Infections preceding diagnosis associated with myositis phenotypes in a national patient registry

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Abstract

Objective

We investigated the association of antecedent infections with clinical subgroups and phenotypes in the idiopathic inflammatory myopathies (IIMs).

Methods

Adult IIM patients (362 with dermatomyositis (DM), 250 with polymyositis (PM), and 256 with inclusion body myositis (IBM)) enrolled in a national myositis patient registry. One hundred thirty-four patients had symptoms of lung disease plus fever and/or arthritis (LD+), and 103 with systemic autoimmune rheumatic disease-associated overlap myositis (OM). Self-reported infections and antibiotic usage within 12 months prior to IIM diagnosis were examined. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated across IIMs. LD+ and OM analyses were performed excluding IBM patients.

Results

Infections before IIM diagnosis were more frequent in DM and PM than IBM. Febrile illness and gastroenteritis were more frequent in DM than IBM (OR 2.82 and 3.30, respectively), and in PM than IBM (OR 3.27 and 3.26, respectively). Patients with LD+ and OM had higher odds of reported infections than those without these phenotypes, with pneumonia the most strongly associated infection (OR 5.26 95% CI 2.59-10.71 in LD+, OR 2.75, 95% CI 1.25-6.06 in OM). Antibiotic usage within 1 year before diagnosis did not differ among DM, PM and IBM patients, nor in OM. Antibiotics were used more frequently used in patients with LD+ compared to no LD, but this was attenuated after adjusting for infections.

Conclusion

Antecedent infections, particularly respiratory and gastrointestinal infections may contribute to adult IIM phenotypes. Pneumonia showed the strongest association with myositis phenotypes accompanied by frequent lung disease.

Key words

idiopathic inflammatory myopathies, dermatomyositis, polymyositis, inclusion body myositis, interstitial lung disease

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Introduction

The idiopathic inflammatory myopathies (IIMs) are a group of rare, chronic autoimmune diseases characterised by muscle inflammation, weakness, and systemic involvement (1). The classical subtypes of adult-onset IIMs include dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM). In addition, anti-synthetase syndrome (ASyS), which consists of myositis, interstitial lung disease (ILD), fever and arthritis, represents a severe clinical phenotype (2). IIMs can also occur in conjunction with other systemic autoimmune diseases (SARDs), a condition broadly referred to as overlap myositis (OM), which has important implications for the presence of ILD, frequent relapse, and higher mortality (3).

Both genetic and environmental factors have been implicated in the pathogenesis of IIMs (4, 5). Case-control and other epidemiologic studies have identified several environmental factors prior to diagnosis of IIMs, including ultraviolet radiation, smoking, infections, and medications (6, 7). Notably, respiratory and gastrointestinal infections have a strong association with IIMs based on national registry data from a population-based case-control study (8).

Several studies have suggested that environmental factors may vary across IIM subtypes and phenotypes, indicating that certain exposures could differentially influence disease presentation (4, 9, 10). For instance, personal exposure to intense sunlight was associated with the development of DM, compared to PM and IBM (11). In addition, occupational and hobby exposures to silica and heavy metals have been identified as contributing factors to DM, OM, and myositis with lung disease accompanied by fever or arthritis (LD+) (12). However, the relationship between specific infections and IIM subtypes has not been examined.

This study aims to address this knowledge gap by investigating infection in the year prior to IIM diagnosis in a large cohort of adult-onset IIM patients as part of a national United States (U.S.) patient registry named MYOVISION. We analysed infectious diseases and antibiotic usage across classical IIM subgroups (DM, PM, and IBM), as well as IIM-associated symptoms of lung disease (LD+) as a proxy for ASyS or other myositis autoantibody-associated lung disease, and OM phenotypes. This study provides a novel approach by using a nationwide U.S. cohort to investigate the association between preceding infections and clinical phenotypes of IIM. It also offers a unique perspective by simultaneously analysing both infection history and antibiotic usage. Understanding the types of infections associated with specific disease phenotypes could provide valuable insights into disease mechanisms and inform prevention strategies for IIMs.

Patients and methods

Participants

The study design and recruitment process for the MYOVISION registry, an U.S. national myositis patient registry, have been previously described (13). Participants were initially contacted between December 2010 and July 2012 through The Myositis Association's national mailing list, study advertisements, and specialty clinics. The study protocol was approved by the institutional review boards at Cincinnati Children's Medical Center and the National Institutes of Health. Written informed consent was obtained from all participants prior to enrolment.

The MYOVISION questionnaire included 83 questions that encompassed patient demographics, disease-related information, environmental exposures prior to diagnosis, and questions regarding work, school, and leisure activities, as well as health-related quality of life. The study questionnaire was developed by two rheumatologists with expertise in myositis (LGR, FWM), an occupational epidemiologist (CP) and the executive director of The Myositis Association (BG). Of 9,211 individuals contacted, 1,956 (22%) returned complete questionnaires. Among these, 1,806 met probable or definite Bohan and Peter criteria for DM or PM (14), or Griggs' criteria for possible IBM (15). To minimise recall bias, this study was restricted to participants diagnosed with IIMs after 2001. A smaller number

Table I. Characteristics of adult-onset myositis patients in the MYOVISION registry by clinical subgroup.

Characteristic	Overall (n=868)	DM (n=362)	PM (n=250)	IBM (n=256)
Demographics:				
Sex, female, n (%)	588 (68)	300 (83)*,†	183 (73)*,†	105 (41)†,†
Race/ethnicity, n (%)				
Non-Hispanic White	746 (86)	306 (85)†	199 (80)†	241 (94)†,†
Non-White	122 (14)	56 (15)	51 (20)	15 (6)
College education rate, median [IQR], %	27 [16– 44]	26 [17 – 42]	26 [14 – 40]‡	30 [16 – 48]‡
Clinical data:				
Age at diagnosis, median [IQR], years	54.2 [43.9 – 62.3]	48.7† [39.2 – 55.8]	49.6† [40.8 – 57.3]	64.0†,† [57.8 – 69.7]
Year of diagnosis, median [IQR], month/year	01/2006 [01/2004 – 03/2008]	02/2006 [01/2004 – 04/2008]	11/2005 [08/2003 – 03/2008]	03/2006 [03/2004 – 02/2008]
Disease duration, median [IQR], years	5.3 [3.2 – 7.5]	5.3 [3.1 – 7.4]	5.5 [3.2 – 7.7]	5.2 [3.3 – 7.1]
Lung disease+§	134 (15)	85 (23)‡,†	39 (16)‡,†	10 (3.9)†,†
Overlap myositis	103 (12)	52 (14)†	37 (15)†	14 (5)†,†

§Lung disease + cases were those exhibiting lung involvement with arthritis and/or fever.
Significant differences: †$p \leq 0.001$, *$p \leq 0.005$, ‡$p \leq 0.05$.
DM: dermatomyositis; IBM: inclusion body myositis; IQR: interquartile range; NA: not applicable; PM: polymyositis.

of patients with juvenile DM (JDM) (n=60) were excluded. The final sample consisted of 868 adults, including 362 patients with DM, 250 with PM, and 256 with IBM.

We defined LD+ as a phenotype characterised by lung disease accompanied by joint swelling (hereafter referred to as 'arthritis') and/or fever (12). This definition was used to reflect features commonly observed in anti-synthetase syndrome or autoantibody-associated interstitial lung disease (16). One hundred thirty-four IIM patients were identified as having LD+. OM was defined as patients meeting criteria for an IIM and reporting a diagnosis of at least one SARD, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren's syndrome (SS) and mixed connective tissue disease (MCTD) (1). One hundred three patients met criteria for OM including 46 patients with RA/JIA, 32 with SLE, 17 with SSc, 22 with SS, or 5 with MCTD. IBM patients were excluded from the phenotype analysis of LD+ and OM, since most IBM patients do not have these phenotypes.

Covariate data included age at diagnosis, sex (male, female), race/ethnicity (non-Hispanic White, non-White), disease duration, and area rate of college-education, which was calculated using census tract data based on geocoded addresses at diagnosis from the American Community Survey of the U.S. Census Bureau. The area rate of college education is a surrogate for socioeconomic status (17), as individual-level educational attainment was not available for most participants.

Participants were asked whether they had experienced specific infections during the 12 months prior to their myositis diagnosis. These included skin infections, colds or upper respiratory infections (URIs), influenza, urinary tract infections (UTIs), strep throat, pneumonia, hepatitis, stomach viruses or gastroenteritis, fever or other febrile illnesses, or other infections (see the Appendix in the Supplementary file). A composite variable, 'Respiratory infections', was defined as a combination of URIs, influenza, strep throat, and pneumonia. Participants were also asked about their use of prescribed antibiotics such as penicillins, tetracycline, trimethoprim/sulfamethoxazole, ciprofloxacin, norfloxacin, isoniazid, and zidovudine, during the 12 months prior to their myositis diagnosis.

Statistical analyses

Demographic and clinical characteristics, as well as specific infections experienced, and antibiotic usage in the year prior to diagnosis were summarised as frequencies and percentages for categorical variables and as medians and interquartile ranges for continuous variables. Statistical significance between pairwise disease subgroups (PM, DM, and IBM) and phenotypes was evaluated using chi-square test for categorical data and the Wilcoxon Rank Sum test for continuous data.

Associations between disease subgroups and individual infections or antibiotic usage were evaluated using logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for age, sex, race/ethnicity, disease duration, and area rate of college-education. Similarly, associations between disease phenotypes (LD+ *vs*. no LD and OM *vs*. no OM) and individual infections or antibiotic usage were assessed using logistic regression models with similar adjustment.

When evaluating the association with clinical subgroups and phenotypes, we also considered that some cases may have been treated with antibiotics. To account for potential confounding, we conducted additional analyses which included infections potentially treated with antibiotics and added antibiotic usage as an additional covariate. In analyses evaluating the association with antibiotic usage, infections were similarly included as a covariate. Furthermore, a composite outcome for antibiotic usage and the presence of infection was examined using a multinomial logistic regression model, with similar adjustment to previous models.

No adjustments for multiple comparisons were made. All statistical analyses were performed using SAS (v. 9.4; SAS Institute, Cary, NC).

Table II. Characteristics of adult-onset myositis patients in the MYOVISION registry by disease phenotype.

Characteristic	Lung disease+*		Overlap myositis	
	Yes (n=124)	No (n=488)	Yes (n=89)	No (n=523)
Demographics:				
Sex, female, n (%)	97 (78)	386 (79)	76 (85)	407 (78)
Race/ethnicity, n (%)				
Non-Hispanic White	95 (77)	410 (84)	78 (88)	427 (82)
Non-White	29 (23)	78 (16)	11 (12)	96 (18)
College education rate, median [IQR], %	20 [13 – 36]†	27 [17 – 43]†	22 [13 – 38]	27 [17 – 42]
Clinical data:				
Age at diagnosis, median [IQR], years	46.8 [40.5 – 56.1]	49.1 [39.4 – 56.1]	47.7 [38.5 – 56.1]	49.0 [39.8 – 56.1]
Year of diagnosis, median [IQR], month/year	11/2005 [09/2003 – 01/2008]	01/2006 [01/2003 – 05/2008]	11/2005 [10/2003 – 07/2007]	02/2006 [02/2004 – 04/2008]
Disease duration, median [IQR], years	5.7 [3.5 – 7.8]	5.3 [3.1 – 7.5]	5.5 [3.7 – 7.8]	5.4 [3.0 – 7.5]

IBM subgroup was removed from the analyses.
*Lung disease+ cases were those exhibiting lung involvement with arthritis and/or fever.
Significant differences: †$p \leq 0.005$; IQR: interquartile range.

Results

The median age at diagnosis was significantly higher in IBM patients (64.0 years) compared to DM and PM patients (median age 48.7 and 49.6 years, respectively, $p<0.001$) (Table I). The gender distribution also varied significantly across subgroups, with a higher proportion of males in the IBM group (59%) compared to DM (17%) and PM (27%), which were predominantly female ($p<0.001$). The majority of patients across all subgroups were Non-Hispanic White (86%), with IBM patients having the highest proportion of Non-Hispanic White individuals (94%). Patients had a median disease duration between 5.2 and 5.5 years across clinical subgroups and a median date of diagnosis between November 2005 and March 2006, with no significant differences. The prevalence of LD+ was higher in DM patients (23%) compared to PM patients (16%). The prevalence of OM was similar in the DM and PM groups, at 14% and 15% respectively, whereas IBM patients had a lower prevalence of OM at 5% ($p<0.001$).

Regarding disease phenotype, there were no significant demographic differences between patients with LD+ and no LD, except area rate of college-education, which was lower in LD+ patients (median 20 *vs*. 27%, $p=0.003$) (Table II). Additionally, there were no significant demographic differences between patients with OM and those without OM.

The prevalence of infections reported during the 12 months prior to diagnosis of IIM varied among myositis subgroups; however, there were no significant differences between DM and PM patients (Fig. 1, Supplementary Table S1). The odds of reporting any infection within 12 months of diagnosis were significantly higher in DM and PM patients compared to IBM (OR 1.85, 95% CI 1.17–2.92, $p=0.008$ for DM *vs*. IBM; OR 1.60, 95% CI 1.01–2.55, $p=0.048$ for PM *vs*. IBM). Febrile illness was notably more frequent in DM and PM patients compared to IBM (OR 2.82, 95% CI 1.11–7.18, $p=0.030$ for DM *vs*. IBM; OR 3.27, 95% CI 1.28–8.37, $p=0.014$ for PM *vs*. IBM). Gastroenteritis, characterised by nausea, vomiting, and/or diarrhoea, was also more frequent in DM and PM patients compared to IBM (OR 3.30, 95% CI 1.37–7.94, $p=0.008$ for DM *vs*. IBM; OR 3.26, 95% CI 1.34–7.94, $p=0.009$ for PM *vs*. IBM). Respiratory infections overall, including colds/URIs and pneumonia, were more common in DM and PM patients compared to IBM patients (OR

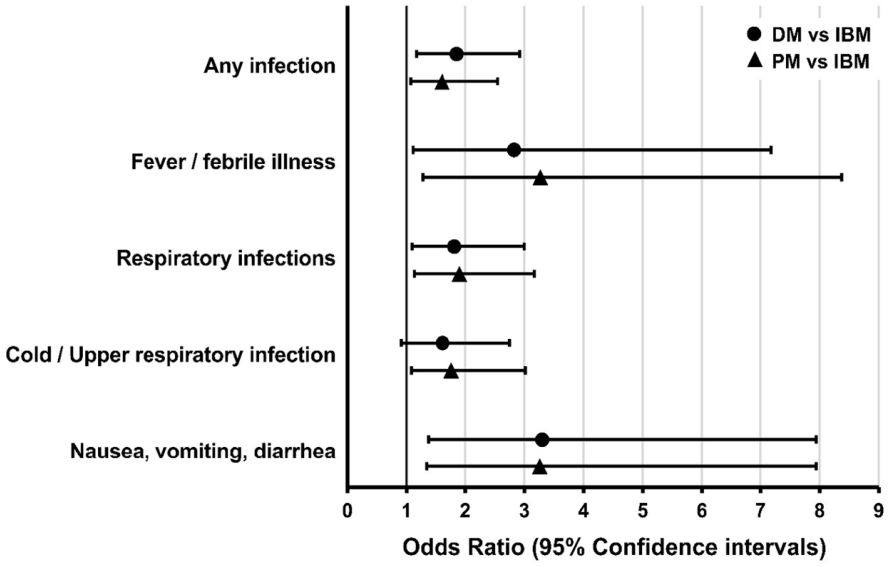

Fig. 1. Reported infections within one year prior to myositis diagnosis in patients in the MYOVISION registry, by clinical subgroup.
Odds ratios (•DM *vs*. IBM; ▲PM *vs*. IBM) and 95% confidence intervals (indicated by horizontal lines) for selected infection types in the year prior to myositis diagnosis. Only infection categories with a statistically significant difference ($p<0.05$) in either DM *vs*. IBM or PM *vs*. IBM comparisons are shown. Full data are shown in Supplementary Table S1.
Respiratory infections include cold / upper respiratory infection, influenza, pneumonia, and strep throat.
DM: dermatomyositis; IBM: inclusion body myositis; PM: polymyositis.

1.81, 95% CI 1.09-3.00, p=0.023 for DM *vs*. IBM; OR 1.90, 95% CI 1.13-3.17, p=0.015 for PM *vs*. IBM).

Patients with LD+ had significantly higher odds of a reported infection preceding diagnosis compared to patients without LD (OR 1.71, 95% CI 1.10-2.66, p=0.017) (Fig. 2, Suppl. Table S2). Pneumonia was the most strongly associated preceding infection in patients with LD+ (OR 5.26, 95% CI 2.59-10.71, p<0.001). Other infections, such as URIs, unspecified febrile illness, gastroenteritis, and skin infection, were all also more prevalent in LD+ compared to patients with no LD (OR ranging between 1.67 and 3.10).

OM patients more frequently reported an infection in the 12-month period prior to IIM diagnosis (58.8%) compared to IIM patients without OM (45.1%) (OR 1.73, 95% CI 1.05–2.88, p=0.033). Specifically, pneumonia was the most strongly associated infection preceding IIM in OM patients (OR 2.75, 95% CI 1.25–6.06, p=0.012). A similar association with antecedent infections was observed in OM patients when excluding patients with overlapping SARDs that were diagnosed prior to IIMs (Suppl. Table S3).

The association between infections potentially treated with antibiotics within the year prior to IIM diagnosis was significant in patients with DM and PM compared to those with IBM (OR 1.99 and 1.92, respectively) (Fig. 3, Suppl. Table S4). After adjusting for antibiotic usage, this association was stronger (OR 2.55 and 2.18, respectively). There was no association of antibiotic usage within 12 months of diagnosis between DM or PM patients compared to IBM, even after adjustment for infection. Additionally, the composite outcome analysis confirmed that infection within 12 months of diagnosis in the absence of antibiotic usage, was associated with DM *vs*. IBM (OR 2.63), while antibiotic usage within 12 months of diagnosis, with or without an infection, was not associated with DM or PM compared to IBM (Suppl. Table S5).

Patients with LD+ had a significantly higher odds of reported infections within the year prior to IIM diagnosis that were potentially treated with antibiotics

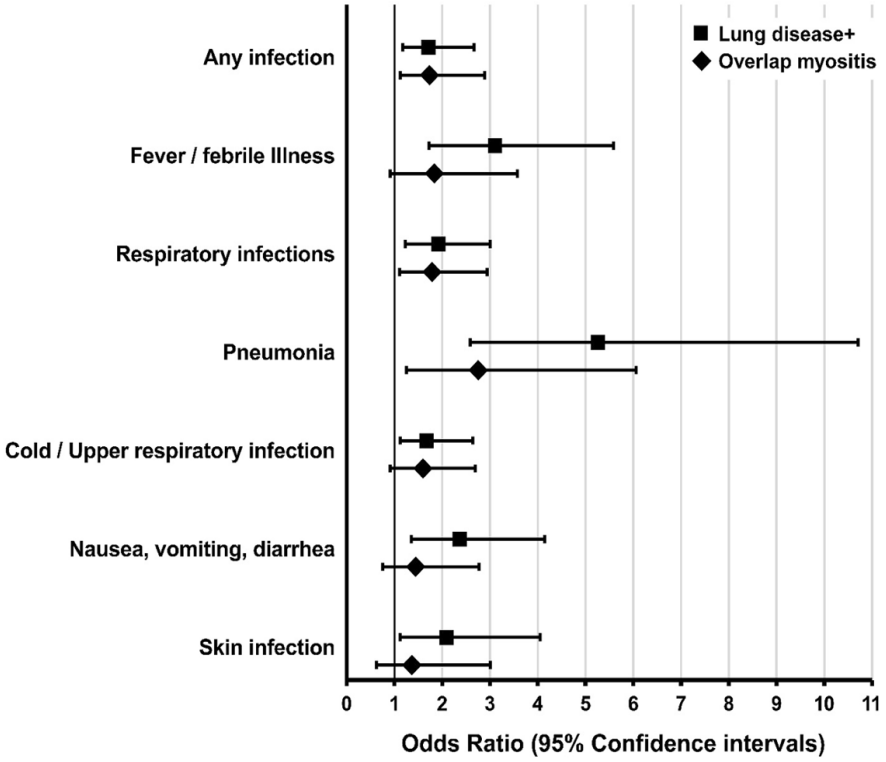

Fig. 2. Reported infections within one year prior to myositis diagnosis in patients in the MYOVISION registry, by disease phenotype.
Odds ratios (■lung disease+ (LD+) *vs*. without LD+; ♦overlap myositis (OM) *vs*. non-OM) and 95% confidence intervals (indicated by the horizontal lines) for selected infection types in the year prior to myositis diagnosis. LD+ cases were those exhibiting lung involvement with arthritis and/or fever. IBM subgroup was removed from the analyses.
Only infection categories with a statistically significant difference (p<0.05) in either comparison are shown. Full results are shown in Supplementary Table S2.
Respiratory infections include cold/upper respiratory infection, influenza, pneumonia, and strep throat.

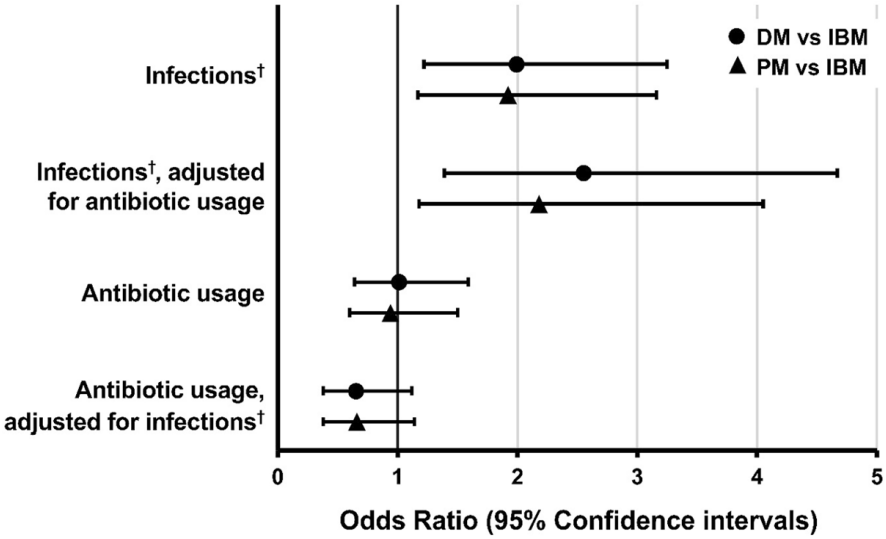

Fig. 3. Frequency of infection and antibiotic usage within one year prior to myositis diagnosis, by clinical subgroup.
Odds rations (•DM *vs*. IBM; ▲PM *vs*. IBM) and 95% confidence intervals (indicated by the horizontal lines) for infections potentially treated with antibiotics and antibiotic usage.
Full results are shown in Supplementary Table S4.
*Infections include those potentially treated with antibiotics, such as febrile illness, pneumonia, strep throat, nausea, vomiting, diarrhoea, hepatitis, urinary tract infection, and skin infection.
DM: dermatomyositis; IBM: inclusion body myositis; PM: polymyositis.

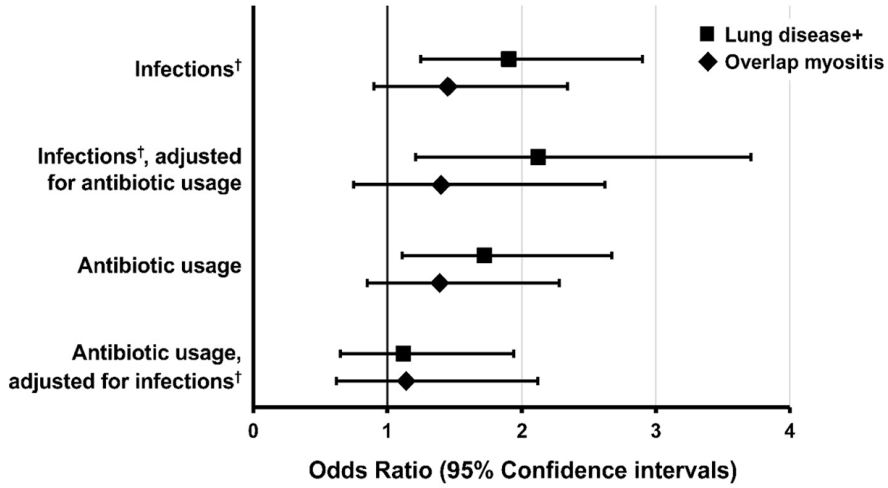

Fig. 4. Frequency of infection and antibiotic usage within one year prior to myositis diagnosis, by clinical phenotype.
Odds ratios (■lung disease+ (LD+) *vs*. without LD+; ♦overlap myositis (OM) *vs*. non-OM) and 95% confidence intervals (indicated by the horizontal lines) for infections potentially treated with antibiotics and antibiotic usage. LD+ cases were those exhibiting lung involvement with arthritis and/or fever. IBM subgroup was removed from the analyses.
Full results are shown in Supplementary Table S6.
*Infections include those potentially treated with antibiotics, such as febrile illness, pneumonia, strep throat, nausea, vomiting, diarrhoea, hepatitis, urinary tract infection, and skin infection.

compared to patients without LD (OR 1.90), even after adjusting for antibiotic usage (OR 2.12) (Fig. 4, Suppl. Table S6). Antibiotic usage was more likely in patients with LD+ within the year prior to diagnosis compared to patients without LD (OR 1.72). However, after further adjusting for the presence of infection, this difference was no longer statistically significant. A composite outcome analysis revealed that patients with LD+ were significantly more likely to encounter infections treated with antibiotics preceding IIM diagnosis compared to patients without LD (OR 2.34) (Suppl. Table S7). This association appeared to be driven more by a preceding infection, rather than by antibiotic usage alone.

No significant differences were observed between patients with and without OM regarding infections potentially treated with antibiotics. This association remained non-significant, even after adjusting for antibiotic usage (Fig. 4, Suppl. Table S6). Additionally, the frequency of antibiotic usage did not differ significantly between patients with and without OM, even after adjustment for infections. However, a composite outcome analysis indicated that antibiotic usage without a preceding infection (OR 2.22) and infection without preceding antibiotic usage were significantly more common in patients with OM compared to those without OM (OR 3.35) (Suppl. Table S7). Although similar trends were observed in examining the combination of infection and antibiotic use, the result was not statistically significant.

Discussion

This national myositis patient registry study found an overall increase in respiratory infections and gastroenteritis prior to IIM diagnosis in patients with DM and PM compared to IBM, as well as in those with the LD+ phenotype. Pneumonia preceding diagnosis was strongly associated with LD+ and OM, which are forms of myositis frequently accompanied by ILD.

Previous evaluation of environmental exposures in the MYOVISION registry identified differences in the association of specific environmental factors with clinical subgroups of IIMs. Ultraviolet radiation exposure was more strongly linked to DM, compared to PM and IBM (11). Additionally, occupational and hobby exposure to silica and heavy metals has been more strongly associated with DM compared to IBM (12). In the current study, respiratory infections and gastroenteritis also emerged as environmental factors associated with DM and PM in comparison to IBM. An increasing prevalence of infections prior to IIM diagnosis has also been reported in paediatric cases. In a U.S. national juvenile IIM (JIIM) cohort, infections within 6 months prior to disease onset were the most reported environmental exposure, affecting 45% of the studied population. Among these, respiratory tract infections were the most prevalent, accounting for 66% of all documented infections, while gastrointestinal infections accounted for only 5% (18). It is also possible that early manifestations of IIM, such as fever, respiratory symptoms, or gastrointestinal complaints, were initially misdiagnosed as infections. Such misclassification could have contributed to an overestimation of the frequency of infections during the period preceding diagnosis.

We also found that respiratory infections and pneumonia frequently preceded a diagnosis of IIM in patients with LD+ and OM. ILD can precede clinical myopathy in 7.2% to 37.5% of IIM patients (19-21). In ASyS cases, 53.6% of patients present with ILD at the onset of symptoms, while 48% of OM patients have ILD at diagnosis (22, 23). Therefore, some patients with preceding ILD could have been misdiagnosed with or had an accompanying infectious pneumonia. OM patients with PM and DM were reported to have experienced more severe infections compared to patients without OM from a large Spanish cohort (23). However, it remains unclear whether these infections prior to IIM diagnosis were complications of the disease itself or environmental triggers for developing phenotypes. We also identified a higher association of gastroenteritis and skin infections within 1 year prior to diagnosis with LD+ patients compared to those without LD. Infections may contribute to disease onset, particularly in patients with lung involvement, which is frequent in these myositis phenotypes (3). Infections are not only frequent preceding events, but have also been identified as a predominant cause of death in patients with IIM, particularly within the first 18 months after diagnosis (24). The lung and intestinal mucosa have been suggested as

potential sites for the initiation of autoimmunity (25). Inflammation of the respiratory tract, including respiratory infections, can induce localised innate immune responses, leading to the expression of autoantibodies that contribute to SARDs, such as RA (26). Previous studies have reported that patients with preceding inflammatory lung diseases, including pneumonia, tuberculosis, or sarcoidosis, have an increased risk of developing myositis, particularly in those with concurrent ILD (27). Similarly, gastrointestinal infections may alter the gut microbiota, triggering autoimmunity through intestinal barrier dysfunction and immune responses disrupted by microbial metabolites, which has been reported in SLE patients as well as a mouse model system (28, 29). Notably, in JIIM patients, gastroenteritis was more frequent in myositis-specific autoantibody negative patients within 1 year before diagnosis compared to those with anti-MDA5 autoantibodies (10). These findings suggest that gut microbiome dysbiosis could contribute to the development or exacerbation of myositis (30, 31). Skin infections may compromise the skin barrier, potentially increasing exposure to environmental antigens and triggering autoimmune responses. A case-control study found an increased frequency of streptococcal infections, including impetigo, in JDM patients compared to matched controls (32). However, skin infections have not been associated with an increased risk of IIM flares (33). A possibility is that skin manifestations preceding myositis were misdiagnosed as skin infections in LD+ patients, although skin infections were not found to be associated with DM.

The overall frequency of antibiotic usage in the year before diagnosis among IIM patients was approximately 35%. Since some infections are treated with antibiotics, we conducted multiple analyses to account for potential confounding, adjusting for antibiotic usage in infection-related analyses and adjusting for infections in antibiotic usage analyses. No significant differences in antibiotic usage were apparent among clinical subgroups in this adult myositis nationwide study, a finding consistent with a previous national cohort study in JIIM (10). Across clinical and serologic subgroups of JIIM, no significant differences were observed in the frequency of antibiotic usage within one year of diagnosis.

Patients with LD+ had higher odds of experiencing infections treated with antibiotics compared to patients without LD. This association persisted even after adjustment, suggesting a stronger link between LD+ and infections requiring antibiotics. Composite outcome analysis further supported this trend, showing LD+ patients were more likely to have infections requiring antibiotics before diagnosis. This was primarily driven by preceding infections rather than antibiotic use alone, suggesting infections may contribute to LD+ pathogenesis. These findings highlight infections as potential environmental factors in the phenotype of LD+.

Infections potentially treated with antibiotics were not significantly associated with OM even after adjusting for antibiotic usage. Similarly, the prevalence of antibiotic usage showed no significant association with OM, including after adjustment for infections. However, composite outcome analysis revealed a notable pattern: antibiotic usage without a preceding infection and infection without prior antibiotic use were both significantly more common in OM. One possible explanation for the high frequency of antibiotic use without reported infections may be related to prescription of antibiotics for conditions not captured in the infection questionnaire, such as chronic sinusitis, dental infections, or for prophylactic use. This suggests that while infections potentially treated with antibiotics may not be a primary environmental factor for OM, in certain clinical circumstances, such as undiagnosed or subclinical infections, non-infectious inflammatory conditions requiring antibiotics, or differences in healthcare utilisation, may contribute to a role for both antibiotics and infections in patients with OM. The lack of statistical significance when analysing the combined presence of infection and antibiotic usage further supports the complexity of this relationship, though this may also be due to limited statistical power.

This study has several limitations. The exposures were evaluated using self-reported questionnaire data, which are subject to recall bias, and were not able to be confirmed through review of medical records or through cultures or microbial testing. Although the response rate in our study may appear low (22%), it is comparable to or higher than typical response rates reported in community-based postal surveys without follow-up contacts, which often range from 7.5% to 10.5% (34). Disease severity and patient self-awareness or advocacy may have influenced participation in the registry, potentially impacting our results, and as such, the study population may not fully represent the broader spectrum of IIM. Because serum samples for myositis-specific autoantibodies and muscle biopsy data were not available, misclassification of some phenotypes may have occurred, biasing the results. Patients with PM were classified according to the Bohan and Peter criteria, which were the validated criteria in use at the time of the study was conducted. This PM subgroup, however, may have included individuals with other inflammatory myopathies, such as immune-mediated necrotising myopathy or ASyS. The LD+ group likely included not only patients with ASyS, but also those with anti-MDA5 and other myositis-specific autoantibodies.

To reduce recall bias, we restricted the sample from MYOVISION to those patients diagnosed within 10 years of enrolment and primarily asked about major infections. The timing of causally relevant exposures before symptom onset and disease diagnosis remains unclear. The median time from disease onset to IIM diagnosis is typically less than one year for DM and PM (5 months for DM and 8 months for PM), while IBM is considerably longer (41 months) (35). Therefore, focusing on exposures within one year prior to diagnosis was considered appropriate for patients with DM and PM to identify potential triggers, while minimising recall bias. However, for IBM, a longer time period may be relevant to illness, onset and risk. Most studies suggesting infections as risk factors for IIM have focused on events occurring in close proximity to

diagnosis, within 3 to 6 months before symptom onset, or within one year of diagnosis (10, 18, 36). However, a previous nationwide study on infections preceding IIM sought to minimise the risk of reverse causality by excluding infections diagnosed within one year of IIM diagnosis and including only those infectious episodes greater than one year prior to diagnosis (8). Therefore, it is essential for future studies to further assess which timeframe may present a greater risk for developing IIMs.

In conclusion, our study identified preceding infections within one year prior to IIM diagnosis that may vary among clinical subgroups and were associated with adult-onset IIM phenotypes. Specifically, we observed an increase in respiratory infections and gastroenteritis in patients with DM and PM compared to IBM, as well as in the LD+ phenotype. Pneumonia was most strongly associated with LD+ and OM, while gastroenteritis and skin infections were identified as novel associations in LD+ patients. Prospective case-control studies conducted in large, well-defined clinical populations, with confirmation of infections through medical records and by molecular and/or serological methods, are needed to further evaluate the impact of infections on disease risk, phenotype development, and clinical outcomes. In addition, future studies should examine the association between specific autoantibodies and prior infections.

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