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Contents

Viral Respiratory Infections and Intensive Care Admissions during the Pandemic

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As the world is slowly coming out from the coronavirus disease 2019 (COVID-19) pandemic, pediatricians and pediatric intensivists are facing new challenges. Young children who have been well protected from various common viral infections are now facing great danger of severe viral respiratory tract infections. Early data from New Zealand and Australia clearly showed a significant rebound of severe respiratory synctial virus infection in young children.[1,2] In addition to respiratory synctial virus, other viral infections are coming back into the community. Asthmatics are at high risk of developing exacerbations precipitated by viral infections. In this issue, Nguyen *et al*.[3] reported a cross-sectional study in Vietnam demonstrating a high percentage of children with asthma exacerbations were found to have concomitant viral infections. The results are in line with results in other parts of the world. Strategies to reduce viral respiratory infections will potentially reduce asthma exacerbations in the population setting. The epidemiology of intensive care admission has experienced dramatic changes during the pandemic. Severe viral respiratory infections other than COVID-19 have decreased dramatically, whereas high rates of diabetic ketoacidosis (DKA) resulting in admission to intensive care units (ICUs) have been observed.[4,5] Whang *et al*.[6] reported, in this issue, a large series of pediatric patients with ICU admission due to DKA within the period of pandemic. Interestingly, nonemergency room admission and younger age were identified as risk factors for longer ICU stay. It was likely that a delay in diagnosis was an important reason for the longer ICU stay for those transferred from other hospital wards instead of admitting directly from the emergency department where the diagnosis of DKA was made promptly. High index of suspicion is needed in order to facilitate early diagnosis of this potentially lethal condition. Pulmonary hemorrhage is an uncommon but potentially lethal condition affecting children especially for those with severe hemorrhage. Nathan *et al*[7] described five interesting cases of children who presented with possible pulmonary hemorrhage and discussed the diagnostic approach including the important differentiation of hemoptysis, hematemesis, or simple bleeding from the nose. I am sure readers will find these cases educational and the approach described will help them to manage future cases of possible pulmonary hemorrhage.

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Review Article

Approach to Pulmonary Haemorrhage in Children: What Could It Be?

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Abstract

Pulmonary haemorrhage is rare in children but can be life-threatening. It is recognised as a triad of haemoptysis, drop in haemoglobin or iron-deficiency anaemia and radiographic evidence of pulmonary infiltrates. Although there can be a myriad of causes, careful history with consideration of co-morbid factors and radio imaging of the chest can help determine the most likely cause. This review will illustrate how to determine the aetiology, types of investigations to perform and management through real-life clinical vignettes.

Keywords: Blood, child, haemoptysis, management, pulmonary haemorrhage

Introduction

Pulmonary haemorrhage (PH), which is the extravasation of blood into the airways and alveoli, is recognised by the triad of a drop in haemoglobin/iron-deficiency anaemia, pulmonary infiltrates and haemoptysis.[1,2] In children with PH, haemoptysis is seen only in 56.2% of cases, resulting in delayed diagnosis.[3,4] A decline in blood haemoglobin levels over a few days without haemolysis or any haemorrhage elsewhere should alert a physician to the possibility of PH.[5]

PH presents insidiously or suddenly: common symptoms are poor growth, reduced effort tolerance, chronic iron deficiency or sudden cyanosis with cardiorespiratory arrest/failure from massive haemorrhage. Massive haemorrhage is defined as blood loss of >8mL/kg within 24 h or if associated with cardiorespiratory arrest/failure.[6] Massive haemoptysis is usually seen in patients with a bleeding from the bronchial circulation, whereas mild bleeds may be seen in pulmonary bleeds.[7] Diffuse disease is usually from a low-pressure, high-volume circulation, for example, within the alveoli, like in diffuse alveolar haemorrhage (DAH). In contrast, the focal disease is usually seen in a high-pressure, low-volume circulation, like from the bronchial circulation.[8]

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Case 1

A 16-year-old girl presented to the hospital with a sudden onset of haemoptysis. She was otherwise well with no weight loss or reduced appetite, no fever, no contact history of tuberculosis (TB), no reduced effort tolerance or shortness of breath or cyanosis, and no rash or symptoms to suggest connective tissue disease. All investigations were normal, including full blood count, chest radiograph (CXR), computer tomography (CT) and auto-immune screen. On further questioning, she had just gone to stay with her mother and stepfather and was stressed by the home situation. In the ward, blood was seen during her retching period. She was diagnosed with Mallory Weiss tear and discharged well.

Discussion: Is It Really from the Lung?

One of the first issues faced by a child with "haemoptysis" is to exclude haematemesis, Mallory Weiss tear, oesophagitis, and nose or throat bleeds versus true blood from the lower airway. Table 1 delineates how we can

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differentiate blood from the upper airway, lower airway and the gastrointestinal system. A detailed history and even pictures are paramount in the initial approach to "haemoptysis" to avoid unnecessary investigations.

Case 2: Haemoptysis in a Child with Down Syndrome

A 3-year-old boy with Down syndrome presented with a massive PH requiring invasive ventilation. He was born term and was diagnosed with a patent ductus arteriosus (PDA) that was managed conservatively. Antenatally, he was diagnosed with a right middle lobe (RML) congenital pulmonary airway malformation. At 3 months of age, he had an elective video-assisted thoracoscopic RML lobectomy and right upper lobe (anterior segmentectomy) as this was deemed suspicious. Subsequently, he continued to have recurrent admissions for pneumonia with persistent changes seen in the right upper and middle zones of the CXR [Figure 1]. Bronchoscopy was performed at 2-years-old and confirmed the diagnosis of chronic suppurative lung disease. This was considered secondary to his severe respiratory syncytial virus pneumonia and silent aspiration due to suck-swallow incoordination. His parents, unfortunately, defaulted treatment and only reappeared when he had a massive haemoptysis with cyanosis and severe anaemia (Hb 47 g/dL). Extensive investigations finally revealed a focal bleed from the right

Table 1: Clinical differences between blood from the airway (haemoptysis) and blood from the gastrointestinal system (haematemesis)* or upper airway

	Haemoptysis	Haematemesis	Nose/throat bleed
History	Absence of nausea and vomiting	Presence of nausea and vomiting/retching	Throat pain/sore throat/inability to swallow
	Presence of lung disease or symptoms	Presence of gastric or hepatic disease	Previous history of epistaxis
Examination	Hypoxia and/or shortness of breath	Hypoxia and shortness of breath is unusual	Hypoxia and shortness of breath is an unusual aspiration of blood that has occurred
	ENT examination is normal	ENT examination is normal Epigastric pain	Presence of ulcers in the oral cavity, tonsils Dysphonia
	Crepitations in the lung	Normal	Normal unless has aspiration of blood
Sputum	Frothy	Rarely frothy	Not frothy
	Liquid or clotted	Coffee ground	Bright red with streaks or clots
	Bright red to pink	Brown to black/streaky red	Coffee ground if aspiration of blood has happened
Lab	Alkaline pH	Acidic pH	Alkaline
	Mixed with macrophages	Mixed with food particle and neutrophils	–

ENT = ear, nose and throat; *Adapted from Gaude[7]

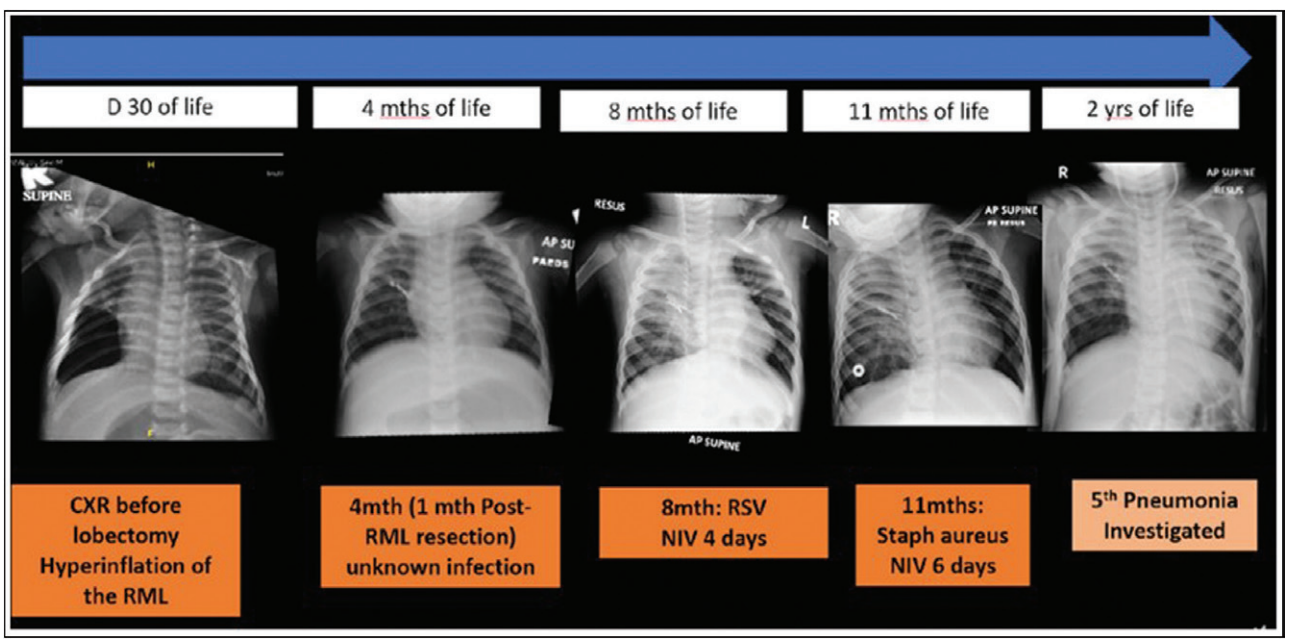

Figure 1: Serial chest radiographs of the patient when he was admitted for pneumonia

upper and remnant middle lobe [Figure 2]. Computerised tomography angiogram (CTA) did not show the source of the bleed. Finally, cardiac catheterisation found abnormally dilated and tortuous aorta-pulmonary collaterals (APCs) supplying these areas. The tortuous APCs and the PDA were coiled. He remains well, nearly after the bleed.

Aetiology of Pulmonary Haemorrhage

Determining the aetiology of PH is challenging, especially in the above case of Down syndrome, where there are so many possibilities. Numerous tests can be done to determine the aetiology [Table 2]. However, these should be prioritised based on the most likely diagnosis and differential diagnoses.

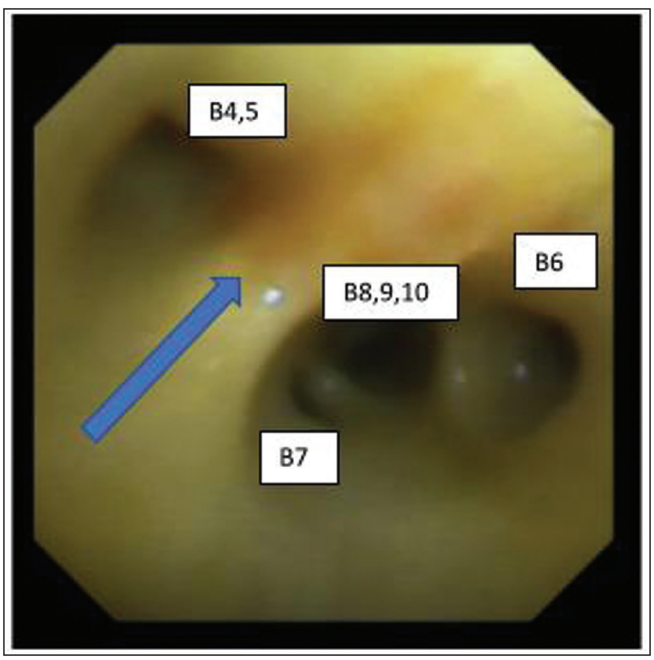

Figure 2: Bronchoscopy red dichromatic imaging (RDI) mode showing blood coming out from the right middle lobe [blue arrow]

The first task is to determine if this is a local versus diffuse bleed. This can be assisted by looking at the CXR. As in case 2, the differential was narrowed down by looking at his serial CXRs [Figure 1] and noting persistent consolidation of the right upper and mid-zone. Flexible bronchoscopy (FB) also confirmed that the PH was focal.

Role Bronchoscopy (Rigid or Flexible)[8]

Bronchoscopy, when performed in a controlled setting, is very useful diagnostically and therapeutically. In a massive bleed, FB should be performed within <48 h of presentation as this will increase the yield to find the source of the bleed, especially if it is a local bleed. Using a scope that can flush and suck adequately, for example, a 2.0 mm working channel, would be ideal to allow clearance of blood clots and improve oxygenation. It will also allow better visualisation of the area to determine or exclude possible aetiologies, for example, tumour, foreign body and airway anomalies. Visualisation using the red diffusion index mode, which enhances the visibility of blood vessels and bleeding sources in deeper tissue by using narrow-band light at two centre wavelengths (600 and 630 nm) in the red band, is very useful, especially when there is a lot of blood[9,10] [Figure 2].

During bronchoscopy, the aims would be to (a) determine the site of bleeding if focal, (b) look for abnormal mucosa, tumour or masses, (c) flush 50–60 mL aliquots of saline × 3 within the same lobe, and inspect the colour of the effluent after each aliquot.[8] If more blood or persistent blood is coming out as you flush, this is more likely a DAH rather than a focal bleed. Finally, using cold saline

Table 2: Investigations that assist in determining the aetiology of PH

Diseases	Investigations
Infective causes	Full blood count (reticulocytes + peripheral blood film) ESR, CRP Sputum/BAL for bacteria, fungus, MTB, PCP, herpes, adenovirus Imaging: CXR, CECT
Bleeding disorder	Coagulation studies, vWF, D-dimer
Immune mediated	Ig GAME ANCA (p-ANCA/MPO, c-ANCA/PR3), anti-GBM antibodies, APLA, ANA, anti-dsDNA, anti-Sm Urine analysis Lung biopsy (later in patients with suspected Idiopathic Pulmonary haemosiderosis) Genetics/WES: *TMEM173, STAT3, COPA genes*
Cardiac causes	Echocardiogram with bubble test
Vascular anomalies	Imaging with CECT, CTA, CTPA or Angiography, MRI angiography
Airway disease/trauma	Bronchoscopy (Flexible or Rigid)

ESR = erythrocyte sedimentation rate, CRP = c-reactive protein, BAL = bronchoalveolar lavage, MTB = Mycobacterium Tuberculosis, PCP = pneumocystis jirovecii, vWF = von Willebrand factor, Ig GAME = immunoglobulin G,A,M,E, ANCA = anti-neutrophilic, WES = whole exome sequencing, ANA = antinuclear antibody, ANCA = anti-neutrophil cytoplasmic antibody, anti-GBM = anti-glomerular basement membrane, anti-B2 GPA = anti-B2 glycoprotein antibody, Anti-CLA = anti-cardiolipin, Anti-dsDNA = anti-double stranded DNA, anti-MPO = anti-myeloperoxidase, APLA = anti-phospholipid antibody, anti-SM = anti-smooth muscle, c-ANCA = cytoplasmic-ANCA, p-ANCA = perinuclear-ANCA, anti-PR3 = anti-proteinase 3, CECT = contrast-enhanced computerised tomography, CTA = computerised tomography angiogram, CTPA = computerised tomography pulmonary angiogram, MRI = magnetic resonance imaging

or adrenaline: 1:10,000–1:20,000 can be therapeutic to control the bleeding.[11] Some have successfully used factor VIIa for massive bleeds.[12] Bronchoscopic alveolar lavage (BAL) samples should be sent for (a) cytology to look for haemosiderin-laden macrophages (including counts) and eosinophil count, (b) bacterial culture, (c) TB smear, culture and polymerase chain reaction/ GeneXpert, (d) fungus for microscopy and culture, (e) galactomannan antigen for Aspergillus and (f) multiplex polymerase chain reaction for viruses.

Role of Imaging to Determine the Aetiology

Radiographic investigations are vital as initial investigations, whether only CXRs or CT [Table 3]. If unable to perform FB immediately, multidetector CT with CTA can determine the source by identifying unusual or aberrant arteries, enlarged pathological bronchial arteries or pseudoaneurysms[13] [Figure 3]. A computed tomography pulmonary angiography (CTPA) is necessary if suspecting pulmonary embolism.[14] In DAH, CT will

Table 3: Aetiology of PH (a) focal (b) diffuse

Focal	Diseases	Examples
Lung	Infection	Tuberculosis, Pneumonia or tracheitis for example, *Staph aureus*, Viruses for example, adenovirus, influenzae, angio-invasive fungal infections for example aspergillosis, mucormycosis.
	Congenital lung malformations	Congenital Pulmonary Airway malformations, bronchogenic cysts, sequestration, duplication cyst
	Bronchiectasis	Cystic fibrosis, inhaled foreign body
	Vascular anomalies	Arteriovenous malformations, haemangioma, pulmonary vein atresia/ stenosis, pulmonary emboli, tracheobronchial varices, tracheo-inominate artery fistula
	Tumours	Mucoepidermoid carcinoma, Bronchial adenoma, carcinoid tumour, Dieulafoy's disease
	Trauma	Foreign body inhalation, artificial suctioning, penetrating chest trauma
Diffuse	**Diseases**	**Examples**
Down syndrome	Pulmonary hypertension	Untreated cardiac shunts for example, Patent ductus arteriosus, Obstructive sleep apnoea
	Congenital cardio-pulmonary malformations	
	Aspiration and infection	
	Auto-immune disease or immune dysregulation	
Immune mediated DAH	Systemic Lupus Erythematosus	
	Granulomatosis-ANCA mediated pulmonary vasculitis	
	GBM disease/Goodpasture	
	Eosinophilic granulomatosis	
	Henoch Schoenlein purpura	
	Idiopathic pulmonary capillaritis	
	Microscopic polyangiitis	
	Celiac disease	
	Monogenic auto-inflammatory diseases for example, SAVI and COPA	
Non-immune DAH	Idiopathic Pulmonary Hemosiderosis	
	Acute idiopathic PH of infancy	
	Heiner syndrome	
	Cardiac disease	Pulmonary telangiectasia, Pulmonary lymphangiomatosis

ANCA= anti-neutrophil cytoplasmic antibody, COPA= coatomer associated protein subunit alpha, DAH = diffuse alveolar haemorrhage, SAVI = STING-associated vasculopathy with onset in infancy

Cardiac disease	Focal	Diffuse
	Pulmonary vein atresia or stenosis/occlusion	Mitral stenosis
		Total anomalous PVD
		Pulmonary veno-occlusive disease

PVD = pulmonary venous drainage

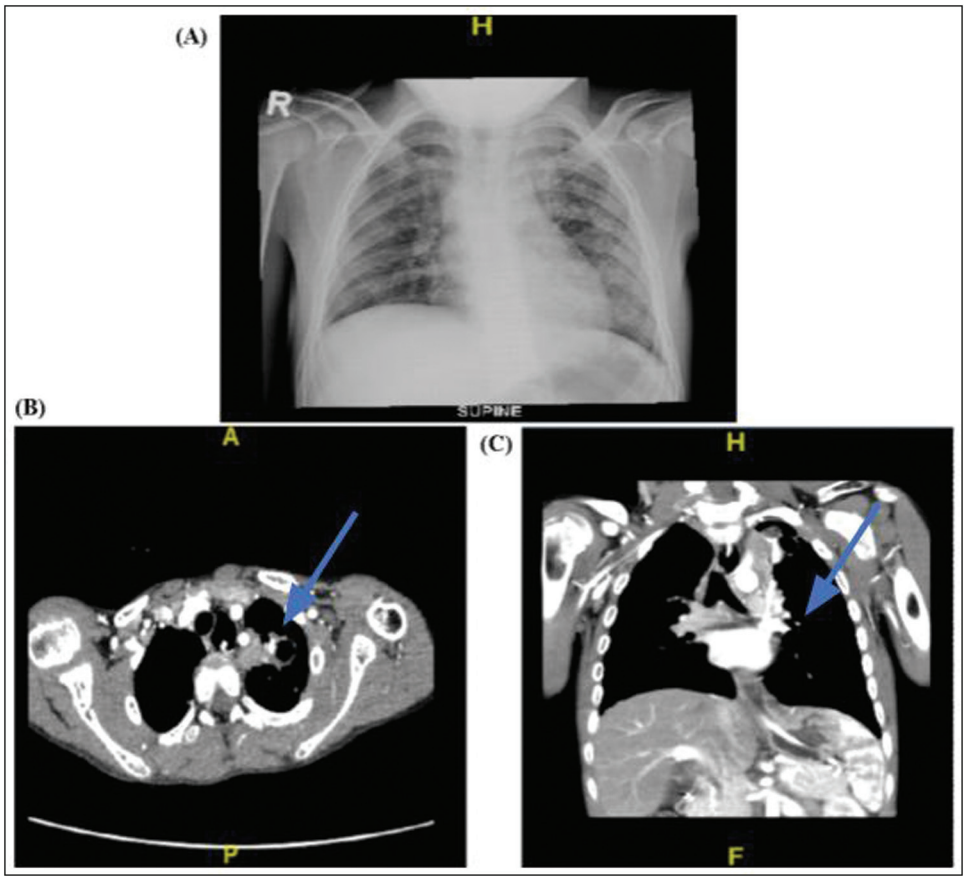

Figure 3: (A) Chest radiograph showed bilateral patchy consolidation and nodular air space opacity at left upper lobe in a patient with haemoptysis and smear positive TB. (B) CT angiography axial view and (C) CT angiography coronal view. Dilated bronchial vessels (blue arrows) adjacent to a cavitation with lack of tapering signifying presence of a pseudoaneurysm. This patient was treated with anti-TB medication and his haemoptysis improved

show diffuse ground glass with thickened septae increasing crazy paving [Figure 4].

An Egyptian study of mainly adults found that CT helped detect the bleeding in 84% of patients.[15] CTA is not always successful, as in our case 2, where two CTAs were performed and had a negative yield. Angiography or cardiac catheterisation is the next step.[16]

Role of Cardiac Catheterisation in the Management of Haemoptysis

Cardiac catheterisation (CC) is not commonly performed for children with haemoptysis.[16,17] However, it can help detect focal bleeding sources from various pathologies such as APCs, arteriovenous malformations (AVMs) and enlarged or pathological bronchial arteries when other conventional radiological techniques have failed. CC can also be therapeutic with the performance of transcatheter interventions. In a retrospective study from the cardiac centre at Children's Hospital of Michigan, over 15 years, only 21 cases were performed for PH.[17] The patients' median (range) age was 17 years (range 0.3–60). CC detected the cause of the bleeding in 81% of patients, and two-thirds had a transcatheter procedure: aortopulmonary collateral embolisation, aortopulmonary, venovenous collateral embolisation and pulmonary arteriovenous malformation embolisation.[17] Although recurrent haemoptysis was frequent (50%) postintervention, the final effectiveness of transcatheter interventions was 79%. In a smaller study published by Zaidi *et al.*,[16] they, too, found CC useful in identifying and treating APCs. Bronchial artery embolisation is also a well-accepted therapy in adults with massive or recurrent haemoptysis and children with cystic fibrosis.[13,18,19] However, this procedure can be more dangerous as inadvertent embolisation of the spinal arteries may cause paraplegia. Unfortunately, the expertise to perform CC in children is only available in some centres.

Case 3: TB or Not TB?

A 14-year-old girl presented with a dry cough for 2 weeks and haemoptysis. There was no fever, but she had lost 2 kg over the past 3 months. Her father had been treated for TB 2 years ago. Initial CXR showed mild infiltration of the right upper lobe. Her CRP was 23 mg/L (normal < 5 mg/L), and she had microcytic hypochromic anaemia.

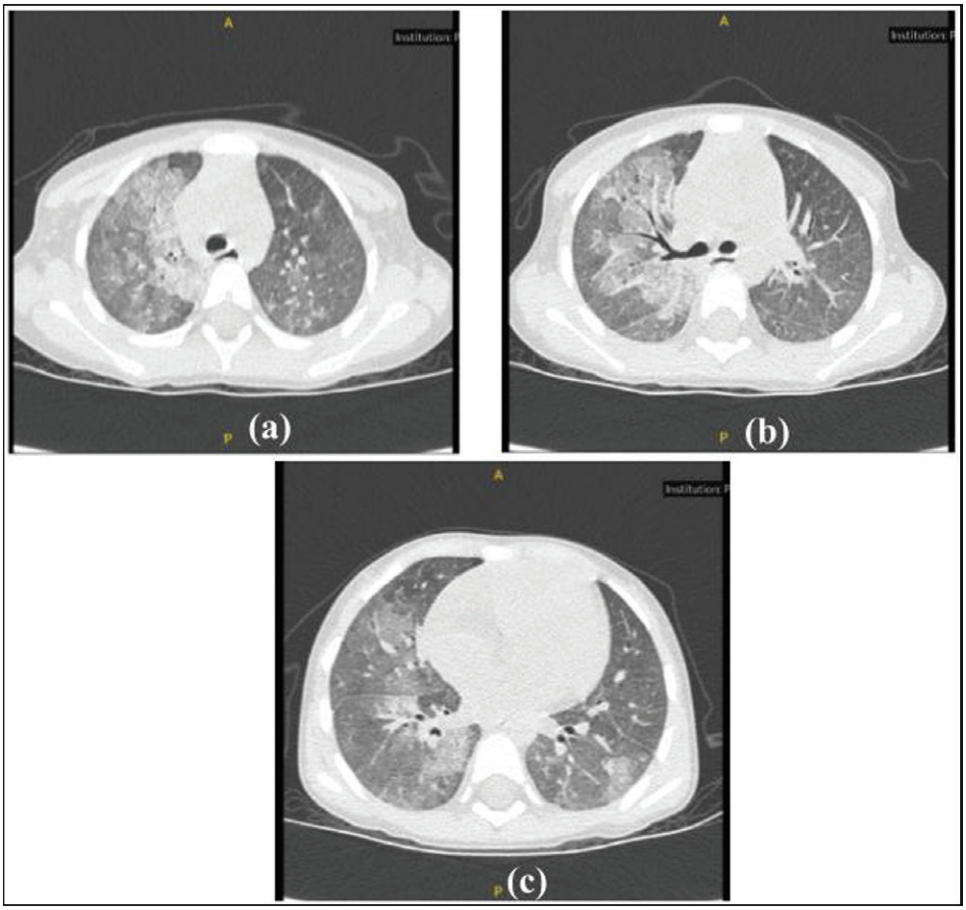

Figure 4: Diffuse bilateral ground glass opacities predominantly in the right upper (A + B) and lower lobes (C) involving the subpleural and central regions with areas of consolidation in the central regions of the right upper lobe. Areas of ground glass opacities with thickened interlobular septa giving rise to a crazy paving pattern seen predominantly in the right upper lobe and apical segment of right lower lobe

Her sputum acid-fast baccilli smear was negative. She had three other visits to the emergency department with haemoptysis over the next 4 weeks. Her repeat CXR showed lung cavities, and she was referred to us for further management. Her TB culture was positive for *Mycobacteria tuberculosis*.

Discussion: Infection in Haemoptysis

Whereas there are many causes of haemoptysis, infection is a common cause. TB is the most common infection associated with haemoptysis in Asia.[20] It is surprising that TB can even be forgotten by many as a cause of haemoptysis, even in the setting of a positive contact history, like the patient above. In a recent review article looking at haemoptysis, TB was not even mentioned as a cause of haemoptysis.[21] de Silva *et al.*[1] looked at 44 children managed in their centre and found TB to be the most common infection associated with PH. In a systematic review by Simon *et al.*,[22] TB was the 3rd most common infectious aetiology. TB can also be associated with complications like bronchial artery pseudoaneurysms, which can cause haemoptysis.[23]

In a review of infections that can cause DAH, the following were identified as possible causes: cytomegalovirus, adenovirus, invasive aspergillosis, *Mycoplasma*, *Legionella*, and Strongyloides in the immunocompromised during influenza A (H1N1) infection, dengue, *Leptospirosis*, Malaria and *Staphylococcus aureus* infection in the immunocompetent patient.[24]

Case 4: Vascular Anomalies

A 5-year-old girl was referred for recurrent bouts of haemoptysis (blood clots) since the age of 2 years. She is a second twin, born at 33 weeks gestational age, complicated with poor weight gain and necrotising enterocolitis. On examination, she was not clubbed, not cyanosed, and tachypnoeic with reduced breath sounds and dullness to percussion over the left lower zone. CTPA revealed an absent left pulmonary vein. Bronchoscopy revealed dilated blood vessels that easily bled, over the carina, and left the main bronchus and left lower lobe [Figure 5]. She was managed conservatively due to parental refusal of treatment and remains well.

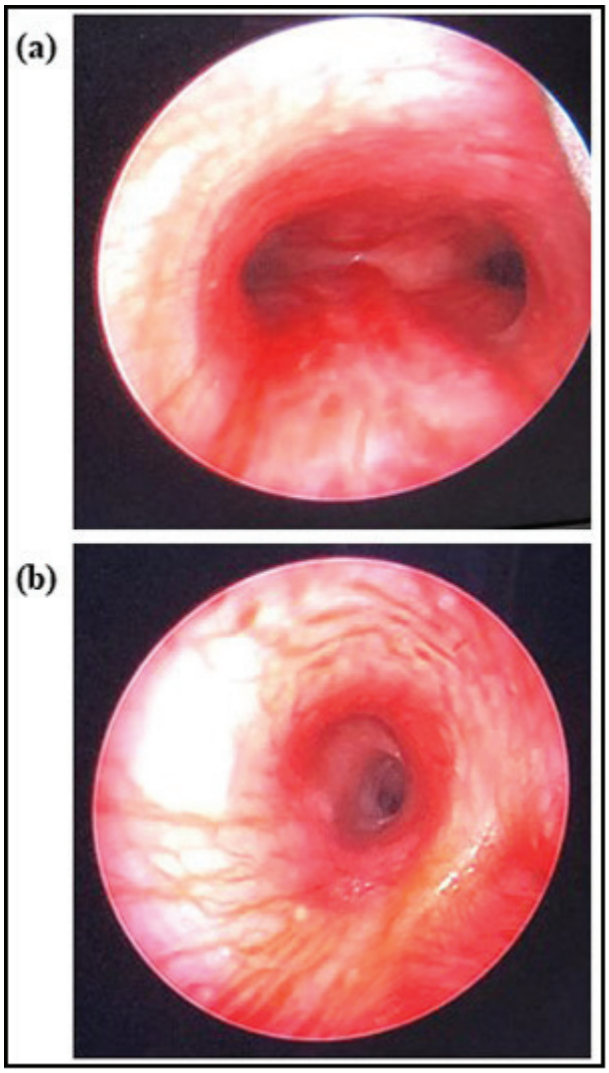

Figure 5: (A) Dilated sub mucosal blood vessels at the carina and leading into the left main bronchus. (B) Dilated blood vessels at the submucosal region of the left main bronchus. Endobronchial changes with dilation of the dense submucosal venous plexus can often be seen in bronchoscopy

Vascular Malformations of the Heart-lung

These can cause both diffuse as well as focal bleeding [Table 3].

Pulmonary vein stenosis

Haemoptysis with a history of mediastinal masses, granulomatous diseases, interventional procedures for atrial fibrillation therapy, lobectomy or right-sided pneumonectomy, pulmonary hypertension, recurrent respiratory infections or after lung transplantation should prompt the suspicion of pulmonary venous stenosis.[25]

The pulmonary and bronchial circulation drain via the pulmonary veins into the left atrium. Thus, in pulmonary vein stenosis, the drainage systems of both lung circulations are blocked. Typical consequences include distended pleural-hilar bronchial veins, alveolar haemorrhage, a friable endobronchial mucosa, reduced lymphatic drainage, interstitial pulmonary oedema, enlarged hilar lymph nodes, enlarged lymph vessels and sometimes a pleural effusion.[25-28]

In pulmonary venous stenosis, the expectorated blood is deoxygenated and, therefore, usually darker compared to haemoptysis with offspring of the systemic bronchial arteries.[29] Other presentations include tussive irritation, exertional dyspnoea, recurrent pulmonary infections and signs of pulmonary venous hypertension. Endobronchial changes with dilatation of the dense submucosal venous plexus can often be seen in bronchoscopy. The alveolar haemorrhage will result in a bloody bronchoalveolar lavage or, if occult, an increased number of haemosiderin-laden macrophages in the cell differentiation.[29] Due to the dense network between the pulmonary and bronchial circulation, extensive collaterals between both circulations may develop, with the possible occurrence of secondary bronchial and pulmonary venous varices in the long run. Misinterpretation of these varices and collaterals as pulmonary arteriovenous malformations has been reported. Bronchial artery embolisation may be deleterious in cases of hindered pulmonary venous drainage.

CT is superior in detecting pulmonary venous stenosis/atresia compared to transthoracic echocardiogram. Phase contrast magnetic resonance imaging also has its advantages of absent radiation, reduced invasiveness and visualisation of mediastinal structures and being able to provide information regarding blood flow. However, CT can give additional information about lung parenchyma.[29]

Arteriovenous malformations

These are defined as abnormal pulmonary arteries to venous connections without interconnecting capillaries.[30] Pulmonary AVMs occur with an incidence of 1 in 2500, with 80% occurring in patients with Hereditary Haemorrhagic Telangiectasia (HHT).[31] Besides haemoptysis, asymptomatic hypoxaemia, stroke, or brain abscess are other presentations of AVMs. AVMs can be simple or complex. Simple AVMs make up 80% of AVMs. Complex AVMs have multiple feeding blood vessels, while diffuse AVMs occupy all lung segments and are associated with cyanosis and clubbing.

HHT is usually inherited in an autosomal dominance trait. Patients present with nose bleeds, iron-deficiency anaemia and an increased risk of pulmonary hypertension.[32]

Aorta-pulmonary collaterals

These are usually blood vessels from the descending aorta, subclavian artery, and bronchial arteries and supply the terminal respiratory unit or bronchioles. It is commonly seen in conditions associated with reduced pulmonary blood flow, for example, tetralogy of Fallot

Table 4: Investigations that support a diagnosis of immune-mediated DAH

Type	Disease	Immune markers	Treatments
ANCA mediated (PC)	Granulomatosis with polyangiitis (Wegener's)	c-ANCA anti-PR3	Immunosuppressants: Steroids Cyclophosphamide Azathioprine MMF Rituximab IV IgG
	Churg Strauss	p-ANCA anti-MPO	
	Microscopic polyangiitis	p ANCA anti-MPO	
Other immune	Anti-phospholipid syndrome	APL/LAC/anti-CL	
	Systemic Lupus Erythematosus (SLE)	ESR/Anti dsDNA/ ANA/Anti-Sm/ Anti-histone ± anti-SSa, anti-SSb and anti-U1-RNP (non-specific)	
	Rheumatoid disease	ESR/RF	
	Henoch Schoenlein Purpura	Anti-Cardiolipin Ig A	Plasmapheresis
	Goodpasture	Anti-GBM	FFP
	Idiopathic pulmonary capillaritis	± p-ANCA anti-MPO	Immunosuppressants
	STING associated Vasculopathy with onset in Infancy (SAVI)	c-ANCA ANA APL STING 1 gene	JAK inhibitor
	COPA	RF/ANA/ANCA COPA gene	

ESR = erythrocyte sedimentation rate, CRP = c-reactive protein, BAL = bronchoalveolar lavage, MTB = Mycobacterium Tuberculosis, PCP = pneumocystis jirovecii, vWF = von Willebrand factor, Ig GAME = immunoglobulin G,A,M,E, ANCA = anti-neutrophilic, WES = whole exome sequencing, ANA = antinuclear antibody, ANCA = anti-neutrophil cytoplasmic antibody, anti-GBM = anti-glomerular basement membrane, anti-B2 GPA = anti-B2 glycoprotein antibody, Anti-CLA = anti-cardiolipin, Anti-dsDNA = anti-double stranded DNA, anto-MPO = anti-myeloperoxidase, APLA = anti-phospholipid antibody, anti-SM = anti-smooth muscle, c-ANCA = cytoplasmic-ANCA, p-ANCA = perinuclear-ANCA, anti-PR3 = anti-proteinase 3, CECT = contrast-enhanced computed tomography, CTA = computed tomography angiogram, CTPA = computer tomography pulmonary angiogram, MRI = magnetic resonance imaging, STING = stimulator of interferon response cGAMP interactor, RF = rheumatoid factor, COPA = COPI coat complex subunit alpha, JAK= Janus kinase

and pulmonary atresia. They have also been identified in premature infants with BPD. Non-bronchial systemic arteries commonly supply the lungs in patients with chronic lung disease.[13] These usually regress and may not require treatment. A review of seven patients, mainly infants with APCs without cardiac disease, presented at a mean age of 3 months and six out of seven required embolisation, which was highly successful. They found that helical CT scans were not useful in detecting these APCs. However, cardiac catheterisation was far superior as diagnostic and therapeutic if embolisation or coiling was performed in one setting.[16]

APC vessels have been reported as a frequent source of bleeding in congenital heart disease (CHD) patients.[33] It is hypothesised that APCs develop due to the need for a secondary source of pulmonary blood flow in CHD patients because of chronic hypoxia and altered pulmonary vasculature.[12] Patients after the Fontan operation are likely to develop significant APCs with an estimated haemoptysis rate of 4%.[33] Interestingly, APCs have also been reported as the source of haemoptysis in children without CHD.[8,13]

Bronchial artery malformations, for example, dieulofoys disease

Bronchial artery malformations are well known for massive bleeds and require treatment in 90% of cases, that is, bronchial artery embolisation or surgical resection.[13] Worldwide, TB is the most common cause of non-massive haemoptysis.[12,33] These malformations are also seen in diseases with chronic inflammation, for example, cystic fibrosis, bronchiectasis and fibrotic scarring, aspergillomas or invasive mycotic infections and fibrotic scarring.[12,34] These can be diagnosed via contrast-enhanced CT, but angiography is more sensitive. This is similar to a pseudoaneurysm.

Another rare but very interesting disease is Dieulofoy's disease.[33,35] These appear small (usually < 1 cm in diameter), smooth and elevated nodules, with white pointed caps and a ridge-like bulge between the nodules. These sessile nodules are usually covered with normal-appearing bronchial mucosa and appear benign. However, they are fed by tortuous dysplastic bronchial arteries in the submucosa, from which vascular branches derive that can be located in the mucosa and biopsy of these lesions can be fatal. Diagnosis is confirmed via angiography.[35] Bronchial artery embolisation can be performed in the same setting and is said to be successful in 96.1% of cases.[33,36]

Case 5: Pulmonary Hemosiderosis

A 14-month-old girl presented with iron-deficiency anaemia requiring multiple blood transfusions. Initially, she did not have any respiratory tract symptoms. At

4-years-old, she presented with haemoptysis, cough, fever and shortness of breath. The initial diagnosis of pneumonia. However, her CT chest showed DAH. All investigations were negative, including her connective tissue screen. No lung biopsy was performed. On the basis of her previous history of persistent iron-deficiency anaemia and CT changes, she was diagnosed with idiopathic pulmonary haemosiderosis and treated with pulses of IV methylprednisolone. Whereas she did seem to respond, her disease relapsed three times over a 15-year period. This was usually associated with the cessation of prednisolone. A lung biopsy was then performed, which showed evidence of capillaritis. Her diagnosis was changed to idiopathic pulmonary capillaritis, and she was treated with pulse cyclophosphamide.

Discussion: Diffuse Alveolar Haemorrhage

DAH occurs due to the disruption of the alveolar-capillary basement membrane in the lung, resulting in bleeding into the alveolar spaces.[37] Injury can be immune- or non-immune mediated, with subsequent involvement of the blood vessels and the alveolar septae.

DAH is best diagnosed when diffuse changes in CT scan plus bronchoscopic evidence of haemosiderin-laden macrophages. Classically, persistent or increasing blood on three sequential lavage aliquots from one affected area of the lung supports the diagnosis of DAH.[8,38] The causes of DAH are shown in Table 3. The majority listed is immune-mediated.

Worth a Mention: Idiopathic Pulmonary Hemosiderosis

Idiopathic pulmonary hemosiderosis (IPH) would be a diagnosis of exclusion in children with an unknown cause of DAH. This would be one of the most common causes of haemorrhage.[1,5] Lung biopsies show bland alveolar haemorrhage, with large amounts of haemosiderin-laden macrophages in the alveoli. There is a distinct absence of inflammation, capillaritis and vasculitis in histology. A review on IPH found it more commonly in girls, with only one-quarter of them having positive auto-antibodies: anti-nuclear antibody, 20.3%; anti-neutrophil cytoplasmic antibody, 17%; anti-dsDNA, 9.1%; RF, 12%; anti-smooth muscle antibody, 23.2%; and celiac antibodies, 25.9%.[39] Cow's milk protein allergy was present in 16.2% of the children.[39] The significance of an association between IPH and the presence of autoantibodies is unclear, as the autoantibodies could be suggestive of an overall immune dysregulation rather than causation. However, limited evidence suggests that the presence of anti-nuclear antibody may be associated with a higher risk of recurrence and worse outcomes.[39]

Immune dysregulation diseases associated with PH. There is mounting evidence of the role of genetic immune dysregulation diseases that cause systemic vasculitis associated with haemoptysis, for example, coatomer associated protein subunit alpha[40,41] and sting-associated vasculopathy of infancy (SAVI)[42,43] [Table 4]. A review of 14 patients with coatomer associated protein subunit alpha syndrome, all had symptoms before 12 years, had a positive family history of disease, and had both diffuse lung disease and arthritis.[40] Symptoms were either respiratory and/or joint manifestations. Only two patients presented with anaemia and fatigue secondary to PH. Eventually, 50% had a PH. All subjects were positive for anti-neutrophil cytoplasmic antibody, antinuclear antibody, or both and 71% of patients were rheumatoid factor positive. The most common pulmonary findings included cysts on chest computed tomography and evidence of follicular bronchiolitis on lung biopsy. All were treated with immunosuppressive medication, that is, methylprednisolone, cyclophosphamide and/or rituximab. Longitudinal data demonstrated improvement in chest radiology but an overall decline in pulmonary function despite chronic treatment.[41]

SAVI, on the other hand, typically manifests as neonatal-onset systemic inflammation, interstitial lung disease (ILD), and severe cutaneous vasculopathy in acral regions, including fingers, toes, ears and nose. The majority present with interstitial lung disease rather than PH and other autoimmune signs.[42,43]

Authors Indications for Lung Biopsy

1. Suspect IPH or autoimmune disease
2. Female
3. Negative CTD markers
4. Poor response to first line immunomodulators for example, steroids
5. Recurrent or relapsing disease > 2 times
6. Inability to wean off steroids due to relapse
7. Need to use steroid sparing medication due to complications from steroids.

Management of Pulmonary Haemorrhage

Management of PH can be divided into general and specific management strategies.[21]

The general management includes the following:

1. **Reducing hypoxia:** May require intubation with adequate PEEP if it is a massive bleed. Can consider non-invasive ventilation if not massive bleeding and the patient is stable.
2. **Correcting the anaemia:** Blood transfusion
3. **Correcting any coagulopathy:** Suggested to correct if platelet count is $<50{,}000 \times 10^6$/L or PT > 1.5
4. **In patients with significant/massive bleeding**: Can consider use of factor VIIa[12] or tranexamic acid (TXA)[44] or IVI vasopressin[12]

Factor VIIa acts via the extrinsic pathway. It can be used either via the intrapulmonary or intravenous route. It has been reported to be useful for the general management of DAH, whether immune or not.[21] However, it may be less effective in children < 1-year-old and those with haematological malignancies.[12]

Both systemic and local administration of TXA have been used in the prophylaxis and treatment of bleeding diathesis, whether the bleeding is congenital or acquired.[25,26] TXA acts by binding to plasminogen, which in turn inhibits its binding to fibrin. Activation to plasmin is thus impaired. TXA has been used in the intravenous, aerosolized and intrapulmonary form to treat PH.[45]

Specific Management Depends on the Aetiology

1. **Treating infections:** anti-bacterial, antifungal or antiviral
2. If suspected or autoimmune or idiopathic pulmonary haemosiderosis:
   a. IVI methylprednisolone (MTP) 30mg/kg 3–5 days then taper over 4 weeks with oral prednisolone or prednisolone 30mg/kg/day then taper. Studies have shown that lower doses of methylprednisolone may be sufficient.[46]
   b. Oral hydroxychloroquine (6–10mg/kg/OD) as a maintenance therapy.[46,47]
3. For resistant or recurrent haemoptysis from an autoimmune cause:
   a. Pulse cyclophosphamide (CYC) has been used in the management of PH associated with SLE and oral azathioprine as an immunosuppressant.[48]
4. Rituximab (RTX) has gained interest, since its success in connective tissue disease or autoimmune vasculitis. RTX is a chimeric monoclonal antibody that targets CD20. Concurrent use of MTP, CYC and RTX has been shown to improve remission compared to use of MTP and CYC alone in patients with anti-neutrophil cytoplasmic antibody +ve connective tissue disease[49,50] as well as in SLE.[48] RTX has also been shown to result in improved survival and long-term remission.[51]
5. Life threatening haemoptysis secondary to autoimmune cause of haemoptysis:
   a. IV Ig G at or plasmapheresis[21]
6. Abnormal vasculature for example, AVM, APCs and Aberrant/dilated bronchial arteries
   a. Ideally embolisation and/or ligation of these abnormal bleeding vessels are essential to stop the bleeding. However, it may be difficult to do it small and require expertise.[13,36]

Summary

Managing a child with haemoptysis is challenging and requires critical analyses of the case to avoid unnecessary tests as well as not to delay the diagnoses. Important steps are first to determine if (a) the blood is from the lung or elsewhere, (b) if from the lung, is it focal or diffuse bleed, (c) exclude infection, as this is common and easily treatable, (d) if this is a DAH, what autoimmune problem could it be and (e) treat the problem depending on the severity of the bleed and cause.

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Conflicts of interest

There are no conflicts of interest.

Authors contribution

AMN, HSY, EKP, NFMG and JdB were involved in writing and editing this article.

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Original Article

Factors Associated with Prolonged Intensive Care Unit Treatment and Organ Failure in Pediatric Patients with Diabetic Ketoacidosis

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Abstract

Context: Patients with diabetic ketoacidosis (DKA) have potential complications, such as respiratory failure, cerebral edema, or acute renal injury, all of which can lead to a prolonged hospital course. **Aims:** This study identified risk factors for prolonged intensive care unit (ICU) stay and organ failure in pediatric patients with DKA. **Materials and Methods:** Patients with DKA aged <19 years admitted to the pediatric ICU of our hospital between June 2011 and May 2021 were enrolled. Demographic characteristics, initial Glasgow Coma Scale score, source of admission, biochemical values, ICU length of stay (LOS), and hospital LOS were collected. The primary outcome was to identify factors associated with prolonged (≥48 h) ICU treatment. The secondary outcomes were to identify factors associated with respiratory failure, cerebral injury, or acute renal failure. **Results:** This study enrolled 137 patients. Nonemergency room admission was associated with longer ICU LOS [adjusted odds ratio (aOR), 3.14; 95% confidence interval (CI) 1.01–9.82] compared with admission from the emergency room. Older age (aOR, 0.89; 95% CI, 0.80–0.99) and underweight (aOR, 0.33; 95% CI, 0.12–0.95) were associated with shorter ICU LOS. **Conclusions:** Recognizing the risk factors associated with prolonged ICU LOS in pediatric patients with DKA may help clinicians with the early identification of critical DKA cases.

Keywords: Diabetic ketoacidosis, intensive care unit, pediatric, length of stay

Key messages: nonemergency room admission is associated with longer icu length of stay, whereas older age is associated with shorter icu length of stay in pediatric dka.

Introduction

A previous study using Taiwan's National Health Insurance Research Database revealed that the diabetes mellitus (DM) prevalence rate in Taiwan from 2000 to 2009 in people younger than 19 years was approximately 0.06%–0.08%.[1] Death in patients with insulin-dependent DM is predominantly due to diabetic ketoacidosis (DKA).[2] Prior to the therapeutic use of insulin, the mortality rate of DKA was close to 100%; at present, it has decreased to 0.15%–0.3%.[2-4] Patients with DKA having complications of cerebral edema, sepsis, shock, or acute kidney injury (AKI) can have a prolonged hospital stay and higher mortality.[5] The median length of stay (LOS) in the hospital in pediatric patients with DKA is 2 days in the United States.[6] However, the treatment of pediatric patients with DKA is different between Taiwan and other countries. A longer hospital course is usually observed due to more affordable medical expenses under

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Taiwan's National Health Insurance program. Most pediatric patients with DKA are admitted to the intensive care unit (ICU) for close monitoring of their possible complications. Once DKA is resolved, thorough education about insulin injection, daily diet arrangement, and long-term follow-up plans are conducted at the ward. In this study, we identified the factors associated with prolonged ICU treatment and organ failure in pediatric patients with DKA.

Subjects and Methods

Study design

This is a retrospective cohort study. This study included all patients aged less than 19 years admitted to our hospital due to DKA between June 2011 and May 2021. A study based on the adult population indicated that the average LOS in the ICU was 2 days.[7] Another pediatric population-based study concluded that prolonged metabolic acidosis, if not corrected within 24 h, in children with DKA led to a mean ICU LOS of 45 h.[8] On the bases of these findings, we used 48 h as a reference to evaluate prolonged ICU LOS. The primary aim of this study was to identify the factors associated with ICU stay for >48 h. The secondary aim was to identify factors associated with respiratory failure, cerebral injury, and AKI. This study was approved by the institutional review board of our hospital, and the requirement of informed consent was waived.

Data collection

Medical records were collected by searching our hospital's medical record database using ICD 9 (ICD 9 250.1 diabetes with ketoacidosis) and ICD 10 (E10.1 type 1 DM with ketoacidosis, E11.1 type 2 DM with ketoacidosis, E12.1 malnutrition-related DM with ketoacidosis, E13.1 other specified DM with ketoacidosis, E14.1 unspecified DM with ketoacidosis) codes. Patients whose laboratory data were missing or did not meet DKA criteria (serum glucose >200 mg/dL, venous pH <7.3 or bicarbonate <15 mmol/L, and presence of ketonemia or ketonuria) were excluded.

The following data were obtained from the medical records of each child: demographic characteristics, initial Glasgow Coma Scale (GCS) score, source of admission, initial biochemical value and creatinine changes, ICU LOS, and hospital LOS.

The patients were classified into three body types based on their body mass index (BMI) using the weight and height collected upon admission. BMI percentile was calculated using the BMI calculator for children and teens (https://www.cdc.gov/healthyweight/bmi/calculator.html). Because the BMI percentile is not recommended for children younger than 2 years of age according to the World Health Organization (WHO), they were evaluated using weight-for-length instead. The patients with BMI or weight-for-length below the 5th percentile were classified as being underweight. The patients with BMI higher than the 85th percentile or weight-for-length more than the 95th percentile were classified as being overweight. Those with intermediate values for these two variables were considered as healthy. Data published by the WHO were used as a reference (https://www.who.int/tools/child-growth-standards/standards/weight-for-length-height).

DKA severity was divided into mild, moderate, and severe according to the initial laboratory results as follows: mild DKA, pH < 7.3 or bicarbonate of 10–15 mmol/L; moderate DKA, pH <7.2 or bicarbonate of 5–10 mmol/L; and severe DKA, pH <7.1 or bicarbonate <5 mmol/L.

Serum sodium was corrected using the following formula: corrected serum sodium concentration = measured serum sodium concentration + 1.6 × (serum glucose concentration (mg/dL) − 100)/100.

Patients with lipase >648 U/L or an increase of more than three times the upper limit were considered with elevated lipase.

The patients were also divided into two groups based on the source of admission: the emergency room and the nonemergency room groups. The following patient groups were included in the nonemergency room group: patients whose DKA diagnosis was delayed and who were admitted to the ward first and those diagnosed as having DKA at other facilities but were unable to receive treatment immediately or required referral.

The ICU LOS of a patient with DKA depended on the time taken to resolve DKA (total CO_2 > 15 mEq/L; pH > 7.30 or sodium stable between 135 and 145 mEq/L). Once DKA was corrected, the patient could start oral intake, and their insulin therapy could be shifted from continuous intravenous infusion to subcutaneous injection; they would then be transferred to the ward.

Regarding secondary outcome data collection, patients who received mechanical ventilation support were considered as having respiratory failure. Those who presented with altered consciousness or signs of increased intracranial pressure received mannitol or glycerol as well as underwent brain imaging if cerebral edema was suspected. Any patient with a creatinine increase of 1.5-fold from the baseline or with decreased urine output, requiring diuretic use or renal replacement therapy, was regarded as having AKI.

Statistical analyses

Median values and interquartile ranges were calculated for all continuous variables. Bivariate analysis was used to identify factors associated with prolonged length of ICU stay (≥48 h). Between-group comparisons of continuous and categorical variables were performed using binary

logistic regression and the chi-square test, respectively. Two-tailed $P < 0.05$ was considered statistically significant. Factors statistically significant associated with the prolonged length of ICU stay were further analyzed using multivariate logistic regression to calculate the adjusted odds ratio (aOR). All analyses were performed using SPSS v22 (IBM, Armonk, New York).

Results

Patient characteristics

We identified 150 admissions by using ICD 9 and ICD 10 codes in our hospital's medical record database between June 2011 and May 2021. One patient was excluded due to incomplete medical records, and 12 patients were excluded because they did not meet the diagnostic criteria of DKA.

A total of 137 patients were included in this study. The median age (IQR) of the study population was 11 (8, 15) years. The study population comprised 50 boys and 87 girls. Approximately 56% ($n = 77$) of patients had new-onset diabetes and presented with DKA for the first time, whereas 46% ($n = 60$) patients were already diabetics on insulin therapy. Furthermore, 56% ($n = 77$) of the study population had healthy body weights, 31% ($n = 43$) were underweight, and 12% ($n = 17$) were overweight. As for DKA severity, 27% ($n = 37$) had mild DKA, 39% ($n = 53$) had moderate DKA, and 34% ($n = 47$) had severe DKA. In all, 86% ($n = 118$) of the patients were admitted from the pediatric emergency room, whereas the remaining were referred from other local hospitals or transferred from the ward. The median ICU LOS (IQR) of the study population was 43 (34, 50) h. The median hospital LOS (IQR) was 8 (6, 10) days.

Primary outcome

In this study, 92 patients (67%) had an ICU stay of <48 h, and 45 (33%) had an ICU stay of >48 h [Table 1]. No significant differences were observed between these groups in terms of sex, height, new diabetes diagnosis, DM type, initial white blood cell count, C-reactive protein elevation, serum osmolality, creatinine elevation, serum potassium level, and lipase elevation.

Compared with the patients with ICU LOS <48 h, the patients with ICU LOS ≥48 h were significantly younger ($P = 0.043$); a lower proportion of these patients were underweight ($P = 0.016$); they had lower glycated hemoglobin (HbA1C, $P = 0.025$) and higher corrected serum sodium ($P = 0.009$) levels; and they had a lower proportion of emergency room admitted cases ($P = 0.012$). In addition, fewer severe DKA cases ($P = 0.037$) were found in this group, indicating that initial DKA severity was not associated with prolonged ICU stay.

In the multivariate logistic regression analysis, the only variable associated with prolonged ICU stay was admission from nonemergency room sources [aOR, 3.14; 95% confidence interval (CI) 1.01–9.82] [Figure 1]. Variables associated with shorter ICU stay were age (aOR, 0.89; 95% CI, 0.80–0.99) and being underweight (aOR, 0.33; 95% CI, 0.12–0.95). With every 1-year increase in age, the risk of ICU stay ≥48 h decreased by 11%.

Table 1: Patient characteristics and demographic for ICU stay more than 48 h

	ICU < 48 h ($n = 92$)	ICU ≥ 48 h ($n = 45$)	*P*-value
Age (years)*	12 (8, 16)	10 (8, 12)	0.043
Male (%)	38 (41.3)	12 (26.7)	0.095
Height (cm)*	151 (129, 157)	142 (127, 153)	0.260
Body type			
Underweight (%)	35 (38)	8 (17.8)	0.016
Healthy (%)	47 (51.1)	30 (66.7)	0.084
Overweight (%)	10 (10.9)	7 (15.6)	0.435
Fresh DM case (%)	53 (57.6)	24 (53.3)	0.636
Type 1 DM	84 (91.3)	41 (91.1)	0.970
DKA severity			
Mild (%)	24 (26.1)	13 (28.9)	0.729
Moderate (%)	31 (33.7)	22 (48.9)	0.086
Severe (%)	37 (40.2)	10 (22.2)	0.037
Laboratory			
HbA1C*	12.7 (11.1, 14.4)	11.2 (9.7, 13.1)	0.025
Cr elevation (%)	52 (58.4)	34 (75.6)	0.051
Na, corrected*	138 (136, 140)	140 (137, 144)	0.009
ER admission	84 (91.3)	34 (75.6)	0.012
Respiratory failure	0 (0)	5 (11.1)	0.001
Suspect cerebral edema	0 (0)	7 (15.6)	<0.001
Acute kidney injury	1 (1.1)	4 (8.9)	0.022
Hospital days*	7 (6, 9)	9 (8, 11)	<0.001

DM: diabetes mellitus, DKA: diabetic ketoacidosis, GCS: Glasgow Coma Scale, Osmo: osmolality, ER: emergency room, ICU: intensive care unit

* Median (interquartile range)

Secondary outcomes

Five patients (3.6%) in this study had respiratory failure and were intubated during the ICU course. This group also had a significantly higher number of patients with newly diagnosed DM ($P = 0.044$) [Table 2]. Seven patients were suspected of having cerebral edema [Table 3], and five were suspected of having AKI. Factors associated with cerebral edema or AKI could not be identified. Although not statistically significant, patients with DKA who developed respiratory failure were suspected of cerebral edema, or had AKI were younger, and the majority of them were newly diagnosed as having DM.

Discussion

In our study, patients admitted from nonemergency room sources exhibited a longer ICU stay, and older age and underweight were associated with a shorter ICU stay. These findings might be related to fluid status, because more severe dehydration at presentation was associated

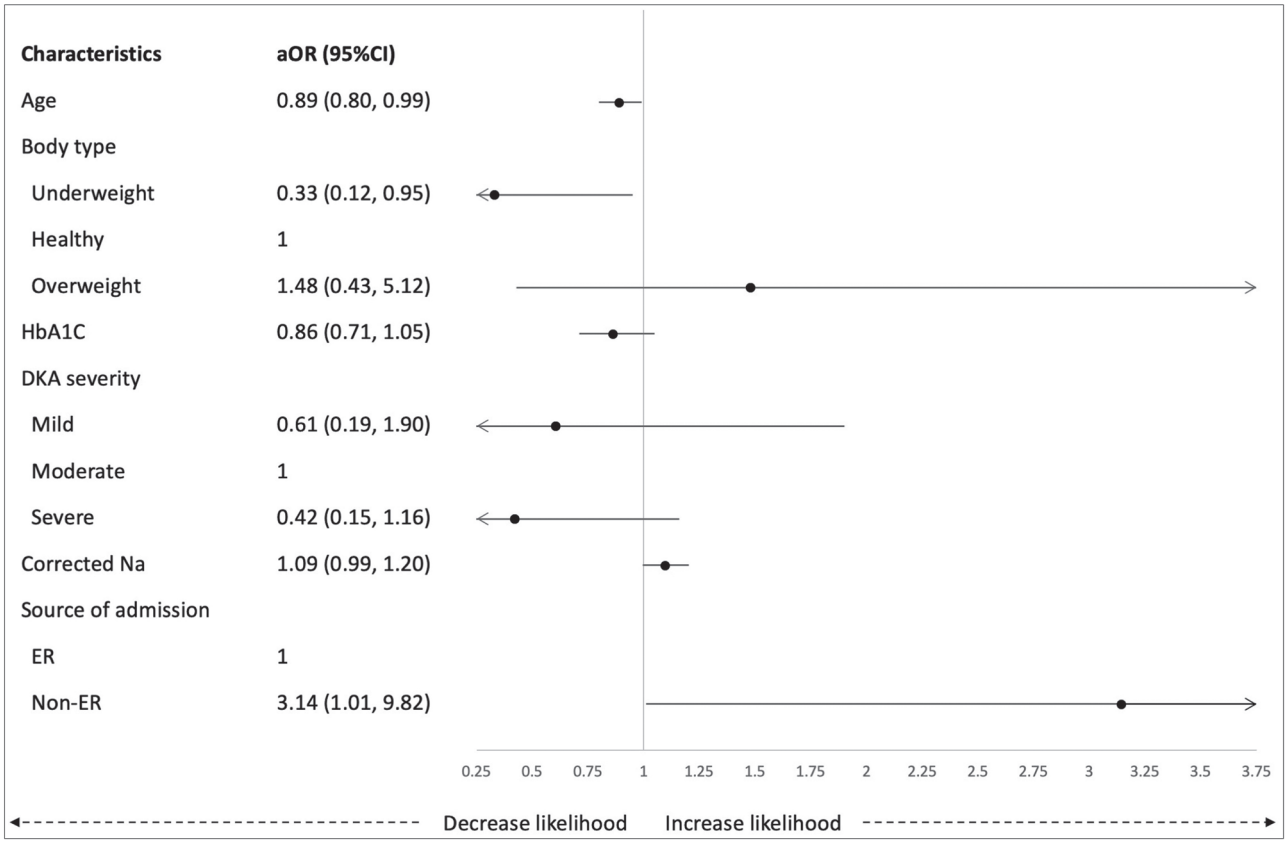

Figure 1: Multivariate adjustment of factors associated with the likelihood of pediatric DKA patients staying in ICU for more than 48 h

Table 2: Characteristics and demographic of patients with acute respiratory failure

	No respiratory failure (n = 132)	Respiratory failure (n = 5)	P-value
Age (years)*	11 (8, 15)	7 (4, 13)	0.155
Male (%)	47 (35.6)	3 (60)	0.266
Height (cm)*	149 (128, 156)	131 (100, 147)	0.145
Body type			
Underweight (%)	42 (31.8)	1 (20)	0.576
Healthy (%)	75 (56.8)	2 (40)	0.457
Overweight (%)	15 (11.4)	2 (40)	0.057
Fresh DM case (%)	72 (54.5)	5(100%)	0.044
Type 1 DM	121 (91.7)	4 (80)	0.365
DKA severity			
Mild (%)	37 (28)	0 (0)	0.116
Moderate (%)	50 (37.9)	3 (60)	0.319
Severe (%)	45 (34.1)	2 (40)	0.785
Initial GCS*	15 (15, 15)	14 (13, 15)	0.442
Laboratory			
HbA1C*	12.5 (10.8, 13.9)	11 (9.8, 11.7)	0.220
Serum Osom*	314(305,324)	318(300,324)	0.297
Cr elevation (%)	83 (64.3)	3 (60)	0.843
Na, initial*	132 (130, 135)	131 (129, 136)	0.916
Na, corrected*	138 (136, 141)	136 (135, 151)	0.219
K*	4.3 (3.6, 4.9)	3.7 (3.3, 4.5)	0.271
Lipase elevation (%)	5 (3.8)	1 (20)	0.082

DM: diabetes mellitus, DKA: diabetic ketoacidosis, GCS: Glasgow Coma Scale, Osmo = osmolality
* Median (interquartile range)

with a longer duration of insulin infusion.[9] In our study, patients with ICU LOS ≥48 h had a higher serum sodium level than those with ICU LOS <48 h, indicating higher dehydration levels.

Patients who were admitted from the ward usually had delayed DKA diagnosis, whereas those referred from other facilities had a longer gap between DKA diagnosis and treatment. These conditions might worsen dehydration status, thereby necessitating a longer insulin infusion time. A study conducted in the adult DKA population revealed a similar result: a longer gap between admission and DKA consultation was associated with a longer hospital LOS.[10] Notably, of the 19 patients from nonemergency room sources, 4 had a delayed diagnosis of DKA: they visited our emergency room but were not diagnosed with DKA and were admitted to the general ward first and then transferred to the pediatric ICU after DKA diagnosis. The remaining 15 patients were diagnosed as having DKA at other hospitals and were referred to our hospital for DKA management. All of the DKA cases admitted from ER were diagnosed during their first ER visit; none of them were diagnosed during the second visit. The delayed diagnosis rate for DKA was 3.2% in our hospital. However, these four patients did not stay in the pediatric ICU for more than 48 h. Therefore, the association of nonemergency room sources with pediatric ICU LOS for more than 48 h was mainly observed in referral patients.

Table 3: Characteristics and demographic of patients suspected of cerebral edema

	No cerebral edema (n = 130)	Suspect cerebral edema (n = 7)	P-value
Age (years)*	11 (8, 15)	9 (6, 11)	0.202
Male (%)	46 (35.4)	4 (57.1)	0.244
Height (cm)*	149 (128, 156)	137 (121, 144)	0.199
Body type			
Underweight (%)	41 (31.5)	2 (28.6)	0.869
Healthy (%)	74 (56.9)	3 (42.9)	0.465
Overweight (%)	15 (11.5)	2 (28.6)	0.183
Fresh DM case (%)	71 (54.6)	6 (85.7)	0.106
Type 1 DM	119 (91.5)	6 (85.7)	0.595
DKA severity			
Mild (%)	35 (26.9)	2 (28.6)	0.926
Moderate (%)	50 (38.5)	3 (42.9)	0.816
Severe (%)	45 (34.6)	2 (28.6)	0.743
Initial GCS*	15 (15, 15)	15 (14, 15)	0.702
Laboratory			
HbA1C*	12.5 (10.7, 13.9)	11.6 (10.2, 12.1)	0.282
Serum Osom*	314 (305, 324)	318 (300, 330)	0.347
Cr elevation (%)	82 (64.6)	4 (57.1)	0.690
Na, initial*	132 (130, 134)	134 (130, 137)	0.401
Na, corrected*	138 (136, 141)	141 (135, 147)	0.075
K*	4.3 (3.6, 4.9)	4.1 (3.6, 4.8)	0.607
Lipase elevation (%)	5 (3.8)	1 (14.3)	0.189

DM: diabetes mellitus, DKA: diabetic ketoacidosis, GCS: Glasgow Coma Scale, Osmo = osmolality

* Median (interquartile range)

Older children were able to access fluids to replenish volume losses, and underweight patients had a lower insensible water loss in terms of the surface area-to-volume ratio.[11] The body surface area formula is the square root of [height (in cm) × weight (in kg)/3600]. Compared with a normal-weight patient, an underweight patient will have a lower body surface area. These measures reduced the likelihood of severe dehydration, resulting in a shorter ICU LOS. Moffett *et al.*[12] found that underweight patients had shorter beta-hydroxybutyrate clearance times, which can cause faster DKA resolution, leading to a shorter ICU LOS.

Glucose level, admission HbA1C level, and initial DKA severity were not significant predictors of hospital LOS in the adult population in a previous study.[10] A similar result was found in the pediatric population; HbA1C was not associated with hospital LOS, and no differences were observed in HbA1C levels between pediatric patients with DKA having newly diagnosed DM and those with known DM.[13] In our study, the initial result indicated that lower HbA1C was associated with longer pediatric ICU LOS (≥48 h), but this association was not significant in the multivariate logistic regression.

In this study, the median ICU and hospital LOS were 43 h and 8 days, respectively. Everett *et al.*[14] reported that the mean hospital LOS in pediatric patients with DKA in the United States was 2.38–2.51 days and was inversely related to medical expenses. The difference between their study and our study was likely due to the more affordable medical expenses under Taiwan's National Health Insurance program.

Most pediatric patients with DKA have type 1 DM. Patients with type 1 DM account for 91% and 94% of the DKA admissions in our study and the aforementioned study in the United States, respectively.[14] DKA is commonly seen in patients with newly diagnosed DM or in those with poor insulin compliance. The median age of newly diagnosed type 1 DM onset is approximately 10 years.[15] Poor insulin compliance resulting in DKA admission is commonly found in the late teenage years.[14] In our study, the majority (56%) of the patients with DKA in pediatric ICUs were newly diagnosed as having DM (median age: 11 years), which is consistent with the results of previous studies.[15]

In our cohort, all five patients with respiratory failure also had unstable hemodynamics that required central line placement and inotropic agent support, and they were all newly diagnosed patients with DKA without a delayed diagnosis of DKA. A previous study listed the following risk factors for respiratory failure in patients with DKA: depletion of primarily intracellular ions (potassium, magnesium, and phosphate), pulmonary edema, respiratory tract infection, neuromuscular disease, and miscellaneous conditions.[16] All patients with DKA and respiratory failure in our study had an electrolyte imbalance, including hypokalemia, hypocalcemia, hypermagnesemia, and hypophosphatemia. However, the small sample size precluded the identification of any of these conditions as risk factors.

According to the ISPAD Clinical Practice Consensus Guidelines 2018, the incidence of cerebral edema is 0.5%–0.9%, and the mortality rate is 21%–24% in patients with DKA.[17] Moreover, cerebral edema is diagnosed when a patient fulfills one diagnostic criterion and two major criteria or one major and two minor criteria. The diagnostic criteria include an abnormal motor or verbal response to pain, decorticate or decerebrate posture, cranial nerve palsy, and abnormal neurogenic respiratory patterns (e.g., grunting, tachypnea, Cheyne–Stokes respiration, and apneusis). The major criteria include altered mentation or fluctuating level of consciousness, sustained heart rate deceleration (a decrease of more than 20 beats/min) not attributable to improved intravascular volume or sleep state, and age-inappropriate incontinence. The minor criteria include vomiting, headache, lethargy or not being easily arousable, diastolic blood pressure >90 mmHg, and age <5 years. These criteria have a sensitivity of 92% and a false-positive rate of only 4% for identifying cerebral edema. Cerebral edema was significantly associated with a lower initial partial

pressure of arterial carbon dioxide and high initial serum urea nitrogen levels.[18] The risk was higher in younger patients and those newly diagnosed as having DKA.[19,20] In our study, the incidence of suspected cerebral edema was 5% because we used broader criteria to identify patients with suspected cerebral injuries in an attempt to increase the case numbers. This led to an unusually high incidence rate, but no associated risk factors were found. However, all seven patients suspected of cerebral injury had hypocapnia (mean $PaCO_2$: 12. 8 ± 3.8 mmHg), and six had high initial serum urea nitrogen levels (mean: 37.2 ± 16.1 mg/dL).

The AKI incidence in our study (3.6%) was much lower than that in another cohort study (43%).[21] Four of the five AKI cases in our study had unstable hemodynamics, but no associated risk factors could be identified. Myers *et al.*[21] evaluated 1359 pediatric patients with admission for DKA, and they found that older age, higher initial blood urea nitrogen levels, higher heart rate, higher glucose-corrected sodium and glucose concentrations, and lower pH were associated with AKI. They defined AKI as an increase in serum creatinine by ≥0.3 mg/dL within 48 h, increase in serum creatinine to ≥1.5 times the baseline value within the last 7 days, or urine output of <0.5 mL/kg/h for 6 h. In addition, they used an estimated glomerular filtration rate of 120 mL/min/1.73 m^2 to calculate the expected baseline creatinine level using the Schwartz estimating equation. This method overcomes the fact that baseline creatinine values were not available for most episodes, which enabled the authors to identify more AKI cases. In our study, those patients who developed AKI had higher glucose-corrected sodium and higher serum glucose concentrations, but these patients were younger, and no difference in heart rate was identified.

Limitations

This was a retrospective study. The ICU LOS might be affected by the DKA treatment protocol at our hospital. Clinical courses and DM education programs are affected by Taiwan's National Health Insurance program; thus, the results might have some differences from those in other countries. Some data, including DKA-associated body weight loss or DKA duration, could not be measured. Insufficient sample size precluded the identification of as risk factors for respiratory failure, cerebral injury, and AKI. Nevertheless, this study provided some insights into pediatric DKA management in Taiwan.

Conclusion

Nonemergency room admission for pediatric DKA patients was associated with prolonged pediatric ICU LOS. Early identification of DKA patients and early treatment initiation are vital for ensuring a short ICU LOS. Being older or underweight was associated with a shorter pediatric ICU LOS. Finally, patients with newly diagnosed DM presented as DKA were more likely to have respiratory failure, unstable hemodynamics, cerebral edema, and AKI.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Virus Infection and Severe Asthma Exacerbations: A Cross-Sectional Study in Children's Hospital 1, Ho Chi Minh City, Vietnam

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Abstract

Context: Virus infection is a well-known risk factor for asthma exacerbations in temperate and subtropical countries, particularly in atopic children. However, the risk has not been well-described in tropical countries including Vietnam. **Aims:** To compare the odds of virus infection in hospitalized children with severe versus moderate asthma exacerbations. **Settings and Design:** A cross-sectional study was conducted at Children's Hospital 1, Ho Chi Minh City, Vietnam. Children who were admitted to the hospital and diagnosed with severe or moderate asthma exacerbations were recruited for the study. **Materials and Methods:** Data were collected from interviews and medical records. Virus infection was confirmed by multiplex real-time polymerase chain reaction. Inhalant allergy was confirmed by a skin prick test with common indoor aeroallergens. **Statistical Analysis Used:** Associations among age, gender, passive smoking, child's history of eczema, family history of asthma, virus infection, and inhalant allergy with the odds of severe asthma exacerbations were tested by binary logistic regressions. Multivariable logistic regression was done to measure the association between virus infection with the odds of severe asthma exacerbations adjusted for passive smoking. The odds ratio (OR) and its 95% confidence interval (CI) were reported to show the strength of the associations. **Results:** Nearly half of the children were infected by a virus (48.5%) and had passive smoking (49.2%). The percentage of children with a positive skin prick test was 83%. The most common indoor aeroallergen was house dust mites (81.1%). The odds of severe asthma exacerbations in children with virus infection was three times higher than that in those without virus infection (OR: 3.21, 95% CI: 1.20-8.60, P = 0.021). **Conclusions:** Immunization and other healthcare programs should be deployed to prevent asthmatic children from virus infection and passive smoking to reduce the risk of severe asthma exacerbations.

Keywords: Asthma exacerbations, hospital-based study, inhalant allergy, viral infection

Key Messages: Virus infection increases the odds of severe asthma exacerbations.

Introduction

Asthma causes 5.1 million disability-adjusted life years among children aged 1-19 years globally.[1] Acute respiratory virus infection is the most common trigger of asthma exacerbations, accounting for 60%-95% of pediatric asthma exacerbations in temperate and subtropical countries.[2-4] Children with atopic asthma, the most prevalent type of childhood asthma,[5] have a high risk of a virus-induced asthma exacerbation.[6,7] However, the prevalence of virus infection as well as an association between virus infection and asthma exacerbations in tropical countries such as Vietnam has not been well-described. Therefore, the study was conducted to measure

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the odds of virus infection in inpatients with severe compared to those with moderate asthma exacerbations at Children's Hospital 1, Vietnam.

Subjects and Methods

Study design and sample

The study was conducted at Children's Hospital 1, a tertiary pediatric hospital, located in Ho Chi Minh City (HCMC) from July 2020 to April 2021. HCMC is the biggest city in the south of Vietnam with a tropical climate and 9 million inhabitants.[8] It has two seasons including rainy (from May to November) and sunny (from December to April). The average temperature is 26.8-27.3°C with a high humidity (64.5%-85.9%) year-round.[9] The study was approved by the Ethics Committee of University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam (Approval Number: 218/*IRB-VN01002*).

A researcher screened medical records of children at the time of admission for eligibility. Parents of eligible children were approached and explained the purpose of the study and persuaded to allow their children to join the study. If they agreed, they were asked to sign the consent forms before data were collected. All eligible children were consecutively recruited to the study to ensure a ratio of one severe to five moderate asthma exacerbations.

Children were included if they were 3-15 years old, admitted to the hospital due to a moderate or severe asthma exacerbation, and their parents allowed them to join the study and receive both multiplex real-time polymerase chain reaction (mqPCR) and a skin prick test (SPT). An asthma exacerbation was identified based on a history of wheezing (at least two episodes of wheezing were applied to under-6-year-old children) related to airflow obstruction, which responded well to asthma rescue medication without other causes of wheezing.[10,11] According to the Global Initiative for Asthma 2010 guideline, a severe asthma exacerbation was determined if a patient had at least two of the following signs including breathless at rest, talking in words, severe retractions of accessory muscles and peripheral oxygen saturation (SpO_2) <92%.[11] A moderate asthma exacerbation was determined if a patient had two of the following signs including breathless at talking, talking in phrases, moderate retractions of accessory muscles, and SpO_2 92%-95%.[11] Children, who have neurologic, metabolic, or genetic diseases, chronic pulmonary diseases other than asthma, cardiopathy, or immuno-suppression, were excluded from the study.

Data collection and tool

Age, gender, passive smoking, family history of asthma, and child's history of eczema were collected from interviews and cross-checked with medical records. Passive smoking was defined as a child inhaling smoke from family members daily.[12] Child's history of eczema was yes if the child's parents confirmed that the child was diagnosed by a physician. Family history of asthma was yes if parents confirmed that they or the child's siblings were diagnosed with asthma by a physician. mqPCR and SPT were performed by accredited laboratories following the standard procedures. Results were read by qualified microbiologists and allergists.

Detection of acute respiratory virus infection

All eligible children were taken nasopharyngeal swabs within 24 h of admission by a well-trained doctor following a standard protocol. All the specimens were placed in dedicated tubes stored in the fridge and then transferred to the micrology laboratory for the detection of respiratory viruses. A validated mqPCR assay and KingFisher™ Flex CFX-96 system were used to detect adenovirus, respiratory syncytial virus, influenza virus (A, B, C), parainfluenza virus (1, 2, 3), human metapneumovirus, enterovirus, human coronavirus, bocavirus, and human rhinovirus. The mqPCR has a sensitivity of 99.5% and specificity of 83.7% and is routinely used to diagnose etiologies of respiratory infection.[13] The virus-positive specimen was coded as "pathogen positive." Co-infection was defined as the presence of at least two pathogens in the specimens.

Detection of inhalant allergy

An SPT was used to diagnose children's inhalant allergy. Its specificity and sensitivity were 70%-95% and 80%-97%, respectively.[14] The participants' thorough history and physical examination were taken before the procedure. The children were eligible for the SPT if they had stable asthma and did not use antihistamines or systemic corticosteroids within the previous week. The indoor allergen extracts, which included *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cockroach, cat, and dog dander, were used in the SPT. An allergen was positive if its wheal diameter was larger than 3 mm compared to that of the negative control.[15]

Statistical analysis

Data were entered using Microsoft Excel 2010 (Redmond, Washington) and analyzed using IBM SPSS Statistics 24.0 (Armonk, New York). Age was described as mean and standard deviation (SD). Gender, child's history of eczema, family history of asthma, passive smoking, virus infection, and inhalant allergy were described as frequency and percentage.

Chi-squared test was used to test the association between demographic, clinical, and laboratory characteristics with the odds of severe asthma exacerbations compared to moderate asthma exacerbations. Model 1, a binary logistic regression, was used to measure the associations between variables including age, gender, child's history of eczema, family history of asthma, passive smoking,

virus infection, and inhalant allergy with the odds of severe asthma exacerbations. The odds ratio (OR) and its 95% confidence interval (CI) were calculated to show the strength of the associations. A *P* value of 0.20 was used to select variables for a multivariable logistic regression.[16] A *P* value of 0.05 was considered statistically significant.

Results

There were 224 records approached and screened for eligibility. Of these, 132 children satisfied the inclusion and had no exclusion criteria, including 23 severe and 109 moderate asthma exacerbations. The mean age of 132 children was 6.25 years (SD 2.64), ranging from 3 to 13.2 years old. A logistic regression showed that age was not associated with severe asthma exacerbations ($P = 0.627$). The percentage of preschool asthma was 51.5% in the whole sample, 53.2% in children with moderate asthma exacerbations and 43.5% in children with severe asthma exacerbations. Chi-squared test showed no significant difference in the percentage of preschool-aged children between moderate and severe groups ($P = 0.396$).

Table 1: Demographic, clinical, and laboratory characteristics of the asthmatic children in the sample (*N* = 132)

	The sample (*N* = 132)	Asthma exacerbations		*P*-value
		Moderate (*n* = 109)	Severe (*n* = 23)	
Age (years)*	6.25 ± 2.64	6.20 ± 2.63	6.50 ± 2.73	0.627[a]
Gender				
Male	82 (62.1)	68 (62.4)	14 (60.9)	0.892
Female	50 (37.8)	41 (37.6)	9 (39.1)	
Child's history of eczema (yes)	25 (18.9)	19 (17.4)	6 (26.1)	0.336
Family history of asthma	13 (9.8)	10 (9.2)	3 (13.0)	0.571
Father	7 (53.8)	6 (60.0)	1 (33.3)	
Mother	5 (38.5)	4 (40.0)	1 (33.3)	
Siblings	1 (7.7)	0 (0)	1 (33.3)	
Passive smoking (yes)	65 (49.2)	50 (45.9)	15 (65.2)	0.092
Virus infection (yes)	64 (48.5)	48 (44.0)	16 (69.6)	0.026
Human rhinovirus (HRV) infection (yes)	41 (31.1)	32 (29.4)	9 (39.1)	0.357
Inhalant allergy (yes)	109 (82.6)	89 (81.7)	20 (87.0)	0.542
House dust mite (HDM) allergy (yes)	107 (81.1)	88 (80.7)	19 (82.6)	0.835
Virus infection + Inhalant allergy (yes)	52 (39.4)	38 (34.9)	14 (60.9)	0.020
Virus infection + HDM allergy (yes)	51 (38.6)	38 (34.9)	13 (56.5)	0.053
HRV infection + inhalant allergy (yes)	37 (28.0)	28 (25.7)	9 (39.1)	0.192
HRV infection + HDM allergy (yes)	37 (28.0)	28 (25.7)	9 (39.1)	0.192

*Mean ± standard deviation; All used Chi-squared test, except stated other

[a] Logistic regression was used

Table 2: Binary and multiple logistic regression measure associations between exploratory variables with the severity of asthma exacerbations (*N* = 132)

	Model 1			Model 2		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age (years)*	1.04	0.88-1.23	0.627			
Gender						
Male	0.94	0.37-2.36	0.892			
Female						
Child's history of eczema (yes)	1.67	0.58-4.80	0.339			
Family history of asthma (yes)	1.49	0.38-5.88	0.573			
Passive smoking (yes)	2.21	0.87-5.65	0.097	2.50	0.95-6.57	0.062
Virus infection (VI) (yes)	2.91	1.11-7.63	0.030	3.21	1.20-8.60	0.021
Inhalant allergy (IA) (yes)	1.50	0.41-5.54	0.544			

OR = odds ratio, 95% CI = 95% confidence interval

Model 1: Binary logistic regressions assessed the associations between variables including age, gender, child's history of eczema, family history of asthma, passive smoking, virus infection, and inhalant allergy with the odds of severe asthma exacerbations compared to moderate asthma exacerbations

Model 2: Multiple logistic regression assessed the association between virus infection with the odds of severe asthma exacerbations compared to moderate asthma exacerbations adjusted for passive smoking

Male represented 62.1% of the sample, 62.4% of moderate asthma exacerbations, and 60.9% of severe asthma exacerbations. The percentage of children having a family history of asthma was 9.8% and parental history of asthma was the most common among these children. Compared to children with moderate asthma exacerbations, those with severe asthma exacerbations had no significant difference in gender ($P = 0.892$), child's history of eczema ($P = 0.336$), and family history of asthma ($P = 0.571$).

Passive smoking was 49.2% in the sample, 45.9% in children with moderate asthma exacerbations, and 65.2% in those with severe asthma exacerbations. No significant difference was observed in passive smoking between the two groups (Chi-squared test, $P = 0.092$) [Table 1].

The children with virus infection are more prone to develop severe exacerbations than those without virus infection.

The percentage of nasopharyngeal specimens positive for any assayed virus was 48.5%, of which 94% were infected by one type of virus. The percentage of virus infection in the severe group was significantly higher than that in the moderate group (69.6% vs. 44%, $P = 0.03$).

The percentage of children having inhalant allergy was 82.6%. House dust mites were the most common (81.1%), followed by cockroach (24.2%), cat dander (9.8%), and dog dander (9.8%). Of those children who were allergic to house dust mites, *D. farinae* and *Dermatophagoides pteronyssinus* accounted for 93.5% and 90.7%, respectively. The percentage of asthmatic children having inhalant allergy was not different between moderate and severe groups (81.7% vs. 87%, $P = 0.542$). However, the percentage of children having both virus infection and inhalant allergy was significantly different between those with moderate asthma exacerbations and those with severe asthma exacerbations (34.9% vs. 60.9%, $P = 0.02$).

Table 2 shows that the odds of severe asthma exacerbations in children with virus infection was 2.9 times higher than that of those without virus infection in a binary logistic regression (OR: 2.91, 95% CI: 1.11–7.63, $P = 0.03$). The adjusted OR (aOR) was 3.21 times higher in the multivariable logistic regression adjusted for passive smoking (aOR: 3.21, 95% CI: 1.20-8.60, $P = 0.02$).

Discussion

This study found that virus infection increased the odds of severe asthma exacerbations in asthmatic children with a moderate or severe asthma exacerbation admitted to a hospital that was consistent with previous evidence.[17] The potential mechanism for this link is related to an upward expression of specific receptors of respiratory viruses such as intercellular adhesion molecule-1 in airway epithelium, deficient, and delayed innate antiviral immune responses, and destruction of the epithelium by cytokines and chemokines derived from responses to allergens.[18-20] Apart from this, synergic impact of acute respiratory virus infection and inhalant allergy on asthma exacerbations was explained by the interaction between high-affinity IgE receptors "FcεRI" as well as anti-virus immune modulation, resulting in excessive inflammatory response.[17,21] A previous study showed that the combination of virus infection and allergic sensitization increased the risk of hospital admission due to asthma exacerbations.[22] Our study did not find any association of this combination, but virus infection was found to act as an independent risk of severe asthma exacerbations in the multivariable logistic regression. Further studies with bigger sample sizes should be conducted to clarify the association.

This study found that nearly 50% of asthmatic children were infected by a virus. This percentage was reported at 61.7% of Canadian children aged 1-17 years, 92.2% of Australian children aged 2-16 years.[4,23] It may be partially related to different climates among regions. Our study was conducted during COVID-19 pandemic. Thus, good habits including washing hands more frequently, wearing masks, and social distancing probably contributed to a lower prevalence of acute respiratory infection.

Human rhinovirus has been found to be the major cause of asthma exacerbations in children older than three in some studies. However, the underlying mechanism remains uncertain. Immune dysregulation via aberrant immune responses, both deficient and exaggerated, as well as a viral affinity for specific receptors required for infection of airway cells, have been proposed as a mechanism for human rhinovirus-induced asthma exacerbations.[24] Our study was unable to confirm whether human rhinovirus infection increases the odds of severe asthma exacerbations in asthmatic children, which was consistent with Merckx's study.[4] The Vietnam National Pediatric Hospital reported that the concentration of Th2-related cytokines, a biomarker of human rhinovirus infection, was higher in children with severe asthma exacerbations compared to those with mild or moderate asthma exacerbations.[25] Another study conducted in Australia found that children with human rhinovirus infection had higher asthma severity scores than those without respiratory virus infection.[23]

Indoor aeroallergens were found to increase the risk of severe asthma exacerbations in children with inhalant allergy.[26] However, the association between inhalant allergy and severe asthma exacerbations was not significant in our study even though most of our children were sensitive to indoor aeroallergens. It is worth noting that the percentage of children having both virus infection and inhalant allergy was significantly higher in children with severe asthma exacerbations compared to those with moderate asthma exacerbations. These findings were consistent with Merckx's study.[4]

Half of our asthmatic children were at preschool age which was consistent with a previous study of the Children's

Hospital 1.[27] It was reported that preschool children in the United Kingdom had the highest rate of asthma exacerbations.[28] A significant increase of peripheral airway resistance was observed in asthmatic children, particularly during asthma exacerbations.[29] The airway resistance is remarkably stronger in preschool children compared to older children.[30] In addition, recent evidence showed that variants in cadherin-related family member 3 may increase the risk of severe asthma exacerbations in children aged 2–6 by altering the integrity of airway epithelium, thus promoting entry and replication of viruses.[26] However, age was not associated with the odds of severe asthma exacerbations in this study.

Our study had some limitations. Firstly, the study was conducted at one hospital with a small sample size; therefore, the findings should be cautiously extrapolated to a more general population. Secondly, data were collected cross-sectionally, and time order of the association between virus infection and severe asthma exacerbation is questionable. The odds of severe asthma exacerbations was underestimated because the study did not include children with mild asthma exacerbations or stable asthma.

In conclusion, among children with a severe or moderate asthma exacerbation admitted to the Children's Hospital 1 in Ho Chi Minh City, Vietnam, half of them had respiratory virus infection. The odds of severe asthma exacerbations was three times higher in children with virus infection compared to those without virus infection. Healthcare programs such as immunization and/or tobacco controls should be considered and focused on asthmatic children to reduce the severity of asthma exacerbations. Vaccines other than influenza viruses should be developed to prevent asthmatic people from virus infection thus reducing the risk of severe asthma exacerbations.

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Conflicts of interest

The authors declare no conflicts of interests.

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