/2020/No.271), Dated: November 2, 2020, and further registered with CTRI vide reference no. CTRI/2020/11/029058. All data were stored with investigators in a password protected computer, with full regard to patient confidentiality.

Data analysis and statistical methods

Categorical data were presented as counts and percentage, and skewed distribution was described as median and interquartile ranges. To test whether the distribution is normal or not, a graph was plotted. For comparison of two unrelated categorical data Chi square was used, and if related McNemar test was used. For comparison of categorical versus quantitative data, if two groups of categorical data were present, then further test was decided by the distribution of quantitative data. For normally distributed data, paired *t* test was used for related samples, and for unrelated samples, Student *t* test, were be used. In non-normal distribution, unrelated, Mann–Whitney *U* test and related Wilcoxon sign rank test were used. For comparison between more than two groups, in normally distributed unrelated data, one way analysis of variance (ANOVA) was used, and for related two-way ANOVA was used. For non-normally distributed, unrelated data, Kruskal–Wallis test was used, and for related data, Friedman test was used for comparison between two quantitative variables; further test choice was decided on the basis of distribution of data, for normal distribution, Pearson correlation coefficient was chosen, and for non-normal distribution, spearman correlation coefficient was used. A subgroup analysis was

done based of PFT findings with presence and absence of ground glass opacifications (as seen on chest radiographs).

Results

Baseline demographics

A total of 326 patients in pediatric age group (0–18 years) were admitted at Lok Nayak hospital between March 2020 and December 2020. As per inclusion criterion, 125 patients were contacted telephonically and informed regarding the study, and the requirement of follow-up. Thirty-seven patients declined participation, whereas 51 patients had given wrong phone numbers in the records, and 17 did not follow-up after consenting. We were able to enroll clinical data of 20 children, as per study criterion [Figure 1]. The mean age of the patients was 12 ± 3.5 years (mean ± standard deviation), with female preponderance (55%, n = 11).

COVID-associated hospital admission: Subjects were further categorized as mild versus moderate/severe diseases based Government of India interim COVID protocol guidelines.[10,18] They were confirmed as COVID based on rapid antigen test/reverse transcriptase polymerase chain reaction.

There were 18 (90%) mild cases and two (10%) moderate/severe category (both being moderate disease). Patients were admitted in general wards or Pediatric intensive care unit (ICU) depending on the severity of the disease. Azithromycin was used as part of treatment in all 20 enrolled patients; however steroids were used in only moderate/severe category (P value = 0.01), which was consistent with recommendations and data available at the time.[10,18-20] Oxygen supplementation was required in two of the twenty enrolled patients (10%) belonging in moderate/severe category, who were both treated in an ICU setting.

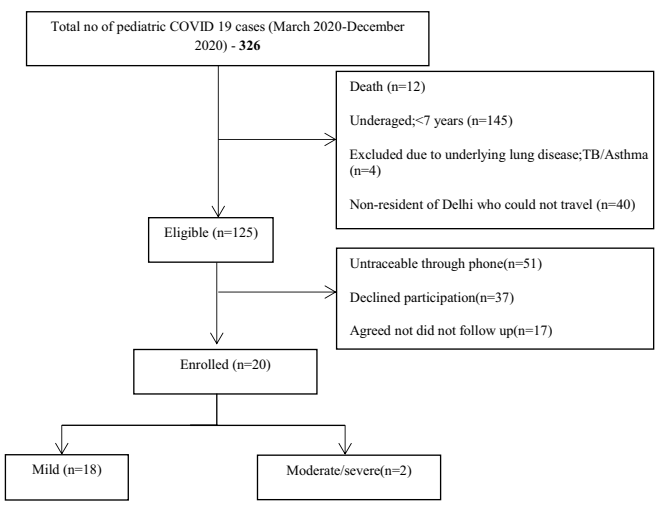

Figure 1: Study flow chart

Clinical and radiological findings

Four of twenty (20%) patients had underlying comorbidities: one patient had abdominal tuberculosis, one had Bell's palsy, and two had meningoencephalitis of non-COVID origin. The most common clinical feature was fever, present in 80% of the subjects. Cough was present in 50% of the cases, whereas coryza was seen in 30% of the cases. Other common findings observed were myalgias, fatigue, and headache in 50%, 60%, and 60% of cases, respectively. Shortness of breath was observed in 40% of total cases and was seen even in 33.3% of mild COVID cases. Gastro intestinal disturbances in form of diarrhea, vomiting, and pain abdomen were identified in 10%, 25%, and 30% of total enrolled cases. Anosmia/ageusia was seen only in 2 cases (10%). All the presenting clinical features were comparable in the two groups [Table 1].

25% of enrolled cases were admitted as COVID pneumonia whereas other 75% cases were upper respiratory illness. Radiological finding in the form of ground glass opacities (GGOs) were found in five cases (25%); however clinical severity was observed in only two of these five patients.

Follow-up visit

Mean duration between positive COVID report and follow-up visit was 8.3 ± 2 months with minimum duration as 7 months and maximum at 14 months. Clinical examination and scoring systems as planned were done using a pre-structured proforma. Of the 20 enrolled children who came for follow-up, none had clinical complaints of dyspnea on exertion during any level of activity. As per the parental questionnaire, all children had attained pre-COVID level of activity and functioning. No readmission was required in any of our subjects and complication like multisystem inflammatory syndrome in children was not reported in any of these cases. Clinical examination was performed in all these children and respiratory rate, SpO_2 and single breath count was noted along with chest auscultation [Table 2].

Spirometry was performed on all these children and the following parameters were measured: FVC, forced expiratory capacity at the first second of exhalation (FEV1) and 0.5s of inhalation (FEV0.5), FEV1/FVC ratio, and PEFR. The group means of forced expiratory volume in 1s (FEV1), 0.5s (FEV0.5), FEV1/FVC, and PEFR were within normal limits (>80% predicted) [Table 2] and were found comparable in both groups (mild vs. moderate/severe; P value ≥ 0.05). However, five cases of FVC abnormality (less than 80% predicted) were detected among 20 enrolled subjects. Four out 18 mild cases (22%) and one out of two moderate cases (50%) had FVC abnormality with a normal or even slightly increased FEV_1/VC [Table 2, Supplementary Table 1].

Subgroup analysis

A subgroup analysis was done with respect to patients who had GGO's on their chest X-ray's during admission versus those who had not [Figure 2], [Tables 3 and 4]. Among clinical features, cough and shortness of breath were

Table 1: Demographic and baseline characteristics of COVID-19 patients

Variable	All patients $N = 20$	Mild cases $n = 18$	Moderate/severe cases $n = 2$	*P* value
Age (years)	12 ± 3.5 years			0.624
7–10 years	6 (30%)	6 (33.3%)	0	
11–14 years	6 (30%)	5 (27.7%)	1 (50%)	
15–18 years	8 (40%)	7 (38.8%)	1 (50%)	
Weight (kg)	41.9 ± 1.4	42.7 ± 16.6	45.5 ± 5.5	0.713
Height (cm)	150.6 ± 17.8	149.7 ± 18.1	158.5 ± 0.5	0.526
BMI (kg/m^2)	17.8 ± 3.8	16.5 ± 3.8	18.1 ± 2.3	0.934
Gender (male)	9 (45%)	9 (50%)	0	0.479
Ward of admission general ward	17 (85%)	17 (94.4%)	0	**0.03**
PICU	3 (15%)	1 (5.5%)	2 (100%)	
Comorbidities present	4 (20%)	3 (16.6%)	1 (50%)	0.447
Clinical features	16 (80%)	14 (77.7%)	2 (100%)	1
Fever	10 (50%)	10 (55.5%)	2 (100%)	0.479
Cough	6 (30%)	5 (27.7%)	1 (50%)	0.52
Coryza	8 (40%)	6 (33.3%)	2 (100%)	0.15
SOB	12 (60%)	10 (55.5%)	2 (100%)	0.19
Fatigue	10 (50%)	10 (55.5%)	0	0.49
Myalgia	2 (10%)	1 (5.5%)	1 (50%)	1
Anosmia/ageusia	2 (10%)	2 (11.1%)	0	0.19
Diarrhea	5 (25%)	5 (27.7%)	0	1
Vomiting	6 (30%)	6 (33.3%)	0	1
Pain abdomen	12 (60%)	11 (61.1%)	1 (50%)	1
Headache				
COVID pneumonia	5 (25%)	3 (16.6%)	2 (100%)	**<0.05**
Oxygen supplementation	2 (10%)		2 (100%)	
Treatment given Azithromycin	20 (100%)	18 (100%)	2 (100%)	**0.01**
Glucocorticoids	2 (10%)	0	2 (100%)	

BMI: body mass index, PICU: pediatric intensive care unit, SOB: shortness of breath

* Data are presented as *n* (percentage [%] and mean ± standard deviation), unless otherwise indicated

Bold value indicates $p < 0.05$.

Table 2: Clinical examination on follow-up

Respiratory rate		**21 ± 1.89**	
SpO_2		**98.5 ± 0.76**	
Single breath count		**31.1 ± 7.56**	
Groups	**Mild cases ($n = 18$)**	**Moderate/severe cases ($n = 2$)**	***P* value**
FEV1%Predicted	94.9 ± 19.5	84 ± 24.0	0.753
FVC %Predicted	90.5 ± 18.6	79.5 ± 17.6	0.377
FEV1/FVC ratio	103.1 ± 6.2	104 ± 7.0	0.899
FEF0.5%predicted	102.7 ± 25.2	86.5 ± 26.1	0.449
PEF	97.6 ± 21.6	80.5 ± 20.5	0.231
FVC percentage (less than 80%) *	4 (22.2%)	1 (50%)	

*Values in number of children (*N*%); remaining median (inter quartile range)

found to be significantly more in those with radiological impairment. Consequently, oxygen supplementation and steroid therapy were required in those having radiological impairment and the difference was significant. However, follow-up clinical parameters (respiratory rate, SpO_2, and single breath count) were comparable. Though there was some degree of impairment, with worse PFTs in those who had radiological impairment, when compared to those who had not, the difference was not statistically significant.

Discussion

COVID-19 predominantly affected the adult population, sparing the children. However many long-term post COVID conditions are coming to light with time.[21] There remains paucity of long-term follow-up data in children. Fever associated with cough, headache, myalgia, and fatigue were the most common presenting clinical features in our study which is in accordance with similar

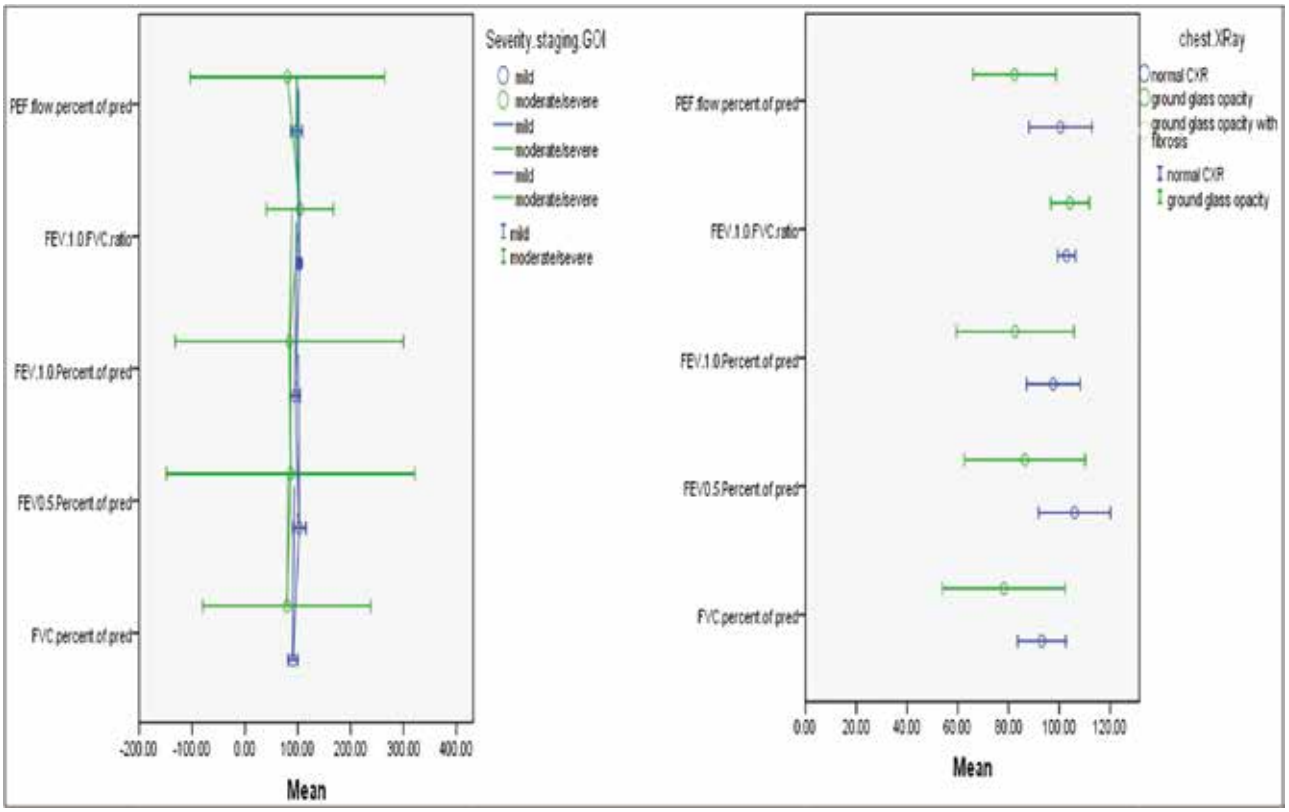

Figure 2: (A) Comparison of PFT parameters between mild versus moderate/severe cases; (B) comparison of PFT parameters between children with or without radiological COVID disease

Table 3: Clinical characteristics of GGO versus non-GGO COVID-19 patients

Variable	All patients $N = 20$	GGO $n = 5$	Non-GGO $n = 15$	*P* value
Ward of admission				0.208
General ward	17 (85%)	3 (60%)	0	
PICU	3 (15%)	2 (40%)	1 (6.6%)	
Clinical features				
Fever	16 (80%)	5 (100%)	11 (73%)	0.208
Cough	10 (50%)	5 (100%)	5 (33%)	0.012
Coryza	6 (30%)	2 (40%)	4 (26%)	0.538
SOB	8 (40%)	4 (80%)	4 (26%)	0.04
Fatigue	12 (60%)	4 (80%)	8 (53%)	0.304
Myalgia	10 (50%)	3 (60%)	7 (46%)	0.615
Diarrhea	2 (10%)	0	2 (13%)	0.402
Vomiting	5 (25%)	0	5 (33%)	0.146
Pain abdomen	6 (30%)	0	6 (40%)	0.099
Headache	12 (60%)	4 (80%)	8 (53%)	0.304
Oxygen supplementation	2 (10%)	2 (40%)	0	0.012
Steroid therapy	2 (10%)	2 (40%)	0	0.00
Respiratory rate (at follow-up)	21 (20–22)	21 ± 1	21 ± 3	0.39
SpO_2	99 (98–99)	99 ± 1	98 ± 1	0.06
Single breath count	30 (26–39)	32 ± 7	28 ± 9	0.89

GGO: ground glass opacity, PICU: pediatric intensive care unit, SOB: shortness of breath, SpO_2: oxygen saturation

*Data are presented as *n* (percentage) (%) and mean ± standard deviation, unless otherwise indicated

pediatric COVID-related studies done recently; however we observed less COVID-associated gastrointestinal disturbances.[22,23]

COVID-related radiological findings in the form of GGOs have been commonly reported in children, in up to a third of the patients, commonly correlating with clinical

Table 4: PFT parameters† in children who had radiological COVID disease

Groups	FEV1% predicted	FVC % predicted	FEV1/FVC ratio	FEF0.5% predicted	PEF
Normal (n = 15)	97.6 ± 18.9	93.1 ± 17	102.8 ± 6.2	106 ± 25.5	100.4 ± 22.3
Radiological COVID disease* (n = 5)	82.6 ± 18.6	78.2 ± 19.5	104.2 ± 6.0	86.4 ± 19.1	82.4 ± 13.2
P value	0.275	0.162	0.726	0.126	0.06

*Radiological COVID disease was predominantly ground glass opacity, as identified on chest X-rays, during admission

† Values in median (inter quartile range)

severity,[24] But our study had commensurate findings in 25% (n = 5/20) cases; however, only 40% (n = 2/5) had clinical severity.

On follow-up of our subjects at a mean duration of 8.3 ± 2 months (range 7–14 months), all patients in our study were fortunately doing well, with no readmissions and normal clinical examinations. This was mirrored in other studies across the globe (Greece, 3 months,[25]; Bangladesh: 2 months[22]).

Pulmonary involvement has been reported quite extensively in COVID, predominantly from adult literature. With early COVID-related changes including edema, capillairitis, with microthrombosis, progressing to exudative diffuse alveolar damage, hyaline membrane formation, pneumocyte type 2 hyperplasia, and superinfections progressing to fibrotic stage of diffuse alveolar damage.[26] Consequently adult literature is rampant with COVID-related PFT abnormalities on follow-up, with total lung capacity (TLC), FEV1, FVC, and DLCO abnormalities reported (at 1 month, n = 57[7] and 3 months, n = 55[27]).

Pulmonary function impairment in children after COVID-19 infection is rare, as was shown by a German study[28] where pulmonary functions of children recovered from covid-19 were compared to those with non-COVID-19 infection after 6 months of diagnosis. It was normal in 75% of the subjects, even in children and adolescents with persistent respiratory symptoms. 7% of these cases had reduced FVC and 5.3% showed impaired DLCO but no patient had pathological FEV1 values. Bottino *et al.*[29] prospectively followed up children less than 18 years who recovered from COVID-19 infection for at least 30 days and performed spirometry and DLCO in seven patients, and in none of them, values <80% of predicted were found. This is in accordance to our study where four out 18 mild cases (22%), and one out of two moderate cases (50%) had FVC abnormality with a normal or even slightly increased FEV_1/VC. Though some patients showed FVC abnormalities, FVC abnormality with a normal or even slightly increased FEV_1/VC [Table 3, Supplementary 1] maybe explained by submaximal inspiratory or expiratory efforts and/or patchy peripheral airflow obstruction and does not reflect a true restrictive pattern. There have been previous studies to prove that FVC alone has poor predictive value.[30]

On comparison between those with and without radiological disease, severity in form of oxygen supplementation and steroid requirement was seen more in the group with radiological disease which is in accordance with a previous study.[24] Other follow-up parameters (both clinical or PFT) did not reveal any significant difference.

The limitations for the study include a small sample size, non-availability of diffusing capacity (DLco), and TLC as a part of PFT and lack of baseline data on pulmonary functions on each of these patients for serial comparison. However, the long follow-up of COVID-affected children, and large screened cohort, in one of largest exclusive COVID hospitals are some of the strengths of our study.

Our study suggests that mild or moderate pediatric COVID infection may not leave residual clinical sequelae, as evaluated by clinical examination and PFT. However, larger studies with longer serial follow-up maybe helpful to validate these findings.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Pulmonary function parameters* of children at follow-up

S.No	Age (years)	Duration between COVID admission and PFT (months)	FVC (% predicted)	FEV1 (%pred)	FEV1/FVC (%pred)	PEF	FEV0.5 (%pred)
1	6	7	104	115	99	158	172
2	11	7	54	61	111	72	65
3	18	7	103	101	97	95	104
4	9	8	81	89	106	97	97
5	8	6	70	66	92	67	71
6	15	8	75	81	105	91	86
7	9	6	75	83	105	84	90
8	13	6	86	89	103	96	96
9	8	7	95	97	100	87	101
10	11	12	83	85	103	78	84
11	11	9	138	141	103	111	140
12	17	8	117	127	108	121	131
13	16	8	102	110	107	104	111
14	15	8	93	96	102	91	93
15	16	8	87	100	115	101	106
16	13	8	86	86	99	75	85
17	15	9	67	67	99	66	68
18	8	14	94	87	91	111	106
19	15	10	86	95	110	119	111
20	12	10	92	101	109	95	105

FVC, Forced Vital Capacity; FEV1, Forced Expiratory Volume in the first Second; FEV0.5, Forced Expiratory Volume in the 0.5 Second; PEF, Peak Expiratory Flows; PFT: pulmonary function tests

*All pulmonary function parameters are presented as % of predicted scores

Supplementary Table 2: Government of India classification used in our study

Suspect case	A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, for example, cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; OR B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset; OR C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, for example, cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.
Probable case	A. A suspect case for whom testing for the COVID-19 virus is inconclusive. OR B. A suspect case for whom testing could not be performed for any reason.
Confirmed case	A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.
Contact	A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case: 1. Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 min; 2. Direct physical contact with a probable or confirmed case; 3. Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment; OR 4. Other situations as indicated by local risk assessments. For confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the *date on which the sample was taken* which led to confirmation.

High-Frequency Ventilation in an Infant with Acute Respiratory Distress Syndrome due to Pneumocystis Jirovecii Pneumonia: A Case Report

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Abstract

Pneumocystis jirovecii could lead to respiratory failure immunocompromised individuals, this pathogen typically causes lung interstitial inflammation and patient hypoxia. For pediatric patients with severe respiratory failure and ventilated with excessively high ventilator settings, high-frequency oscillatory ventilation (HFOV) might serve as an alternative treatment. HFOV is a lung protective strategy, which provides an increased mean airway pressure to maintain patient's oxygenation, and theoretically decrease ventilator-associated lung injury. We present a 9-month-old female infant with Kaposiform hemangioendothelioma and Kasabach–Merritt syndrome, she received chemotherapy and took prednisolone for disease control. She developed acute respiratory distress syndrome after *P. jirovecii* infection. Conventional ventilation with pressure control mode was applied at the beginning, the peak airway pressure was 28 cmH_2O and highest mean airway pressure was 17 cmH_2O before we shift to HFOV. The highest mean airway pressure was 22 cmH_2O during the treatment course under HFOV. Although the patient developed a pneumomediastinum but was successfully extubated on 28th day of admission and was safely discharged on 45th day of admission. We suggest clinicians consider early HFOV intervention in pediatric patients with *P. jirovecii* infection.

Keywords: Acute respiratory distress syndrome, high-frequency oscillatory ventilation, pediatric, *Pneumocystis jirovecii*

Key Messages: High-frequency oscillatory ventilation could be used in Pneumocystis jirovecii pneumonia

Introduction

Pneumocystis jirovecii is a fungal pathogen that is primarily transmitted through the inhalation of airborne particles. Healthy individuals are unlikely to become ill when exposed to *P. jirovecii*. However, immunocompromised individuals, such those who are human immunodeficiency virus (HIV) positive, those who have hematologic malignancies, those who have undergone stem cell or organ transplantation, and those who have been on long-term immunosuppressants or steroids, are susceptible to developing life-threatening *P. jirovecii* pneumonia (PJP).[1,2] In immunocompetent individuals, *P. jirovecii* infection is typically associated with no symptoms. However, in immunocompromised individuals, severe inflammation may occur, particularly in the form of pneumonia. Compared with HIV-positive patients, immunocompromised individuals who are not infected with HIV but have PJP may experience a more rapid disease progression and may be at a greater risk of respiratory failure.[3,4]

When patients experience respiratory failure, they require ventilatory support. For patients with severe respiratory

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failure who have encountered conventional mechanical ventilation (CMV) failure or have been ventilated with excessively high settings, high-frequency oscillatory ventilation (HFOV) can serve as an alternative treatment.[5] In theory, HFOV reduces ventilator-induced lung injury (VILI) to a greater extent compared with CMV. It also provides patients with an increased mean airway pressure (MAP), which helps maintain alveolar expansion and prevents lung collapse during exhalation. This process improves oxygenation and reduces damage resulting from the repetitive alveolar expansion and collapse (i.e., atelectrauma). It also involves the use of small tidal volumes, which prevent volume-induced injuries caused by excessive alveolar expansion (i.e., volutrauma).[6]

In the past, HFOV was predominantly used in preterm infants or newborns, particularly in preterm infants with respiratory distress syndrome. Multiple studies have indicated that HFOV improves the survival rate of newborns with severe respiratory problems.[7] However, research indicates that while HFOV improves oxygenation in children with acute respiratory distress syndrome (ARDS) (pediatric ARDS), it does not reduce their mortality rate.[8] Therefore, further research on the use of HFOV in older children or children with different diseases is required. Only a few reports have examined the effectiveness of HFOV in treating *P. jirovecii*-induced respiratory failure.

In this article, we present the case of a 9-month-old female infant with kaposiform hemangioendothelioma on the right side of her face. After treatment with prednisolone, she developed fever and mild cough and received a diagnosis of PJP. Later, she experienced severe hypoxemia and developed pediatric ARDS. After HFOV was introduced, she eventually recovered.

Case Presentation

Background and initial presentation

A 9-month-old female infant with a height of 64 cm and a weight of 7.4 kg presented with kaposiform hemangioendothelioma on the right side of her face [Figure 1], accompanied by Kasabach–Merritt syndrome. The patient had undergone five courses of chemotherapy with vincristine and was on oral propranolol and prednisolone. On the day following her discharge from the hospital after completing her fifth vincristine treatment, she developed intermittent fever, mild cough, and decreased appetite, prompting a hospital visit. Upon arrival, she had a heart rate of 132 bpm, a respiratory rate of 34 bpm, and blood pressure of 87/66 mmHg, with no signs of cyanosis, and was admitted to the general ward for further inspection. Blood bacterial culture tests yielded negative results, and renal ultrasonography revealed mild hydronephrosis. A combination of ampicillin and sulbactam was, therefore, administered as an antibiotic.

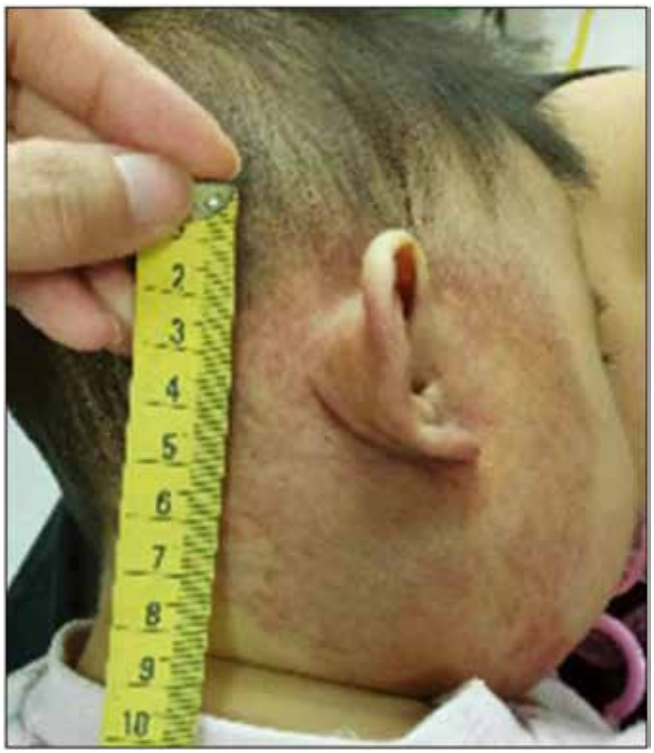

Figure 1: Kaposiform hemangioendothelioma on the right side of the patient's face

Because the patient's urine culture revealed *Escherichia coli* at 34000 CFU/mL, urinary tract infection was suspected. Therefore, gentamicin was added to her treatment on the 2nd day of hospitalization. On the fifth evening, the patient had a respiratory rate of 40–79 bpm, a heart rate of 190–220 bpm, a body temperature of 38.5°C, and blood pressure of 91/63 mmHg, with saturation on room air (SpO_2) of 94%. Auscultation revealed rales, and chest X-ray (CXR) revealed mild infiltrates [Figure 2A]. Respiratory syncytial virus, adenovirus antigen, pneumococcal urinary antigen, and rapid influenza diagnostic tests all yielded negative results. Abdominal ultrasound revealed no abnormalities, and cardiac ultrasound revealed no signs of heart failure. Because the patient's clinical symptoms were suggestive of PJP, a combination of trimethoprim (TMP) and sulfamethoxazole (SMX) was intravenously injected, and oxygen was supplemented through a nasal cannula at 0.5 L/min. Subsequently, the patient was transferred to the pediatric intensive care unit. On the 6th day, the patient had a respiratory rate of 50–74 bpm, a heart rate of 193 bpm, and an SpO_2 of 95%–98%. A grunting sound was detected during expiration, indicating respiratory distress, and thus, intubation was performed for ventilation.

Ventilator support

Pressure control ventilation (PCV) was initially used with a control pressure of 13 cmH_2O. The positive end-expiratory pressure (PEEP) was set to 5 cmH_2O, and the fraction of inspired oxygen (FiO_2) was set to 50%.

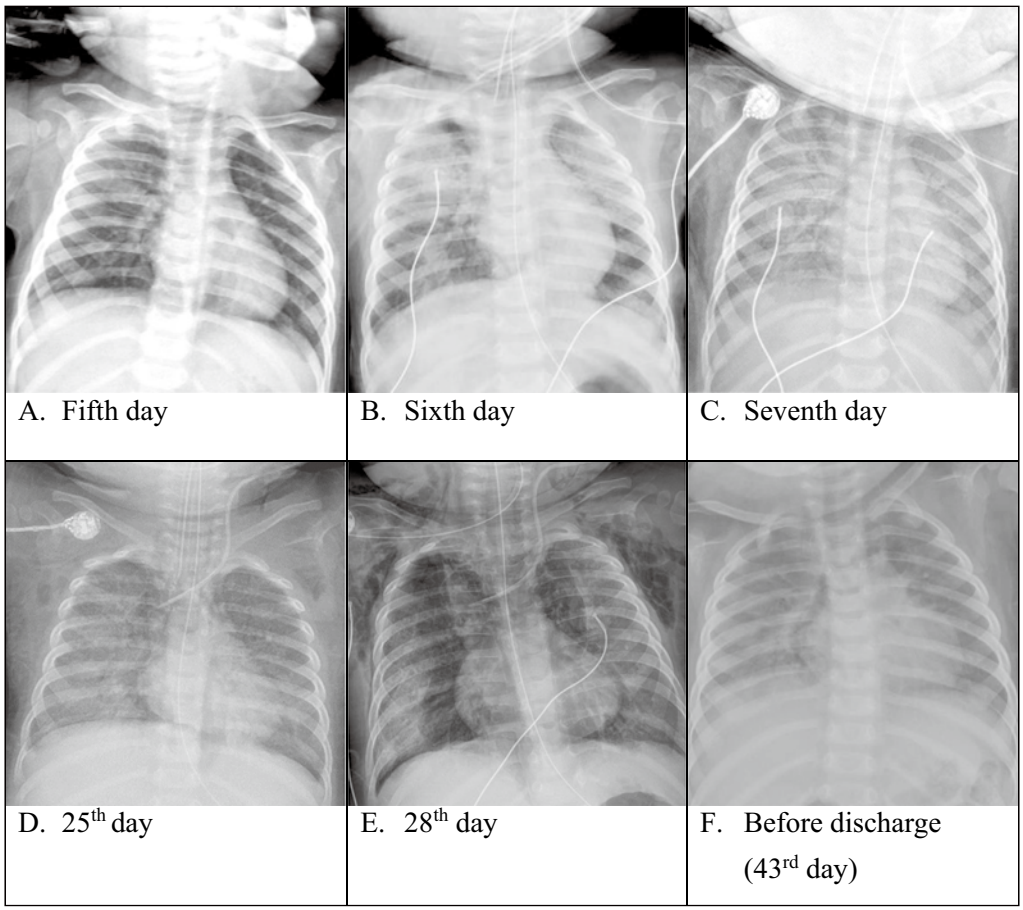

Figure 2: (A) Hyperaeration of the lungs. (B) Airspace opacities in the bilateral lung fields. (C) Progression with appearance of more airspace opacities. (D) Pneumomediastinum and subcutaneous emphysema in bilateral chest walls. (E) Increased amount of the pneumomediastinum with mild right pneumothorax. (F) Small amount of residual pneumomediastinum

Laboratory tests revealed an albumin level of 2.7 g/dL (reference range: 3.5–4.8 g/dL). Therefore, albumin was administered at 1 g/kg/day for 3 days, and furosemide was administered to control the patient's pulmonary edema. Nevertheless, the CXR results continued to deteriorate [Figure 2B], and therefore, the parameter settings on the ventilator were increased. On the 7th day, CXR revealed increased bilateral ground-glass opacities [Figure 2C], and therefore, steroids were intravenously administered. On the 10th day, the patient was ventilated in PCV mode, with an MAP of 17 cmH_2O, a peak inspiratory pressure (P_{peak}) of 28 cmH_2O, and an FiO_2 of 85%. Because the patient's SpO_2 dropped to 90%, the ventilation mode was switched from PCV to HFOV with the following settings: MAP = 22 cmH_2O, FiO_2 = 85%, respiratory frequency = 10 Hz, and pressure amplitude (ΔP) = 35 cmH_2O. Following this treatment strategy, the patient's SpO_2 gradually increased. On the next day, her FiO_2 dropped to 60%. On the 18th day, a sputum test report for *P. jirovecii* DNA revealed positive results, confirming a diagnosis of PJP. On the 25th day, the ventilator settings were reduced to an MAP of 10 cmH_2O and an FiO_2 of 55%. Follow-up CXR revealed both mediastinal and subcutaneous emphysema [Figure 2D]. Subsequently, the ventilator settings were gradually reduced again. On the 28th day, the patient was successfully extubated. Table 1 summarizes the patient's clinical course and treatments over time.

After extubation

The patient was transitioned to nasal continuous positive airway pressure (CPAP) mode, with the PEEP set to 6 cmH_2O and FiO_2 set to 60%. Following her extubation, CXR revealed a progressive air leak [Figure 2E], and the PEEP was further reduced to 3 cmH_2O. On the 30th day, the administration mode of TMP, and SMX was switched from intravenous to oral. On the 33rd day, the patient was successfully weaned off the CPAP device. On the 35th day, antibiotic therapy was discontinued, and PJP treatment was complete. Finally, on the 45th day, the patient was discharged.

Discussion

PJP clinically presents with fever, dry cough, dyspnea, and hypoxemia. In patients with PJP, lung auscultation may be normal or may reveal rales. Up to 39% of cases may

Table 1: Ventilation parameter settings, arterial blood analysis results, and medications

Days of hospitalization	Day 6	Day 7	Day 9	Day 10	Day 10	Day 11	Day 14	Day 16	Day 19	Day 24	Day 25	Day 28	Day 28	Day 28
Ventilation Mode	PCV	PCV	PCV	PCV	HFOV	HFOV	HFOV	HFOV	HFOV	HFOV	HFOV	HFOV	nCPAP	nCPAP
FiO_2 (%)	50	100	80	85	85	60	65	60	65	55	55	40	60	60
P_{peak} (cmH_2O)	23	25	24	28										
P_{mean} (cmH_2O)	14	16	16	17	22	22	22	19	16	12	10	8	6	3
PEEP (cmH_2O)	5	8	9	9										
PC level (cmH_2O)	15	16	15	15										
Rate/Hz	30/	30/	30/	30/	/10	/10	/10	/10	/8	/8	/10	/10		
Amplitude					35	20	22	22	24	24	22	20		
ABG														
PH	7.453			7.470	7.382		7.465	7.415	7.403	7.394	7.399		7.431	
$PaCO_2$ (mmHg)	28.1			29.1	41.6		37.7	43.5	53.1	35.6	38.6		41.3	
PaO_2 (mmHg)	52			58.1	91.7		61.5	66.5	96.2	86.6	82.5		154.9	
P/F ratio	104			68.4	107.9		94.6	110.8	148	157.5	150		258.2	
Methylprednisolone		7th–10th day				11th–18th day			19th–23th day	24th–27th day			28th day	
		1.08 mg/kg/day				0.54 mg/kg/day			0.27 mg/kg/day	0.14 mg/kg/day			1.89 mg/kg/day	

ABG = arterial blood gas test, HFOV = high-frequency oscillatory ventilation, nCPAP = nasal continuous positive airway pressure, P/F ratio = PaO_2/FiO_2 ratio, PC level = pressure control level above PEEP, PCV = pressure control ventilation, PEEP = positive end-expiratory pressure, P_{mean} = mean airway pressure, P_{peak} = peak airway pressure.

Trimethoprim/sulfamethoxazole: 16.2/81.1 mg/kg/day, 5th–30th day: intravenous administration, 31st–35th day: oral administration

have normal CXR results at the initial diagnosis. High-resolution computed tomography is more sensitive than CXR in detecting PJP, which may involve round-glass opacities, reticular opacities, or septal thickening.[2,9] In HIV-infected individuals with PJP, the course of the disease is typically subacute. However, immunocompromised individuals without HIV may experience a more rapid disease progression, which may result in sudden respiratory distress, hypoxia, and respiratory failure.[1-3] Multiple retrospective studies have indicated that the mortality rate of non-HIV-infected individuals ranges between 20% and 50%, which is evidently higher than that of HIV-infected individuals (between 10% and 20%).[10-17]

At a microscopic level, *P. jirovecii* attach to type I alveolar epithelial cells and transform from a small trophic form to a larger cystic form. Pathologically, *P. jirovecii* infection is associated with two types of manifestations: typical manifestations and atypical manifestations.[18,19] In typical manifestations, interstitial inflammation and infiltration result in diffuse lung injury and the proliferation of hyaline membranes and alveolar epithelial cells, especially of type II pneumocytes. Eosinophilic foamy substances are also discharged as exudates into the alveolar spaces. These exudates predominantly consist of *P. jirovecii* trophozoites, cysts, cellular debris, and fibrin. In atypical manifestations, dense lymphocytic infiltration is observed in the interstitial cells of the lungs. This process results in the formation of multiple cavities following interstitial cell breakdown and necrosis, leading to localized calcification and confluent parenchymal necrosis, which present as a fibrocaseous nodular pattern.[18] Nevertheless, regardless of the type of manifestation, *P. jirovecii* targets the patient's lung interstitial tissues.[18,20]

Overall, the imaging findings of PJP are consistent with its pathological findings. CXR of a typical PJP manifestation normally reveals increased diffused interstitial infiltration, concentrated around the perihilar area and lower lung lobes during the early stages of the disease, which later expands to the entire lungs.[18,21,22] This form of interstitial pneumonia differs from conventional bacterial pneumonia (alveolar damage is more predominant in conventional bacterial pneumonia).[20] Both types of pneumonia are associated with inadequate blood oxygen saturation. However, in patients with alveolar damage, the cause of hypoxemia is a reduced gas exchange surface area, whereas in patients with interstitial damage, the cause of hypoxemia is the change that occurs to the pathway through which oxygen passes to enter the alveolar vessels after its exchange through the alveolar–capillary membrane. Hence, the mechanisms underlying hypoxemia for the two patient groups are slightly different.[18,20]

The combination of TMP and SMX is regarded as the first-line treatment for PJP in both adults and children.[3] The recommended dosages of TMP and SMX are 15–20 and 75–100 mg/kg/day, respectively, either orally or intravenously, for a period of 21 days.[1,10] Research has indicated that corticosteroids are useful in treating HIV-infected patients with PJP. According to a literature review by Ding *et al.*,[23] the use of corticosteroids as an adjunctive therapy in immunocompromised patients without HIV may reduce their mortality rates.[1,10,23] In our case, we started our patient on a combination of TMP and SMX from the 5th day of hospitalization. Later, we performed intubation and used a ventilator because the patient experienced respiratory failure. When the patient's oxygen demand increased, we gradually

increased her airway pressure. Moreover, CXR revealed an increase in bilateral lung opacities. Therefore, we started steroid treatment from the 7th day. The patient's oxygen level could be gradually decreased after the 9th day of hospitalization. Nevertheless, the patient still required high ventilator settings. On the 10th–14th days, the patient's MAP reached 22 cmH_2O, indicating that, despite receiving effective treatment, she required proper respiratory treatment to maintain her stability.

Lung infectious diseases often result in uneven lung compliance. VILI refers to the risk of overdistention in mechanically ventilated lungs with high compliance, which results in volume trauma or barotrauma. By contrast, in mechanically ventilated lungs with low compliance, atelectrauma may occur because of the repetitive alveolar expansion and collapse during the respiratory cycle. Hence, avoiding VILI is regarded as a great challenge in clinical practice.[24,25] Unlike CMV, HFOV requires a constant MAP. It also requires a respiratory frequency that exceeds physiological levels to provide patients with tidal volumes smaller than the dead space, which is typically referred to as *ΔP*.[25] In addition, it enables the use of an increased MAP to prevent alveolar collapse and provides an extremely low tidal volume to prevent alveolar rupture due to overdistension. Therefore, HFOV is often considered a lung protective strategy.[5,6,25] Conventionally, in preterm infants or newborns with respiratory distress syndrome, HFOV is used as a rescue strategy when CMV fails to maintain adequate oxygenation or when the parameters are set to be too high.[7,8,25-27]

Most cases of pneumonia-induced ARDS occur as a result of reduced alveolar compliance secondary to bacterial alveolar damage. However, the extent of damage in each alveolus varies, leading to a unique compliance level in each alveolus. Conventional ventilation with a high airway pressure may result in an excessive airway pressure on relatively compliant alveoli when the highest airway pressure is applied, leading to barotrauma. To avoid this drawback, a high-frequency ventilation mode with a stable MAP can be used. In patients with PJP, interstitial damage is more obvious than alveolar damage, and interstitial inflammation reduces lung compliance. Multiple studies have indicated that patients with interstitial pneumonia become prone to air leaks and barotrauma when they are placed on ventilatory support.[28-30] In many studies, HFOV has been used as a preventive therapeutic strategy for managing infant air leaks.[31-34] For instance, Aurilia *et al.*[35] proposed adopting HFOV as a first-line treatment for pneumothorax in hemodynamically stable preterm infants who do not require chest tube insertion.[35] Nonetheless, only a few studies have investigated whether high-frequency ventilation is suitable for use in cases of interstitial pneumonia. In our case, we used conventional ventilation with a peak airway pressure of 28 cmH_2O (MAP = 17 cmH_2O). However, we were unable to maintain a stable oxygen concentration. Generally, a peak airway pressure of 28 cmH_2O may result in barotrauma in the alveoli of infants. In our case, after we used HFOV, the effect of peak airway pressure on the patient's lungs decreased, and we were able to gradually increase the patient's MAP to 22 cmH_2O under poor oxygen conditions. On the 25th day of hospitalization, the patient developed pneumomediastinum, even at a ventilation MAP of 10 cmH_2O. This finding is consistent with a previous argument that interstitial pneumonia is prone to air leaks. Therefore, in patients with interstitial pneumonia, excessive positive air pressure must be avoided. Under relatively stable conditions, we switched the ventilation mode to noninvasive negative-pressure ventilation (CPAP) on the 28th day of hospitalization, and we subsequently observed a gradual improvement in pneumomediastinum.

Overall, we recommend that clinicians consider the early implementation of high-frequency ventilation strategies in cases of interstitial pneumonia with high ventilator settings, reduce the peak airway pressure, and closely monitor their patients to prevent air leaks.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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