

## Objective Measurement of Cough during Pulmonary Exacerbations in Adults with Cystic Fibrosis

Jaclyn A. Smith<sup>1</sup>, Emily C. Owen<sup>1</sup>, Andrew M. Jones<sup>2</sup>, Mary E. Dodd<sup>2</sup>, A. Kevin Webb<sup>2</sup> and Ashley Woodcock<sup>1</sup>

<sup>1</sup>North West Lung Centre, South Manchester University Hospitals Trust, Manchester, UK

<sup>2</sup>Manchester Adult Cystic Fibrosis Centre, South Manchester University Hospitals Trust, Manchester, UK

### Correspondence:

Dr Jaclyn A. Smith,  
North West Lung Research Centre,  
Wythenshawe Hospital,  
Southmoor Rd,  
Wythenshawe,  
Manchester M23 9LT  
Telephone +44 161 291 4198  
Fax +44 161 291 5057  
Email [jackyannsmith@hotmail.com](mailto:jackyannsmith@hotmail.com)

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## ABSTRACT

**Background** Little is known about cough frequency in adults with cystic fibrosis (CF). This study aimed to determine 1) daytime and overnight cough rates in patients with CF at the beginning and end of a course of antibiotics for treatment of an exacerbation; 2) the relationship between cough frequencies and standard clinical measures of disease; 3) the relationship between objective cough rates and the subjective assessment of cough.

**Methods** 19 adult patients admitted with a pulmonary exacerbation performed daytime and overnight sound recordings on admission; 13 had repeat recordings prior to discharge. Coughs were manually quantified in cough seconds (time spent coughing). Patients subjectively scored their cough using a visual analogue scale (VAS) and numerical score. Lung function, C-reactive protein levels (CRP) and sputum weights were recorded.

**Results** Cough rates fell substantially with treatment; median fall in cough rate was 51.3% (IQR 32.3-77.5) ( $p < 0.001$ ) for daytime and 72.2% (28.6-90.1) ( $p = 0.049$ ) for overnight. Multivariate regression analyses examined the influence of lung function, sputum volume and CRP on cough rates. On admission, FEV<sub>1</sub> and CRP predicted overnight cough rates. On discharge, sputum volume predicted daytime cough rates. Only the change in overnight VAS correlated with the change in objective cough rates.

**Conclusions** Cough rate significantly decreased with treatment of a pulmonary exacerbation in adults with CF. Lung function, sputum volume and CRP influenced cough rates; the effects differed from day to night and between admission and discharge. Subjective reporting of a nocturnal cough may indicate a pulmonary exacerbation of CF in adults.

## INTRODUCTION

Pulmonary exacerbations are frequently used as an outcome measure in clinical trials of CF.<sup>1</sup> Exacerbations are defined based upon clinical criteria, usually an acute worsening in respiratory function and symptoms e.g. a change in sputum production, and an increased cough, which resolve with intensive treatment.<sup>2,3</sup>

Due to the difficulties in measuring cough, little is known about the frequency of coughing in CF, either in stable disease or the changes associated with an exacerbation. However, a study of cough in children with CF surprisingly did not to find any difference in cough epochs with treatment of a pulmonary exacerbation.<sup>4</sup>

The causes of cough in CF are likely to be multiple including airway inflammation, mucus, airway instability, sinus disease, and perhaps also gastro-oesophageal reflux. The relative contributions of these factors remain unknown.

We hypothesised that in-patient treatment for a pulmonary exacerbation of CF would reduce airway inflammation and sputum production and consequently coughing would be reduced. The primary outcome measure was the objective monitoring of cough before and after treatment. We have quantified cough as the time spent coughing per hour. If coughing occurs in prolonged bursts this measure takes account of the length of these bursts as well as the number.

Secondary outcome measures were spirometry, CRP levels and sputum weight. Based on previous work we predicted that these clinical markers of an exacerbation would be related to time spent coughing<sup>5</sup>. We also examined the relationships between subjective estimates of cough severity and cough frequency.

## METHODS

### Subjects

Subjects were recruited from consecutive admissions with a pulmonary exacerbation of CF. Clinical parameters were used to define a CF exacerbation including change in sputum load and colour, increased breathlessness, cough and wheeze, and a fall in FEV<sub>1</sub> of > 10%, compared to baseline. Subjects under 16 years of age, current smokers (3 were ex-smokers) and subjects requiring high flow oxygen or non-invasive ventilation were excluded. Those infected with *Burkholderia cepacia*, methicillin resistant *Staphylococcus aureus* and multi-drug resistant *Pseudomonas* species were also excluded due to the potential risk of infection transfer via the cough recording equipment. The study was approved by the local ethics committee and informed written consent was obtained from all subjects.

All patients received standard treatment for their pulmonary exacerbation including intravenous antibiotics, chest physiotherapy and an overnight intravenous aminophylline infusion, commenced on the day of admission. Measurement of spirometry, sputum weight and CRP was performed as part of routine monitoring.

## Study Procedures

Each patient had ambulatory daytime and overnight sound recordings on the day after admission and again prior to discharge. On each study day, the daytime recording commenced at approximately 1000 hrs and the overnight recording at 2200 hrs; each was 10 hours in length. Sound recordings were obtained by using digital recording devices (Nomad Jukebox 3™, Creative Technology Ltd, Singapore) and a lapel microphone (AOI, ECM-1025) positioned 30cm from the mouth. The digital files were transferred to a personal computer for analysis and archiving. Custom written software was used to compress the sound files (remove silence and low amplitude sounds) and to assist manual counting of the time spent coughing. Time spent coughing was defined as the numbers of seconds per hour that contained at least one explosive cough sound. Coughing induced by physiotherapy was excluded from the analyses. Each recording takes approximately 2.5 to 3 hours to process. We have previously validated this methodology by comparing coughs counted from digital sound recordings with those counted from video recordings and found excellent agreement between the two methods.<sup>6</sup> To check reliability of the manual counting, 10 randomly selected tracks were recounted by a second trained observer. To examine the relationships between time spent coughing (cough seconds, cs) and cough epochs, the first 3 hours of each daytime recording was recounted in cough epochs. Cough epochs are defined as a period of coughing with less than 2 seconds interruption.<sup>4 7 8 9 10</sup>

Sputum was collected during the day and night, and weighed at the end of each recording period. Clinical assessment routinely includes sputum collection, spirometry and CRP levels (normal <5mg/l).

Patients were asked to subjectively score the severity of their cough, by day and by night. Two methods of subjective assessment were used; a visual analogue scale (100mm line marked “no cough” to “worst cough”) and a cough score chart with a range of scores from 0-5 (Table 1).<sup>4 7</sup>

## Statistical Analysis

A power calculation to determine sample size could not be performed due to the lack of existing data on time spent coughing in CF; after consultation with a statistician it was decided to recruit 20 subjects. Both day and night cough data were positively skewed. For clarity, the median and interquartile ranges are reported for day and night, on admission and discharge. However for the primary outcome i.e. the comparison of time spent coughing before and after treatment, the  $\log_{10}$  transforms were used, and means compared using a paired t test (two-sided).

For the secondary hypotheses, multivariate linear regression analyses were performed to examine the influence of FEV<sub>1</sub>, CRP and sputum weight on cough frequency. Again data was log transformed for these analyses. Subjective measures of cough were also skewed but could not be improved by transformation and hence Spearman’s correlations were used to examine the relationships between subjective and objective measures of cough. Statistics were performed using SPSS version 11.0 (SPSS Inc, Chicago) and Prism 4.0 (Graphpad Software Inc, San Diego).

**Table 1.** Cough Symptom Scores for daytime and night

Score	Daytime	Night-time
0	No cough during the day	No cough during the night
1	Cough for one short period	Cough on waking only
2	Cough for more than two short periods	Wake once or early due to cough
3	Frequent coughing which did not interfere with usual daytime activities	Frequent waking due to coughs
4	Frequent coughing which did interfere with usual daytime activities	Frequent coughs most of the night
5	Distressing cough most of the day	Distressing cough most of the night

## RESULTS

Twenty patients with CF and an exacerbation of their chest disease entered the study. Median age was 23 years (inter-quartile range 19-30), 9 patients were male, and median body mass index was 19.6 (18.2-22.3). After the study was completed one patient was found to be a current smoker and so was excluded. Of the remaining 19 subjects, one patient only performed recordings on admission and withdrew from further study for personal reasons. Of the 74 recordings performed 5 were technically faulty; hence cough recording data was available for 19 subjects on admission and 13 subjects prior to discharge. Each analysis was performed on the fullest data set available. The average time between admission and discharge recordings was 8.0 days (SD  $\pm$ 3.0 days). Agreement between manual cough counts for two trained observers was excellent with a mean difference of 0.25cs between observers (95% limits of agreement -2.17cs and 2.67cs).<sup>11</sup>

### Daytime and overnight cough during and after exacerbation

After treatment there was a significant fall in time spent coughing for both day and night recording periods; median fall in cough rate was 51.3% (32.3-77.5) for daytime and 72.2% (28.6-90.1) for overnight, Figure 1 and Table 2. A paired t-test of the log transformed cough rates found the fall in cough rate to be statistically significant for day ( $p < 0.001$ , mean 2.29 fold difference (95%CI 2.29-3.26) and night ( $p = 0.049$ , mean 2.51 fold difference (95%CI 1.02-6.31) . Two patients had an increase in daytime cough rate and 4 patients had an increase in nocturnal cough rate however for total cough rates (cumulative day and night) all patients cough rates fell. These patients did not have a different clinical outcome to the remainder of the group. Patients had a wide range of cough rates and there was a significant diurnal variation in cough rate on both study days ( $p < 0.001$  admission,  $p = 0.002$  discharge), Table 2.

The temporal change in cough seconds over each recording period is demonstrated in Figure 2. The median cough rate at each time point is higher and more variable on admission compared to discharge, during the day. Coughing virtually stops overnight.

When  $\log_{10}$  cough epochs are compared to  $\log_{10}$  cough seconds there are significant linear relationships (admission  $r = 0.92$   $p < 0.001$ , discharge  $r = 0.92$   $p < 0.001$ ). However, the length of cough epochs (to the nearest second) significantly reduces with treatment (on admission median length 2 seconds (interquartile range 1-2), on discharge 1 second (interquartile range 1-1),  $p = 0.009$ ). Statistical analysis (linear regression) did not find a statistically significant difference between the relationships between cough seconds and cough epochs over the short period analysed.

**Table 2.** Cough frequencies and clinical parameters on admission and discharge (medians and inter-quartile ranges).

		Admission	Discharge	p value
FEV <sub>1</sub> (% predicted)		41.8 (32-67.8)	56.1 (40.2-76.8)	0.002
FEV <sub>1</sub> /FVC (%)		60.5 (54.2-73.6)	65.0 (58.2-75.3)	0.213
CRP (mg/dl)		16 (1-31)	5 (1-13)	0.050
Cough Rate (cs/hr)	Day	21.2 (14.0-34.9)	9.0 (5.8-12.8)	<0.001
	Night	4.8 (1.0-6.8)	1.5 (0.8-5.0)	0.049
Sputum (g)	Day	7.1 (3.8-21.8)	2.8 (0.0-4.5)	0.041
	Night	2.2 (0.0-9.3)	0.0 (0.0-4.5)	0.959
Cough score	Day	3.0 (2.0-3.0)	1.5 (1.0-2.8)	0.002
	Night	1.0 (0.0-2.0)	1.0 (0.0-1.0)	0.216
Visual analogue scale	Day	60 (43-73)	18 (12-53)	0.005
	Night	20 (3-46)	7 (2-27)	0.064

### Relationships between coughs and clinical measures

There were improvements in lung function, a decrease in daytime sputum weight and a decrease in CRP levels with treatment of the infective exacerbation (Table 2).

Multivariate regression analyses were performed to examine the predictive value of FEV<sub>1</sub>, sputum weight and CRP for time spent coughing during the day and night, on admission and on discharge. Variables were again log<sub>10</sub> transformed for analysis to allow the use of parametric statistics. FEV<sub>1</sub> (B=-0.321 [95%CI -0.459 to -0.184], p=<0.001) and CRP (B=0.006 [95%CI 0.001 to 0.012], p=0.026) were significant predictors of overnight cough frequency on admission. Together they accounted for 74.4% of the variance in time spent coughing overnight (adjusted R<sup>2</sup>=0.744). A 100ml increase in FEV<sub>1</sub> was associated with a 4.7% fall in cough frequency and a 1 unit increase in CRP was associated with a 1.4% increase in cough frequency.

Statistically significant models could not be produced with these parameters for daytime cough frequency on admission, or night cough frequency on discharge. Day cough frequency on discharge was predicted by sputum volume alone (B=0.411 [95%CI 0.144 to 0.678], p=0.005). A 1g increase in sputum weight was associated with a 4.0% increase in daytime cough frequency.

## Subjective Assessment of Cough

Subjective assessments of cough fell from admission to discharge in keeping with the change in time spent coughing (Table 2). Day scores were higher than night scores before and after treatment.

The relationships between the change in subjective cough scores, visual analogue scales and the change in time spent coughing are shown in Table 3. The changes in cough scores were not significantly correlated with objective coughing for the day or the night. Visual analogue scales however are strongly and significantly correlated with objective cough overnight and show a trend for a moderate correlation for change in daytime objective cough.

**Table 3.** Correlations between changes in subjective estimates of cough frequency (cough scores and VAS) and time spent coughing for day and night.

	Change in Day Cough Rate	Change in Night Cough Rate
Change in Cough Score	r=0.34 p=0.204	r=0.19 p=0.510
Change in Visual Analogue Scale	r=0.47 p=0.070	<b>r=0.81</b> <b>p=0.001</b>



## DISCUSSION

This is the first study to quantify the effects of in-patient treatment on cough, in adults with an infective exacerbation of CF. We have shown that in adult subjects with an infective exacerbation, time spent coughing significantly falls with inpatient treatment including intravenous antibiotics and chest physiotherapy.

The precise mechanisms by which coughing occurs in CF are not understood. The most obvious candidates are airway inflammation related to chronic infection and the accumulation of purulent airway secretions; extra-pulmonary diseases such as sinusitis and gastro-oesophageal reflux could also contribute<sup>12 13</sup>. In subjects suffering from chronic dry cough increased inflammatory mediators have been demonstrated in induced sputum<sup>14 15</sup> and have been implicated in increasing the sensitivity of the cough reflex<sup>16</sup>. In children with stable CF however, the cough reflex sensitivity to inhaled tussigenic agents has been shown to be similar to or less sensitive than in healthy controls.<sup>17</sup> This may not be the case in adults where pulmonary disease has progressed further. Whether cough reflex sensitivity increases during an exacerbation has not been studied in CF, but adults with non-CF bronchiectasis do have an increased cough reflex during exacerbations.<sup>18</sup>

Our secondary outcome measures suggest overnight cough frequency is influenced by FEV<sub>1</sub> and CRP in exacerbating patients, implying cough may be driven mainly by airway inflammation. Sputum weight did not influence cough frequency whilst the subjects were unwell, but after treatment the daytime cough rates increased with increasing with sputum weight.

These were not the primary endpoints in this study and so must be interpreted cautiously; however CRP and FEV<sub>1</sub> explain such a large proportion of the variation in cough rates, this finding is difficult to ignore. Overnight, subjects are less likely to be exposed to environmental irritants or changes in temperature that may independently provoke coughing. The coughing that occurs overnight with exacerbations may therefore be a better reflection of airway inflammation than daytime cough. Furthermore, factors which then adversely affect the ability of subjects to clear secretions when coughing (such as impaired FEV<sub>1</sub>) would also be expected influence to the frequency and pattern of cough. In this respect sputum viscosity, airway instability and degree of airflow obstruction are all likely to be important<sup>19</sup>.

Prior to discharge the only statistically significant predictor of cough rate was daytime sputum volume. Subjects do not always expectorate, hence sputum volumes are known to be poor markers of changes in disease and additionally this finding was limited to daytime cough rate. A similar effect would be difficult to identify overnight as the majority of overnight sputum volumes fell to zero after treatment.

Although adults with CF cough much more during the day than overnight they are poor at subjectively estimating the severity of their daytime cough. Subjects may become so accustomed to high daytime cough rates that they do not perceive cough as interfering with their daily activities and are not able to estimate changes well. It is also possible that when scoring cough severity subjects take into account other factors not measured in this study such as intensity of the cough. Visual analogue scales are clearly superior to cough scores for subjective estimation of changes in cough frequency in adults with CF.

Discrepancies between subjective and objective assessments of cough frequency have been reported in other conditions where cough is a predominant symptom. In a

group of adults with cough variant asthma there was no relationship between objective and subjective measures.<sup>7</sup> Poor agreement for reporting of nocturnal cough compared to tape recordings was also found in a group of children with asthma.<sup>20</sup> However, adults with seasonal allergic rhinitis had a significant moderate correlation between objective and subjective cough frequency.<sup>21</sup> In children with chronic recurrent cough there was an excellent correlation between objective cough frequency and diary card visual analogue scales scored by the children and their parents.<sup>22</sup> The usefulness of subjective measures of cough seems to vary with subject groups and the tools employed.

The only significant correlation for subjective measures this study occurred between changes in time spent coughing overnight and visual analogue scales overnight. We speculate that sleep disruption may be the explanation for this. As subjects are most aware of overnight cough, clinicians should pay particular attention to reporting of worsening overnight cough as an indicator of an exacerbation.

Our findings of a substantial fall in cough rate in adults treated for an exacerbation of CF are in contrast to a similar study in children with CF. In that study the cough was identified from sound and EMG signals and cough epochs (i.e. bursts of coughing) were counted<sup>4</sup>. In children with CF, cough and sputum production may be less responsive to treatment. We found that the length of cough epochs significantly shortened from admission to discharge. A device counting only epochs could not appreciate this change and hence cough epochs may be an inferior method for quantifying cough. Measuring epoch frequency may underestimate the reduction in coughing with treatment in CF. However, we could not demonstrate a significant difference between the measures analysed over a 3 hour period.

The main limitation of this study is that available digital recording equipment does not currently allow continuous 24 hour sound recordings of adequate quality. Rapid improvements in storage capacity and battery life should make this possible soon. Manual counting to quantify cough is time-consuming, and hence studies are restricted to relatively small numbers of subjects, however algorithms to automatically identify cough are showing promise.

In conclusion, we have employed an accurate although labour intensive method for objectively quantifying cough in adults with CF. We were able to quantify the change in cough frequency associated with treatment of an acute exacerbation. Cough rates during an exacerbation may be more influenced by airway inflammation and FEV<sub>1</sub> than sputum volume but the relationships may be reversed after treatment. An accurate 24 hour automated cough monitor would greatly improve the evaluation of the burden of cough in all respiratory diseases.

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### **Competing Interests**

None

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## Figure legends

**Figure 1.** Time spent coughing with a pulmonary exacerbation, on admission and prior to discharge; daytime (A) and overnight (B)

**Figure 2.** Temporal distribution of coughs during daytime and overnight on admission and before discharge (median time spent coughing per 30 minute period)

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Figure 1A

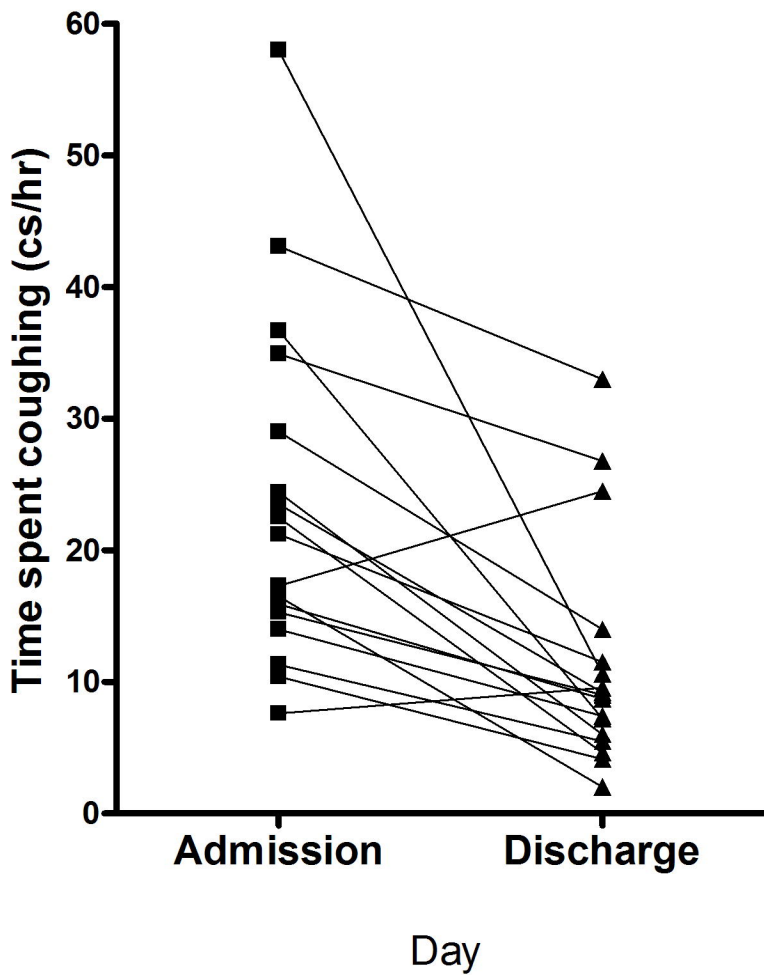
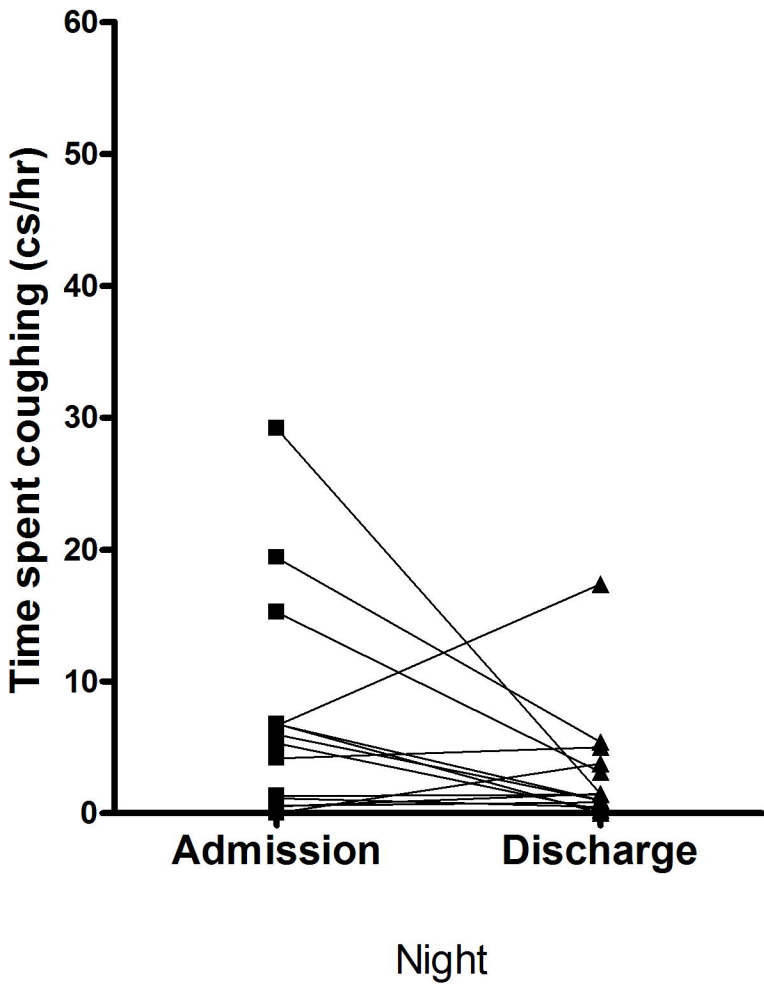
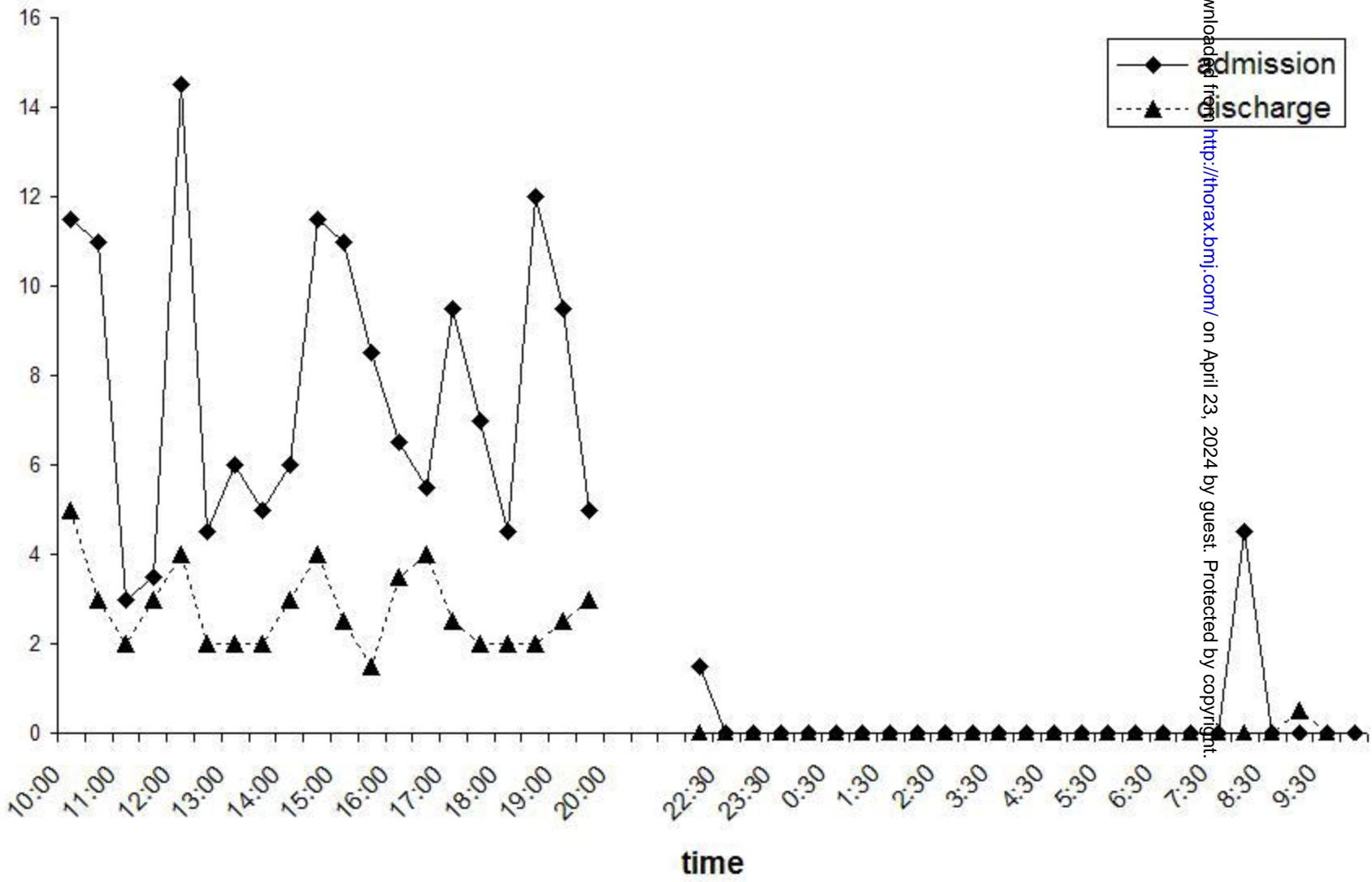


Figure 1B





median time spent coughing cs/hr



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