

# A novel approach to the diagnosis and treatment of hemoptysis in infants: A case series

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## Abstract

**Introduction:** Hemoptysis in children is an uncommon presenting symptom but can be life-threatening if massive. Cardiac catheterization and coil embolization of aorto-pulmonary collateral vessels (APCs) is uncommon in pediatric hemoptysis patients without congenital heart disease.

**Methods:** We present a series of seven infants ( $\leq 12$  months of age) with hemoptysis, all of whom underwent cardiac catheterization to look for and intervene upon APCs, if found. Only those patients who underwent both bronchoscopy as well as cardiac catheterization from January 1995 to January 2015 were included in this retrospective review.

**Results:** Seven patients met inclusion criteria, and three had a history of recurrent hemoptysis. The mean age was 3 months. Four had evidence of bleeding on bronchoscopy. All seven had respiratory distress which necessitated ICU admission; five required mechanical ventilation. Cardiac catheterization showed significant APCs ( $>2$  mm) in six of the seven studied patients, all of which were coil embolized. One patient had no significant APCs and therefore, no embolization. All patients had complete resolution with no recurrences during the 10-20-year outpatient follow-up period. Chest CT scans were not helpful in delineating the site or etiology of bleeding in any patient.

**Conclusions:** APCs should be considered as a differential diagnosis for pulmonary hemorrhage in infants after more common causes have been ruled out.

## KEYWORDS

aorto-pulmonary, cardiac catheterization, coil embolization, hemoptysis, collateral vessels, infants

## 1 | INTRODUCTION

Hemoptysis, the coughing up of blood that arises from the lower respiratory tract, is a rare condition in infants and children, but it is potentially life-threatening and may cause significant morbidity. Overall mortality was found to be close to 13%. When massive and untreated, mortality rate may rise to 32%.<sup>1</sup> Unless the volume of blood

is considerable, hemoptysis may be difficult to detect because younger children, especially infants, swallow their sputum. However, once identified, the source and underlying pathology must be investigated in a systematic manner.<sup>2</sup>

Treatment is initiated as with other bleeds with stabilization of the patient and protection of the airway. Mild hemoptysis may be treated symptomatically while a diagnostic workup is underway. Massive

hemoptysis in children needs immediate hospitalization and stabilization. The risk of asphyxiation though exsanguination remains a possibility,<sup>3</sup> underscoring the need for rapid diagnosis and intervention.

The differentiation of bronchial arteries from aortopulmonary collateral (APC) vessels is an anatomic one. These terms are often erroneously used interchangeably. APCs arise from the systemic arteries and supply the pulmonary circulation. These vessels, in the setting of congenital heart disease (CHD), can cause a significant systemic to pulmonary shunt.<sup>4</sup> They typically arise from the descending aorta, subclavian artery or its branches, bronchial and intercostal arteries. They often supply blood to the terminal respiratory unit and unlike bronchial arteries do not necessarily travel in close proximity to the bronchial tree.<sup>4</sup> They have been known to be associated with lesions associated with decreased pulmonary blood flow (tetralogy of Fallot, pulmonary atresia)<sup>5</sup> but have also been seen in premature neonates with bronchopulmonary dysplasia.<sup>6-9</sup> They are usually small and regress spontaneously in this latter group rarely needing intervention.<sup>10,11</sup>

APCs are synonymous with broncho-pulmonary arterial anastomoses and there are very few reports of coil embolization of these vessels for pediatric hemoptysis<sup>2</sup> aside from those associated with known CHD. Prominent APCs are more prevalent with cyanotic structural cardiac lesions.<sup>4</sup> Though massive hemoptysis is rare after palliated congenital cardiac lesions, there have been multiple reports of post-Fontan patients who present with massive hemoptysis, resolving after embolization of multiple aorto-pulmonary collateral vessels.<sup>12-14</sup>

Bronchial arteries are a known cause of massive and recurrent hemoptysis in adults and are often intervened upon in this setting. According to Bruzzi et al,<sup>15</sup> bronchial arteries are responsible for massive hemoptysis requiring treatment in over 90% of cases. Bronchial artery embolization (BAE) is the most frequently performed endovascular procedure and promptly brings bleeding under control in 66-90% of patients. BAE is now considered to be most effective nonsurgical treatment of massive AND recurrent hemoptysis, either as first-line treatment or as an adjunct to elective surgery.<sup>10</sup> APCs may be a neglected source of bleeding in children except those with CHD.

This case series focuses on infants, a small subset of hemoptysis patients, to underscore the importance of the presence of APCs in this cohort. All patients examined in this series were 12 months of age and younger and underwent cardiac catheterization after a work-up did not reveal the cause of bleeding. The aim of this study was to assess how many infants presenting with hemoptysis would have APCs and to assess the recurrence of hemoptysis after cardiac catheterization and coil embolization of these APCs, if found.

## 2 | METHODS

After IRB approval was received, a retrospective review of the pediatric pulmonology and cardiology databases at our tertiary children's hospital was performed to identify patients with hemoptysis as their reason for hospitalization and who also underwent a

bronchoscopy and subsequent cardiac catheterization between January 1995 and January 2015. All patients with a history of congenital heart disease (except foramen ovale) and/or older than 12 months of age were excluded. Data collection from the electronic medical record (EMR) included: demographics, symptoms, comorbid conditions, laboratory, and radiologic test results, as well as interventions and outcomes.

Due to our institution's long-standing hemoptysis guidelines, all patients received the same standard diagnostic assessment that comprised the following testing: 1) routine and immunologic/rheumatologic bloodwork (complete blood count, chem profile, anti-nuclear antibodies with reflex anti-double stranded DNA, rheumatoid factor, anticentromere antibody, Sjogren's antibody, Scl-70 antibody, anti-glomerular basement membrane antibody, anti-myeloperoxidase antibody, anti-proteinase 3 antibody, prothrombin time, activated partial thromboplastin time, international normalized ratio, fibrinogen, D-dimer, lupus anticoagulant, Von Willebrand factor assay, protein C and S activity, Factor V Leiden, B2-glycoprotein, C-reactive protein, and procalcitonin); 2) a respiratory viral panel and bronchial culture with acid fast bacilli testing; 3) consultation with a pediatric pulmonologist; and 4) bronchoscopy with bronchoalveolar lavage—essential to help localize the site and possibly identify the etiology. In addition, each lung was lavaged separately for assessment of hemosiderin-laden macrophages.

Our hospital's hemoptysis management also requires consultation with a pediatric cardiologist and cardiac catheterization (once hemoptysis and its location are confirmed and other common causes of hemoptysis are ruled out). Cardiac catheterization is performed to detect significant (>2 mm) APCs and occlude them, if found. Therefore, consistent with our standard of care, all patients described in this case series underwent a cardiac catheterization under general anesthesia to allow for better angiography with accurate digital subtraction; this has been noted to be less distressing for patients.<sup>16</sup> This entailed right and left heart catheterization, right pulmonary artery angiography, left pulmonary artery angiography and ascending and descending aortography using biplane angiography to reduce radiation dosage in all cases. If significant APCs were found, coil embolization was performed with 3 × 3 cm stainless steel or platinum coils.

## 3 | RESULTS

Of the 16 patients initially identified in the combined databases, nine patients were excluded due to age and/or congenital heart defect. The remaining seven patients who met inclusion criteria were studied. The mean age was 3 months (range 1-12 months). Four patients (47%) were female. A summary of the number and percentage of infants with hemoptysis-related characteristics can be found in Table 1.

### 3.1 | Clinical presentation and history

Although the quantity of blood loss was not consistently documented in the EMR, the volume was qualified to be significant based

**TABLE 1** Hemoptysis-related characteristics

	Characteristic	N (percent)
Patient history	History of prior hemoptysis	3 (43%)
Respiratory condition at time of hemoptysis presentation (pre-bronchoscopy)	Respiratory distress/failure necessitating ICU admission	7 (100%)
	Required intubation and mechanical ventilation	5 (71%)
	Respiratory distress and placement on high flow nasal cannula	2 (29%)
Laboratory testing	Antinuclear antibodies	1 (6%)
	p-ANCA/c-ANCA	1 (14%)
Radiology	Abnormal chest X-ray	7 (100%)
	Chest CT scan performed	5 (71%)
	Chest CT scan non-diagnostic	5 (71%)
Bronchoscopy	Active bleeding on bronchoscopy	4 (57%)
	Significant hemosiderin laden macrophages (>35% HLM index; 5)	1 (14%)
Cardiac catheterization	Significant APCs (>2 mm in diameter)	6 (86%)
	Coil embolization of APCs	6 (86%)
Outcome	Resolution of hemoptysis immediately post-embolization	7 (100%)
	Long-term hemoptysis recurrence post-embolization	0 (0%)

on the necessity of Intensive Care Unit (ICU) admission and respiratory support for all seven patients. Prior to bronchoscopy, intubation, and mechanical ventilation were required in five of the seven children, and two were placed on oxygen via high flow nasal cannula. None of the children had tracheostomies or a diagnosis of chronic lung disease. Three patients had a history of recurrent hemoptysis (2 or more) episodes during the week immediately preceding their ICU admission. Five patients had a patent foramen ovale, which was not considered as structural cardiac disease. Non-cardiovascular hemoptysis-associated comorbidities included failure to thrive, eczema, asthma, and anemia.

### 3.2 | Diagnostic work-up

The respiratory viral panel was positive for *Coronavirus* in one patient. On culture of bronchial washings, none of the patients showed specific infectious agents. All remaining cultures were negative for bacterial, fungal, and mycobacterial organisms. One patient's anti-nuclear antibodies were positive. The hemoglobin range of the entire study population was between 9.5 and 13.1 g/dL. No patients required blood transfusions.

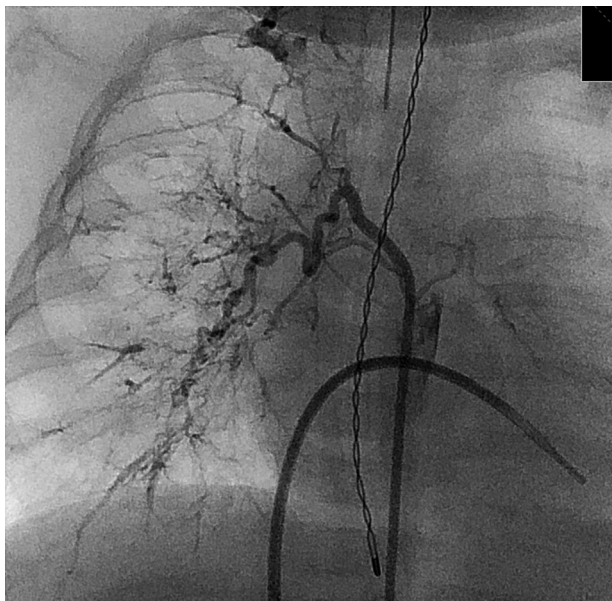
Chest radiography had positive findings in all seven patients, and five of them demonstrated either bilateral hilar or bibasilar interstitial streaky opacification. In the remaining two patients, the chest x-ray was not diagnostic for a specific site or etiology, however it did accurately reveal which lung was affected as confirmed by subsequent bronchoscopy. In one patient with right pulmonary opacification, right bronchus bleeding was found. In the other, bilateral pulmonary opacification was consistent with visualization of bleeding from both lungs on bronchoscopy.

Helical chest CT angiograms with intravenous contrast were also performed in all patients but were unsuccessful in detecting the site of bleeding or identifying specific etiologies. A majority of the chest CT scan findings were reported as nonspecific bilateral ground glass opacities, patchy or confluent heterogenous infiltrates or multi-segment atelectasis. No specific pulmonary pathology was mentioned, and no abnormal bronchial vessels were noted on the scans. No anomalous branches were seen arising from the aorta in the chest or abdomen. Visualized segments of the pulmonary arteries and pulmonary veins were unremarkable. No dilated pulmonary venous structures were visualized.

On bronchoscopy, four patients had either active bleeding from one lobe/segment or pink frothy lavage fluid returned on suction. One patient had bleeding from both left and right bronchi. One patient had a significant percentage of hemosiderin-laden macrophages on bronchoalveolar lavage.

### 3.3 | Cardiac catheterization

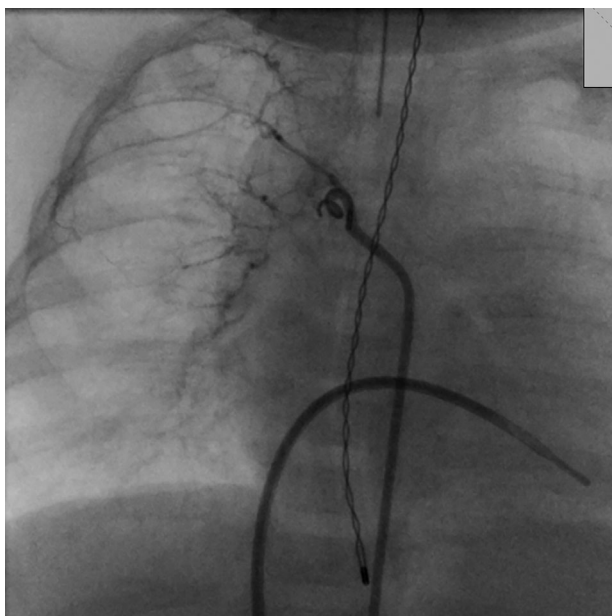
Cardiac catheterization was performed in all seven patients after their workup failed to reveal specific hemoptysis etiology. General diagnostic information including hemodynamic and saturation measurements were performed and within the normal range for all patients. There was no evidence of pulmonary hypertension in any of the cohort patients. Significant APCs (defined as vessels >2 mm in diameter at take-off from the descending aorta) were found in six of the seven patients, and coil embolization using 3 mm coils was performed in all six of these patients (see Figures 1 and 2). In one patient, no significant APCs were seen; therefore, no embolizations were performed during cardiac catheterization.



**FIGURE 1** Large aortopulmonary collateral vessel to the right lung on cardiac catheterization

### 3.4 | Short and long-term follow-up

No adverse events related to bronchoscopy or cardiac catheterization occurred at any time. All six patients who had coil embolization of their APCs [including the three with prior hemoptysis episode(s)], had complete resolution. Hemoptysis in the one patient without APCs also resolved. The EMRs of all seven patients were followed long-term for a time period between 10 and 20 years post-hemoptysis ICU hospitalization. There were no hemoptysis recurrences in any of the seven patients through their last EMR-documented clinic visit.



**FIGURE 2** Decreased flow in this collateral vessel after coil embolization

## 4 | DISCUSSION

Although hemoptysis is rare in the pediatric age group, it can be a significant cause of morbidity and possible mortality in addition to being a source of anxiety for infants, their guardians and their caregivers. A systematic approach should be followed to arrive at an etiology to guide appropriate management. The amount of hemoptysis can be deceptive as children, especially infants, tend to swallow the blood.<sup>2</sup>

In previous studies in the literature, involvement of the pediatric cardiologist has been limited to patients with CHD. The early consultation and involvement with pediatric cardiology in patients with or without congenital heart disease (CHD) is a novel approach wherein if significant APCs (>2 mm) are discovered, they are coil occluded/embolized. Additionally, the longest follow up period after coil embolization (in this case, of the bronchial arteries), was 42 months.<sup>2</sup> Our study has the longest follow up of patients intervened upon (10-20 years). Our small sample size precludes generalizations, but it is possible that early intervention prevented subsequent recurrent or massive hemoptysis episodes in the patients found to have APCs. Chun et al<sup>17</sup> stated that recurrent bleeding is not uncommon after BAE. Our experience with coil embolization of APCs in our small subset of infants was different with no recurrent bleeding episodes noted.

A chest x-ray or, when indicated, a CT scan may provide additional information but were not helpful in our study with all patients getting a chest CT but none of the scans being diagnostic for the site or etiology of bleeding. A 2012 study from Egypt,<sup>18</sup> using multi-detector chest CT scans identified the cause in 84% of cases, and the site and vascular origin in 76% of patients presenting with hemoptysis (mean age 50 years). However, this study was in the adult population and different from our cohort. Its applicability to the pediatric population is unknown. This modality offers the advantage of being non-invasive, but the disadvantage is the inability to perform interventions, unlike cardiac catheterization. Both modalities lend themselves to radiation exposure. However, with recent advances in technology, operators in both fields strive to minimize this exposure.

Bronchoscopy is an essential tool to help aid the localization of bleeding and possible etiology. In addition, bronchoscopy can be used for therapeutic interventions<sup>19,20</sup> mostly in older children, which include CO<sub>2</sub> laser bronchoscopy, Nd-YAG laser bronchoscopy, endoscopic balloon occlusion of a lobe or main bronchus, topical airway vasoconstrictors, endoscopic tumor excision, and lobectomy.<sup>4,13</sup>

As expectorated blood often originates from the bronchial arteries, selective bronchial arteriography, and bronchial artery embolization (BAE) has been found to be the safest and most effective therapy for hemoptysis in adults.<sup>21</sup> It is now considered the procedure of choice for the management of massive and recurrent hemoptysis, either as a first-line therapy or as an adjunct to elective surgery.<sup>17,22-24</sup> Non-bronchial systemic artery embolization has also been reported in the treatment of hemoptysis in adults.<sup>17</sup> Inadvertent embolization in spinal branches of the bronchial arteries is the

most serious complication of a BAE.<sup>25</sup> Surgery is the most definitive form of therapy for these patients if endoscopy or embolization fails repeatedly. Bronchial artery embolization has also been reported in children with hemoptysis though this practice is not common.<sup>2,16,26</sup> This procedure requires technical skills not usually available in pediatric hospitals unless they have ready availability of pediatric cardiologists or interventional radiologists. The interventional cardiologist at our institution has over 20 years of experience in all manner of cardiac catheterization in children with and without CHD. Roebuck and Barnacle<sup>16</sup> state that although BAE is regarded as relatively safe, complications may be severe or even fatal. Therefore, if unavailable, transfer of children with severe hemoptysis to a tertiary care center with more experience in the performance of these procedures should be considered. Continuous improvements in techniques and embolization material has led to success rates up to 1-month post-BAE being 73–99%.<sup>25</sup> On the other hand, longer term success rates have been lower (1–46-month post-treatment recurrence rates of 10–55% of cases).<sup>25</sup>

The known complications from bronchial artery embolization in adults include chest pain, dysphagia, and very rarely transverse myelitis due to spinal cord ischemia.<sup>27</sup> Mal et al<sup>21</sup> have stated that the true frequency of spinal cord injury after BAE is probably underestimated by medical literature, the latter reporting mainly the experience of centers overspecialized in BAE. The patients in our series did not have any adverse events related to bronchoscopy or cardiac catheterization. Cardiac catheterization was performed in all seven patients and significant APCs were found in six with complete resolution of hemoptysis in all including those with recurrent hemoptysis episodes.

Coss-Bu et al<sup>1</sup> have also mentioned in their study that there was a higher mortality in recipients of blood products in all three groups. Of note, none of our patients needed blood transfusions. Roebuck and Barnacle<sup>16</sup> also stated that metal coils are rarely appropriate for BAE despite some published recommendations. They occlude large arteries, meaning that recurrent hemoptysis is likely because of revascularization by collaterals. However, in our cohort, we did not have a recurrence of hemoptysis, though they did not have a repeat cardiac catheterization to exclude revascularization.<sup>16</sup> It is theoretically possible that coils placed in these APCs would hamper embolization of distal vessels if revascularization did occur.<sup>28</sup>

Additionally, a significant correlate was that the site of bleeding on bronchoscopy correlated with the site of the APCs on catheterization. All six of the patients were found to have right sided APCs. Bronchoscopic bleeding was observed on the right side in two and on both sides in two. All our patients were <12 months of age and all required escalation of care to the ICU prior to bronchoscopy with most requiring intubation and mechanical ventilation. The natural history of pediatric hemoptysis is unknown, and it is hard to know if the APCs contributed significantly to the hemoptysis. The one patient in our series with hemoptysis who did not have any APCs could possibly have had smaller ones not clearly visible on cardiac catheterization and not amenable to coil embolization. It is also possible that there was a different etiology for the hemoptysis which was undiagnosed on the standard workup. The risks and benefits of general anesthesia,

procedural complications and radiation exposure need to be considered prior to cardiac catheterization. Moreover, this is a single center study and our sample size is very small precluding broad generalizations. These collateral vessels may need additional attention, especially in infants, who do not have a cause identified on a standard workup.

#### 4.1 | Limitations

The retrospective nature of our study has well known limitations and may preclude assessment of subtle differences between our patients. Our sample size was typical for a single center but not large enough to provide conclusive results that can be applied to the general population. We had an inclusion bias due to our institutional policy wherein all infants who presented with hemoptysis in whom a cause could not be determined on standardized testing underwent cardiac catheterization. One infant in our study who presented with hemoptysis did not have APCs and had no recurrence of hemoptysis on follow up. The natural history of hemoptysis in infants is not well studied and it is not possible to conclusively associate our intervention with no recurrences. A larger multicenter study may be necessary to overcome both the sample size and selection bias.

## 5 | CONCLUSIONS

Aorto-pulmonary collateral vessels should be considered as a differential diagnosis for pulmonary hemorrhage in an infant after other more common causes of hemoptysis have been ruled out. In addition to early consultation with pediatric pulmonology, a consultation with pediatric cardiology should be considered. Many of these events may possibly be related to these vessels. A bronchoscopy with differential lavage of right and left lungs would confirm and help localize the site of bleeding allowing for selective embolization of these collateral vessels when present during cardiac catheterization. Other imaging modalities may be helpful but cardiac catheterization would have the advantage of being able to perform interventions if needed.

#### CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

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