

Initial drug regimen for active tuberculosis cases in Montreal, 1995 to 1998

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OBJECTIVES: To evaluate the proportion of tuberculosis (TB) cases initially treated with the recommended four-drug regimen of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB) or streptomycin; and to identify factors associated with the choice of initial therapy.

DESIGN: Descriptive analysis of surveillance data obtained by TB case notifications from physicians and microbiology laboratories.

SETTING: The island of Montreal (with a population of 1,854,435 people).

STUDY POPULATION: All TB cases reported between January 1, 1995 and December 31, 1998.

OUTCOME MEASURE: The proportion of TB cases initially treated with a four-drug regimen by sex, age, country of birth, site of disease and year of reporting.

MAIN RESULTS: Seven hundred forty-one cases were reported during the study period. Among the 687 analyzed cases, 406 (59.1%) received the recommended initial four-drug regimen (INH-RIF-PZA-EMB), 187 (27.2%) received an INH-RIF-PZA regimen, 61 (8.9%) received an INH-RIF-EMB regimen and 33 (4.8%) received an INH-RIF regimen only. In a logistical regression model, a four-drug regimen was significantly associated with respiratory disease (odds ratio [OR] 4.48; 95% CI 3.15 to 6.39), age younger than 65 years (OR 2.32; 95% CI 1.55 to 3.45), being foreign-born (OR 1.62; 95% CI 1.06 to 2.48) and later year of reporting (OR 1.27; 95% CI 1.09 to 1.47).

CONCLUSIONS: The proportion of TB cases initially treated with a four-drug regimen has increased steadily since 1995, reaching 65% in 1998. However, given the rate of INH resistance in Montreal, efforts to promote the use of the initial four-drug regimen must continue.

Key Words: *Antitubercular agents; Communicable disease control; Disease notification; Microbial drug resistance; Multidrug-resistant tuberculosis; Population surveillance; Public health; Tuberculosis*

Régime thérapeutique initial pour les cas de tuberculose active, Montréal, 1995 à 1998

OBJECTIF: Évaluer la proportion des cas déclarés de tuberculose qui reçoivent le régime initial recommandé comportant quatre médicaments (isoniazide [INH], rifampicine [RIF], pyrazinamide [PZA] et éthambutol [EMB]); et déterminer les facteurs associés au choix du régime thérapeutique initial.

CONCEPTION : Analyse descriptive des données de surveillance obtenues à partir de la déclaration des cas de tuberculose par les médecins traitants et les laboratoires de microbiologie des hôpitaux.

CONTEXTE : Île de Montréal (population: 1 854 435).

POPULATION ÉTUDIÉE: Tous les cas de tuberculose déclarés entre le 1^{er} janvier 1995 et le 31 décembre 1998.

MESURE DE RÉSULTATS : Proportion des cas ayant reçu quatre médicaments en début de traitement mesurée en fonction du sexe, de l'âge, du pays de naissance, du type d'atteinte du patient et de l'année de la déclaration.

RÉSULTATS: De 1995 à 1998, 741 cas de tuberculose ont été déclarés. Sur les 687 cas analysés, 406 (59,1 %) ont reçu le régime thérapeutique recommandé (INH-RIF-PZA-EMB), 187 (27,2 %) un régime comportant INH-RIF-

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PZA, 61 (8,9 %) un régime comportant INH-RIF-EMB et 33 (4,8 %) un régime comportant INH-RIF seulement. Dans un modèle de régression logistique, la quadruple thérapie était associée de façon significative à une atteinte respiratoire (RC 4,48; IC 95 % 3,15-6,39), à un âge inférieur à 65 ans (RC 2,32; IC 95 %: 1,55-3,45), au fait d'être né à l'extérieur du Canada (RC 1,62; IC 95 % 1,06-2,48) et à une année de déclaration plus tardive (RC 1,27; IC 95 % 1,09-1,47).

CONCLUSION : La proportion de cas de tuberculose recevant un traitement de départ comportant quatre antituberculeux a augmenté constamment depuis 1995 et atteint 65 % en 1998. Cependant, compte tenu du taux de résistance à l'INH à Montréal, la promotion de l'utilisation d'emblée d'un tel régime thérapeutique quadruple doit se poursuivre.

In the United States, since 1985, dramatic changes in tuberculosis (TB) morbidity prompted the Centers for Disease Control and Prevention and the American Thoracic Society to update their recommendations for the treatment of TB among adults and children (1,2). These recommendations promoted the in vitro drug susceptibility testing of *Mycobacterium tuberculosis* isolates from all patients, the reporting of these results to the health department and an initial four-drug regimen for the treatment of TB.

Although Canada did not experience the same rate increase as the United States, the Canadian Thoracic Society, in the *Canadian Tuberculosis Standards, 4th edition*, made similar recommendations (3). These recommendations included the use of a four-drug regimen of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB) or streptomycin (SM) for the initial treatment of active TB. In communities where overall INH resistance exceeds 4%, all patients with active TB should be treated initially with INH, RIF, PZA and EMB or SM. When susceptibility to INH and RIF has been demonstrated, EMB or SM can be stopped, and PZA may be discontinued after the initial eight weeks of treatment (1-3).

In Montreal, between 1992 and 1995, the proportion of TB cases resistant to INH was greater than 4% in almost all age groups among both foreign-born and Canadian-born cases (4). This article presents data on the initial drug regimen prescribed by clinicians between 1995 and 1998 and on factors that may have influenced the choice of initial treatment.

DATA AND METHODS

Throughout Canada, active TB is a reportable disease. In Montreal, all cases of active TB are reported to the Department of Public Health (DPH). Each case is investigated by a public health nurse who obtains clinical and epidemiological information and ensures that appropriate treatment is initiated, that the patient adheres to the treatment regimen, and that close contacts of the patient are tested and referred for further evaluation when necessary.

The DPH maintains a nominal database of all reported patients having active TB who reside in the region at the time of diagnosis. This database contains epidemiological data and the results of drug susceptibility testing.

Since 1995, the public health nurses have been systematically identifying all medications prescribed at the beginning of therapy. This allowed the authors to assess clinicians' adherence to the recommended four-drug regimen.

Logistical regression was performed to identify predictors of the use of a four-drug regimen. The SAS statistical software program (SAS Institute Inc, USA) was used for statistical analyses. Odds ratios (ORs) with 95% CIs were calculated.

RESULTS

During the study period, 741 cases of active TB were reported to the DPH (with an average annual rate of 10 cases/100,000 people). Of these, 672 (90.7%) were confirmed cases: 670 by culture and two by polymerase chain reaction only. All culture-confirmed isolates of *M tuberculosis* were tested for susceptibility to the first-line drugs by the Quebec Public Health Laboratory, using the BACTEC 460 (Becton Dickinson, Canada) radiometric method.

The analysis excluded 15 cases that were diagnosed post-mortem, 10 cases whose initial therapy began after the receipt of results of susceptibility testing and five cases that did not have adequate information on the initial drug regimen. Also excluded were 24 cases in children under age 12 years, because the use of ethambutol in young children is somewhat controversial.

Among the 687 analyzed cases, 406 (59.1%) received the recommended four-drug regimen (INH-RIF-PZA-EMB), 187 (27.2%) received a regimen of INH-RIF-PZA, 61 (8.9%) received a regimen of INH-RIF-EMB and 33 (4.8%) received a regimen of INH-RIF only. The percentage of cases with a four-drug regimen increased from 53.1% in 1995 to 64.9% in 1998 (χ^2 for linear trend 5.39, $P=0.02$) (Table 1).

A four-drug regimen was prescribed for 70.0% of cases with

TABLE 1
Number and percentage of tuberculosis cases by initial drug regimen in Montreal from 1995 to 1998

Type of regimen	Number of patients by year (%)				Total
	1995	1996	1997	1998	
INH-RIF-PZA-EMB	103 (53.1)	99 (58.2)	108 (61.7)	96 (64.9)	406 (59.1)
INH-RIF-PZA	56 (28.9)	53 (31.2)	46 (26.3)	32 (21.6)	187 (27.2)
INH-RIF-EMB	22 (11.3)	11 (6.5)	17 (9.7)	11 (7.4)	61 (8.9)
INH-RIF	13 (6.7)	7 (4.1)	4 (2.3)	9 (6.1)	24 (4.8)
Total	194 (100)	170 (100)	175 (100)	148 (100)	687 (100)

EMB Ethambutol; INH Isoniazid; PZA Pyrazinamide; RIF Rifampin

TABLE 2
Number and percentage of tuberculosis cases on a four-drug regimen in Montreal from 1995 to 1998

Variables	Number of patients	Percent of patients isoniazide-resistant	Number of patients on four-drug regimen (%)	Odds ratio (95% CI)*	Odds ratio (95% CI)†
Sex					
Male	375	8.3	236 (62.9)	1.42 (1.04 to 1.93)	1.16 (0.83 to 1.61)
Female	312	9.1	170 (54.5)	1.0	1.0
Age					
<65	527	9.7	333 (63.2)	2.05 (1.43 to 2.93)	2.32 (1.55 to 3.45)
65	160	5.3	73 (45.6)	1.0	1.0
Origin					
Foreign-born	559	9.5	341 (61.0)	1.52 (1.03 to 2.23)	1.62 (1.06 to 2.48)
Canadian-born	128	3.5	65 (50.8)	1.0	1.0
Site					
Respiratory	456	9.8	319 (70.0)	3.85 (2.76 to 5.38)	4.48 (3.15 to 6.39)
Nonrespiratory	231	6.4	87 (37.7)	1.0	1.0
Year					
1998	148	7.1	96 (64.9)	1.63 (1.03 to 2.59)	1.27 (1.09 to 1.47)
1997	175	7.0	108 (61.7)	1.42 (0.92 to 2.20)	1.27 (1.09 to 1.47)
1996	170	11.6	99 (58.2)	1.23 (0.80 to 1.91)	1.27 (1.09 to 1.47)
1995	194	8.8	103 (53.1)	1.0	1.0
Total	687	8.7	406 (59.1)		

*Univariate analysis; †Multivariate analysis

pulmonary (including miliary) disease, compared with 32.7% of cases with peripheral adenitis and 42.2% of cases with other sites of disease. Of the 456 cases of pulmonary disease, those with a positive smear examination were more likely to receive a four-drug regimen (181 of 249 patients [72.7%]) than were those with a negative smear examination (138 of 207 patients [66.7%]).

In a logistical regression model, the four-drug regimen was significantly associated with the presence of a respiratory disease (OR 4.48; 95% CI 3.15 to 6.39), age younger than 65 years (OR 2.32; 95% CI 1.55 to 3.45), being foreign-born (OR 1.62; 95% CI 1.06 to 2.48) and later year of reporting (OR 1.27; 95% CI 1.09 to 1.47) (Table 2).

In the present review, of the 670 culture-positive cases, there were 60 cases (9.0%) with resistance to at least one of the four first-line drugs – 51 (7.6%) with INH resistance and six (0.9%) with multidrug-resistant TB. For 20 (33.3%) of the 60 patients, the initial treatment did not include the recommended four-drug regimen (Table 3). Thirteen were treated with INH-RIF-PZA, five with INH-RIF-EMB and two with INH-RIF.

DISCUSSION

The present study was limited to information that was recorded routinely on the TB surveillance database. All susceptibility testing was performed at the provincial reference laboratory, and the reference laboratory staff was able to verify that the information in the provincial database coincides with laboratory results. Therefore, the authors are confident that the information on drug sensitivities is valid. Information on initial drug treatment was also collected systematically by public health nurses who are dedicated to TB control. This information can be obtained from several sources – the hospital chart, the patient and/or the pharmacy. Therefore, the authors feel that this information is also valid.

In Montreal, between 1995 and 1998, 40% of TB patients

TABLE 3
Initial drug regimen according to pattern of resistance for tuberculosis cases in Montreal from 1995 to 1998

Pattern of resistance	Initial drug regimen	Number resistant (%)
INH	INH-RIF-PZA-EMB	27 (45.0)
	INH-RIF-PZA	8 (13.3)
	INH-RIF-EMB	3 (5.0)
	INH-RIF	2 (3.3)
PZA	INH-RIF-PZA-EMB	3 (5.0)
	INH-RIF-PZA	4 (6.7)
	INH-RIF-EMB	1 (1.7)
RIF	INH-RIF-EMB	1 (1.7)
INH-PZA	INH-RIF-PZA-EMB	1 (1.7)
	INH-RIF-PZA	1 (1.7)
INH-EMB	INH-RIF-PZA-EMB	3 (5.0)
Multidrug-resistant TB	INH-RIF-PZA-EMB	6 (10.0)
Total		60 (100.0)

EMB Ethambutol; INH Isoniazid; PZA Pyrazinamide; RIF Rifampin; TB Tuberculosis

were treated initially with fewer than four drugs. The age, site of TB and country of origin were associated with the use of four-drug regimens. However, even when one of these factors was present, between 30% and 39% of patients received three drugs or less. This implies that clinicians in Montreal were unaware of the recommendations, were unaware of the extent of INH resistance in Montreal or did not agree with the treatment recommendations.

Surveillance data provide only limited information on treatment decisions; individual patient factors that may have led the treating physicians to choose the specific drug regimen cannot be fully appreciated. It is possible that, although the physicians were aware of the recommendations, some chose to exclude one of the medications because of anticipated side effects, the presence of minimal disease or possible interaction with other medications that the patient was taking.

However, many surveys in the United States have revealed poor adherence to recommended treatment guidelines (5-7). In Toronto, of 141 culture-confirmed pulmonary TB cases diagnosed between 1992 and 1993, only 32 (22.7%) received an initial four-drug treatment, and 90 (63.8%) received a regimen of three drugs (8). According to the authors, in 25% of cases, the initial treatment was a regimen not considered standard by the 1993 current guidelines (INH-RIF-PZA with or without EMB), but the study looked at patients who were started on therapy before the four-drug guidelines of 1993 (1,2). From 1994 to 1995 in New Jersey, where almost all TB patients (98%) were reported from counties with an INH-resistant proportion of 4% or more, 35.5% of the 1230 culture-positive cases were not initially treated with the four-drug regimen. Nonhispanic white patients were more likely to be treated with fewer than four drugs than nonhispanic black patients. Private practitioners and physicians at chest clinics were approximately five times more likely to prescribe fewer than four drugs initially than physicians at the hospital where a national TB centre is located (9).

The fact that younger age and being foreign-born were associated with initial treatment with four drugs suggests that physicians were less likely to suspect resistance in Canadian-born patients and perhaps were less likely to fear secondary effects in young patients. In fact, of the 20 patients with resistance to at least one of the first-line drugs who did not receive four drugs initially, 50% were either Canadian-born or elderly.

Inadequate treatment strategies may contribute to poor outcomes for TB patients and to the emergence of drug resistance. Unfortunately, the TB surveillance database presently does not contain information that would allow the comparison of outcomes among cases having initial four-drug regimens with cases having nonstandard regimens. These outcomes include the development of secondary resistance or side effects to the medication.

However, among the 406 patients treated with an initial four-drug regimen, no relapse was identified in the surveillance database as of January 2000. A relapse case is defined as a new episode of active TB in an individual who received a complete course of treatment, was free of disease for six months or was lost to care for more than 12 months. Such a case would be entered as a new episode of active TB in the database. Among the other 281 patients, one patient who was initially treated with INH-RIF for nine months had a relapse eight months after the completion of the initial treatment.

Although information is limited, the public health files did not identify any deaths, relapses or development of secondary resistance among the 20 patients who were not started on four drugs and whose strain was resistant to at least one of the four first-line drugs.

In Montreal, from 1995 to 1998, the proportion of INH resistance was less than 4% among Canadian-born patients. But because the annual number and the total number of INH-resistant cases among Canadian-born patients are small, the proportion of INH resistance may fluctuate from year to year. From 1992 to 1995, the percentage of INH-resistant cases

among Canadian-born patients was 8.7% (4), and over the seven-year period of 1992 to 1998, the percentage of INH-resistant cases was 5.9% and was greater than 4% among all age groups.

In Quebec, any physician may treat patients with TB, and since 1997, medication can be dispensed by any community pharmacy. Public health departments, therefore, do not become aware of individual treatment regimens before the case is declared, which may occur several weeks after treatment has been initiated. In this type of health care system, it is necessary for public health departments to ensure that clinicians are aware of resistance levels in their community and treatment guidelines. It is also necessary for public health departments to monitor treatment regimens and ensure that the regimens used are appropriate for the susceptibility patterns of the individual patient and that they are in accordance with guidelines. Since 1995, several guidelines have been published and disseminated by the public health department and other bodies. In addition, a report on the epidemiology of TB in Montreal has been disseminated, and public health physicians have met with various groups of physicians. It is possible that these efforts contributed to the increase in the use of the initial four-drug regimen in Montreal. However, the results of the present study demonstrate that physicians have not adopted the optimum treatment regimen and that efforts to increase the use of these regimens must continue.

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