4.7 Hemoptysis in Cystic Fibrosis

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1. INTRODUCTION

- The blood supply to the lungs is provided by the bronchial arteries, which, in contrast to the low-pressure system of the pulmonary circulation, have systemic blood pressure levels.
- Chronic inflammation and infection of the CF lung result in **hypertrophy of bronchial arteries and neovascularization derived from bronchial and non-bronchial arteries**. These mechanisms predispose these arteries to leakage and rupture resulting in hemoptysis.
- Hemoptysis is characterized as
  - mild (<100ml and no life-threatening respiratory or hemodynamic instability)
  - moderate (100-240ml and no life-threatening respiratory or hemodynamic instability) or
  - massive (>240ml and/or life-threatening respiratory or hemodynamic instability or recurrent bleeding of >100ml over several days).
- The quantification in ml is arbitrary and probably not very useful in clinical practice, better alternatives, however, are lacking. Massive hemoptysis is generally used to describe the expectoration of a large amount of blood and/or a rapid rate of bleeding but the precise threshold that constitutes massive hemoptysis is controversial. Respiratory instability, abnormal gas exchange and hemodynamic instability should also be part of the definition of massive hemoptysis.
- Hemoptysis is a common complication in CF:
  - the annual incidence is estimated to 0.87%
  - up to 10% of CF patients have one episode of hemoptysis during lifetime
  - almost 5% have a massive bleeding
- Hemoptysis in CF patients is associated with high morbidity (i.e. need for hospitalization, accelerated loss of lung function) and mortality (5.8 – 16.1%).

2. RISK FACTORS FOR HEMOPTYSIS (TABLE 1)

- **Increasing age:** The first episode of hemoptysis occurs at 24.2 ± 8.7 years. Hemoptysis in pediatric patients is rare. Female and male patients are equally affected.
- **Declining lung function**: 60% of patients with hemoptysis have a FEV_1 < 40%. However, it should be kept in mind that 20% of patients have normal or mildly impaired lung function at first occurrence of hemoptysis.
- **Chronic pulmonary infections**:
  - Chronic pulmonary infection with *Staphylococcus aureus* has been identified as a risk factor for massive hemoptysis (Odds ratio 1.3) probably due to a special virulence factor ("Panton-Valentine Leukocidin").

- Whether chronic pulmonary infection with *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex confers an additional risk, or, in contrast, might be "protective" for massive hemoptysis is controversial.

- **Acute pulmonary infections** are the most common trigger for the development of scant hemoptysis.
- **Additional risk factors** include coagulopathies, vitamin K deficiency and the presence of CF-related diabetes mellitus (Odds ratio 1.1).

Table 1: Risk factors for massive hemoptysis

Increasing age
Severe disease, low FEV1 (<40%)
Staphylococcus aureus
Coagulopathies (including vitamin K deficiency)
Diabetes mellitus

3. PATIENT ASSESSMENT AND MANAGEMENT

- **Management** will depend on the quantity/frequency of hemoptysis and on whether the patient develops airway compromise or hemodynamic instability. **Figure 1** proposes an algorithm for the management of hemoptysis in CF.
- Localization of the bleeding source:
  - **CT angiography** may localize the bleeding source, may identify enlarged bronchial arteries or a new consolidation (indicating bleeding and/or an associated infection). Whenever possible, CT angiography should be performed before further intervention but should not delay embolization in life-threatening hemoptysis.
  - **Bronchoscopy** is not considered to be helpful and is rarely indicated in the context of CF-associated hemoptysis because localization of the bleeding is difficult and delays further management.

3.1 *Management of massive hemoptysis associated with airway compromise/ hemodynamic instability (Figure 1)*

- Protection of the airway and hemodynamic stabilization
  - Position the patient in anti-Trendelenburg (to prevent formation of thrombi in main airways and trachea) and, if the side of the bleeding is known → bleeding side down (to prevent blood aspiration in the non-bleeding lung).
  - Administer oxygen, hemodynamic and $SatO_2$ surveillance, IV access → fluid resuscitation
  - When emergency intubation is performed,
    - bronchoscopy may help intubation and permeabilisation of the airway, selective intubation of the non-bleeding lung or occlusive baloon placement in the bleeding lung but, as mentioned before, in CF hemoptysis, bronchoscopy is rarely helpful for the localisation of the bleeding source.

  - Endobronchial hemostatic treatments applied bronchoscopically **(Table 2)** may be considered in selected cases, but their efficacy is not established and **they shouldn't delay management with bronchial arterial embolization (BAE)**.
  - For more information on the risks of intubation in CF **see Chapter *"ICU care and invasive ventilation".***

- Blood cross-match, CBC, coagulation check, liver function tests, renal function. Arterial blood gas and controled oxygen administration ($SatO_2$>92%).
- **Proceed to bronchial arterial embolization to control the bleeding.**
- After protection of the airway and hemodynamic stabilisation follow recommendations of paragraph 3.2.

3.2 *Management of moderate or massive hemoptysis without airway compromise/hemodynamic instability (Figure 1)*

- Patients with moderate and massive hemoptysis should be hospitalized (monitoring in a high dependency unit or in the ICU). **See also Chapter *"ICU care and invasive ventilation".***
- Hemodynamic and $SatO_2$ surveillance, IV access, blood cross-match, complete blood count, coagulation check, liver function tests, renal function. Arterial blood gas and controled oxygen administration if necessary ($SatO_2$>92%). Monitor frequency/quantity of hemoptysis, sputum culture. CT angiography.
- Patients with massive hemoptysis should be advised to
  - **discontinue aggressive airway clearance techniques** and
  - **stop inhalation therapy with hypertonic saline and dornase alpha**

  Note: Whether this recommendation holds true also for patients with moderate hemoptysis is controversial. The duration of the discontinuation should be individualized depending on the quantity and recurrence of hemoptysis.
- **Evaluate withholding drugs associated with a bleeding risk,** such as nonsteroidal anti-inflammatory drugs (NSAIDs), antiplatelets, anticoagulants and selective serotonin reuptake inhibitors (SSRIs).
- **Antibiotic treatment should be introduced** based on recently obtained sputum cultures.
- **Vitamin K substitution is recommended**
  - Start empirical treatment with vitamin K (for example Konakion® 10mg IV once daily, at least until hospital discharge).
  - Vitamin K deficiency may be present due to malabsorption or liver disease. Prolonged prothrombin time is usually measured but it is a relatively late marker of vitamin K deficiency.
- **Hemostatic treatment regimens** that may be considered are presented in **Table 2.** Data on these regimens are limited and available information is based on retrospective clinical studies, case reports and institutional guidelines.

3.3 *Minor hemoptysis and minor recurrent hemoptysis*

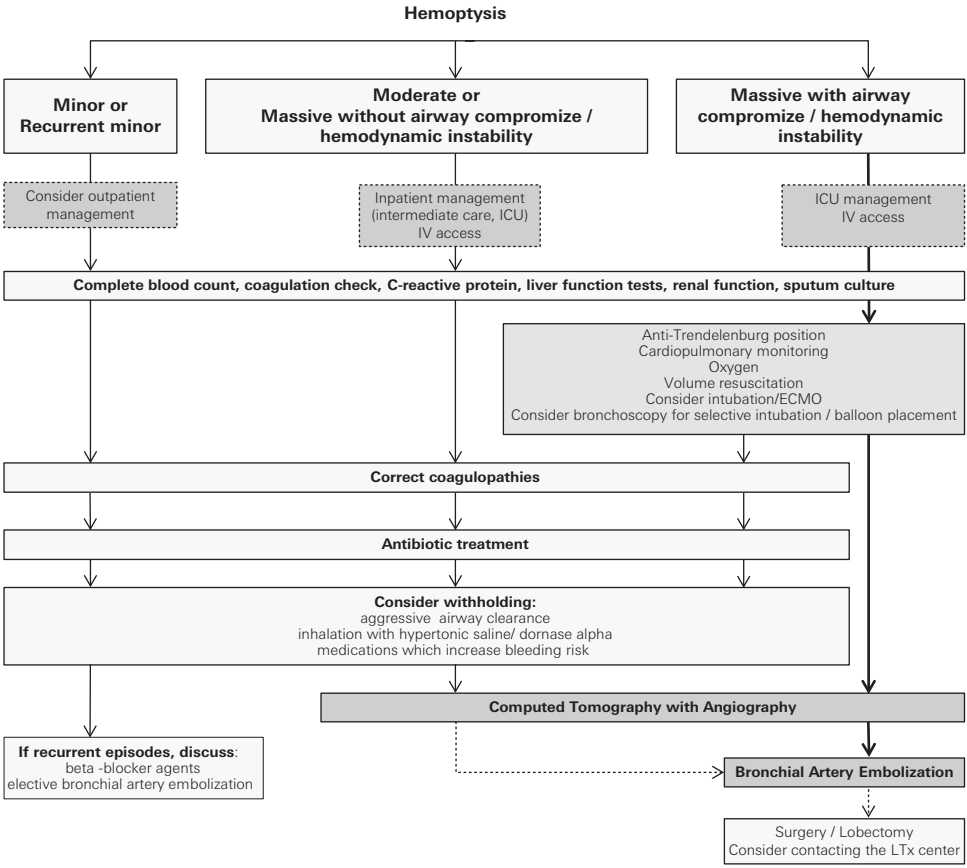
- Minor hemoptysis is a common finding in CF patients and frequently indicates ongoing infection.

- Patients with minor hemoptysis can be considered for outpatient management
  - Patients with a first episode of minor hemoptysis should be evaluated for infection and bleeding predisposition with CBC, coagulation check, C-reactive protein, liver function tests, renal function, sputum culture, CT angiography.
  - CT angiography might be omitted in patients with recurrent episodes of minor hemoptysis if an imaging study has been performed recently.
- Antibiotic treatment should be introduced in all patients according to the last available antibiogram.
- Spirometry, aggressive airway clearance techniques and drugs associated with increased bleeding risk should be withheld. Whether inhalation therapy with hypertonic saline and dornase alpha should be stopped is controversial but suggested by some experts.
- In a small pilot study, empirical administration of a beta-blocker (specifically atenolol) in CF patients with recurrent hemoptysis refractory to conservative treatment was found to be safe and to have a positive effect, decreasing the volume and the frequency of hemoptysis reported by the patients. Although promising, these results await confirmation in a larger study.
- In a patient with minor recurrent hemoptysis not responding to conservative treatment and/or negatively affecting the quality of life, bronchial artery embolization should be discussed.

3.4 Bronchial arterial embolization (BAE)

- **Indications**
  - There are no specific guidelines for BAE in CF patients. Accepted and recommended indications result from the efficacy of the BAE in controlling bleeding and potential risks of the BAE procedure in the general population.
  - **There is a consensus that patients with massive hemoptysis who are clinically unstable should be treated by BAE.**
  - **BAE should be discussed for:**
    - **patients with massive hemoptysis but who were deemed clinically stable**
    - **patients with recurrent severe episodes of hemoptysis**
    - **patients with bronchial arterial aneurysms**
  - Prophylactic BAE in CF patients with hypertrophic bronchial arteries is still a controversial indication.
  - BAE should be performed in a tertiary care center by an experienced interventional radiologist and using dedicated facilities.
- **Strategies for embolization**
  - Pre-BAE evaluation may include CT angiography, especially in patients with recurrent hemoptysis. Patients with massive hemoptysis should not undergo bronchoscopy before BAE.
  - No consensus exists on which arteries should be embolized. As CF lung disease is diffuse with a high risk of recurrence, it is usually advocated to treat all abnormal bronchial arteries from both sides provided that there is no identified specific risk related to a specific branch (e.g. spinal artery arising from a bronchial artery). However, at least the culprit artery should be treated if a partial BAE is decided.
  - Systematic embolization of systemic non-bronchial arteries (SNB) should be considered only in case of recurrence or uncontrolled bleeding.

Figure 1: Hemoptysis management algorithm (adapted from[1])



- Different materials can be used for BAE and SNB embolization **(Table S1 in the supplement)**. Particles are the most common material for BAE. Usually the recommended sizes are 500 to 700 microns. However, CF patients have frequently broncho-pulmonary shunts that require the use of larger particles (e.g. 1300 microns) or coils. Resorbable materials are used as adjuvant agents for temporary occlusion of non targeted SNB branches.

- **Contraindications:** No absolute contraindication
- **Surveillance after BAE**
  - Vital signs and saturation
  - Pain control
  - Surveillance of the catheter insertion point for signs of infection, development of aneurysms or fistulas.

Table 2: Hemostatic regimens[2-9]

Drug	Swiss tradename	Administration route	Dosage	Comment
Adrenaline (syn. epinephrine)	Adrenaline® *amp 1mg / 1mL (= 1:1000 =0.1%)*	Nebulized	1 mg (1 mL) + 5 mL NaCl 0,9 % nebulized over 20 min - If no recurrence after the 1st dose: administer a dose every 4h for 12 h (i.e. 3 doses) -If recurrence before 4 h: administer an additional dose	Vasopressor Very limited evidence Store adrenaline between 15-25°C and protect from light Prepare solution for nebulization at the moment of use
Tranxenamic acid	Cyklokapron® *tab 500mg, efferv tab 1g*	Oral	0.5 – 1 g up to 4x/day (usually 1 g 3x/day) Dose adjustment in renal failure: -Creat 120-250 µmol/L: 15 mg/kg every 12h -Creat 250-500 µmol/L: 15 mg/kg every 24h -Creat >500 µmol/L: 7.5 mg/kg every 24h	Antifibrinolytic agent *Main adverse reactions*:* hypotension, allergic reactions, thromboembolic complications, headache, nausea, vomiting, diarrhea, visual disturbances.
	Tranexam® *amp 500 mg / 5mL* *amp 1g / 10mL*	IV	0.5-1 g every 8h or 12h (up to 3x/day) Slow administration: 1 g over 15-20min (max 100 mg/min) Dose adjustment in renal failure: -Creat 120-250 µmol/L: 10 mg/kg every 12h -Creat 250-500 µmol/L: 10 mg/kg every 24h -Creat >500 µmol/L : 5 mg/kg every 24h	Increased risk of hypotension if administered too quickly Do not administer IM Do not mix with other drugs (e.g. penicillin)
	amp 500 mg / 5 ml	Nebulized (off label route)	250-500 mg (corresponding to 2.5-5 ml) every 8h or 12h (up to 3x/day) Jet nebulizer, duration of administration about 15 min	Limited case report evidence in non-CF moderate hemoptysis May cause bronchospasm

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Terlipressin acetate	Glypressine® Haemopressin® *vial 1 mg + solvent vial 5 mL*	IV	Weight < 50 kg: 1 mg every 4h or 6h Weight > 50 kg: 1-2 mg every 4h or 6h Slow IV administration Max treatment duration: 5 days	Vasopressor. **Patient monitoring!** Incompatible with dextrose solutions *Contraindications:* septic shock, angina, uncontrolled hypertension, severe arteriopathy, arrhythmias, pregnancy *Main adverse reactions*:* angina, hypertension, bradycardia, hyponatremia Of note, in the clinical setting of CF-related hemoptysis, previous administration of terlipressin is not expected to render subsequent BAE more technically challenging.
Atenolol	Atenolol® , Tenormin® *tab 25, 50 or 100 mg*	Oral	Initiate at 12.5 mg/day, then titrate	Beta-blocker. Based on a retrospective study on 12 CF patients: decreased the frequency and amount of hemoptysis, generally well tolerated. *Main adverse reactions**: bradycardia, hypotension, syncope, dizziness, bronchospasm.

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Recombinant human activated factor VII (rFVIIa)	Novoseven® *vial 1, 2, 5 or 8 mg + solvent syringe*	IV	90 µgr/kg (80-120 µgr/kg) may be repeated 4-6h later if ongoing bleeding Slow administration over 2-5min	Based on 4 patients. As a salvage therapy when significant hemoptysis despite BAE. *Main adverse reactions**: thromboembolic complications, fever, skin eruption

BAE=bronchial arterial embolization

* for more details see product information (**www.swissmedicinfo.ch**)

Note: When emergency bronchoscopy is performed, endobronchial tamponade or bronchoscopic installation of cold (4°C) NaCl 0.9%, adrenaline, terlipressine or tranexamic acid may be considered in selected cases (for more information see Ref 8). However their efficacy is not established and they shouldn't delay management with BAE.

- **Complications**
  - Potential complications of BAE are presented in **Table 3**.
  - A serious but rare complication is the paradoxical embolization (occlusion) of the anterior spinal artery. To prevent non targeted embolization, which may lead to this complication, it is recommended to assess on the angiogram the presence of spinal and esophageal branches before embolization, to check for this regularly during the procedure and to use a microcatheter when the bronchial artery arises from an intercostal trunk. The microcatheter should be placed distal to the intercostal branch.
- **BAE outcome**
  - Using modern approaches, immediate control of bleeding is obtained in 90 to 100% of CF patients.
  - The 30-day bleeding control is more than 85%.
  - However a high recurrence of bleeding was reported in CF patients (up to 50%). Two peaks of recurrence were reported: 1 to 6 months (possibly related to incomplete embolization) and 1 to 2 years (probably related to secondary recanalisation of vessels or development of new collaterals). Some CF patients require multiple procedures.

Table 3: Potential complications of bronchial artery embolization

Chest pain (24-91%): usually self-limiting, responds well to analgesics
Dysphagia (1-18%): usually self-limiting
Very rare: – Inadvertent embolization of the anterior medullary artery → spinal cord ischemia → paralysis (0.1%) – Transient cortical blindness, stroke – Pulmonary infarction, bronchial stenosis or necrosis – Ischemic colitis
Associated to the endovascular catheter insertion
Associated with the use of contrast agent

3.5 Surgical lobectomy

- Surgical lobectomy is the final option in patients with refractory bleeding. It is rarely needed.

3.6 Lung transplantation

- Due to high associated morbidity and mortality, repetitive moderate or massive hemoptysis despite multiple embolizations is an indication for referral and evaluation for lung transplantation (LTx) regardless of pulmonary function tests **(see also Chapter "*Transplantation*").**

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S4.7 Hemoptysis

Table S1: Examples of materials used for bronchial artery embolization

Material	Characteristics	Comment
PVA particles	Different sizes, non-absorbable	
Gelatin sponge	Absorbable	Recanalization and recurrent bleeding
Gelatin cross-linked particles (tris-acryl microspheres)	More uniform in diameter than PVA particles, hydrophilic coating prevents clumping of the microcatheters	The preferred materials
Glue (N-BCA)	Rapid polymerization in the blood	Difficult to use, instant occlusion
Coils and plugs	Metallic devices with different predefined 2D or 3D shapes	When embolization of large feeding arteries or large shunts is required. They preclude further embolization of the treated vessel if bleeding recurs.
Ethylene-vinyl Alcohol Copolymer	Liquid non-adhesive agent	Potential agent to be used in a case of broncho-pulmonary shunts. A learning curve needed.