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Addresses

Editorial Correspondence
Prof. Gary Wing-kin Wong
Hong Kong Society of Paediatric Respirology and Allergy
4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wan Chai, Hong Kong.
E-mail: wingkinwong@cuhk.edu.hk
Website: www.prccm.org

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Contents

Editorial

This edition of the journal contains three articles that highlight different but important aspects of respiratory diseases.

Pertussis is the most common vaccine-preventable disease causing respiratory infections.[1] Pertussis is frequently under-diagnosed as it presents in older children and adults in a similar manner as any other viral respiratory tract infection.[2] Infants are the ones at greatest risk of severe infection especially those below the age of 6 months of age and in particular below 2 months of age as they are not protected by primary immunization and a single dose of the vaccine is insufficient to confer adequate protection. Furthermore, the current acellular vaccines are safer with fewer serious side effects but we traded safety for efficacy as the period of protection conferred by the acellular vaccines are shorter compared to the whole cell vaccines and immunity wanes faster.[3] Children and adults will require booster doses after vaccination with the acellular vaccine.

Treatment is with the early initiation of macrolides if recognized. As it is frequently missed, prevention becomes paramount. The various strategies have included cocoon strategy which includes immunizing the mother and household contacts of the newborn. This stems from the fact that the majority of transmission of infection is from household contacts which can be as high as 64%, the most frequent being parents at 45% and older siblings (29%).[4] The cocoon strategy is difficult to implement as it is difficult to get all the relevant household contacts to be vaccinated. Maternal immunization with Tdap in the 3rd trimester of pregnancy is a more feasible option and has been shown to be effective with a vaccine efficacy of 78%–91%.[5,6]

Another important area in paediatrics is the role of hyperoxia in the development of acute lung injury. Oxygen is given very frequently in the management of respiratory illnesses and especially in the premature infants where the lung is not well developed. This study by Jiang *et al*.[7] hopes to find solutions to reduce the effects of hyperoxia on the neonatal lung with the use of early surfactant instillation. Hyperoxic acute lung injury is postulated to be caused by the induction of inflammation and oxidative stress causing impaired development of the lung brought on by prolonged exposure to high levels of oxygen. There is a lack of consensus on the treatment of neonatal hyperoxic lung injury. Corticosteroids, have anti-inflammatory effects and have been used.[8] Early selective surfactant administration has also been shown to be decrease the overall risk of bronchopulmonary dysplasia.[9] Other potential treatment options include mesenchymal stem cell transplant to improve alveolization and pulmonary vascular development, IL-1 receptor antagonists by inhibiting inflammatory cytokines, caffeine and Vit D which down-regulates IL-1β and IFN-γ and thereby decreasing inflammatory responses.[10]

The last article reports a rare condition in children which is hypersensitivity pneumonitis. Though uncommon, it is seen in children and must be thought of as it can have severe consequences if not properly managed. Lentil aspiration causing hypersensitivity pneumonitis has only been reported from India so far.[11] This highlights some differences in feeding practices which is important to be communicated to the parents in India so that this condition can be prevented.

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There are no conflicts of interest.

Anne Goh

Allergy and Respiratory Service, KK Women's and Children's Hospital, Singapore, Singapore

Address for correspondence: Dr. Anne Goh, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899, Singapore.
E-mail: anne.goh.e.n@singhealth.com.sg

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Review Article

Critical Pertussis: "Prevention is better than cure"

M. Jayashree[1], T. K. Kavitha[2]

[1]Pediatric Critical Care Unit, Advanced Pediatrics Centre, PGIMER Chandigarh, [2]Pediatric Intensive Care Unit, Department of Pediatrics, Malabar Medical College Hospital and Research Centre, Calicut, Kerala, India

Abstract

The global incidence of pertussis has increased in the last two decades. Critical pertussis (cases necessitating intensive care unit admission or resulting in death) is a major health concern, especially among infants. Inadequately transferred maternal immunity, high susceptibility to disease before completion of the primary immunization schedule, and differential expression of pertussis toxins are some of the proposed reasons for higher disease burden in infancy. Adolescent children with waning immunity and susceptible adults contribute to the transmission of the disease. Siblings and parents are a major source of infection in infants. Multisystem involvement includes respiratory failure, central nervous system manifestations, shock, and pulmonary artery hypertension. Hyperleukocytosis, a characteristic feature of critical pertussis, is a proven risk factor for increased mortality. Other predictors of mortality include pulmonary artery hypertension, requirement of mechanical ventilation, and vasoactive requirements. Early macrolide antibiotics and organ support measures are the major domains of management. Intensive care needs include mechanical ventilation, inotropic support, and leukodepletion measures. Studies regarding optimal management strategies are scarce, and strategies like leukapheresis or ECMO have shown variable mortality benefit in literature. Routine immunization along with adolescent booster dose and immunization of pregnant mothers have shown promising impacts on reducing pertussis-related morbidity and mortality. We describe the updates regarding the risk factors for resurgence, disease morbidity, and management strategies in children with critical pertussis.

Keywords: Critical pertussis, vaccine preventable, hyperleukocytosis, pertussis vaccine, pulmonary artery hypertension

Introduction

Periodic outbreaks of pertussis and an overall increase in the incidence of pertussis have been reported from various parts of the world, including India, in the last two decades. Although introduction of vaccine in the 1940s led to a decrease in the incidence of pertussis, a worrisome trend of resurgence of pertussis cases and outbreaks has been reported from many countries since the 1980s.[1-4] Despite achieving 85% vaccine coverage, the disease burden in children continues to be high.[5] Inadequate surveillance systems and reduced awareness regarding the disease are major impediments in generating pertussis-related data from low- and middle-income countries (LMICs). Similarly, the data related to critical pertussis are also scarce, with few reports from LMICs including India.[6] The exact cause of resurgence of this vaccine-preventable disease remains unclear, although multiple postulations like bacterial antigenic shifts; waning immunity in adolescents, especially after acellular pertussis vaccine; and reduced maternal antibody levels, limiting its transfer to infants, have been put forth.[1] The diagnosis of pertussis can often be missed as it tends to masquerade as any other common acute respiratory infection. Due to similar symptomatology, many viral infections such as RSV, adenovirus, influenza, and para influenza get clubbed together as "pertussoid illnesses." Identifiable sources of infection have been seen in about 27%–43% of infant with pertussis, which is usually mother or siblings.[7-9]

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Address for correspondence: Dr. M. Jayashree, Pediatric Critical Care Unit, Advanced Pediatrics Centre, PGIMER Chandigarh, Chandigarh 160012, India.
E-mail: mjshree64@gmail.com

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Risk factors

Recent studies reflect a higher burden of pertussis among infants, with critical pertussis predominantly affecting infants younger than 3 months of age. The median age of children with critical pertussis ranges between 45 days and 3.5 months.[6,10-12] Low maternally transferred passive immunity and incomplete primary pertussis vaccination are some of the reasons postulated for both increased burden and severity in younger infants.[13] Although regarded as a childhood disease, many pertussis cases are also being reported among adults and adolescents, suggesting a high prevalence and disease susceptibility in the community.[14,15] Skoff *et al.* in a study published from the US in 2015, showed that the sources of infection in infantile pertussis were siblings, followed by parents.[9] The reason for increased severity of disease in infants is unclear; pertussis toxin-mediated leukocytosis and leukostasis might be responsible for worse treatment outcomes in this age group.[16] Animal studies on mice suggest an age-dependent effect of pertussis toxin. Neonatal mice showed increased toxin-mediated leukocytosis, bacterial colonization, cardiac remodeling, pulmonary artery hypertension, and death as compared to adult mice. Pertussis toxin surprisingly inhibited lung inflammation in younger mice in comparison to promotion of lung inflammation in adult mice.

Pertussis toxin-mediated extrapulmonary bacterial dissemination was severe in neonatal mice as compared to adult mice, in whom it was negligible. Studies have also proposed that mortality in neonatal mouse models might be related more often to non-pulmonary rather than pulmonary effects of pertussis toxin.[17,18]

Clinical and laboratory diagnosis

Clinically probable pertussis is defined as "any patient with cough lasting ≥2 weeks with at least one of the following symptoms – paroxysmal cough, inspiratory whoop or post-tussive vomiting or any duration cough with contact with a lab confirmed case of pertussis."[5]

The chest X-ray findings described are usually diffuse infiltrates, hyperinflated lung fields, or atelectatic changes.[19] Confirmation requires detecting *Bordetella pertussis* in the clinical specimen by polymerase chain reaction (PCR) or culture. Critical pertussis is defined as pertussis resulting in death or needing admission to an intensive care unit (ICU).[20] Life-threatening complications include respiratory failure, hyperleukocytosis, shock, and pulmonary arterial hypertension (PAH). Total leukocyte count (TLC) > 50,000/μL is regarded as hyperleukocytosis. The mortality rate in critical pertussis cases ranges from 4.8% to 34%.[21,22]

In a retrospective case series published from Level 3 PICU of the author's tertiary care center, the clinical profile, complications, intensive care needs, and predictors of mortality in 36 cases with critical pertussis over a period of 3 years were described.[10] Infants were commonly affected (31, 86.1%), and 10 (27.7%) were less than 6 weeks and had not yet started their primary pertussis immunization. Among the remaining 26 children (beyond 6 weeks of age), 16 (61.5%) were either partially immunized or unimmunized. The symptoms at presentation were rapid breathing [n = 32 (88.9%)], typical paroxysmal cough [n = 31 (86.1%)], and apnea [n = 15 (41.7%)]. Most patients (35, 97.2%) had hypoxemia (SPO2 < 94% in room air) at admission. Common complications included hypoxemia (97.2%), hyperleukocytosis (61.1%), and encephalopathy (52.8%). Mechanical ventilation in 11 (30.6%), vasoactive support in 7 (19.4%), and exchange transfusion (ET) in 3 (8.3%) were major intensive care needs. This cohort had a significantly higher prevalence of hyperleukocytosis, seizures, and encephalopathy as compared to previously published reports; one-third had PAH.[10] A study by Peters *et al.* postulated that hyperleukocytosis, leukostasis, and lymphocytic aggregation in the pulmonary vasculature results in pulmonary vessel obstruction, leading to pulmonary artery hypertension in pertussis.[23] Higher TLC of 315,00/cumm was shown to be a predictor for developing critical pertussis.[24] Female gender, hyperleukocytosis, apnea, need for vasoactive support and mechanical ventilation, and encephalopathy were predictors of poor outcomes in the cohort of critical pertussis from the author's center.[10] Out of the seven deaths, only one child had secondary bacterial infection. In fact, none of the patients in that cohort were suspected or diagnosed with pertussis nor were started on macrolide antibiotics before referral. Missed diagnosis can change the course of "benign pertussis to critical" due to evolving complications.

Treatment

Treatment modalities of critical pertussis remain largely supportive and mainly focus on organ support measures along with timely initiation of antibiotics such as erythromycin, azithromycin, or clarithromycin. Since hyperleukocytosis is a major risk factor for mortality, early leukodepletion/leukoreduction by ET or hemofiltration have been tried in few case series and studies with variable outcomes.[25-28] In a study from China, out of 12 infants who underwent ET for critical pertussis, eight children survived.[27] Another case series reported survival in five out of 10 children who underwent ET for leukocytosis.[28] Although leukodepletion for mortality reduction in critical pertussis requires further exploration, pre-extracorporeal membrane oxygenation (ECMO) leukodepletion was shown to be beneficial in improving survival of critical pertussis requiring ECMO.[29] In a study done in 200 critical pertussis patients treated with ECMO, the mortality benefit was observed in 58 children (26% survival), suggesting not so favorable

outcomes even after ECMO in such children. Use of vasoactive agents, renal or neurological dysfunction, and PAH were associated with increased mortality in them.[29] Use of hydroxyurea for critical pertussis leukocytosis was reported in few case reports.[30,31] Management in the PICU includes screening for PAH and other complications such as apnea, shock, or encephalopathy and ensuring organ support measures like mechanical ventilation, neuroprotection, inotropic support, renal replacement therapy, or extracorporeal membrane oxygenation (ECMO) as and when required.[6]

Prevention

Resurgence of a vaccine preventable disease such as pertussis with high mortality and morbidity, especially among young infants, is a major concern, which demands a detailed relook at our current immunization strategies.[13,32] The higher incidence of critical pertussis in very young infants, before initiation or completion of their primary immunization schedule, brings the spotlight on the need for maternal immunization against pertussis. In a study by Marcellini *et al.*, mothers of healthy infants were found to have low serum IgG anti-pertussis toxin antibody and low IgA reacting to pertussis bacteria in breast milk, suggesting low potential for transfer of passive immunity from mothers to infants.[33] Acellular pertussis vaccines result in rapid weaning immunity, thus making adolescents prone to infection.[34,35] Introduction of booster adolescent vaccination with aP (acellular pertussis) vaccine, and immunization of pregnant mothers with Tdap (tetanus, diphtheria, and acellular pertussis) have shown promising results in reducing disease burden in infants and in adolescents.[36-38] A study from Columbia reported drastic reduction of pertussis incidence and mortality in infants after introduction of maternal immunization with TdaP vaccination.[36] Critical pertussis poses a serious health threat to children, especially young infants. Since treatment options are limited, preventive measures, booster vaccinations, maternal immunization, and surveillance are the keys to tackling it.

Author contributions

M. Jayashree and Kavitha TK drafted the initial manuscript and critically reviewed and revised the manuscript. They approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data availability

Our previous study data are available in the following publication "Kavitha TK, Samprathi M, Jayashree M, Gautam V, Sangal L. Clinical Profile of Critical Pertussis in Children at a Pediatric Intensive Care Unit in Northern India. Indian Pediatr 2020;57: 228–31."

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Conflicts of interests

There are no conflicts of interest.

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Original Article

Intratracheal Surfactant Administration Attenuates Hyperoxia-Induced Lung Injury and Fibrosis in Neonatal Rats

Jiunn-Song Jiang, Chi-Chun Hsieh[1], Hsiu-Chu Chou[2], Chung-Ming Chen[3,4]

Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, [1]Department of Pediatrics, Hsiang Ann Clinic, Miaoli, [2]Department of Anatomy and Cell Biology, School of Medicine, College of Medicine, Taipei Medical University, [3]Department of Pediatrics, Taipei Medical University Hospital, [4]Department of Pediatrics, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

Abstract

Background: Hyperoxia decreases surfactant production and suggests exogenous surfactant may be a potential treatment for hyperoxia-induced lung injury. This study aimed to investigate the effects of an animal-derived surfactant on hyperoxia-induced lung injury and fibrosis in newborn rats. **Methods:** Sprague Dawley rat pups were randomly reared either in room air (RA) or hyperoxic conditions (85% O_2) from postnatal days 1–14. On postnatal day 4, the rats received an intratracheal injection of either 20 μL of normal saline (vehicle) or 20 μL of surfactant (Survanta). Our study included four study groups: RA + vehicle, RA + surfactant, 85% O_2 + vehicle, and 85% O_2 + surfactant. Body weights were recorded at birth and on postnatal days 4 and 14. On postnatal day 14, the lungs were dissected for histology, Western blotting, and cytokine measurements. **Results:** The hyperoxia-reared rats exhibited significantly higher lung injury scores, tumor necrosis factor-α (TNF-α) expression, transforming growth factor-β1 (TGF-β1) expression, and collagen deposition compared with the RA-reared rats. The surfactant alleviated hyperoxia-induced lung injury, inflammation, and fibrosis, as evidenced by the lower lung injury score, TNF-α expression, TGF-β1 expression, and collagen deposition in the lungs. **Conclusion:** The intratracheal administration of the surfactant ameliorated hyperoxia-induced lung injury and fibrosis and downregulated TNF-α and TGF-β1 expression, most likely by inhibiting lung inflammation and collagen deposition.

Keywords: Collagen, lung, newborn, transforming growth factor-β1, tumor necrosis factor-α

Introduction

A pulmonary surfactant is a compound composed of phospholipids, surfactant proteins (SPs), and a neutral lipid that helps maintain the health of alveoli by lowering surface tension and controlling lung inflammation.[1] Each SP serves a specific function.[2,3] SP-A and SP-D play a role in local immune modulation, whereas SP-B and SP-C contribute to reducing surface tension.[4] Hyperoxia significantly alters the expression of SPs,[5] downregulates surfactant phospholipid synthesis, induces surfactant dysfunction in adult murine lungs, and modifies the phosphatidylcholine synthesis pathway in newborn rats.[6-8] These findings suggest that hyperoxia decreases surfactant production and that exogenous surfactants may be a potential treatment for hyperoxia-induced lung injury.

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Surfactant delivery reduces the risks of pulmonary air leak, bronchopulmonary dysplasia, and mortality in preterm babies with established respiratory distress syndrome.[9-11] Rescue surfactants have similarly been recommended for infants with hypoxic respiratory failure due to secondary surfactant deficiency, pulmonary hemorrhage, meconium aspiration syndrome, sepsis/pneumonia, and ventilator-induced lung injury.[12,13] Prophylactic intranasal administration of an animal-derived surfactant

Address for correspondence: Dr. Chung-Ming Chen, Department of Pediatrics, Taipei Medical University Hospital, Taipei, 110 Taiwan.
E-mail: cmchen@tmu.edu.tw

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(Curosurf) prevents lung injury induced by hyperoxia in adult mice (100% for 24 h).[14] However, the long-term effects of surfactant use on hyperoxia-induced lung injury in newborn rats remain unknown.

Neonates with respiratory distress at birth are at risk of hyperoxic injury due to the clinically recommended supraphysiological supplementation of oxygen to reverse hypoxemia. Type II cell proliferation and pulmonary surfactant production were disrupted in neonatal mice subjected to hyperoxia for 4 days.[15] Exposure to hyperoxic conditions (85% O_2 for 7 days) altered the mRNA levels of lipid metabolism enzymes in neonatal rats.[8] In neonatal Sprague Dawley rats, hyperoxia during the first 3 days of life increased inflammatory cell infiltration in alveolar gaps as well as the wet-to-dry lung weight ratio.[16] Surfactants attenuate air embolism-induced lung injury by suppressing the nuclear factor-κB activation and decreasing proinflammatory cytokine expression in isolated-perfused rat lungs.[17] According to these findings, hyperoxia reduces surfactant synthesis and causes lung inflammation, indicating that the administration of a surfactant may be a treatment modality for hyperoxia-induced lung injury in neonatal rats. This study aimed to investigate the effects of intratracheal administration of an animal-derived surfactant (Survanta) on hyperoxia-induced lung injury and fibrosis in neonatal rats.

Materials and Methods

Animal model and experimental groups

Pregnant Sprague Dawley rats were housed in individual cages with *ad libitum* access to laboratory food and water, maintained on a 12-h/12-h light/dark cycle, and permitted to deliver vaginally at term.[18] Within 12-h post-delivery, the litter was pooled and randomly redistributed among the mothers who had recently given birth. From postnatal days 1–14, the pups were randomly exposed either to room air (RA) or an oxygen-enriched atmosphere (85% O_2). The nursing mothers alternated between the 85% O_2 and RA groups every 24 h to prevent the development of oxygen toxicity and to eliminate the effect of individual mothers between the groups. An oxygen-rich atmosphere was maintained by continuously delivering O_2 at 4 L/min to a transparent plexiglass chamber measuring 40 cm × 50 cm × 60 cm. The oxygen concentration inside the hyperoxic chamber was continuously monitored by using an oxygen sensor (Coy Laboratory Products, Grass Lake, MI, USA). On postnatal day 4, the rats received an intratracheal injection of either 20 μL of normal saline (vehicle) or 20 μL of the surfactant (Survanta; AbbVie, North Chicago, IL, USA), approximately corresponding to 50 mg/kg of phospholipids. Though the dose was half that for humans (100 mg phospholipids/kg), we chose this dose because intratracheal injection of 20 μL of the surfactant administered on postnatal days 4 or 5 decreased lung cytokine levels on postnatal day 14.[19,20] The intratracheal injections were administered as described by Chen *et al.*[21] Briefly, the rats were anesthetized with isoflurane and immobilized on a board at a fixed angle. A 0.3-cm vertical midline neck incision was made above the trachea using microscissors to avoid damaging the carotid arteries, and the trachea was located with the help of curved-tip tapered tweezers without a hook. A 100-μL syringe was held upright, and 20 μL of vehicle or surfactant was slowly injected into the trachea through a 30-G needle during the inspiratory phase. The incision was sutured with a 6-0 silk stitch. A knot was tied, and the end was cut as short as possible. We designed four study groups: RA + vehicle, RA + surfactant, 85% O_2 + vehicle, and 85% O_2 + surfactant. Body weights were recorded at birth and on postnatal days 4 and 14. On postnatal day 14, the rats were anesthetized with 2% isoflurane (Halocarbon Laboratories, River Edge, NJ, USA) in an anesthesia chamber and euthanized by cardiac puncture. The lungs were subjected to histological studies, Western blotting, and cytokine measurements.

Lung histology

Before being embedded in paraffin, the lungs were soaked in 4% paraformaldehyde, rinsed with phosphate-buffered saline, and serially dehydrated in increasing concentrations of ethanol. Lung tissues were collected from the right middle lobe to standardize the analyses. A pathologist who was blinded to the procedure and experimental groups assessed lung morphology and fibrosis by evaluating 5-μm sections of lung tissue stained with hematoxylin and eosin and Masson's trichrome. Following the recommendations of the American Thoracic Society Official workshop report, we examined changes in the extracellular hyaline material (glassy eosinophilic substance accumulation between cells in the interstitium), hemorrhage, infiltration of inflammatory cells, and intactness of the alveolar epithelium.[22-24] Lung injury was scored using a 5-point severity scale (0 = within normal limits, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe).[24] The optical density values of Masson's trichrome-stained sections were determined to evaluate the presence of collagen in 10 nonoverlapping microscopic fields per animal. The images were processed using Image-Pro Plus 6.0 (Media Cybernetics; Bethesda, MD, USA).[25]

Lung volume fraction

The volume fraction was determined using digitized images with five nonoverlapping fields (four corners and one central region) selected from each section. The images were printed and examined at a final magnification of 200×. A total of 10 regions were randomly observed per animal. The number of points along the alveolar airspace and alveolar walls was counted by superimposing 49-point transparent grids onto the enlarged printed images. The volume fraction was defined as P_i/P_t, where P_i is the number of test points coinciding with the structure of interest and P_t is the total number of points coinciding with the reference space.[26]

Lung cytokine level

Lung tissue was homogenized in 1 mL of ice-cold lysis buffer containing 1% Nonidet P-40, 0.1% sodium dodecyl sulfate, 0.01 M deoxycholic acid, and a complete protease inhibitor cocktail. The cell extracts were centrifuged, and the level of tumor necrosis factor-α (TNF-α) in the supernatant was measured using an enzyme-linked immunosorbent assay kit (Cloud-Clone Corp., Houston, TX, USA).

Immunohistochemistry of transforming growth factor-β1 (TGF-β1)

After routine deparaffinization and rehydration, the slides were immersed in 0.01 M sodium citrate buffer (pH 6.0) for heat-induced epitope retrieval. The sections were incubated for 1 h at room temperature with 0.1 M phosphate-buffered saline containing 10% normal goat serum and 0.3% H_2O_2 to block endogenous peroxidase activity and nonspecific antibody binding. Subsequently, the sections were probed for 20 h at 4°C with mouse monoclonal anti-TGF-β1 primary antibody (1:50; Santa Cruz Biotechnology, CA, USA), treated for 1 h at 37°C with biotinylated goat anti-mouse IgG (1:200; Jackson ImmunoResearch Laboratories, PA, USA), and subjected to a reaction involving the reagents from an avidin–biotin complex kit (Vector, CA, USA). The brown reaction products were visualized using a diaminobenzidine substrate kit (Vector) as per the manufacturer's recommendations. All immunostained sections were viewed and photographed using an Olympus BX43 microscope.

Western blotting of TGF-β1

Lung tissues were homogenized in ice-cold buffer containing 50 mmol/L Tris·HCl (pH 7.5), 1 mmol/L ethylene glycol tetraacetic acid, 1 mmol/L ethylenediaminetetraacetic acid, and a protease inhibitor cocktail (cOmplete mini-tablets; Roche, Mannheim, Germany). Proteins (30 μg) were resolved through 12% sodium dodecyl sulfate–polyacrylamide gel electrophoresis under reducing conditions and electroblotted onto a polyvinylidene difluoride membrane (Immobilon P, Millipore, Bedford, MA, USA). The membrane was blocked with 5% nonfat dried milk, probed with anti-TGF-β1 (1:500, 3C11 Sc-130348; Santa Cruz Biotechnology) and anti-β-actin (1:1000, C4 sc-47778; Santa Cruz Biotechnology) antibodies, and incubated with horseradish peroxidase-conjugated goat anti-mouse antibody (Pierce Biotechnology, Rockford, IL, USA). Protein bands were detected using the BioSpectrum AC System (Pierce Biotechnology). β-Actin was used as an internal control. The densitometry unit of protein expression in the RA + vehicle group was assigned as 1 after normalizing it to the expression of β-actin.

Statistical analysis

Lung injury score data are presented as the medians (range); other data are presented as the means ± standard deviations. Statistical analyses were performed using a two-way analysis of variance with the Bonferroni *post hoc* test for multiple-group comparisons. The survival rate was evaluated using the Kaplan–Meier method, and the log-rank test was used for intergroup comparisons. Correlations between lung injury scores and volume fractions were analyzed using Pearson's correlation coefficients. Differences were considered statistically significant if $P < 0.05$.

Results

Intratracheal surfactant administration improved the survival rate

All the rats reared in RA and treated with vehicle ($n = 13$) or surfactant ($n = 11$) survived [Figure 1A]. The rats reared in hyperoxia exhibited respiratory distress. The survival rate of rats reared in hyperoxia and treated with surfactant (8/10 = 80%) was significantly higher than that of rats reared in hyperoxia and treated with vehicle (5/11 = 45.5%, $P < 0.05$).

Body-weight and lung-to-body-weight ratio

The body weights at birth and on postnatal days 4 and 14 and the lung-to-body-weight ratios on postnatal day 14 were comparable among the four study groups [Figure 1B–E].

Intratracheal surfactant administration ameliorated hyperoxia-induced lung injury

Vehicle-treated rats reared in hyperoxia exhibited large thin-walled air spaces [Figure 2A], significantly higher lung injury scores [Table 1] and alveolar airspace volume fractions, and significantly lower alveolar wall volume fractions compared with vehicle- or surfactant-treated rats reared in RA [Table 2]. Surfactant treatment significantly mitigated the hyperoxia-induced increase in the lung injury score but did not improve hyperoxia-induced alterations in volume fraction.

The lung injury score was significantly negatively correlated with alveolar wall volume fraction ($r = -0.549$, $P < 0.0001$) and significantly positively correlated with alveolar airspace volume fraction ($r = 0.542$, $P < 0.001$).

Intratracheal surfactant administration reduced hyperoxia-induced increase in TNF-α

On postnatal day 14, vehicle-treated rats reared in hyperoxic environment exhibited significantly higher TNF-α levels than vehicle- or surfactant-treated rats reared in RA [Figure 2B, $P < 0.05$]. TNF-α levels were lower in surfactant-treated rats compared with untreated rats.

Intratracheal surfactant administration attenuated hyperoxia-induced increase in TGF-β1

TGF-β1 immunoreactivity was primarily detected in epithelial cells [Figure 3A]. Vehicle-treated rats reared

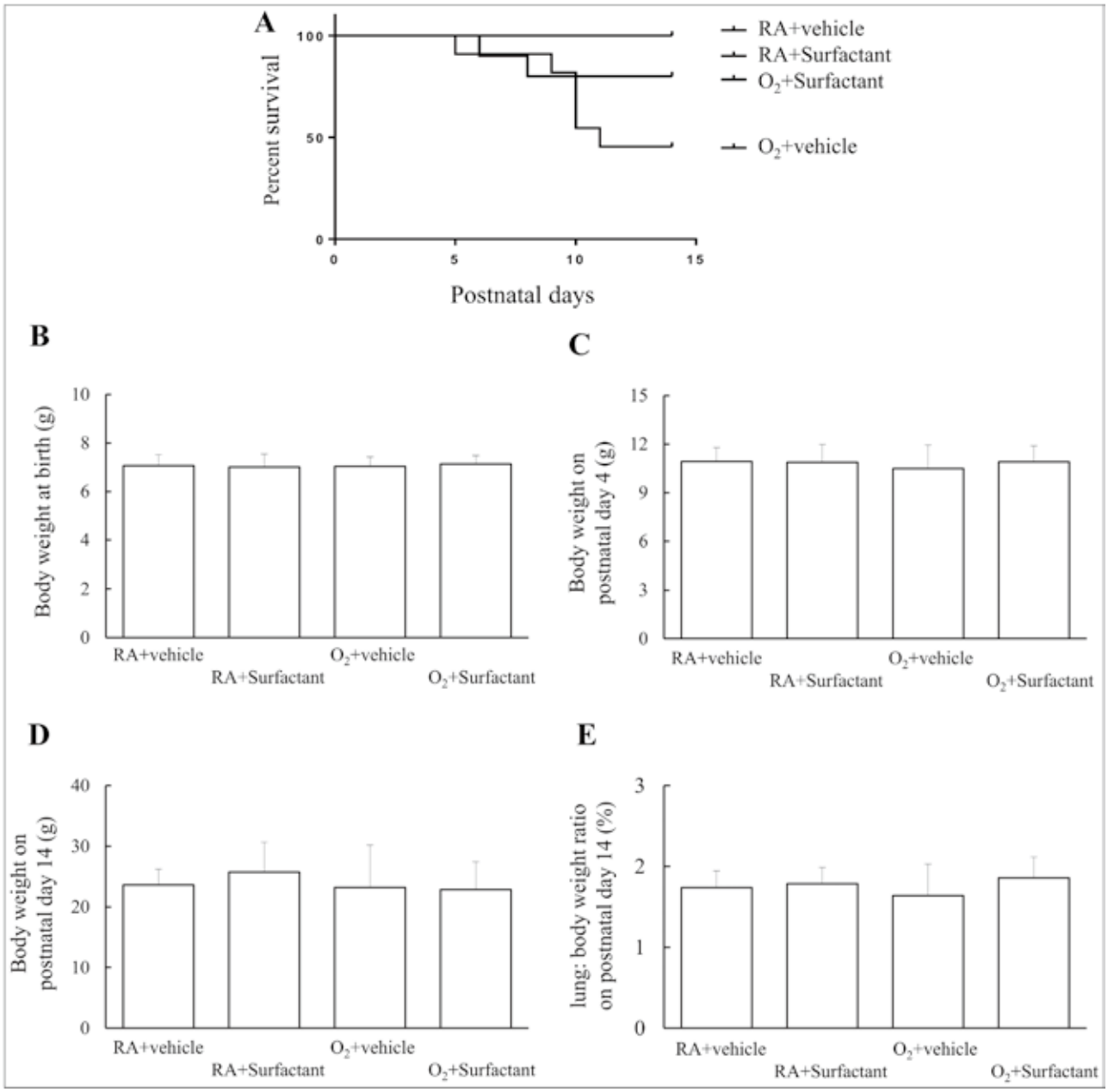

Figure 1: Survival rate (A), body weight at birth (B) and on postnatal days 4 (C) and 14 (D), and the lung-to-body-weight ratios (E) on postnatal day 14 for the four study groups. RA: room air, O_2: oxygen-enriched atmosphere

in hyperoxic environment exhibited significantly higher TGF-β1 protein expression than vehicle- or surfactant-treated rats reared in RA [Figure 3B, $P < 0.001$]. However, surfactant treatment significantly lowered the hyperoxia-induced increase in TGF-β1 protein expression ($P < 0.05$).

Intratracheal surfactant administration reduced the hyperoxia-induced increase in collagen deposition

Masson's trichrome staining revealed that collagen fibers were primarily deposited around the respiratory passage, alveolar interstitium, and pulmonary vessels in vehicle-treated rats reared in hyperoxic environment. The optical density of collagen in these rats was significantly higher than that in vehicle- or surfactant-treated rats reared in RA [Figure 4A and B, $P < 0.001$]. Surfactant treatment mitigated hyperoxia-induced collagen fiber deposition and significantly decreased the optical density of collagen compared with that in vehicle-treated rats reared in hyperoxic environment ($P < 0.001$).

Discussion

The salient findings of this *in vivo* study are that exposure of newborn rats to hyperoxic environment damaged the lung structure, increased lung inflammation and fibrosis, and resulted in a lower survival rate on postnatal day

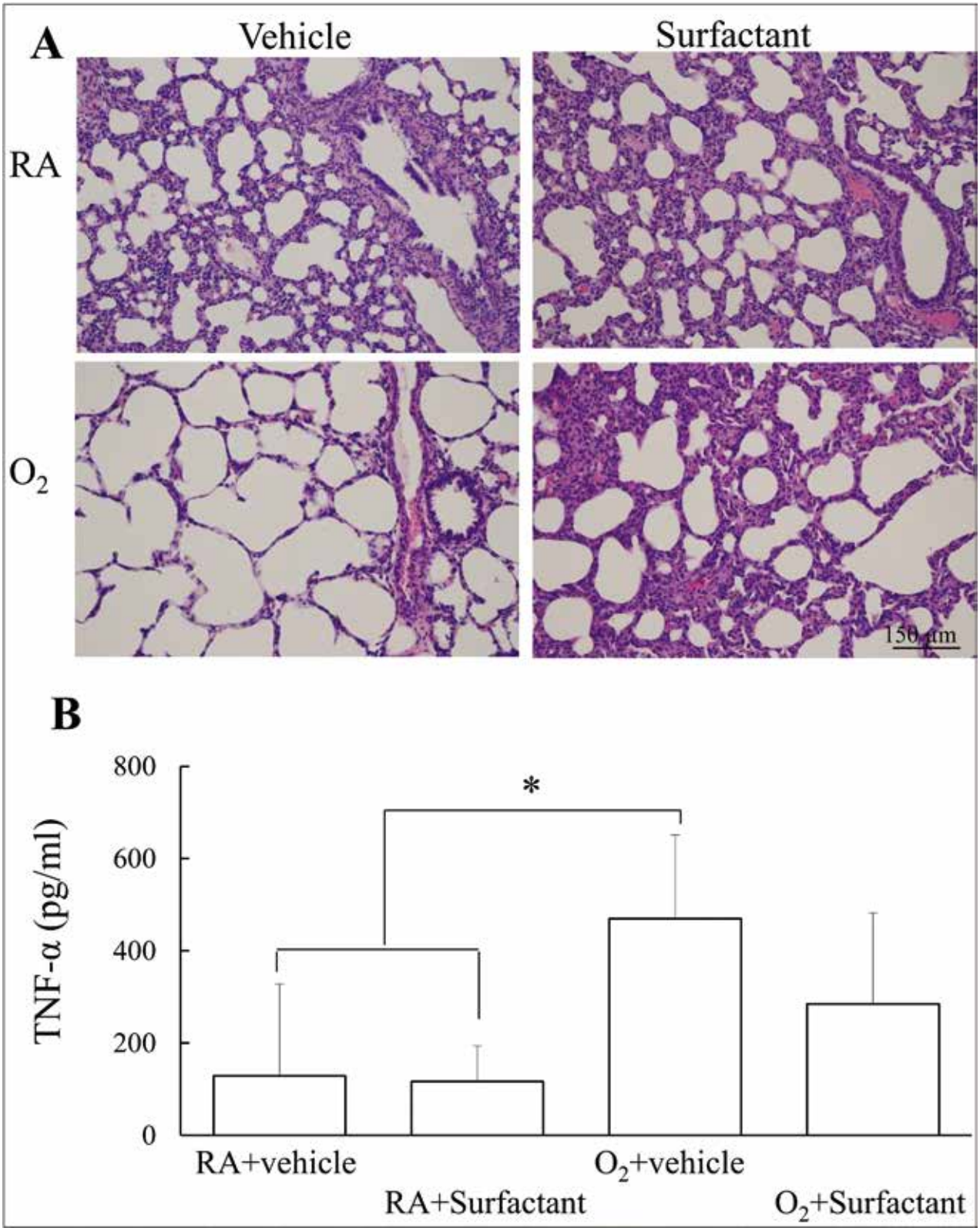

Figure 2: (A) Representative histology and (B) TNF-α levels in 14-day-old rats exposed to either postnatal RA or hyperoxia and treated with either vehicle or surfactant on postnatal day 4. Vehicle-treated rats reared in hyperoxic environment exhibited large thin-walled air spaces than vehicle- or surfactant-treated rats reared in RA. Vehicle-treated rats reared in hyperoxic environment showed significantly higher TNF-α expression than vehicle- or surfactant-treated rats reared in RA. Treatment with surfactants decreased TNF-α expression, but the effect was not significant. *$P < 0.05$. RA: room air, O_2: oxygen-enriched atmosphere. $n = 5–8$ rats

Table 1: Lung injury score in 14-day-old rats exposed to RA or hyperoxia and treated with vehicle or surfactant on postnatal day 4

Treatment	*n*	Extracellular hyaline changes	Hemorrhage	Infiltration of inflammatory cell	Intactness of the alveolar epithelium
A + vehicle	13	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–0)
RA + surfactant	11	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–0)
O_2 + vehicle	5	2 (2–2)***	1 (1–1)***	2 (1–2)***	2 (2–2)***
O_2 + surfactant	8	0 (0–1)$^{\#}$	0 (1–1)$^{\#}$	1 (0–1)$^{\#}$	1 (0–1)$^{\#}$

Values are presented as mean ± standard deviation. RA = room air

$^{***}p < 0.001$ vs. RA + vehicle and RA + surfactant groups.

$^{\#}p < 0.001$ vs. O_2 + vehicle group

Table 2: Lung volume fraction in 14-day-old rats exposed to RA or hyperoxia and treated with vehicle or surfactant on postnatal day 4

Treatment	*n*	Alveoli (%)	Alveolar wall (%)	Vessel (%)	Bronchus (%)
RA + vehicle	13	52.35 ± 2.54	44.22 ± 2.18	2.04 ± 0.96	1.38 ± 0.56
RA + surfactant	11	51.96 ± 3.39	44.74 ± 3.73	2.24 ± 1.13	1.06 ± 0.65
O_2 + vehicle	5	57.35 ± 2.54**	38.96 ± 2.90**	2.46 ± 0.95	1.23 ± 0.58
O_2 + surfactant	8	54.32 ± 2.00	41.84 ± 2.13	2.51 ± 0.74	1.34 ± 0.58

Values are presented as mean ± standard deviation. RA = room air.

$^{**}p < 0.01$ vs. RA + vehicle and RA + surfactant groups

14; however, intratracheal administration of an animal-derived surfactant on postnatal day 4 reversed these adverse outcomes. These findings suggest that the animal-derived surfactant can alleviate lung injury and fibrosis in neonatal rats exposed to hyperoxic conditions by suppressing lung inflammation and TGF-β1 expression.

The rat model is appropriate for studying the effects of hyperoxia on preterm infants with respiratory distress because rats are born at the saccular stage, equivalent to the human gestational age from 26 to 28 weeks.[27] We used 85% O_2 exposure of rat pups from postnatal days 1–14 because murine alveolar development begins on postnatal day 4, and saccular division is complete by postnatal day 14, which is roughly similar to the human alveolar stage. In this study, we euthanized the animals on postnatal day 14 because previous research has reported that the effects of hyperoxia peak on postnatal day 14.[27] We observed that the intratracheal administration of the surfactant ameliorated hyperoxia-induced lung fibrosis in neonatal rats. The pulmonary surfactant Survanta downregulates type I collagen expression in normal human lung fibroblasts, which may explain these findings.[28] The other possible mechanism is that the pulmonary surfactant may alleviate lung inflammation and improve lung fibrosis.[29]

A pulmonary surfactant, which is composed of both a phospholipid and a neutral lipid, stabilizes the alveoli by reducing surface tension.[1] In addition to its biophysical characteristics, a pulmonary surfactant possesses anti-inflammatory properties. An imbalance between the proinflammatory and anti-inflammatory processes and the persistence of the proinflammatory mechanisms are crucial factors leading to the development of bronchopulmonary dysplasia.[30] The ability of surfactants to minimize surface tension and exert anti-inflammatory effects suggests them as an alternative therapeutic option to treat inflammation-induced lung injury associated with chorioamnionitis, meconium aspiration syndrome, and pneumonia.[31-33]

TGF-β1 is a pleiotropic growth factor involved in the activation and migration of fibroblasts and in the upregulation of extracellular matrix components.[34] After 3 days of exposure to hyperoxia, TGF-β1 expression increases in the lungs of neonatal rats, and lung fibrosis is induced.[35,36] In the present study, we exposed neonatal rats to hyperoxic conditions after birth and administered the surfactant on postnatal day 4, after TGF-β1 expression had increased. We discovered that the surfactant reduced TGF-β1 expression as well as lung fibrosis. These findings corroborate those of Beike *et al.* who reported that animal-derived surfactant replacement therapy stabilized the alveoli and reduced collagen deposition in the septal walls in mice overexpressing TGF-β1.[37]

Our study demonstrated that intratracheal surfactant administration on postnatal day 4 alleviated hyperoxia-induced lung injury, inflammation, and fibrosis on postnatal day 14 in newborn rats. These findings are consistent with results from our previous studies. Previously, we reported that a single intratracheally administered dose of a natural surfactant (Survanta) on postnatal days 4 or 5 ameliorated hyperoxia-induced lung inflammation and impaired lung development on postnatal day 14.[19,20] However, these results differ from those of Salaets *et al.* who reported that daily intratracheal surfactant injections for 7 days did not improve lung structure and function or survival in hyperoxia-exposed (95% O_2) preterm rabbit

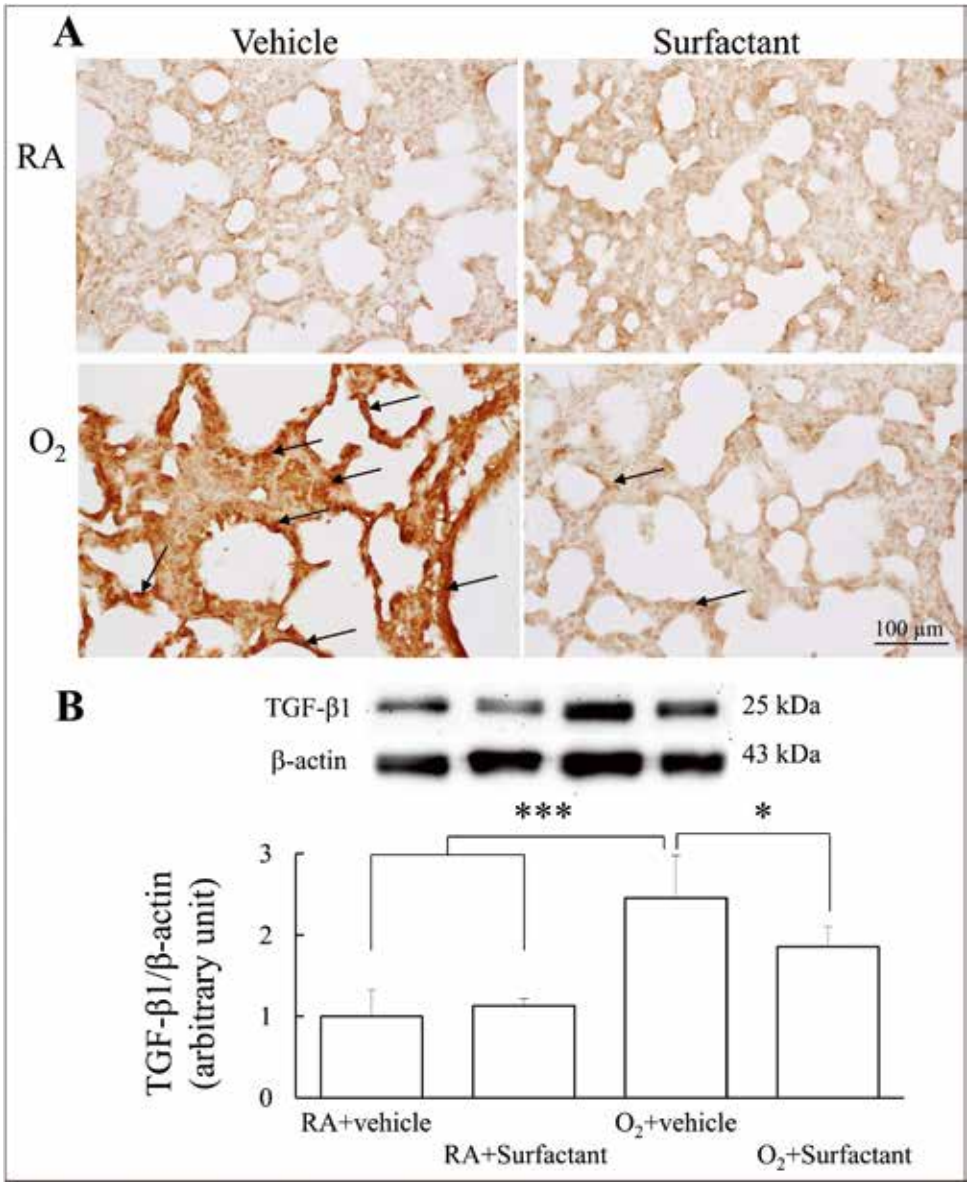

Figure 3: (A) Representative immunohistochemistry images for TGF-β1 and (B) representative Western blots and quantitative data obtained through densitometry for TGF-β1 protein expression in 14-day-old rats exposed to postnatal RA or hyperoxia and treated with vehicle or surfactant on postnatal day 4. The black arrows indicate the epithelium was positively stained with TGF-β1. Vehicle-treated rats reared in hyperoxic environment exhibited significantly higher TGF-β1 protein expression than vehicle- or surfactant-treated rats reared in RA. Treatment with surfactants significantly reduced the hyperoxia-induced increase in TGF-β1 protein expression compared with treatment with vehicle. Blot images were cropped for clarity of presentation. *$P < 0.05$ and ***$P < 0.001$. RA: room air, O_2: oxygen-enriched atmosphere, TGF-β1: transforming growth factor-β1. $n = 5$–8 rats

pups.[38] We surmise that the discrepancy in findings is due to different animal species, oxygen concentrations, and exposure times.

Our research has several limitations. First, we did not evaluate the effects of surfactants on lung function, surfactant phospholipids, or SP expression, although hyperoxia significantly altered SP expression and decreased surfactant phospholipid synthesis in newborn rats.[5,8] Second, we measured the levels of only TNF-α, which is the most potent proinflammatory cytokine in the TNF superfamily and is a well-known mediator of the pulmonary inflammatory response.[39] Third, we did not assess pulmonary function in this study. Future studies should explore the role of TGF-β1/Smads signaling, induction of epithelial-to-mesenchymal transition, and collagen content in surfactant-attenuated hyperoxia-induced lung injury and fibrosis in neonatal rats.

In conclusion, we demonstrated that the surfactant used in this study attenuated hyperoxia-induced lung injury and lung fibrosis, as evidenced by decreased lung injury score, TNF-α expression, and collagen deposition. Moreover, surfactants did not adversely affect natural lung

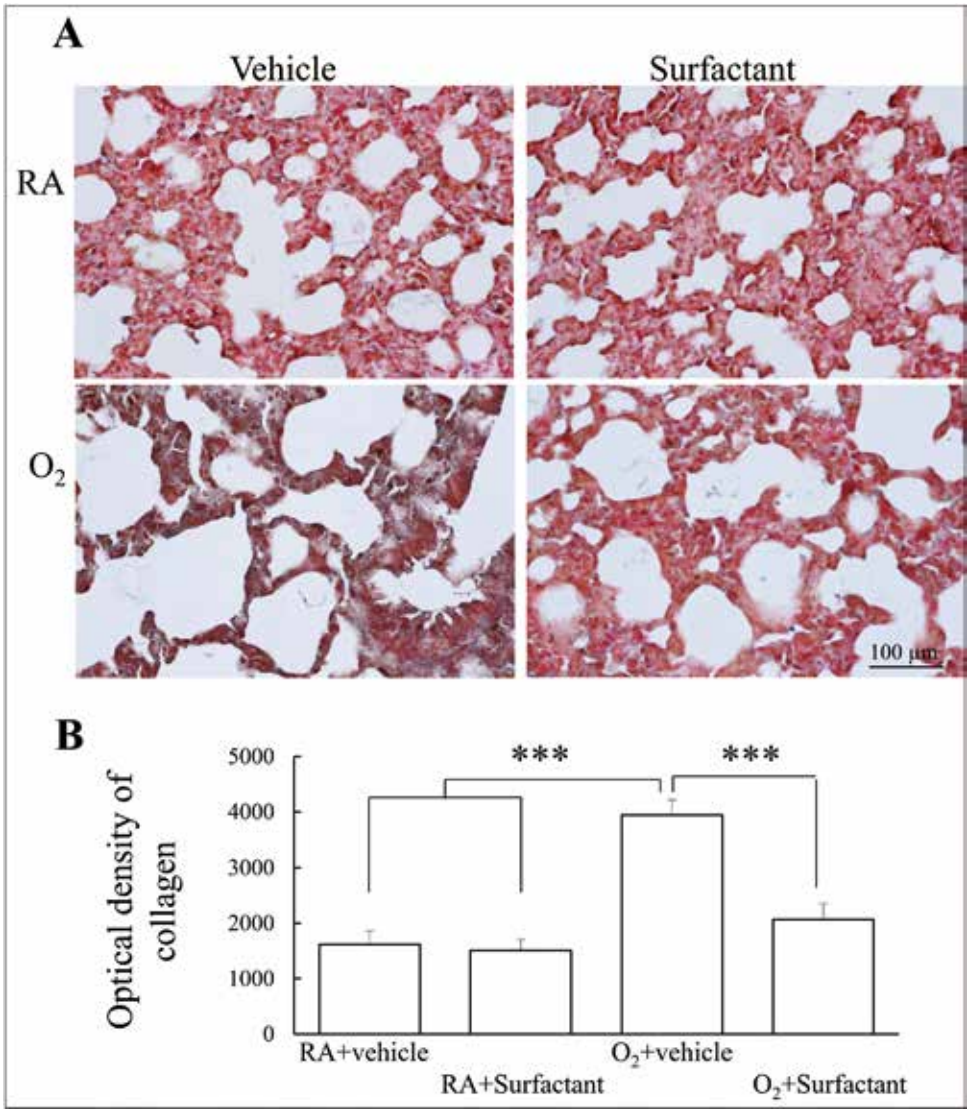

Figure 4: (A) Representative photomicrographs of Masson's trichrome staining and (B) optical density of collagen in 14-day-old rats exposed to postnatal RA or hyperoxia and treated with vehicle or surfactant on postnatal day 4. Collagen fibers were mainly deposited in the alveolar septum and interstitium. Vehicle-treated rats reared in hyperoxic environment exhibited significantly higher collagen deposition than vehicle- or surfactant-treated rats reared in RA. Treatment with surfactants significantly reduced the hyperoxia-induced increase in collagen deposition relative to treatment with vehicle. ***$P < 0.001$. RA: room air, O_2: oxygen-enriched atmosphere. $n = 5–8$ rats

development in neonatal rats. These positive effects of surfactants on hyperoxia-induced lung injury and fibrosis are likely facilitated by a decrease in cytokine and TGF-β1 expression. Intratracheal surfactant administration may offer a unique approach to treating hyperoxia-induced lung injury and avoiding lung fibrosis. Further studies are needed to explore the potential long-term impacts and effectiveness of surfactant therapy beyond the 14-day postnatal period.

Author contributions

CMC: conceived and designed research; JSJ, CCH, HCC, and CMC: analyzed the data; JSJ, CCH, HCC, and CMC interpreted the results of the experiments and drafted the manuscript. All authors reviewed the manuscript.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author at a reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Hypersensitivity Pneumonitis Due to Lentil Aspiration in Children: A Case Series

Deepak Kumar, Anil Sachdev, Samarjit Singh Ghuman[1], Dhiren Gupta

Department of Pediatrics, Institute of Child Health, [1]Department of CT & MRI, Sir Ganga Ram Hospital, New Delhi, India

Abstract

Hypersensitivity pneumonitis (HP) in children is a common cause of interstitial lung disease. HP has been seen in the patient due to the inhalation of different bacteria, fungi, and other particles, such as feathers of various types of birds. In our study, we observed that children who were forced to feed themselves with lentil-based weaning food had respiratory symptoms and radiology similar to HP. Here, we are reporting nine patients admitted over 13 months with symptoms of persistent cough, breathing difficulty, not responding to antibiotics, and persistent radiological changes in chest radiographs and computerized tomography. The median age of the cases was 12 months, with male predominance. Flexible bronchoscopy was done to rule out any structural anomalies in the airways and to obtain broncho-alveolar lavage, which yielded no results for pyogenic and tubercular infections. The immunoglobulin G (IgG) specific for lentils ranges from 17.6 to > 200 mgA/L. All children received oral steroids for up to 8 weeks and showed remarkable improvement in clinical and radiological status. In conclusion, lentil-induced HP in infants during weaning should be considered in cases with persistent cough and non-resolving pneumonia.

Keywords: Children, hypersensitivity pneumonitis, interstitial lung disease, lentil, persistent pneumonia

Introduction

Hypersensitivity pneumonitis (HP), also named extrinsic allergic alveolitis, is the most frequent cause of chronic interstitial lung disease in children. The HP is caused by exposure to a wide variety of organic particles of sizes <5 µm, which induce type III/IV hypersensitivity reaction in alveoli.[1]

In adults, HP is mainly due to occupational exposure to allergens, whereas childhood HP is associated with exposure to the antigen from home, school, or playground environments.[1] The antigen may be fungi, bacteria, protozoa, animals, birds, insects, and sometimes inorganic antigens such as inhaled paints, wax, and talcum. The classic farmer's lung disease is due to the thermophilic *Actinomyetes*. Other types of bacteria and fungi responsible for HP are *Aspergillus* sp., *Candida* sp., *Cephalosporium*, *Aurreobasidium pulludans*, *Naregleria gruberi*, *Acanthamoeba polyphagia*, *Acanthamoeba castellahi*, *Bacillus* sp., *Trichospron* sp., *Crypticocus albidus*, and *Mycobacterium avium* complex.

Some plant proteins are also responsible for HP, such as soybeans and coffee.[1] Over time, as our knowledge and understanding of the disease is increasing, more and more suspected antigens are implicated as causative agents. In some studies, it was shown that in the pediatric age group, aspiration of food in the airways may also be one of the important causes of chronic lung disease with fibrosis.[2]

In India, it is recommended that complementary feeds be started at the age of 4 to 6 months, and lentils are usually initiated as a weaning meal in infants.[3] At this age, oro-pharyngeal coordination may not be completely developed, and patients with neurological disability or

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Address for correspondence: Dr. Anil Sachdev, Department of Pediatrics, Institute of Child Health, Sir Ganga Ram Hospital, New Delhi 110060, India. E-mail: anilcriticare@gmail.com

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gastroesophageal reflux disease (GERD) or forceful feeding may lead to aspiration in the airways.[4]

Histologically, lentil HP appears as a granulomatous inflammatory response with giant cells, while radiologically, a nodular appearance with centrilobular nodules is seen, which is highly suggestive of HP.[5-7]

Case Series

Clinical and laboratory data of all cases of non-resolving pneumonia with positive lentil IgG levels admitted in the Pediatric Department of Sir Ganga Ram Hospital from January 2022 to February 2023 were collected from the Hospital Information System (HIS). Details of all cases with age at presentation, sex, clinical symptoms and signs, laboratory reports, radiological reports, and other relevant laboratory reports were captured on an Excel datasheet.

We identified 9 cases from our database [Table 1]. Out of 9 cases, 5 patients (55.5%) received oxygen therapy in view of respiratory distress. All patients reported here had normal neurological examination and normal screening 2D echocardiography. The median (IQR) age at presentation was 12 (9,17) months with a male-to-female ratio of 2:1. The most prominent and consistent symptom in all cases was prolonged cough, which did not report to a prolonged course of antibiotics and inhaled bronchodilators. Fever was the second most common symptom reported in 7 patients (77.7%), followed by shortness of breath in 5 cases (55.5%). All the patients had a significant history of forceful feeding. The feed was mainly in the form of dal or dal-based food items. On auscultation, crackles and wheeze were audible in 3 (33.33%) and 2 (22.2%), respectively, and in the remaining 4 cases, there were no added sounds on auscultation.

Investigations revealed anemia in 7 patients as per the World Health Organization (WHO) age-related cut-off.[8] The leukocytosis and thrombocytosis were also

Table 1: Summary of hypersensitivity pneumonitis cases

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age (months)	9	22	12	12	36	9	10	9	17
Sex	Male	Male	Female	Male	Male	Female	Male	Male	Female
Chief Complaints	Fever, cough-1.5 mo RD-1 mo	Cough, Coryza-1 mo. Fever-11 days	Cough-1 mo. RD-7 days	Fever, Cough-2 mo	Cough-22 days. RD-7 days	Fever, Cough-20 days	Fever, cough-1 mo	Cough, coryza & RD-1.5 months. Fever-3days	Fever, cough- 20 days
Chest auscultation	Vesicular breathing. Bilateral crepitations	Vesicular breathing. Bilateral wheeze	Vesicular breathing. Bilateral crepitations	Clear	Vesicular breathing. Bilateral rhonchi	Vesicular breathing	Vesicular breathing	Vesicular breathing. Bilateral crepitations	Vesicular breathing
Hb (gm/dL)	8.8	8.2	10.6	10.2	12.4	9.4	10.2	12.3	10
TLC/mm^3	27.43	3.5	13.2	39.26	21.76	22.4	23.92	19.2	30.5
CRP (mg/dL) ($N < 6$)	60	48	44	66	5	2	93	4	33
IgG (mg/dl)	1071	2440	1119	1864	896	1631	998	839	978
BAL TLC & DLC	665; N 75%, L 25%	454; N 65%, L35%	744; N80%, L20%	490; N70%, L30%	312; N65%, L35%	213; N60%, L40%	938; N70%, L30%	571; N80%, L20%	1236;N40%, L60%
Lentil-specific IgG (mgA/L)	28.9	45.1	124	>200	17.6	178	>200	187	25
CT chest	Ill-defined non-homogenous opacity in bilateral and perihilar region with retico-nodular opacity	Diffuse Bilateral ill-defined, non-homogenous opacities present in hilar and perihilar areas	Ill-defined opacity, non-homogenous present in hilar and perihilar area	Non-homogenous opacities present in hilar and perihilar areas. In some areas ground glass opacities were also noted	Not done	Opacities present in bilateral hilar areas and perihilar areas spreading to the bilateral lower lobes sparing upper lobes. Retico-nodular opacity was also noted	Bilateral opacities were noted in hilar and perihilar opacities also involving right lower and middle lobes	Non-homogenous opacities were seen in bilateral hilar and perihilar areas. Also involving Rt middle and lower lobes and in left lower lobes	Opacities present in the bilateral hilar and perihilar areas along with left lower lobes

present in 7/9 (77.7%) patients each. Elevated levels of C-reactive protein (CRP) and IgG immunoglobulins were observed in 6 (66.6%) and 7 (77.7%) patients, respectively. The flexible fiber-optic bronchoscopy (FFB) was done to assess any congenital airway anomalies and to obtain broncho-alveolar lavage (BAL). All BAL fluid samples were sterile pyogenic or fungal organisms and tuberculosis work-up, including Zeil Nelson stain, Cartridge-based nucleic acid amplification test (CBNAAT), and culture was negative. The lipid-laden macrophages were not present in any BAL sample. Two ml of blood was sent to the Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India, for estimation of lentil-specific IgG antibodies. The technique was based on a sandwich enzyme-linked immunosorbent assay (ELISA) (ImmunoCAP, Phadia AB, Uppsala, Sweden) analyzed with Phadia 100 immunoassay analyzer (Phadia AB, Uppsala, Sweden). The serum IgG lentil was positive in all the cases, ranging from 17.6 to >200 mgA/L. Chest radiographs showed non-homogenous opacity in the perihilar area, some extending to the right lower and mid zone, and also some cases showed left lower zone involvement. Chest × ray of one of the cases, before and after oral steroid treatment [Figure 1A and B]. Contrast-enhanced computerized tomography (CECT) findings revealed predominantly perihilar pneumonia extending to adjacent lobes [Figure 2].

Parents or caretakers of all children were advised to modify feeding practices in the form of no forceful feeding. All patients were started on oral prednisolone

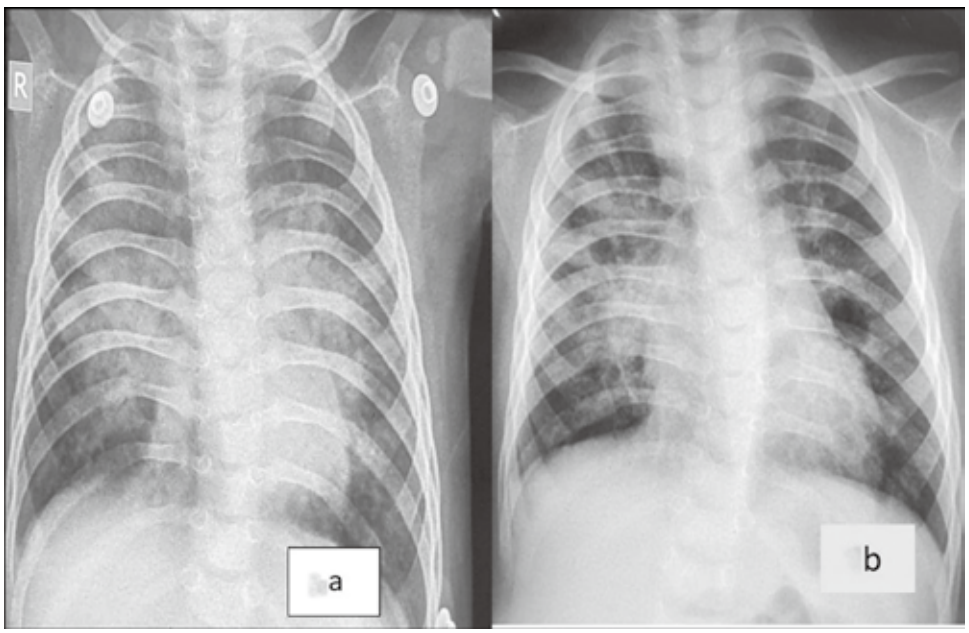

Figure 1: Chest radiograph frontal view (a) showing bilateral hilar and parahilar non-homogeneous opacities with air bronchogram. (b) in same child remarkable resolution of opacities especially on left side after 2 months of treatment with oral steroids.

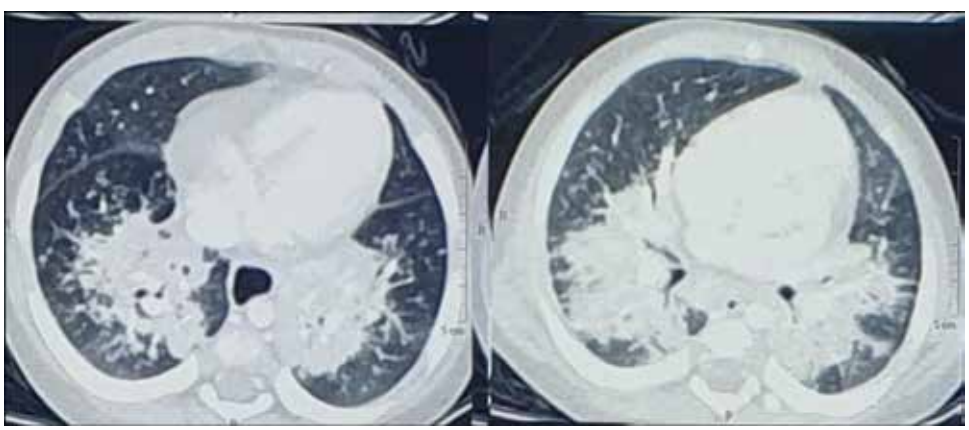

Figure 2: Axial computerized tomography images (lung window setting) reveal almost symmetrical areas of consolidation in lower lobes bilaterally. The changes seem centered around main bronchi with some subpleural sparing

(1 mg/kg/day) in two divided doses for 2 weeks and tapered over the next 6–8 weeks except in two cases. These two children required prolonged oral steroids for 3 months due to clinical and radiological deterioration during tapering. All patients were followed closely for clinical and radiological response [Figure 1B]. We did not evaluate the esophagus and stomach by contrast imaging studies, 24 h pH monitoring for gastroesophageal reflux, and swallowing dysfunction.

Discussion

There are numerous causes of HP, among which one of the known but less discussed etiology is lentil aspiration pneumonia. The first case report of lentil aspiration dates back to 1974, while the second case report was published after 10 years in 1984.[5,6] In recent years, a case series of 9 patients was published, which shed light on this well-known and existent etiology.[9]

In our study, a total of 9 patients were included over a period of 13 months. There was male preponderance. In previous studies of childhood interstitial lung disease (chILD) and HP, there was a similar pattern with male predominance.[10] The exact reason for this male predilection is not known. It was described that airway resistance is higher in males than in females, which may lead to more exposure to the antigen.[11] Another possible social reason may be due to feeding practices in our country, where male babies receive preferential attention and are fed, maybe forcefully, by the mother or other family members in the household.

The HP results from massive or repeated exposure to allergens. In the cohort of HP due to lentil aspiration, there was slow and repetitive exposure due to occult aspirations. The radiological impression is indistinguishable from infections like tuberculosis, bacterial pneumonia, or viral pneumonia like cytomegalovirus.[12] Therefore, it is important to rule out the infective etiology, even in patients with a positive history of forceful feeding. In our study, FFB and BAL were done in all patients, but the microbiological yield was negative. FFB also helped us to rule out any anatomical defect in the form of H-type fistula.

Radiologically, primarily perihilar and paracardiac pulmonary areas were involved, but in some cases, lower zone involvement was also noticed. It occurs possibly due to continuous exposure through recurrent aspirations. The computed tomography (CT) findings include small, indistinct, centrilobular nodules, multifocal ground glass opacities, and evidence of air trapping in the expiratory phase of respiration. Though all of these findings are non-specific and overlap with other conditions like respiratory bronchiolitis, follicular bronchitis, and asthma, but a combination of these findings is highly suggestive of HP.[13]

On the basis of clinical presentation, HP can be categorized as acute, subacute, or chronic. Acute hypersensitivity may present with flu-like symptoms in the form of chills, fever, malaise, dyspnea, and cough. The symptoms may occur within 2 h post-exposure, sometimes up to 12 h to a few days. The symptoms may resolve after removing the exposure. The subacute form may have symptoms of sputum production, cough, anorexia, and weight loss, whereas chronic HP is characterized by progressive dyspnea due to prolonged and continuous exposure to the offending allergen.[14] Even on examination, none of our patients had clubbing since it is a sign of chronic HP. Anemia was noted to be 77.9%, but there is no such evidence or literature suggesting any co-relation between anemia and HP. Since the prevalence of iron deficiency anemia is high in children in India, it would be difficult to relate the presence of anemia to HP. Complete detailed investigations are required to rule out deficiency or hereditary causes of anemia.

The earlier two pediatric case reports of lentil HP, described in the literature, were diagnosed on the basis of lung biopsy.[3,4] The biopsy in both cases revealed foreign body granulomas with a center made of starch-rich lentil core. Subsequent studies used lentil-specific IgG levels to diagnose the disease. The pulmonary function test is helpful in the initial assessment and further progression of the disease. Lower forced vital capacity (FVC) or a decline in FVC on spirometry reflects the progression of the disease and has been associated with a high risk of mortality in patients with HP.[15] As our patient cohort included a younger age group, a pulmonary function test could not be performed. The other modality to ascertain pulmonary function is the inhalation test/challenge test, which is also not a safe test, particularly in young children.

The mainstay of treatment for HP is avoidance of antigen. The same strategy was followed in our cohort by advising parents to stop forceful feeding and thickening of feed to minimize the risk of aspiration. The medical management includes prednisolone at 1 mg/kg/day in two divided doses given for a total duration of 6 to 8 weeks with gradual tapering every 1-2 weeks after assessing clinical and radiological response. In our study, all the patients showed both clinical and radiological improvement after the treatment. There is a paucity of literature on other treatment modalities. The HP patients may require immunosuppressive drugs like Azathioprine and mycophenolate mofetil (MMF) in case of steroid failure.[16]

The present case series has a few limitations. We did not perform investigations to rule out swallowing defects and gastroesophageal reflux disease, which are rather common in infants. We relied on clinical history and examination to rule out these entities. So, we suggest that these investigations must be considered in the clinical context. Also, as discussed previously, relevant investigations may be conducted in the presence of anemia to rule out a particular etiology. Future

multicenter studies may focus on establishing cause-effect relation between HP and anemia.

Our case series throws fresh light on the entity of lentil-induced HP in young children due to forced feeding at wean age. There is a need for more awareness among pediatricians and pediatric pulmonologists to consider HP in young infants with non-resolving pneumonia.

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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.

Author contributions

Deepak Kumar — Data collection and compilation
Anil Sachdev — Manuscript preparation, critical review, and final draft preparation
Samarjit Singh Ghuman — Radiology inputs
Dhiren Gupta — Manuscript preparation.

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Conflicts of interest

There are no conflicts of interest.

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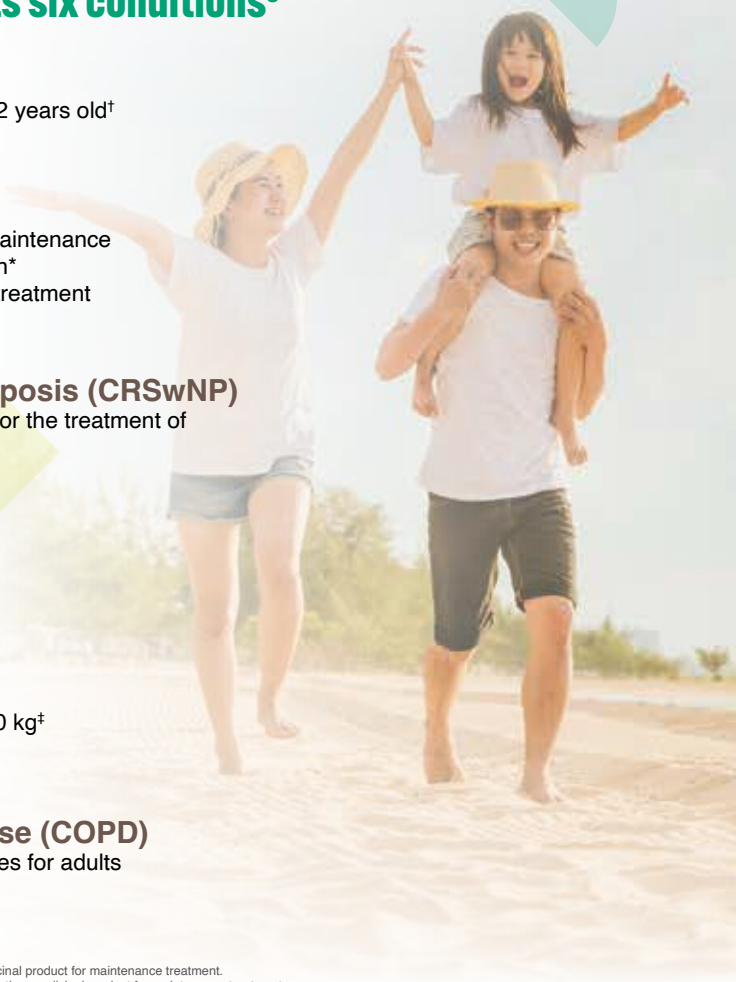

Atopic Dermatitis (AD)
- Moderate-to-severe AD in adults and adolescents ≥12 years old†
- Severe AD in children 6 months to 11 years old†

6+ months

Asthma
- In adults and adolescents ≥12 years old as add-on maintenance treatment for severe asthma with Type 2 inflammation*
- In children 6 to 11 years old as add-on maintenance treatment for severe asthma with Type 2 inflammation^

6+ years

Chronic rhinosinusitis with nasal polyposis (CRSwNP)
- As an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP#

18+ years

Prurigo Nodularis (PN)
- Moderate-to-severe PN in adults who are candidates for systemic therapy

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^ Characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with medium to high dose ICS plus another medicinal product for maintenance treatment.
# For whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.
‡ Those who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.
§ Characterised by raised blood eosinophils, on a combination of an inhaled corticosteroid (ICS), a long acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate.

Abbreviations: AD=atopic dermatitis; COPD = chronic obstructive pulmonary disease; CRSwNP= chronic rhinosinusitis with nasal polyps; EoE= eosinophilic esophagitis; FeNO=fractional exhaled nitric oxide; ICS=inhaled corticosteroids; LABA = long acting beta2-agonist; LAMA = long acting muscarinic antagonist; PN=prurigo nodularis.

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1. Guttman-Yassky E, et al. J Allergy Clin Immunol. 2019;143(1):155-172. 2. Gandhi NA, et al. Nat Rev Drug Discov. 2016;15(1):35-50 3.DUPIXENT® Hong Kong Prescribing Information

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 months 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. In children 6 to 11 years old 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 medium to high dose ICS plus another medicinal product for maintenance treatment. For 300 mg only – 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. Prurigo Nodularis (PN): Moderate-to-severe PN in adults who are candidates for systemic therapy. Eosinophilic esophagitis (EoE): In adults and adolescents ≥12 years, weighing ≥40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy. Chronic obstructive pulmonary disease (COPD): In adults as add-on maintenance treatment for uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate. **Dosage & Administration:** Subcutaneous injection. AD adults: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg Q2W. AD adolescents (12-17y/o): Body weight <60 kg- initial dose of 400 mg (two 200 mg injections), followed by 200 mg Q2W. Body weight ≥60 kg- same dosage as adults. AD children (6-11y/o): Body weight 15kg-~<60 kg- initial dose of 300 mg on Day 1 follow by 300 mg on Day 15, then 300mg Q4W. 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. AD children (6 months-5y/o): Body weight 5kg-~<15 kg- initial dose of 200 mg, then 200 mg Q4W. Body weight 15kg-~<30 kg- initial dose of 300 mg, then 300 mg Q4W. 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. Asthma adults and adolescents: Initial dose of 400 mg, followed by 200 mg Q2W. 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 Q2W. Asthma children (6-11y/o): Body weight 15kg-~<30 kg- 300 mg Q4W. Body weight 30kg-~<60 kg- 200 mg Q2W; or 300 mg Q4W. Body weight ≥60 kg- 200 mg Q2W. For paediatric patients (6-11y/o) with asthma and co-morbid severe atopic dermatitis, as per approved indication, the recommended dose should follow AD children (6-11y/o). 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: Initial dose of 300 mg, followed by 300 mg Q2W. Consider discontinuing treatment in patients who have shown no response after 24 weeks. PN: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg Q2W. Dupilumab can be used with or without topical corticosteroids. Consider discontinuing treatment in patients who have shown no response after 24 weeks. EoE: 300 mg QW. Dupilumab 300 mg QW has not been studied in patients with EoE weighing <40 kg. Dosing beyond 52 weeks has not been studied. COPD: 300 mg Q2W. Consider discontinuing treatment in patients who have shown no response after 52 weeks. For Missed dose instructions, please refer to the full prescribing information. **Contraindications:** Hypersensitivity to dupilumab or any of the excipients. **Precautions:** Not be used to treat acute symptoms, acute exacerbations of asthma or COPD, 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. Cases of enterobiasis were reported in children 6 to 11 years old in the paediatric asthma development program. Advise patients to promptly report new onset or worsening eye symptoms. Patients who develop conjunctivitis, dry eye and keratitis that does not resolve following standard treatment should undergo ophthalmological examination. Sudden changes in vision or significant eye pain that does not settle warrant urgent review. Patients with comorbid asthma should not adjust or stop asthma treatments without consultation with physicians. Carefully monitor patients after discontinuation of dupilumab. Avoid using 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, conjunctivitis allergic, arthralgia, oral herpes, eosinophilia and injection site bruising. Safety profile observed in adolescents and children 6 months to 11 years old 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.**

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Synagis abridged prescribing information
Presentation: 50mg/0.5ml, and 100 mg/1ml, for solution for injection. **Indications:** Treatment prevention of serious lower respiratory tract disease requiring hospitalization caused by respiratory syncytial virus (RSV) in children at high risk for RSV disease including: • Children born at ≤ 35 weeks of gestation and ≤ 6 months of age at the onset of RSV season. • Children <2 years of age who require treatment for bronchopulmonary dysplasia within the last 6 months. • Children < 2 years of age and with hemodynamically significant congenital heart disease. **Dosage:** 15 mg/kg of body weight administered as an intramuscularly, given once a month during anticipated periods of RSV risk in the community. **Contraindications:** Hypersensitivity to the active substance or to the excipients or to other humanized monoclonal antibodies. **Precautions:** Allergic reactions including very rare cases of anaphylaxis and anaphylactic shock have been reported following palivizumab administration. In some cases, fatalities have been reported. A moderate to severe acute infection or febrile illness may warrant delaying the use of palivizumab, unless, in the opinion of the physician, withholding palivizumab incurs a greater risk. A mild febrile illness, such as mild upper respiratory infection, is not usually reason to defer administration of palivizumab. Palivizumab should be given with caution to patients with thrombocytopaenia or any coagulation disorder. **Undesirable effects:** Rash, pyrexia, apnoea and injection site reaction. **Full local prescribing information is available upon request. API.HK.SYN.0421**

References: 1. Synagis® Hong Kong Prescribing Information 2019. 2. Resch B. Product review on the monoclonal antibody palivizumab for prevention of respiratory syncytial virus infection. Hum Vaccin Immunother. 2017;13(9):2138-2148. doi:10.1080/21645515.2017.1337614

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in conjunction with

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2nd–4th April

Bangkok, Thailand

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HIGHLIGHT SESSIONS:

- Advancements in Asthma Management
- RSV in Pediatrics: Prevention and Management Strategies
- Genetics and Environment: Dual Impact on Pediatric Lung Health
- Non-invasive Respiratory Support: New Technologies and Approaches
- Vaping and E-Cigarettes: Protecting Youth Lung Health
- Telemedicine in Respiratory Care: Transforming Pediatric Pulmonology
- Chronic Cough in Children: Comprehensive Diagnostic and Treatment
- Approaches Managing Allergic Respiratory Diseases
- Sleep-Disordered Breathing: Diagnosis and Management
- Emerging Therapies in Sepsis Management Innovations in PICU Care
- Neurocritical Care in Pediatrics
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