Clinical outcomes of cystic fibrosis patients with hemoptysis treated with bronchial artery embolization

Marília Amaral Peixoto da Silveira[1,2], Patrícia Amaral Peixoto da Silveira[3],
Flávia Gabe Beltrami[1,2], Leandro Armani Scaffaro[4],
Paulo de Tarso Roth Dalcin[1,2]

1. Programa de Pós-Graduação em Ciências Pneumológicas, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
2. Serviço de Pneumologia, Hospital de Clínicas de Porto Alegre – HCPA – Porto Alegre (RS) Brasil.
3. Faculdade de Medicina, Universidade Federal de Pelotas, Pelotas (RS) Brasil.
4. Serviço de Radiologia, Hospital de Clínicas de Porto Alegre – HCPA – Porto Alegre (RS) Brasil.

ABSTRACT

Objective: Massive hemoptysis is one of the most serious complications in patients with cystic fibrosis (CF). This study aimed to evaluate the hemoptysis-free period following bronchial and non-bronchial artery embolization (BAE/non-BAE) in CF patients and to investigate predictors of recurrent bleeding and mortality by any cause. **Methods:** This was a retrospective cohort study of CF patients ≥ 16 years of age undergoing BAE/non-BAE for hemoptysis between 2000 and 2017. **Results:** We analyzed 39 hemoptysis episodes treated with BAE/non-BAE in 17 CF patients. Hemoptysis recurrence rate was 56.4%. Of the sample as a whole, 3 (17.6%) were hemoptysis-free during the study period, 2 (11.8%) underwent lung transplantation, and 3 (17.6%) died. The median hemoptysis-free period was 17 months. The median hemoptysis-free period was longer in patients with chronic infection with *Pseudomonas aeruginosa* (31 months; 95% CI: 0.00-68.5) than in those without that type of infection (4 months; 95% CI: 1.8-6.2; p = 0.017). However, this association was considered weak, and its clinical significance was uncertain due to the small number of patients without that infection. **Conclusions:** BAE appears to be effective in the treatment of hemoptysis in patients with CF.

Keywords: Cystic fibrosis; Hemoptysis; Bronchial arteries; Embolization, therapeutic.

INTRODUCTION

Cystic fibrosis (CF) is a recessive genetic disease that mostly affects Whites and predominantly involves the lungs by impairing mucociliary clearance of airways.[1,2] This results in inflammation and chronic infection, leading to progressive obstructive lung disease, bronchiectasis, and recurrent respiratory infections.[3,4] One of the most serious complications in patients with CF is massive hemoptysis, present in approximately 4.1% of CF patients in their lifetime, with an average annual incidence of nearly 1%.[5] Bronchial artery embolization (BAE) is the current recommended treatment for patients with massive hemoptysis.[6]

The pathogenesis of hemoptysis is multifactorial.[7] Chronic inflammation and hypoxia have potential proliferative effects on bronchial circulation.[8] Arteries become tortuous, enlarged, and friable, favoring bleeding to the airways. Although there are risk factors for massive hemoptysis, such as advanced age, impairment of pulmonary function, and chronic infection with *Staphylococcus aureus*, the condition is often associated with airway infection and acute pulmonary exacerbation.[5] Therapeutic approaches depend on hemoptysis volume and patient health status. Management of hemoptysis includes conservative medical treatment and BAE/non-BAE; surgery is the final treatment option.[8]

The choice of treatment largely depends on the severity and urgency of the clinical conditions. The quantity of hemoptysis has been defined as scant (< 5 mL), mild-to-moderate (5–240 mL), and massive (> 240 mL).[6] Other authors consider that hemoptysis is massive when bleeding is > 240 mL/day or > 100 mL/day for several days.[5,9] An unequivocal indication for arterial embolization is massive hemoptysis together with clinical instability. In addition, patients who present with massive hemoptysis, become clinically stable, and no longer cough up blood should always be treated with BAE.[6] More recently, however, embolization of bronchial and non-bronchial arteries has been recommended in patients presenting with smaller hemoptysis volumes, decreased lung capacity, and difficulty to maintain airway patency.[10,11] This procedure is also recommended in patients with recurrent hemoptysis when their bronchial hygiene, respiratory physiotherapy, and lifestyles are compromised.[12,13] Bronchoscopy is not part of the routine approach prior to definitive treatment with embolization. However, chest angiotomography may be helpful in providing a thorough understanding of the anatomy and bleeding sites of bronchial arteries and non-bronchial collaterals, making embolization more effective.[14]

BAE for hemoptysis control was first described by Remy et al. in 1974.[15] Since then, several publications have

suggested different strategies for the treatment of hemoptysis with embolization, whose main purpose is to block the blood flow from the artery causing the bleeding. The success rate in controlling hemoptysis with embolization has increased in recent years due to improvements in embolic materials and catheter technology.[16,17] Arterial embolization has been particularly effective in patients with CF. In these patients, immediate control of hemoptysis has been achieved in over 90% of the cases.[12,18] However, recurrent bleeding after arterial embolization is a well-known complication, affecting 18% and 21% of the patients at 30 days and at 1 year, respectively,[17] illustrating a limitation of this technique in mid- and long-term outcomes.

The objective of the present study was to evaluate the hemoptysis-free period following BAE/non-BAE in CF patients, as well as to investigate predictors of recurrent bleeding and mortality by any cause.

METHODS

This was a retrospective cohort study including CF patients ≥ 16 years of age admitted to the Porto Alegre *Hospital de Clínicas* (HCPA), located in the city of Porto Alegre, Brazil, due to massive hemoptysis (> 240 mL/day or > 100 mL/day for 3 or more days) and submitted to BAE/non-BAE between January 1st, 2000 and December 31st, 2017. The clinical diagnosis of CF fulfilled the Cystic Fibrosis Foundation consensus criteria.[19] Data were obtained by reviewing the electronic records of the patients.

Data on the following variables were collected at the study entry date in the study: sex; ethnicity; age; presence of F508del mutation; BMI; spirometry results; six-minute walk distance; use of inhaled medications; use of azithromycin; pulmonary artery systolic pressure (estimated by Doppler echocardiography); liver transplantation; and presence of chronic respiratory bacterial infections, CF-related diabetes, pancreatic insufficiency, liver disease, previous pneumothorax, previous hemoptysis without BAE, and previous allergic bronchopulmonary aspergillosis. Spirometry records were obtained at the HCPA Pulmonary Physiology Unit, and FEV_1, FVC, and the FEV_1/FVC ratio were expressed in liters and in percentages of predicted values for sex, age, and height.[20] Prothrombin time, activated partial thromboplastin time, and platelet count were also collected at the time of bleeding. Chronic bacterial infections with *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex, or *S. aureus* were defined as patients having three or more positive isolates of these bacteria during the previous 12 months.

All of the patients underwent BAE/non-BAE performed by an interventional radiologist for hemoptysis treatment. The Seldinger technique[21] was used for vascular access via femoral artery, followed by selective catheterization of bronchial arteries. In this procedure, a 2.8-F coaxial microcatheter was used for superselective catheterization, and polyvinyl alcohol particles, ranging from 300-500 μ and 500-700 μ, were used for superselective embolization. All abnormal vessels supplying the area of interest were embolized if technically possible. Non-bronchial systemic arterial collateral supply from intercostal, phrenic, internal mammary, and subclavian arteries was also approached. The total number of specific arteries that received embolization was reviewed in the electronic medical records. In addition, anomalous bronchial artery diameter (≥ 4 mm), anomalous extrabronchial circulation, and previous embolization were recorded, as were complications and adverse effects.

The present study was approved by the Research Ethics Committee of the HCPA (Protocol no. 18-0297) and *Plataforma Brasil* (Protocol no. 64430516.0.0000.5327) and was in accordance with international and national standards for clinical studies in humans (Declaration of Helsinki and Brazilian governmental regulation– *Plataforma Brasil*). Informed consent was waived by the Research Ethics Committee of the HCPA because of the retrospective nature of the study. The authors signed a commitment to privacy and personal data protection statement.

Statistical analysis

The collected data were processed using the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA). A descriptive analysis was carried out for demographic characteristics and other variables of interest. The Kaplan-Meier method was used for plotting bleeding-free intervals and survival over time.

Data were analyzed from the date of patient inclusion (study entry date), that is, when the patient first underwent BAE. Outcomes were evaluated until March of 2018, which was defined as the study closing date. Patients who underwent lung transplantation or died along the study period were censored on the date of the event.

Cox proportional hazards regression was used in order to identify risk factors for repeat massive hemoptysis events and to determine the association between the baseline characteristics of the patients and outcomes. Two-tailed statistical tests were used, and significance was set at 5%. On the basis of two previous studies that reported recurrence rates of 47% and 46%,[22,23] the sample size should include approximately 41 cases within a 95% confidence interval.

RESULTS

During the study period, there were 39 hemoptysis episodes requiring BAE in 17 CF patients. General characteristics of the patients at their first hemoptysis event requiring BAE are listed in Table 1. All patients were White. The mean age was 25.0 ± 10.6 years, and 9 patients (53%) were female. Chronic bacterial infection with *P. aeruginosa* was the most prevalent (88%), followed by infection with methicillin-resistant *S. aureus* (35%), methicillin-susceptible *S. aureus*

(29%), and *B. cepacia* complex (17%). Mean values of FVC (% of predicted), FEV_1 (% of predicted), and FEV_1/FVC ratio were 56 ± 25%, 44 ± 25%, and 64.0 ± 12.5, respectively. Mean six-minute walk distance was 438 ± 123 m (Table 1).

During the study period, 9 (53%) and 8 (47%) of the patients were submitted to BAE only once and more than once, respectively (twice, in 2 patients; three times, in 2; four times, in 3; and eight times, in 1). There were no statistical differences between the patients that required one versus more than one procedure during the study regarding sex (p = 0.953), age (p = 0.139), BMI (p = 0.414), FEV_1 in % of predicted (p = 0.391), and FVC in % of predicted (p = 0.366).

Of the 39 hemoptysis episodes requiring BAE, 4 (10.3%) and 6 (15.4%) were censored due to lung transplantation and death, respectively. There was no death due to hemoptysis. The hemoptysis-free period following each procedure was determined using the Kaplan-Meier analysis (median = 17 months; mean = 46 months; Figure 1). There was no immediate recurrence (< 24 h); however, most patients (72%) developed late recurrence (after 30 days).

Results from the univariate logistic regression analysis for the risk of novel hemoptysis episodes are shown in

Table 1. Characteristics of the patients at the first hemoptysis episode requiring bronchial artery embolization (N = 17).[a]

Variable	Patients
Sex	
Female	9 (53%)
Male	8 (47%)
Age, years	25 ± 10.6
Age at diagnosis, years	2 [18]
Ethnicity	
White	17 (100%)
BMI, kg/m^2	20.0 ± 2.2
Pancreatic Insufficiency	12 (70.6%)
CFRD	2 (11.8%)
Liver disease	4 (23%)
Liver transplantation	1 (5.9%)
Chronic respiratory infection	
Pseudomonas aeruginosa	15 (88.2%)
Burkholderia cepacia complex	3 (17.6%)
MSSA	5 (29.4%)
MRSA	6 (35.3%)
Pulmonary function	
FVC, % predicted	56 ± 25
FEV_1, % predicted	44 ± 25
FEV_1/FVC, %	64 ± 12.5
6MWD, m	438.8 ± 123.3
PASP, mmHg	22 [13]

CFRD: cystic fibrosis-related diabetes; MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *S. aureus*; 6MWD: six-minute walk distance; and PASP: pulmonary artery systolic pressure (estimated by Doppler echocardiography). [a]Qualitative data are expressed as absolute (n) and relative (%) frequencies. Quantitative data are expressed as mean ± SD or median and [IQR].

Table 2. The only variable statistically associated with hemoptysis recurrence was chronic infection with *P. aeruginosa* (hazard ratio = 0.28; p = 0.028). Patients with chronic bacterial infection with *P. aeruginosa* had a longer hemoptysis-free period, with a median of 31 months (95% CI: 0.00-68.52) and a mean of 52 months (95% CI: 31.15-74.25) in comparison with those without that infection (median = 4 months; 95% CI: 1.8-6.2; p = 0.017).

Adverse effects following embolization occurred in 20% of the procedures. Chest discomfort, fever, and dyspnea were present after 6, 3, and 1 procedures, respectively. No dysphagia, neurological disorders, or serious complications were reported.

Flexible bronchoscopy and endobronchial irrigation with cold saline were performed in 10 hemoptysis events (8 subjects), and a balloon catheter for bronchus blocking was inserted in only 1 event prior to BAE. Chest CT scanning was performed in 4 hemoptysis events (4 subjects) prior to BAE. None of these procedures were statistically associated with the outcomes (p < 0.05).

Intravenous tranexamic acid was used as an additional therapy in 17 hemoptysis events (9 subjects). No patient was treated with nebulized epinephrine, terlipressin, or beta blockers.

DISCUSSION

This retrospective cohort study evaluated CF patients with massive hemoptysis submitted to BAE/non-BAE in a referral hospital in southern Brazil. Of the 39 hemoptysis episodes requiring BAE/non-BAE, 22 (56.4%) evolved to novel massive hemoptysis episodes. The median hemoptysis-free period following BAE/non-BAE was 17 months. This procedure was first adopted at the HCPA in 2000. Since then, it has been playing an important role in the treatment of hemoptysis in CF patients. BAE/non-BAE was an effective treatment, with immediate hemoptysis control in all cases, since

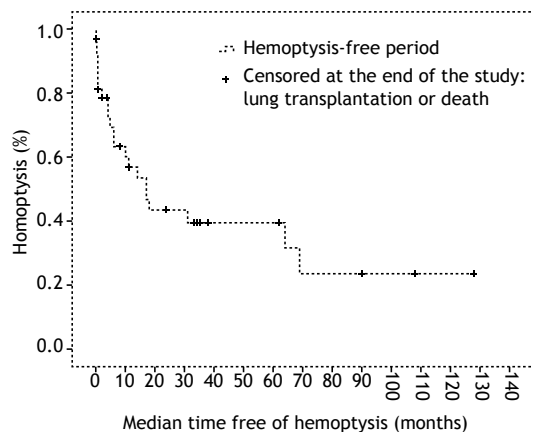**Figure 1.** Kaplan-Meier analysis of hemoptysis-free period in cystic fibrosis patients undergoing bronchial artery embolization. Median survival period was 17 months (95 CI: 8.1-25.9) and mean survival period was 46.2 months (95 CI: 26.8-65.6).

Table 2. Univariate logistic regression analysis for a repeat hemoptysis episode.

Variable	ß	Wald	p	HR	95% CI
Sex	0.28	0.42	0.517	1.33	0.55-3.18
Age, years	−0.06	2.65	0.103	0.94	0.87-1.01
Age at diagnosis, years	−0.05	1.65	0.199	0.94	0.86-1.03
F508del mutation	0.73	1.42	0.232	2.08	0.62-6.96
BMI, kg/m^2	−0.09	1.02	0.310	0.90	0.75-1.09
Pancreatic insufficiency	1.22	2.62	0.105	3.93	0.77-14.85
CFRD	−0.57	0.59	0.440	0.56	0.13-2.42
Previous pneumothorax	0.71	1.18	0.277	2.03	0.56-7.35
Previous hemoptysis with no BAE	0.49	0.75	0.386	1.63	0.53-5.00
ABPA	−0.55	0.55	0.458	0.57	0.13-2.48
Liver disease	0.25	0.26	0.606	1.28	0.49-3.31
Liver transplantation	−0.36	0.24	0.623	0.69	0.16-2.99
Chronic respiratory infection					
Pseudomonas aeruginosa	−1.26	4.80	0.028	0.28	0.09-0.87
Burkholderia cepacia complex	0.98	3.67	0.055	2.67	0.97-7.29
MSSA	−0.43	0.68	0.407	0.64	0.23-1.80
MRSA	0.25	0.29	0.587	1.28	0.51-3.20
Medication					
Inhaled dornase alpha	−0.56	0.80	0.368	0.56	0.16-1.94
Inhaled colistin	0.26	0.32	0.567	1.30	0.52 -3.24
Inhaled tobramycin	0.43	0.90	0.341	1.54	0.63-3.76
Azithromycin	0.60	0.66	0.414	1.83	0.42-7.89
Pulmonary function					
FVC, % predicted	−0.02	3.36	0.067	0.98	0.95-1.00
FEV$_1$, % predicted	−0.02	3.35	0.067	0.97	0.957-1.000
FEV$_1$/FVC, %	−0.02	1.77	0.183	0.97	0.94-1.01
6MWD, m	−0.00	2.80	0.094	0.99	0.99-1.00
PASP, mmHg	0.01	0.67	0.412	1.01	0.97-1.06
Platelet count	0.00	0.02	0.864	1.00	0.99-1.00
INR	1.57	1.17	0.278	4.83	0.28-83.0
Number of embolized arteries	−0.25	2.31	0.128	0.77	0.55-1.07
BAE	0.75	0.53	0.464	2.12	0.28-16.05
Non-BAE	−0.65	2.32	0.127	0.52	0.22-1.21
Anomalous bronchial artery diameter (≥ 4 mm)	0.27	0.322	0.570	1.31	0.51-3.35
Anomalous extrabronchial circulation	−0.64	0.978	0.323	0.526	0.15-1.88
Previous embolization	−0.50	1.26	0.260	0.60	0.25-1.45
Required more than one BAE procedure during the study period	−0.51	1.26	0.260	0.60	0.25-1.45

HR: hazard ratio; CFRD: cystic fibrosis-related diabetes; BAE: bronchial artery embolization; ABPA: allergic bronchopulmonary aspergillosis; MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *S. aureus*; 6MWD: six-minute walk distance; PASP: pulmonary artery systolic pressure; and INR: international normalized ratio.

no new bleeding was observed within the first 24 h. Moreover, similarly to previous studies, the long-term recurrence rate was 56%. Barben et al.[21] reported a 95% success rate in immediate bleeding control in 38 cases, whereas other studies have described long-term recurrence rates ranging from 42% to 55%.[12,17,21-24]

In a 14-year-long retrospective cohort study, Vidal et al.[25] evaluated 30 CF patients with major or persistent hemoptysis that required 42 embolization sessions. In that study, 8 patients relapsed and required a new embolization procedure. Of those, 4 and 4 patients had one and two relapses each, respectively. The mean period between the first embolization and recurrence

was 27.8 months (1-49 months), and 38% relapsed within 5 years after embolization. Of the 30 patients, 8 (26.7%) died from respiratory failure and 9 (30.0%) underwent lung transplant. The failure rate in that study was comparatively higher than in our study, whose mortality and transplant rates were 17.6% and 11.8%, respectively.

In another long-term retrospective study, Barben et al.[26] investigated 52 BAE procedures in 28 CF patients. In that sample, 13 patients required more than one BAE (re-embolization rate = 46%). Of the 13 patients, 3, 1, and 2 required 3, 4, and 5 BAE procedures. The median time between the first and

second BAE procedure was 4 months. The sample in that study was younger (mean age = 15 years) than in the present study (mean age = 25 years). However, despite the age difference, those patients showed similar pulmonary function results. Advances in technology and materials used for BAE might thus justify the longer hemoptysis-free period in our study.

Pathak et al.[27] evaluated long-term outcomes following BAE to treat different lung diseases. In their study, CF was the most common cause of hemoptysis requiring BAE. The recurrence rate was 50%, similar to that in our study. The 10-year survival rate was 85% in CF patients undergoing the procedure. Neither the median nor the mean hemoptysis-free period was described.

Flight et al.[24] described 27 adult CF patients that underwent 51 BAE procedures for massive and submassive hemoptysis over a median follow-up period of 26 months. Hemoptysis recurred after 31 BAE procedures (61%). Mortality after the first BAE at 30 days and at 12 months were 3.9% and 14.8%, respectively. No significant predictors of mortality were identified.

Martin et al.[17] studied 38 BAE procedures for the treatment of hemoptysis in 28 adult patients with CF and reported 30-day, 1-year, and 3-year outcomes. Technical (freedom from repeat embolization and hemoptysis-related mortality) and clinical (freedom from repeat embolization and mortality from any cause) success rates at 30 days were 89% and 82%, respectively, whereas they were 86% and 79% at 1 year and 82% and 75% at 3 years.

When we assessed clinical features that might predict hemoptysis recurrence, we found that the presence of chronic infection with *P. aeruginosa* was the only variable that correlated with longer hemoptysis-free periods, causing a protective effect (median = 31 months). However, this association was considered weak, and its clinical significance was uncertain due to the low number of patients in the group without that type of infection (only 2 patients). Additional studies involving larger numbers of patients are needed to clarify this finding. One hypothesis that might justify this association could be the continuous use of inhaled antibiotics by patients with chronic infection with *P. aeruginosa*, reducing bacterial colonization of the airways, controlling inflammation, and improving the prognosis for hemoptysis recurrence. Respiratory bacterial infection (detected by sputum bacteriology) is often mentioned in studies regarding BAE in CF patients, because *P. aeruginosa* occurs in 56% of the cases. However, to date, there have been no studies correlating this chronic airway infection with hemoptysis recurrence.[9,28,29]

Vidal et al.[25] found that the risk of hemoptysis recurrence was higher in patients with a large number of collateral arteries. There is a lack of information regarding the risks associated with hemoptysis recurrence after BAE. In the present study no correlation was found between the prevalence of this type of arteries and recurrent bleeding.

Previous studies[17,24,30] have described severe adverse effects following BAE, including transverse myelitis, circulation stroke, and paraplegia. However, these rare complications were not identified in our study. New technologies in catheters, guidewires, and embolic agents have likely resulted in safety improvements in BAE. The prevalence of mild adverse events in the literature[17,25] ranges from 5.2% to 50.9%, and the most common symptom is chest pain. Although chest discomfort, fever, and dyspnea occurred in 20% of the cases in the present study, these adverse effects were easily controlled with medication; hence, they did not compromise the clinical outcomes.

The present study has several limitations. First, it was conducted in a single medical center with a relatively small sample size, limiting its statistical power. However, we should notice that the studies published about this subject[10,15-18,23-26] also have a small sample size. Second, the study had a retrospective design, using data obtained from a review of medical records, which are not likely to be as complete and accurate as data collected in prospective studies. Third, the BAE procedures did not follow a strict protocol in this retrospective study.

In conclusion, this retrospective cohort study showed that BAE was an effective treatment for immediate and long-term hemoptysis in CF patients. Successful control was achieved within 24 h in 100% of the cases, with a median hemoptysis-free period of 17 months. The only predictor of recurrent bleeding following BAE was the presence of chronic infection with *P. aeruginosa*, but this association was considered weak and its clinical significance was uncertain due to the small number of patients.

AUTHOR CONTRIBUTIONS

MAPS: study conception and design; data collection, analysis, and interpretation; drafting the manuscript and tables; critical review of content; and approval of the final version. PAPS and FGB: analysis and interpretation of data; drafting the manuscript; critical review of content; and approval of the final version. LAS: study conception and design; data interpretation; drafting the manuscript and figures; critical review of content; and approval of the final version. PTRD: study conception and design; data collection, analysis, and interpretation; drafting the manuscript and figures; critical review of content; and approval of the final version.

REFERENCES

1. Riordan JR, Rommens JM, Kerem B, Alon NO, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA [published correction appears in Science 1989 Sep 29;245(4925):1437]. Science. 1989;245(4922):1066-1073. https://doi.org/10.1126/science.2475911

2. Skolnik K, Quon BS. Recent advances in the understanding and management of cystic fibrosis pulmonary exacerbations. F1000Res. 2018;7:F1000 Faculty Rev-575. https://doi.org/10.12688/f1000research.13926.1

3. Konstan MW, Hilliard KA, Norvell TM, Berger M. Bronchoalveolar lavage findings in cystic fibrosis patients with stable, clinically mild lung disease suggest ongoing infection and inflammation [published correction appears in Am J Respir Crit Care Med 1995 Jan;151(1):260]. Am J Respir Crit Care Med. 1994;150(2):448-454. https://doi.org/10.1164/ajrccm.150.2.8049828

4. Birrer P, McElvaney NG, Rüdeberg A, Sommer CW, Liechti-Gallati S, Kraemer R, et al. Protease-antiprotease imbalance in the lungs of children with cystic fibrosis. Am J Respir Crit Care Med. 1994;150(1):207-213. https://doi.org/10.1164/ajrccm.150.1.7912987

5. Flume PA, Yankaskas JR, Ebeling M, Hulsey T, Clark LL. Massive hemoptysis in cystic fibrosis. Chest. 2005;128(2):729-738. https://doi.org/10.1378/chest.128.2.729

6. Flume PA, Mogayzel PJ, Robinson KA, Rosenblatt RL, Quittell L, Marshall BC, et al. Cystic fibrosis pulmonary guidelines: pulmonary complications: hemoptysis and pneumothorax. Am J Respir Crit Care Med. 2010;182(3):298-306. https://doi.org/10.1164/rccm.201002-0157OC

7. Hurt K, Simmonds NJ. Cystic fibrosis: management of haemoptysis. Paediatr Respir Rev. 2012;13(4):200-205. https://doi.org/10.1016/j.prrv.2012.01.003

8. Stern RC, Wood RE, Boat TF, Matthews LW, Tucker AS, Doershuk CF. Treatment and prognosis of massive hemoptysis in cystic fibrosis. Am Rev Respir Dis. 1978;117(5):825-828.

9. Smyth AR, Bell SC, Bojcin S, Bryon M, Duff A, Flume P, et al. European Cystic Fibrosis Society Standards of Care: Best Practice guidelines. J Cyst Fibros. 2014;13 Suppl 1:S23-S42. https://doi.org/10.1016/j.jcf.2014.03.010

10. Hemoptysis in Israeli CF patients--prevalence, treatment, and clinical characteristics. J Cyst Fibros. 2008;7(4):301-306. https://doi.org/10.1016/j.jcf.2007.11.007

11. Antonelli M, Midulla F, Tancredi G, Salvatori FM, Bonci E, Cimino G, et al. Bronchial artery embolization for the management of nonmassive hemoptysis in cystic fibrosis. Chest. 2002;121(3):796-801. https://doi.org/10.1378/chest.121.3.796

12. Cohen AM, Doershuk CF, Stern RC. Bronchial artery embolization to control hemoptysis in cystic fibrosis. Radiology. 1990;175(2):401-405. https://doi.org/10.1148/radiology.175.2.2326467

13. Andersen PE. Imaging and interventional radiological treatment of hemoptysis. Acta Radiol. 2006;47(8):780-792. https://doi.org/10.1080/02841850600827577

14. Monroe EJ, Pierce DB, Ingraham CR, Johnson GE, Shivaram GM, Valji K. An Interventionalist's Guide to Hemoptysis in Cystic Fibrosis. Radiographics. 2018;38(2):624-641. https://doi.org/10.1148/rg.2018170122

15. Rémy J, Voisin C, Dupuis C, Beguery P, Tonnel AB, Denies JL, et al. Treatment of hemoptysis by embolization of the systemic circulation [Article in French]. Ann Radiol (Paris). 1974;17(1):5-16.

16. Panda A, Bhalla AS, Goyal A. Bronchial artery embolization in hemoptysis: a systematic review. Diagn Interv Radiol. 2017;23(4):307-317. https://doi.org/10.5152/dir.2017.16454

17. Martin LN, Higgins L, Mohabir P, Sze DY, Hofmann LV. Bronchial Artery Embolization for Hemoptysis in Cystic Fibrosis Patients: A 17-Year Review. J Vasc Interv Radiol. 2020;31(2):331-335. https://doi.org/10.1016/j.jvir.2019.08.028

18. Fellows KE, Khaw KT, Schuster S, Shwachman H. Bronchial artery embolization in cystic fibrosis; technique and long-term results. J Pediatr. 1979;95(6):959-963. https://doi.org/10.1016/S0022-3476(79)80283-8

19. Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: a consensus statement. Cystic Fibrosis Foundation Consensus Panel. J Pediatr. 1998;132(4):589-595. https://doi.org/10.1016/S0022-3476(98)70344-0

20. Pereira CA, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. J Bras Pneumol. 2007;33(4):397-406. https://doi.org/10.1590/S1806-37132007000400008

21. Barben J, Robertson D, Olinsky A, Ditchfield M. Bronchial artery embolization for hemoptysis in young patients with cystic fibrosis. Radiology. 2002;224(1):124-130. https://doi.org/10.1148/radiol.2241010654

22. van den Heuvel MM, Els Z, Koegelenberg CF, Naidu KM, Bolliger CT, Diacon AH. Risk factors for recurrence of haemoptysis following bronchial artery embolisation for life-threatening haemoptysis. Int J Tuberc Lung Dis. 2007;11(8):909-914.

23. Bronchial arteriography and embolotherapy for hemoptysis in patients with cystic fibrosis. Cardiovasc Intervent Radiol. 1991;14(4):241-246. https://doi.org/10.1007/BF02578470

24. Flight WG, Barry PJ, Bright-Thomas RJ, Butterfield S, Ashleigh R, Jones AM. Outcomes Following Bronchial Artery Embolisation for Haemoptysis in Cystic Fibrosis. Cardiovasc Intervent Radiol. 2017;40(8):1164-1168. https://doi.org/10.1007/s00270-017-1626-0

25. Vidal V, Therasse E, Berthiaume Y, Bommart S, Giroux MF, Oliva VL, et al. Bronchial artery embolization in adults with cystic fibrosis: impact on the clinical course and survival. J Vasc Interv Radiol. 2006;17(6):953-958. https://doi.org/10.1097/01.RVI.0000222822.82659.50

26. Barben JU, Ditchfield M, Carlin JB, Robertson CF, Robinson PJ, Olinsky A. Major haemoptysis in children with cystic fibrosis: a 20-year retrospective study. J Cyst Fibros. 2003;2(3):105-111. https://doi.org/10.1016/S1569-1993(03)00066-3

27. Pathak V, Stavas JM, Ford HJ, Austin CA, Aris RM. Long-term outcomes of the bronchial artery embolization are diagnosis dependent. Lung India. 2016;33(1):3-8. https://doi.org/10.4103/0970-2113.173059

28. Spoonhower KA, Davis PB. Epidemiology of Cystic Fibrosis. Clin Chest Med. 2016;37(1):1-8. https://doi.org/10.1016/j.ccm.2015.10.002

29. Håkanson E, Konstantinov IE, Fransson SG, Svedjeholm R. Management of life-threatening haemoptysis. Br J Anaesth. 2002;88(2):291-295. https://doi.org/10.1093/bja/88.2.291

30. Ivanick MJ, Thorwarth W, Donohue J, Mandell V, Delany D, Jaques PF. Infarction of the left main-stem bronchus: a complication of bronchial artery embolization. AJR Am J Roentgenol. 1983;141(3):535-537. https://doi.org/10.2214/ajr.141.3.535