The impact of different antibiotic treatment regimens on mortality in *Mycobacterium avium* complex pulmonary disease: a population-based cohort study

To the Editor:

Evidence-based guidelines recommend the combination of macrolide–ethambutol–rifamycin as first-line treatment for *Mycobacterium avium* complex pulmonary disease (MAC-PD) [1]. Whether this regimen results in improved survival is unknown.

We conducted a retrospective cohort study of older adults treated for MAC-PD using linked laboratory and health administrative databases in Ontario, Canada; these datasets were linked using unique encoded identifiers and analysed at ICES. We included all Ontario residents aged ⩾66 years with incident MAC-PD (defined using American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) microbiological criteria) [1] from 2001 to 2013 and followed them until December 31, 2014 or death, whichever occurred first. The index date was the date of the first positive culture, and the date of death was captured from the Registered Persons Database. We excluded patients who met ATS/IDSA microbiological criteria for a nontuberculous mycobacteria (NTM) species other than MAC any time during the study period, and patients who had culture-confirmed TB within 18 months before, and any time after, MAC-PD diagnosis.

We used the Ontario Drug Benefit database to review oral drug claims for antibiotics commonly used to treat MAC-PD (macrolides, ethambutol, rifamycins, fluoroquinolones, linezolid). Treatment regimens were categorised as: no treatment, macrolide monotherapy, macrolide–ethambutol–rifamycin with or without other antibiotics (regimen group A), macrolide–ethambutol with or without other antibiotics except rifamycins (regimen group B), or another combination of at least two drugs (regimen group C). For each patient, information on their treatment regimen was obtained at index date and updated throughout follow-up. Patients had to be dispensed ⩾180 continuous overlapping days of treatment (either daily or intermittent) for each regimen to qualify. To allow for patients who refilled their prescriptions late, we defined treatment as continuous if the patient filled their next prescription for the same antibiotic class within 1.5 times the number of days supplied for their last prescription.

We used Cox proportional hazards regression models to compare mortality across treatment regimens. We used statistical contrasts using regression parameter estimates to compare survival of patients receiving regimen group A and regimen group B to patients receiving regimen group C. We hypothesised that these regimens would rank in the following order in terms of superiority and potential survival benefit: A>B>C, and modelled antimycobacterial treatment as a five-level categorical time-varying exposure. The main regression analysis allowed patients to switch arms and contribute follow-up time to a presumably superior regimen (*i.e.*, "step-up") once meeting exposure criteria (*i.e.* dispensed 180 days of that regimen), after contributing follow-up time to an inferior regimen. However, patients who "stepped-down" to an inferior regimen continued to contribute follow-up time to the most superior regimen they received. In sensitivity analysis 1, we excluded those who "stepped-up" in regimen group. In sensitivity analysis 2, we excluded patients who met exposure criteria for more than one regimen grouping (*i.e.* "stepped-up" or "stepped-down"). In another sensitivity analysis, we limited follow-up to 5 years. As secondary analyses, we

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contrasted survival of patients receiving regimen groups A, B and C to no treatment and macrolide monotherapy. The multivariable models were adjusted for demographics and comorbidities (table 1) [2–10].

We identified 3148 older Ontarians with incident MAC-PD during the study period. Sustained treatment with at least two anti-MAC drugs was prescribed to 500 (16%) patients; initial regimens included 163 (33%) group A, 108 (22%) group B, 135 (27%) group C, as well as 94 (19%) who received macrolide monotherapy and later met criteria for regimen groups A, B or C. We observed no significant differences between groups A, B and C at baseline in age (mean 75.0, 76.4, and 75.4 years, respectively; p=0.31), sex (female 66%, 56%, and 62%, respectively; p=0.31), or other baseline characteristics.

In the primary analysis, median time (interquartile range) from MAC-PD diagnosis to starting treatment was 99 (26–340), 98 (36–357), and 104 (37–312) days for regimen groups A, B, and C respectively. Crude death rates per 1000 person-years (number of deaths) during follow-up were 111.1 (109), 106.3 (49), and 122.4 (50) for regimens A, B, and C, respectively.

Compared to patients treated with regimen group C, we observed no significant differences in unadjusted or adjusted mortality among patients treated with regimen group A or B (table 1). Patients treated with either regimen group A or B also did not have a significant difference in mortality than patients treated with regimen group C. Sensitivity analyses yielded similar results, though point estimates favoured regimen groups A and B. In secondary analyses, patients treated with regimen group A had an increased hazard for adjusted mortality compared to patients receiving no treatment, and there was no significant difference in mortality observed with the other comparisons.

Our observational study did not detect a survival benefit to the guidelines-recommended antibiotic combination compared to an alternative antibiotic regimen. Prior studies of this question are limited. Jenkins *et al.* [11] performed a prospective randomised trial comparing clarithromycin–ethambutol–rifamycin to ciprofloxacin–ethambutol–rifamycin in NTM-PD, including 170 patients with MAC-PD. They found higher mortality in the clarithromycin arm than the ciprofloxacin arm among MAC-PD patients (48% *versus* 29%), but no differences in mortality among all patients (including those infected with other NTM species) or MAC-PD-specific mortality.

TABLE 1 Proportional hazards mortality estimates comparing different antibiotic regimens in MAC-PD

Regimen group comparison	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[#]
Main analysis		
A *versus* C	0.91 (0.65–1.27)	1.11 (0.79–1.56)
B *versus* C	0.87 (0.59–1.29)	0.88 (0.59–1.30)
(A or B) *versus* C	0.93 (0.69–1.26)	1.04 (0.77–1.40)
Sensitivity analysis 1[¶]		
A *versus* C	0.68 (0.46–1.01)	0.76 (0.51–1.14)
B *versus* C	0.70 (0.45–1.09)	0.77 (0.49–1.21)
(A or B) *versus* C	0.69 (0.49–0.99)	0.78 (0.54–1.11)
Sensitivity analysis 2[+]		
A *versus* C	0.75 (0.49–1.14)	0.80 (0.53–1.22)
B *versus* C	0.73 (0.45–1.191	0.78 (0.48–1.28)
(A or B) *versus* C	0.75 (0.52–1.10)	0.82 (0.56–1.20)
Secondary analyses		
A *versus* no treatment	1.11 (0.91–1.35)	1.26 (1.03–1.54)
B *versus* no treatment	1.06 (0.79–1.41)	0.99 (0.74–1.33)
C *versus* no treatment	1.22 (0.92–1.62)	1.13 (0.85–1.50)
A *versus* macrolide monotherapy	0.71 (0.50–1.01)	0.84 (0.58–1.19)
B *versus* macrolide monotherapy	0.68 (0.45–1.03)	0.66 (0.4–1.00)
C *versus* macrolide monotherapy	0.78 (0.52–1.18)	0.75 (0.50–1.14)

Regimen group A: macrolide–ethambutol–rifamycin with or without other antibiotics. Regimen group B: macrolide–ethambutol with or without other antibiotics, except for rifamycins. Regimen group C: other combinations or two or more drugs. [#]: the multivariable models were adjusted for age, sex, income, rurality, and comorbidities (time-varying adjustment, updated every 6 months or at treatment change) including asthma, chronic kidney disease, COPD, diabetes, HIV infection, interstitial lung disease, lung cancer, rheumatoid arthritis, and ACG System Aggregated Diagnosis Groups (ADGs; a general measure of comorbidity; The Johns Hopkins ACG System Version 1]) [2–10]. [¶]: excluded patients who "stepped-up" in regimen group. [+]: excluded patients who "stepped-up" or "stepped-down".

Our study also did not detect a survival benefit to antibiotic treatment when compared to no treatment. However, this comparison likely suffers from confounding by treatment indication. We suspect that treated patients had more severe MAC-PD than untreated patients, but we could not statistically control for disease severity, because we lacked chest imaging results, acid-fast bacilli smear results, and symptom data. Prior single-centre retrospective observational studies that evaluated the association of antibiotic therapy with mortality in MAC-PD, compared to no treatment, found mixed results. Similar to us, Hayashi *et al.* [12] reported that two or more antibiotics given for ⩾3 months within 6 months of diagnosis was associated with a slight increase in all-cause mortality in 634 patients, compared to treatment with no or one antibiotic (HR 1.43, 95%CI 1.01–2.05). Ito *et al.* [13] found that treatment with two or more antibiotics given for ⩾6 months was associated with lower 5-year mortality than no treatment among 164 patients, but the difference was not statistically significant (22% *versus* 33%; p=0.30).

Our study has limitations. We defined NTM-PD on microbiological criteria alone, and therefore may have misclassified some patients as having true disease, perhaps most likely among untreated patients and biasing comparisons with treated patients. We only included adults aged ⩾66 years, so our findings may not apply to younger patients. We do not have cause of death; this older cohort may have died primarily from causes unrelated to MAC-PD. We were unable to study clofazimine or injectable aminoglycoside usage because this information is not in our databases. Our results may be impacted by confounding by treatment indication; we think this bias explains the higher mortality associated with standard triple therapy compared to no treatment, and may also impact our comparison of different antibiotic regimens, as patients treated with standard triple therapy may have had more severe disease or fewer unmeasured comorbidities than patients treated with other regimens. Finally, we were limited by the small number of patients treated with a sustained regimen of interest. Frequent adjustments in MAC-PD treatment make studying the effects of a single regimen challenging.

We could not identify an association between survival and antimicrobial drug regimen among patients with MAC-PD. Prospective randomised trials are needed to determine the impact of different antibiotic regimens on mortality.

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