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Crichton, Megan L.; Shoemark, Amelia; Chalmers, James D.

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The Impact of the COVID-19 Pandemic on Exacerbations and Symptoms in Bronchiectasis: A Prospective Study

Megan L Crichton, BSc, Amelia Shoemark, PhD, James D Chalmers, MD, PhD

Division of Molecular and Clinical Medicine, University of Dundee, Dundee, United Kingdom

Corresponding author: James D. Chalmers, MD, PhD, Division of Molecular and Clinical Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee, DD1 9SY.

jchalmers@dundee.ac.uk

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The underlying mechanisms leading to bronchiectasis symptoms and exacerbations are poorly understood. Recent data suggests that daily symptoms such as cough and sputum are linked to airway bacterial load and corresponding neutrophilic inflammation.[1–3] In contrast, recent data suggests bronchiectasis exacerbations arise due to changes in the interactions between pathogens in the airway microbiome that may be disrupted by viral infections.[4] Respiratory viruses can be identified during exacerbations in up to 50% of bronchiectasis patients.[5] The COVID-19 pandemic resulted in the introduction of social distancing and mitigation measures that have reduced person to person interactions worldwide.[6] This has reduced the circulation of respiratory viruses such as influenza and rhinovirus which are commonly identified in exacerbations of bronchiectasis.[5] The COVID-19 pandemic therefore represents a "natural experiment" to test the hypothesis that many bronchiectasis exacerbations are related to external exposures while daily chronic symptoms such as cough and sputum are more "intrinsic". In this study we therefore hypothesised that social distancing during 2020 would be associated with reduced reported exacerbations but no change in chronic symptoms typically experienced during stable state.

We performed a prospective observational study embedded within the EMBARC registry of patients with CT confirmed bronchiectasis, enrolled at Ninewells Hospital, Dundee, UK. Patients were enrolled between June 2019 and February 2020 as part of a study to validate a novel patient reported outcome measure (the Bronchiectasis Impact Measure - BIM) which has recently been reported (Ethical approval: 19/NW/03/64).[7]

An amendment to the protocol was made at the onset of the COVID-19 pandemic to administer additional BIM and quality of life bronchiectasis questionnaires during the UK first lockdown period as a measure of symptoms during a period of social distancing. COVID-19 data collection for symptoms took place May-July 2020. Patients symptoms during lockdown were compared to their most recent stable pre-lockdown symptom questionnaire. All questionnaires were performed while patients were clinically stable and free from exacerbation. Exacerbation frequency during 23rd March

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to 22nd March 2018/19, 2019/20 and 2020/21 were recorded through the EMBARC registry.[8] Dates were selected so that the 2020/21 period started with the beginning of the first national lockdown in the UK. Exacerbations were reported by patients and verified by prescription for antibiotics. Symptom and exacerbation data were not normally distributed and so are compared using Wilcoxon paired signed rank test. Negative binomial regression was used to model exacerbation rates over time.

We included 173 patients in the original study. 19 patients were lost to follow-up and 7 patients had died, resulting in 147 patients included in the present analysis. The median age (interquartile range) was 70 years (64-75), 84 (57.1%) patients were female. The mean baseline FEV_1 was 84.0% predicted (standard deviation 28.4). The median bronchiectasis severity index score was 6 (4-9). 64 (43.5%) had *Haemophilus influenzae* chronic infection and 25 (17.0%) had *Pseudomonas aeruginosa* chronic infection. 82.1% of the patients reported to be "shielding" during the pandemic. 'Shielding' was used to describe recommended additional protective measures encouraged in the UK for people who were at high-risk and extremely vulnerable, this included leaving their homes as little as possible and minimising all person to person contact. Only 2 patients in the cohort had PCR confirmed SARS-CoV-2 infection.

There was a statistically significant reduction in the frequency of reported exacerbations during the lockdown period. The number of exacerbations per patient per year was 2.08 in 2018/19, 2.01 in 2019/20 and 1.12 in 2020/21. Figure 1 shows that the number of patients experiencing no exacerbations over a 12 month period increased from 22.4% in 2018/19, 25.6% in 2019/20 to 52.3% in 2020/21. Paired data between years was compared using the Wilcoxon matched pair sign rank test, demonstrating a significant reduction in exacerbations between 2020/21 and both 2018/19 and 2019/20 ($p<0.0001$ for both comparisons). The proportion of patients experiencing a hospitalization due to severe exacerbation was 8.8%, which was lower than 14.3% and 16.3% in the two previous years respectively. We analysed which clinical parameters were associated with continuing to have

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exacerbations during 2020/21 in a negative binomial model and significant associations were found for prior exacerbation frequency (rate ratio 1.20 (1.07-1.35,p=0.002) and chronic *P. aeruginosa* infection (RR 1.78 95% 1.01-3.14,p=0.047).

After adjusting for prior exacerbation history, patients with more severe symptoms were more likely to experience exacerbations during 2020/21 including sputum production RR 1.14 95%CI 1.05-1.24,p=0.002, dyspnoea RR 1.11 95%CI 1.02-1.21,p=0.018, tiredness RR 1.14 95%CI 1.04-1.24,p=0.004, activity RR 1.13 95%CI 1.03-1.23,p=0.007, overall health RR 1.11 95%CI 1.02-1.21,p=0.022 and control RR 1.12 95%CI 1.03-1.22,p=0.006. The only domain not significantly associated with exacerbations was cough RR 1.08 95%CI 0.99-1.18,p=0.07.

Comparing patients symptoms using the BIM pre- and during lockdown, there were no significant differences in the impact of cough, sputum, dyspnoea, tiredness, activity, overall health, control and exacerbations on quality of life (table 1). This was also noted in the QOL-B where no significant change was seen in the respiratory symptoms score which was completed alongside the BIM at each timepoint. It should be noted that the BIM questionnaire asks about the impact of exacerbations on quality of life, not the frequency of exacerbations.

In summary, bronchiectasis exacerbation frequency was markedly reduced between March 2020 and March 2021 compared to the same time periods in the previous 2 years. Respiratory symptoms were unchanged during the pandemic from the pre-pandemic period. Our data support a key role for external environmental factors in the pathogenesis of bronchiectasis exacerbations. While a reduction in circulating viruses is the most likely reason for reduced exacerbation frequency[5], there are other potential contributors to our findings including reductions in traffic related air pollution which were documented during the lockdown periods.[9] Although reduced access to healthcare, or avoidance of healthcare contacts by patients are a potential alternative explanation for our findings, this seems less likely because access to primary and secondary care were largely maintained in the region via virtual appointments during the study period. We might also expect that if patients had

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exacerbations which were not treated, we would see a deterioration in symptoms or an increase in severe exacerbations requiring hospitalisation, neither of which were observed. Results of our study are consistent with observations in other diseases such as COPD where exacerbation frequency has reduced during lockdown periods.[10] Our study has limitations including single centre design, the relatively small sample size and the lack of data on viruses at exacerbation to confirm the mechanism of exacerbation reduction. Our study also has unique strengths in that we could perform symptom and exacerbations assessments in a standardised fashion within a cohort established before the pandemic.

In summary, social distancing measures during the first 12 months of the COVID-19 pandemic were associated with a marked reduction in bronchiectasis exacerbations but no change in individual chronic respiratory symptoms.

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References

1. Crichton ML, Lonergan M, Barker AF, et al. Inhaled aztreonam improves symptoms of cough and sputum production in patients with bronchiectasis: a post hoc analysis of the AIR-BX studies. *Eur Respir J*. 2020;56(1). doi:10.1183/13993003.00608-2020

2. Sibila O, Laserna E, Shoemark A, et al. Airway Bacterial Load and Inhaled Antibiotic Response in Bronchiectasis. *Am J Respir Crit Care Med*. May 2019. doi:10.1164/rccm.201809-1651OC

3. Gao Y-H, Abo Leyah H, Finch S, et al. Relationship between Symptoms, Exacerbations, and Treatment Response in Bronchiectasis. *Am J Respir Crit Care Med*. 2020;201(12):1499-1507. doi:10.1164/rccm.201910-1972OC

4. Mac Aogáin M, Narayana JK, Tiew PY, et al. Integrative microbiomics in bronchiectasis exacerbations. *Nat Med*. 2021;27(4):688-699. doi:10.1038/s41591-021-01289-7

5. Gao Y-H, Guan W-J, Xu G, et al. The role of viral infection in pulmonary exacerbations of bronchiectasis in adults: a prospective study. *Chest*. 2015;147(6):1635-1643. doi:10.1378/chest.14-1961

6. Prem K, Liu Y, Russell TW, et al. The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: a modelling study. *Lancet Public Heal*. 2020;5(5):e261-e270. doi:10.1016/S2468-2667(20)30073-6

7. Crichton ML, Dudgeon EK, Shoemark A, Chalmers JD. Validation of the Bronchiectasis Impact Measure (BIM) - a novel patient reported outcome measure. *Eur Respir J*. November 2020. doi:10.1183/13993003.03156-2020

8. Chalmers JD, Aliberti S, Polverino E, et al. The EMBARC european bronchiectasis registry: Protocol for an international observational study. *ERJ Open Res*. 2016;2(1). doi:10.1183/23120541.00081-2015

AJRCCM Articles in Press. Published July 15, 2021 as 10.1164/rccm.202105-1137LE

9. Goeminne CP, Cox B, Finch S, et al. The impact of acute air pollution fluctuations on bronchiectasis pulmonary exacerbation. A case-crossover analysis. *Eur Respir J*. June 2018. doi:10.1183/13993003.02557-2017

10. Tan JY, Conceicao EP, Wee LE, Sim XYJ, Venkatachalam I. COVID-19 public health measures: a reduction in hospital admissions for COPD exacerbations. *Thorax*. December 2020. doi:10.1136/thoraxjnl-2020-216083

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Questionnaire	Symptom	Pre-lockdown	lockdown	p-value
Bronchiectasis Impact Measure	Cough	4.0 (1.1-7.0)	3.1 (1.0-7.0)	0.19
	Sputum	3.7 (1.0-7.0)	3.8 (1.0-7.0)	0.89
	Dyspnoea	5.0 (1.5-75)	4.9 (2.0-7.5)	0.19
	Tiredness	6.0 (2.0-8.0)	5.0 (2.6-8.0)	0.79
	Activity	4.0 (1.0-8.0)	4.0 (1.0-7.0)	0.67
	Overall health	3.0 (1.0-7.0)	4.0 (1.0-7.0)	0.31
	Control	3.0 (1.0-7.0)	3.0 (1.0-7.0)	0.95
	Impact of exacerbations	3.0 (1.0-8.0)	3.9 (1.0-7.0)	0.82
Quality of Life Bronchiectasis questionnaire	Respiratory symptoms score	70.4 (55.6-81.5)	70.4 (51.9-81.5)	0.56

Table 1. Change in disease impact during the pre- and pandemic periods. Patients most recent stable BIM questionnaire and their "lockdown" questionnaire performed during June/July 2020 are compared. Symptom data are presented as median (interquartile range) p-values calculated by Wilcoxon paired sign rank test.

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Figure 1. Absolute number of patients experiencing 0, 1, 2 and 3 or more exacerbations per year during the 3 years of observation. (n=147 total patients for each year).

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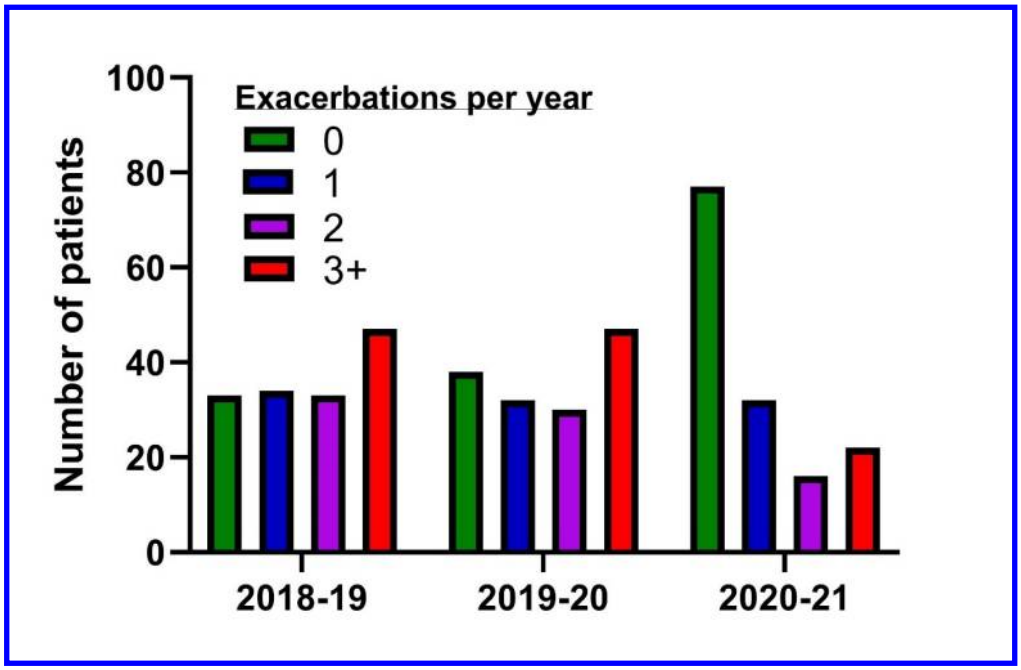

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