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Effect of long-term primary aerosolized pentamidine prophylaxis on breakthrough *Pneumocystis carinii* pneumonia

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Effect of long-term primary aerosolized pentamidine prophylaxis on breakthrough Pneumocystis carinii *pneumonia. S. Ewig, H. Schäfer, J.K. Rockstroh, A. Pickenhain, B. Lüderitz. ©ERS Journals Ltd 1996.*

ABSTRACT: Aerosolized pentamide is a well-tolerated primary prophylaxis regimen for *Pneumocystis carinii* pneumonia (PCP) in human immunodeficiency virus (HIV)-infected patients. It is now commonly administered for prolonged periods. We therefore studied the effect of long-term inhalation on breakthrough PCP.

We recorded clinical, immunological, radiological and microbiological data, as well as therapy and clinical course of all episodes with confirmed PCP diagnosed at our institution between January 1, 1990 and June 30, 1995. Furthermore, data of all patients on primary aerosolized pentamidine since May 1, 1989 were retrieved. Prophylaxis failures were subdivided into "early" (≤12 months of inhalation time) and "late" (>12 months of inhalation time) failures and were compared with episodes without any prophylaxis.

Thirty patients without any prophylaxis, six with early and 14 with late failures represented the study population. Mean±SD inhalation times were 4.9±4.8 and 26.3±14.1 months, respectively. No significant differences could be detected with regard to clinical presentation, severity of PCP, and in-hospital as well as long-term outcome. Early as well as late prophylaxis failures had a higher incidence of upper lobe infiltrates on chest radiography (50% without prophylaxis *versus* 100% with early and 83% with late failure, respectively; $p<0.05$). No extrapulmonary or disseminated pneumocystosis was observed in either group. The sensitivity of site-directed bronchoalveolar lavage was conserved after long-term inhalation (86% *versus* 100% without prophylaxis and 97% in early failure; p=NS).

The severity and outcome of *Pneumocystis carinii* pneumonia is not altered by long-term primary aerosolized pentamidine prophylaxis. Presentation with upper lobe infiltrates is a radiographic pattern also of late failures. Bronchoalveolar lavage should, therefore, be performed using the site-directed technique in this setting.
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Aerosolized pentamidine continues to represent an effective and safe prophylaxis for human immunodeficiency virus (HIV)-associated *Pneumocystis carinii* pneumonia (PCP) [1–3]. Although oral co-trimoxazole has proved to be superior in patients with severe CD4-cell depletion (<100 CD4 cells·μL^{-1}) and is also effective in preventing central nervous system (CNS) toxoplasmosis in patients with positive *Toxoplasma gondii* serology, the important advantages of aerosolized pentamidine are its minimal toxicity and its lack of interaction with other drugs. These qualities prove to be of growing clinical relevance in the long-term administration, as concurrent medications with its inherent considerable toxicities are frequently indicated in advanced HIV disease. Accordingly, a study comparing regimens for primary prophylaxis with 48 months of observation time reported that 88% of patients on aerosolized pentamidine but only 23% on co-trimoxazole and dapsone, respectively, were still receiving the drug which they were prescribed originally when they completed the study [4].

Thus, aerosolized pentamidine is expected to be administered especially as primary prophylaxis for prolonged periods in large HIV-infected populations with an expected longer survival. This raises the question of the effect of long-term aerosolized pentamidine on the clinical presentation, severity, and outcome of breakthrough PCP episodes. The comparative studies on this subject published so far have not exceeded a mean observation period of 12 months [5, 6]. Others have not reported the inhalation time at all [7–11]. Moreover, most studies have not been controlled for primary or secondary prophylaxis [6, 7, 9–11].

Late primary prophylaxis failures may have a more complicated and severe presentation because they occur later in the course of HIV disease with a more profound immune depletion. Additionally, as a result of a smouldering infection with progressive degenerative lung damage [12, 13], bronchoalveolar lavage (BAL) may only achieve a decreased yield in diagnosing PCP.

An analysis of the effect of primary prophylaxis on PCP should, therefore, include a comparison of the natural history of PCP with "early" (≤12 months of inhalation time) and "late" (>12 months of inhalation time) prophylaxis failures. We therefore performed a corresponding analysis in our patient population on primary aerosolized pentamidine prophylaxis.

Methods

The clinical charts of all proven first episodes of HIV-associated *Pneumocystis carinii* pneumonia (PCP) diagnosed at our institution between January 1, 1990 and June 30, 1995 were reviewed. HIV infection was documented by enzyme-linked immunosorbent assay (ELISA) and immunofluorescence or Western-blot tests. A diagnosis of PCP was based on demonstration of the organisms in Giemsa and/or Grocott stains of BAL or transbronchial biopsy as described previously [14]. BAL was regularly performed in the area most prominently affected in the chest radiograph throughout the observation period.

Data were extracted manually, recorded on study forms and entered into a computerized data base. In detail, the analysis included the following parameters: 1) epidemiological data: age and sex; 2) data from history: staging according to Centers for Disease Control (CDC) [15], history of acquired immune deficiency syndrome (AIDS)-defining opportunistic infections; date of diagnosis of PCP; cough, dyspnoea, fever, duration of symptoms prior to diagnosis; loss of weight in the last 3 months prior to diagnosis; current and prior PCP-prophylaxis regimens, including dose, dosing interval and length of administration, as well as antiretroviral therapy; 3) clinical examination: height, weight, body mass index; 4) laboratory data: haemoglobin, haematocrit, leucocyte count, relative and absolute neutrophils and lymphocytes, platelet count, albumin, γ-globulins, lactate dehydrogenase (LDH); 5) immune status: CD3, CD4, CD8 (within 3 months prior to diagnosis); 6) capillary blood gas values without supplemental oxygen on room temperature with an inspiratory oxygen fraction (F_{I,O_2}) of 0.21: arterial oxygen tension (P_{a,O_2}), arterial carbon dioxide tension (P_{a,CO_2}), calculated alveolar to arterial pressure difference for oxygen ($P_{(A\text{-}a),O_2}$); 7) May-Grünwald differential cytological stains of BAL specimens; 8) microbiological: medium of diagnosis of PCP; pulmonary or systemic co-infections; 9) therapy: anti-pneumocystis regimen; change of therapy and reason for changes made; 10) in-hospital outcome: days of hospital treatment and stay; survival or fatal outcome; causes of death (respiratory failure attributable to PCP or other); 11) long-term survival. All data of initial clinical and laboratory investigations refer to the 24 h before diagnosis of PCP.

The radiographs of the chest were reviewed by one of the research group (A.P.), who was otherwise blinded for clinical information. The distribution of the infiltrates was evaluated, dividing the chest by a vertical line and two horizontal lines originating above and below the hilus, respectively, resulting in six areas. Patterns of parenchymal infiltrates were graded as either: absent (0); reticular or reticular-nodular (1); ground-glass (2); or airspace filling (3). A severity score was calculated by multiplying the type of the parenchymal infiltrate and the number of areas affected.

A presentation of PCP was considered as "atypical" if one of the following patterns was present: predominant or isolated apical infiltrates; presence of cysts and/or cavitations; pneumothorax; extrapulmonary or disseminated infection.

A BAL was considered to be falsely negative if within 60 days of follow-up PCP was documented by a repeated diagnostic procedure.

In order to ensure a representative population of breakthrough PCP for analysis, all patients with breakthrough PCP were derived from the population having received primary aerosolized pentamidine prophylaxis at our institution. All relevant data of these patients were recorded. The database included: 1) epidemiological data: age, sex; 2) data from history: history of AIDS-relating complex (ARC) or AIDS-defining illnesses; 3) immune status (within 3 months prior to the initiation of prophylaxis): CD4-cell count at entry; 4) data on prophylaxis: inhalation device and dosing schedule; date of first inhalation; 5) record of endpoints: change of prophylaxis regimen, breakthrough PCP; death; and censored observation.

Primary aerosolized pentamidine prophylaxis was started in case of repeated CD4-cell counts <200 CD4-cells·μL^{-1} or presence of clinical signs of ARC, or a history of another AIDS-defining illness. Aerosolized pentamidine was administered by a handheld jet-nebulizer (Lifetec-Respirgard or Pari IS2). The patients initially received 60 or 200 mg biweekly or 300 mg monthly, dissolved in 6 mL of sterile water. All patients on 60 mg were switched to 200 mg biweekly or 300 mg monthly after January 1, 1991. Inhalation was performed in a sitting position with breathing at tidal volume around the functional residual capacity.

Statistical analysis was performed using Statistical Package for Social Sciences for Windows ™. Categorical data were compared with the Chi-squared test and the Fisher's exact test in case of small expected frequencies, respectively (at least one frequency <2 or more than half of the frequencies <5 [16]). Descriptive statistics for continuous variables are expressed as the mean±the standard deviation. Analysis of variance and Kruskal-Wallis test were used to compare multiple groups of normally distributed and nonparametric data, respectively. Further comparisons between two groups were subject to Bonferroni correction. In all cases, p-values of less than 0.05 were considered to be significant.

The sensitivity of BAL was calculated as the number of true positive results divided into the number of proven cases.

Time-to-event distributions were estimated using the method of KAPLAN and MEIER [17]. The efficacy of aerosolized pentamidine was analysed on an intention-to-treat basis. Survival distributions were compared using the log-rank test. Sixty days was chosen as the observation time for in-hospital treatment.

Results

Study population

Overall, 95 patients (91 males and 4 females) had received primary aerosolized pentamidine prophylaxis since May 1, 1989. The population included 61 haemophiliacs, 17 homosexuals, 14 bisexuals, and three intravenous drug-abusers. The mean±SD age was 36±9 yrs (range 22–71 yrs), the mean CD4-cell count at entry 128±7 CD4-cells·mL^{-1} (range 8–378 CD4-cells·mL^{-1}). The mean inhalation time was 29.7±15.9 months (range 1–65 months). Eight patients received an additional oral drug with anti-pneumocystis activity, including four co-trimoxazole,

three dapsone, and one Fansidar after a mean of 15, 21 and 20 months of inhalation, respectively and were censored accordingly.

The total failure rate was 20 out of 95 (21%). The estimated cumulative risks of PCP were 8% at 12 months, 18% at 24 months, 23% at 36 months, 32% at 48 months, and 39% at 60 months. Prophylaxis failures did not reveal a significant relationship to different dosing schedules.

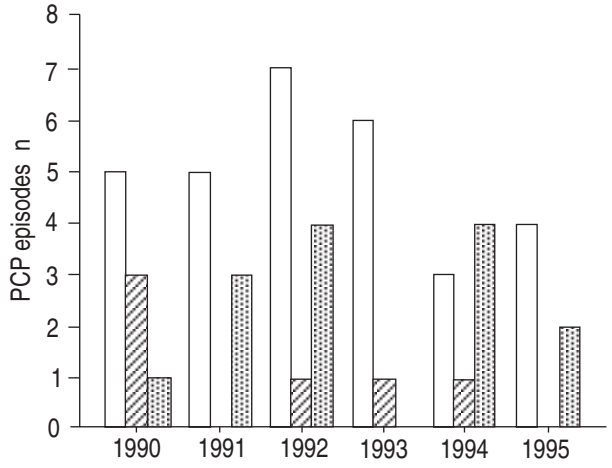

Fig. 1. – Distribution of PCP episodes January 1, 1990 until June 30, 1995. ☐: without prophylaxis; ▨: early failures; ▦: late failures.

Six breakthrough episodes occurred as "early" (≤12 months of inhalation), and 14 as "late" failures (>12 months of inhalation). The mean±SD inhalation time was 4.9±4.8 months for early and 26.3±14.1 months for late failures. No patient in the prophylaxis failure groups had received an additional prophylactic medication.

Thirty patients developed *Pneumocystis carinii* pneumonia without any prophylaxis. Six were episodes with previously unknown HIV-serostatus, and 24 refused any prophylaxis but were regularly investigated clinically and immunologically at our institution.

The distribution of PCP episodes during the observation period is shown in figure 1. The main baseline characteristics of the study populations are summarized in table 1. Importantly, only 10% of the group without prophylaxis and 5% in the prophylaxis group were intravenous drug abusers. Epidemiological as well as clinical data were comparable in all groups.

Sensitivity of BAL

BAL was diagnostic in 29 out of 30 episodes without any prophylaxis. The only negative result was achieved in a patient presenting with extensive cystic and cavitating disease. This case was confirmed in a repeated bronchoscopic procedure by transbronchial biopsy. In the prophylaxis group, two cases were negative in BAL, whilst confirmed in a repeated BAL and transbronchial biopsy, respectively. Both patients belonged to the late

Table 1. – Baseline epidemiological and clinical characteristics of the group without any prophylaxis, early failures, late failures and all failures taken together

	Without prophylaxis	Early failures	Late failures	All failures
Patients n	30	6	14	20
Sex M/F	26/4	6/0	13/1	19/1
Age# yrs	39±12	37±11	36±10	36±10
Risk group n (%)				
Haemophiliac	8 (27)	4 (66)	10 (72)	14 (70)
Homosexual	15 (50)	1 (17)	3 (22)	4 (20)
IVDA	3 (10)	0	1 (6)	1 (5)
Hetero-/Bisexual	3 (10)	1 (17)	0	1 (5)
Central African	1 (3)	0	0	0
PCP as AIDS-defining illness n (%)	22 (73)	3 (50)	12 (86)	15 (75)
Number of AIDS manifestations prior to PCP n				
1	8	2	1	3
2	0	1	1	2
AIDS staging (according to CDC 1992) n (%)				
A3	9 (30)	3 (50)	3 (22)	6 (30)
B3	13 (43)	0	9 (64)	9 (45)
C3	8 (27)	3 (50)	2 (14)	5 (25)
Kaposi sarcoma n (%)	4 (13)	0	1 (7)	1 (5)
Nebulizer n	-			
Respirgard II		4	9	13
Pari IS II		2	5	7
Dosing schedule of aerosolized pentamidine n	-			
60 mg biweekly		2	2	4
200 mg biweekly		1	3	4
300 mg monthly		3	9	12
Antiretroviral therapy* n (%)	7 (23)	3 (50)	7 (50)	10 (50)
Zidovudine	6	3	6	9
Zidovudine plus DDI	0	0	1	1
Zidovudine plus DDC	1	0	0	0

#: mean±SD; *: history of antiretroviral therapy at any time or concurrent medication. M: male; F: female; IVDA: intravenous drug abuser; PCP: *Pneumocystis carinii* pneumonia; AIDS: acquired immune deficiency syndrome; CDC: Centres for Disease Control. DDI: didesoxyinosin; DDC: didesoxycytiolin.

failure group. No further patient with symptoms suggestive of pneumonia who underwent bronchoscopy had a falsely-negative result for PCP during the observation period. Thus, BAL sensitivity was 97% in the group without prophylaxis, 100% in the early failure group and 86% in the late failure group. These differences were not statistically significant.

Pulmonary and systemic co-infections

Additional investigations of BAL for co-infections were performed in 25 out of 30 patients without prophylaxis and 18 out of 20 cases with prophylaxis. Five pulmonary co-infections were present in the group without any prophylaxis (three bacterial, one *Mycobacterium avium-intracellulare* (MAI)). *Streptococcus pneumoniae* was detected in significant amounts (10^6 colony forming units (cfu)·mL^{-1}) in one case. Cytomegalovirus (CMV) was isolated in two further cases. In the late failure group, pulmonary co-infections with MAI were detected in two cases. Two further cases revealed positive cultures for (CMV). These differences were not statistically significant.

Clinical, immunological and laboratory characteristics

The clinical performance at diagnosis of PCP was very similar in all groups. The mean duration of symptoms prior to the diagnosis of PCP as well as the proportion of patients with acute onset of disease (symptoms <5 days) was not significantly different in any group. There was also no difference in mean lymphocyte counts and CD4-cell counts, with late failures revealing lower levels as compared to patients without prophylaxis as well as to early failures. $P_{(A\text{-}a),O_2}$ as the variable most closely associated with the severeity of PCP [18] was not significantly different between the groups. Severe hypoxaemia defined as an $P_{(A\text{-}a),O_2}$ >8 kPa (>60 mmHg) at presentation was observed in only a minority of cases (17% in the group without any prophylaxis, 0% in the early failure group, and 21% in the late failure group). Furthermore, other parameters known to bear prognostic significance for the outcome of PCP, such as haemoglobin [19], albumin [20], LDH [21] and percentage of neutrophils in BAL [22], did not reveal any difference between the groups. Table 2 summarizes the most important data with regard to general clinical performance, severity of immunodeficiency, and severity of PCP in the three groups.

Chest radiographs

Thirty five chest radiographs, including 18 from the group without any prophylaxis and 17 (5 early/12 late failures) of the prophylaxis group were available for analysis. Upper lobe infiltrates were present in 50% of the group without any prophylaxis and 100% and 83% in the early and late failure group, respectively. This difference was significant. However, the radiographic score revealed no significant differences when the group without prophylaxis was compared with early or late failures (table 3).

Incidence of atypical, extrapulmonary and disseminated Pneumocystis carinii *infection*

Overall, atypical presentations other than upper lobe infiltrates were rare. Cysts and cavitations were found to

Table 2. – Comparison of clinical performance, severity of immunodeficiency and severity of PCP between the study groups

	Without prophylaxis	Early failures	Late failures	All failures
Clinical parameters				
Duration of symptoms days	22±18	18±16	16±11	17±12
Duration of symptoms <5 days n (%)	3 (10)	0	3 (22)	3 (15)
Body mass index kg·m^{-2}	20.5±4.2	20.9±3.9	20.2±2.8	20.4±3.1
Loss of weight kg	4.7±4.4	3.5±3.2	3.0±3.5	3.2±3.3
Immunology				
CD4 (%) cells·µL^{-1}	59±52	50±42	34±36	39±38
	(7±3)	(7±3)	(4±3)	(5±3)
CD8 (%) cells·µL^{-1}	615±507	375±324	555±636	492±545
	(55±50)	(51±16)	(50±20)	(50±18)
Lymphocytes cells·µL^{-1}	1162±988	997±703	743±725	819±710
(%)	(20±19)	(24±15)	(19±12)	(20±13)
γ-globulins g·dL^{-1}	1.8±0.7	1.6±0.6	1.3±0.5	1.4±0.5
Laboratory parameters				
Haemoglobin g·dL^{-1}	12.1±2.2	12.1±2.1	11.9±2.2	11.9±2.2
Albumin g·dL^{-1}	3.4±0.6	3.5±0.4	3.2±0.6	3.3±0.6
LDH U·L^{-1}	428±189	279±88	427±203	383±187
Oxygenation				
$P_{(A\text{-}a),O_2}$ kPa	6.0±2.3	5.1±2.3	6.2±2.0	5.7±2.0
mmHg	45±17	38±17	46±15	43±15
BAL				
Lymphocytes %	22±22	23±18	20±22	21±21
Neutrophils %	16±24	10±16	17±29	15±26

Values are presented as mean±SD, with percentage values in parentheses. LDH: lactate dehydrogenase; BAL: bronchoalveolar lavage; $P_{(A\text{-}a),O_2}$: alveolar to arterial pressure difference for oxygen.

Table 3. – Comparison of radiographic patterns between the study groups

	Without prophylaxis (n=18)	Early failures (n=5)	Late failures (n=12)	All failures (n=17)
Upper lobe infiltrates n (%)*	9 (50)	5 (100)	10 (83)	13 (77)
Cavities n (%)	1 (6)	0	1 (8)	1 (6)
Pleural effusion n (%)	1 (6)	0	2 (17)	2 (12)
Pneumothorax n (%)	1 (6)	0	0	0
Mean radiographic score	8.3±6.8	6.8±3.3	11.4±7.7	10.1±6.9

*: Chi^2=6.4; p<0.05.

Table 4. – Summary of therapeutic regimen in the four groups

	Without prophylaxis	Early failures	Late failures	All failures
First-line therapy n (%)				
Intravenous co-trimoxazole*	28 (93)	6 (100)	13 (93)	19 (95)
Intravenous pentamidine-isethionate**	2 (7)	-	1 (7)	1 (5)
Change of regimen to:				
Intravenous pentamidine-isethionate* n	2	1	3	4
Inhalative pentamidine-isethionate# n	3	-	-	-
Adjunctive steroids## n (%)	19 (63)	5 (83)	9 (64)	14 (70)
Mechanical ventilation n (%)	1 (3)	-	-	-

*: 100 mg·kg^{-1} sulphamethoxazole and 20 mg·kg^{-1} daily; **: 4 mg·kg^{-1} daily; #: 300 mg daily; ##: 1–2 mg·kg^{-1} daily.

be present in one patient from the group without any prophylaxis and in one patient with late failure. One pneumothorax occurred in the group without prophylaxis, and none in the prophylaxis groups. Extrapulmonary and disseminated pneumocystosis were not detected in any patient (table 3).

Therapeutic regimens

No significant differences could be detected between the groups with regard to drug treatment regimens and dosing schedules. The main therapeutic data are summarized in table 4. The pulmonary and systemic co-infections diagnosed *intra vitam* at the same time as PCP could be successfully treated in all groups.

In-hospital and long-term outcome

Two patients without any prophylaxis and two patients in the prophylaxis group (both late failures) had a fatal outcome. Death was attributable to PCP resulting in respiratory failure in one case from each group. The remaining two cases died of uncontrolled oesophageal variceal bleeding with underlying chronic hepatitis C and liver cirrhosis and of staphylococcal sepsis during long-term mechanical ventilation. The differences in survival were not significant (log-rank 1.32; p=0.52).

Long-term survival after successfully treated PCP could be determined in 23 patients without any prophylaxis (two in-hospital deaths, five lost to follow-up) and 17 patients on aerosolized pentamidine (two in-hospital deaths, one lost to follow-up). The median±SD survival time was 23.5±5.4 as compared to 26.5±10.7 months. The differences in survival were also not significant (log-rank 0.17; p=0.68). When early and late failures were compared the median survival was 11.6±3.4 in the early failure group and 26.5±3.4 months in the late failure group. Again, this difference was not significant (log rank 0.22; p=0.64).

Discussion

We found no difference in clinical presentation and severity of PCP after long-term primary aerosolized pentamidine prophylaxis as compared to episodes without any prophylaxis and to early failures. Episodes during prophylaxis had upper lobe infiltrates on chest radiograph significantly more frequently. Other patterns of "atypical" PCP did not reveal a higher incidence in any prophylaxis group. The sensitivity of BAL as diagnostic test for PCP was also found to be unaffected by long-term inhalation. In-hospital outcome as well as long-term survival after successful treatment of PCP were comparable in all groups.

The overall failure rates of this study were comparable with other reports. The recently reported estimated 36 month cumulative risks of PCP were 21% [4] and 22% [23], as compared to 23% in our analysis. Thus, our breakthrough episodes can be regarded as representative and valid cases for analysis of our subject. Moreover, no episode of PCP diagnosed at our institution during the observation period was treated on an outpatient basis. These two facts exclude important potential selection bias. It is important to recognize, however, that the 24 patients with known HIV-serostatus but without any prophylaxis were nevertheless regularly investigated at our institution. Data on severity of PCP at presentation, therefore, largely refer to informed patients known to be HIV-infected with close contact to an experienced treatment centre.

The baseline characteristics of our patients were homogenous with regard to sex, age, PCP as first AIDS manifestation, and clinical staging. In addition, the percentage

of intravenous drug-abusers was low and comparable in all groups. This is an important fact as intravenous drug abuse may be associated with pre-existing or concurrent lung damage independently of PCP [24]. Also the therapeutic regimens and dosing schedules of PCP were very similar in all groups. Our observations and conclusions, therefore, seem well-substantiated despite the limited number of patients studied.

The absence of significant differences in clinical presentation as well as in diagnostic yield of BAL between early and late failures establishes further evidence against the hypothesis that aerosolized pentamidine is causally involved in the pathogenesis of atypical presentations of first episodes of PCP. Pneumothorax, cyst-formation, and cavitation were all observed in the group without prophylaxis. Conversely, only one case presented with cavitating disease in the late failure group. These observations correspond to reports about pneumothorax as well as cavitations with and without aerosolized pentamidine prophylaxis [23, 25, 26].

Although only a limited number of chest radiographs were available for analysis, there was a pattern of upper lobe infiltrates in about 80% of the cases of late failures on primary pentamidine prophylaxis and this should certainly be taken into account when performing BAL. This incidence is clearly different from that reported for the natural history of PCP [25]. On the other hand, it corresponds to the incidence reported in early failures [5, 6, 27]. This observation indicates that late breakthrough PCP frequently presents as localized rather than diffuse infection. Inhomogenous distribution patterns of pentamidine aerosol, therefore, remain the central concern with regard to the safety of this prophylaxis regimen.

The favourable results of BAL as diagnostic test for PCP in both prophylaxis groups were achieved using the site-directed lavage technique. Accordingly, all studies on PCP during aerosolized pentamidine in which BAL was performed in an upper lobe segment or in the segment most prominently affected in the chest radiograph conserved a diagnostic yield for the diagnosis of PCP of 90–100% [6–8, 10, 11]. An initial report on a reduced diagnostic yield, on the other hand, relied on BAL in a standard segment [5]. BAL should therefore no longer be performed in a standard segment in the setting of aerosolized pentamidine.

Mortality attributable to respiratory failure of PCP was low in all groups. The favourable prognosis of first episodes of PCP, including those patients with profound immunodeficiency for prolonged periods or other chronic debilitating AIDS manifestations, is probably the result of an early diagnosis of PCP. Accordingly, severe hypoxaemia defined as $P_{(A\text{-}a),O_2}$ >8 kPa (>60 mmHg) at presentation was observed only in a minority of cases. The long-term prognosis of PCP in all groups was also well comparable with data reported in the literature [28, 29]. A median survival of 26.5±3.4 months in the late failure group expected to have developed PCP later in the course of the AIDS-disease suggests a benefit in long-term survival for patients on primary aerosolized pentamidine prophylaxis as was proven for secondary prophylaxis [30].

In conclusion, using the site-directed technique of bronchoalveolar lavage, *Pneumocystis carinii* pneumonia remains a condition which can be reliably diagnosed after long-term primary aerosolized prophylaxis. Moreover, the severity of *Pneumocystis carinii* pneumonia appears to remain unchanged and complications remain infrequent. Our findings support the option of aerosolized pentamidine as long-term primary prophylaxis for *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected patients.

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