

# Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis

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## ABSTRACT

**Background** Despite advances in treatment of cystic fibrosis (CF), pulmonary exacerbations remain common. The aim of this study was to determine if frequent pulmonary exacerbations are associated with greater declines in lung function, or an accelerated time to death or lung transplantation in adults with CF.

**Methods** A 3-year prospective cohort study was conducted on 446 adult patients with CF from Ontario, Canada who could spontaneously produce sputum. Patients enrolled from 2005 to 2008 and were stratified into groups based upon their exacerbation rates over the 3 year study: <1 exacerbation/year (n=140), 1–2 exacerbations/year (n=160) and >2 exacerbations/year (n=146). Exacerbations were defined as acute/subacute worsening of respiratory symptoms severe enough to warrant oral or intravenous antibiotics. Patient-related factors associated with frequent exacerbations were determined, and clinical outcomes were compared among the three exacerbation groups.

**Results** Patients with frequent exacerbations were more likely to be female, diabetic and have poorer baseline lung function. Patients with >2 exacerbations/year had an increased risk of experiencing a 5% decline from baseline forced expiratory volume in 1 s (FEV<sub>1</sub>); unadjusted HR 1.47 (95% CI 1.07 to 2.01, p=0.02), adjusted HR 1.55 (95% CI 1.10 to 2.18, p=0.01) compared with patients with <1 exacerbation/year. Patients with >2 exacerbations/year also had an increased risk of lung transplant or death over the 3 year study; unadjusted HR 12.74 (95% CI 3.92 to 41.36, p<0.0001), adjusted HR 4.05 (95% CI 1.15 to 14.28, p=0.03).

**Conclusions** Patients with CF with frequent exacerbations appear to experience an accelerated decline in lung function, and they have an increased 3 year risk of death or lung transplant.

## INTRODUCTION

Despite advances in understanding the molecular basis and the development of new treatments for cystic fibrosis (CF), pulmonary exacerbations continue to contribute to significant clinical burden among patients with CF. In a large observational study of >11 000 patients, 42% of patients with CF experienced a pulmonary exacerbation over a 6 month period.<sup>1</sup> Although currently there are no consensus diagnostic criteria which define a pulmonary exacerbation, typically a pulmonary exacerbation is diagnosed based upon a constellation of patient symptoms and signs including dyspnoea,

## Key messages

### What is the key question?

- Do adults with cystic fibrosis (CF) who experience frequent pulmonary exacerbations have greater declines in lung function or an accelerated progression to death or lung transplant?

### What is the bottom line?

- Patients with CF with frequent pulmonary exacerbations appear to experience an accelerated decline in lung function, and they have an increased 3 year risk of death or lung transplant.

### Why read on?

- To learn about the potential impact of CF pulmonary exacerbations on the overall health status of adults with CF.

cough, sputum production, decreased energy level and appetite, weight loss and decreases in lung function.<sup>2</sup> Treatment usually involves commencement of intravenous or oral antibiotics, and intensification of sputum clearance via chest physiotherapy.<sup>3</sup>

Several studies have shown that pulmonary exacerbations negatively impact on quality of life in patients with CF<sup>4–6</sup> and are associated with significant cost.<sup>7</sup> Pulmonary exacerbations of CF, chronic obstructive pulmonary disease (COPD) and asthma are clearly serious events and have recently been coined 'lung attacks'.<sup>8</sup> Studies have shown that the annual prevalence of CF pulmonary exacerbations increases with age.<sup>1–9</sup> Despite advances in CF care, pulmonary exacerbation rates have not declined over the last two decades.<sup>10</sup>

Studies using data from the US CF Patient registry have found a negative correlation between pulmonary exacerbation rates and values of forced expiratory volume in 1 s (FEV<sub>1</sub>), suggesting that lung function is lower in patients who experience more exacerbations.<sup>2</sup> A small retrospective single-centre study of 51 patients recently suggested that FEV<sub>1</sub> decline is associated with the number of pulmonary exacerbations/year.<sup>11</sup>

It has been hypothesised that exacerbations might induce greater airway inflammation and provoke subsequent accelerated declines in lung function<sup>11–12</sup>; however, this theory has not been conclusively proven. Our hypothesis was that

patients with frequent pulmonary exacerbations might experience greater long-term morbidity. The objective of our study was to determine if frequent pulmonary exacerbations are associated with greater declines in lung function and body mass index (BMI), and an accelerated time to death or lung transplantation in adults with CF.

## METHODS

### Study design

This was a secondary analysis of a 3 year prospective observational cohort study involving an inception cohort of adult patients with CF from Ontario, Canada who could spontaneously produce sputum at the time of entry. The original study was designed to determine whether infection with transmissible strains of *Pseudomonas aeruginosa* was associated with poor clinical outcomes. Primary clinical outcomes in the original study included pulmonary exacerbation rates, survival and lung function, and these same outcomes are presented here in the current study.<sup>13</sup>

### Patients and data collection

Adult patients attending each of the seven Ontario adult CF clinics were approached for participation in the study between September 2005 and September 2008. Patients were included if they were  $\geq 18$  years of age and had a confirmed diagnosis of CF with genetic testing and/or sweat testing. Patients were excluded if they were unable to produce sputum at enrolment (since the primary objective of the original study was to examine transmissible strains of *P. aeruginosa*). The research ethics boards of the participating centres approved the study, and participants provided written informed consent.

Pulmonary exacerbations were defined as acute or subacute worsening of respiratory symptoms severe enough to warrant oral or intravenous treatment with antibiotics. Treatment was at the discretion of the treating physicians.

Patients were seen at baseline and annually for three consecutive years. At each visit we collected height, weight, BMI, spirometry and exacerbation history. Information on exacerbations and exacerbation treatment was collected each year for events in the preceding 12 month period. Exacerbation events were ascertained through a review of the patient's clinic and hospital charts. Direct patient interviews were conducted at baseline and then annually to determine if there were exacerbations that had not been captured in the health record. We specifically collected data on: number of pulmonary exacerbations in the past year requiring oral or intravenous antibiotics, number of inpatient pulmonary exacerbations requiring intravenous antibiotics, number of pulmonary exacerbations treated exclusively at home with intravenous antibiotics and number of pulmonary exacerbations treated exclusively on an outpatient basis with oral antibiotics.

We also collected data on baseline chronic infections at the time of study entry, including infection with both unique and transmissible strains of *P. aeruginosa*. *P. aeruginosa* transmissible strains are genetically identical strains that infect unrelated patients with CF. Co-morbidities (pancreatic insufficiency, CF-related diabetes and CF-related liver disease) and medical treatments were recorded from each patient at baseline and at each subsequent follow-up clinic visit.

Patients who underwent lung transplantation before completion of the study did not contribute spirometry, BMI or exacerbation data after their lung transplant date. Spirometry was performed according to American Thoracic Society (ATS)

standards, and predicted values from Crapo *et al* were used.<sup>14</sup> Patients completed measurements of lung function at each annual prescheduled visit (0, 12, 24 and 36 months).

### Statistical analysis

Patients were grouped according to their mean exacerbation status over the 3 year follow-up period: (1)  $<1$  exacerbation/year; (2) 1–2 exacerbations/year; and (3)  $>2$  exacerbations/year. The groupings were made a priori before commencing study analysis, based on the distribution of the data so that three approximately equal sized groups could be assigned. We selected three exacerbation groupings to determine if there was a graded response to pulmonary exacerbations. Once established, the exacerbation groupings were used as predefined cut-off points and subsequent analyses were run using only these cut-off points. Baseline continuous variables between the groups were compared using analysis of variance (ANOVA) and categorical variables were compared using  $\chi^2$  tests as appropriate, with p values reflecting the difference between the three groups (table 1).

We assessed decline in lung function using two methods. The slope of the rate of decline of FEV<sub>1</sub> % predicted over the 3 year study period was compared between the reference group ( $<1$  exacerbation/year) and the other two groups using random effects mixed linear models. Group–time interactions were analysed using the SAS PROC.MIXED program. Potential confounding effects of age, sex, BMI, infection with *Burkholderia cepacia* complex and transmissible *P. aeruginosa* strains, baseline FEV<sub>1</sub> % predicted, CF co-morbidities (diabetes, liver disease and pancreatic insufficiency) and medical treatments (inhaled tobramycin, inhaled colistin, azithromycin, dornase  $\alpha$ ) were assessed using linear mixed models. We adjusted all of our analyses for the same covariates which were determined a priori. These covariates were selected because they have previously been shown to be statically associated with either mortality or health outcomes in CF.

We also assessed FEV<sub>1</sub> decline by using Cox proportional hazards models to compare the time to 5% decline of patient's FEV<sub>1</sub> % predicted relative to their baseline lung function in the reference group compared with the other two groups. The time to lung transplant or death was compared using Kaplan–Meier survival methods and Cox proportional hazards models. Mortality was also examined as a stand-alone variable. Lastly, we assessed for trends by determining if the interaction trend between time and group was linear across the three groupings.

We performed a secondary analysis examining the effect of exacerbations requiring intravenous antibiotics on rate of decline of FEV<sub>1</sub> and time to lung transplant or death. Patients were again stratified based on mean annual number of exacerbations requiring intravenous antibiotics over the 3 year study: (1) 0 exacerbation/year; (2) 0.01–0.99 exacerbations/year; and (3)  $\geq 1$  exacerbations/year. Statistical analyses were performed using the same methods as described above. All statistical testing was two-sided and was performed at the 5% significance level using SAS software version 9.0.

## RESULTS

### Patient selection and baseline characteristics

Five hundred and eighty patients were approached to enter the study, and in total 446 patients enrolled (figure 1). Of the 446 enrolled patients, 140 patients averaged  $<1$  exacerbation/year, 160 patients had 1–2 exacerbations/year and 146 patients had  $>2$  exacerbations/year during the study period. These patients

**Table 1** Patient baseline characteristics

	<1 Exacerbation/ year n = 140	1–2 Exacerbations/ year n = 160	>2 Exacerbations/ year n = 146	Between-group p value
Average follow-up time, years	2.17	2.27	2.34	
Total no. of exacerbations	158	710	1512	
Average no. of exacerbations/year	0.52	1.95	4.43	
Mean age (SD), years	28.5±9.7	29.1±9.1	30.2±10.1	0.33
Sex (% male)	96 (68.6%)	92 (57.5%)	67 (45.9%)	0.0005
Mean height (SD), cm	169.8±9.4	169±9.3	167.6±8.3	0.11
Mean weight (SD), kg	65.5±12.5	64.1±12.6	61.9±14.1	0.06
Mean BMI (SD), kg/m <sup>2</sup>	22.6±2.9	22.4±3.6	21.9±4	0.25
Lung function				
FEV <sub>1</sub> measured (SD), litres	2.70±1.00	2.26±0.87	1.81±0.85	<0.0001
FEV <sub>1</sub> % predicted (SD)	67.5±20.7	59.0±20.8	49.1±20.4	<0.0001
FVC measured (SD), litres	4.71±0.86	5.47±0.83	4.37±0.76	0.002
FVC % predicted (SD)	83.4±17.8	77.7±20.6	67.9±21.6	<0.0001
Chronic infections, n (%)				
<i>Achromobacter</i> species	0 (0%)	7 (4.4%)	4 (2.7%)	0.05
<i>Aspergillus</i> species	25 (18.4%)	36 (22.5%)	56 (38.4%)	0.0003
<i>Burkholderia cepacia</i> complex	17 (12.5%)	24 (15%)	22 (15.1%)	0.78
<i>Staphylococcus aureus</i>	39 (28.7%)	44 (27.7%)	37 (25.5%)	0.83
<i>Stenotrophomonas maltophilia</i>	6 (4.4%)	14 (8.8%)	15 (10.3%)	0.17
Transmissible <i>Pseudomonas aeruginosa</i> strains	42 (30.0%)	28 (17.5%)	32 (21.9%)	0.11
<i>Pseudomonas aeruginosa</i> (all strains)	101 (72.1%)	101 (68.8%)	109 (74.7%)	0.67
Co-morbidities, n (%)				
CF-related diabetes	23 (16.4%)	28 (17.5%)	41 (28.1%)	0.02
Pancreatic insufficiency	116 (82.9%)	132 (82.5%)	127 (87%)	0.50
CF-related liver disease	4 (2.9%)	8 (5%)	11 (7.5%)	0.20
Medications, n (%)				
Azithromycin	30 (21.4%)	52 (32.5%)	61 (41.8%)	0.001
Inhaled colistin	5 (3.6%)	8 (5%)	16 (11%)	0.03
Dornase $\alpha$	10 (7.1%)	16 (10%)	31 (21.2%)	0.0007
Inhaled tobramycin	86 (61.4%)	94 (58.8%)	98 (67.1%)	0.31

BMI, body mass index; CF, cystic fibrosis; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity.

were followed for a mean of 791, 827 and 855 days, respectively. Full 3 year follow-up was not available for 101 patients (50 with <1 exacerbation/year, 32 with 1–2 exacerbations/year and 19 with >2 exacerbations/year), who enrolled in the study after January 2007. Late enrollees were mostly paediatric patients who transitioned to adult CF clinics during the latter half of the study. These patients were followed until December 2009. Vital status (death or lung transplant) was assessed for all enrolled

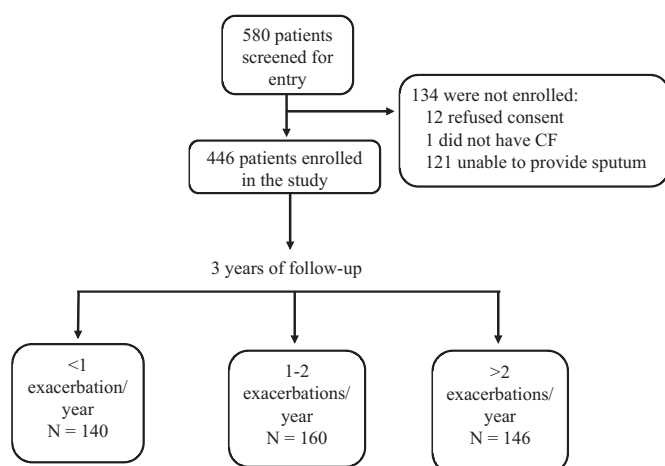
patients 3 years after entry into the study or, for those who enrolled late, up to 31 December 2009.

Table 1 outlines the baseline characteristics of patients included among the three pulmonary exacerbation groupings. Patients with frequent exacerbations were more likely to be female, diabetic and have poorer baseline lung function.

### Exacerbation frequency and decline in FEV<sub>1</sub> and BMI

Patients with more frequent exacerbations had lower lung function at entry into the study, and all three groups experienced a decline in their FEV<sub>1</sub> over the course of the study. Over the 3 year study the mean decline from baseline in FEV<sub>1</sub> % predicted was –4.85% (95% CI –8.01% to –1.69%) for patients with <1 exacerbation/year, –5.44% (95% CI –8.33% to –2.55%) for patients with 1–2 exacerbations/year, and –6.49% (95% CI –10.10% to –2.91%) for patients with >2 exacerbations/year. The slopes of rate of decline were not significantly different between the three groups and the p value for trend across the three groups was not significant (p=0.36).

The analysis of rate of decline in FEV<sub>1</sub> was also undertaken using survival analysis to try to correct for differences in between-group rates of premature censoring of patients who experienced death or lung transplant. Sixty-seven (48%) patients with <1 exacerbation/year, 93 (58%) patients with 1–2 exacerbations/year and 93 (64%) patients with >2 exacerbations/year experienced a ≥5% decline in FEV<sub>1</sub> from baseline. Compared with patients who had <1 exacerbation/year, patients with 1–2 exacerbations/year did not have a significantly increased risk of experiencing a 5% decline in FEV<sub>1</sub> %



**Figure 1** Flow diagram of entry of patients into the study. CF, cystic fibrosis.



predicted from baseline over the study period; unadjusted HR 1.29 (95% CI 0.95 to 1.77,  $p=0.11$ ), adjusted HR 1.33 (95% CI 0.96 to 1.84,  $p=0.08$ ). However, patients with  $>2$  exacerbations/year did experience a more rapid progression to 5% decline in FEV<sub>1</sub> % predicted from baseline compared with patients with  $<1$  exacerbation/year; unadjusted HR 1.47 (95% CI 1.07 to 2.01,  $p=0.02$ ), adjusted HR 1.55 (95% CI 1.10 to 2.18,  $p=0.01$ ) (table 2). The  $p$  value for trend was statistically significant across the three groups ( $p=0.02$ ).

There was no difference in change in BMI when comparing patients with  $<1$  exacerbation/year versus 1–2 exacerbations/year (unadjusted difference in decline of BMI of 0.14 per year, 95% CI  $-0.1$  to 0.46) or for patients with  $<1$  exacerbation/year versus  $>2$  exacerbations/year (unadjusted difference in decline of BMI of 0.04 per year, 95% CI  $-0.29$  to 0.35). The  $p$  value for trend for BMI was non-significant ( $p=0.89$ ).

### Exacerbation frequency and risk of death or lung transplantation

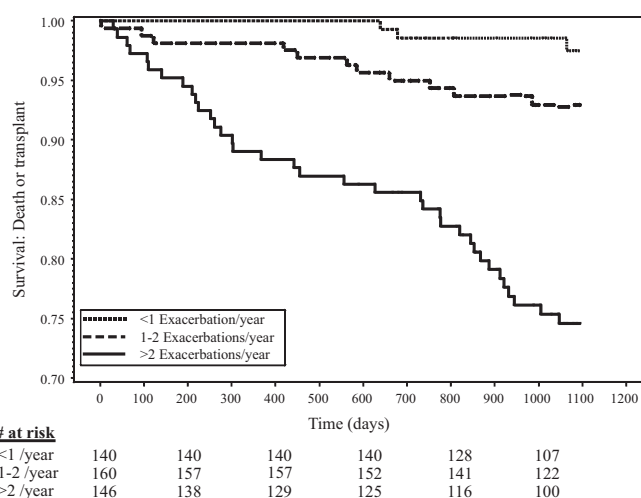
Over the 3 year study period 50/446 (11.2%) patients died or received a lung transplant. All deaths were respiratory deaths. Death or lung transplant occurred in 3/140 (2.1%) patients in the  $<1$  exacerbation/year group, 11/160 (6.9%) in the 1–2 exacerbations/year group and 36/146 (24.7%) in the  $>2$  exacerbations/year group. Patients with  $>2$  exacerbations/year experienced a greater 3 year risk of death or lung transplant compared with patients with  $<1$  exacerbation/year; unadjusted HR 12.74 (95% CI 3.92 to 41.36,  $p<0.0001$ ), adjusted HR 4.05 (95% CI 1.15 to 14.28,  $p=0.03$ ). Patients with 1–2 exacerbations/year did not experience a significantly accelerated risk of death or lung transplant versus those with  $<1$  exacerbation/year; unadjusted HR 3.25 (95% CI 0.91 to 11.66,  $p=0.07$ ), adjusted HR 2.02 (95% CI 0.53 to 7.73,  $p=0.30$ ) (figure 2).

### Exacerbation frequency and risk of death

A Kaplan–Meier analysis of time to death was performed, independently of lung transplant. Death occurred during the 3 year study follow-up period in 2/140 (1.4%) patients in the  $<1$  exacerbation/year group, 4/160 (2.5%) in the 1–2 exacerbations/year group and 16/146 (11.0%) in the  $>2$  exacerbations/year group (Kaplan–Meier log rank  $p$  value=0.0002). Patients with  $>2$  exacerbations/year did experience an increased 3 year risk of death compared with patients with  $<1$  exacerbation/year; unadjusted HR 7.86 (95% CI 1.81 to 34.2,  $p=0.006$ ). However, patients with 1–2 exacerbations/year did not have a statistically increased risk of death compared with patients with  $<1$  exacerbation/year; unadjusted HR 1.73 (95% CI 0.32 to 9.45,  $p=0.53$ ).

### Secondary analysis of exacerbations requiring intravenous antibiotics

FEV<sub>1</sub> % predicted was significantly lower at baseline in patients who experienced more frequent exacerbations requiring intra-



**Figure 2** Kaplan–Meier plot comparing time to death or lung transplant over the 3 year study period for exacerbation groups. Survival analyses were adjusted for age, sex, body mass index, infection with *Burkholderia cepacia*, transmissible *Pseudomonas aeruginosa*, baseline forced expiratory volume in 1 s (FEV<sub>1</sub>), cystic fibrosis co-morbidities and maintenance therapies.

venous antibiotics. The baseline FEV<sub>1</sub> % predicted was 67.4% in the 0 intravenous exacerbation/year group, 56.6% in the 0.01–0.99 intravenous exacerbations/year group and 42.0% in those with  $\geq 1$  intravenous exacerbations/year;  $p<0.0001$ .

Compared with patients who had 0 intravenous exacerbations/year, patients with CF with 0.01–0.99 intravenous exacerbations/year had a significantly increased risk of experiencing a 5% decline in FEV<sub>1</sub> % predicted from baseline over the study period; unadjusted HR 1.45 (95% CI 1.08 to 1.95,  $p=0.01$ ), adjusted HR 1.58 (95% CI 1.15 to 2.16,  $p=0.004$ ). Patients with  $\geq 1$  intravenous exacerbations/year also experienced a more rapid progression to 5% decline in FEV<sub>1</sub> % predicted from baseline compared with patients with 0 intravenous exacerbation/year; unadjusted HR 1.46 (95% CI 1.08 to 1.97,  $p=0.02$ ), adjusted HR 1.78 (95% CI 1.24 to 2.54,  $p=0.002$ ).

Death or lung transplant occurred in 6/228 patients (2.6%) in the 0 intravenous exacerbation/year group, 5/104 patients (6.9%) in the 0.01–0.99 intravenous exacerbations/year group and 39/114 (34.2%) patients in the  $\geq 1$  intravenous exacerbations/year group. Patients requiring  $\geq 1$  intravenous course of antibiotics/year experienced a significantly increased 3 year risk of death or transplant compared with patients with 0 intravenous exacerbation/year; unadjusted HR 15.68 (95% CI 6.64 to 37.06,  $p<0.0001$ ), adjusted HR 3.36 (95% CI 1.30 to 8.73,  $p=0.01$ ). Patients requiring 0.01–0.99 intravenous exacerbations/year did not experience an increased 3 year risk of death or lung transplant compared with patients with 0 intravenous exacerbations/year; unadjusted HR 1.77 (95% CI 0.54 to 5.80,  $p=0.35$ ), adjusted HR 0.93 (95% CI 0.27 to 3.15,  $p=0.90$ ) (figure 3).

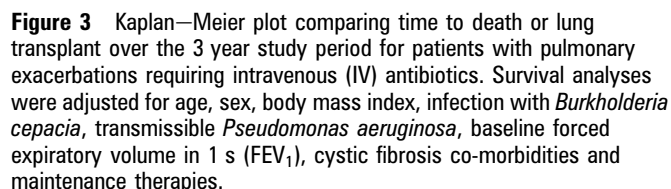
### DISCUSSION

The results of our study suggest that patients with CF who experience frequent pulmonary exacerbations are at increased risk of experiencing a decline in their lung function by 5% from baseline and that frequent pulmonary exacerbations are associated with an increased 3 year risk of death or lung transplant. Patients who experienced  $>2$  exacerbations/year were also at significantly increased risk for death, independent of lung transplant. The results were similar whether we considered

**Table 2** Analysis of time to 5% decline of baseline FEV<sub>1</sub> % predicted

	Unadjusted HR	Adjusted HR*
$<1$ exacerbation/year	1.29	1.33
versus	95% CI 0.95 to 1.77	95% CI 0.96 to 1.84
1–2 exacerbations/year	$p=0.11$	$p=0.08$
$<1$ exacerbation/year	1.47	1.55
versus	95% CI 1.07 to 2.01	95% CI 1.10 to 2.18
$>2$ exacerbations/year	$p=0.02$	$p=0.01$

\*Adjusted for age, sex, body mass index, infection with *Burkholderia cepacia*, transmissible *Pseudomonas aeruginosa*, baseline forced expiratory volume in 1 s (FEV<sub>1</sub>), cystic fibrosis co-morbidities and maintenance therapies.



We found that patients with frequent pulmonary exacerbations were more likely to be female and diabetic. Female gender has been previously identified as a risk factor for

We demonstrated that more frequent pulmonary exacerbations in patients with CF are associated with a significantly higher risk of death or lung transplant. Patients with >2 pulmonary exacerbations/year have reduced lung function at baseline which continues to decline progressively over time. Patients with CF who regularly experience >2 pulmonary exacerbations/year are clearly at high risk, and they warrant diligent clinical monitoring and timely consideration for lung transplant.

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## Journal club

### Oxygen therapy is equivalent to room air for alleviating refractory dyspnoea

Palliative oxygen is commonly used for the treatment of dyspnoea in individuals with life-limiting illness who are ineligible for long-term oxygen therapy despite insufficient evidence for symptomatic benefit. This multicentre study investigated the effectiveness of oxygen compared with room air in this population group.

Between 2006 and 2008, 239 patients from Australia, the USA and the UK were randomly assigned to receive at least 15 h of oxygen (n=120) or room air (n=119) for 7 days. The primary outcome measured was 'breathlessness' using a 0–10 numerical rating scale recorded by the patient twice daily.

There was no significant difference in breathlessness between the two groups. Symptomatic improvement was appreciable in the first 72 h of intervention. A greater response was seen in the morning with oxygen therapy than with room air, but the response remained the same in the evening for both groups. The side effects of treatment and change in quality of life were similar in the two groups.

The authors conclude that oxygen is not superior to room air in palliative treatment of breathlessness; however, this study is limited by the lack of representation of the sickest patients in palliative care as only outpatients were recruited. In ineffective cases, alternative measures should be sought as medical gas therapy is restricted by cost, availability and logistic burdens.

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