Predicting recovery from acute severe asthma

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ABSTRACT Fifty-two patients admitted to hospital with acute severe asthma took part in a prospective study investigating the rate and pattern of their subsequent recovery. Clinical assessment of the severity of the acute attack on admission (according to pulse rate, degree of pulsus paradoxus, and peak expiratory flow rate) did not reliably predict the results of arterial blood gas analysis. Subjects were divided into three groups according to the speed of recovery of peak expiratory flow rate. Historical features associated with slow recovery were: age over 40 years, non-atopic asthma, and the use of maintenance oral corticosteroids. The degree of pulsus paradoxus on admission and the improvement in PEFR at six hours and arterial oxygen tension (Pao2) at 48 hours were also useful in predicting speed of recovery. The severity of the attack, assessed on admission by arterial blood gas analysis and PEFR, did not differ between the three groups of recovering patients. Hyperinflation was still present in 15 out of 44 patients investigated five days after admission even though PEFR had returned to more than 80% of predicted normal in seven of these 15 subjects. The recovery of hypoxia was also commonly delayed with 12 out of 52 patients having Pao2 values of less than 80 mmHg at five days. Persistent hypoxia was more common in those with delayed recovery of PEFR.

The increase in asthma deaths during the 1960s emphasised the significant risks of acute exacerbations in this disease and attention has been drawn to a number of factors which may have contributed to the increased mortality. The fall in death rate in more recent years is almost certainly the result of improved clinical and physiological assessment of the acute attack together with the increased use of corticosteroids. Since the late 1960s, a number of studies of recovery from acute severe asthma have been performed showing that hypercapnia and pulsus paradoxus disappear within hours of the institution of vigorous therapy, hyperinflation, and forced expired volume in one second (FEV1) recover over about one week and recovery of arterial oxygen tension (Pao2) is often delayed for two weeks or more. A wide variation in the rate of recovery has been a consistent feature in these reports but few investigations into factors which might predict the speed of recovery have been performed. The ability to differentiate patients who will recover slowly from an acute attack of asthma would be of obvious clinical and therapeutic significance and we have studied asthmatic subjects with exacerbations of their disease in an attempt to identify those in whom delayed recovery is likely.

Methods

Over a 10-month period, patients with exacerbations of asthma sufficiently severe to require admission to hospital and with PEFRs on admission of less than 50% of predicted normal were entered into the study. Patients fulfilling the Medical Research Council definition of bronchitis or giving a history of smoking were excluded.

Detailed clinical information was obtained on admission, together with features of the current attack of asthma. Arterial blood gas analysis, performed immediately on arrival, was compared with the pulse rate, degree of pulsus paradoxus, and PEFR. All patients were treated with intravenous aminophylline (6 mg/kg loading dose, 1 mg/kg/hour by infusion) and hydrocortisone (250 mg loading dose, 250 mg six-hourly by infusion), nebulised salbutamol, oral prednisolone (40 mg daily), and 35% oxygen. Antibiotics were administered when indicated.

The rate and pattern of recovery was assessed by

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six-hourly measurements of PEFR, before and after nebulised salbutamol, continued throughout the patient's stay in hospital. Arterial blood gas analysis was repeated at six-hourly intervals with the patient breathing air for 15 minutes beforehand and was continued until a PaO$_2$ of more than 80 mmHg on air was attained. Physiological measurements were performed more frequently as the clinical situation demanded. The maximum PEFR was recorded as a percentage of the predicted normal and the time taken to achieve this level of PEFR with no additional improvement after nebulised salbutamol was also noted. Lung volumes were measured by the helium dilution technique$^{12}$ five days after admission.

Patients were classed into three groups according to the speed of recovery of PEFR. Slow responders reached maximum PEFR in more than seven days, intermediate responders in three to seven days, and rapid responders in less than three days from admission (fig 1). The three groups were then compared regarding historical, clinical, and physiological findings on admission. Paired sample Student $t$ tests were applied to each pair of groups for parametric data and four-fold table tests were used to investigate pairs of groups with regard to non-parametric data. In addition, the statistical test of trend, $X^2_1$, was applied to each of the non-parametric features studied.$^{18}$ Probability values of less than 0.05 were considered to be statistically significant.

**Results**

Fifty-two patients (15 male), aged between 15 and 77 years, entered the study.

There was no correlation between arterial blood gases on admission and clinical features of the attack which might be used to define severity. Neither pulse rate nor the degree of pulsus paradoxus correlated with the initial measurements of PaO$_2$ and Pco$_2$. Five patients had pulse rates of 100/min or less despite having PaO$_2$ values lower than 70 mmHg (fig 2) and two of these patients were younger than 25 years. Similarly, seven patients whose PaO$_2$ was less than 70 mmHg had less than 15 mm of paradox on admission (fig 3), five of these patients being younger than 25 years. In addition, there was no consistent relationship between the PEFR on admission and PaO$_2$, Pco$_2$, or the degree of paradox.

Of the 52 patients, nine were slow responders (group A), 24 were included in the intermediate group (group B), and 19 recovered rapidly from their attack of asthma (group C). Attacks were of equal severity in these three groups of responders in that no difference was found between them in PaO$_2$, Pco$_2$, or PEFR on admission. The three groups were also comparable with regard to the maximum PEFR achieved during their stay in hospital. Delayed recovery did not occur merely in those patients who were more severely ill on arrival.

![Fig 1 Admission PEFR and time taken to achieve maximum PEFR for individual patients.](http://thorax.bmj.com/Downloaded from)
therefore, and rapid responders did not recover more quickly simply because their maximum PEFR achieved was significantly less. Other features which did not influence speed of recovery included the sex of the patient, associated respiratory tract infection, the length of time for which a patient had been asthmatic, and pulse rate on admission. There was no difference in the frequency of “morning-dipping” between the three groups.

Table 1 lists the historical features which were significantly related to the subsequent speed of recovery. Slow recovering patients were older than rapid responders and the intermediate group occupied an intermediate position with regard to age. Non-atopic asthmatics manifested delayed recovery more frequently. That this factor acted independently of age in influencing speed of recovery was suggested by the fact that non-atopic asthmatics in the slow responding group were still significantly older (mean age 62 years) than non-atopic individuals.
who were intermediate responders (mean age 47 years, \( p = < 0.05 \)). Similarly, when ages of atopic individuals were compared between the groups, slow responders were significantly older than rapid responders (mean ages 48 years and 23 years respectively, \( p = < 0.0001 \)), and the intermediate group again occupied an intermediate position (mean age 38 years).

Slow responding patients were found to have suffered their acute attack for a longer period before admission to hospital (table 1). In addition, the use of maintenance oral steroids and the presence of poor maintenance control of asthma (defined as regular wheeze throughout the day or more than three admissions to hospital in the preceding 12 months or both) both occurred more frequently in slow responders and a statistically significant trend was found for these features between the three groups. Finally, the degree of paradox on admission differed significantly between the three groups, greater paradox being found in those patients whose recovery was subsequently delayed.

The three groups also behaved differently during the early phase of recovery (table 2). Thus, the increase in PEFR at six hours (expressed both in litres/min and as a percentage of predicted maximum PEFR) was significantly greater in rapid responders. Similarly, a significant trend was found between the groups regarding the number of patients whose \( \text{Pao}_2 \) was more than 80 mmHg after 48 hours treatment.

Total lung capacity, functional residual capacity, and residual volume (RV) measured in 44 patients at five days did not differ significantly between the groups. There was a weak correlation between the fall in RV and the rise in PEFR but in several patients recovery of the former was delayed beyond that of the latter: seven patients had PEFR values of greater than 80% of their predicted normal at five days but were still hyperinflated with RVs of greater than 130% of predicted normal (fig 4). Similarly, the recovery of FEV\(_1\) was often quicker than that of RV (fig 5).

Return of \( \text{Pao}_2 \) to levels of greater than 80 mmHg

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**Table 1  Clinical differences on admission found between patients grouped according to speed of recovery of PEFR**

<table>
<thead>
<tr>
<th>Group A &gt; 7 days</th>
<th>Group B 3-7 days</th>
<th>Group C &lt;3 days</th>
<th>( A ) versus ( B )</th>
<th>( B ) versus ( C )</th>
<th>( A ) versus ( C )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.4 ± 4.6</td>
<td>39.3 ± 3.5</td>
<td>25.7 ± 2.9</td>
<td>( p = 0.008 )</td>
<td></td>
</tr>
<tr>
<td>Age &gt; 40 years</td>
<td>9/9</td>
<td>11/24</td>
<td>3/19</td>
<td>( p = 0.01 )</td>
<td>( p = &lt; 0.0001 )</td>
</tr>
<tr>
<td>Intrinsic asthma</td>
<td>6/9</td>
<td>7/24</td>
<td>1/9</td>
<td>( p = &lt; 0.002 )</td>
<td>( p = &lt; 0.005 )</td>
</tr>
<tr>
<td>Length of attack (days)</td>
<td>9.5 ± 2.4</td>
<td>4.6 ± 1.2</td>
<td>3.2 ± 1.1</td>
<td>( p = &lt; 0.01 )</td>
<td>( p = &lt; 0.001 )</td>
</tr>
<tr>
<td>Maintenance oral steroid</td>
<td>4/9</td>
<td>6/24</td>
<td>2/19</td>
<td>( p = )</td>
<td>( p = &lt; 0.05 )</td>
</tr>
<tr>
<td>Poor maintenance control</td>
<td>4/9</td>
<td>9/24</td>
<td>2/19</td>
<td>( p = )</td>
<td>( p = &lt; 0.05 )</td>
</tr>
<tr>
<td>Paradox on admission (mmHg)</td>
<td>27 ± 5</td>
<td>18 ± 2</td>
<td>15 ± 3</td>
<td>( p = 0.04 )</td>
<td>( p = 0.02 )</td>
</tr>
</tbody>
</table>

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**Table 2  Differences in the early stages of recovery in the three groups of patients**

<table>
<thead>
<tr>
<th>Group A &gt; 7 days</th>
<th>Group B 3-7 days</th>
<th>Group C &lt;3 days</th>
<th>( A ) versus ( B )</th>
<th>( B ) versus ( C )</th>
<th>( A ) versus ( C )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in PEFR at 6 hours (litres/min)</td>
<td>27 ± 8</td>
<td>57 ± 8</td>
<td>106 ± 14</td>
<td>( p = 0.05 )</td>
<td>( p = 0.003 )</td>
</tr>
<tr>
<td>Increase in PEFR at 6 hours (% max pred pefr)</td>
<td>6.2 ± 2.0</td>
<td>13.2 ± 2.1</td>
<td>21.8 ± 3.2</td>
<td>( p = 0.023 )</td>
<td>( p = 0.008 )</td>
</tr>
<tr>
<td>( \text{Pao}_2 ) ≥ 80 mmHg at 48 hours</td>
<td>4/9</td>
<td>13/24</td>
<td>16/19</td>
<td>( p = )</td>
<td>( p = &lt; 0.025 )</td>
</tr>
</tbody>
</table>

\( \chi^2 \)
was delayed beyond five days in 12 of our 52 subjects (23%); four of these were slow-recoverers with regard to PEFR (44%), seven were in the intermediate group (29%), and only one patient was a rapid responder (5%).

Discussion

Both the pulse rate and the degree of pulsus paradoxus are generally believed to reflect the severity of hypoxia in acute exacerbations of asthma. No reliable relationship was observed in our asthmatics, however, nor was the lack of correlation confined to the older patient. Arterial oxygen tension did not correlate with PEFR on admission, and these observations emphasise the need for full clinical assessment in acute asthma together with prompt arterial blood gas analysis.

In keeping with the results of other studies, there was a wide variation in the speed of recovery of our patients but we have observed several factors which are useful in predicting the rate of recovery.
Apart from a slight difference in age, Petheram et al\textsuperscript{18} failed to find clinical differences between fast and slow responders in a study of acute severe asthma. The severity of the attack in their patients, assessed by peak flow rates and arterial blood gas analysis, was comparable with our findings but their definition of quick recovery was different. Patients who had achieved 50\% of their eventual improvement in PEFR within 24 hours were called fast responders and an intermediate group was not included. In contrast, we have looked at the time taken to reach maximum improvement in PEFR. Our inclusion of an intermediate group and the fact that significant trends have been shown between the three groups validates our observation of important differences between rapidly and slowly recovering asthmatics.

The severity of the attack on admission does not necessarily influence the subsequent speed of recovery but recovery delayed beyond one week may be expected in a patient over 40 years with non-atopic asthma who has suffered an acute attack for longer than seven days before arrival in hospital. A similar observation was made by Bellamy and Collins,\textsuperscript{16} whose 11 patients followed through the course of their illness, all of whom had prolonged poor control before the acute attack, would have been allocated to the slow recovering group. Poor long-term asthma control and the use of maintenance steroids also suggest delayed recovery. If PEFR has increased by less than 40 litres/min (or less than 10\% of predicted maximum PEFR) after six hours of vigorous therapy then prolonged recovery is likely, and this also applies to the patient whose Pao\textsubscript{2} is less than 80 mmHg on air 48 hours after admission.

Twelve patients (23\%) were significantly hypoxic five days after admission to hospital but only one of these was a rapid responder. This means that patients who had features on admission which predicted delayed recovery of PEFR were also more likely to suffer persistent hypoxia after their acute attack of asthma. Delayed recovery of Pao\textsubscript{2} has previously been described\textsuperscript{7-9} and indicates continuing ventilation-perfusion ratio inequality in asthmatics when large airway obstruction has often fully recovered. In 1971, Cade et al\textsuperscript{17} investigated the recovery of both small and large airways obstruction in asthmatic subjects after provocation with methacholine. Frequency dependence of compliance was used as an assessment of small airways resistance and total pulmonary resistance was measured as predominantly reflecting changes in the larger airways. The response of the latter to methacholine was of faster onset and of shorter duration than that of small airways. This observation was supported by McFadden and Lyons\textsuperscript{18} who showed that after a spontaneous attack of asthma, small airways were involved to a greater and more prolonged extent than larger ones. In the present study, slower recovery of small airways function is illustrated by the poor correlation between PEFR and RV at five days. Hypoxia and hyperinflation frequently persist when other parameters of severity have returned to normal, and it should be remembered, therefore, that recovery from an acute exacerbation of asthma is not necessarily complete when PEFR and other clinical findings are within normal limits.

The differentiation of rapid and slow responders in the way in which we have described should help in identifying a high-risk group of patients recovering from acute severe asthma. The importance of age as a risk factor in acute asthma is supported by the analysis of asthma deaths in the South Glamorgan area in 1976\textsuperscript{19} when 17 of the total 19 deaths occurred in patients over 45 years of age and no deaths were reported in patients under 35 years. Macdonald et al\textsuperscript{5} retrospectively studied 53 hospital deaths from asthma which occurred in Cardiff between 1963 and 1974 and found that the mean age of patients who died was 46 years for men and 60 years for women. Delayed hospital admission, maintenance use of steroids, and previous admission to hospital in the preceding 12 months were common features in these patients, and this supports our observation that these factors predict delayed recovery from acute severe asthma.

The early modification of treatment regimens in rapid responders, identified by the findings on admission and during the early phase of recovery which we have described, might reduce treatment morbidity in these patients without influencing the eventual speed of recovery. This aspect of the management of acute severe asthma requires further study.

References

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Thorax 1981 36: 835-841
doi: 10.1136/thx.36.11.835

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