

# Pseudomembranous and obstructive *Aspergillus* tracheobronchitis – optimal diagnostic strategy and outcome

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## Summary

Pseudomembranous and obstructive *Aspergillus* tracheobronchitis (PMATB/OATB) are still considered to be refractory to therapy and to have a fatal outcome. To evaluate the optimal diagnostic strategy and to describe factors affecting the outcome of PMATB and OATB. Retrospective analysis of four new cases of PMATB and OATB combined with 16 previously reported cases over a 10-year period (1995–2004). Among the four new cases reported and the 16 published cases, four patients survived their infection. The mortality rate was significantly higher in the group of ventilated patients [94% (15 of 16 patients)] than in the group of non-ventilated patients [25% (1 of 4 patients),  $P < 0.05$ , Fisher's exact test]. In all 20 patients, diagnosis was established by bronchoscopy. Culture examination of mucous plugs was positive in 8 of 10, culture of the tracheobronchial aspirate was positive in 8 of 12, and bronchoalveolar lavage was diagnostic in 7 of 13 patients. All bronchoscopic techniques were complementary in improving the yield of bronchoscopy. However, microscopy of mucous plugs and/or necrotic material was the best diagnostic modality [positive in 94% (17 of 18 patients)]. Prognosis of PMATB and OATB remains poor. Microscopy of respiratory specimens is the most sensitive tool to confirm the diagnosis. The characteristic appearance of the disease makes it possible to start antifungal therapy immediately.

**Key words:** *Aspergillus*, pseudomembranous, obstructive, tracheobronchitis, immunodeficiency, bronchoscopy, mechanical ventilation.

## Introduction

*Aspergillus* tracheobronchitis (ATB) is an uncommon clinical presentation of pulmonary aspergillosis (PA). Predisposing factors are similar to those for invasive pulmonary aspergillosis (IPA). Neutropenic or immunocompromised patients including patients with cytotoxic chemotherapy or corticosteroid therapy are at particular risk.

In 1995, Denning proposed a classification of three forms of ATB in predominantly immunocompromised hosts. Obstructive ATB (OATB), described initially in

patients with AIDS and heart transplantation, is characterised by thick mucous plugs full of *Aspergillus* spp. without macroscopic evidence of bronchial inflammation. Pseudomembranous ATB (PMATB) typically shows extensive inflammation of the tracheobronchial tree, with a membrane overlying the mucosa containing *Aspergillus* spp. The term ulcerative ATB (UATB) is reserved for patients with limited involvement of the tracheobronchial tree, typically found around the suture line in lung transplant recipients.<sup>1</sup> Cases of UATB have a favourable outcome in lung transplant patients due to surveillance bronchoscopy and prompt initiation of antifungal therapy in the posttransplantation course. Up to 82% of the published patients respond to antifungal therapy and/or surgical debridement.<sup>2</sup> In contrast, OATB and PMATB are still considered by many to be refractory to therapy and to have a fatal outcome, especially in ventilated patients. Since 1995,

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only four patients have been reported to survive PMATB and OATB.<sup>3–6</sup> Here, we describe our experience with four new cases of PMATB. In addition, we analyse our cases and 16 more cases described by others<sup>7–18</sup> with regard to outcome and best diagnostic strategy.

## Materials and methods

Three patients with underlying haemato-oncological disease and one patient with immunosuppression for glomerulonephritis presented in our department between July 2002 and March 2004 with PMATB. PMATB was diagnosed during mechanical ventilation by bronchoscopy.

A MEDLINE search (<http://www.pubmed.org>) and cross-references identified English-language articles addressing cases of OATB and PMATB since 1995. Only studies and case reports that allowed classifications of cases according to the criteria established by Denning were included in the analysis. In brief, Denning characterised PMATB as extensive inflammation of the tracheobronchial tree, with a pseudomembrane overlying the bronchial mucosa. Cases of OATB were characterised to show thick mucous plugs without macroscopic evidence of bronchial inflammation.<sup>1</sup>

The data were analysed with regard to clinical and diagnostic characteristics. The primary end point was survival at discharge.

## Statistical analysis

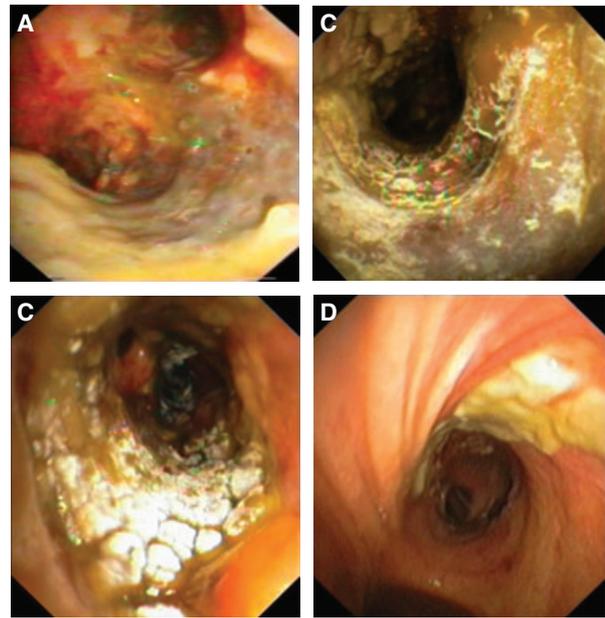
The statistical analyses were performed using SPSS statistical software (SPSS version 11.0, SPSS Inc., Chicago, IL, USA). Fisher's exact test was used to analyse the relationship between categorical variables. Continuous variables between groups were compared using the Mann–Whitney *U*-test. An error level of  $P < 0.05$  was considered significant. Appropriate adjustments for multiple comparisons were made.

## Results

### Clinical characteristics of patients

#### Case reports

**Case 1:** A 58-year-old man with stage IIIB multiple myeloma developed respiratory failure and neutropenic sepsis (neutrophils  $400 \mu\text{l}^{-1}$ ). He was admitted to the ICU and required mechanical ventilation (MV). Three weeks before he had received the second course of high-dose chemotherapy with 400 mg melphalan and autologous stem cell transplantation. Bronchoscopy performed on



**Figure 1** Bronchoscopic appearance of Pseudomembranous *Aspergillus* tracheobronchitis (four new cases presented in this series). Bronchoscopic images: distal trachea and main carina with cream-coloured and ulcerative pseudomembranes (Panel A, case 1), widespread pseudomembranous formation of the trachea (Panel B, case 2) and right main bronchus (Panel C, case 3), right main bronchus lined by a yellowish pseudomembrane (Panel D, case 4).

day 10 of MV for microbiological studies showed severe inflammation with yellow-greyish pseudomembranes of the trachea and multiple circumscribed lesions suspicious of mould infection (Fig. 1, Panel A). Forceps biopsy of the pseudomembranes yielded *Aspergillus* hyphae. Two days later *Aspergillus fumigatus* was isolated from a tracheal aspirate and a CT scan showed consolidations in both lungs. Despite liposomal amphotericin-B therapy ( $4 \text{ mg kg}^{-1}\text{day}^{-1}$ ) the patient died 5 days later due to septic shock. An autopsy was not permitted by his family.

**Case 2:** A 64-year-old female was admitted for pancytopenia. Shortly after admission, brisk upper gastrointestinal bleeding and hypovolemic shock developed. After volume resuscitation endotracheal intubation for airway protection during endoscopy was performed. Disseminated Burkitt's lymphoma could be identified as the underlying disease. Polychemotherapy (cyclophosphamide, ifosfamide, vincristin, steroids, rituximab) was started while the patient was still intubated. Subsequently, septic shock and multi-organ failure ensued. Despite broad-spectrum antibiotics and antifungal prophylaxis with itraconazole ( $400 \text{ mg day}^{-1}$ ), gas exchange worsened. Bronchoscopy on day 13 of MV revealed PMATB (Fig. 1, Panel B). *Aspergillus* antigen

detection in serum showed a borderline result (1.0). After oxygenation could not be sustained using conventional ventilation and extracorporeal membrane oxygenation was ruled out in this poor-risk patient, therapy was discontinued 16 days after initiation of mechanical ventilation. An autopsy was not permitted by her family.

**Case 3:** A 67-year-old female who had been immunocompromised (cyclophosphamide, steroids) for 3 months because of rapidly progressive glomerulonephritis developed bilateral pneumonia and had to be intubated. BAL cultures were negative and therapy with broad-spectrum antibiotics did not result in clinical improvement. On the seventh day of MV, bronchoscopy surprisingly revealed macroscopic, microscopic and cultural evidence of PMATB (Fig. 1, Panel C). Antimycotic combination therapy with conventional amphotericin B ( $1 \text{ mg kg}^{-1}\text{day}^{-1}$ ) and caspofungin ( $1 \text{ mg kg}^{-1}\text{day}^{-1}$ ) did not result in clinical improvement. Two days later a positive *Aspergillus* antigen was detected in a serum specimen (4.7). The therapy was discontinued on day 12 of MV when major intracerebral bleeding ensued. An autopsy was not permitted by her family.

**Case 4:** A 34-year-old male with Burkitt's lymphoma with extensive bone marrow infiltration was started on chemotherapy. During the first phase of induction therapy (having received only steroids, vincristin and rituximab) he developed septic shock and pulmonary leakage. He was intubated and received amphotericin B in addition to broad-spectrum antibiotics. On day 5 of MV bronchoscopic evidence of PMATB could be found (Fig. 1, Panel D). *Aspergillus* antigen detection in serum was negative (0.2). Additional caspofungin treatment was started. Even though the PMATB improved according to bronchoscopic and computer tomographic criteria, the lymphoma progressed and necessitated repeated courses of rituximab and vincristin (which were deemed to be less prone to promote fungal growth than steroids and cyclophosphamide). Fatal intracranial bleeding complicated the clinical course 49 days after initiation of mechanical ventilation. An autopsy was not permitted by his family.

Another 16 patients reported as case reports in the literature since 1995 were also analysed. Clinical characteristic of all 20 cases are specified in Table 1. The overall mortality rate of the pooled patients was 80% (16 of the 20 patients died). However, the mortality rate was significantly higher in ventilated patients [94% (15 of 16 patients)] than in non-ventilated patients [25% (1 of 4 patients)],  $P < 0.05$  (Table 2). There were no statistically significant differences in age, sex, underlying disease, the presence of

severe neutropenia, the presence of wheezing prior to bronchoscopy, and the time between the first symptoms and therapy between survivors and non-survivors. PMATB/OATB associated with HIV was not reported between 1995 and 2004.

In all 20 patients diagnosis was established by bronchoscopy. Culture examination of mucous plugs was positive in 80% (8 of 10 patients for whom data were available in this regard, case numbers 2, 4, 10, 12, 15–18), the tracheobronchial aspirate was positive in 67% (8 of 12 patients, case numbers 2, 3, 5, 7, 8, 11, 16 and 19), and BAL was positive in 54% (7 of 13 patients, case numbers 7, 8, 10, 13, 15, 18 and 20). Microscopy or histology of biopsies of pseudomembranes, mucous plugs or necrotic material established the diagnosis in 94% (17 of 18 patients, case numbers 1–5, 9, 10, 12–19). Abnormal radiographic findings before diagnostic bronchoscopy were found in 76% (12 of 18 patients, case numbers 3, 5, 7, 9, 11–17, 20). The mortality rate was not different in patients who received amphotericin B as compared to antifungal combination therapy.

## Discussion

The main findings of this pooled analysis of our own cases of ATB and of cases described in the literature over a 10-year period (1995–2004) were (i) the mortality of patients with PMATB and OATB remains high; (ii) the need for mechanical ventilation indicates a fatal outcome in PMATB/OATB; (iii) age, sex, and underlying disease do not predict survival; (iv) ATB typically is an unexpected diagnosis; (v) the characteristic bronchoscopic macroscopic appearance leads to the diagnosis; and (vi) the most sensitive diagnostic test is microscopy of material obtained at bronchoscopy.

The aetiology of ATB and the reason for its restriction to the tracheobronchial tree remain unclear. Probably, inoculation of airborne spores of *Aspergillus* spp. and colonisation of the respiratory tract is the first step. This may be facilitated by the host's immunodeficiency and altered local defence mechanisms such as the prolonged presence of an endotracheal tube.<sup>1</sup> The susceptibility of the bronchial anastomosis in lung transplant recipients to ATB supports this assumption.<sup>2</sup> Immunosuppression may then result in invasive disease.

Recent studies have shown that IPA is increasingly recognised in ICU patients with chronic obstructive pulmonary disease (COPD),<sup>19</sup> and in patients without haemato-oncological malignancy.<sup>20</sup> It can be speculated that PMATB and OATB are underdiagnosed in ICU patients due to a lack of characteristic clinical and radiological appearance. Furthermore, non-invasive

**Table 1** Clinical characteristics, therapy and outcome of presented and reviewed cases of PMATB and OATB (1995–2004).

Ref., year	Case no.	Age, sex	Underlying disease/therapy	WBC count of <1000 cells mm <sup>-3</sup>	Indication for FB	MV (days)	Classification	<i>Aspergillus</i> spp.	FB image	Therapy	Outcome
This series	1	58, m	Multiple myeloma, HSCT, CT	Yes	SOI	17	PMATB	<i>A. fumigatus</i>	Yes	IAmB	Fatal
This series	2	64, w	Burkitt lymphoma, CT	Yes	SOI	16	PMATB + OATB	<i>A. fumigatus</i>	Yes	Amb	Fatal
This series	3	67, w	Ig-A nephropathy, CT	Yes	PTF	12	PMATB	<i>A. fumigatus</i>	Yes	Amb, CAS	Fatal
This series	4	34, m	Burkitt lymphoma, CT	Yes	SOI	49	PMATB	<i>A. fumigatus</i>	Yes	Amb, CAS	Fatal
[7], 2004	5	22, w	Lymphoma, CT, ST	Yes	AT	7	OATB	<i>A. terreus</i>	Yes	IAmB, VCZ	Fatal
[5], 2004	6	70, m	COPD, ST	No	nm	–	PMATB	nm	Yes	nm	Cured
[4], 2002	7	59, w	Hodgkin lymphoma, CT	No	SP	–	PMATB	<i>A. fumigatus</i>	Yes	IAmB	Cured
[8], 2002	8	23, w	Lupus erythematosus, ST, CT	No	nm	9	PMATB	<i>A. fumigatus</i>	Yes	Amb	Fatal
[9], 2001	9	60, m	Erythroleukaemia, CT	Yes	AT	3	OATB	<i>A. fumigatus</i>	No	Amb	Fatal
[10], 2000	10	56, w	BMT, CT, ST	Nm	wheezing, ARD	1	PMATB	<i>A. fumigatus</i>	No	I/nAmB, ITR	Fatal
[11], 2000	11	54, w	Malaria	No	SP	4	PMATB	<i>A. fumigatus</i>	No	Amb	Fatal
[12], 2000	12	54, w	Multiple myeloma, CT	Yes	ARD	8	PMATB + OATB	<i>A. fumigatus</i>	No	Amb	Fatal
[13], 2000	13	20, m	Leukaemia, post HSCT, IST	No	Unclear opacity	8	PMATB	<i>A. fumigatus</i>	No	Amb, ITR	Fatal
[14], 1999	14	56, m	AML, CT	Yes	nm	–	PMATB	nm	No	Amb	Fatal
[6], 1999	15	35, m	Influenza	No	ARD	33	PMATB + OATB	<i>A. niger</i>	No	IAmB, ITR, FC	Cured
[15], 1999	16	38, m	NTX, IST	No	SP	8	PMATB	<i>A. flavus</i>	No	ITR	Fatal
[16], 1999	17	44, w	Leukaemia, post BMT, CT, IST	No	ARD	2	PMATB	nm	Yes	Amb	Fatal
[17], 1998	18	64, w	ALL, CT	No	ARD	18	PMATB + OATB	<i>A. flavus</i>	No	Amb	Fatal
[3], 1998	19	44, m	T-cell lymphoma, CT	Yes	Hoarseness	–	PMATB	nm	No	Amb	Cured
[18], 1995	20	66, w	COPD	No	ARD	11	PMATB	nm	No	FC	Fatal

FB, bronchoscopy; HSCT, haematopoietic stem cell transplantation; NTX, renal transplantation; BMT, bone marrow transplantation; COPD, chronic obstructive pulmonary disease; CT, chemotherapy; ST, steroid therapy; IST, immunosuppressive therapy; SOI, suspected opportunistic infection; SP, suspected pneumonia; PTF, pneumonia treatment failure; ARD, acute respiratory distress; AT, atelectasis; MV, total days of mechanical ventilation; nm, not mentioned; Amb, amphotericin B (l, lipid formulation; n, nebulised); FC, flucytosine; ITR, itraconazole; CAS, caspofungin; VCZ, voriconazole.

**Table 2** Differences between survivors and non-survivors with PMATB and OATB.

Characteristics	Survivors (n = 4)	Non-survivors (n = 16)	Significance
Age, year	52.0 ± 15.6	48.8 ± 16.4	ns
Sex (male)	3	10	ns
Underlying disease			
HOD	2 (3)	9 (11)	ns
Other	1 (3)	2 (11)	ns
Neutropenia ( $<1000$ cells $\text{mm}^{-3}$ )	1 (3)	8 (14)	ns
Abnormal radiographic finding before bronchoscopy	2 (3)	12 (15)	ns
Mechanical ventilation Therapy	1	15	$P = 0.013^*$
AmB	2 (3)	9 (16)	ns
Combination including AmB	1 (3)	5 (16)	ns
Other	0 (3)	2 (16)	ns
Wheezing prior bronchoscopy	2 (3)	1 (11)	ns
Day of bronchoscopy post first symptoms	5.6 ± 5.2 (3)	9.3 ± 13.6 (14)	ns

Values in parentheses represent the number of patients for whom data were available. Continuous variables are described as mean (and standard deviation), categorical variables are described as *n*. Fisher's exact test for categorical data.

\*Mann-Whitney *U*-test.

AmB, amphotericin B formulations; HOD, haemato-oncological disease.

approaches in the diagnostic strategy of suspected ventilator-associated pneumonia may decrease bronchoscopic examinations in ICU patients.

Unlike IPA, radiological evaluation may not be helpful in the diagnosis of PMATB and OATB. While 12 patients showed pathological radiographs prior to bronchoscopy, only two patients had characteristic peribronchial findings<sup>6, 14</sup> and two patients showed atelectasis.<sup>8, 9</sup> In contrast, bronchoscopy was diagnostic of PMATB and OATB in all cases. In this survey, we found that the sensitivity of microscopic examination techniques of tracheobronchial specimens is much greater than that of sole culture of BAL and TBAS. The value of surveillance bronchoscopies is unclear. Interestingly, in addition to the cases described here (Fig. 1), several reports included those characteristic bronchoscopic images.<sup>4, 5, 7, 8, 16</sup>

This analysis has several limitations. The retrospective design and the inclusion of cases reported over a period of one decade does introduce some selection bias and may not be representative of the outcome of all patients with PMATB and OATB. However, due to the rarity of PMATB and OATB, a pooled analysis is

currently the only way to study this disease. Likewise, the timing of performing bronchoscopy was different for each patient. This could explain the differences in outcome between ventilated and non-ventilated patients. The data reviewed do not justify recommendations with regard to the kind of therapy one should use to treat PMATB/OATB. However, new antifungal agents with better tissue penetration and new diagnostic procedures may improve outcome of patients with PMATB and OATB. The bronchoscopic evidence for regression of PMATB in case 4 after addition of caspofungin to conventional amphotericin B treatment may demonstrate the efficacy of this substance.

In conclusion, the prognosis of PMATB and OATB remains poor, especially in ventilated patients with underlying immunodeficiency. However, in view of the patient's underlying disease, it is often almost impossible to distinguish mortality attributable to PMATB/OATB from mortality due to underlying disease. Moreover, early diagnosis and prompt antifungal therapy including new antifungal agents may significantly improve the outcome.

Performing bronchoscopy with microscopic examination of tracheal or bronchial specimens is the most sensitive diagnostic test for early diagnosis of PMATB/OATB. Cultural evaluation of non-bronchoscopic samples alone may result in underdiagnosis. Further, multicentric prospective studies are necessary to assess the optimal therapy of these uncommon clinical presentations of PA.

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