Bronchopulmonary complications therapy

Hemoptysis in cystic fibrosis

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Background

Hemoptysis occurs as a complication of lung disease in CF and is believed to result from erosion of abnormal bronchial vessels (Mingora CM, Flume PA, 2021). Haemoptysis occurs in up to 25 % of young people with CF (Sheppard m et al, 2022). An increased risk of hemoptysis in pwCF has been associated to several factors including older age, advanced lung disease (forced expiratory volume in 1s (FEV1) <70% predicted), airway colonisation by Pseudomonas aeruginosa, CF-related diabetes, portal hypertension, and liver cirrhosis. Recently (Pavaut G et al, 2020) an observational retrospective study including 85 adult patients with CF identified ABPA and diabetes as factors for the development of massive haemoptysis in CF patients who have previously experienced an episode of mild-to-moderate haemoptysis.

Hemoptysis s defined as minor or major based on the amount of bleeding that generally occurs in more severely damaged lung regions. Hemoptysis can be an acute medical emergency. Region of erosion can be localized angiographically and controlled by therapeutic intervention. Recently (Bozkanat KM et al, 2021) four cases (age range: 25–34?years) of catamenial haemoptysis have been described representing thoracic endometriosis related to hormonal variations in airway inflammation or infection resulting in bronchial artery bleeding.

A classification of severity of haemoptysis is generally accepted as massive (>240 ml/24h or >100 ml/day for ?2 days), moderate-severe (>20 ml/24h) or mild (<20 ml/24h). Minor hemoptysis - that is, blood streaking in sputum - is relatively common and has been reported in up to 60% of adolescents and adults with CF. It usually requires no specific therapy other than treatment of a CF pulmonary exacerbation, correction of contributing factors such as coagulation abnormalities (for example vitamin K deficiency) and breaking the chronic use of medications which can promote hemorrhage.

Major hemoptysis is defined as the expectoration of gross blood, usually more than 240ml in 24h, or recurrent bleeding of less volume (>100 mL/day) for a few days or weeks. Major hemoptysis is a life–threatening condition (because of asphyxiation or hypotension) requiring aggressive therapies to control the bleeding. It occurs in approximately 1% of all patients with CF and is rarely seen in children younger than 10 years. Observational studies show that major hemoptysis is more common as the patient aged and in patients with Staphylococcus aureus infection.

Cystic Fibrosis Pulmonary Guidelines for Pulmonary Complications (Flume PA et al, 2010) have been published in the past to help clinicians in clinical practice.

Concerning medical therapy of hemoptysis, anedoctal cases (Hurley M et al, 2011) reported the successful use at low doses of tranexamic acid (TXA), a synthetic derivative of the amino acid lysine, for controlling recurrent severe hemoptysis episodes in people with CF. TXA is a well-known antifibrinolytic drug with established efficacy in prohibiting connections between fibrin and plasmin, which is activated by t-PA release from endothelial cells derived from ruptured bronchial arteries. TXA has been used in patients with haemoptysis to reduce the amount of expectorated blood, by decreasing the fibrinolytic activity and thereby improving the clinical outcomes. Tranexamic acid may reduce both the duration and volume of bleeding, with low risk for short-term thromboembolic complications (Moen CA et al, 2013).

BAE has become an increasingly used therapeutic option for major hemoptysis, although conservative therapy has been demonstrated to be as effective. Multiple complications from embolization have been reported, including transverse myelitis, bronchoesophageal fistulas, systemic emboli, recurrent hemorrhage, bronchial necrosis, and paralysis.

Use of pro?coagulants, hormone contraceptives, anti?inflammatories, bronchial artery embolization, and recently the use of modulators have been discussed as management strategies.

Issues

1. What is the best diagnostic tool to identify earlier the site of bleeding.
2. What are both benefits and side effects or disadvantages for medical and surgical treatment of hemoptysis in pwCF.
3. Whether BAE is effective and safe.

What is known

A systematic literature search (Karlafti E et al, 2023) was conducted in PubMed and Scopus from January 2017 until May 2023 for studies reporting massive hemoptysis in non-CF people. All studies that included technical and clinical success rates of hemoptysis management, as well as rebleeding and mortality rates, were included. A proportional meta-analysis was conducted using a random-effects model. Of the 30 studies included in this systematic review, 26 used bronchial artery embolization as a means of treating

hemoptysis, with very high levels of both technical and clinical success (greater than 73.7% and 84.2%, respectively). Alternative methods such as dual-vessel intervention (80% technical success rate and 66.7% clinical success rate), customized endobronchial silicone blockers (92.3% technical success rate and 92.3% clinical success rate), antifibrinolytic agents (50% clinical success rate), and percutaneous transthoracic embolization (93.1% technical success rate and 88.9% clinical success rate) had high success rates apart from antifibrinolytic agents. Of the 2467 patients included in these studies, 341 experienced rebleeding during the follow-up period, while 354 other complications occurred, including chest discomfort, fever, dysphagia, and paresis. A total of 89 patients died after an episode of massive hemoptysis or during the follow-up period. The results of the meta-analysis showed a pooled technical success of bronchial artery embolization equal to 97.22% and a pooled clinical success equal to 92.46%. The pooled recurrence was calculated to be 21.46%, while the mortality was 3.5%. These results confirm the ability of bronchial artery embolization in the treatment of massive hemoptysis but also emphasize the high rate of recurrence following the intervention, as well as the risk of death.

Regarding the issue 1:

a recent study (Dohna M et al, 2024) determined whether morphological lung changes differ between pwCF who have massive hemoptysis (MH) and pwCF without MH. Chest computed tomography (CT) scans of pwCF and MH acquired at a maximum of 4 months prior to MH were evaluated for morphological changes and bronchial artery (BA) diameters. Lung lobes with MH were compared with lobes without MH and with matched control patients with end-stage CF and no hemoptysis using the Helbich scoring system. 26 patients with MH (P_{MH}; 15 female, median age 29 years, interquartile range [IQR]: 25-33.75) and 17 matched control patients (11 male, median age 24 years, IQR: 19.5-30) were included. No difference in Helbich score was detected between lobes with MH and matched control patients ($p = 0.051$). Higher scores were detected in lobes with MH compared to lobes without MH in P_{MH} ($p = 0.021$), but no difference was detected in the subscores. The BA diameters were larger in P_{MH} ($p = 0.02$); 85% of P_{MH} had unilateral MH, with 65% of MH involving only one or two lobes. Theseresults show that morphological changes are more severe in lobes with MH in the same patient, but there is no difference when compared with matched control patients. Other factors such as BA hypertrophy might play a pivotal role in the pathogenesis of MH in pwCF such as alternative scores to evaluate chest CT could be suitable for assessing the risk for MH.

Regarding the issue 2 and 3:

1 CDSR (Prutsky G et al, 2016) is available to evaluate the effectiveness and safety of antifibrinolytic agents in reducing the volume and duration of haemoptysis in adult and paediatric patients with different etiologies including CF. TXA did not affect remission of haemoptysis evaluated at seven days after the start of treatment. No significant difference in the incidence of mild side effects was registered between active and placebo groups (OR 3.13, 95% CI 0.80; 12.24). There is insufficient evidence to judge whether antifibrinolytics should be used to treat haemoptysis from any cause, though limited evidence suggests they may reduce the duration of bleeding.

A japanese observational study (Kinoshita T et al, 2019), including almost 30000 subjects with hemoptysis for different etiologies covering also CF, showed that TXA may reduce in-hospital mortality among patients with haemoptysis requiring emergency admission compared with patients did not.

A study (Al-Samkari H et al 2019) was performed to examine the use of antifibrinolytic agents in managing adult in-patients and outpatients with CF and hemoptsysis, and rates of admission for bleeding prior to and following implementation of these drugs. Effectiveness of the pathway was evaluated via comparison of annualized hemoptysis admission rates prior to and following pathway enrollment over 54 months period. Main results including 72 distinct episodes of hemoptysis treated with antifibrinolytic agents as tranexamic acid or epsilon aminocaproic acid in a total of 21 adult patients with CF showed that systemic antifibrinolytic therapy was associated with a reduction in hospital admissions. No serious adverse events were observed.

A series of four anedoctal cases are consistent with other studies that propose inhaled TXA as an alternative for hemoptysis treatment, reducing bleeding (Segrelles Calvo G et al, 2016).

A 3-year retrospective audit of inhaled TA in pwCF with haemoptysis was performed (Merchant A et al, 2025). Baseline demographics, hospitalisation status, haemoptysis volume, adverse events, adjuvant therapies and time to resolution of haemoptysis were evaluated. Twenty-six adults [female, 12; age (yrs), 27.2 ± 3.1 95 % CI] with haemoptysis were treated on nebulised TXA, in addition to standard therapy. Nebulised TA was generally well tolerated. In 65.4 % of cases, haemoptysis resolved within 48 h with TXA use. A home haemoptysis management plan, with guidance for outpatient TA use was provided to 19 adults. Nebulised TXA is a well-tolerated, non-invasive and inexpensive pharmacological option for in- and outpatient management of haemoptysis in CF supporting its use to minimise further bleeding in CF outpatients. A personalised home haemoptysis management plan should be provided prior to use.

An observational study (Flight WG et al, 2017) showed that among twenty-seven patients undergoing to 51 BAE procedures over a median follow-up period of 26 months BAE was effective in controlling haemoptysis, but this procedure is associated with considerable morbidity and high recurrence rates.

A case of temporary unilateral diaphragmatic paralysis associated to lung consolidation following BAE has been registered in a pediatric CF female patient. This complication worsened the lung function of the patient who underwent lung transplantation after 9?months (Terlizzi V et al, 2020) .

Recently (Gavioli EM et al, 2021) a retrospective observational study including 38 adult patients with CF was performed in order to evaluate the use of vitamin K therapy at a average daily dose of 10 mg in the setting od hemoptysis during an acute pulmonary exacerbation. The median lenght of stay, the median time until next hospital admision and the 30-day readmission rates were evaluated. Results on the potential role of vitamin K in the setting of hemoptysis were inconclusive.

Based on a retrospective review at an Australian tertiary paediatric centre (The Children's Hospital Westmead, Sydney, New South Wales) 67 episodes of haemoptysis were revised in patents with CF between 2010 and 2020. Sixty episodes met inclusion criteria, including 31 patients. Using the US CF Foundation guidelines, episodes were classified as scant (53.3 %), moderate (38.3 %) or massive (8.3 %). Fifty-two percent of patients were female, mean age at presentation was 15.4 years (SD+/- 2.4) and 58 % were homozygous for the Fdel508 genotype. Twelve episodes (9 patients) required BAE. BAE was used in all cases of massive haemoptysis 5/5 (100 %), 6/23 (22 %) episodes of moderate and 1/32 (3 %) episode of scant haemoptysis as an elective procedure for recurrent

haemoptysis. An algorithm was proposed to guide the management of haemoptysis in CF (Sheppard m et al, 2022).

A retrospective study described experience of an Italian CF Centre for treatment of sub-massive hemoptysis with BAE to understand if early treatment of sub-massive hemoptysis can reduce the volume of any subsequent bleedings. Thirteen patients were included from March 2016 to December 2021 for assessing at least one BAE with microspheres or coils after sub-massive hemoptysis, for a total of 19 procedures. Technical success was 94.7% (Floridi C et al, 2022).

Unresolved questions

Clinical studies are needed to determine whether TXA should be routinely used as an adjunctive therapy of hemoptysis in CF, or whether it should be reserved for patients who have failed conventional therapies. No conclusive data are available concerning the benefits or the disadvantages of both medical and surgical treatments.

There is still no consensus on the agents which should be used for preventing recurrence of hemoptysis in people with CF.

No trials have been detected in order to define the role of BAE in CF.

Keywords

Hemoptysis;