Diffuse alveolar haemorrhage in children hospitalised in a tertiary-level hospital: A retrospective descriptive study

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Diffuse alveolar haemorrhage (DAH) is considered a rare condition in children. There is no consensus on the management of DAH syndromes in Africa or other low- and middle-income countries. In this brief report, the clinical characteristics, management and outcomes of children treated for DAH in the Chris Hani Baragwanath Academic Hospital paediatric pulmonology unit in Johannesburg, South Africa are described. Fifteen children were included in this case series, of whom 11 (73.3%) presented with severe microcytic anaemia. Of the 11 children who had bronchoalveolar lavage, 9 (81.8%; 60.0% of the total) had haemosiderin-laden macrophages on microscopy. Only 5 children had a lung biopsy, of whom 3 (60.0%) had capillaritis. All the children were started on oral prednisone at presentation, and 11 (73.3%) received additional complementary treatment. Nine children (60.0%) had normal haemoglobin levels 1 year after initiation of treatment. Our series supports previous reports that DAH is uncommon in children. A large proportion of our patients responded well to treatment despite some resource limitations.

Keywords. Diffuse alveolar haemorrhage, pulmonary haemosiderosis, pulmonary capillaritis.

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Study synopsis

What the study adds

The study provides additional data on children presenting with diffuse alveolar haemorrhage in a South African tertiary hospital.

What are the implications of the findings

There is a need for South African pulmonologists to come together and conduct a national audit of these patients in different hospitals to determine the incidence in our country, as well as to inform a management plan in the presence or absence of specialised tests.

Diffuse alveolar haemorrhage (DAH) is a potentially life-threatening condition that can present acutely with respiratory failure or more insidiously with microcytic anaemia and diffuse radiological changes.[1,2] DAH in children is considered to be a rare condition, and most of the literature is limited to case reports or case series from developed countries.[3]

DAH is suspected if >20% of alveolar macrophages (minimum count of 200) stain positive for haemosiderin on a bronchoalveolar lavage (BAL) or sputum sample.[1] The Golde score may also be used to diagnose and assess the severity of DAH.[4] There are many causes of DAH, which can broadly be catergorised into those with or without immune-mediated pulmonary capillaritis.

Pulmonary capillaritis describes a histological pattern of lung injury in which autoantibodies are generated against neutrophilic components, causing enzymatic damage to the endothelium of the alveolar capillary. Pulmonary capillaritis may present as part of a systemic condition (such as systemic lupus erythematosus, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) or Goodpasture syndrome), or occur in isolation.[1,5,6] Antineutrophilic cytoplasmic antibodies (ANCAs), antiglomerular basement membrane antibodies (AGBMAs), anti-smooth-muscle antibodies (ASMAs), antinuclear antibodies (ANAs) and rheumatoid factor may be measured, but generally lack specificity.[7] DAH not associated with pulmonary capillaritis can either be idiopathic pulmonary haemosiderosis (IPH) or secondary to causes such as mitral stenosis, pulmonary venous hypertension or veno-occlusive disease.

Corticosteroid therapy is generally accepted as the initial treatment for DAH. Additional therapies such as azathioprine, cyclophosphamide and hydroxychloroquine are often required.[1] Another option is rituximab, a monoclonal antibody that acts on the CD20 receptor on B lymphocytes, preventing immunoglobulin binding to antigens in pulmonary capillaries.[1]

There are currently no published data on children hospitalised with DAH in South Africa (SA). We therefore describe the clinical characteristics, management and outcomes of children treated for DAH in the Chris Hani Baragwanath Academic Hospital (CHBAH) paediatric pulmonology unit in Johannesburg, SA.

A retrospective audit of children (aged 28 days - 16 years) with DAH who were managed in the CHBAH paediatric pulmonology unit from 1 January 2011 to 30 April 2022 was undertaken. Children referred from

the general paediatric wards at CHBAH or from other hospitals in the CHBAH's catchment area are seen in the paediatric pulmonology unit and their details are captured on a database.

The paediatric pulmonology database was searched for patients fulfilling the description of DAH. The criteria used were any two of the following: bilateral diffuse infiltrates on the chest radiograph, anaemia, and haemosiderin-laden macrophages (HLMs) in sputum or BAL fluid. Clinical, laboratory and radiological information was extracted from patient records and entered onto data collection forms before being entered onto an Excel sheet (Windows 10; Microsoft Inc., USA).

There are no guidelines or protocols for investigation or management of children with DAH at CHBAH. Generally, the following laboratory investigations are carried out: a full blood count, serum urea and electrolytes, erythrocyte sedimentation rate, tests for immune-mediated diseases such as cytoplasmic ANCAs (c-ANCAs) and perinuclear ANCAs (p-ANCAs), AGBMAs, ASMAs and ANAs, and a screen for coeliac disease with anti-gliadin, anti-tissue transglutaminase and anti-endomysial antibodies. A bronchoscopy with BAL is undertaken to identify HLMs. Chest radiographs and computed tomography (CT) scans are performed as indicated. Paediatric surgery and postoperative intensive care unit beds required for lung biopsies are limited, so most children are diagnosed on the basis of clinical, haematological and radiological findings, and treated without complete histological investigations.

Data are reported as proportions for categorical variables, and medians and interquartile ranges (IQRs) for continuous variables. Ethical approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (ref. no. M200828).

Of 2 614 children in the database, 18 (0.7%) who met the description of DAH were identified. Three cases were excluded: 2 had severe iron deficiency anaemia only, and 1 was lost to follow-up with no clinical data. A total of 15 children (0.6%) were therefore included in the analysis.

Twelve of the children (80.0%) were female, with a median (IQR) age of 35 (15 - 84) months (Table 1). All the children were of black African descent and HIV uninfected. Thirteen children (86.7%) lived in Gauteng Province, 1 child (6.7%) was from North West Province and 1 (6.7%) was from Limpopo Province. Three children (20.0%) were underweight and 4 (26.7%) were stunted. Most children (n=12; 80.0%) had had multiple previous admissions (median of 4) to hospital. Eleven (73.3%) presented with severe anaemia. Three children (20.0%) were referred from other institutions where they had received blood transfusions and were therefore not anaemic on presentation (Supplementary Table 1, https://www.samedical.org/file/2036). Four children (26.7%) were hypoxic at presentation, and 1 child required invasive ventilation.

All the children had diffuse bilateral opacification on the chest radiograph noted by the attending clinician. Two children had CT scans on presentation which were reported by radiologists; the first showed multiple tiny cysts throughout the lung fields, and the second bilateral alveolar opacification. No organisms were cultured on sputa.

Four children (26.7%) were c-ANCA positive and 1 (6.7%) was p-ANCA positive (Table 1). Of the 13 children who had an ANA, C3 and C4 test, all were negative or had results within the normal range. Rheumatoid factor was measured in 4 cases, and all the results were within the normal range. Five children screened negative for coeliac disease. Tests for autoimmunity were repeated annually for symptomatic children.

Five (33.3%) of the 15 children had HLMs observed on sputum microscopy. Eleven children (73.3%) had a BAL, of whom 9 (81.8%; 60.0% of the total) were positive for HLMs. Five children (33.3%) had a lung biopsy; 3 (60.0%) had evidence of capillaritis, while 2 (40.0%) had intra-alveolar HLMs without any evidence of capillaritis (Supplementary Table 1, https://www.samedical.org/file/2036). Those who had no antibodies detected and had no capillaritis, or had not had a biopsy done yet, were treated for IPH. One child was c-ANCA positive with capillaritis on histology, and was diagnosed with GPA.

All the children were started on oral prednisone 2 mg/kg/d at presentation; 5 (33.3%) also received three pulses of intravenous methylprednisolone 500 mg/m^2 per day on alternate days for a duration of 5 days. Four (26.7%) remained on prednisone alone throughout their management, while 11 (73.3%) received further complementary treatment, including azathioprine (n=7; 46.7%), cyclophosphamide (n=5; 33.3%), rituximab (n=2; 13.3%), mycophenolate mofetil (MMF) (n=2; 13.3%) and hydroxychloroquine (n=7; 46.7%) (Table 1). The decision to initiate complementary therapy was made at the discretion of the treating clinician. It was generally based on a continuous dropping of haemoglobin coupled with elevated reticulocytes, and clinical symptoms such as hypoxia (Supplementary Table 2, https://www.samedical.org/file/2037). One patient complained of blurring vision, and was reported to have developed retinopathy of the left eye that was thought to be caused by hydroxychloroquine. The drug was subsequently stopped and her vision returned to normal.

Nine children (60.0%) had normal haemoglobin concentrations 1 year after initiation of treatment. Three (20.0%) were discharged from the service, 5 (33.3%) are still being followed up and on treatment, and 7 (46.7%) were lost to follow-up.

In this retrospective study, we investigated the clinical presentation and management of 15 (0.5%) children with DAH over an 11-year period at a tertiary-level paediatric pulmonology service. Similar to reports in high-income countries,[3,8] DAH is an uncommon clinical condition in SA children, and there is a paucity of studies describing the clinical characteristics and outcomes of these patients. In our study, most children had a delayed diagnosis and presented with multiple hospital admissions for anaemia or lower respiratory tract infections before DAH was suspected. The delay in referral and presentation may be due to lack of awareness about this condition among clinicians.

Five children (33.3%) had serological findings suggestive of an immune-mediated condition. Negative serology does not exclude an immune-mediated cause of DAH, so repeat testing after initial screening may be necessary.[5,9] In cases where an immune-mediated capillaritis is suspected and serological investigations are not helpful, a lung biopsy is indicated.[10]

Only 5 children had a lung biopsy; 3 had histological features of pulmonary capillaritis, of whom only 1 was c-ANCA positive. A further 3 children without a biopsy were c-ANCA positive and another was p-ANCA positive. We were therefore only confident of an underlying immune-mediated cause in 7 (46.7%) of the 15 children with DAH; the main differential diagnoses were GPA and MPA. A systematic review found that >90% of children with GPA or MPA had ANCAs detected and that they were predominantly female.[11] Despite its being

Table 1. Characteristics, investigations, treatment and outcomes of children with diffuse alveolar haemorrhage (*N*=15)

	n (%)*
Characteristics	
Female gender	12 (80.0)
Black African	15 (100)
HIV negative	15 (100)
Stunting (HAZ <–2)	4 (26.7)
Age at presentation (months), median (IQR)	35 (15 - 84)
Number of admissions before diagnosis was made (*n*=12), median (IQR)	4 (2 - 5)
Investigations	
Haemoglobin (g/dL), median (IQR)	5.8 (2.7 - 9.5)
Platelets ($\times 10^9$/L), median (IQR)	438 (361 - 542)
Creatinine (μmol/L), median (IQR)	35 (22 - 44)
INR (*n*=11), median (IQR)	1.03 (0.92 - 1.10)
ESR (mm/h) (*n*=9), median (IQR)	10 (8 - 11)
C3 (g/L) (*n*=13), median (IQR)	1.26 (1.17 - 1.41)
C4 (g/L) (*n*=13), median (IQR)	0.30 (0.21 - 0.40)
ANA	
Positive	0
Negative	13 (86.7)
Unknown	2 (13.3)
c-ANCA	
Positive	4 (26.7)
Negative	8 (53.3)
Unknown	3 (20.0)
p-ANCA	
Positive	1 (6.7)
Negative	11 (73.3)
Unknown	3 (20.0)
AGBMA	
Positive	1 (6.8)
Negative	7 (46.7)
Unknown	7 (46.7)
HLMs	
Sputum	5 (33.3)
Bronchoalveolar lavage (*n*=11)	9 (81.8)
Negative	1 (6.7)
Histological findings (*n*=5)	
Capillaritis	3 (60.0)
No capillaritis	2 (40.0)
Treatment†	
Steroids	15 (100)
Cyclophosphamide	5 (33.3)
Hydrochloroquine	7 (46.7)
Azathioprine	7 (46.7)
MMF	2 (13.3)
Rituximab	2 (13.3)
Outcome	
On treatment	4 (26.7)
In remission	3 (20.0)
Transfer to another hospital	1 (6.7)
Lost to follow-up	7 (46.7)

HAZ = height-for-age *z*-score; IQR = interquartile range; INR = international normalised ratio; ESR = erythrocyte sedimentation rate; C3 = complement component 3; C4 = complement component 4; ANA = antinuclear antibody; c-ANCA = cytoplasmic antineutrophilic cytoplasmic antibody; p-ANCA = perinuclear antineutrophilic cytoplasmic antibody; AGBMA = antiglomerular basement membrane antibody; HLMs = haemosiderin-laden macrophages; MMF = mycophenolate mofetil.
*Except where otherwise indicated.
†Some children were on more than one treatment.

a tertiary-level hospital, there are resource constraints at CHBAH. Consequently, a lung biopsy in all children with DAH was not possible. In some instances, parents refused this procedure for cultural reasons, or concerns around pain and the risk of complications. Some experts believe that a lung biopsy should be mandatory and the gold standard for identifying the cause of DAH.[5,12]

Immunosuppressive therapy was initiated even when the cause of DAH was not known. All the patients were started on oral or intravenous steroids, and those who remained symptomatic, with dropping haemoglobin, respiratory distress and/or bilateral diffuse infiltrates on the chest radiograph, received additional immunosuppressive treatment in a stepwise manner. This was done in consultation with the rheumatologist when an underlying immune-mediated condition was present or suspected. Two challenging patients were ultimately treated with MMF and rituximab. The first was a girl who had histological features of capillaritis and was serologically positive for c-ANCAs. The working diagnosis was GPA, as she subsequently developed symmetrical polyarthritis of the small joints as well as a diffuse pattern of nodular infiltrates on the chest radiograph.[1] She has not had haematuria and her renal function has remained normal. She has had multiple relapses with a low haemoglobin level and respiratory distress. The second patient, also a girl, was serologically positive for p-ANCAs. Despite receiving intravenous methylprednisolone and cyclophosphamide pulsing, plus azathioprine, her haemoglobin level would drop to as low as 3 g/dL during bleeding episodes. Both patients were clinically stable at the time of submission of this report.

Most children in our series had a normal haemoglobin concentration 1 year after treatment, with no other signs to suggest continued alveolar haemorrhaging. However, long-term follow up is required, as those who do not go into remission may develop fibrosis with reduced lung capacity.[13] We recommend investigating all cases with a meticulous, systematic and stepwise approach to avoid essential tests being omitted. Antibody tests should ideally be repeated annually, as some children with immune-mediated disease may not initially be seropositive. Efforts should be made to confirm a histological diagnosis, but where there are resource constraints, treatment can be initiated based on the findings of clinical and laboratory investigations.

There were many limitations to this study. As it was a retrospective review, there was missing information, and no uniform investigational approach was undertaken. We had a small number of cases, and almost half (n=7) were lost to follow-up. Possible reasons for loss to follow-up may include the effect of poor socioeconomic circumstances, which make it difficult for patients to come for ongoing check-ups, as well as inadequate counselling or understanding of the seriousness of the condition.

DAH is an uncommon clinical condition in children that often responds to immunosuppressive therapy. However, there are no evidence-based guidelines in the literature on how to investigate and treat children with DAH, particularly in a setting where there are resource constraints. Pragmatically, children need to be investigated based on the availability of specialised testing, bronchoscopy and surgical lung biopsy. Treatment should ideally be in collaboration with rheumatologists when an immune-mediated condition is the likely cause. There is a need for SA pulmonologists to come together and conduct a national audit of these patients in different hospitals to determine the incidence in our country, as well as to inform a management plan in the presence or absence of specialised tests.

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1. Parris D, van Niekerk A, Jeevarathnum AC, Green RJ. An approach to pulmonary haemorrhage in children. S Afr Respir J 2017;23(3):63-70. https://doi.org/10.7196/SARJ.2017.v23i3.152
2. Collard HR, Schwarz MI. Diffuse alveolar hemorrhage. Clin Chest Med 2004;25(3):583-592. https://doi.org/10.1016/j.ccm.2004.04.007
3. Nuesslein TG, Teig N, Rieger CH. Pulmonary haemosiderosis in infants and children. Paediatr Respir Rev 2006;7(1):45-48. https://doi.org/10.1016/j.prrv.2005.11.003
4. Golde D, Drew W, Klein H, Finley T, Cline M. Occult pulmonary haemorrhage in leukaemia. BMJ 1975;2(5964):166-168. https://doi.org/10.1136/bmj.2.5964.166
5. Susarla S, Fan L. Diffuse alveolar hemorrhage syndromes in children. Curr Opin Pediatr 2007;19(3):314-320. https://doi.org/10.1097/MOP.0b013e3280dd8c4a
6. Wang H, Sun L, Tan W. Clinical features of children with pulmonary microscopic polyangiitis: Report of 9 cases. PLoS ONE 2015;10(4):e0124352. https://doi.org/10.1371/journal.pone.0124352
7. Taytard J, Nathan N, de Blic J, et al. New insights into pediatric idiopathic pulmonary hemosiderosis: The French RespiRare® cohort. Orphanet J Rare Dis 2013;8:161. https://doi.org/10.1186/1750-1172-8-161
8. Fullmer JJ, Langston C, Dishop MK, Fan LL. Pulmonary capillaritis in children: A review of eight cases with comparison to other alveolar hemorrhage syndromes. J Pediatr 2005;146(3):376-381. https://doi.org/10.1016/j.jpeds.2004.10.025
9. Chin CI, Kohn SL, Keens TG, Margetis MF, Kato RM. A physician survey reveals differences in management of idiopathic pulmonary hemosiderosis. Orphanet J Rare Dis 2015;10:98. https://doi.org/10.1186/s13023-015-0319-5
10. Specks U. Diffuse alveolar hemorrhage syndromes. Curr Opin Rheumatol 2001;13(1):12-17. https://doi.org/10.1097/00002281-200101000-00003
11. Ludici M, Quartier P, Terrier B, Mouthon L, Guillevin L, Guillevin L. Childhood-onset granulomatosis with polyangiitis and microscopic polyangiitis: Systematic review and meta-analysis. Orphanet J Rare Dis 2016;11:141. https://doi.org/10.1186/s13023-016-0523-y
12. Zhang Y, Luo F, Wang N, Song Y, Tao Y. Clinical characteristics and prognosis of idiopathic pulmonary hemosiderosis in pediatric patients. J Int Med Res 2019;47(1):293-302. https://doi.org/10.1177/0300060518800652
13. Saha BK. Idiopathic pulmonary hemosiderosis: A state of the art review. Respir Med 2021;176:106234. https://doi.org/10.1016/j.rmed.2020.106234

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