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Major haemoptysis in children with cystic fibrosis: a 20-year retrospective study

Juerg U. Barben[a], Michael Ditchfield[b], John B. Carlin[c], Colin F. Robertson[a], Philip J. Robinson[a,*], Anthony Olinsky[a]

[a]*Department of Respiratory Medicine, Royal Children's Hospital, Parkville, Melbourne, Victoria 3052, Australia*
[b]*Department of Radiology, Royal Children's Hospital, Parkville, Melbourne, Victoria 3052, Australia*
[c]*Clinical Epidemiology and Biostatistics Unit, Royal Children's Hospital, Parkville, Melbourne, Victoria 3052, Australia*

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Abstract

Background: Major haemoptysis occurs in approximately 1% of children with cystic fibrosis (CF). This report describes management and follow-up of these children at a tertiary centre in Australia. *Methods*: Retrospective review of medical records from 1980–1999. *Results*: Fifty-one children (45% female) had major haemoptysis (102 episodes). Mean age at first episode was 15 years (range 7–19) and mean FEV_1 was 56% predicted (range 14–98). Massive life-threatening haemoptysis was not confined to those with severe lung disease ($FEV_1 < 50\%$ predicted). Bronchial artery embolisation (BAE) was more likely to be the initial treatment for those with massive haemoptysis and chronic recurrent bleeding tended to be treated conservatively ($P = 0.01$). Overall, 52 BAE were performed in 28 children with an immediate success rate of 98%; 13 children (46%) had repeated BAE. Four patients died as a direct result of severe haemoptysis. Mean follow-up was 54 months (range 0.5–183). Median survival time (Kaplan–Meier estimate) after first haemoptysis was 70 months, with a significantly longer survival for male patients independent of age (RR 3.8; 95% CI 1.7–8.8; $P = 0.001$). Median survival time following initial treatment with BAE was longer (103 months) compared to conservative treatment (52 months, $P = 0.09$). *Conclusions*: Massive haemoptysis was unrelated to the severity of lung disease and was more likely to be treated with embolisation. BAE was highly effective, however, 46% of the children required re-embolisation at some time, which is similar to the recurrence risk for major hemoptysis treated conservatively on longer term follow-up.

Keywords: Cystic fibrosis; Haemoptysis; Bronchial artery embolisation; Children

1. Introduction

Haemoptysis is uncommon in the paediatric population, however, it is a potentially life-threatening condition [1,2]. With the decreasing incidence of tuberculosis and bronchiectasis, cystic fibrosis (CF) has become the principal cause of major haemoptysis in older children and young adults in developed countries [3,4]. Episodes of minor bleeding (blood streaking) are common and have been reported in up to 60% of patients with CF over 18 years of age [5]. Major haemoptysis occurs in approximately 1% of all patients with CF and is more frequent as their disease progresses. It is rarely seen in children younger than 10 years and occurs up to 1.5% in the age group of 16–20 years [6].

The generally used definition of major haemoptysis, however, arbitrary, is acute bleeding of more than 240 ml/day or recurrent bleeding of substantial volumes (> 100 ml/day) over a few days or weeks [7–9]. Chronic or recurrent, small haemoptysis (<100 ml/day) interfering with patients lifestyle (e.g. sporting activities) and/or preventing effective physiotherapy or home management is also considered by some to represent a significant haemoptysis [9,10]. Haemoptysis in CF is

Abbreviations: ATS, American Thoracic Society; BAE, Bronchial artery embolisation; CF, Cystic fibrosis; CI, Confidence interval; FEV_1, Forced expiratory volume in 1 s; FVC, Forced vital capacity; IPPV, Intermittent positive pressure ventilation; MRSA, Multi resistant staphylococcus aureus; RCH, Royal Children's Hospital; RR, Relative risk.

*Corresponding author. Tel.: +61-3-9345-5818; fax: +61-3-9349-1289.

E-mail address: philrob@rch.org.au (P.J. Robinson).

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believed to result from erosion of enlarged, thin walled, tortuous and newly developed abnormal bronchial vessels found in areas of bronchiectasis secondary to chronic infection [11–14].

There are several reported approaches to the management of haemoptysis in children and young adults with CF[7]. Minor haemoptysis (blood streaked sputum) usually requires no specific treatment. In many patients with major haemoptysis, the bleeding stops spontaneously within a few days. At times, conservative treatment (e.g. bedrest, intensive IV antibiotics, vitamin K, blood replacement, temporary discontinuation of positive pressure chest physiotherapy) is sufficient to control the symptoms [11]. There are two case reports published about the use of a tranexamic acid [15,16], an antifibrinolytic agent (lysine analogue), in the treatment of major haemoptysis in children with CF including one from our clinic [16].

Percutaneous bronchial artery embolisation (BAE) has been shown to be a safe and effective method of controlling haemoptysis in both CF [9,10,12,14,17–20] and non-CF populations [21,22]. No controlled studies have been conducted examining its superiority over conservative therapy in reducing long-term rate of major haemoptysis and in improving patient's survival [20]. Rarely, when severe pulmonary bleeding fails to respond to medical treatment and BAE, surgical intervention, e.g. bronchial artery ligation or local pulmonary resection may be necessary [8,23–25].

This report describes our experience in the management and long-term follow up of children with CF and major haemoptysis at the Royal Children's Hospital in Melbourne, Australia, from 1980 to 1999.

2. Methods

In the last 20 years, the CF Unit at the Royal Children's Hospital has managed the care of approximately 750 children with CF. By the end of 1999 there were approximately 340 children at the CF Unit. This represents over 90% of the children in the state of Victoria with a diagnosis of CF. Until 1989, the diagnosis of CF was made on the basis of clinical presentation and a positive sweat test [26]. Neonatal screening was introduced in Victoria in March 1989. We retrospectively reviewed all available medical records with the discharge diagnosis of haemoptysis and CF from January 1980 to December 1999.

Haemoptysis was considered to be major and by inference, clinically relevant, on the basis of following criteria: (1) massive haemoptysis as a single event ($>$ 250 ml/day), (2) recurrent bleeding of substantial volume ($>$100 ml/day) over a few days or (3) recurrent or chronic small haemoptysis ($<$100 ml) interfering with patient's lifestyle (e.g. sporting activities) and/or preventing effective physiotherapy or home management [9]. Children with minor bleeding (blood streaked sputum) were excluded.

Lung function tests (FVC and FEV_1) were obtained from the laboratory database. All lung function had been obtained by a trained respiratory technician using ATS criteria for paediatric lung function testing [27]. CF lung disease was classified into mild ($FEV_1 > 75\%$ predicted), moderate (FEV_1 50–75% predicted) and severe ($FEV_1 < 50\%$ predicted).

Sputum culture and sensitivity results were obtained from the medical records. Multi-resistant strains were defined as resistant to ≥ 2 classes of antibiotics: Aminoglycosides (tobramycin, gentamicin), third-generation cephalosporins (ceftazidime), penicillins (ticarcillin with clavulanic acid), quinolones (ciprofloxacin), polymyxins (colistin) and/or monobactams (aztreonam).

Prior to 1985 all BAE were performed in an adjacent adult hospital, thereafter the majority were performed at the RCH. The embolic material used was polyvinyl alcohol (Ivalon®, Pacific Medical Industries, La Mesa, California) containing particles ranging in size from 150 to 550 mm, gelatin pledgets (Gelfoam®, Upjohn, Kalamazoo) and/or Gianturco coils (Cook). As a routine the descending thoracic aorta and intercostal arteries were examined for bronchial arteries by a femoral artery catheter. Vessels that were enlarged and/or abnormally tortuous were embolised. If catheter placement could not be secured, embolisation was not performed. The presence of spinal artery circulation arising from a bronchial artery was a relative contraindication or absolute if the origin was distal to the catheter tip. A postembolisation angiogram was usually obtained. BAE was considered successful if the patient's haemoptysis stopped or significantly reduced. If significant haemoptysis persisted or recurred, the procedure was repeated and considered as a separate procedure in the results.

Statistical analysis was performed using Stata 6.0. Survival curves were estimated using the Kaplan–Meier method and crude comparisons between groups performed with the log-rank test. The proportional hazards regression model was used to estimate hazard ratios or relative risks adjusted for potential confounding effects.

3. Results

Fifty-one patients with cystic fibrosis had major haemoptysis over the last 20 years (approx. 6% of all CF patients). There were a total of 102 significant bleeding episodes with a mean of two episodes per child (range 1–7). Twenty-three (45%) were female and 28 (55%) were male. Age at first bleeding ranged from 7 to 19 years (mean age 15 years), however, only 4 children (8%) were younger than 10 years. Males were older (mean age 16.2 years) compared to the females (mean age 13.5 years). Twelve patients (24%) had a massive bleeding ($>$240 ml) and four of them presented with

Table 1
Severity of lung disease and type of bleeding at presentation

Severity of lung disease	Type of bleeding			Total
	Massive	Moderate	Chronic recurrent	
FEV_1 <50%	3	4	15	22 (43%)
FEV_1 50–75%	7	2	7	16 (31%)
FEV_1 >75%	2	7	4	13 (26%)
Total	12 (24%)	13 (25%)	26 (51%)	51 (100%)

pulmonary haemorrhage of greater than 500 ml of blood loss in 24 h. Mean FEV_1 at first haemoptysis was 56% predicted (range: 14–98). Massive life-threatening haemoptysis was not confined to those with severe lung disease (FEV_1 <50% predicted), however, 58% of the children with chronic recurrent bleeding had severe lung disease (Table 1).

Resistant mucoid *Pseudomonas aeruginosa*, was grown in the sputum of 24 (47%) children, 15 (29%) had a sensitive mucoid *Pseudomonas aeruginosa* and six (12%) had a resistant rough *Pseudomonas aeruginosa* combined with a sensitive mucoid *Pseudomonas aeruginosa*. Only two children (4%) had a methicillin *Staphylococcus aureus* (MRSA). *Burkholderia cepacia* was not identified in any of the children.

The first episode of haemoptysis was conservatively treated in 29 patients (57%) and 22 patients (43%) had an embolisation as first treatment (Figs. 1 and 2). The majority of massive bleeding was treated by embolisation (83%) and chronic recurrent haemoptysis tended to be treated conservatively (81%) (Table 2). A total of 52 embolisations were performed in 28 children. Six children had an embolisation following initial conservative treatment due to recurrence of bleeding after an average time of 27.3 months (median 19.5, range 3–67). The immediate success rate after BAE defined as no recurrent bleeding within 24 h was 98%. Thirteen children required more than one BAE (re-embolisation rate 46%) with a median time between first and second embolisation of 4 months (mean 18.9, range: 5 days–

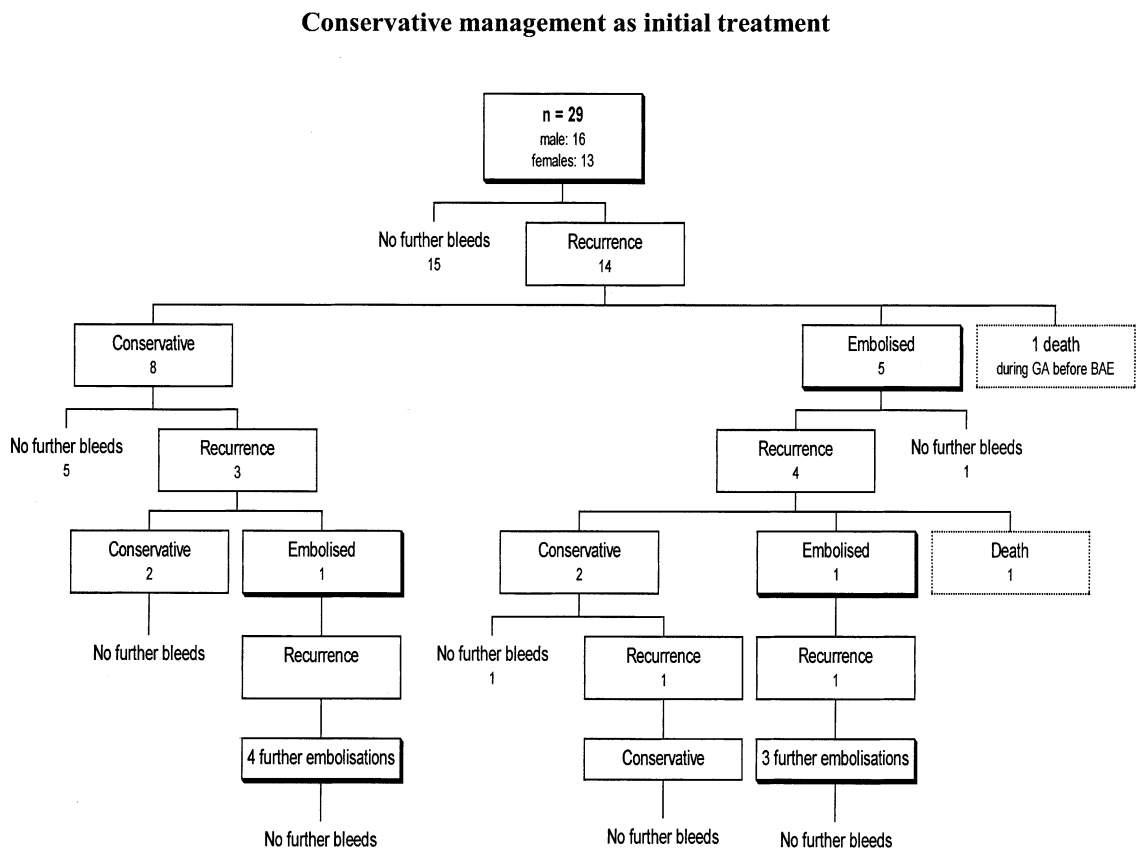

Fig. 1. Conservative management as initial treatment.

83 months). Three children required 3, one 4 and two 5 embolisations.

Two patients had angiography but BAE was not performed because the catheter could not be safely placed in the bronchial arteries. The majority (89%) of BAE was performed using polyvinyl alcohol (Ivalon®). Gelatin pledgets (Gelfoam®) were only used in few procedures as well as Gianturco coils. At our institution a coil has not been used since 1988 as their use has been found to hamper further embolisation in the distribution of vessels that have been previously coiled. In two patients bleeding could not be controlled by BAE and lobectomy was performed, one because of massive pulmonary haemorrhage (>1 l) and the other because of a persistent bleeding despite three embolisations as a result of multiple aberrant bronchial arteries [16].

A bronchoscopy to localise and identify the specific site of haemorrhage was only performed on four occasions (4%) out of 102 bleeding episodes.

Four patients died as a consequence of severe haemoptysis. One died as a result of a fatal pulmonary haemorrhage during anaesthetic induction for BAE and two children died soon after a massive haemoptysis during anaesthetic induction for BAE, which has been reported elsewhere [28]. The fourth patient was initially managed conservatively but required embolisation for major bleeding 42 months after initial haemoptysis. He had a fatal haemoptysis 10 months later.

Table 2
Type of bleeding and initial treatment at presentation

Type of bleeding	Initial treatment	
	Conservative	Embolisation
Massive	2	10
Moderate	6	7
Chronic recurrent	21	5
Total	29 (57%)	22 (43%)

The median survival time in the whole group (Kaplan–Meier estimate) was 70 months with significantly greater survival in males than females (relative risk = 3.8; 95% confidence interval 1.7–8.8; $P = 0.001$ by log-rank test) (Fig. 3). Rates of embolisation treatment were identical between the sexes (43% each). There was a weak evidence of improved survival time following initial treatment with BAE (103 months) vs. conservative treatment (52 months), which was not statistically significant by log-rank test ($P = 0.09$) (Fig. 4). After adjustment for the potential confounding effect of differences in sex—severity of initial lung disease and bleeding type between the conservatively treated and embolisation group—the estimated treatment difference

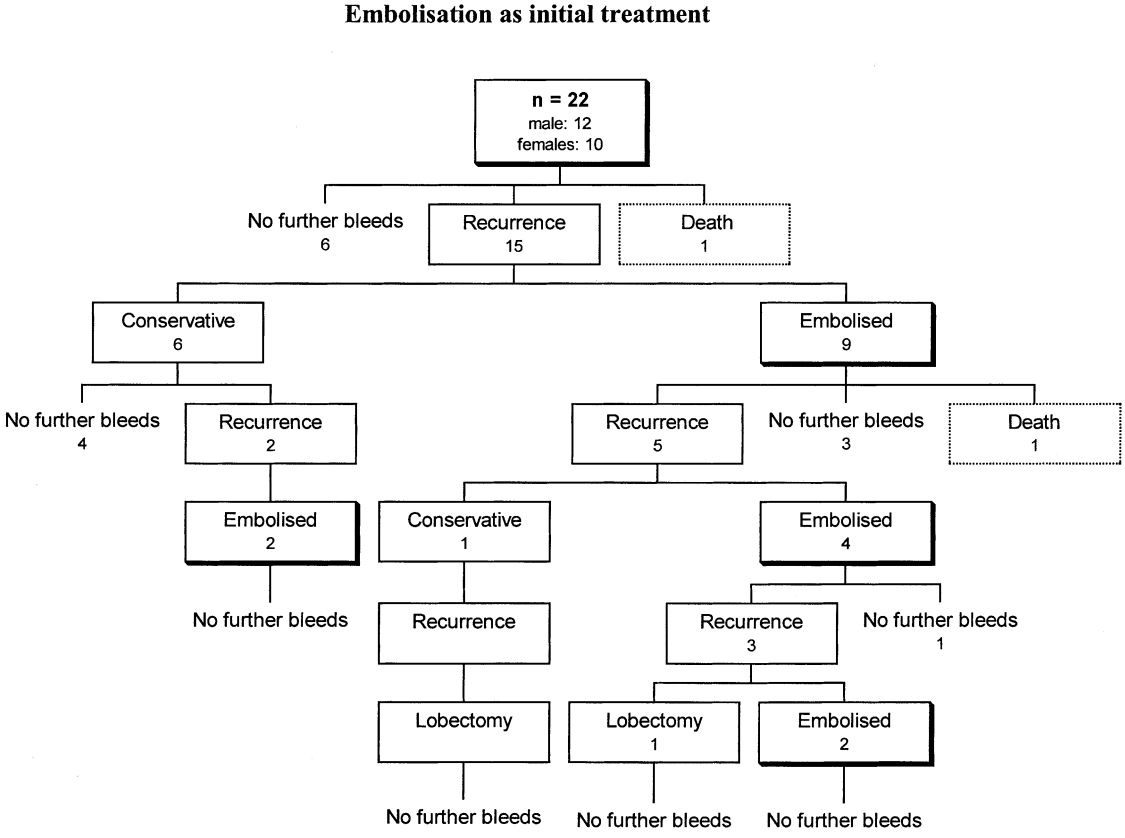

Fig. 2. Embolisation as initial treatment.

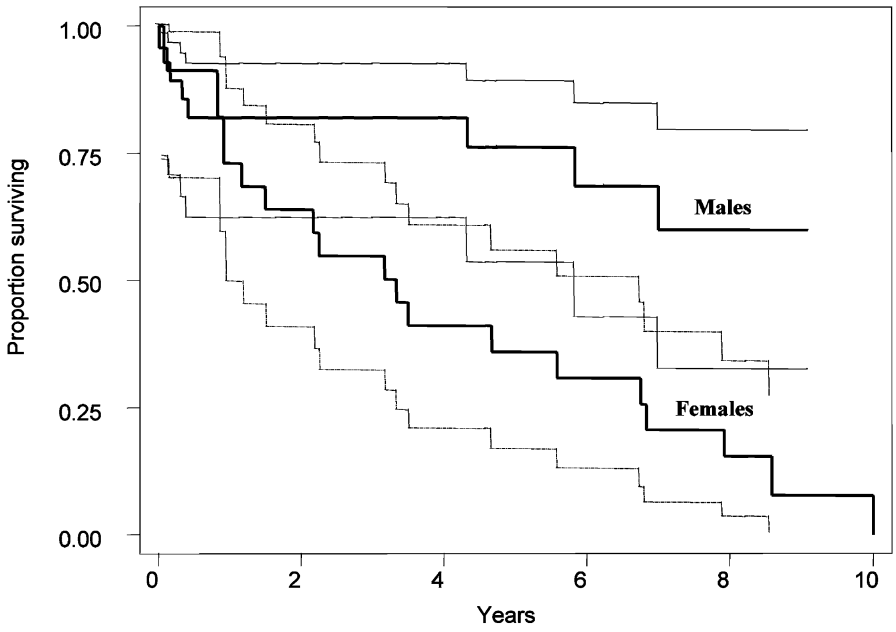

Fig. 3. Kaplan–Meier survival estimates, by sex (95% pointwise confidence band shown).

was little changed (RR = 0.47; 95% CI 0.16–1.38; P = 0.17). In this regression model, the sex difference remained large (RR = 3.0; 95% CI 1.2–7.4), while amongst the three bleeding types, the lowest mortality was in the moderate category (RR = 0.35; 95% CI 0.1–1.2 compared to the severe group).

4. Discussion

This retrospective study describes the longest follow up of children with CF and major haemoptysis in the literature. BAE was highly effective as well as more likely to be used in patients with massive haemoptysis. However, 46% of the children required re-embolisation at some time, which is similar to the recurrence risk for major hemoptysis treated conservatively on longer term follow-up and is slightly higher than the reported re-embolisation rate in other published studies (Table 3).

In 1970, Holscaw et al. [3] published a survival study of 19 CF-patients with severe haemoptysis and described a mortality rate of 32% after the first episode. All

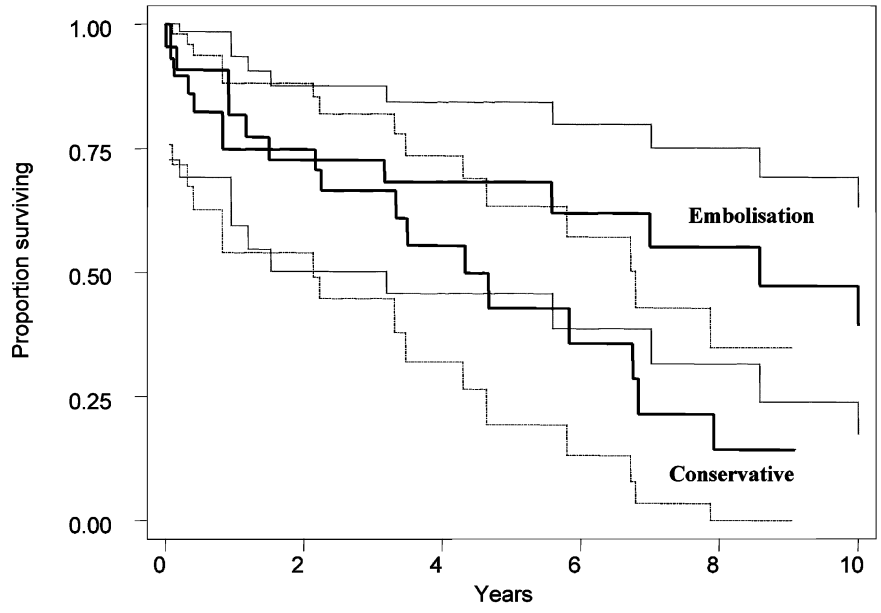

Fig. 4. Kaplan–Meier survival estimates, by initial treatment (95% pointwise confidence band shown).

Table 3
Studies on bronchial artery embolisation in patients with CF

Study	No.	Age (range) (years)	Follow-up (month)	Re-embolisation (%)
Fellows et al. (1979)	13	7–24	11 (1–30)	31
Sweezy et al. (1990)	25	7–35	35 (1–101)	36
Cohen et al. (1990)	19	6–43	34 (7–62)	42
Tonkin et al. (1991)	11	7–36	42 (4–96)	45
Cipolli et al. (1995)	14	15–39	15 (0.5–38)	21
Present study	28	7–19	54 (0.5–183)	46

patients were conservatively treated. Six of the 13 survivors had recurrent haemoptysis (recurrence rate of 46%) and another 7 patients died within 6 months. A few years later, Stern et al. [11] reported an average survival time of 2.5 years (range: 3 months–6 years) in 38 CF-patients with conservatively treated massive haemoptysis. This figure was not significantly different from matched controls (equally severe lung disease) without haemoptysis. The reported recurrence rate was 45%. Twenty-six percent of the CF-patients with major haemoptysis died during the study period, however, no patient died as a direct result of haemoptysis.

BAE was first reported by Remy and colleagues in 1974 [17]. Since then, many reports have been published describing this technique including its use in patients with CF [9,10,12,19,20]. BAE is an effective method for controlling haemoptysis in cystic fibrosis with a reported immediate success rate up to 96% [22]. In our hospital, catheter embolisation of bronchial arteries was first used for our patients in 1980. In the early years, the policy was more in favour of conservative treatment, however, interventional procedures were favoured in the latter years.

The re-embolisation rate of our patients of 46% was similar to other published studies (Table 3). Fellows et al. [12] reported 13 patients with severe haemorrhage treated by BAE with a follow-up of an average 11 months. Their immediate success rate was 62%. Four patients (31%) required repeat embolisations within 10 days and 5 patients (38%) had recurrent minor haemoptysis. Sweezy and Fellows [19] studied the long-term outcome after BAE of 25 CF-patients with massive haemoptysis with an average follow-up of 35 months. Nine patients had a repeated BAE (re-embolisation rate of 36%, interval between 5 days and 24 months). Twenty-four percent of the 25 patients died within three month of BAE (in two of them haemoptysis was a contributing cause) and the mean survival of the survivors (remaining 19 patients) was 3.5 years. The re-embolisation rate reported by Cohen et al. [10] was 42% in 19 patients with CF. Cipolli et al. [20] had a low re-embolisation rate of 21% in 14 CF-patients, however, his average follow-up was only 15 months. In the latter report, 50% were free of major haemoptysis one year after BAE. The longest reported follow-up to date is by Tonkin et al. [9] who describes a re-embolisation rate of 45% that is very similar to ours.

The superiority of BAE over conservative therapy in reducing the long-term recurrence rate of massive haemoptysis and improving the survival time has not yet been proven [20]. In our data there was a trend towards reduced mortality in those initially treated with embolisation (after adjustment for sex and severity differences), but the confidence interval around this estimate was very wide, indicating the need for larger samples to make definite conclusions. In addition, our study was not a direct comparison of conservative treatment vs. embolisation as there was neither randomisation to each group nor clear clinical indications for inclusion in either group.

In our study, 3 children died following massive pulmonary haemorrhage during anaesthesia for BAE, which is described in detail elsewhere [28]. It is believed that factors associated with intermittent positive pressure ventilation (IPPV) were important in precipitating these bleedings. Other possible explanations for rebleeding, such as hypertension due to inadequate anaesthesia at intubation and laryngoscopy, or bronchial artery vasodilatation seem less likely. As a result of these events the practice of anaesthesia for BAE at the RCH was changed to a combination of intravenous sedation and local anaesthesia whenever possible, thus avoiding the use of IPPV.

Major haemoptysis in CF is believed to occur in those patients with diffuse severe lung disease [3]. In our study we did not find any relationship between massive haemoptysis and the severity of lung disease (FEV_1), however, the majority of children with chronic recurrent bleeding had severe lung disease. Severe bleeding can also be associated with mild disease [29], possibly arising in a localised area of more severe inflammation or as a result of multiple aberrant arteries [16]. This emphasises the need to identify each of the bronchial arteries and to search for any aberrant arteries by an aortogram before performing selective catheterisation and embolisation of all abnormal bronchial vessels [10].

In patients with major haemoptysis as a life threatening event, the first priority is to maintain the airway,

optimise oxygenation and stabilise the hemodynamic status followed by BAE or surgical intervention [30]. At our institution, BAE is always considered if there is a massive or moderate bleeding. However, chronic or recurrent haemoptysis interfering with patient's lifestyle and/or preventing effective physiotherapy is usually treated conservatively before considering BAE. While some patients will settle with conservative treatment, BAE should always be considered earlier than later if conservative treatment fails.

In summary, this retrospective study has demonstrated that massive haemoptysis is unrelated to the severity of lung disease and was more likely to be treated with embolisation. Despite its efficiency, the superiority of BAE over conservative therapy in reducing recurrent bleeding and long-term mortality remains unproven.

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