Risk factors for breakthrough *Pneumocystis carinii* pneumonia on aerosol pentamidine prophylaxis

RA McIvor MD FRCPC MRCP, AR Rachlis MD FRCPC, P Berger MD CCFP, LR Lee Pack, CK Chan MD FRCPC FCCP FACP

Department of Medicine, The Wellesley and Sunnybrook Hospitals, University of Toronto, and The Toronto Central Aerosol Pentamidine Clinic, Toronto, Ontario

RA McIvor, AR Rachlis, P Berger, LR Lee Pack, CK Chan. Risk factors for breakthrough *Pneumocystis carinii* pneumonia on aerosol pentamidine prophylaxis. Can Respir J 1995;2(1):49-54.

Objective: To identify baseline characteristics of human immunodeficiency virus (HIV)-infected individuals on aerosol pentamidine for *Pneumocystis carinii* prophylaxis that are predictive of subsequent breakthrough *Pneumocystis carinii* pneumonia (PCP).

Design: Nested case-control study assembled from a cohort of patients enrolled in the Toronto aerosol pentamidine program.

Methods: Subjects were selected from a cohort of HIV-infected individuals were enrolled in a community based aerosol pentamidine program between May 1989 and May 1992 in Toronto, Ontario. Cases – individuals who had breakthrough PCP – were matched with up to two controls enrolled in the same week. Risk factors examined for development of PCP for both primary and secondary prophylaxis included age, sex, smoking history, evidence of bronchospasm during aerosol pentamidine administration (fall of forced expiratory volume [FEV] 15% or more), administration of salbutamol before aerosol pentamidine, pulmonary function tests including lung volumes, flow rates and diffusing capacity for carbon monoxide. In the primary prophylaxis group, CD4 count at enrolment and in the secondary prophylaxis group, time from the most recent episode of PCP to enrolment for aerosol pentamidine and total time from the most recent episode of PCP to breakthrough PCP were examined as additional risk factors.

Results: A total of 1344 patients were enrolled in the aerosol pentamidine program, 78% for primary prophylaxis and 22% for secondary prophylaxis. At the time of census at the end of 1992 there had been 96 episodes of breakthrough PCP, 5% on primary prophylaxis and 14.5% on secondary prophylaxis. In the primary prophylaxis group, enrolment CD4 count was significantly lower in the cases developing breakthrough PCP: 116±74 compared with 175±85 cells/mm^3 in the control group (P=0.001). There was no difference in any other variable. In the secondary prophylaxis group, time from the most recent episode of PCP to initiation of aerosol pentamidine therapy was longer in the cases developing breakthrough PCP: mean delay 6.1±6.6 months compared with 3.1±2.1 in controls (P=0.02). There was no difference in the other variables examined.

Conclusions: The results of this study support immune augmentation for patients receiving aerosol pentamidine for primary prophylaxis, and aerosol pentamidine should be recommenced as soon as possible following an episode of PCP, for secondary prophylaxis. *(Pour résumé, voir page 50)*

Key Words: *Acquired immunodeficiency syndrome (AIDS), Human immunodeficiency virus (HIV), Pentamidine,* Pneumocystis carinii *pneumonia*

Correspondence and reprints: Dr CK Chan, The Wellesley Hospital, 160 Wellesley Street East, #242 Jones Building, Toronto, Ontario M4J 1J3

Facteurs de risque pour l'apparition d'une pneumonie à *Pneumocystis carinii* pendant une prophylaxie à la pentamidine en aérosol

Objectif : Identifier les caractéristiques de base des individus infectés par le virus de l'immunodéficience humaine (VIH) et traités en prophylaxie avec de la pentamidine en aérosol contre le *Pneumocystis carinii*, et qui sont prédictives pour le développement d'une pneumonie à *Pneumocystis carinii* (PPC) subséquente.
Modèle : Étude cas/témoins emboîtés réalisée à partir d'une cohorte de patients recrutés dans le programme de pentamidine en aérosol de Toronto.
Méthodes : Les sujets ont été choisis dans une cohorte d'individus infectés par le VIH qui avaient été recrutés pour un programme de pentamidine en aérosol basé dans la communauté entre mai 1989 et mai 1992 à Toronto, en Ontario. Les cas – individus qui ont développé une PPC – ont été appariés avec un ou deux sujets contrôles recrutés dans la même semaine. L'analyse des facteurs de risque pour le développement d'une PPC au cours des deux types de prophylaxie, primaire et secondaire, comprenaient l'âge, le sexe, le tabagisme, la présence d'un bronchospasme lors de l'administration de la pentamidine en aérosol (chute du volume expiratoire maximal/seconde [VEMS] de 15% ou plus), l'administration de salbutamol avant la pentamidine en aérosol, les tests de fonction pulmonaire, notamment les volumes pulmonaires, les débits et la capacité de diffusion du monoxyde de carbone. Un autre facteur de risque analysé était, pour le groupe soumis à une prophylaxie primaire, la numération CD4 au moment du recrutement tandis que pour le groupe soumis à une prophylaxie secondaire, les facteurs de risque additionnels comprenaient l'intervalle de temps entre l'épisode le plus récent de PPC et la date du recrutement pour le traitement à la pentamidine en aérosol et l'intervalle de temps entre l'épisode de PPC le plus récent jusqu'à une récidive de PPC.
Résultats : Au total, 1344 patients ont été recrutés dans le programme de pentamidine en aérosol dont 78 % pour une prophylaxie primaire et 22 % pour une prophylaxie secondaire. Au moment du recensement à la fin de 1992, on a dénombré 96 épisodes de PPC sous prophylaxie, soit 5 % des cas de prophylaxie primaire et 14,5 % des cas de prophylaxie secondaire. Dans le groupe soumis à une prophylaxie primaire, la numération CD4, au moment du recrutement, était nettement inférieure chez les cas développant une PPC : 116±74 cellules/mm^3 comparativement à 175±85 cellules/mm^3 dans le groupe contrôle (P=0,001). Il n'y avait aucune différence dans les autres variables. Dans le groupe soumis à une prophylaxie secondaire, l'intervalle de temps entre l'épisode le plus récent de PPC et le début du traitement à la pentamidine en aérosol était plus long chez les cas présentant une récidive de PPC : retard moyen 6,1±6,6 mois comparativement à 3,1±2,1 chez les sujets contrôles (P=0,02). Aucune autre différence n'a été observée pour les autres variables.
Conclusions : Les résultats de cette étude appuient l'utilisation d'immunostimulants chez les patients recevant de la pentamidine en aérosol pour une prophylaxie primaire. De plus, on devrait recommencer le plus tôt possible à administrer la pentamidine en aérosol à la suite d'un épisode de PPC, pour une prophylaxie secondaire.

Pneumocystis carinii pneumonia (PCP) remains the most prevalent infectious complication of AIDS in North America. PCP in Ontario still represents the index disease in approximately 53% of cases (1).

As the human immunodeficiency virus (HIV) epidemic develops into a chronic illness in the 1990s, the focus of treatment has changed towards prophylaxis rather than acute salvage therapy for both PCP and many other opportunistic infections that were lethal in the early 1980s.

Trimethoprim-sulfamethoxazole (TMP-SMX) remains the 'gold' standard prophylaxis against PCP in the 1990s. This has been confirmed in recent trials of both primary and secondary PCP prophylaxis (2-3). Approximately 30% of HIV individuals are intolerant to long term TMP-SMX, and for these individuals aerosol pentamidine remains a strong and proven second-line alternative (2-3). Thus, even with early diagnosis and therapy directed towards reversal of the underlying immune dysfunction, there is still a substantial pool of patients who require aerosol pentamidine prophylaxis over many months or years.

In the late 1980s, two main aerosol pentamidine prophylaxis regimens were validated in clinical trials and are still widely used in the 1990s (4). Some centres have adopted the jet nebulizer Respirgard II system, using 300 mg of pentamidine monthly to minimize the number of clinic visits (5). Ultrasonic nebulizers such as Fisoneb, Porta-sonic and Aerosonic, using pentamidine at 60 mg every two weeks, are being used to reduce the amount and cost of drug used (6).

Aerosol pentamidine is clearly not 100% effective, and as time passes we are faced with increasing numbers of episodes of breakthrough PCP (7-9).

In an effort to identify risk factors for breakthrough PCP, with an emphasis on pulmonary function abnormalities, we carried out a nested case-control study in a large cohort of patients followed for three-and-a-half years in a central aerosol pentamidine program in Toronto.

PATIENTS AND METHODS

Aerosol pentamidine program clinic population: Individuals were enrolled in the aerosol pentamidine program for primary prophylaxis if they had CD4 counts below 300 cells/mm^3. Primary prophylaxis was also commenced for HIV-infected individuals with constitutional symptoms, eg, unexplained persistent fever (greater than 37.8°C) for two weeks or more, or oropharyngeal candidiasis (unrelated to antibiotic or corticosteroid therapy), regardless of the CD4 count.

Secondary prophylaxis was initiated as soon as possible following completed therapy for one or more acute episodes of PCP.

In all cases, HIV status was confirmed by both the enzyme-linked immunosorbent assay (ELISA) and Western blot methods.

Aerosol pentamidine protocol: All patients received 60 mg pentamidine every two weeks via Fisoneb (Fisons Corp, New York) following a loading period of five doses over a two-week period according to the Canadian multicentre study protocol (6). Patients were monitored for cough and pen-

TABLE 1
Primary prophylaxis

	Cases Mean ± SD (n=53)	Controls Mean ± SD (n=98)	P value
Baseline characteristics			
Age (years)	39.8±8	41.6±9	0.14
T4 (cells/mm^3)	116±74	175±85	0.001
First treatment to breakthrough PCP or last treatment (months)	16.7±9.1	20.5±8.6	0.016
Smokers	43%	54%	0.28
Spirometry and bronchodilator use			
% Fall in FEV_1	−9.4±11	−9.5±9 5	0.96
Fall of ≥15% FEV_1	26%	26%	0.84
Regular bronchodilator before aerosol pentamidine	68%	54%	0.28
Baseline pulmonary function tests			
Total lung capcity (% predicted)	86±14	88±15	0.5
Forced vital capacity (% predicted)	90±13	93±14	0.09
FEV_1 (% predicted)	87±14	90±13	0.12
DLCO (% predicted)	81±22	84±20	0.37

DLCO Single breath diffusion capacity for carbon monoxide; FEV_1 Forced expiratory voume in 1 s; PCP Pneumoncystis carinii *pneumonia*

tamidine-induced bronchospasm during aerosol pentamidine therapy with pre- and postspirometry. Prophylactic salbutamol was administered 20 mins before aerosol pentamidine if a fall in forced expiratory volume in 1 s (FEV_1) of 15% or more occurred between pre- and postaerosol pentamidine therapy. Salbutamol was also available for individuals who experienced cough, wheeze or chest tightness but did not have a reduction in FEV_1 of 15% or more.

All treatments were administered at a single out-patient treatment facility in Toronto.

Selection of patients for the case-control study: The cases and controls were identified from the cohort of all HIV-infected patients enrolled in the aerosol pentamidine program between May 1989 and May 1992. All breakthrough cases occurring up to the date of census, December 31, 1992, were matched with up to two controls.

Selection of cases: Cases of PCP were defined as either: confirmed PCP episodes from cytopathologically proven samples obtained from sputum, bronchoscopy or biopsy; or highly probable episodes of PCP without cytopathological proof but with clinical and radiological response to a course of anti-PCP therapy, or cause of death directly attributed to breakthrough PCP. No cases of extrapulmonary *P carinii* infection were identified.

Selection of controls: Controls were individuals who had not developed breakthrough PCP and were selected from the longitudinal aerosol pentamidine program database. They were matched to the cases for primary or secondary prophylaxis. All cases were also matched for date of enrolment with up to two controls enrolled in the aerosol pentamidine program within one week of the case. Controls had no documented episodes of breakthrough PCP or treatment for presumed PCP. These criteria for control selection ensured comparable length of aerosol pentamidine treatment and length of time at risk of breakthrough PCP after initiation of aerosol pentamidine in the two groups.

Baseline risk factors: Risk factors examined were age, sex, smoking history, evidence of bronchospasm during aerosol pentamidine administration (fall of FEV_1 15% or more), requirement for salbutamol before pentamidine administration and baseline complete pulmonary function, and all were recorded at patient enrolment. In the primary prophylaxis group CD4 count was also recorded at enrolment, before commencement of aerosol pentamidine. In the secondary prophylaxis group, the time from the most recent episode of PCP to enrolment in the aerosol pentamidine program was also assessed, as was the total time from the most recent episode of PCP to either breakthrough PCP (cases) or the end of the study period.

Surveillance protocol for PCP: Baseline assessment at enrolment and follow-up was coordinated through the HIV primary care physicians who were responsible for the patients. The HIV primary care physicians were prompted by the HIV Project Centre (Sunnybrook Health Sciences Centre, Toronto) and were responsible for the completion of follow-up assessments at three- to six-month intervals. A team of three data collection nurse/monitors made regular visits to the physicians' offices to ensure adequate documentation on all patients in the aerosol pentamidine program. Data related to investigation and treatment of PCP episodes were obtained and confirmed from source documents in physicians' offices.

Pulmonary function tests: Complete pulmonary function tests were performed by a single technician on a computerized MMC Horizon 4400 system (SensorMedics, California) and results expressed as percentage predicted using Knudsen 1983 values (10). Complete pulmonary function tests included spirometry performed in accordance with American Thoracic Society guidelines (11), lung volumes by nitrogen washout and single breath diffusion capacity for carbon monoxide (DLCO) corrected for hemoglobin (12). Baseline pulmonary function tests were performed on all patients before commencement of aerosol pentamidine therapy.

Statistical analysis: Baseline results are presented as the

TABLE 2
Secondary prophylaxis

	Cases Mean ± SD (n=43)	Controls Mean ± SD (n=77)	P value
Baseline characteristics			
Age (years)	39.8±8	40.0±9	0.45
Latest PCP to first aerosol pentamidine treatment (months)	6.1±6.6	3.1±2.1	0.02
First treatment to breakthrough PCP or last treatment (months)	10.8±6	15.3±7	0.002
First episode of PCP to breakthrough PCP or last treatment (months)	14.8±6.5	17.9±8.2	0.04
Smokers	42%	36%	0.69
Spirometry and bronchodilator use			
% fall in FEV_1	−10.8±10.1	−6.5±10.4	0.21
Fall of ≥15% FEV_1	25%	18%	0.9
Regular bronchodilator before aerosol pentamidine	58%	23%	0.052
Baseline pulmonary function tests			
Total lung capacity (% predicted)	89±16	85±15	0.34
Forced vital capacity (% predicted)	88±13	88±13	0.83
FEV_1 (% predicted)	87±13	88±13	0.87
DLCO (% predicted)	64±15	71±20	0.11

DLCO Single breath diffusion capacity for carbon monoxide; FEV_1 Forced expiratory voume in 1 s; PCP Pneumoncystis carinii *pneumonia*

means and standard deviations. An unpaired two-tailed Student's *t* test was used to compare continuous variables, and a χ^2 test with correction for continuity was used for categorical variables. $P<0.05$ was considered significant.

RESULTS

A total of 1344 individuals were enrolled during this period. Seventy-eight per cent (1048) were receiving aerosol pentamidine as primary PCP prophylaxis (CD4 count less than 300 cells/mm^3). Twenty-two per cent (296) were receiving aerosol pentamidine as secondary PCP prophylaxis (one or more previous episodes of PCP). Ninety-seven per cent of patients were receiving concurrent antiretroviral therapy with zidovudine (AZT) or didanosine (ddI) during the time of this study. Due to the flexible clinic hours and schedule, compliance was excellent in all groups with more than 90% of individuals attending more than 90% of scheduled visits.

Primary prophylaxis Fifty-three cases of breakthrough PCP occurred in the group receiving primary prophylaxis (53 of 1048, 5%). They were matched with 98 controls. Mean age was 40 years in the cases compared with 42 years in controls (P=0.14). Mean CD4 count was 116±74 cells/mm^3 in the cases compared with 175±85 in the controls (P=0.001). Time from initiation of aerosol pentamidine to breakthrough PCP in the cases was 16.7±9.1 months. To ensure that control subjects were at the same risk of breakthrough PCP, the controls were followed for a significantly longer period of time, compared with the time to breakthrough PCP for the cases, a mean of 20.5±8.6 months (P=0.016) (Table 1). Forty-three per cent of the cases were smokers, compared with 54% of the controls (P=0.28). Spirometry before and after aerosol pentamidine therapy showed a mean reduction in FEV_1 of −9.4±11.0 in the cases compared with −9.5±9.5 in the controls (P=0.96). Twenty-six per cent of cases and 26% of controls had a documented fall in FEV_1 of 15% or more (P=0.84). In both the case (68%) and control (54%) groups (P=0.28), approximately twice as many individuals took regular bronchodilators 20 mins before administration of aerosol pentamidine compared with those who had a documented fall in FEV_1 of 15% or more. Baseline pulmonary function tests showed no statistical difference in lung volumes, flow rates or DLCO corrected for hemoglobin between cases and controls (Table 1).

Secondary prophylaxis: Forty-three cases of breakthrough PCP in the group receiving secondary prophylaxis (43 of 296, 14.5%) were matched with 77 controls. Mean age was 40 years in both groups (P=0.45). The time from the latest episode of PCP to initiation of aerosol pentamidine therapy was 6.18±6.6 months in the cases compared with 3.1±2.1 months in the controls (P=0.02). The cases occurred at a mean of 10.8±6 months on aerosol pentamidine, and control subjects were followed for a significantly longer period by design, for 15.3±7 months (P=0.002) (Table 2). Subsequent cases of breakthrough PCP occurred at 14.8±6.5 months following the previous episode; control subjects were followed for 17.9±8.2 months following the previous episode (P=0.04), a significantly longer period, during which time they remained PCP free. Forty-two per cent of the cases were smokers compared with 36% of controls (P=0.69). Spirometry before and after aerosol pentamidine therapy showed a mean reduction in FEV_1 of −10.8±10.4% in the cases compared with −6.5±6.4% in the controls (P=0.21). Twenty-five per cent of the cases and 18% of controls had a documented fall in FEV_1 of 15% or more (P=0.9). Approximately twice as many cases required regular bronchodilation before aerosol pentamidine, compared with 23% of controls (P=0.052). Baseline pulmonary function tests showed no

statistically significant difference in lung volumes, flow rates or DLCO corrected for hemoglobin, between cases and controls (Table 2).

DISCUSSION

One of the major thrusts in HIV management in the second half of the first decade of the HIV epidemic has been the attempt to prevent or delay PCP (4).

We had a unique opportunity to monitor a large cohort of individuals on aerosol pentamidine in Toronto. In this study, we wanted to ascertain whether there were any prognostic indicators, particularly with respect to underlying lung function, identifiable at enrolment that may predict subsequent breakthrough PCP in patients receiving aerosol pentamidine for PCP prophylaxis. The Multicenter Aids Cohort Study (8) suggested that the CD4 count was an important predictor of subsequent development of PCP in individuals not receiving PCP prophylaxis. However, with secondary prophylaxis no strong predictor for breakthrough PCP has been identified; breakthrough PCP was felt not to be related to the CD4 count in this group, and CD4 counts were not obtained in the secondary prophylaxis group.

In the present study, the only identifiable risk factor for development of breakthrough PCP in primary prophylaxis was a lower CD4 count at inception. Baseline pulmonary function test profiles were similar; in particular there was no evidence of worse airflow obstruction or reduced DLCO in the cases compared with controls.

In the secondary prophylaxis group, a delay in the time from the last episode of PCP to initiation of aerosol pentamidine therapy was highly predictive for subsequent breakthrough PCP. The mean time to the loading doses of aerosol pentamidine in the cases was six months, almost double the delay in the controls. The main reason for this delay was that aerosol pentamidine therapy was not widely available until May 1989 in Toronto, and patients intolerant to TMP-SMX before this had not been receiving adequate prophylaxis, because dapsone with or without TMP was not widely used in 1989 or 1990 at our centre. We now encourage commencement of aerosol pentamidine therapy as soon as possible following completion of a full course of anti-PCP therapy. Controls receiving secondary prophylaxis were followed and remained free from breakthrough PCP for longer – 17.9 months compared with 14.8 months for cases (P=0.04). Also in the secondary prophylaxis group, there were no differences between cases and controls with respect to enrolment lung volumes, flow rates or DLCO.

We particularly focused on baseline pulmonary function tests and spirometry pre- and postaerosol pentamidine as risk factors, since aerosol pentamidine is an inhaled medication and is known to cause bronchospasm (5-6). Our data do not suggest that airflow obstruction was a major factor for breakthrough PCP on aerosol pentamidine. However, there was a trend towards increased bronchodilator use in cases receiving aerosol pentamidine for secondary prophylaxis, although this did not reach statistical significance. Approximately twice as many individuals took regular bronchodilator before aerosol pentamidine as those who had a documented fall in FEV_1 of 15% or more. This may in part reflect the aggressive monitoring of the aerosol pentamidine program for cough and bronchospasm, with the use of an inhaled beta-agonist as premedication for aerosol pentamidine.

Pulmonary function abnormalities are felt to be important in identifying subclinical PCP. A reduction in lung volume or a reduced DLCO may suggest subclinical pneumonitis, or perhaps for those on secondary prophylaxis, unresolved or persistent PCP. There was no significant difference between the pulmonary function tests of cases and controls enrolled for primary or secondary prophylaxis in this study. It should, however, be noted that the DLCO in both cases and controls enrolled for secondary prophylaxis is reduced compared with those receiving primary prophylaxis. Whether the findings suggest adequate suppression of *P carinii* before initiation of aerosol pentamidine in our population or merely indicate the lack of sensitivity of pulmonary function testing in detecting subclinical PCP is open to debate.

Our study strongly suggests that in patients receiving primary prophylaxis as much effort as possible should be directed towards obtaining and maintaining a high CD4 count, because even on adequate aerosol pentamidine prophylaxis a high CD4 count is an important prognostic factor in the delay of subsequent PCP. In patients with one or more episodes of PCP, prophylactic therapy should be commenced as soon as possible after treatment for PCP.

Risk factors for breakthrough PCP identified in this study may not be generalizable to other systemic PCP prophylaxis protocols. However, the risk factors identified in this study appear to reflect underlying immune dysfunction or a delay in the initiation of PCP prophylaxis rather than being directly linked to aerosol pentamidine treatment. Thus, until similar analysis is conducted on patients on systemic prophylaxis for PCP, one should apply the same principles of early initiation of PCP prophylaxis when the CD4 starts falling or as soon as possible after recovery from an episode of PCP.

ACKNOWLEDGEMENTS: This program was funded by the Ministry of Health of Ontario.

REFERENCES

1. Ontario AIDS Bulletin 1993. Toronto: Ministry of Health, Ontario, 1993.
2. Hardy WD, Feinberg J, Finklestein D, Power ME, He W, Koczka C. ACTG Protocol 021. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia (PCP) in patients with the acquired immunodeficiency syndrome. N Engl J Med 1992;327:1842-8.
3. Schneider MME, Hoepelman AIM, Eeftinck Schattenkerk JKM, et al. A controlled trial of aerosolized pentamidine or trimethoprim sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus infection. N Engl J Med 1992;327:1836-41.
4. National Institute of Allergy And Infection Diseases Important Therapeutic Information on Prevention of Recurrent *Pneumocystis carinii* Pneumonia in Persons With AIDS. Executive Summary Clinical Alert Oct 21, 1991.

5. Leoung GS, Fiegal DW, Montgomery AB, et al. Aerosol pentamidine for prophylaxis against *Pneumocystis carinii* pneumonia. The San Francisco Community Prophylaxis Trial. N Engl J Med 1990;323:769-75.
6. Montaner JSG, Lawson L, Gervais A, et al. Aerosolized pentamidine for secondary prophylaxis of AIDS related *Pneumocystis carinii* pneumonia. Ann Intern Med 1991;114:948-53.
7. Graham NMH, Zeger SL, Park LP, Phair JP, Detels R, Vemund SH. Effect of zidovudine and *Pneumocystis carinii* pneumonia prophylaxis on progression of HIV-1 infection to AIDS. Lancet 1991;338:265-9.
8. Phair JP, Munoz A, Detels R, et al. The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. N Engl J Med 1990;332:161-5.
9. Graham NMH, Zeger SL, Park LP Vermud SH, Detels R, Renaldo CR. The effects on survival of early treatment of human immunodeficiency virus infection. N Engl J Med 1992;323:1037-42.
10. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am Rev Respir Dis 1983;127:725-34.
11. American Thoracic Society. Snowbird workshop on standardization of spirometry. Am Rev Respir Dis 1979;119:831-8.
12. Crapo RO, Morris AH. Standardized single breath normal values for carbon monoxide diffusing capacity. Am Rev Respir Dis 1981;123:185-9.