An approach to pulmonary haemorrhage in children

D Parris, BSc, MB BCh, FCP (Paeds), Dip Allergy; **A van Niekerk**, MB ChB, MMed;
A C Jeevarathnum, MB BCh, FCP (Paeds), Dip Allergy, MMed, Cert Paed Pulm; **R J Green**, PhD, DSc

Department of Paediatrics and Child Health, School of Medicine, Faculty of Health Sciences, University of Pretoria, South Africa, and Steve Biko Academic Hospital, Pretoria, South Africa

Corresponding author: *D Parris (drdeniseparris@gmail.com)*

Pulmonary haemorrhage in children is very rare and the exact incidence remains unknown. Children usually swallow blood that has been coughed up and unless the haemoptysis is substantial, it can go unnoticed. Pulmonary haemorrhage can occur as a result of diffuse or local pathology. Diagnosis is based on a thorough history and examination, with laboratory, radiological, bronchoscopic findings, and lung biopsies in some cases. Treatment is directed at the underlying condition. On review of the available literature, the authors provide an approach to investigating pulmonary haemorrhage in children.

S Afr Respir J 2017;23(3):63-70. DOI:10.7196/SARJ.2017.v23.i3.152

Pulmonary haemorrhage (PH) can affect children of all ages. It can present surreptitiously, which delays the diagnosis, or as an acute life-threatening event requiring resuscitation. Bleeding may be diffuse or localised.[1] Diffuse alveolar haemorrhage (DAH) occurs as a result of the disruption of the alveolar-capillary basement membrane in the lung, with resultant bleeding into the alveolar spaces. Injury can be immune- or non-immune mediated, with subsequent involvement of the blood vessels and the alveolar septae.[2] DAH can sometimes present as a life-threatening event, with haemoptysis and hypoxaemic respiratory failure, as well as falling haematocrit measurements and diffuse pulmonary infiltrates. A triad of haemoptysis, anaemia and airspace opacities on chest radiographs is suggestive of pulmonary haemorrhage.[3]

Focal pulmonary haemorrhage is restricted to the lung, and is sub-segmental, segmental or lobar.[4] It can occur due to undiagnosed congenital lung malformation, or secondary to infection, trauma, vascular disorders, underlying lung disease, coagulopathies or neoplasms of the lung. When assessing pulmonary haemorrhage, it is important to determine the origin of the bleeding. It is important to assess the upper airways and the gastrointestinal tract as possible sources of bleeding. Furthermore, as the diagnostic workup varies for local and diffuse DAH, it is necessary to distinguish between the two entities.[1]

Pathophysiology

The lungs receive blood from two separate circulations. The bronchial circulation, which is a high-pressure, low-volume circuit, supplied by the bronchial arteries arising from the aorta and the pulmonary circulation, which is a low-pressure, high-capacitance circuit arising from the right ventricle. Blood flows to the acinar units and is involved with gas exchange.[5] Bleeding from the bronchial circulation is profuse, with massive haemoptysis and the likelihood of death. Bleeding from the pulmonary circulation is low grade, chronic and diffuse.

Table 1. Causes of focal pulmonary haemorrhage in children

Condition	Precipitating pathology
Infection	Pneumonia (*Staphylococcus aureus*)
	Lung abscess
	Viral infections, e.g. influenza A H1N1
	Chronic bronchitis
Bronchiectasis	Cystic fibrosis
	Primary ciliary dyskinesia
	Primary immunodeficiency
	Secondary immunodeficiency
Congenital lung malformations	Sequestration
	Bronchogenic cyst
	Congenital pulmonary airway malformations
Trauma	Foreign-body inhalation
	Lung contusion
	Lung laceration
	Artificial airway suction catheters
	Inhalation injury
Vascular disorders	Pulmonary haemangioma
	Arteriovenous malformations
	Pulmonary emboli
Coagulopathy	Von Willebrand's disease
	Thrombocytopenia
	Anticoagulants
Neoplasms	–

Aetiology

Focal pulmonary haemorrhage

Focal pulmonary haemorrhage is generally restricted to a focal region in the lung, but can involve an entire lobe (Table 1).[1] In some situations, the bronchial circulation may give rise to bleeding, which causes massive haemoptysis, but the low-pressure, high-capacitance circuit that supplies the alveoli is spared, with no consequent alveolar bleeding.

Diffuse alveolar haemorrhage

DAH arises from the pulmonary circulation, which is a low-pressure, high-capacitance circuit providing blood to the acinar units. DAH can be immune- or non-immune mediated (Table 2).[1]

Immune-mediated alveolar haemorrhage

Understanding the immune-mediated mechanism of DAH requires a basic understanding of the anatomy of blood vessels and the role of neutrophils in immune-mediated pathogenesis. Blood vessels consist of arteries, arterioles, capillaries, venules, and veins. Arteries and veins are composed of three tissue layers.

The inner layer (tunica intima) is composed of endothelial cells and a layer of elastic lamina, forming the basement membrane of the blood vessel. The bulky middle layer (intima media) contains elastin and smooth muscle, which regulates the diameter of the blood vessel.

Table 2. Causes of DAH in children

Immune-mediated DAH	Idiopathic pulmonary capillaritis
	Granulomatosis with polyangiitis[6]
	Microscopic polyangiitis
	Goodpasture's syndrome
	Systemic lupus erythematosus
	Henoch-Schönlein purpura
	Behçet's disease
	Cryoglobulinaemic vasculitis
	Juvenile idiopathic arthritis
Non-immune-mediated	Idiopathic pulmonary haemosiderosis
	Acute idiopathic pulmonary haemorrhage of infancy:
	• Coagulation disorders
	• Asphyxiation
	• *Stachybotrys chartarum*
	Heiner syndrome
	Cardiovascular causes:
	• Pulmonary vein atresia/stenosis
	• Total anomalous pulmonary venous return
	• Pulmonary veno-occlusive disease
	• Pulmonary capillary haemangiomatosis
	• Pulmonary telangiectasia
	• Mitral stenosis

DAH = diffuse alveolar haemorrhage; GPA = granulomatosis with polyangiitis (Wegener's granulomatosis).

The outermost layer (tunica externa) consists of areolar or fibrous connective tissue that provides structural support and protection (Fig. 1).[6]

Neutrophils are white blood cells that play an important role in innate immunity. They circulate in the bloodstream and are the first line of defense against invading organisms. Neutrophils defend by phagocytosis, antigen presentation, and activating T-cells, which stimulate the humoral immune response.[4,8] Neutrophils either circulate, or bind to the vascular endothelium as marginating neutrophils. Damaged neutrophils leak enzymes, which damage vessels as they migrate toward the site of injury or infection – a process called diapedesis.

Pathophysiology of pulmonary capillaritis

Pulmonary capillaritis (PC) is an immune-mediated disorder that targets the cytoplasmic components of neutrophils, subsequently developing antineutrophil cytoplasmic antibodies (ANCA).

Two neutrophil proteins are involved in the immune response: the myeloperoxidase (MPO), and proteinase 3 (PR3) granules. Autoantibodies are generated against the neutrophil components. The damaged neutrophils leak enzymes as they migrate through the vascular system, which damages the endothelium of the blood vessels, with subsequent exposure of the sub-endothelial structures.

Damaged endothelial cells elicit an antibody response, which develops anti-endothelial cell antibodies (AECA). AECAs bind to

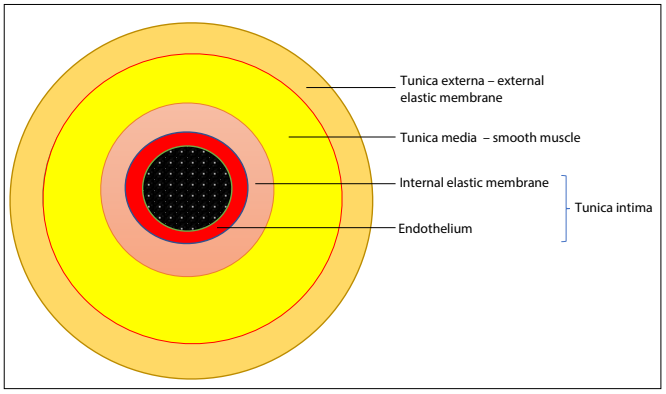

Fig. 1. Structure of blood vessels. (Courtesy of Dr D Parris, Department of Paediatrics and Child Health, Steve Biko Academic Hospital)

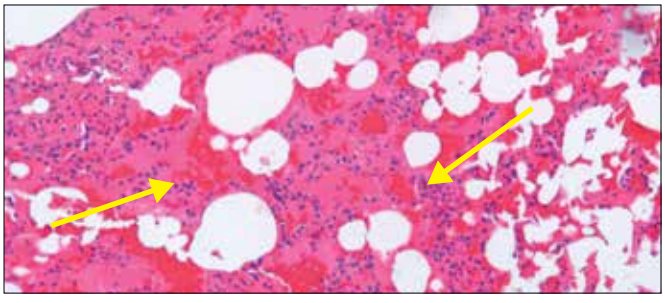

Fig. 2. H&E lung biopsy specimen showing increased numbers of polymorphonuclear leukocytes (yellow arrows) and fibrinoid necrosis in the interstitium, with erosion of the alveolar epithelium in a child with Behçet's disease. (Courtesy of Dr Dinkel, Department of Histopathology, University of Pretoria)

the vessel, progressively exposing its basal components, to which antibodies are also synthesised. These include anti-endothelial cell antibodies (AECA), antiglomerular basement membrane antibodies (anti-GBM), antibasal membrane laminin antibodies (ABLA), and antiphospholipid antibodies (APLA).[4,8]

Aetiology of PC

PC is an inflammatory process involving capillaries, with subsequent inflammation and necrosis of these vessels. It involves a histological diagnosis without identifying the disorder.[9] It may present in isolation or as part of a systemic disorder (Fig. 2).

The most frequently isolated forms of PC are ANCA-associated vasculitides and systemic lupus erythematosus. Other diseases associated with PC include microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA; Wegener's granulomatosis), Henoch-Schönlein purpura, Behçet's disease, cryoglobulinaemic vasculitis, and juvenile idiopathic arthritis.

Histological assessment can distinguish between underlying systemic vasculitis and immune-mediated vasculitis.[1] Cytoplasmic ANCA-associated disorders include GPA, MPA and eosinophilic granulomatosis with polyangiitis (EPGA; Churg-Strauss syndrome).[6]

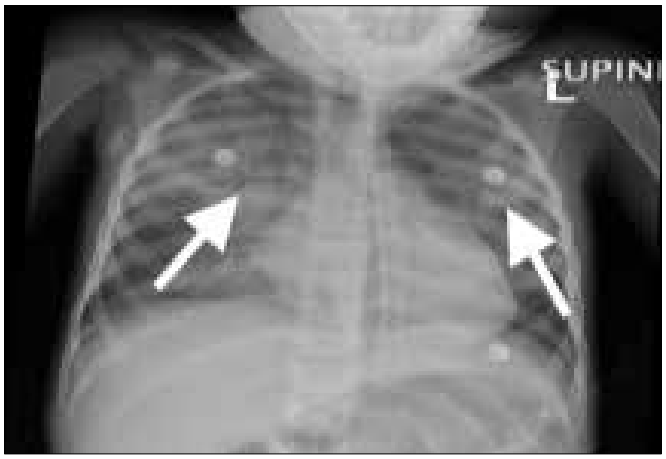

Fig. 3. Frontal chest X-ray showing alveolar infiltrates (white arrows) bilaterally consistent with alveolar haemorrhage. (Courtesy of Dr D Parris, Department of Paediatrics and Child Health, Steve Biko Academic Hospital)

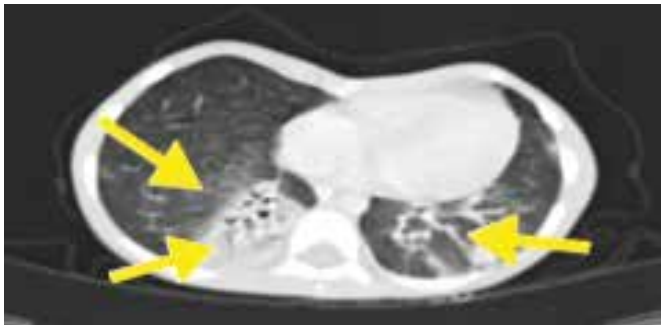

Fig. 4. High-resolution contrast scan of the chest, axial views at the level of the heart (yellow arrows) depicting ground-glass appearance, septal thickening and inhomogeneous opacification. (Courtesy of Dr D Parris, Department of Paediatrics and Child Health, Steve Biko Academic Hospital)

Although there is some overlap between disease entities, proteinase 3 (PR-3) is associated with GPA, and MPO is associated with microscopic angiitis. Goodpasture's disease (GPD) differs from the other immune-mediated disorders, as the antibodies are directed against the glomerular basement membrane.[10]

Granulomatosis with polyangiitis (GPA; Wegener's granulomatosis)

GPA is a systemic vasculitic disease. It is distinguished by its necrotising granulomatous inflammation, affecting both upper and lower respiratory tracts, the kidneys, and small and medium-sized vessels to varying degrees. The antibodies are directed against the PR-3 neutrophil granulocytes.

Upper respiratory symptoms include otitis media, sinusitis, chronic rhinitis and nasal cartilage destruction, which results in a saddle nose deformity. Salivary glands are often swollen and painful; subglottic stenosis and tracheobronchial ulceration are associated complications.

Parenchymal lung nodules coalesce and form cavities, which erode blood vessels, causing DAH. Clinically, patients present with a cough, dyspnoea, haemoptysis and hypoxaemia. Other organ systems, particularly the kidneys, may be involved, causing haematuria. Chest radiographs show nodules, with or without cavitation, pulmonary haemorrhage, a reticulonodular pattern, and wedge-like consolidations (Fig. 3). Computed tomography (CT) scans are better at delineating the nodules and cavities, and characterising ground-glass opacities, densities and consolidations (Fig. 4).[11]

Pulmonary involvement MPA

MPA is a rare pauci-immune, small-vessel vasculitis, involving the skin, joints, kidneys and lungs. It may present in childhood with haemoptysis, anaemia, hypoxaemia, pulmonary haemorrhage, or severe respiratory disease requiring ventilation. MPA is distinguished from GPA by the presence of high titres of anti-myeloperoxidase (MPO)-ANCA, and the absence of granulomatous inflammation.[11,12] Lung histology demonstrates infiltration of neutrophils in small blood vessels, with associated fibrinoid necrosis. Imaging studies show diffuse alveolar infiltrates, tree-in-bud patterns, and septal thickening.

Goodpasture's disease (GPD)

GPD is a rare, systemic autoimmune disease that causes DAH and a progressive crescentic glomerulonephritis. It is characterised by anti-GBM antibody-mediated damage, and the antibody response is IgG1 subtype. The autoantibodies are directed at the a3 and a5 domains of the type IV collagen fibres present in the basement of blood vessels and glomeruli. Approximately one-third of patients with GPD have perinuclear antineutrophil cytoplasmic autoantibodies, directed against either the MPO or the PR3 protein of the neutrophil (Fig. 5).[10]

Coughing, haemoptysis, dyspnoea, and fatigue are common presenting features. Chest X-rays (CXR) and CT scans show features of nonspecific DAH. A definitive diagnosis is made by immunofluorescent staining, demonstrating the presence of anti-GBM antibodies. Early diagnosis is important, as plasmapheresis, immunosuppression with corticosteroids, and the addition of cyclophosphamide can successfully induce remission in 90% of patients who survive acute presentation.[10]

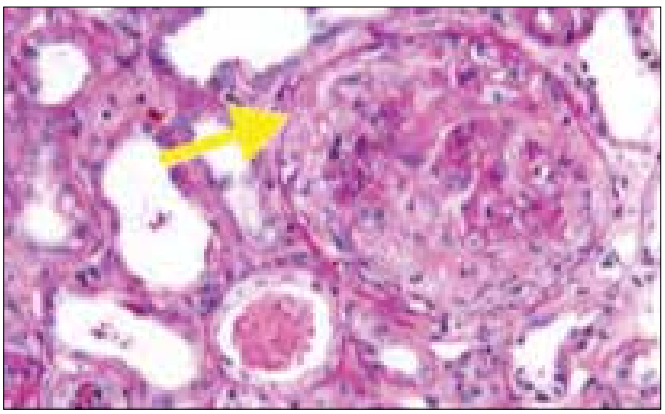

Fig. 5. H&E stain of renal biopsy. Histology depicts diffuse, high-intensity, linear staining of the glomerular basement membrane (yellow arrow) in a patient with antiglomerular basement membrane disease. (Courtesy of the Department of Nephrology Steve Biko Academic Hospital)

Isolated PC

Isolated pauci-immune PC is a rare disorder with a poorly understood aetiology. Clinically, patients present with signs and symptoms of alveolar haemorrhage, but lack the renal and systemic manifestations. The histopathologic pattern shows disruption of the integrity of the alveolar-capillary basement membranes, with blood-filled alveoli. Haematological testing demonstrates low haemoglobin and elevated erythrocyte sedimentation rate (ESR) and C-reactive protein. The renal function is completely normal. Bronchoalveolar lavage (BAL) specimens contain haemosiderin-laden macrophages. If ANCA is isolated, it is usually of the MPO type, as the PR-3 variation is rarely identified. Diagnostic imaging demonstrates diffuse alveolar opacities. In the absence of ANCA, a lung biopsy is imperative, as PC can present with fulminant haemorrhage, where implementing early therapy is crucial.[12]

Idiopathic pulmonary haemosiderosis

Idiopathic pulmonary haemosiderosis (IPH) is a lung disease with unknown aetiology. It is characterised by alveolar capillary bleeding, with a subsequent accumulation of haemosiderin in the lungs. It is a diagnosis of exclusion, and appears to have a better prognosis than PC. Clinically the symptoms are nonspecific, with malaise, cough and tachypnoea, with or without haemoptysis. The diagnostic criteria for IPH is an iron deficiency anaemia and diffuse alveolar infiltrates on imaging studies (Figs 6 and 7). Haemosiderin-laden macrophages are isolated from sputum, gastric aspirates or BAL specimens.[13] The aetiopathogenesis of IPH remains contentious. Environmental causes in children with IPH who developed pulmonary haemorrhage following exposure to *Stachybotrys chartarum*. This theory has subsequently been disproved. The allergic theory, based on the correlation between pulmonary haemorrhage and cow's milk protein (Heiner syndrome) remains contentious. Evidence for an autoimmune aetiology is surfacing.[14-16] Autoimmune antibodies cited to have a role include smooth-muscle antibodies, antinuclear antibodies, and ANCA. The antibodies are thought to elicit a primitive vasculitis, as well as systemic disease. A strong correlation exists between celiac disease and IPH. These patients have antibodies to endomysium, transglutaminase and gliadin. Genetic testing demonstrates a positive HLA-DQ2 association in patients with IPH and celiac disease. Down syndrome children are more prone to developing celiac disease. This autoimmune disease appears to be more prominent in children with underlying genetic disorders.[14,17] However, lung biopsies show bland alveolar haemorrhage, with large amounts of haemosiderin-laden macrophages in the alveoli (Figs 8 A and B). There is a distinct absence of any inflammation, capillaritis and vasculitis on histology.[13,18] IPH is essentially a diagnosis of exclusion in a patient with DAH.

Distinguishing PC from IPH

Treatment modalities for PC and IPH differ, and therefore it is imperative to distinguish between the two disease entities. PC is immune-mediated, more difficult to treat, and often requires cytotoxic therapy to induce remission and circumvent recurrence. IPH is classically treated with steroids, with hydroxychloroquine or azathioprine used as adjuncts for their steroid-sparing effect.[14,15]

Acute idiopathic pulmonary haemorrhage of infancy (AIPH)

AIPH is a disease that occurs in previously healthy infants.[4,19] Clinical presentation is severe, with acute respiratory failure, diffuse infiltrates on imaging, and marked pulmonary haemorrhage. This disease was previously ascribed to the mycotoxin-producing mould, *Stachybotrys chartarum*, found in patients' dwellings. This theory has subsequently been disproved and coagulopathies, such as Von Willebrand's disease, appear to have a stronger correlation with the disease. Thus, coagulation screening is essential.

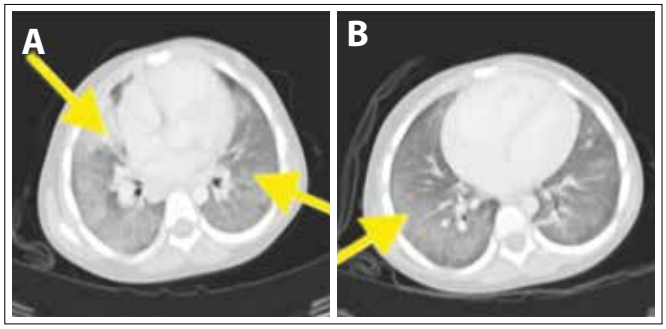

Fig. 6. High-resolution computed tomography (HRCT) chest axial views of the patient. A fine reticular pattern and consolidation (yellow arrows) were noted. (Courtesy of Dr D Parris, Department of Paediatrics and Child Health, Steve Biko Academic Hospital)

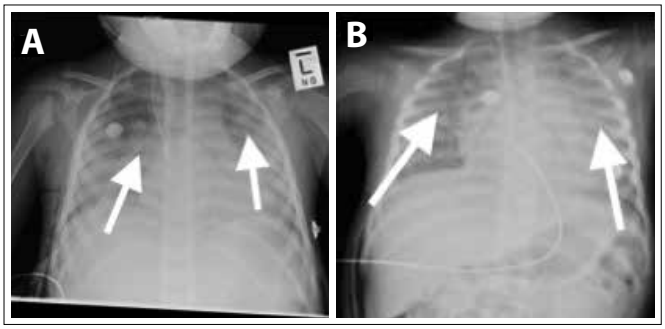

Fig. 7. Frontal chest X-rays of a patient with idiopathic pulmonary haemosiderosis (A and B). X-rays depict bilateral diffuse reticular infiltrates (white arrows) that involve both lung fields. (Courtesy of Dr D Parris, Department of Paediatrics and Child Health, Steve Biko Academic Hospital)

Table 3. List of investigations to elicit the aetiology directed by the history and examination

Aetiology	Investigation
Tuberculosis/HIV-mediated underlying lung disease	Infective markers
Cystic fibrosis (CF)	Sweat test, faecal elastase
Primary ciliary dyskinesia	Light phase microscopy, mucociliary clearance, nasal biopsy and electron microscopy
Non-CF mediated bronchiectasis	Sputum, laboratory studies
Primary immunodeficiency disorder	Immune screen, immunoglobulins, lymphocytes, antibody responses to capsulated and non-capsulated vaccines
Bleeding diathesis	Coagulation screening
Cardiac disease	Echocardiography
Vascular malformations	Angiography

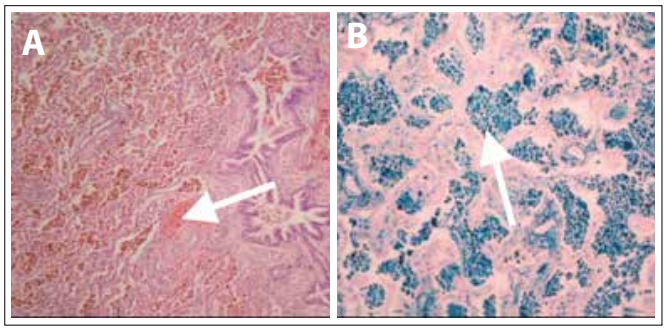

Fig. 8. Lung biopsy specimens. (A) H&E staining; (B) Prussian blue staining (white arrows). A large number of haemosiderin-laden macrophages and foci of fresh haemorrhage were observed. (Courtesy of Dr Dinkel, Department of Histopathology, University of Pretoria)

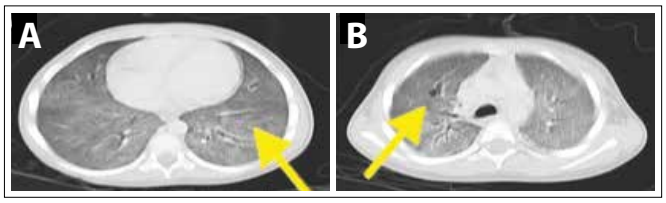

Fig. 9. Diffuse alveolar infiltrates, with ground-glass attenuation in both lung fields (yellow arrows) (A and B).

Other important considerations are underlying cardiac disease, with mandatory echocardiography. Potential child abuse is excluded with skeletal surveys and a retinal assessment.

Cow's milk sensitivity

Cow's milk sensitivity (Heiner syndrome) is a rare disorder in infants and young children. The disease is considered to be a non-IgE-mediated allergy to cow's milk protein. The disease manifestation is variable, resulting in diagnostic delay. Infants and young children present with a history of chronic upper and lower respiratory tract infections. The classic triad of anaemia, haemoptysis, and diffuse alveolar infiltrates on imaging is frequently absent, and the patchy infiltrates on CXR are often misdiagnosed as pneumonia. HRCT is required to make a definitive diagnosis (Figs 9A and B).

Diagnosis is based on a high index of suspicion. Laboratory findings may demonstrate elevated IgE levels, and high titres of serum IgG precipitins to various milk proteins may be present. However, a definitive diagnosis is based on the withdrawal of cow's milk with a clinical improvement. Early re-introduction of cow's milk is subsequently associated with clinical deterioration.[17,18]

Cardiovascular abnormalities

Pulmonary vein atresia and stenosis, total anomalous pulmonary venous return and pulmonary veno-occlusive disease have been associated with DAH. Left ventricular failure and mitral stenosis cause pulmonary venous hypertension, and an increased risk of bleeding. Vascular malformations, either congenital, as those seen in hereditary haemorrhagic telangiectasia, or acquired post Glen or Fontan procedure for cyanotic cardiac lesions, can present with catastrophic pulmonary haemorrhage, or septic emboli and abscesses.

Approach to pulmonary haemorrhage

History, examination and laboratory evaluation

A detailed history and examination is necessary as this may influence the investigations required to confirm a diagnosis. Full blood count, serum creatinine levels, and urinalysis are basic laboratory investigations that should be ordered on presentation. Pulmonary-renal syndrome can be identified by elevated ESR and creatinine levels, as well as microscopic haematuria. Other important tests to consider are the autoimmune markers, including serum ANCA, anti-GBM, and antinuclear antibodies for collagen vascular disease. The tests are based on patient history.

Other investigations (Table 3) to consider based on the patient's history include a diagnostic workup for infective causes of pulmonary haemorrhage (TB, HIV), underlying structural lung damage occurring in cystic fibrosis, and non-immunodeficiency-mediated bronchiectasis.

Chest X-ray

CXR is imperative in trying to elicit whether the pulmonary haemorrhage is as a result of a diffuse or localised aetiology.

Bronchoscopy

Flexible bronchoscopy and consecutive lavage specimens are hallmarks of DAH diagnosis. Radiographic evaluation is useful in assessing the areas for lavage. Once identified, the bronchoscope is wedged into the associated subsegmental bronchus. Three separate 50 - 60 mL aliquots of sterile saline are instilled into the segments, and recouped. The diagnosis of DAH is confirmed by increasing haemorrhagic aliquots being retrieved. Samples should be sent for routine bacterial, fungal and viral studies to rule out infection. Cytology samples should also be sent, as haemosiderin-laden macrophages can be demonstrated on BAL specimens by staining with Prussian blue. A diagnosis of DAH is confirmed if >20% of 200 macrophages stain positive for haemosiderin.[2]

Biopsy

Transbronchial biopsies are controversial as the patient may be too ill, and the sample size is frequently too small to make a diagnosis. Open lung biopsies may be warranted, but the role in diagnosing DAH is not well established. Renal biopsy may be more valuable in collagen vascular disorders, like granulomatosis with polyangiitis.[19]

Histology

Histology identifies three different patterns. Fig. 10A demonstrates the blood present both in the alveoli and the interstitium. Haemosiderin-laden macrophages are visible in the parenchyma and alveolar septae with a Prussian blue stain.

DAH

Histology identifies the specific histological patterns in DAH. In 1985, Mark and Ramirez[20] identified specific histological features associated with pulmonary capillaritis, which is the most common cause of DAH: (*i*) fibrin thrombi occlude the capillaries in the inter-alveolar septae; (*ii*) fibrin clots adhere to the inter-alveolar septae in a pedunculated manner; (*iii*) fibrinoid necrosis of the capillaries; (*iv*) neutrophils and nuclear dust are found in the fibrin, the interstitium, and in the alveolar blood; (*v*) red blood cells, and haemosiderin-laden macrophages are present in the alveoli. Not all features are present in every patient (Fig. 10B).

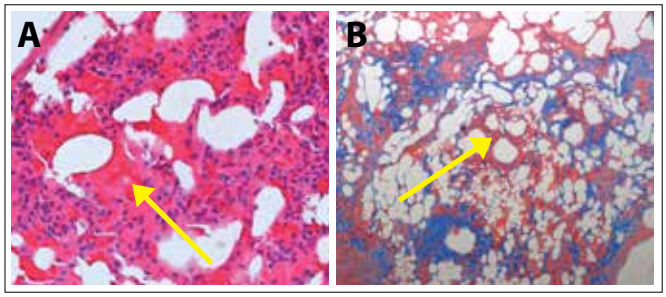

Fig. 10. Pulmonary capillaritis. (A) A pleural biopsy of a patient with Behçet's disease. Pulmonary capillaritis of the lung shows diffuse acute and organising haemorrhage. Neutrophils and necrotic debris are within inter-alveolar septa supportive of necrotising capillaritis (yellow arrow); (B) The ongoing haemorrhage is supported by intra-alveolar fibrin associated with plugs and clusters of intra-alveolar haemosiderophages and extensive fibrosis of the interalveolar septae (yellow arrow).

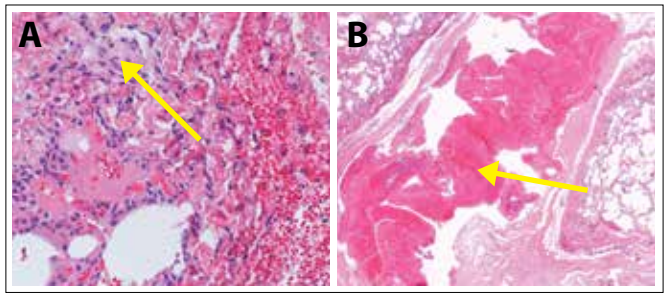

Fig. 11. Acute stage diffuse alveolar damage (DAD). (A) Hyaline membranes are plastered against alveolar septae thickened by oedema, scattered mononuclear inflammatory cells, and a few fibroblasts (yellow arrow); (B) Extensive thrombus formation, fibrinoid necrosis and interstitial fibrosis (yellow arrow).

Diffuse alveolar damage

Diffuse alveolar damage (DAD) resembles the histopathological findings seen in acute respiratory distress syndrome, with oedema, capillary congestion and microthrombi present in the alveolar septae (Fig. 11).

Bland pulmonary haemorrhage

The last histological pattern is bland PH. This pattern demonstrates haemorrhage in the alveolar spaces, without alveolar damage, and is found in idiopathic pulmonary hypertension, congestive cardiac failure, anticoagulant therapy, and GP.

Treatment

Treatment instituted for PH is based on the clinical presentation and the associated underlying aetiology. Despite the underlying aetiology, massive haemoptysis and respiratory failure require intubation, with high positive end-expiratory pressure utilised to recruit alveoli. Patients often require blood transfusions and stabilisation of haemodynamic status as a priority. All known or suspected coagulopathies should be corrected. Platelet counts should be >50 000/uL, and an acceptable prothrombin time <1.5 s. Bronchial artery embolisation may be an option in patients with localised focal PH.

Unfortunately, the literature offers no standard guidelines to approaching patients with DAH. To arrest the bleeding there are a few options, which include pulsed methylprednisone. Corticosteroids are the initial modality of therapy, especially in patients with either immune- or inflammatory-mediated DAH. They act in therapeutic doses to suppress the inflammatory process by inhibiting migration of inflammatory mediators to the site of bleeding, which would otherwise exacerbate the disease process. Corticosteroids also act by suppression of the immunological process. This process involves direct inhibition of antigen-antibody complex formation that, once formed, damages the vascular endothelium and aggravates bleeding. High-dose methylprednisone is initiated at a dose of 30 mg/kg/day for 3 - 5 days. The dose is gradually tapered. Corticosteroids on their own usually fail to control the bleeding, with consequently high fatalities. Complementary therapies are thus required to control bleeding.[20,21] Immunosuppressant therapies that have been successfully used include agents like cyclophosphamide and hydroxychloroquine, among others, over a 3 - 6-month period. Rituximab has been used with some success. This is a monoclonal antibody that binds CD20, which is expressed on beta-cells. It acts in three very precise ways: antibody-dependent cytotoxicity, complement-mediated cytotoxicity, and apoptosis of beta-cells. This results in a decrease in the number of beta-cells, and less immunoglobulin formation (IgG), which binds the antigens on capillaries in the lungs and results in pulmonary haemorrhage.[22-24] If this fails, plasmapharesis and intravenous immunoglobulins may play a role in removing the circulating antigens from the circulation, or binding of the antigens to the exogenously administered immunoglobulins and prevent further binding to the exposed antigens on the capillaries.

Newer treatment modalities

Other novel therapies attempted include the use of antifibrinolytics. The two most commonly used agents are tranexamic acid (TXA)

and epsilon-aminocaproic acid (EACA). TXA acts by binding to plasminogen, which in turn inhibits its binding to fibrin. Activation to plasmin is thus impaired. Both systemic and local administration of TXA have been used in the prophylaxis and treatment of bleeding diatheses, whether the bleeding is congenital or acquired.[25,26] TXA has been used successfully in the intravenous, aerosolised and intrapulmonary form to treat pulmonary haemorrhage. However, side-effects like seizures have rendered it less favourable for treatment. EACA in conjunction with corticosteroids has demonstrated variable results, and more studies are required to assess its value in DAH.[27]

There is, however, increasing evidence for the use of recombinant factor VIIa (rFVIIa).[28,29] This drug was initially developed to control bleeding in haemophiliac patients, who were either FVII deficient, or had inhibitors to FVII. rFVIIa exerts its action via two mechanisms. The first involves activating factors X and IX at the sites of injury. Factors X and IX bind to tissue factor (TF) and activated platelets, and this promotes thrombin generation. The second method is through a TF-independent pathway, where rFVIIa directly activates factor X on the surface of activated platelets. rFVIIa is used to achieve haemostasis in a number of life-threatening bleeding situations. The drug has been successfully used in patients with bleeding diatheses secondary to platelet dysfunction or thrombocytopenias and in bleeding following haematopoeitic stem cell transplantation (HSCT), coagulopathies associated with liver failure, as well as trauma-mediated haemorrhage.

There are insufficient data in the literature to support the use of rFVIIa for DAH. However, it has been used successfully in DAH patients with incalcitrant pulmonary haemorrhage, both in immune and non-immune cases of DAH associated with connective tissue disorders, vasculitides with associated pulmonary haemorrhage, post HSCT, and pulmonary haemorrhage associated with infections. The optimal dose for therapy is not clearly established, and the ideal route of administration is not clearly defined. However, favourable results have been achieved both with intravenous and bronchoscopic administration. Intravenous administration with dosages of between 35 and 200 µg/kg, either as a single bolus dose or repeated 2 - 4-hourly. Intrapulmonary administration, achieved bronchoscopically, requires a total dose of 50 - 90 µg/kg of rFVIIa. This dose of rFVIIa requires dilution in normal saline, which can either be dispensed as a single dose, or if bleeding fails to abate, as repeated doses over a 24-hour period.[28] In children, the evidence currently seems to favour intrapulmonary administration to achieve effective haemostasis.[30]

Using TXA, and rVIIa in a two-step approach in children with unremitting DAH

Based on the mechanism of action of both drugs discussed above, a combination of the two would yield the best results in intractable DAH; studies are currently underway to assess this theory. To date, administering TXA, followed by rFVIIa, has demonstrated improved clot stability, resilience to fibrinolysis, cessation of pulmonary bleeding, and improved outcomes. This theory requires further testing.[29]

Conclusion

PH is a potentially life-threatening condition that could present as fulminant haemoptysis from the high-pressure bronchial circulation, or as an insidious bleed from the low-pressure pulmonary circulation. Both pathologies are associated with significant morbidity and mortality and treatment requires a thorough patient history, examination, and goal-directed investigations to make the diagnosis. For patients with focal PH, it is imperative to rule out structural lung disorders that occur from underlying disorders, like bronchiectasis, CF, and primary immunodeficiency disorders. DAH requires a systemic workup for autoimmune disease. A bronchoscopy should be performed early and, where definitive diagnosis remains a problem, renal and lung biopsies may be imperative to establish a diagnosis and implement therapy.

Acknowledgements. Dr Dinkel, Department of Histopathology, University of Pretoria for the histology slides.
Author contributions. AvN, ACJ and RJG all proofread and edited the manuscript.
Funding. None
Conflicts of interest. None

1. Vece TJ, de Guzman MM, Langston C, Fan LL. Diffuse alveolar hemorrhage in children. In: Wilmott RW, Boat TF, Bush A, Chernick V, Deterding RR, Ratjen F. eds. Kendig and Chernick's disorders of the respiratory tract in children. Philadelphia: Elsevier, 2012:848-857. https://doi.org/10.1016/b978-1-4377-1984-0.00058-9
2. Schwarz MI. Diffuse alveolar haemorrhage syndrome. http://www.uptodate.com/contents/the-diffuse-alveolar-hemorrhage-syndromes (accessed 21 December 2016).
3. Collard HR, Schwarz MI. Diffuse alveolar haemorrhage. Clin Chest Med 2004;25(3):583-592. https://doi.org/10.1016/j.ccm.2004.04.007
4. Avital A, Springer C, Godfrey S. Pulmonary haemorrhagic syndromes in children. Pediatr Resp Rev 2000;1(3):266-273. https://doi.org/10.1053/prrv.2000.0058
5. Editors of Encyclopaedia Britannica. Pulmonary circulation. https://www.britannica.com/science/pulmonary-circulation (accessed 21 December 2016).
6. Khan I, Watts RA. Classification of ANCA-associated vasculitis. Curr Rheumatol Rep 2013;15(12):383. https://doi.org/10.1007/s11926-013-0383-6
7. Antranik. Blood Vessels. 2016. http://antranik.org/blood-vessels (accessed 21 December 2016).
8. Németh T, Mócsai A. The role of neutrophils in autoimmune diseases. Immunol Let 2012;143(1):9-19. https://doi.org/10.1016/j.imlet.2012.01.013
9. Franks TJ, Koss MN. Pulmonary capillaritis. Curr Opin Pulm Med 2000;6(5):430-435. https://doi.org/10.1097/00063198-200009000-00008
10. Chan AL, Louie S, Leslie KO, Juarez MM, Albertson TE. Cutting edge issues in Goodpasture's disease. Clin Rev Allergy Immunol 2011;41(2):151-162. https://doi.org/10.1007/s12016-010-8222-2
11. Ludici M, Quartier P, Terrier B, Mouton L, Guillevin L, Puéchal X. Childhood-onset granulomatosis with polyangiitis and microscopic polyangiitis: Systematic review and meta-analysis. Orphan J Rare Dis 2016;11:141. https://doi.org/10.1186/s13023-016-0523-y
12. Mehorotra AK, Gupta PR, Khublani TK, Anupam, Soni S, Feroz A. Isolated pauci-immune pulmonary capillaritis. Lung India 2015;32(1):56-59. https://doi.org/10.4103/0970-2113.148453
13. Castellazzi L, Patria MF, Frati G, Esposito AA, Esposito S. Idiopathic pulmonary haemosiderosis in paediatric patients: How to make an early diagnosis. Ital J Paediatr 2016;42(1):86. https://doi.org/10.1186/s13052-016-0296-x
14. Taytard J, Nathan N, de Blic J, et al. New insights into pediatric idiopathic pulmonary hemosiderosis: The French RespiRare cohort. Orphan J Rare Dis 2013;8(1):161. https://doi.org/10.1186/1750-1172-8-161
15. Sigua JA, Zacharisen M. Heiner syndrome mimicking an immune deficiency. Wiscon Med J 2013;112(5):215-217.
16. Newsome BR, Morales JE. Diffuse alveolar haemorrhage. South Med J 2011;104(4):269-274. https://doi.org/10.1097/SMJ.0b013e3182126d3b
17. Bakalli I, Kota L, Sala D, et al. Idiopathic pulmonary haemosiderosis – a diagnostic challenge. Ital J Paediatr 2014;40:35. https://doi.org/10.1186/1824-7288-40-35
18. Poggi V, Lo Vecchio A, Menna F, Menna G. Idiopathic pulmonary haemosiderosis - a rare cause of iron-deficiency anaemia in childhood. J Pediatr Haematol Oncol 2011;33(4):160-162. https://doi.org/10.1097/MPH.0b013e3182a6df
19. Moo SP. Diffuse alveolar hemorrhage. Tuberc Res Dis 2013;74(4):151-162. https://doi.org/10.4046/trd.2013.74.4.151
20. Mark EJ, Ramirez JF. Pulmonary capillaritis and hemorrhage in patients with systemic vasculitis. Arch Pathol Lab Med 1985;109(5):413-418.
21. Susarla SC, Fan LL. Diffuse alveolar hemorrhage syndromes in children. Curr Opin Pediatr 2007;19(8):314-320. https://doi.org/10.1097/MOP.0b013e3280dd8c4a
22. Alberici F, Jayne DR. Impact of rituximab trials on the treatment of ANCA-associated vasculitis. Nephrol Dial Transplant 2014;29(6):1151-1159. https://doi.org/10.1093/ndt/gft318

23. Kallenberg CG, Hauser T. B-cell therapy in antineutrophil cytoplasmic antibody associated vasculitis. Nephrol Dial Transplant 2015;30(1):119-122. https://doi.org/10.1093/ndt/gfv056
24. Yates M, Watts RA, Bajema IM, et al. Eular/ERA_EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2016;75(9):1583-1594. https://doi.org/10.1136/annrheumdis-2016-209133
25. Solomonov A, Fruchter O, Zuckerman T, et al. Pulmonary haemorrhage: A novel mode of therapy. Respir Med 2009;103(8):1196-1200. https://doi.org/10.1016/j.rmed.2009.02.004
26. Wanko SO, Broadwater G, Folz RJ, Chao NJ. Diffuse alveolar haemorrhage: Retrospective review of clinical outcomes in allogeneic transplant recipients treated with aminocaproic acid. Biol Blood Marrow Transplant 2006;12(9):949-953. https://doi.org/10.1016/j.bbmt.2006.05.012
27. Rathi NK, Tanner AR, Dinh A, et al. Low-, medium- and high-dose steroids with or without aminocaproic acid in adult hematopoietic patients with diffuse alveolar haemorrhage. Bone Marrow Transplant 2015;50(3):420-426. https://doi.org/10.1038/bmt.2014.287
28. Park JA. Diffuse alveolar haemorrhage and recombinant factor VIIa treatment in pediatric patients. Korean J Pediatr 2016;59(3):105-113. https://doi.org/10.3345/kjp.2016.59.3.105
29. Bafaqih H, Chehab M, Almohaimeed S, et al. Pilot trial of a novel two-step therapy protocol using nebulized tranexamic acid and recombinant factor VIIa in children with intractable diffuse alveolar hemorrhage. Ann Saudi Med 2015;35(3):231-239. https://doi.org/10.5144/0256-4947.2015.231