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The burden of disease in pediatric non-cystic fibrosis bronchiectasis

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Abstract

Background: The burden of disease in children with non-cystic fibrosis (CF) bronchiectasis is unknown. Our study aimed to identify the determinants of quality of life (QOL) and parental mental health in this group of patients and their parents; and to evaluate the effect of exacerbations on these parameters.

Methods: Parents of 69 children (median age 7 years) with non-CF bronchiectasis prospectively completed two questionnaires [parent-proxy cough-specific QOL (PC-QOL) and Depression, Anxiety and Stress scale (DASS)] at stable and exacerbation states. Data on clinical, investigational and lung function parameters were also collected.

Results: During stable-state, the median [Inter-quartile range (IQR)] PC-QOL was 6.5 (5.3-6.9) and DASS-21 was 6 (0-20). Young age of children correlated with worse QOL (r_s=0.242, p=0.04) but radiological extent, lung function, underlying etiology, environmental tobacco smoke exposure and chronic upper-airway disease did not influence these scores. Exacerbations caused significant worsening in PC-QOL [median (IQR) 4.6 (3.8-5.4); p=<0.001] and DASS scores [22 (9-42); p<0.001; 38% with elevated anxiety 54% abnormal depression/stress scores during exacerbation]. Presence of viral infection, hypoxia and hospitalization did not influence exacerbation PC-QOL and DASS scores.

Conclusions: There is a significant burden of disease, especially during exacerbation, on parents of children with bronchiectasis. Prevention, early detection and appropriate management of exacerbations are likely to reduce psychological morbidity in this group.

Abbreviation List:

CF	Cystic Fibrosis
COPD	Chronic Obstructive Pulmonary Disease
DASS	Depression Anxiety and Stress
ETS	Environmental Tobacco Smoke
HRCT	High Resolution computerised tomography
HRQOL	Health related quality of life
hs-CRP	High sensitivity C-reactive protein
IOS	Impulse Oscillometry System
IQR	Interquartile range
NPA	Nasopharyngeal aspirate
PC-QOL	Parent proxy cough specific quality of life
PCR	Polymerase Chain Reaction
QOL	Quality of life

INTRODUCTION

Non-cystic fibrosis (CF) bronchiectasis continues to be an important cause of respiratory morbidity in both children and adults of developed[1] and developing[2] countries. Despite its importance, non-CF bronchiectasis remains neglected. Traditionally, outcomes of children with bronchiectasis have been assessed with parameters such as pulmonary function, growth[3] and radiological extent of bronchiectasis[1] though their correlation with clinical severity may not be ideal.[1,4] Since one goal of healthcare is to improve quality of life (QOL), it is increasingly used as an important outcome in chronic diseases such as asthma, CF and chronic obstructive pulmonary disease (COPD).[5,6] To date there is no published data on health related QOL (HRQOL) in children with non-CF bronchiectasis. Also, in childhood illnesses the family, and particularly the primary caregiver, may face considerable burden,[7,8] causing stress, anxiety and depression.[9] These are important since maternal depression may be an important factor in non-adherence to therapy and morbidity.[10,11]

As in other chronic pulmonary conditions, pulmonary exacerbations in bronchiectasis impact the short and long term morbidity,[3,12] though it remains under researched. Recurrent exacerbations (in the preceding year) in adults have been reported to predict poor QOL in stable bronchiectasis,[13] though similar pediatric data and data on acute effect of exacerbation on burden of disease are unavailable. Further, in 15 adults with bronchiectasis, Courtney et al.[14] reported a significant improvement in chronic respiratory QOL scores after treatment of pulmonary exacerbations. Similar improvements have also been reported with treatment in adolescents with CF[5] but no data in children with non-CF bronchiectasis exist. In addition to the paucity of quantitative studies addressing the burden of disease on parents of children with bronchiectasis, there are no studies that have examined acute changes in these

parameters with pulmonary exacerbations. The objectives of our prospective study in a cohort of children with non-CF bronchiectasis were 1) to identify the determinants of parent-proxy cough-specific QOL (PC-QOL) and parental mental health [using Depression Anxiety and Stress Score (DASS) questionnaire][15] during stable-state and 2) to assess the magnitude of changes in these parameters with pulmonary exacerbations.

Methodology

Study population

Children (aged <18 years) with high resolution CT (HRCT) based diagnosis of bronchiectasis without CF attending the respiratory clinic at the Royal Children's Hospital, Brisbane, were prospectively enrolled from 1st February 2008 to 31st January 2010 and followed until 31st July 2010. This was part of a larger prospective cohort study to delineate a validated definition of pulmonary exacerbation in children with non-CF bronchiectasis. Parents were asked to contact the primary investigator (NK) when their child was suspected of experiencing an exacerbation. Children were reviewed at the hospital clinic every three months and when suspected of experiencing an exacerbation. Information on demography, underlying etiology, extent of radiological bronchiectasis, presence of upper airway disease (middle ear disease, sinusitis or allergic rhinitis) and environmental tobacco smoke (ETS) exposure were collected at the initial consultation. All children had a sweat chloride level of less than 35meq/L. Informed parental consent was obtained at the time of enrolment. The Queensland Health Children's Health Services Ethics Committee approved the study (Number 2008/038).

Each participating parent (primary caregiver for the child) completed two questionnaires [Parent–proxy Quality of Life Cough specific Questionnaire (PC-QOL) and Depression, Anxiety and Stress 21-item scale (DASS 21)] during stable state and within 72-hours of start of a pulmonary exacerbation. Parent reported QOL scores were used as proxy for the QOL of the children. Exacerbation was diagnosed by the treating pediatric pulmonologist based on the Aspen workshop[16] definition of pulmonary exacerbation as "a sustained worsening of the

patient's condition from stable state and beyond normal day to day variations that is acute in onset and necessitates a change in regular medication". In the absence a validated definition of pulmonary exacerbation in pediatric bronchiectasis (CF or non-CF), we used this definition as the "Gold Standard". We have previously used this definition[12] in a retrospective study on clinical features of pulmonary exacerbations in children with non-CF bronchiectasis. The most recent stable-state data related with exacerbation data was included. These events were within 6-months of each other. Blood investigations and airway resistance measurement using Impulse Oscillometry System (IOS) (Jaeger, Germany) were performed in each child during stable-state and exacerbation state. Extended viral screen by polymerase chain reaction (PCR) was also performed on the nasopharyngeal aspirates (NPA) obtained during each exacerbation (Details online).

Scales for measurement of burden of disease

In the absence of any suitable QOL measures for children with non-CF bronchiectasis, we used a validated cough-specific QOL for children[17] since cough-specific QOL scales have been proven valid and useful in adults with bronchiectasis.[18] In the young (usually under 6 years), parent-proxy QOL is usually reported.[8,17] PC-QOL is a validated[17] 27 item scale with a 7 point Likert- type scale with a minimum important difference of 0.9.[19] PC-QOL is further divided into three subscales – psychological (11 items), physical (11 items) and social (5 items). Lower scores reflect worse QOL.

DASS-21: This is a self-reported scale with 21-items measuring three dimensions of emotional distress construct: depression, anxiety and stress (7 items each).[15] Participants

respond to each item on a 4 point severity scale from 0 (did not apply to me) to 3 (applied to me most of the time), with past week as the referent period. Scores from DASS-21 were compared to normative population data[15] and z-scores calculated. Higher scores indicate worse mental health and z-scores of >0.5 are considered abnormal,[15] corresponding with a depression score of 10, anxiety score of 7 and stress score of 14, with respect to normative data.

Statistical Analysis

For PC-QOL, mean values per child were first calculated for the total score, as well as for each domain (psychological, physical and social). For DASS-21, sum of the total scores as well as sum of each domain (depression, anxiety and stress) were separately calculated. As these data were not normally distributed, results for the whole cohort were expressed as medians and their interquartile range (IQR). Paired data were compared by Wilcoxon signed ranks test when continuous and conditional logistic regression when categorical. Independent data were compared by Mann Whitney test. Correlations were examined using the Spearman rank signed test. Statistical analysis was performed on SPSS 13.0. A p-value <0.05 was considered statistically significant.

Results

Study population

The demographic profile of the 69 children prospectively enrolled and followed for 900 child-months is presented in ***Table 1***. PC-QOL scores were available from all 69 children during stable state and 64 children during exacerbation state (4 children did not have an exacerbation, 1 questionnaire was not returned). Three parents declined to respond to the DASS-21 questionnaire and thus data was available from 66 children during stable-state and 61 children during exacerbation-state. Thirty-one (48%) exacerbations had virus-positive PCR on the NPA (Details online).

Table 1- General characteristics of 69 children enrolled in the study

Characteristic	**Data**
Male:Female	33:36
Age at diagnosis (years)*	5.7 (3.1-8.1)
Age at enrollment (years)*	7 (3.8-10.9)
Ethnicity	
Caucasian	59 (85%)
Indigenous	4 (6%)
Asian	4 (6%)
Maori	2 (3%)
Etiology	
Primary Immunodeficiency	12 (18%)
Aspiration	11 (16%)
Post Infectious	10 (14.5%)
Primary Ciliary Dyskinesia	2 (3%)
Others	4 (6%)

Idiopathic	30 (43.5%)
Multilobar disease on HRCT	51 (73%)
Chronic upper airway disease	16 (23%)
ETS exposure	19 (27%)
Stable-state hs-CRP (n=67)* (mg/L)	0.22 (0.2-0.8)
Stable state R5 (n=50)* (% of predicted)	96 (84-112)

*Median (IQR)

ETS: Environmental Tobacco Smoke; hs-CRP: high sensitivity C-reactive protein; R5: resistance at 5 Hz

Assessment during stable-state

The median (IQR) PC-QOL score during the stable state in the 69 children were: total score 6.5 (5.3-6.9); psychological 6.6 (4.8-7); physical 6.5 (5.7-7) and social 6.6 (5.5-7). The three sub-scales of the PC-QOL all correlated highly with one another during the stable-state (psychological with physical: $r=0.724$, $p<0.001$; psychological with social: $r=0.768$, $p<0.001$ and physical with social: $r=0.882$, $p<0.001$).

The median (IQR) DASS-21 score during the stable state in the 66 children were: total score 6 (0-20); depression 2 (0-6); anxiety 0 (0-4) and stress 2 (0-10). When compared to normative data, the median (IQR) z-scores for the three sub-components were: depression -0.62 (-0.91, -0.05); anxiety -0.96 (-0.96, -0.14) and stress -1.03 (-1.28, -0.01). The three sub-components of the DASS-21 all correlated highly with one another during the stable-state (depression with anxiety: $r=0.790$, $p<0.001$; depression with stress: $r=0.801$, $p<0.001$ and anxiety with stress: $r=0.603$, $p<0.001$).

PC-QOL total score, but not DASS, was significantly related to older age but the correlation coefficient was small (***Table 2***). PC-QOL was significantly and negatively correlated with total DASS-21 scores (***Table 2***). PC-QOL and DASS did not significantly correlate with time since diagnosis, CRP or airway resistance (R_5 measured on IOS).

Table 2- Factors associated with Total PC-QOL and Total DASS-21 scores during stable-state

Factor	Correlation coefficient for Total PC-QOL	p#	Correlation coefficient for Total DASS-21	p#
Age	0.242	**0.04**	-0.098	0.4
Time since diagnosis	0.17	0.16	-0.046	0.7
Stable-state CRP	0.039 (n=63)	0.7	-0.026 (n=62)	0.8
Stable-state R5	0.09 (n=46)	0.5	-0.05 (n=44)	0.7
Total DASS-21 score	-0.388	**0.001**	-	-

Spearman's rank correlation

CRP: C-reactive protein; R5: Airway resistance at 5 Hz

There was also no significant difference in the total PC-QOL or DASS-21 score between children exposed to ETS [PC-QOL median (IQR) 6.25 (4.6-6.7); DASS-21 median (IQR) 4 (0-26)] and those not exposed [PC-QOL median (IQR) 6.6 (5.9-6.9); p=0.26 & DASS-21 median (IQR) 6 (0-20); p=0.9]. Similarly, no significant difference was seen between children grouped by extent of radiological bronchiectasis. [Unilobar bronchiectasis: PC-QOL median (IQR) 6.53 (4.9-6.9); DASS-21 median (IQR) 6 (0-18) vs. Multilobar: PC-QOL median (IQR) 6.4 (5.3-6.9); p=0.78 & DASS-21 median (IQR) 6 (0-20); p=0.62] Further, there was no significant difference in total or any sub-component PC-QOL or DASS-21 score

based on underlying etiology or presence of chronic upper airway disease (middle ear disease, sinusitis or allergic rhinitis) (data not shown).

Assessment during exacerbation-state

Pulmonary exacerbation significantly worsened total PC-QOL and all three subscales when compared with stable state scores (***Figure 1***). There was no difference in the exacerbation state PC-QOL total scores between exacerbations caused by viral agents [virus-positive: n=31, median (IQR) 4.4 (3.1-5.3); virus negative: n=33, median (IQR) 4.9 (3.4-5.5); p=0.3] or exacerbations requiring hospitalization [requiring hospitalization: n=32, median (IQR) 4.7 (2.9-5.1); not requiring hospitalization: n=32, median (IQR) 4.6 (3.7-5.5); p=0.3]. There was further no difference in the score during exacerbation with the extent of radiological bronchiectasis, underlying etiology or presence of hypoxia during exacerbation (data not shown). Similarly, DASS-21 total score, depression, anxiety and stress sub-scores were all significantly worse during an exacerbation than in stable state (***Figure 2 and Table 3***).

Table 3 – Comparison of DASS-21 scores between stable and exacerbation state (n=61 pairs)

	Number of carers with stable state z-score >0.5 [n (%)]	Number of carers with exacerbation state z-score >0.5 [n (%)]	OR (95% CI)	p#
Depression	8 (12%)	23 (37.7%)	4.0 (1.6-9.9)	0.003
Anxiety	10 (15%)	33 (54.1%)	6.0 (2.6-14)	<0.001
Stress	10 (15%)	23 (37.7%)	3.1 (1.3-7.2)	0.013

Univariate conditional logistic regression

There was no difference in the exacerbation state DASS-21 score between virus positive and negative exacerbations [virus-positive: n=30, median (IQR) 15 (8-22.5); virus negative: n=31, median (IQR) 8 (3-18.5); p=0.1] or those requiring hospitalization [requiring hospitalization: n=30, median (IQR) 14 (3-20.5); not requiring hospitalization: n=31, median (IQR) 9.5 (4.7-21.5); p=0.8]. There was further no difference in the DASS-21 score with extent of radiological bronchiectasis, underlying etiology or presence of hypoxia during exacerbation (data not shown).

Discussion

We describe for the first time QOL and mental health data (depression, stress, anxiety) reported by carers of children with non-CF bronchiectasis. In our prospective cohort of 69 children with non-CF bronchiectasis, parents of younger children with bronchiectasis were more likely to report an impaired QOL but radiological extent, baseline lung function, underlying etiology and chronic upper airway disease did not influence the burden of disease scores. A small but important number (12-15%) of mothers had abnormal scores reflecting anxiety, stress or depression above population norms. Acute pulmonary exacerbations caused significant worsening in both QOL and DASS scores with 38-54% having scores reflecting abnormal depression, anxiety and stress. Presence of viral infection and severity of exacerbation (hospitalized vs. non-hospitalized; hypoxia vs. no hypoxia) did not influence QOL and DASS scores during an exacerbation.

In this first study to prospectively examine the magnitude of parent-proxy burden of disease in children with non-CF bronchiectasis and its determinants, we found that young age was the only significant factor associated with worse burden of disease. Factors that govern QOL in adults with bronchiectasis include *Pseudomonas aeruginosa* infection,[20] dyspnea, sputum production[21] and frequency of exacerbations[13] though similar pediatric data is not available. However adult features such as sputum production, sputum bacteriology and spirometric parameters are of limited use in young children who cannot perform spirometry and do not expectorate. We had found that lung airway resistance (by spirometry or IOS) contributed little value when defining pulmonary exacerbations of bronchiectasis[22] though due to the relatively young cohort, spirometric data was unavailable from nearly half the cohort limiting assessment of this parameter. In pediatric cohorts with chronic respiratory illness (asthma,

CF, chronic cough); upper airway disease,[23] recurrent doctor visits[7] and high frequency of cough[24] worsen QOL. In our cohort, radiological extent, stable-state lung function (measured as airway resistance by IOS) and ETS exposure were not associated with the overall burden of disease measures, a finding similar to other pediatric and adult studies.[10,20] The correlation coefficient for age and PC-QOL scores was small (0.24), even though statistically significant. Due to the small coefficient and no clear clinical plausibility, we can only speculate reasons for this correlation. These reasons include parental fear of lung disease deterioration when the child becomes older and the effects of sleep deprivation on the young child. It is also possible that the parents of older children are more adjusted to the medical condition than those of younger children.

In adults with bronchiectasis, elevated scores for anxiety and/or depression have been described in up to a third of patients.[25] In contrast the majority of parents of children with bronchiectasis in our cohort were not depressed (<15% had DASS z-scores >0.5) during stable-state. It is possible that this difference could reflect differences in symptomatology between pediatric and adult populations. Whereas adult bronchiectasis is considered a disease of chronic cough and sputum production, children with bronchiectasis in stable-state are likely to be minimally symptomatic when managed appropriately for exacerbations.[12] However, during pulmonary exacerbations, a high proportion of parents reported significant worsening in the QOL and psychological burden of disease. Thus, in addition to data showing that severe exacerbations are associated with accelerated lung function decline,[3] our study's finding supports the contention that reduction of exacerbations should be one of the treatment goals in the management of children with non-CF bronchiectasis. Recurrent exacerbations

are known to worsen QOL in adults with bronchiectasis[13] and QOL scores have been shown to improve after treatment of pulmonary exacerbations in adults.[14]

DASS-21 is a commonly used tool to measure the variations in emotional state in adults though there is limited data on parents of children with chronic disease. Data from a cohort of children with chronic cough[7] - shows that the median DASS-21 score was 10 and the median PC-QOL score was 3.38. Both these parameters improved significantly with cessation of cough. In comparison, our cohort in exacerbation had worse DASS score (median 22) but better PC-QOL scores (median 4.6). The differences in age may explain some of these differences [Marchant et al's cohort was much younger (median age 2.56 years)], though it is possible that factors other than cough may be governing the burden of disease in our cohort of non-CF bronchiectasis.

A further implication of our findings in the depression, stress and anxiety scores, particularly during an exacerbation, is that physicians should be cognizant that irrespective of underlying cause or severity of bronchiectasis, some parents are substantially burdened. Detecting depressive symptomatology in the primary caregivers of children is important since it is reported to influence medication adherence. In a pediatric asthma study, Bartlett and colleagues[10] reported maternal depression to be associated with decreased medication adherence and increased emergency department visits. In 39 children with CF aged 7-17 years, parental depression was reported to be an important factor for poor adherence to airway clearance.[26] Also, data suggests that addressing the psychosocial aspects early improves functioning and minimizes the parental burden of illness.[11]

Decline in clinical symptoms such as dyspnea and sputum production is associated with worsening QOL in adults with chronic respiratory illnesses.[6,21] Acute events such as pulmonary exacerbations that aggravate symptoms are therefore likely to worsen the quality of life. This is especially relevant in light of the fact that recurrent stress is a risk factor for major depression in adults[27] and stressful states such as a pulmonary exacerbation could have a compounding effect on making parental mental state worse.

In the context of the finding that adult cough-specific QOL is valid for adults with bronchiectasis[18], we used the sole validated cough-specific QOL for children. There is no QOL specific for non-CF bronchiectasis. In adults, the St George's Respiratory Questionnaire (SGRQ) is often used.[21] The SGRQ is not appropriate in our cohort of children that includes the very young. As young children are unable to verbally express themselves adequately, it is standard practice for parents to be proxy assessors of their child.[8] Although proxy HRQOL measurements have been validated for assessing outcomes in children and adolescents[28] it remains unknown if use of child QOL would have resulted in the similar findings. Of note, in 62 adolescents with CF, Britto and colleagues[29] reported that HRQOL scores from children were comparable to their parents' proxy rating across most domains. Also, the fact that the PC-QOL scores in our cohort during stable state correlated well with the DASS scores, gives further strength to the role of this tool in understanding parental QOL and mental health. The correlation between DASS and PC-QOL is not surprising as we had previously described this finding in the development of the PC-QOL in 190 children.[7] In children with chronic cough, parental DASS scores significantly reduced when cough ceased and the reduction was

primarily related to the stress factor. Reasons for this explanation can only be speculated and have been described in our previous paper.[7]

In conclusion our study highlights the need for the treating physician to be sensitive to the emotional distress of parents thereby addressing this early in the consultative process. This is especially relevant during periods of clinical deterioration such as an exacerbation that constitutes a psychologically "vulnerable period". Efforts should also be made for prevention, early detection and appropriate management of exacerbation since recurrent stressors, such as exacerbations, could be a risk factor for long term caregiver depression.

Contributions

Drs. Kapur and Chang contributed to the study concept and design. Dr Kapur collected all the data. Drs Kapur and Newcombe contributed to the analysis and interpretation of the data. Drs. Kapur, Newcombe, Masters and Chang contributed to the drafting of the article. Dr Kapur is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

Figure Legend

Figure 1- Comparative analysis showing effect of pulmonary exacerbation on PC-QOL total and sub-component scores (Empty box indicates stable state and filled box indicates exacerbation state)

Figure 2- Comparative analysis showing effect of pulmonary exacerbation on DASS-21 total and sub-component scores (Empty box indicates stable state and filled box indicates exacerbation state)

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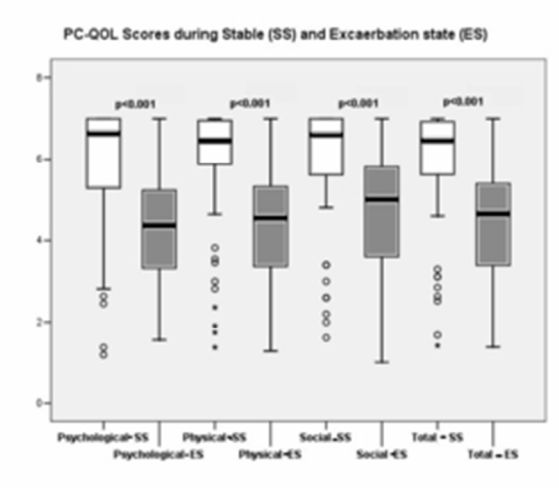

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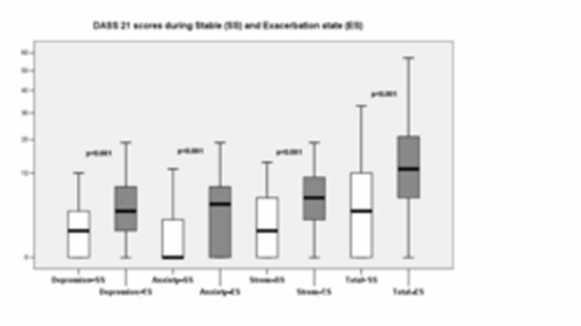

12x6mm (600 x 600 DPI)

Online Supplement

Virus identification

The nasopharyngeal aspirate (NPA) was assessed using an extended respiratory viruses polymerase chain reaction (PCR) screen that detected Influenza viruses A and B; Human parainfluenza viruses 1, 2, 3 and 4; Adenovirus; Human respiratory syncytial virus (RSV); Human metapneumovirus (hMPV); Human rhinoviruses (HRV) A, B and C; Human coronaviruses (HCoV); Human bocavirus (HBoV) and Human enteroviruses (HEV). Nucleic acids were extracted from 0.2 ml of each specimen using the High Pure Viral Nucleic Acid kit (Roche Diagnostics Australia) according to the manufacturer's instructions. Primary specimen and purified nucleic acid extracts were stored at −70 ◦C. Extracts (2μL) were tested by RT-PCR (Reverse Transcriptase PCR) (OneStep, QIAGEN®) or PCR (HotStarTaq, QIAGEN) as appropriate for the viral genome.

Impulse Oscillometry System (IOS)

Resistance at 5 and 20 Hz was measured using IOS (MasterScreen®, Jaeger, Germany) in accordance to the ERS task force guidelines. Percentage predicted values were calculated using Frei et al's reference and its extrapolation for children above 150 cm in height.

Table E1- Point prevalence of viruses detected by PCR from NPAs in bronchiectasis exacerbation (n=65)

Virus	Frequency*	Proportion
Human rhinovirus (HRV)	**15**	**23%**
A	7	
B	2	
C	1	
Non-typable	5	
Human parainfluenza virus	**5**	**8%**
1	1	
3	2	
4	2	
Human bocavirus (HBoV)	**4**	**6%**
Human enterovirus	**2**	**3%**
Adenovirus	**2**	**3%**
Human metapneumovirus (HMPV)	**2**	**3%**
Influenza A virus	**2**	**3%**
Human respiratory syncytial virus (RSV)	**2**	**3%**
Human corona virus (HCoV)	**1**	**1.5%**

*Four exacerbations had viral co-detection (HRV-B with HBoV, RSV with HMPV, HRV with HCoV and HBoV with adenovirus)