BMJ Open Respiratory Research

Prevalence and risk factors for chronic co-infection in pulmonary *Mycobacterium avium* complex disease

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To cite: Fujita K, Ito Y, Hirai T, *et al*. Prevalence and risk factors for chronic co-infection in pulmonary *Mycobacterium avium* complex disease. *BMJ Open Resp Res* 2014;**1**:e000050. doi:10.1136/bmjresp-2014-000050

Received 26 May 2014
Accepted 15 August 2014

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ABSTRACT

Background: Patients with pulmonary *Mycobacterium avium* complex (MAC) disease are often co-infected with various pathogenic microorganisms. This study aimed to determine the prevalence of co-infection with non-MAC pathogens and the risk factors associated with co-infection in patients with pulmonary MAC disease.

Methods: We retrospectively reviewed the patient characteristics, microbiological results and chest CT findings in 275 patients with pulmonary MAC who visited the Kyoto University Hospital from January 2001 to May 2013. We defined chronic pathogenic co-infection as the isolation of non-MAC pathogens from sputum samples taken on more than two visits that occurred at least 3 months apart.

Results: The participants were predominantly female (74.5%) and infected with *M. avium* (75.6%). Chronic co-infection with any pathogen was observed in 124 patients (45.1%). Methicillin-sensitive *Staphylococcus aureus* (MSSA; n=64), *Pseudomonas aeruginosa* (n=35) and *Aspergillus* spp (n=18) were the most prevalent pathogens. The adjusted factors were chronic obstructive pulmonary disease (COPD; OR=4.2, 95% CI 1.6 to 13.1) and pulmonary *M. intracellulare* disease (OR=2.2, 95% CI 1.1 to 4.4) in chronic co-infections; COPD (OR=4.2, 95% CI 2.1 to 31.4), long duration of MAC disease (OR=2.2, 95% CI 1.2 to 4.4) and nodules (OR=3.5, 95% CI 1.2 to 13.2) in chronic MSSA co-infection; COPD (OR=7.5, 95% CI 2.1 to 31.4) and lower lobe involvement (OR=9.9, 95% CI 2.0 to 90.6) in chronic *P. aeruginosa* co-infection; and use of systemic corticosteroids (OR=7.1, 95% CI 1.2 to 50.9) and pulmonary *M. intracellulare* disease (OR=4.0, 95% CI 1.1 to 14.5) in chronic *Aspergillus* spp co-infection.

Conclusions: Patients with pulmonary MAC disease frequently had chronic co-infections with pathogenic microorganisms such as MSSA, *P. aeruginosa* and *Aspergillus*. The risk factors for chronic co-infection were COPD and pulmonary *M. intracellulare* disease.

KEY MESSAGES

- Patients with pulmonary *Mycobacterium avium* complex (MAC) disease are often co-infected with various other pathogenic microorganisms, but the factors associated with microorganism co-infection in patients with pulmonary MAC remain unclear.
- Patients with pulmonary MAC disease frequently had chronic co-infections with pathogenic microorganisms such as methicillin-sensitive *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Aspergillus*, and the adjusted risk factors for chronic co-infection were chronic obstructive pulmonary disease (COPD) and pulmonary *M. intracellulare* disease.
- Chronic co-infection is common in patients with pulmonary MAC disease, and COPD and pulmonary *M. intracellulare* disease increase the risk of co-infection.

INTRODUCTION

As the prevalence of pulmonary non-tuberculous mycobacterial (NTM) disease, especially pulmonary *Mycobacterium avium* complex (MAC) disease, has been increasing worldwide,[1–3] more patients have an opportunity to be followed in a medical institution.[4 5] Pulmonary MAC disease has a prolonged course and often manifests as bronchiectasis and cavitation in high-resolution CT (HRCT) images.[6] In patients susceptible to bronchiectasis, chronic inflammation causes damage primarily to the bronchi. Damaged airways are susceptible to infection, resulting in further destruction and dilation of the bronchi and leading to bronchiectasis.[7 8] NTM infection has been shown to stimulate the development of or worsen pre-existing bronchiectasis, although causality has not been definitively established.[9–11]

Chronic infections with bacteria such as *Pseudomonas aeruginosa* and *Haemophilus influenzae* are associated with bronchiectasis and cystic fibrosis, causing recurrent exacerbations of these diseases and leading to lung function decline and premature death.[12–14] Although these pathogenic microorganisms

can be isolated intermittently, chronic infections are known to have a higher clinical impact.[15–18]

During the course of pulmonary NTM disease, co-infections with various bacteria other than NTM such as *P. aeruginosa, H. influenzae* and *Aspergillus* are occasionally observed.[19 20] However, previous studies of these infections included a relatively small number of participants with MAC disease, and patients with single NTM isolates were most likely only temporarily colonised.[6] Furthermore, although some host traits, such as chronic lung disease and autoimmune disease, and the use of immunosuppressive agents are known risk factors for infection in patients with bronchiectasis and cystic fibrosis,[18 21 22] the factors associated with microorganism co-infections in patients with pulmonary MAC remain unclear.

The aim of this study was to determine the prevalence of co-infection with non-MAC pathogenic microorganisms and to identify risk factors for co-infection among clinical, microbiological and radiological findings in patients with pulmonary MAC disease.

METHODS

Study design and population

This was a retrospective cohort study of 645 patients with pulmonary MAC, who fulfilled the American Thoracic Society diagnostic criteria and who visited the Kyoto University Hospital from January 2001 to May 2013.[6] We reviewed patient characteristics, microbiological results and chest (HRCT) findings from institutional medical records. We excluded 370 patients: 295 patients who were unable to provide sputum samples at least two times in a year, medical history and/or CT scan data; 74 patients who were followed up for less than 12 months from the first visit to the last visit and 1 patient who had complications with disseminated MAC infection and HIV infection. Finally, we analysed 275 patients with pulmonary MAC in this study. Laboratory and HRCT data from patients with any co-infecting microorganism were collected around the time that the co-infecting microorganism was first isolated, and the data collected from patients without co-infection by microorganisms were collected at the time of the first visit.

Microbiological classification

We defined chronic pathogenic microorganism co-infection (chronic co-infection) as the isolation of non-MAC potential pathogens from two or more sputum samples taken on two separate visits at least 3 months apart. Cultures did not necessarily have to be consecutive. Patients were defined as having an intermittent pathogenic microorganism co-infection (intermittent co-infection) when the potential pathogen had been isolated only once in the past. Patients with no pathogenic microorganism co-infection (no co-infection) did not have any potential pathogens isolated from any of the sputum samples at any time.[15] Since *Staphylococcus aureus* often colonises the human oropharynx, the sputum quality was checked according to the Geckler classification to distinguish between infection and colonisation.[23] Only sputum with a Geckler classification of 4 or 5 was selected for analysis. In addition, making a clear distinction between *Aspergillus* infection and colonisation is not feasible. Therefore, we have chosen to use the term infection throughout this article.[18]

Radiological findings

We assessed four cardinal HRCT findings (nodule, bronchiectasis, cavity and consolidation). We counted the extent and location of lung involvement and thoracic abnormalities (scoliosis and pectus excavatum) in the HRCT. We classified the following four radiographic forms according to previous reports: nodular/bronchiectatic (NB), fibrocavitary (FC), NB+FC and unclassified.[4] One board-certified thoracic radiologist who had no prior knowledge of the patients' profiles or laboratory test results read the HRCT images.

Statistical analysis

JMP V.9.0.0 was used for all statistical analyses. Group comparisons were made using the χ^2 test or Fisher's exact test for categorical values and the Wilcoxon test for continuous values. To adjust for confounders, variables with a p value less than 0.05 on univariate analysis were entered into a multivariate logistic regression analysis. ORs and their respective 95% CIs were computed as estimates of relative risk. For all analyses, p values less than 0.05 were considered statistically significant.

RESULTS

Characteristics of the study population

The participants were predominantly female (205 patients, 74.5%) and infected with *M. avium* (208 patients, 75.6%). The mean age at diagnosis was 61.9 ±11.6 years, and the mean duration of MAC disease from diagnosis was 7.2±7 years. Bronchiectasis was the most frequent host trait (234 patients, 85.1%), followed by severe pneumonia (81 patients, 29.6%), malignant disease (57 patients, 20.7%) and prior tuberculosis (34 patients, 12.4%). Since it is often difficult to distinguish which comes first, the bronchiectasis or the pulmonary MAC disease, we counted bronchiectasis as an underlying disease when it was detected in the first HRCT. Autoimmune disease was recorded in 36 patients (13.1%), with 19 (52.8%) having rheumatoid arthritis (table 1). In the HRCT scans, nodules and bronchiectasis were the most common findings (86.2% and 85.1%), and they were predominantly located in the right middle lobe or lingula.

Patients with pulmonary *M. intracellulare* were older in age and had significantly lower body mass indices. These patients more frequently had host traits of severe

Table 1 Characteristics of the study population

Clinical characteristics	n=275
Age at diagnosis, years	61.9±11.6
Gender (female)	205 (74.5)
Body mass index, kg/m^2	19.4±2.8
Smoking status (never)	219 (79.6)
Chronic microorganism co-infection	124 (45.1)
Intermittent microorganism co-infection	41 (14.9)
Number of sputum samples, numbers/year	
All patients	4.43±2.4
Patients with chronic co-infection	4.51±2.4
Patients with intermittent co-infection	4.54±2.3
Underlying disease	
Bronchiectasis	234 (85.1)
Severe pneumonia (hospitalisation)	81 (29.6)
COPD	28 (10.2)
Asthma	24 (8.7)
History of tuberculosis	34 (12.4)
History of malignant disease	57 (20.7)
Diabetes mellitus	26 (9.5)
Autoimmune disease	36 (13.1)
Rheumatoid arthritis	19 (6.9)
GORD symptom	44 (16.1)
Use of systemic corticosteroids	22 (8.0)
Use of immunosuppressant agent	24 (8.7)
Use of inhaled corticosteroids	19 (6.9)
Infected MAC strain (*Mycobacterium avium*)	208 (75.6)
Duration of MAC disease, years	7.2±7.0

Data show either the number (%) of patients or the mean±SD. COPD, chronic obstructive pulmonary disease; GORD, gastro-oesophageal reflux disease; MAC, *M. avium* complex.

pneumonia, malignant disease and autoimmune disease and used more systemic corticosteroids than patients with pulmonary *M. avium* (table 2). In the HRCT analysis, patients with pulmonary *M. intracellulare* had significantly more cavity findings and the NB+FC form of lung involvement than patients with *M. avium* (table 2).

Type of co-infection and isolated microorganisms

Of the 275 patients with pulmonary MAC, 124 (45.1%) had chronic co-infections, 41 (14.9%) had intermittent co-infections and 110 (40.0%) had no co-infection. Among the 277 detected microorganisms, methicillin-sensitive *S. aureus* (MSSA; 89 patients, 32.4%), *P. aeruginosa* (45 patients, 16.4%) and *Aspergillus* spp (29 patients, 10.5%) were the most prevalent co-pathogens. These three species were more frequently isolated from patients with a chronic co-infection than from those with an intermittent co-infection (64 and 25 patients with MSSA infection, 35 and 10 patients with *P. aeruginosa* infection and 18 and 11 patients with *Aspergillus* infection, respectively). In contrast, intermittent co-infections were observed more frequently than chronic co-infections for *Serratia marcescens* (12 and 2 patients, respectively), *Moraxella catarrhalis* (7 and 1 patients, respectively), *Acinetobacter baumannii* (6 and 1 patients, respectively) and *Klebsiella oxytoca* (2 and 0 patients, respectively) (figure 1).

Characteristics of patients and factors associated with chronic and intermittent co-infection

Compared with patients who did not have a co-infection, chronic co-infection was significantly associated with a history of severe pneumonia, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, use of systemic corticosteroids and pulmonary *M. intracellulare* disease. Intermittent co-infection was associated with pulmonary *M. intracellulare* disease alone. There was no significant difference in the history of MAC treatment and a negative conversion rate of MAC sputum cultures during the study period between patients with chronic co-infections and those without co-infection (table 3). There were no significant differences in the HRCT findings, the location of areas of lung involvement and thoracic abnormalities between patients with chronic or intermittent co-infection and those without co-infection. (table 4).

In the multivariate analysis, COPD (OR 4.2; 95% CI 1.6 to 13.1; p=0.0029) and pulmonary *M. intracellulare* disease (OR 2.2; 95% CI 1.1 to 4.4; p=0.026) were independently associated with chronic co-infection. Pulmonary *M. intracellulare* disease (OR 3.0; 95% CI 1.3 to 7.1; p=0.01) was also independently associated with intermittent co-infection (table 5).

Characteristics of patients and factors associated with chronic MSSA co-infection

COPD, the use of inhaled corticosteroids and a longer duration of MAC disease were significantly associated with chronic MSSA co-infection in patients (table 6).

In the HRCT findings, nodule findings and the NB form were predominantly found in patients with chronic MSSA co-infection (table 7). In the multivariate analysis, COPD (OR 4.2; 95% CI 1.3 to 15.2; p=0.017), longer duration of MAC disease (OR 2.2; 95% CI 1.2 to 4.4; p=0.017) and having nodules on the HRCT (OR 3.5; 95% CI 1.2 to 13.2; p=0.019) were significantly associated with chronic MSSA co-infection (table 8).

Of 64 patients with chronic MSSA co-infection, 41 patients (64.1%) had a MAC-positive sputum culture. Thirty-seven patients (57.8%) had a history of MAC treatment, and only two of these patients (5.4%) had a positive MSSA sputum culture during MAC treatment. After 46 patients had converted sputum cultures of MAC, 32 patients (69.6%) had a positive MSSA sputum culture (tables 6 and 9). Thirty-two of 64 (50%) patients with chronic MSSA co-infection had received antibiotic treatment for their co-infection.

Characteristics of patients and factors associated with chronic *P. aeruginosa* co-infection

A history of severe pneumonia, COPD or autoimmune disease including rheumatoid arthritis; the use of systemic corticosteroids and immunosuppressive agents and pulmonary *M. intracellulare* disease were significantly associated with the development of chronic *P. aeruginosa* co-infections (table 6). The areas of lung involvement in

Table 2 Characteristics and HRCT findings of patients with pulmonary *Mycobacterium avium* and *M. intracellulare*

	Pulmonary *M. avium* disease (n=208)	Pulmonary *M. intracellulare* disease (n=67)	p Value
Age at diagnosis, years	61.0±11.6	64.7±11.5	0.0029
Gender (female)	158 (76.0)	47 (70.2)	0.34
Body mass index, kg/m^2	19.6±2.6	18.7±3.2	0.012
Smoking status (never)	163 (78.4)	56 (83.6)	0.36
Chronic microorganism co-infection	87 (41.8)	37 (55.2)	0.055
Intermittent microorganism co-infection	27 (13.0)	14 (20.9)	0.11
Underlying disease			
Bronchiectasis	177 (85.1)	57 (85.1)	>0.99
Severe pneumonia (hospitalisation)	53 (25.5)	28 (41.8)	0.011
COPD	22 (10.6)	6 (9.0)	0.81
Asthma	19 (9.1)	5 (7.5)	0.81
History of tuberculosis	23 (11.1)	11 (16.4)	0.25
History of malignant disease	36 (17.3)	21 (31.3)	0.014
Diabetes mellitus	19 (9.1)	7 (10.5)	0.81
Autoimmune disease	22 (10.6)	14 (20.9)	0.029
Rheumatoid arthritis	11 (5.3)	8 (11.9)	0.092
GORD symptom	34 (16.4)	10 (14.9)	0.77
Use of systemic corticosteroids	12 (5.8)	10 (14.9)	0.016
Use of immunosuppressant agent	15 (7.2)	9 (13.4)	0.14
Use of inhaled corticosteroids	14 (6.7)	5 (7.5)	0.79
Duration of MAC disease, years	7.3±6.6	7.0±8.1	0.34
HRCT findings			
Nodule	179 (86.1)	58 (86.6)	>0.99
Consolidation	114 (54.8)	38 (56.7)	0.78
Bronchiectasis	177 (85.1)	57 (85.1)	>0.99
Cavity	66 (31.7)	32 (47.8)	0.017
Radiographic pattern			
NB form	125 (60.1)	27 (40.3)	0.0072
FC form	17 (8.2)	8 (11.9)	0.34
NB+FC form	48 (23.1)	24 (35.8)	0.039
Unclassified	18 (8.7)	8 (11.9)	0.47
Thoracic abnormality			
Scoliosis	49 (23.6)	23 (34.3)	0.08
Pectus excavatum	25 (12.0)	6 (9.0)	0.66
Location of HRCT findings			
Right/left upper lobe	157 (75.5)	51 (76.1)	0.92
Right middle lobe/lingula	189 (90.9)	64 (95.5)	0.3
Right/left lower lobe	135 (64.9)	57 (85.1)	0.0018

Data show either the number (%) of patients or the mean±SD.
COPD, chronic obstructive pulmonary disease; FC, fibrocavitary; GORD, gastro-oesophageal reflux disease; HRCT, high-resolution CT; MAC, *M. avium* complex; NB, nodular/bronchiectatic.

patients with chronic *P. aeruginosa* co-infections were predominantly located in the lower lobe (table 7). In the multivariate analysis, COPD (OR 7.5; 95% CI 2.1 to 31.4; p=0.0017) and lung involvement in the lower lobe on HRCT (OR 9.9; 95% CI 2.0 to 90.6; p=0.0027) were significantly associated with chronic *P. aeruginosa* co-infection (table 8).

Of the 35 patients with chronic *P. aeruginosa* co-infection, 9 (25.7%) had *P. aeruginosa* detected in a MAC-positive sputum culture. Of the 24 patients with a history of MAC treatment, 18 (75%) had a positive *P. aeruginosa* sputum culture during MAC treatment. After 29 patients had a converted sputum culture of MAC, 27 (93.1%) also had a positive *P. aeruginosa* sputum culture (tables 6 and 9). Seventeen of 35 (48.6%) patients with chronic *P. aeruginosa* co-infection had received antibiotic treatment for their co-infection.

Characteristics of patients and factors associated with chronic *Aspergillus* co-infection

Of the 18 patients with chronic *Aspergillus* co-infection, 15 (83.3%) had a chronic necrotising pulmonary aspergillosis (CNPA), with 5 (33.3%) having pulmonary aspergilloma and 3 (16.7%) having an allergic bronchopulmonary aspergillosis (ABPA). Of the 6 patients using systemic corticosteroids, 5 had CNPA and 1 had ABPA.

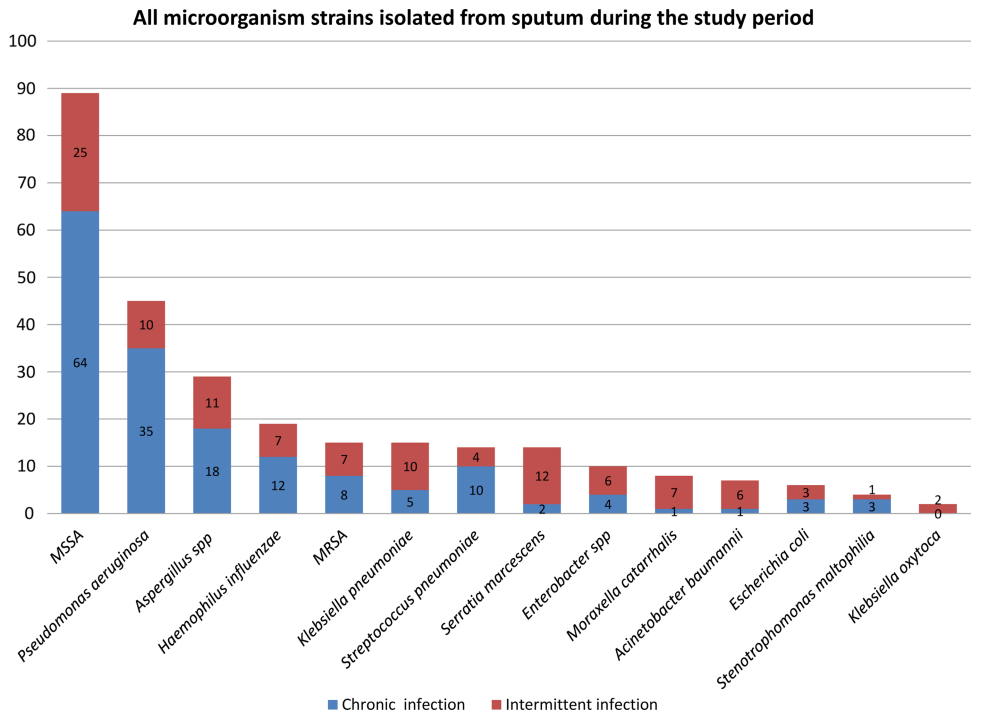

Figure 1 All microorganism strains isolated from the sputum during the study period. The graph shows the number of patients with chronic and intermittent microorganism co-infections. The blue and red bars show chronic and intermittent infections, respectively (MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*).

Table 3 Characteristics of patients with pulmonary MAC with chronic and intermittent co-infection

Variables	No co-infection (n=110)	Chronic co-infection (n=124)	p Value	Intermittent co-infection (n=41)	p Value
Age at diagnosis, years	61.9±11.5	61.6±12.3	0.91	62.8±9.7	0.62
Gender (female)	88 (80.0)	87 (70.2)	0.084	30 (73.2)	0.37
Body mass index, kg/m^2	19.1±2.9	19.6±2.8	0.37	19.8±2.5	0.13
Smoking status (never)	92 (83.6)	93 (75.0)	0.11	34 (82.9)	0.92
Underlying disease					
Bronchiectasis	92 (83.6)	108 (87.1)	0.45	34 (82.9)	>0.99
Severe pneumonia (hospitalisation)	26 (23.6)	45 (36.3)	0.036	10 (24.4)	0.92
COPD	5 (4.6)	21 (16.9)	0.0030	2 (4.9)	0.99
Asthma	7 (6.4)	14 (11.3)	0.25	3 (7.3)	0.99
History of tuberculosis	13 (11.8)	18 (14.5)	0.54	3 (7.3)	0.56
History of malignant disease	17 (15.5)	30 (24.2)	0.096	10 (24.4)	0.20
Diabetes mellitus	9 (8.2)	11 (8.9)	0.99	6 (14.6)	0.24
Autoimmune disease	9 (8.2)	19 (15.3)	0.11	8 (19.5)	0.079
Rheumatoid arthritis	3 (2.7)	12 (9.7)	0.034	4 (9.8)	0.087
GORD symptom	17 (15.5)	18 (14.5)	0.86	9 (22.5)	0.33
Use of systemic corticosteroids	4 (3.6)	16 (12.9)	0.017	2 (4.9)	0.66
Use of immunosuppressant agent	5 (4.6)	13 (10.5)	0.14	6 (14.6)	0.07
Use of inhaled corticosteroids	4 (3.6)	13 (10.5)	0.074	2 (4.9)	0.73
Infected MAC strain (*Mycobacterium intracellulare*)	16 (14.6)	36 (29.3)	0.0053	13 (33.3)	0.011
Duration of MAC disease, years	6.3±5.0	8.5±8.6	0.15	5.7±5.3	0.39
History of MAC treatment	76 (69.1)	81 (65.3)	0.54	27 (65.9)	0.70
MAC sputum culture conversion	74 (67.3)	87 (70.2)	0.63	31 (75.6)	0.32

Data show either the number (%) of patients or the mean±SD.
COPD, chronic obstructive pulmonary disease; GORD, gastro-oesophageal reflux disease; MAC, *M. avium* complex.

Table 4 HRCT findings of patients with pulmonary *Mycobacterium avium* complex with chronic and intermittent co-infections

Variables	No co-infection (n=110)	Chronic co-infection (n=124)	p Value	Intermittent co-infection (n=41)	p Value
HRCT findings					
Nodule	89 (80.9)	110 (88.7)	0.095	38 (92.7)	0.086
Consolidation	60 (54.6)	76 (61.3)	0.30	16 (39.0)	0.09
Bronchiectasis	92 (83.6)	108 (87.1)	0.45	34 (82.9)	0.99
Cavity	42 (38.2)	45 (36.3)	0.79	11 (26.8)	0.19
Radiographic pattern					
NB form	55 (50.0)	71 (57.3)	0.27	26 (63.4)	0.14
FC form	14 (12.7)	9 (7.3)	0.19	2 (4.9)	0.24
NB+FC form	28 (25.5)	36 (29.0)	0.54	9 (22.0)	0.83
Unclassified	13 (11.8)	9 (7.3)	0.27	4 (9.8)	0.99
Thoracic abnormality					
Scoliosis	28 (25.5)	34 (27.4)	0.73	10 (24.4)	0.89
Pectus excavatum	12 (10.9)	15 (12.1)	0.84	4 (9.8)	0.99
Location of HRCT findings					
Right/left upper lobe	81 (73.6)	95 (76.6)	0.60	32 (78.1)	0.68
Right middle lobe/lingula	98 (89.1)	117 (94.4)	0.16	38 (92.7)	0.76
Right/left lower lobe	71 (64.6)	91 (73.4)	0.14	30 (73.2)	0.32

Data show the number (%) of patients.
FC, fibrocavitary; HRCT, high-resolution CT; NB, nodular/bronchiectatic.

Male sex; a history of severe pneumonia, asthma, tuberculosis or autoimmune disease including rheumatoid arthritis; the use of systemic corticosteroids and pulmonary *M. intracellulare* disease were significantly associated with chronic *Aspergillus* co-infection in patients (table 6). In the multivariate analysis, the use of systemic corticosteroids (OR 7.1; 95% CI 1.2 to 50.9; p=0.034) and pulmonary *M. intracellulare* disease (OR 4.0; 95% CI 1.1 to 14.5; p=0.036) was significantly associated with chronic *Aspergillus* co-infection (table 8).

Of the 18 patients with chronic *Aspergillus* co-infection, 9 (50%) were positive for *Aspergillus* spp at the time of MAC-positive sputum culture. Of the 11 patients with a history of MAC treatment, 9 (81.8%) had a positive *Aspergillus* sputum culture during MAC treatment. After 11 patients converted a sputum culture of MAC, 9 (81.8%) had a positive *Aspergillus* sputum culture (tables 6 and 9). Ten of the 18 (55.6%) patients with chronic *Aspergillus* co-infection had received antibiotic treatment for their co-infection.

DISCUSSION

Previous studies in patients with bronchiectasis have shown that *H. influenzae* and *P. aeruginosa* were the more prevalent pathogens and that *S. aureus* was a less common pathogen.[12 19 24 25] In contrast, a previous study in patients with bronchiectasis and NTM infection reported that *P. aeruginosa* (51%) and *S. aureus* (28%) were often isolated, whereas *H. influenzae* (12%) was rarely isolated.[19] As compared with these previous studies, our study showed that chronic and intermittent microorganism co-infection was observed in 45.1% and 14.9%, respectively, of patients with pulmonary MAC disease. The majority of co-infecting microorganisms were MSSA, followed by *P. aeruginosa* and *Aspergillus* spp. We found that co-infection with *Aspergillus* spp is the third most prevalent infection in patients with pulmonary MAC disease.

CNPA was occasionally complicated during a long course of MAC disease.[26] Kunst *et al* reported that *Aspergillus*-related lung disease was more common in

Table 5 Factors associated with chronic and intermittent co-infections

Variables	Chronic co-infection OR (95% CI)	p Value	Intermittent co-infection OR (95% CI)	p Value
Severe pneumonia	1.5 (0.8 to 2.7)	0.22	–	–
COPD	4.2 (1.6 to 13.1)	0.0029	–	–
Rheumatoid arthritis	1.8 (0.38 to 9.9)	0.48	–	–
Use of systemic corticosteroids	2.1 (0.55 to 9.6)	0.28	–	–
Infected *Mycobacterium intracellulare* strain	2.2 (1.1 to 4.4)	0.026	3.0 (1.3 to 7.1)	0.01

Variables were included if the probability values were less than 0.05 by univariate analysis.
COPD, chronic obstructive pulmonary disease.

Table 6 Characteristics of patients with pulmonary MCA with chronic MSSA, *Pseudomonas aeruginosa* and *Aspergillus* co-infections

Variables	No co-infection (n=110)	Chronic MSSA co-infection (n=64)	p Value	Chronic *P. aeruginosa* co-infection (n=35)	p Value	Chronic *Aspergillus* co-infection (n=18)	p Value
Age at diagnosis, years	61.9±11.5	61.4±11.8	0.84	61.9±11.6	0.78	64.3±13.4	0.16
Gender (female)	88 (80.0)	46 (71.9)	0.22	25 (71.4)	0.29	10 (55.7)	0.035
Body mass index, kg/m^2	19.1±2.9	19.6±2.7	0.34	20.0±2.7	0.26	18.7±2.6	0.54
Smoking status (never)	92 (83.6)	48 (75.0)	0.17	25 (71.4)	0.11	14 (77.8)	0.51
Underlying disease							
Bronchiectasis	92 (83.6)	53 (82.8)	0.89	32 (91.4)	0.41	15 (83.3)	>0.99
Severe pneumonia (hospitalisation)	26 (23.6)	20 (31.3)	0.27	16 (45.7)	0.012	11 (61.1)	0.0034
COPD	5 (4.6)	10 (15.6)	0.022	10 (28.6)	0.0003	3 (16.7)	0.084
Asthma	7 (6.4)	7 (10.9)	0.39	5 (14.3)	0.16	4 (22.2)	0.049
History of tuberculosis	13 (11.8)	6 (9.4)	0.80	4 (11.4)	0.99	6 (33.3)	0.029
History of malignant disease	17 (15.5)	14 (21.9)	0.29	10 (28.6)	0.083	5 (27.8)	0.19
Diabetes mellitus	9 (8.2)	4 (6.3)	0.77	2 (5.7)	0.99	2 (11.1)	0.65
Autoimmune disease	9 (8.2)	4 (6.3)	0.77	10 (28.6)	0.0038	5 (27.8)	0.028
Rheumatoid arthritis	3 (2.7)	2 (3.1)	0.99	7 (20.0)	0.0019	3 (16.7)	0.036
GORD symptom	17 (15.5)	13 (20.3)	0.41	4 (11.4)	0.78	1 (5.6)	0.47
Use of systemic corticosteroids	4 (3.6)	3 (4.7)	0.71	9 (25.7)	0.0004	6 (33.3)	0.0005
Use of immunosuppressant agent	5 (4.6)	3 (4.7)	0.99	7 (20.0)	0.0086	3 (16.7)	0.084
Use of inhaled corticosteroids	4 (3.6)	8 (12.5)	0.033	5 (14.3)	0.023	3 (16.7)	0.057
Infected MAC strain (*Mycobacterium intracellulare*)	16 (14.6)	16 (25.0)	0.086	11 (34.3)	0.01	9 (50.0)	0.0016
Duration of MAC disease, years	6.3±5.0	9.0±6.9	0.017	8.5±10.8	0.96	8.1±10.2	0.91
History of MAC treatment	76 (69.1)	37 (57.8)	0.13	24 (68.6)	0.95	11 (61.1)	0.59
MAC sputum culture conversion	74 (67.3)	46 (71.9)	0.53	29 (82.9)	0.09	11 (61.1)	0.60

Data show either the number (%) of patients or the mean±SD.
COPD, chronic obstructive pulmonary disease; GORD, gastro-oesophageal reflux disease; MAC, *M. avium* complex; MSSA, methicillin-sensitive *Staphylococcus aureus*.

patients with bronchiectasis and NTM. Although they used serological markers but not sputum culture for the diagnosis of *Aspergillus*-related lung disease, they showed that NTM infection predisposed patients with bronchiectasis to *Aspergillus*-related lung disease.[20] In this study, most of our participants had bronchiectasis, and all 18 patients with chronic *Aspergillus* infection had culture-proven *Aspergillus*-related lung disease (15 patients with CNPA and 3 patients with ABPA).

In patients with cystic fibrosis, chronic Methicillin-resistant *Staphylococcus aureus* (MRSA) infection caused a rapid decline in lung function, and chronic *Aspergillus* infection was more frequently associated with both low lung function and increased risk of hospitalisation than intermittent *Aspergillus* infection or no infection.[17 18] In patients with bronchiectasis, the baseline lung function of patients with chronic *P. aeruginosa* infection was lower than that of patients either with intermittent *P. aeruginosa* infection or without an infection.[16] Others reported that chronic *P. aeruginosa* infection was associated with an accelerated decline in lung function.[13 27] Therefore, we divided our group of co-infected patients into those with chronic co-infections and those with intermittent co-infections. In this study, we found that these three microorganisms were predominantly isolated from chronically co-infected patients (71.9% with an MSSA infection, 77.8% with a *P. aeruginosa* infection and 62.1% with an *Aspergillus* infection).

Previous studies have demonstrated that the risk factors for microorganism infection in patients with bronchiectasis and cystic fibrosis include COPD,[21] rheumatoid arthritis,[22] a long duration of the disease[12] and the use of immunosuppressive agents.[18 22] Compared with these previous studies, our study found that patients with COPD were at an increased risk of

Table 7 HRCT findings of patients with pulmonary *Mycobacterium avium* complex with chronic MSSA, *Pseudomonas aeruginosa* and *Aspergillus* co-infections

Variables	No co-infection (n=110)	Chronic MSSA co-infection (n=64)	P value	Chronic *P. aeruginosa* co-infection (n=35)	P value	Chronic *Aspergillus* co-infection (n=18)	P value
HRCT findings							
Nodule	89 (80.9)	60 (93.8)	0.024	26 (74.3)	0.47	15 (83.3)	0.99
Consolidation	60 (54.6)	37 (57.8)	0.68	24 (68.6)	0.14	14 (77.8)	0.076
Bronchiectasis	92 (83.6)	53 (82.8)	0.89	32 (91.4)	0.41	15 (83.3)	0.99
Cavity	42 (38.2)	18 (28.1)	0.18	16 (45.7)	0.43	9 (50.0)	0.44
Radiographic pattern							
NB form	55 (50.0)	43 (67.2)	0.028	17 (48.6)	0.99	7 (38.9)	0.45
FC form	14 (12.7)	1 (1.6)	0.011	3 (8.6)	0.76	3 (16.7)	0.71
NB+FC form	28 (25.5)	17 (26.6)	0.87	13 (37.1)	0.18	6 (33.3)	0.48
Unclassified	13 (11.8)	4 (6.3)	0.30	3 (8.6)	0.59	2 (11.1)	0.99
Thoracic abnormality							
Scoliosis	28 (25.5)	16 (25.0)	0.95	11 (31.4)	0.49	8 (44.4)	0.15
Pectus excavatum	12 (10.9)	8 (12.5)	0.81	3 (8.6)	0.99	2 (11.1)	0.99
Location of HRCT findings							
Right/left upper lobe	81 (73.6)	45 (70.3)	0.64	27 (77.1)	0.82	15 (83.3)	0.56
Right middle lobe/lingula	98 (89.1)	62 (96.9)	0.086	32 (91.4)	0.99	15 (83.3)	0.44
Right/left lower lobe	71 (64.6)	45 (70.3)	0.44	33 (94.3)	0.0007	14 (77.8)	0.42

Data show the number (%) of patients.
FC, fibrocavitary; HRCT, high-resolution CT; MSSA, methicillin-sensitive *Staphylococcus aureus*; NB, nodular/bronchiectatic.

chronic infection with any pathogenic microorganisms or with MSSA or *P. aeruginosa* individually. A long duration of MAC disease (≥8 years) was significantly associated with chronic MSSA co-infection. The use of systemic corticosteroids was significantly associated with chronic *Aspergillus* spp co-infection. These factors for microorganism co-infection in patients with pulmonary MAC disease are similar to those in patients with bronchiectasis and cystic fibrosis.

Since COPD and systemic corticosteroid use also increased the risk of pulmonary NTM disease,[28–30] close attention to pulmonary MAC disease and other co-infections is needed in these patients.

A recent study comparing the features of patients with pulmonary *M. avium* and *M. intracellulare* disease showed that patients with pulmonary *M. intracellulare* disease had more severe symptoms including the FC form of the disease and a worse prognosis.[5] In this study, we found that pulmonary *M. intracellulare* disease was significantly associated with intermittent co-infection and chronic co-infection, especially *Aspergillus* co-infection. Patients with pulmonary *M. intracellulare* disease more frequently

Table 8 Factors associated with chronic MSSA, *Pseudomonas aeruginosa* and *Aspergillus* co-infections

Variables	Chronic MSSA co-infection OR (95% CI)	p Value	Chronic *P. aeruginosa* co-infection OR (95% CI)	p Value	Chronic *Aspergillus* co-infection OR (95% CI)	p Value
Male gender	–	–	–	–	2.3 (0.6 to 8.7)	0.21
History of severe pneumonia	–	–	1.5 (0.57 to 3.8)	0.41	3.2 (0.93 to 12.0)	0.064
COPD	4.2 (1.3 to 15.2)	0.017	7.5 (2.1 to 31.4)	0.0017	–	–
Asthma	–	–	–	–	3.2 (0.53 to 18.2)	0.19
History of tuberculosis	–	–	–	–	1.8 (0.37 to 7.7)	0.46
Rheumatoid arthritis	–	–	3.4 (0.59 to 21.0)	0.17	1.9 (0.17 to 19.5)	0.58
Use of systemic corticosteroids	–	–	3.5 (0.74 to 18.0)	0.11	7.1 (1.2 to 50.9)	0.034
Use of inhaled corticosteroids	2.7 (0.74 to 11.1)	0.13	4.6 (0.92 to 25.1)	0.062	–	–
Infected *Mycobacterium intracellulare* strain	–	–	1.8 (0.61 to 5.1)	0.29	4.0 (1.1 to 14.5)	0.036
Long duration of MAC disease	2.2 (1.2 to 4.4)	0.017	–	–	–	–
Nodule finding	3.5 (1.2 to 13.2)	0.019	–	–	–	–
Lung involvement at lower lobe	–	–	9.9 (2.0 to 90.6)	0.0027	–	–

Variables were included if the probability values were less than 0.05 by univariate analysis.
COPD, chronic obstructive pulmonary disease; MAC, *M. avium* complex; MSSA, methicillin-sensitive *Staphylococcus aureus*.

Table 9 Isolation of chronic microorganisms of interest during positive MAC sputum culture, during MAC treatment and after MAC sputum conversion

	Chronic MSSA co-infection (n=64)	Chronic *Pseudomonas aeruginosa* co-infection (n=35)	Chronic *Aspergillus* co-infection (n=18)
During positive MAC sputum culture	41 (64.1)	9 (25.7)	9 (50.0)
During MAC treatment	2 (5.4)*	18 (75.0)*	9 (81.8)*
After MAC sputum conversion	32 (69.6)†	27 (93.1)†	9 (81.8)†

*MAC treatment was received in patients with chronic MSSA co-infection (n=37), chronic *P. aeruginosa* co-infection (n=24) and chronic *Aspergillus* co-infection (n=11).
†Patients with chronic MSSA co-infection (n=46), chronic *P. aeruginosa* co-infection (n=29) and chronic *Aspergillus* co-infection (n=11) converted sputum culture of MAC.
MAC, *Mycobacterium avium* complex; MSSA, methicillin-sensitive *Staphylococcus aureus*.

had the host traits of severe pneumonia, malignant disease and autoimmune disease, systemic corticosteroid use and more cavity findings (FC form and NB+FC form) in the HRCT than patients with pulmonary *M. avium* disease (table 2). Therefore, patients with pulmonary *M. intracellulare* disease potentially may have more lung deterioration than patients with pulmonary *M. avium* disease and thus be predisposed to the development of microorganism co-infection.

In our study participants, clarithromycin, rifampicin and ethambutol were the most commonly used drugs for MAC treatment. The historical use of these antibiotics in patients with MAC disease did not differ among patients with MSSA, *P. aeruginosa* and *Aspergillus* co-infections (table 6). However, since clarithromycin and rifampicin decrease susceptibility to MSSA, MAC treatment markedly suppressed the sputum isolation of MSSA but only during MAC treatment. In contrast, *P. aeruginosa* and *Aspergillus* were isolated during MAC treatment due to the lack of susceptibility of *Pseudomonas* and *Aspergillus* to these drugs.

Recently, Binder *et al*[31] reported that cystic fibrosis patients with MAC were less likely than those without MAC to be colonised with *P. aeruginosa*. Winthrop *et al* also showed that non-cystic fibrosis bronchiectasis patients with NTM were less likely than those without NTM to be colonised with *Pseudomonas* spp as indicated in the US Bronchiectasis Registry.[32] In this study, MSSA was similarly isolated in MAC-positive sputum cultures and after MAC sputum conversion (table 9). However, we found that *P. aeruginosa* was less frequently isolated from positive MAC sputum cultures and more often isolated after MAC sputum conversion (tables 6 and 9). Although we investigated only patients with pulmonary MAC disease and did not include patients without MAC disease in this study, we found that *P. aeruginosa* was increasingly isolated after negative sputum conversion of MAC in patients who were originally MAC-positive and that *P. aeruginosa* was less likely to be isolated concurrently with MAC. Therefore, our data support these previous studies.[31 32]

The existence of lung nodules was associated with chronic MSSA co-infection in this study. Morikawa *et al* previously reported that centrilobular nodules (63.9%) were more common than consolidation (51.8%) and bronchiectasis (12.0%) in patients with MSSA pneumonia. Since MSSA was rarely isolated during the antibiotic treatment of MAC in this study, some of the nodules found in patients with chronic MSSA co-infection might have been associated with MSSA pneumonia.[33]

Patients with chronic *P. aeruginosa* infection had greater areas of lung involvement in the lower lobes than patients without co-infection in this study. Previous studies showed that *P. aeruginosa* pneumonia was predominantly involved in the lower lung zone.[34 35] Even after negative sputum conversion of MAC, *P. aeruginosa* remained positive in sputum cultures (table 9), and these areas of lower lung involvement were observed in follow-up CTs (data not shown). Therefore, some of the areas of lower lobe involvement in patients with chronic *P. aeruginosa* infection were most likely due to *P. aeruginosa* infection.

This study had the limitation of retrospective observation. We could not regularly follow sputum examination or chest CT evaluation for every participant. More than half of the patients were excluded from our cohort due to missing sputum examinations and chest CT evaluations. These excluded patients might have had a different frequency of microorganism isolation from the participants in this study. Therefore, the recruitment of additional patients and collection of additional sputum samples might allow more pathogenic microorganisms to be isolated and thus alter the prevalence of specific co-infections. However, since most of the excluded patients had few symptoms and less expectoration of sputum, the results in this study would reflect a symptomatic population. Also, since the university hospital is the tertiary referral hospital, more patients with severe conditions or with multiple complications are likely to be referred. Furthermore, this study was conducted only at a single centre. These may cause the patient selection bias. In this study, multiple statistical tests were applied to the different co-infection subgroups, and this carries a risk of false-positive associations—hence, the findings of this subgroup analysis should be viewed as hypothesis-generating rather than definitive. Finally, since we did not analyse an association of co-infection with the outcome or prognosis, we could not show the clinical significance of co-infection in this study.

In conclusion, we showed a high prevalence of chronic co-infections of pathogenic microorganisms in patients with pulmonary MAC disease. MSSA, *P. aeruginosa* and *Aspergillus* were the most prevalent isolated microorganisms. COPD and pulmonary *M. intracellulare* disease were risk factors for chronic co-infection.

Contributors KF conducted the study design, collected and analysed the data and drafted the manuscript. YI was principally responsible for the study design, recruited patients, collected and interpreted the data and critically revised the manuscript. TH recruited patients, collected and interpreted the data and revised the manuscript. TK analysed the data and revised the manuscript. KT, SI and MM contributed to the interpretation of data.

Funding This study was supported by Grants-in-Aid for Scientific Research by the Japanese Society for the Promotion of Science grant 24591479.

Competing interests None.

Ethics approval This study was approved by the Kyoto University Medical Ethics Committee (Approved number: E-1863).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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