Supplementary material

Antibiotic Maintenance and Redevelopment of *Mycobacterium avium* Complex Pulmonary Disease

Sungmin Zo¹, Hojoong Kim¹, O Jung Kwon¹, Byung Woo Jhun¹

¹Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.

Correspondence: Byung Woo Jhun, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea. E-mail: byungwoo.jhun@gmail.com
| Original etiology | M. avium | M. intracellulare | M. abscessus | M. massiliense | M. abscessus complex | M. kansasii | Mixed | Etc.* |
|-------------------|----------|------------------|--------------|----------------|---------------------|-------------|-------|-------|
| M. avium (n=45)   | -        | 21               | 10           | 6              | -                   | -           | 6     | 2     |
| M. intracellulare (n=42) | 20      | -                | 7            | 2              | 1                   | 2           | 10    | -     |

Etc.* included M. fortuitum complex and M. shimoidei.
**Table S2** Characteristics of study patients at the time of diagnosis with MAC-PD according to phenotype

| Characteristics                                                                 | Nodular bronchiectatic (n=520) | Fibrocavitary (n=111) | p-value |
|---------------------------------------------------------------------------------|---------------------------------|-----------------------|---------|
| **BACES**                                                                       |                                 |                       |         |
| Body mass index <18.5 kg/m²                                                      | 113 (22)                        | 38 (34)               | 0.007   |
| Age ≥65 years                                                                   | 92 (18)                         | 31 (28)               | 0.019   |
| Cavity                                                                          | 113 (22)                        | 107 (96)              | <0.001  |
| Elevated erythrocyte sedimentation rate                                         | 361 (69)                        | 92 (83)               | 0.006   |
| Sex, male                                                                       | 135 (26)                        | 72 (65)               | <0.001  |
| **BACES severity**                                                              |                                 |                       |         |
| Mild                                                                             | 258 (50)                        | 4 (4)                 | <0.001  |
| Moderate                                                                        | 242 (46)                        | 73 (66)               |         |
| Severe                                                                          | 20 (4)                          | 34 (31)               |         |
| **Comorbidity**                                                                 |                                 |                       |         |
| Previous pulmonary tuberculosis                                                  | 159 (31)                        | 66 (60)               | <0.001  |
| Chronic obstructive pulmonary disease                                           | 47 (9)                          | 26 (23)               | <0.001  |
| Chronic pulmonary aspergillosis                                                  | 3 (1)                           | 9 (8)                 | <0.001  |
| Lung cancer                                                                     | 5 (1)                           | 8 (7)                 | <0.001  |
| Ever-smoker*                                                                   | 94 (18)                         | 58 (52)               | <0.001  |
| Acid-fast bacillus smear positivity                                             | 174 (34)                        | 81 (73)               | <0.001  |
| **Etiology**                                                                    |                                 |                       | 0.005   |
| M. avium                                                                       | 281 (54)                        | 43 (39)               |         |
| M. intracellulare                                                               | 239 (46)                        | 68 (61)               |         |
| **Time between initiation of antibiotics and culture**                          | 1.0 (1.0-3.0)                   | 3.0 (1.0-5.0)         | <0.001  |
|                          | Current (n=191) | Former (n=106) | p-value |
|--------------------------|----------------|----------------|---------|
| Overall treatment duration, months | 17.0 (15.0-23.0) | 23.0 (16.0-24.0) | <0.001 |
| Total follow-up duration, months | 35.0 (24.0-51.0) | 38.0 (24.5-62.0) | 0.193  |

Redevelopment

|      | Current (n=191) | Former (n=106) | p-value |
|------|----------------|----------------|---------|
|      | 179 (34)       | 26 (23)        | 0.033   |

Data are presented as number (%) or median (interquartile range). MAC-PD, *Mycobacterium avium* complex-pulmonary disease; BACES, body mass index <18.5kg/m², age ≥65 years, cavity, erythrocyte sedimentation rate (men >15 mm/h, women >20 mm/h), and sex (male). †Includes current and former smokers. ‡Time from culture conversion to treatment completion.
**Table S3** Characteristics of study patients at the time of diagnosis with MAC-PD according to etiology

| Characteristics                                      | M. avium (n=324) | M. intracellulare (n=307) | p-value |
|------------------------------------------------------|-------------------|---------------------------|---------|
| **BACES**                                            |                   |                           |         |
| Body mass index $<18.5$ kg/m$^2$                     | 61 (19)           | 90 (29)                   | 0.003   |
| Age $\geq$65 years                                   | 40 (12)           | 83 (27)                   | $<0.001$|
| Cavity                                               | 95 (29)           | 125 (41)                  | 0.004   |
| Elevated erythrocyte sedimentation rate              | 216 (67)          | 237 (77)                  | 0.004   |
| Sex, male                                            | 97 (30)           | 110 (36)                  | 0.136   |
| **BACES severity**                                   |                   |                           | $<0.001$|
| Mild                                                 | 160 (49)          | 102 (33)                  |         |
| Moderate                                              | 152 (47)          | 163 (53)                  |         |
| Severe                                                | 12 (4)            | 42 (14)                   |         |
| **Comorbidity**                                      |                   |                           |         |
| Previous pulmonary tuberculosis                       | 104 (32)          | 121 (39)                  | 0.067   |
| Chronic obstructive pulmonary disease                | 31 (10)           | 42 (14)                   | 0.136   |
| Chronic pulmonary aspergillosis                      | 5 (2)             | 7 (2)                     | 0.700   |
| Lung cancer                                           | 4 (1)             | 9 (3)                     | 0.223   |
| Ever-smoker*                                         | 64 (20)           | 88 (29)                   | 0.012   |
| Acid-fast bacillus smear positivity                  | 121 (37)          | 134 (44)                  | 0.126   |
| **Radiological form**                                |                   |                           | 0.005   |
| Nodular bronchiectatic form                          | 281 (87)          | 239 (78)                  |         |
| Fibrocavitary form                                   | 43 (13)           | 68 (22)                   |         |
| Time between initiation of antibiotics and culture conversion, months | 1.0 (1.0-3.0) | 2.0 (1.0-4.0) | 0.206 |
| Maintenance period‡, months | 14.0 (12.0-18.0) | 14.0 (12.0-20.0) | 0.974 |
|----------------------------|------------------|------------------|-------|
| Overall treatment duration, months | 18.0 (15.0-24.0) | 18.0 (15.0-24.0) | 0.226 |
| Total follow-up duration, months | 38.0 (25.0-57.0) | 34.0 (24.0-50.5) | 0.105 |
| Redevelopment | 102 (32) | 103 (34) | 0.639 |

Data are presented as number (%) or median (interquartile range). MAC-PD, *Mycobacterium avium* complex-pulmonary disease; BACES, body mass index <18.5kg/m², age ≥65 years, cavity, erythrocyte sedimentation rate (men >15 mm/h, women >20 mm/h), and sex (male). †Includes current and former smokers. ‡Time from culture conversion to treatment completion.
Figure S1 Cumulative rate of redevelopment of MAC-PD according to phenotype (NB, nodular bronchiectatic; FC, fibrocavitary).
Figure S2 Cumulative rate of redevelopment of MAC-PD according to etiology.

| Time (years) | Etiology | M. avium | M. Intracellulare |
|-------------|----------|----------|------------------|
| 0           |          |          |                  |
| 1           |          |          |                  |
| 2           |          |          |                  |
| 3           |          |          |                  |
| 4           |          |          |                  |
| 5           |          |          |                  |

Number at risk

| Year | 324  | 204  | 137  | 85   | 57   | 34   |
|------|------|------|------|------|------|------|
| 0    | 307  | 168  | 102  | 64   | 39   | 25   |

p = 0.151
**Figure S3** Cumulative rate of redevelopment of each phenotype of MAC-PD, according to maintenance period (NB, nodular bronchiectatic; FC, fibrocavitary).

**A. NB form**

Cumulative redevelopment rate (%)

| Time (years) | 0 | 1 | 2 | 3 | 4 | 5 |
|-------------|---|---|---|---|---|---|
| Maintenance period | > 12 months | ≤ 12 months |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 |

Number at risk: 447, 276, 182, 110, 71, 48

**B. FC form**

Cumulative redevelopment rate (%)

| Time (years) | 0 | 1 | 2 | 3 | 4 | 5 |
|-------------|---|---|---|---|---|---|
| Maintenance period | > 12 months | ≤ 12 months |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 |

Number at risk: 97, 56, 37, 27, 18, 7

**Figure 3** Cumulative rate of redevelopment of each phenotype of MAC-PD, according to maintenance period (NB, nodular bronchiectatic; FC, fibrocavitary).

**A. NB form**

Cumulative redevelopment rate (%)

| Time (years) | 0 | 1 | 2 | 3 | 4 | 5 |
|-------------|---|---|---|---|---|---|
| Maintenance period | > 12 months | ≤ 12 months |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 |

Number at risk: 447, 276, 182, 110, 71, 48

**B. FC form**

Cumulative redevelopment rate (%)

| Time (years) | 0 | 1 | 2 | 3 | 4 | 5 |
|-------------|---|---|---|---|---|---|
| Maintenance period | > 12 months | ≤ 12 months |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 |

Number at risk: 97, 56, 37, 27, 18, 7
Figure S4 Cumulative rate of redevelopment of MAC-PD according to etiology.

A. *M. Intracellulare*

B. *M. avium*
Table S4-1 Risk factors related to redevelopment of MAC-PD in 631 study patients (*Model 1*)

| Characteristics                                                                 | Univariate analysis                  | Multivariate analysis                  |
|--------------------------------------------------------------------------------|--------------------------------------|----------------------------------------|
|                                                                                | HR (95% CI)                          | p-value                                | HR (95% CI)                          | p-value |
| **BACES**                                                                      |                                      |                                        |                                      |         |
| Mild                                                                           | reference                            |                                        | reference                            |         |
| Moderate                                                                       | 1.06 (0.80-1.41)                     | 0.686                                  | 0.97 (0.71-1.31)                     | 0.832   |
| Severe                                                                         | 0.77 (0.41-1.44)                     | 0.416                                  | 0.63 (0.30-1.31)                     | 0.216   |
| Acid-fast bacillus smear positivity                                            | 1.09 (0.83-1.44)                     | 0.533                                  | 1.08 (0.81-1.44)                     | 0.594   |
| Previous pulmonary tuberculosis                                                | 1.09 (0.82-1.44)                     | 0.549                                  | 1.09 (0.81-1.47)                     | 0.562   |
| Chronic obstructive pulmonary disease                                          | 0.94 (0.61-1.43)                     | 0.765                                  | 0.89 (0.57-1.37)                     | 0.595   |
| Chronic pulmonary aspergillosis                                                | 0.59 (0.19-1.85)                     | 0.363                                  | 0.70 (0.20-2.42)                     | 0.575   |
| Lung cancer                                                                    | 1.03 (0.38-2.78)                     | 0.950                                  | 1.06 (0.39-2.88)                     | 0.908   |
| Ever-smoker*                                                                   | 1.20 (0.87-1.66)                     | 0.256                                  | 1.28 (0.90-1.82)                     | 0.162   |
| **Etiology**                                                                   |                                      |                                        |                                      |         |
| *M. avium*                                                                     | reference                            |                                        | reference                            |         |
| *M. intracellulare*                                                            | 1.24 (0.94-1.63)                     | 0.124                                  | 1.26 (0.95-1.67)                     | 0.112   |
| **Maintenance period**                                                         |                                      |                                        |                                      |         |
| ≤12 months                                                                     | reference                            |                                        | reference                            |         |
| >12 months                                                                     | 0.99 (0.63-1.58)                     | 0.976                                  | 0.99 (0.61-1.59)                     | 0.961   |

BACES, body mass index <18.5kg/m², age ≥65 years, cavity, erythrocyte sedimentation rate (men >15 mm/h, women >20 mm/h), and sex (male). *Includes current and former smokers. ‡Time from culture conversion to treatment completion.
| Characteristics                                           | Univariate analysis | Multivariate analysis |
|-----------------------------------------------------------|---------------------|-----------------------|
|                                                           | HR (95% CI)         | p-value               |
|                                                           | HR (95% CI)         | p-value               |
| Body mass index <18.5 kg/m²                                | 1.05 (0.77-1.43)    | 0.769                 |
|                                                           | 1.08 (0.76-1.52)    | 0.678                 |
| Age ≥65 years                                              | 1.12 (0.77-1.64)    | 0.552                 |
|                                                           | 0.98 (0.66-1.48)    | 0.940                 |
| Cavity                                                    | 0.86 (0.64-1.16)    | 0.331                 |
|                                                           | 0.78 (0.55-1.10)    | 0.153                 |
| Elevated erythrocyte sedimentation rate*                  | 1.00 (0.74-1.34)    | 0.977                 |
|                                                           | 1.03 (0.75-1.41)    | 0.860                 |
| Sex, male                                                 | 1.19 (0.89-1.60)    | 0.239                 |
|                                                           | 1.21 (0.74-1.99)    | 0.445                 |
| Acid-fast bacillus smear positivity                       | 1.09 (0.83-1.44)    | 0.533                 |
|                                                           | 1.12 (0.83-1.51)    | 0.446                 |
| Previous pulmonary tuberculosis                           | 1.09 (0.82-1.44)    | 0.549                 |
|                                                           | 1.10 (0.82-1.49)    | 0.520                 |
| Chronic obstructive pulmonary disease                     | 0.94 (0.61-1.43)    | 0.765                 |
|                                                           | 0.88 (0.57-1.37)    | 0.569                 |
| Chronic pulmonary aspergillosis                          | 0.59 (0.19-1.85)    | 0.363                 |
|                                                           | 0.53 (0.16-1.77)    | 0.300                 |
| Lung cancer                                               | 1.03 (0.38-2.78)    | 0.950                 |
|                                                           | 1.03 (0.38-2.78)    | 0.959                 |
| Ever-smoker‡                                              | 1.20 (0.87-1.66)    | 0.256                 |
|                                                           | 1.06 (0.62-1.80)    | 0.835                 |
| Etiology                                                  |                     |                       |
| M. avium                                                 | reference           |                       |
| M. intracellulare                                         | 1.24 (0.94-1.63)    | 0.124                 |
|                                                           | 1.24 (0.93-1.66)    | 0.135                 |
| Maintenance period‡                                       |                     |                       |
| ≤12 months                                                | reference           |                       |
|                                                           | reference           |                       |
| >12 months                                                | 0.99 (0.63-1.58)    | 0.976                 |
|                                                           | 1.05 (0.65-1.71)    | 0.838                 |

*Men >15 mm/h, women >20 mm/h. ‡Includes current and former smokers. †Time from culture conversion to treatment completion.
Table S4-3 Risk factors related to redevelopment of MAC-PD in 631 study patients (Model 3)

| Characteristics                                      | Univariate analysis |                      | Multivariate analysis |                      |
|-------------------------------------------------------|---------------------|----------------------|-----------------------|----------------------|
|                                                       | HR (95% CI)         | p-value              | HR (95% CI)           | p-value              |
| Body mass index <18.5 kg/m²                            | 1.05 (0.77-1.43)    | 0.769                | 1.10 (0.78-1.55)      | 0.594                |
| Age ≥65 years                                          | 1.12 (0.77-1.64)    | 0.552                | 1.00 (0.67-1.51)      | 0.983                |
| Elevated erythrocyte sedimentation rate*              | 1.00 (0.74-1.34)    | 0.977                | 1.01 (0.74-1.37)      | 0.960                |
| Sex, male                                             | 1.19 (0.89-1.60)    | 0.239                | 1.22 (0.74-2.00)      | 0.428                |
| Acid-fast bacillus smear positivity                   | 1.09 (0.83-1.44)    | 0.533                | 1.13 (0.84-1.51)      | 0.417                |
| Previous pulmonary tuberculosis                       | 1.09 (0.82-1.44)    | 0.549                | 1.11 (0.82-1.49)      | 0.496                |
| Chronic obstructive pulmonary disease                 | 0.94 (0.61-1.43)    | 0.765                | 0.91 (0.58-1.41)      | 0.672                |
| Chronic pulmonary aspergilosis                        | 0.59 (0.19-1.85)    | 0.363                | 0.64 (0.18-2.20)      | 0.476                |
| Lung cancer                                           | 1.03 (0.38-2.78)    | 0.950                | 1.14 (0.42-3.12)      | 0.795                |
| Ever-smoker‡                                          | 1.20 (0.87-1.66)    | 0.256                | 1.10 (0.65-1.88)      | 0.718                |
| Phenotype                                             |                     |                      |                       |                      |
| Fibrocavitary form                                     | reference           |                      | reference             |                      |
| Nodular bronchiectatic form                           | 1.39 (0.92-2.09)    | 0.120                | 1.61 (1.01-2.57)      | 0.047                |
| Etiology                                              |                     |                      |                       |                      |
| M. avium                                              | reference           |                      | reference             |                      |
| M. intracellulare                                     | 1.24 (0.94-1.63)    | 0.124                | 1.22 (0.92-1.63)      | 0.173                |
| Maintenance period‡                                    |                     |                      |                       |                      |
| ≤12 months                                            | reference           |                      | reference             |                      |
| >12 months                                            | 0.99 (0.63-1.58)    | 0.976                | 1.05 (0.65-1.71)      | 0.839                |
Men >15 mm/h, women >20 mm/h. ‡Includes current and former smokers. ¶Time from culture conversion to treatment completion.
Figure S5 Study patients. MAC-PD, *Mycobacterium avium* complex-pulmonary disease; BACES, body mass index, age, cavity, erythrocyte sedimentation rate, and sex.