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Original Article

# Risk of hemoptysis in cystic fibrosis clinical trials: A retrospective cohort study

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**Abstract**

*Background:* Cystic fibrosis (CF) is characterized by airway infection and inflammation resulting in respiratory complications including hemoptysis. The objectives of this study were to characterize the risk of hemoptysis attributable to underlying disease and in the presence of standard of care therapy.
*Methods:* This retrospective cohort study estimated hemoptysis rates overall and by relevant risk factors utilizing adverse event data from longitudinal prospective CF clinical trials.
*Results:* Of the 1008 participants, 73% were ≤18 years old; of 929 with available spirometry, 27% had an $FEV_1$ < 70% predicted. During the average 8.2 months of follow-up, 8% experienced ≥1 hemoptysis events (95% CI: 6%, 10%). Of the 125 events, 76% were mild in severity and only 9% were serious. Hemoptysis rates were greater among adults than children, those with $FEV_1$ < 70% predicted, and participants infected with *P. aeruginosa* but not with *S. aureus*.
*Conclusions:* Hemoptysis is a common adverse event among CF clinical trial participants, and particularly in adults with more severe lung disease. These results can be used to predict event occurrence in future clinical trials.


*Keywords:* Cystic fibrosis; Clinical trial; Hemoptysis

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## 1. Introduction

Cystic fibrosis (CF) is a genetic condition associated with the deterioration of lung function due to the impaired clearance of airway mucus, resulting in chronic infection and inflammation [1]. The natural history of the lung disease is marked by an exaggerated inflammatory response [2,3] causing injury to the airways and progressive airway obstruction. There are acute complications attributable to airway infection and inflammation, including hemoptysis, which can range from a minor streaking of blood in the sputum to massive bleeding that can be life-threatening [4]. The pathogenesis of hemoptysis is multi-factorial [5], although there are risk factors shown to be associated with massive hemoptysis, such as older age, more severe pulmonary impairment, and the presence of *Staphylococcus aureus* in sputum cultures [6].

There are published guidelines on the management of hemoptysis in individuals with CF [4]. In the setting of massive hemoptysis, it is recommended withholding inhaled medications under the assumption that they could aggravate hemoptysis. It is understandable how one might attribute hemoptysis events to an inhaled medication if the event occurred temporally to its use. However, tobramycin and dornase alfa are aerosolized medications currently administered as a part of standard of care and neither of which has been identified as risk factors for hemoptysis; rather they have been associated with a lower incidence of massive hemoptysis [6]. Although hemoptysis is thought to be a common event, there are few published studies reporting rates of hemoptysis in the CF population. The CF Patient Registry has long tracked the occurrence of massive hemoptysis with an annual incidence of approximately 4% [6] but it has not tracked all hemoptysis events. In a retrospective study of 440 Israeli individuals with CF, there was an overall 9.1% incidence of hemoptysis events recorded in the medical charts during a 5-year observation period; 25% of these participants were younger than 13 years of age [7]. A few clinical trials have reported the prevalence of hemoptysis in the placebo-treated participants (tobramycin inhaled solution TIS: 31% over 6 months [8], dornase alfa: 21% over 6 months [9], and ivacaftor: 22% over 12 months [10]). Another analysis of the placebo-treated participants in clinical trials reported that hemoptysis events were rare in both children and adults in short-term trials (0–1 weeks) but not uncommon in long term trials (1–6 months), with adults nearly four times more likely to experience hemoptysis than children [11]. However, none of these analyses have assessed risk factors, other than age, that could further elucidate the expected rate of hemoptysis in the CF population. While it is realistic to anticipate that the rates increase in older patients with more advanced lung disease, being able to estimate expected occurrence of hemoptysis based on risk factors is of great value for assessing risk in future drug development.

Because hemoptysis is an expected adverse event in CF clinical trials, understanding the anticipated rates of hemoptysis due to underlying disease and in the presence of standard of care is important for assessing the safety of new therapies in CF clinical trials, particularly for the pediatric population in whom the even rate is not well established. Also as CF therapies have evolved over the last decade with the introduction of more therapies to standard of care, there is a need to evaluate the incidence of hemoptysis using data from a more contemporary cohort than has previously been studied. Utilizing a diverse cohort of children and adults with CF who underwent comprehensive longitudinal monitoring for adverse events, the objectives of this study were (1) to obtain estimates of the frequency and rate of hemoptysis events in the presence of standard of care therapy, and (2) to characterize hemoptysis rates by possible risk factors include age, disease severity as defined by lung function, and microbiologic results.

## 2. Methods

### 2.1. Study design

Recently completed placebo controlled trials were selected for this retrospective cohort study. It utilized existing data from eight completed prospective, longitudinal randomized trials in CF ranging from 2 to 18 months duration between 2000 and 2012. Trial therapies and key eligibility criteria, along with trial duration, visits, and key clinical and safety outcomes are summarized in the Online Supplement (Table E1). For 5 of 8 [12–16] trials, only subjects randomized to placebo were included in the analyses. Pooled data from the treatment and placebo arms were included for 2 trials of azithromycin which led to the adoption of azithromycin into standard of care [17–19], and because comparable hemoptysis rates were observed between treatment arms. The final trial included in our study for the treatment of new onset *Pseudomonas aeruginosa* [20] included all participants receiving tobramycin inhalation solution (TIS) monotherapy and not in combination with oral ciprofloxacin. This analysis was approved by the Institutional Review Board at Seattle Children's Hospital, Seattle, Washington.

All trials collected adverse event (AE) data, which was standardized using MedDRA or COSTART coding. Follow-up time used for the computation of event rates was defined as the date of randomization or the date of first dose of study drug (denoted "baseline") through the end of follow-up. Adverse event severity grades and treatment outcomes were collected in all trials (Online Supplement, Table E1). Treatment outcomes of the AEs were reported differently across trials; thus, for this study a hemoptysis event was considered "treated" if any of the following treatment options were selected on the trial case report forms: concomitant medications, non-drug therapies, concomitant medications in combination with non-drug therapies, or hospitalization.

Baseline $FEV_1$ % predicted was calculated for subjects $\geq 6$ years using either the Wang [21] (females $\leq 16$, males $\leq 18$ years old) or Hankinson [22] (females $> 16$, males $> 18$ years old) equations. Three of the eight trials did not collect respiratory microbiology cultures or history of infection at baseline (Online Supplement, Table E1) and were therefore excluded from analyses of the association between microbiology parameters and hemoptysis.

### 2.2. Statistical analyses

Demographic and baseline characteristics were descriptively summarized by trial and overall. Negative binomial regression