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The cost of medical management of pulmonary nontuberculous mycobacterial disease in Ontario, Canada

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Abstract

Background: Treatment of pulmonary nontuberculous mycobacterial (NTM) infection is complex, requiring multiple antibiotics and a prolonged treatment course. We determined the monthly cost of treating patients with pulmonary NTM infections in our clinic, a tertiary care centre in Toronto, Canada.

Methods: We reviewed records of a single clinic at the University Health Network, Toronto, Canada, for all patients with pulmonary NTM isolates. Pharmacological and non-pharmacological treatment costs were calculated using a number of Canadian references.

Results: One hundred, seventy-two patients were reviewed, 91 of whom were treated pharmacologically. The median (quartiles) total duration and cost per treated patient was 14 months (9-23) and $4,916 (2,934- 9,063) respectively. Median (quartiles) monthly drug treatment cost was $321 (254-458) for all patients, $289 (237, 341) for patients receiving exclusively oral antibiotics, and $1,161 (795, 1,646), for patients whose treatment included intravenous antibiotics. The most costly oral regiment consisted of a fluroquinolone, macrolide and rifampin. In multivariable analysis, Mycobacterium abscessus infection, intravenous therapy, and M. xenopi infection were all associated with increased monthly treatment costs.

Conclusion: The direct medical costs of NTM infections are substantial. Less expensive alternative therapies might be most helpful for M. abscessus infection and when intravenous antibiotics are deemed necessary.

Abbreviations:

American Thoracic Society (ATS)
Angiotensin Converting Enzyme Inhibitors (ACEI)
Body Mass Index (BMI)
Canadian dollars (CD)
Infectious Diseases Society of America (IDSA)
Multi-drug resistant tuberculosis (MDR-TB)
Mycobacterium avium complex (MAC)
Nontuberculous Mycobacterial (NTM)
University Health Network (UHN)
US dollars (USD)

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Keywords:
Cost effectiveness
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BACKGROUND:

Nontuberculous mycobacteria (NTM) cause pulmonary infections which can be clinically challenging at several levels. Proposed diagnostic criteria for pulmonary NTM disease are rigorous and include clinical, radiological and microbiological criteria[1]. These guidelines are meant to prevent false positive diagnoses due to the contamination of respiratory samples with these ubiquitous organisms and the consideration of taxing therapy in patients without significant disease. The treatment is equally complex and requires a prolonged, multi-drug regimen. Treatment is frequently complicated by drug intolerances to first line agents[2] (as recommended by American Thoracic Society guidelines[1]) especially in the elderly, which can result in chronic, continuous use of second line anti-microbials to control the infection. Recent studies have described a significant increase in the prevalence of pulmonary NTM disease worldwide[3], making NTM an important consideration for practicing clinicians and health care administrators.

The long and complex therapy used in NTM pulmonary disease suggests that treatment costs are likely significant and the increasing frequency of pulmonary NTM, suggests that treatment costs will have a mounting impact on the health resources. The cost of treating NTM infection is largely unknown. One study has been published, reporting a median annual treatment cost of close to twenty thousand dollars, however the number of cases evaluated was relatively small and not all treatment costs were examined[4]. We sought to determine the monthly costs for the ambulatory treatment of patients with pulmonary NTM infection at a tertiary hospital clinic in Toronto, Canada.

METHODS AND MATERIALS:

A retrospective chart review was completed of all patients treated for pulmonary NTM in one clinic at the University Health Network (UHN), a large teaching hospital in Toronto, Canada. We included all patients who received a prolonged regimen (greater than one month duration) of antimicrobial therapy, starting from September 2003 until October 2008. Patients who did not meet American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) criteria for NTM pulmonary disease were excluded. We reviewed all records in the clinic of one of the authors (TKM) to identify every eligible patient. Patients were generally treated according to ATS guidelines for therapy of pulmonary NTM disease, including the allowance for the significant proportion of patients who do not tolerate intensive multi-drug therapy, but may benefit from variably less intense regimens.[1] The treatment goal was not the same for all patients and did not remain the same for all patients throughout their treatment course. For some patients, the goal was to cure the infection, with a plan to treat patients for 12 months after the last positive sputum culture. Among patients for whom the initial goal of therapy was to cure the infection, some patients tolerated a prolonged course of aggressive multi-drug therapy and experienced improvement, while other patients did not tolerate therapy or did not improve, so the goals of therapy were either changed to suppression of the infection or therapy was discontinued. Among patients for whom the initial goal of therapy was to suppress the infection, some patients tolerated suppressive antibiotic therapy and experienced clinical improvement, so therapy was continued, sometimes with a plan for indefinite therapy. Other patients treated with suppressive intent did not tolerate therapy or did not improve, so therapy was discontinued. We have found that this approach to pulmonary NTM disease is appropriate in our setting and report on the cost of treating patients using this flexible, inclusive approach.

Medication costs were calculated to estimate the total number of doses of each drug that was used. All clinic records were reviewed to determine the drugs and doses that patients were taking during every month of treatment. Oral antibiotic costs included dispensing fees, and were calculated based on Ontario retail costs provided by a large Canadian retail pharmacy chain. We rarely used rifabutin, reflecting the relatively high toxicity compared with rifampin, as highlighted by the latest American Thoracic Society guidelines[1]. None of the patients in this series was treated with rifabutin. Clofazimine (Lamprene; Novartis Pharmaceuticals Corporation, East Hanover New Jersey, U.S.A.) is not commercially available in Canada. It is currently being provided free of charge on compassionate grounds, through Health Canada's Special Access Program, by its manufacturer. The cost of clofazimine was not made available to us and is therefore not included in our calculations. Parenteral antibiotic acquisition costs and the associated nursing fees for home administration were determined using a Toronto area home care program and their contracted pharmacy. Costs of central line insertion and associated infusion costs were also designated as drug costs.

Non-medication costs, included physicians' fees, medical facility fees, and patient monitoring. Physicians' fees, including the pulmonary specialist, radiologists, and interventional radiologists were calculated using the schedule of benefits from the Ontario Ministry of Health and Long Term Care and counting every applicable patient encounter. Thoracic CT scans were routinely performed initially, after 4-6 months of therapy, at the time of significant clinical deterioration, and at the end of therapy. Chest radiographs were used predominantly in the setting of acute changes. All of these radiographic costs were included. In-person (reimbursed) pulmonology assessments were generally performed every three months. Costs incurred by the hospital for clinic visits, infusion centre administration of antibiotics, radiological tests and

interventional procedures were calculated using the UHN 'case costing' database for every applicable patient encounter. The costs of monitoring patients on therapy, according to costs for monthly complete blood counts, AST, ALT and total bilirubin levels (for patients receiving a rifamycin), monthly sputum acid-fast staining and mycobacterial culture were also designated as non-drug costs. We studied medical treatment costs, so the costs of initial diagnostic investigations were not included in the analysis. The costs of baseline investigations at the initiation of therapy were however included as part of our analysis. A small proportion of our patients had surgical therapy for their NTM disease. The costs of this intervention were not available to us and so are not included.

All costs were calculated according to 2008 rates and are presented in Canadian dollars and summarized rounded to the nearest dollar. Given the variable treatment length for pulmonary NTM, the monthly treatment cost was the focus of study, and was calculated as the total treatment cost during the observation period, divided by the total number of treatment months. Total treatment costs are also presented, but do not include only completed courses of intensive "curative" therapy. We included data for all patients who were treated during the study period, regardless of whether they had completed therapy with curative intent, discontinued potentially curative therapy because of toxicity or futility, utilized ongoing suppressive therapy or discontinued suppressive therapy because of toxicity or futility.

Bivariate comparisons for categoric variables were made with continuity-corrected chi-square tests or Fisher's exact tests as appropriate. Bivariate comparisons for cost (which was not normally distributed) were made with Mann-Whitney U tests. After assessment for collinearity, multiple linear regression, using backward model selection, was used to model log-transformed monthly treatment cost (outcome variable), using gender, age, presence of cavitation on CT,

acid-fast stain status, use of intravenous therapy, and NTM species as predictor variables. Data were entered into an electronic database (Access 2000, Microsoft, Redmond, Washington U.S.A.) and were analyzed using statistical software (SAS 8.02, SAS Institute, Cary, North Carolina, U.S.A.). This study was approved by our institutional review board, without requiring informed consent.

Results:

A total of 172 patients, seen at the UHN respiratory clinic for pulmonary NTM infection between 2003-2008, were reviewed. Ninety-one patients were followed for a minimum of 1 month and treated with prolonged anti-microbial therapy and therefore included in subsequent analysis. Baseline characteristics of the 91 patients are presented in table 1. The majority of patients were thin, elderly females, in keeping with previously reported results[1] Physician-defined pre-existing chronic obstructive pulmonary disease was present in approximately 40% of cases; however obstructive airway disease, as defined by pulmonary function testing, was present in a much higher proportion. This discrepancy could be due to the direct effect of NTM infection on the airways, the development of bronchiectasis, or a pre-existing but undetected abnormality of the airways that predisposes patients to pulmonary NTM infection.

All patients met ATS criteria for pulmonary NTM disease. The patients' clinical, radiological and microbiological features are illustrated in Table 1. Radiologic nodular bronchiectasis was two- to three-fold more common than cavitation. The majority of patients were infected with MAC (70%), followed by *M. xenopi* (17%) and others (11%). The median (quartiles) duration of treatment was 14 months (9-23). Median treatment duration was not significantly different between MAC and *M. xenopi* (15.5 months versus 12 months, p=0.06).

The small number of patients infected with other species of NTM limited further comparisons. Cavitation on CT was not significantly associated with the duration of treatment in bivariate analysis (14 months with cavitation vs. 12 months without cavitation, p=0.66).

The majority of patients were treated with one of six different oral antibiotic regimens, the choice of which was largely determined by patient tolerability and medication toxicities. Intravenous therapy usually comprised amikacin, which was used in 23 cases. The individual costs of antibiotics and non-medication treatment component costs are presented in the online supplement. Daily drug costs, for average doses of the commonly used medications, are macrolides 2.77-4.94 (varies by agent), ethambutol 0.62, rifampin 2.48, and fluoroquinolones 2.82-6.21 (varies by agent). Two patients with *Mycobacterium abscessus* received three months of carbepenem therapy (approximate wholesale cost of $50 per dose) in conjunction with intravenous amikacin. This cost was not included in the analysis. No other intravenous antibiotics were used. The frequency of commonly prescribed antibiotic regimens is shown in Figure 1a. The median monthly cost of common antibiotic regimens is shown in Figure 1b. Clofazimine was used in 18 patients; however, it was not included in cost calculations as it is made available free of charge and cost information was not made available to us. There was no significant difference in cost between the different oral antibiotic regimens. A significant increase in cost occurred with intravenous amikacin.

The median monthly and total medication and non-medication costs are shown in Table 2. Greater than two-thirds of the cost was incurred from medications. Table 3 highlights cost differences between patients treated with exclusively oral therapy and patients treated with parenteral plus oral therapy. The difference in cost of nearly $900 monthly was driven almost exclusively by the increase in drug acquisition and administration costs. In multivariable

analysis, total monthly cost was significantly associated only with infection with *M. abscessus*, use of IV antibiotics, and infection with *M. xenopi*. Multivariable model results and interpretation are summarized in Table 4.

DISCUSSION:

In our study of the treatment cost of pulmonary NTM infections, we observed an average monthly cost of approximately 500 Canadian dollars. Drug costs were responsible for approximately 70% of the total treatment cost. As expected, treatment costs rose dramatically with the use of intravenous antibiotics and in the presence of *M abscessus*, two variables that were often, but not always associated (intravenous therapy was invariably used for *M. abscessus* but also for numerous patients with other NTM species). In multivariable modeling, parenteral therapy added approximately $700 to the monthly treatment cost, independent of other variables. Additional results from multivariable modeling included finding that *Mycobacterium xenopi* was associated with greater treatment costs than MAC, but there was no clear cost association with cavitation on CT scan, age or gender.

A recently published retrospective cohort study[4] examining the medication costs associated with the treatment of 25 cases of pulmonary NTM infection in the United States found monthly and annual medication costs 44% and 15% higher respectively, compared to our study. There are several factors that likely contributed to the large cost difference. The prior study had a higher prevalence of *M abscessus* (22%, compared with 7% in the present study), an organism that is associated with a high treatment cost. In addition, the median number of antimicrobials employed in the prior study was five, compared with only three in our study and we did not include the treatment cost of clofazimine in eighteen patients. Finally, the drug costs were

much higher in the prior study. The monthly cost of a standard first-line regimen comprising a macrolide, rifampin and ethambutol was approximately 470 USD in the prior study, compared with 245 CD in our study. The present study differed from the prior study as we included all readily-quantifiable treatment costs, rather than focusing exclusively on drug acquisition costs. We think that our study provides a reasonable estimate of the total costs of treating pulmonary NTM infection in Ontario, Canada.

Particularly relevant to the overall financial burden of treating pulmonary NTM disease in a population, is choosing the appropriate patients to treat. In our NTM database only 91 of the 172 patients were actively treated with antibiotic therapy. It is well recognized that making the distinction between pulmonary "colonization" and "disease" is not always easy, and has been addressed through the creation of explicit diagnostic guidelines. Despite these guidelines, the decision to treat patients with pulmonary NTM disease remains difficult, even for experts in the field[1]. Therefore, we feel that obtaining the expertise of specialized physicians during the course of diagnosis and/or treatment would better identify those who required treatment and could have a substantial impact on the overall disease cost.

In considering whether the financial cost of a medical treatment is acceptable, it can be helpful to compare it with other accepted therapies. Pulmonary NTM infections are likely less expensive to treat than other treatment resistant infections like multidrug-resistant tuberculosis (MDR-TB) or chronic infections like HIV. The median outpatient costs of treating MDR-TB in seven HIV seronegative patients in San Francisco was $21,929, over a mean duration of therapy of 98 weeks[5]. National (US) AIDS surveillance data from 2002-03 estimated the annual average cost of anti-retroviral therapy was $12,665 per patient[6].

We feel the cost of treating pulmonary NTM disease is closer in cost to the outpatient treatment of more common chronic diseases such as diabetes mellitus and congestive heart failure. In a large cross sectional study published by the American Diabetes Association in 2007, the annual per capita expenditure for outpatient care (not including emergency room visits) for individuals with diabetes greater than 65 years of age was $3,319 (US dollars)[7]. In 2004, the average annual cost of outpatient treatment of over 1500 patients with congestive heart failure was $3,837 (US)[8]. We estimated the drug cost of treating COPD, type 2 diabetes mellitus and symptomatic coronary artery disease, using common drug combinations and doses. In Ontario, Canada, the approximate monthly drug costs for treating COPD (using fluticasone/salmeterol, tiotropium and salbutamol) is $323, symptomatic coronary artery disease [using a beta-blocker, acetylsalicylic acid, statin and an angiotensin converting enzyme inhibitor (ACEI)] is $196, and type 2 diabetes mellitus (using a biguanide, sulfonylurea, thiazolidinedione, statin, ACEI and acetylsalicylic acid) is $319. In a similar cost range, we observed that a standard first line regimen for treating pulmonary NTM infection (using a macrolide, rifampin and ethambutol) was $245 monthly. Although data regarding objective benefits in treating pulmonary NTM disease are not very well established, the cost of treatment does not appear to be out of keeping with accepted costs of ongoing treatment of common chronic diseases.

We speculate that the use of 'guideline therapy', namely a macrolide, rifampin and ethambutol, as first-line treatment is the most cost effective approach to the treatment of NTM disease in Canada. Assuming an 18 month course of treatment, the cost savings (based on our observed costs) of 'guideline therapy' per treatment course versus other regimens such as floroquinolone / rifampin / ethambutol, macrolide / fluroquinolone / ethambutol or fluroquinolone / rifampin / macrolide is $1,026, $198, $1,566 respectively. Obviously the

effectiveness of the regimen must be considered when considering cost saving approaches. However, at present, there is a paucity of studies that compare the effectiveness of different regimens. Jenkins et al.[9] compared the efficacy of a two year treatment course of clarithromycin, rifampin and ethambutol vs ciprofloxacin, rifampin, and ethambutol. There was no statistically significant difference between the two regimens in their primary end points of death due to NTM and treatment failure (defined as positive sputum cultures on two separate occasions during the last three months of treatment). As a secondary endpoint Jenkins et al.[9] compared the tolerability of these regimens and again found no statistically significant difference in the two regimens. Accepting the results from this complex study at face value, we would conclude that the combination of a macrolide, rifampin and ethambutol is the most cost effective regimen due to its lower price, effectiveness and tolerability profile. It is even more difficult to address the cost effectiveness of amikacin (or another aminoglycoside), the major factor driving large increases in cost of therapy. Guidelines recommend considering the use of injectable aminoglycosides in initial therapy of cavitary MAC disease, and advise their use in severe, advanced or recurrent disease. However, controlled data regarding the effectiveness of aminoglycosides in pulmonary NTM are limited. Kobashi et al. randomized patients with pulmonary MAC to clarithromycin / rifampin / ethambutol plus either streptomycin or placebo injections.[10] Patients in the streptomycin group did slightly better, although the differences were not statistically significant. Streptomycin appeared to be particularly beneficial (for clinical and microbiologic outcomes) among patients with radiographically extensive disease. It appears that an injected aminoglycoside is beneficial in extensive pulmonary MAC, but there are inadequate data to assess its cost-effectiveness.

It is interesting to note that a minority of patients were receiving the first-line recommended therapy for MAC (macrolide / rifampin / ethambutol). This observation was present despite our general practice to introduce a three-drug first-line regimen when possible. Even when including regimens that additionally contained amikacin or a fluoroquinolone, the total number of patients with these regimens comprised only 44%. There are probably several reasons for this observation. Although we did not formally study regimen tolerability, we think that a siginificant proportion of patients had been intolerant of rifampin, explaining the substantial proportion of patients using non-rifampin containing regimens. Further, a very small proportion could not tolerate ethambutol, usually due to ocular toxicity. Also, patients with *M. abscessus* were not prescribed rifampin in general, due to the resistance of the isolates and often received carbapenem therapy. Finally, many of our patients had recurrent or difficult to treat disease that led to the addition of more drugs, including fluoroquinolones, amikacin and clofazimine. Our regimen choice is therefore reflective of the spectrum of NTM species treated in our clinic and possibly drug intolerance that is common in treating pulmonary NTM[2].

The frequency of pulmonary NTM has been increasing substantially in Ontario[3], suggesting that the cost of treatment will have a mounting impact on the health resources, underscoring the relevance of studies like the present investigation. We think that our results are generally applicable in Canada, and, with some modification for differences in health care costs, in other jurisdictions as well. Our study is the largest and most comprehensive investigation of the cost of treating pulmonary NTM disease to date, including drug acquisition and administration costs, as well as physician, facility, and testing fees (audiology, biochemistry, hematology, microbiology, radiology). Our patients are probably representative of other populations of pulmonary NTM patients as we ensured that all cases met the ATS diagnostic

criteria for NTM disease. The drug regimens also were generally in close accordance with ATS/IDSA guidelines, although fluoroquinolones, drugs not recommended in first-line regimens, were used extensively. The fraction of patients in our clinic who were treated (53%) is probably in accordance with the observation that pulmonary NTM disease, even in the presence of significant symptoms, radiographic abnormalities and microbiologic evidence of disease, may be relatively indolent and progress only very slowly. Patients were offered antimycobacterial drug treatment if the clinical opinion was such that the benefits of therapy were likely to outweigh the toxicities. Generally, patients were not treated if they had relatively mild and non-progressive symptoms and non-progressive lesions on serial chest imaging.

Although our study offers the first comprehensive analysis of the cost of treating pulmonary NTM, there are several limitations. We did not have the cost of clofazimine available to us, so this cost was omitted from our analysis. The impact of these missing data is probably small however, since fewer than 20% of our patients were treated with this drug. We also did not include the cost of treatment periods with inhaled amikacin, since this therapy is less commonly used and we had few patients who received it. The latter would likely make our costs estimates thereof unreliable. Because only three patients received inhaled amikacin during the study period, it is unlikely that omitting the periods of inhaled amikacin greatly affected our results. Although we did not determine the costs surrounding the use of inhaled amikacin, we think its use would be less than for IV (assuming similar doses), despite the costs of an air compressor, saline and nebulizers, since inhaled therapy eliminates nursing costs and, in our practice, reduces biochemical and audiographic monitoring for toxicity. Also, if amikacin is used exclusively by inhalation, costs of central line insertion are avoided. We did not include the cost of the adverse effects of treatment. The multi-drug regimen and prolonged course of

therapy of pulmonary NTM is well known for high rates of adverse reactions[2]. Prevots et al.[4] recorded the frequency of adverse drug reactions ranged from 18% with azithromycin to 75% with levofloxacin. Adverse drug reactions may lead to more clinic visits, additional diagnostic tests, and the use of more expensive, second line agents, but this cost would have been captured using our methodology. In our cohort, most toxicities were managed by telephone, the costs of which are not included, since this is not a reimbursable service in our health system. One of our patients developed rifampin-related systemic illness, diffuse petichiae and ecchymoses with severe thrombocytopenia, for which hospitalization was required. The inpatient costs of this toxicity were not available to us and not included in our analysis Although the inpatient cost of pulmonary NTM disease was also not explored, hospitalization for initiation or modification of therapy did not occur in patients, outside of the unusual situation of pulmonary resection for localized disease, an intervention that is used in the minority of patients. The majority of patients probably do not require hospitalization; however hospitalization in even a small proportion of patients could raise the average costs substantially. Of note, in our population eight patients underwent surgery (surgical biopsy, lobectomy, pneumonectomy) as part of their assessment or treatment. In our total treatment cost measurements, and our cost estimates for a single, uncomplicated 18-month treatment course (Table 5), we did not account for the high rates of treatment failure and disease recurrence that are known to occur[1] and undoubtedly contribute heavily to the overall economic burden of pulmonary NTM. However, we did find that monthly costs of oral-only therapy are not out of keeping with the commonly accepted costs of treating chronic diseases, where therapy is continued indefinitely. We suggest that it may be just as important to focus on monthly costs, because treatment is often recurrent and sometimes chronic. Finally, the modeling of treatment cost may have been limited by the absence of information

regarding the extent of radiographic disease (we had only data regarding cavitation) and macrolide resistance (most of our patients' isolates were not tested for drug susceptibility).

The generalizability of our work to other health care systems may be questioned. A limited comparison to the United States was made above, regarding only drug costs. The applicability of comparisons between the United States and Canada is not clear, given the differences in medical cost payers (society as a while versus individuals). Regardless, we have expanded the comparison between the costs of treatment in Ontario, Canada, with those of treatment in the United States in Table 5, wherein the cost of a projected uncomplicated 18-month treatment course for pulmonary *M. avium* complex is presented. The modeled cost in the United States was 1.7-2.3 fold greater than the cost in Ontario, Canada, a difference driven largely by medication costs, which comprise the bulk of treatment costs and were expected to be 1.9-2.4 fold greater in the United States. The difference between the United States and Ontario, Canada may be even greater than we modeled, since we used Medicare reimbursement rates for non-drug costs, which are lower than reimbursed rates from private insurers - a study in 1993 estimated that Medicare reimbursement was 76% that of private insurance carriers[12]. Even though our model is likely a gross simplification, it appears to be clear that the cost of treating pulmonary NTM disease in the United States would be at least double the cost in Ontario, Canada.

The Applicability of our work to systems where medical costs are generally borne by society is much greater. Our health care system in Ontario, Canada provides most prescription drugs free-of-charge to patients who are at least 65 years old, or who are receiving social assistance. Further, the provincial drug plan includes automatic substitution of generic drugs and our calculations utilized costs of generic drugs when available. Thirty-eight of our patients were

at least 65 years old and several additional patients were receiving provincial drug benefits as part of their social income assistance. Finally, the costs of physicians' visits, hospital facility fees, home nursing visits, ambulatory parenteral drug therapy, and diagnostic tests requested by a physician are borne completely by the Ontario Ministry of Health and Long Term Care. As a result, nearly half of our patients' treatment comprised exclusively societal costs, rather than costs borne by an individual or a private health insurance program. In this context, we think that our costs reflect very well societal costs of the ambulatory medical management of pulmonary NTM disease. Based on differing recommendations between the American[1] and British[11] Thoracic Societies' NTM guidelines regarding choice of specific drugs, we have presented in Table 5 projected costs of an 18-month course of therapy. It is evident that the "first-line" regimen from the British guidelines (rifampin and ethambutol) is by far the least expensive. However, because the choice of regimen usually depends more upon tolerability and goals of therapy (cure vs suppression), and because we cannot adequately assign relative toxicity or efficacy of these regimens (greater toxicity or less effective regimens may lead to additional costs), the values in Table 5 should not be used to make clinical decisions.

The rising prevalence of pulmonary NTM infections will have an increasingly large impact on population health and heath expenditures. We observed that the cost of treating this disease is substantial, but not out of keeping with the costs of well established therapies for other chronic diseases. Furthermore, the cost varied greatly with the use of parenteral therapy and with the presence of *M. abscessus* infection. In light of our findings, we do not think that the cost of treating pulmonary NTM disease should discourage therapy. The identification of new, less expensive alternative therapies may be most helpful for *M. abscessus* infection and when intravenous antibiotics are deemed necessary.

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Figure Legends

Figure 1a: Frequency of commonly prescribed antibiotic regimens

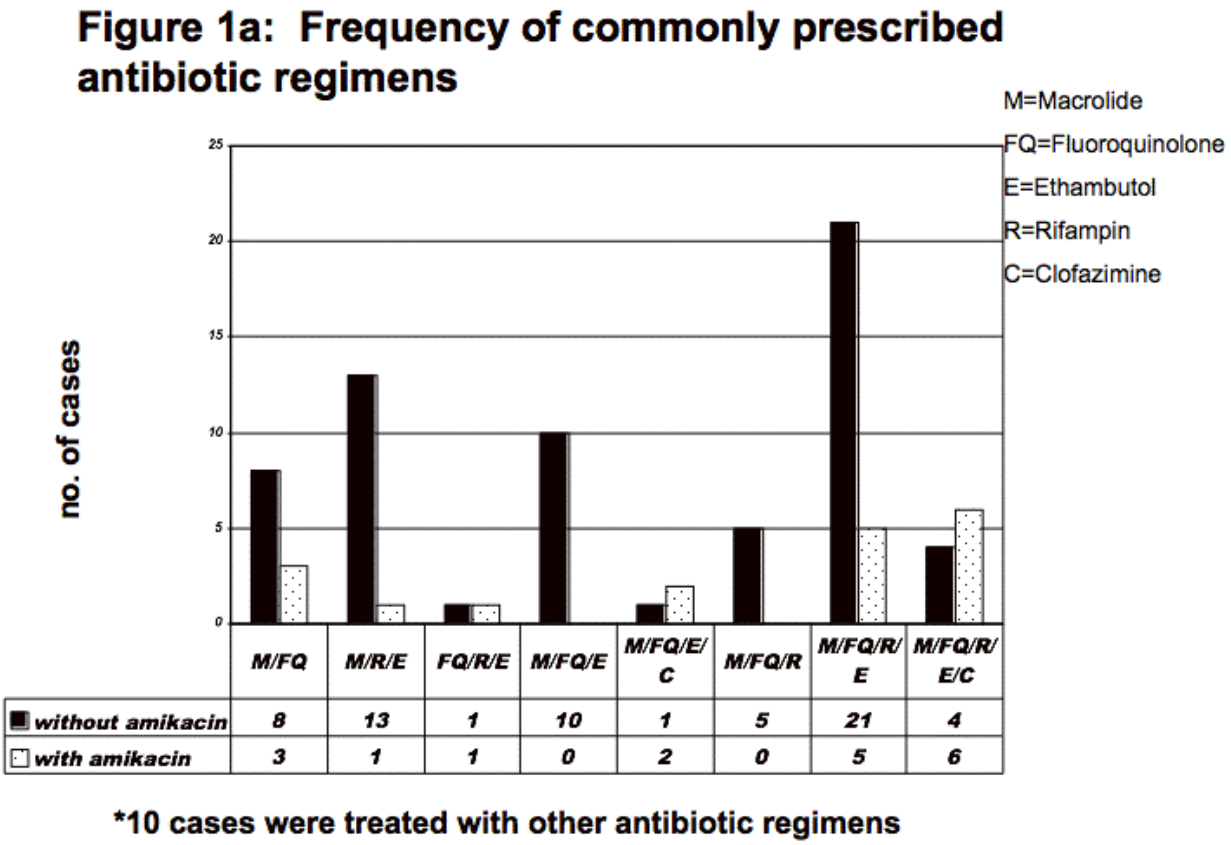
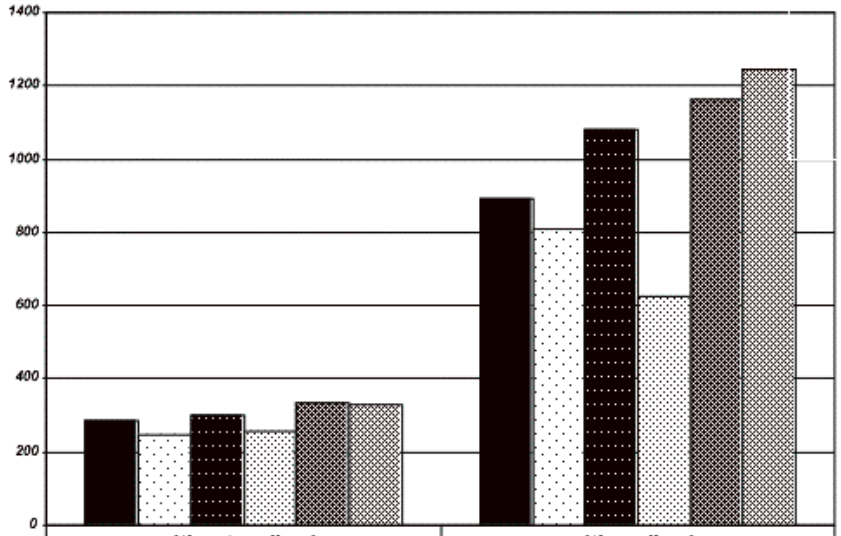


Figure 1b: Monthly cost of common antibiotic regimens (drug acquisition and administration costs only)

Figure 1b: Monthly cost of common antibiotic regimens (drug acquisition and administration costs only)



M=Macrolide

FQ=Fluoroquinolone

E=Ethambutol

R=Rifampin

	without amikacin	with amikacin
M/FQ	285	892
M/R/E	245	808
FQ/R/E	302	1078
M/FQ/E	256	626
M/FQ/R	332	1161
M/FQ/R/E	328	1244

Table 1: Characteristics of study subjects with pulmonary NTM disease

Characteristic	Total; N=91	Men; N=31	Women; N=60
Mean Age +/-SD (years)	61.7+/-13.6	62.3+/-16.0	61.5+/-12.4
Concomitant Lung Disease- N(%)			
COPD	21 (23%)	9 (29%)	12 (20%)
Asthma	16 (18%)	9 (29%)	7 (12%)
Interstitial lung disease	5 (5%)	4 (13%)	1 (2%)
Previous NTM infection-N(%)			
Previous diagnosis	28 (31%)	5 (16%)	23 (38%)
Previous diagnosis and treatment	23 (25%)	4 (13%)	19 (32%)
Mean BMI +/-SD	22.2+/-4.5	23.0+/-4.1	21.9+/-4.7
Pulmonary Function Tests-N(%)			
Obstructive*	55 (60%)	22 (71%)	33 (55%)
Restrictive†	10 (11%)	4 (13%)	6 (10%)
Impaired diffusion capacity††	49 (54%)	21 (68%)	28 (47%)
Clinical Manifestations of NTM-N(%)			
Constitutional symptoms‡	50 (55%)	18 (58%)	32 (53%)
Cough	82 (90%)	26 (84%)	56 (93%)
Dyspnea	33 (36%)	12 (39%)	21 (35%)
Hemoptysis	29 (32%)	8 (26%)	21 (35%)
Chest Pain	6 (7%)	2 (6%)	4 (7%)
Radiological Manifestations of NTM-N(%)			
Multifocal Bronchiectasis	60 (66%)	14 (45%)	46 (77%)
Multiple Nodules	75 (82%)	22 (71%)	53 (88%)
Cavity	25 (27%)	9 (29%)	16 (27%)
Microbiological Manifestations of NTM-N(%)			
3 positive sputum cultures§	53 (58%)	14 (45%)	39 (65%)
Bronchial wash and positive culture	36 (40%)	17 (55%)	19 (32%)
Surgical biopsy/resection	2 (2%)	0 (0%)	2 (3%)
Acid-fast stain positive	55 (60%)	19 (63%)	36 (59%)
NTM Speciation**			
MAC (avium or intracellulare)	74 (81%)	22 (71%)	52 (87%)
M. *xenopi*	17 (19%)	7 (12%)	10 (17%)
M. *abscessus*	6 (7%)	2 (6%)	4 (7%)
M. *fortuitum*	3 (3%)	1 (3%)	2 (3%)
M. gordonae	3 (3%)	1 (3%)	2 (3%)
M. *kansasii*	1 (1%)	1 (3%)	0 (0%)

*FEV1/FVC < 0.7

† FEV1/FVC > 0.7, TLC < 80% of predicted

‡ Fever, weight loss, malaise, fatigue

**some cases were infected with more than one organism

†† Diffusion capacity < 75% of predicted

§ Three positive sputa were required according to the prior version of American Thoracic Society NTM guideline (2003), contemporary with treatment of most patients in the cohort. This criterion differs from current (2007) guidelines, requiring only two positive sputa.

Table 2: Total and monthly medication and detailed non-medication treatment costs of pulmonary NTM infection

Costs	Total cost median (quartiles)	Monthly cost median (quartiles)
Medication		
Total-all patients (n=91)	$ 4,916 (2,934-9,063)	$ 321 (254-458)
IV & oral antibiotics (n=23)	$20,143 (9,451-31,109)	$1,161 (795-1,646)
Oral antibiotics only (n=68)	$ 3,603 (2,306- 5,436)	$ 289 (237-341)
Non-Medication		
Total-all patients (n=91)	$ 2,029 (1,461-2,667)	$ 144 (99-204)
• Physician visits	$ 865 (496-1,269)	$ 57 (38-101)
• Radiology	$ 585 (390- 780)	$ 33 (23- 55)
• Sputum testing*	$ 263 (106- 536)	$ 21 (10- 42)
• Drug toxicity monitoring†	$ 144 (12- 366)	$ 12 (1- 12)
Grand Total costs	$ 6,694 (4,460-11,761)	$ 499 (387-711)

* Smear and culture

† Blood tests and audiograms

Table 3: Treatment costs for pulmonary NTM infection, by use of parenteral therapy

Costs - median (quartiles)	Patients			P value*
	Total (N=91)	Oral only therapy (N=68)	Combined parenteral and oral therapy (N=23)	
Medication				
• Monthly	$ 321 (254-458)	$ 289 (237-341)	$ 1,161 (795-1,646)	<0.0001
• Total	$ 4,916 (2,934-9,063)	$ 3,603 (2,306-5,436)	$ 20,143 (9,451-31,109)	<0.0001
Non-Medication				
• Monthly	$ 144 (99-204)	$ 132 (93-184)	$ 192 (148-222)	0.01
• Total	$ 2,029 (1,461-2,667)	$ 1,915 (1,324-2,308)	$ 2,642 (2,080-4,217)	<0.0001
Total				
• Monthly	$ 499 (387-711)	$ 423 (357-538)	$ 1,300 (989-1,813)	<0.0001
• Total	$ 6,694 (4,460-11,761)	$ 5,388 (4,088-7,584)	$ 23,022 (11,761-33,791)	<0.0001

*P value for difference between patients treated with oral only versus parenteral plus oral therapy

Table 4: Results of multiple linear regression for total monthly treatment cost

Variable	Parameter Estimate	Final p value	Approximate associated increase in total monthly treatment cost
M. abscessus	1.27	<0.0001	$ 2,700*
IV	0.90	<0.0001	$ 700†
M. xenopi	0.28	0.0325	$ 250‡
Intercept	5.69	<0.0001	Not applicable

Multiple linear regression using backward model selection, modeling log-transformed monthly treatment cost (outcome variable), using gender, age, presence of cavitation on CT, acid-fast stain status, use of intravenous therapy, and NTM species as predictor variables; variables that remained in the model with a p value of < 0.05 are included above; model $R^2=0.71$.

* Presence of *M. abscessus* compared with other organisms

† Addition of IV therapy in cases of MAC or *M. xenopi*

‡ Presence of *M. xenopi* compared with MAC

Table 5: Projected costs of 18-month course of guidelines-recommended oral therapy for NTM disease

Guideline / Regimen	Total costs (2008 Canadian dollars)			Total costs (US dollars)		
	Drugs	Non-drug	Total	Drugs*	Non-Drug†	Total
ATS / IDSA[1]						
Daily Azithromycin 250 mg Rifampin 600 mg Ethambutol 800 mg	3,817.80	2,010.50	5,828.30	8,942.40	2,702.91	11,645.31
Daily Clarithromycin 1000 mg Rifampin 600 mg Ethambutol 800 mg	4,989.60	2,010.50	7,000.10	9,622.80	2,702.91	12,325.71
Thrice weekly Clarithromycin 1000 mg Rifampin 600 mg Ethambutol 1200 mg	2,601.90	2,010.50	4,612.40	4,953.60	2,702.91	7,656.51
Thrice weekly Azithromycin 500 mg Rifampin 600 mg Ethambutol 1200 mg	2,742.30	2,010.50	4,752.80	6,479.28	2,702.91	9,182.19
BTS[11]						
Daily Rifampin 600 mg Ethambutol 800 mg	2,106.00	2,010.50	4,116.50	4,525.20	2,702.91	7,228.11
Daily Clarithromycin 1000 mg Rifampin 600 mg Ethambutol 800 mg	4,989.60	2,010.50	7,000.10	9,622.80	2,702.91	12,325.71
Daily Ciprofloxacin 1500 mg Rifampin 600 mg Ethambutol 800 mg	3,844.80	2,010.50	5,855.30	10,832.40	2,702.91	13,535.31

Non-drug cost include once monthly assessment of CBC and liver enzymes, two sputum specimens every two months, CT scan at beginning and end of therapy (otherwise CXR every

three months), physicians' and facility fees (Canadian costs differ from our primary analysis in that facility fees for physician visits and chest radiography have been removed, to model treatment in a non-hospital setting and facilitate comparison with Medicare reimbursement structure; facility fees for CT scans have been retained, since CT scanners are generally operated and maintained by hospitals in Ontario, financed out of hospital global budgets)

Because the choice of regimen will depend more upon tolerability and goals of therapy (cure versus suppression), and because we cannot adequately assign a relative toxicity or efficacy of the regimens (greater toxicity or less effective regimens may lead to additional costs), the Table should not be used to make clinical decisions

* US drug costs derived according to the methods of Ballarino GJ, et al. (Pulmonary nontuberculous mycobacterial infections: Antibiotic treatment and associated costs. Resp Med. 2009; 103(10):1448-1455.) and from personal communication with the authors

† Sources of non drug costs are Medicare reimbursement rates calculated as the median of national non-facility limiting charges from the center for Medicare and Medicaid services (for physician fees and imaging) and midpoint costs from the 2008 Medicare Clinical Laboratory Fee Schedule (microbiology and blood tests). Medicare reimbursement rates are generally lower than those of private insurers, so the costs may be substantially higher for patients in the USA whose care is being charged to private insurance.