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Independent risk of mechanical ventilation for AIDS-related *Pneumocystis carinii* pneumonia associated with bronchoalveolar lavage neutrophilia

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Abstract The use of mechanical ventilation (MV) for AIDS-related *Pneumocystis carinii* pneumonia (PCP) has varied over time. The introduction of adjunctive corticosteroid therapy has changed the patophysiology of PCP. In the present study, we attempted to identify factors predictive of severe respiratory failure requiring MV amongst patients with PCP treated in the era of adjunctive corticosteroid therapy. Furthermore, we studied factors associated with survival in relation to MV. Of 170 consecutive patients with AIDS-related PCP, 18 (11%) required MV. Thirteen of 18 ventilated patients died (72%). In a logistic regression analysis, higher age, increased brnchooalveolar lavage (BAL) neutrophilia and a positive BAL cyto megalovirus CMV culture were associated with the need of MV. In multivariate analyses, only BAL neutrophilia remained independently predictive of mechanical ventilation. In conclusion, short-term mortality remained high after the introduction of adjunctive corticosteroid therapy. BAL neutrophilia may be a useful prognostic marker to identify patients at high risk of requiring mechanical ventilation.

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INTRODUCTION

Despite the availability of effective prophylactic regimens, *Pneumocystis carinii* pneumonia (PCP) continues to be the most common AIDS-defining disease (1). Since the early stages of the HIV epidemic the indication of mechanical ventilation (MV) for PCP-associated severe respiratory failure has been debated. It is an issue of great clinical, ethical and economical importance. Outcome of severe PCP-associated respiratory failure requiring mechanical ventilation has evolved through several stages over the last decades of the HIV epidemic. Previously, the short-term mortality was unacceptably high (2–5), but in more recent times the mortality rate has decreased (6–11). It was speculated that this was possibly due to factors such as the introduction of adjunctive corticosteroids, better knowledge of the disease and refrainment of intensive care use for patients with severe PCP, thus selecting healthier patients for endotracheal intubation (12).

In order to identify factors that may be predictive of respiratory failure requiring MV and thereby offer the possibility of intervention before respiratory failure, we studied a cohort of consecutive patients with AIDS-related PCP for clinical baseline variables associated with MV.

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METHODS

A total of 170 HIV-1-related PCP episodes diagnosed and admitted to the Department of Infectious Diseases, Hvidovre Hospital, Copenhagen were studied. The study of events between June 1990 and January 1999 was conducted prospectively. Clinical and laboratory data was collected prospectively. A retrospective study was conducted of events in the period from 1985 to June 1990.

Only microbiologically confirmed cases of PCP were included. Details of diagnostic evaluation and treatment have been previously described (13).

Statistics

All values are expressed as median and range. Differences between groups were tested by the Mann–Whitney test or χ^2 test, where appropriate. Odd ratios, with the 95% confidence interval, for the progression of respiratory failure requiring MV, were estimated by logistic regression analyses. $P < 0{\cdot}05$ was considered statistically significant. Statistical analyses were carried out using SPSS 9·0 software (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, U.S.A.)

RESULTS

In the era of adjunctive corticosteroid therapy, we identified 170 HIV-1 related PCP episodes. Of these, 18 (11%) were intubated and received MV due to severe respiratory failure. None of the MV-treated patients had prior episodes of PCP. All study participants were male. The demographic, clinical and laboratory data are shown in Table 1.

Factors associated with the need of mechanical ventilation

We first compared the mechanically-ventilated PCP patients in the historical era with the adjunctive corticosteroid era and found that the only difference associated with MV was age ($P < 0{\cdot}023$). The following variables were not different between the two groups: HIV-status at PCP diagnosis. PaO_2 $PaCO_2$, haemoglobin, lymphocytes, CD4 cell counts, serum LDH and serum albumin levels on admission.

In the era of adjunctive corticosteroid therapy, the following significant characterstics of PCP episodes requiring mechanical ventilation were found: age, the relative amount of bronchoalveolar lavage (BAL) neutrophilia and a positive BAL cytomegalovirus (CMV) culture (Table 2). To explore further the independent risk of each factor, the data were entered into a logistic regression model. In a univariate analysis, age, the relative amount of BAL neutrophilia (percentage) and BAL CMV culture were significantly associated with an increased need of MV. Transmission group was also found to be significantly associated with MV, however this was explained by the large number of patients in the subgroup other/unknown, which excludes this result from being valid. The following were not associated with MV: sex, HIV-status at PCP diagnosis, PaO_2, $PaCO_2$, haemoglobin, lymphocytes, CD4 cell counts, serum LDH, BAL cell counts, absolute amount of BAL neutrophils, BAL macrophages, BAL lymphocytes, BAL bacterial culture, TMP–SMZ therapy and pentamidine therapy. This is an observational study and the results rely on discrepancies between clinicians to employ MV. One patient with a very low PaO_2 value of 4·2 kPa was not offered MV due to a rapid response to nasal oxygen supply and treatment. After adjustment in a multivariate model including all significant factors from the univariate model, only BAL neutrophilia ($P < 0{\cdot}0076$) remained independently predictive of progression to mechanical ventilation (Table 3).

Outcome of mechanical ventilation

In the era of adjunctive corticosteroid therapy, 13 of the 18 MV patients died within 3 months, giving a short-term

TABLE 1. Baseline characteristics of 170 patients with PCP between 1990–1999

			n	%	
Sex	Total		170	100	
	Male		161	95	
	Female		9	5	
Transmission group	Homo/bisexual		118	70	
	Heterosexual		28	16	
	Intravenous drug use		7	4	
	Other/unknown		17	10	
AIDS index diagnosis	PCP		150	88	
	Oesophageal candida		11	7	
	Other		9	5	
			n	Median	Range
Age			170	37	22–76
Variables	PaO_2	kPa	158	8·7	4·2–13·8
	$PaCO_2$	kPa	158	4·5	3·0–6·0
	Haemoglobin	mmol l^{-1}	169	7·3	3·4–10·0
	Lymphocyte	10^9 l^{-1}	161	0·7	0·1–3·3
	CD4	count μl^{-1}	165	16	0–259
	Serum LDH	units l^{-1}	100	762	186–2830
BAL fluid	Macrophages	%	137	59	0–97
	Lymphocytes	%	137	20	0–76
	Neutrophils	%	136	11	0–95

Table 2. Mechanical ventilation *vs.* non-mechanical ventilation of PCP episodes in the era of adjunctive corticosteroids expressed as median and range

		No MV		MV		*P*-value
		n	%	*n*	%	
Sex	Total	152	100	18	100	0·600
	Male	143	94	18	100	
	Female	9	6	0	0	
Transmission group	Homo/bisexual	106	70	12	67	0·029
	Heterosexual	27	18	1	6	
	Intravenous drug use	7	5	0	0	
	Other/unknown	12	8	5	28	
HIV status at PCP diagnosis	Unknown	66	45	9	50	0·803
	Known	81	55	9	50	
PCP therapy	TMP-SMZ	135	89	16	89	0·579
	Intravenous pentamidine	12	8	2	11	
	Others	5	3	0	0	
BAL, CMV culture	Positive	57	39	11	73	0·013
	Negative	89	61	4	27	
BAL culture	Positive	26	18	3	23	0·709
	Negative	118	82	10	77	

			No MV		MV		*P*-value
			Median	Range	Median	Range	
Age			36	22–76	47	28–69	0·008
Variables	PaO_2	kPa	8·9	4·2–13·8	7·9	4·4–13·0	0·227
	$PaCO_2$	kPa	4·5	3·0–6·0	4·0	3·3–5·6	0·080
	Haemoglobin	mmol l^{-1}	7·3	5·0–10·0	7·0	3·4–8·4	0·123
	Lymphocyte	10^9 l^{-1}	0·7	0·1–3·3	0·5	0·2–1·7	0·147
	CD4	count μl^{-1}	18	0–259	10	0–102	0·237
	Serum LDH	units μl^{-1}	728	186–2830	905	469–1466	0·148
BAL fluid	Cell count	10^3 ml^{-1}	27	1–1615	29	14–55	0·976
	Macrophages	%	60	0–97	46	3–85	0·127
	Lymphocytes	%	21	0–76	15	5–42	0·305
	Neutrophils	%	10	0–93	31	1–95	0·005

Table 3. Relative prognostic significance of baseline variables on progression to mechanical ventilation amongst 170 PCP patients in the era of adjunctive corticosteroids

		n	Univariate analysis Odd's ratio (95% CI)	Multivariate analysis Odd's ratio (95%CI)
Age		170	1·1 (1·0–1·1)	1·05 (0·99–1·12)
Bal neutrophilia per 10% increment		136	5·6 (1·5–21·5)	8·46 (1·8–40·7)
BAL CMV culture	Positive	68	4·3 (1·3–14·1)	3·3 (0·8–12·6)
	Negative	93	1·0	1·0

mortality rate of 72%. In the era prior to adjunctive corticosteroid therapy we found that 12 of 26 MV patients died, giving a short-term mortality rate of 46%. The comparison of mortality rates prior to and after the introduction of corticosteroids did not reach statistical significance ($P = 0·079$). In order to investigate possible factors associated with a poor outcome of MV, we combined MV patients from groups before and after the introduction of adjunctive corticosteroids. This comparison of survivors and non-survivors of MV showed no differences in laboratory variables, demographics or therapy, apart from initial choice of PCP prophylaxis, which was statistically significantly associated with mortality ($P < 0·05$). However, in the steroid era

we found a statistical significant increase in the short-term mortality rate in the second half of the study period (1995–1999) as compared to the first half (1990–1994) 100% (8/8) *vs.* 50% (5/10) (P=0·036, χ^2).

DISCUSSION

The main finding of the present study was that the presence of BAL neutrophilia was the only factor independently related to the requirement of MV for AIDS-associated PCP. There are few published studies regarding factors associated with the need of MV for AIDS-associated PCP. Curtis *et al.* have recently studied 155 of 1660 (9%) MV patients with confirmed or presumed PCP and found that African–American ethnicity as oposed to hispanic whites and geographical location predicted MV (14). These findings may be attributed to different practises in providing endotracheal intubation to patients.

We found that concurrent BAL neutrophilia was predictive of MV. The relative amount of neutrophilia present in BAL fluid was associated with an 8·5-fold increased risk of mechanical ventilation. The role of the neutrophil in the respiratory tract of patients with AIDS is unclear. The presence of this cell type in excess may be due to PCP infection, but may be associated with concurrent bacterial infection (15). In the present study, a positive BAL bacterial culture was not associated with an increased risk of MV, and is therefore a less likely explanation of the BAL neutrophilia. Azoulay *et al*. (16) have recently conducted a retrospective study including 144 subjects treated after 1990. In support of our study, they found an independent correlation between BAL neutrophilia and the need for MV. Several studies conducted prior to the introduction of corticosteroids demonstrated an association between BAL neutrophilia and mortality (15,17–19). After the exclusion of patients with concomitant pulmonary infections, BAL neutrophilia remained associated with mortality (19). The role of neutrophils in the pathogenesis of disease is unresolved. Once triggered the neutrophil has been described to implement tissue destruction, where host regulatory defence mechanisms have failed in a paradox mechanism participated by oxidants, proteases and antiproteases (20,21). It has been proposed that BAL neutrophilia is related to the severity of the infection, neutrophilia thus appearing in the BAL fluid only in the most advanced stages of PCP (17). Neutrophils have been recovered in BAL fluid from patients with the adult respiratory distress syndrome (ARDS) due to other causes, and increased BAL neutrophilia has been found to correlate with the severity of ARDS (22). It is unclear whether the excess BAL neutrophilia present in severe PCP is due to the pathogenesis of ARDS. Interestingly, elevated levels of the neutrophil chemotactant interleukin-8 in BAL fluid has been found to correlate with the clinical severity of PCP-associated pneumonia and to predict mortality (23). If neutrophils contribute significantly to disease in PCP through the release of proteases and oxygen metabolites, modulating therapies directed against these mediators may prove beneficial in patients with elevated BAL neutrophilia.

In the era of adjunctive corticosteroid therapy, we found that the short-term mortality of the MV PCP patients was higher (72%) than in the period before the introduction of corticosteroids (46%) but the difference did not reach statistical significance. A previous study conducted in our department found a mortality rate of 50% for the MV PCP patients, survival was however in this study defined as discharge from hospital (24). Surprisingly, we observed a mortality rate of 100% in the latter half of the study period. We are uncertain of whether our results represent a local phenomenon as recent studies of mortality for MV PCP are lacking. This increase in of mortality observed in our study group, could not be explained by corticosteroid therapy, as the policy for adjunctive corticosteroid therapy had remained unchanged throughout the period. It would appear that severe respiratory failure requiring MV due to AIDS-related PCP, despite adequate anti-PCP microbial and adjuvent corticosteroid therapy, selected a subgroup of patients with a very poor prognosis. Possibly this reflected more advanced HIV disease on admission to the intensive care unit. However, our results were limited by a small study sample.

Severe PCP requiring MV has been well documented to be independently associated with a worse prognosis (6,16,25,26). Several predictors of short-term mortality for MV patients with PCP have been identified: longer duration of known HIV seropositivity (27), decreased arterial oxygenation on admission (9), lower serum albumin levels on admission (8,28), lower CD4 counts (28–30), longer duration of symptoms prior to admission (9), lower body weight (28), longer duration of PCP treatment combined with corticosteroids prior to MV (27), higher APACHE II score (28,31,32). In the present study, only the use of PCP prophylaxis was a predictor of mortality among ventilated patients. Curtis *et al*. have recently confirmed these findings (14). One explanation may be the selection of resistant strains of *P. carinii* when taking prophylaxis for PCP, leading to infections with more virulent strains. This is supported by a recent study, in which PCP resistance to sulpha-drugs has been found to be associated with increased mortality (33). Alternatively, prophylaxis against PCP may be a marker of patients with more advanced HIV infection due to longer duration of HIV seropositivity. However, neither CD4 cell count nor a prior AIDS defining illness were associated with a poor prognosis for MV patients. Furthermore, neither of these variables were predictors of respiratory failure.

Limitations of this study include a relatively small sample size of patients requiring MV. We may therefore lack

sufficient statistical power to identify other factors that may have had prognostic significance.

In conclusion, we confirmed high short-term mortality of the mechanically ventilated PCP patients. We found that increased BAL neutrophilia was associated with the need of mechanical ventilation. BAL neutrophilia is therefore a useful prognostic marker to identify PCP patients at high risk of requiring MV. The role of BAL neutrophilia in severe respiratory failure to PCP however still remains to be determined. Further studies are required to determine whether BAL neutrophilia is a cause or a consequence of respiratory failure. Future therapies may include neutrophil protease inhibitors.

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