PAPERS AND SHORT REPORTS

Respiratory symptoms and bronchial reactivity: identification of a syndrome and its relation to asthma

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Abstract

Two postal questionnaire surveys were carried out among the adult population of Southampton aimed at clarifying the diagnostic criteria for asthma (study 1) and at testing the validity of symptoms so identified as diagnostic of bronchial hyper-reactivity (study 2). The questionnaires asked about respiratory symptoms and included three questions thought likely to disclose increased bronchial reactivity. Laboratory measurements on subsamples of respondents included spirometry and bronchial challenge with increasing doses of histamine till a concentration was reached provoking a fall of more than 20% ($PC_{>20}$) in forced expiratory volume in one second.

In the first study no normal subject (that is, one who did not report shortness of breath or wheezing on the questionnaire) had a $PC_{>20}$ below 0.5 g/l. Of 51 subjects who reported shortness of breath or wheezing, or both, nine had a cluster of abnormalities consisting of one or more symptoms of bronchial irritability, nocturnal dyspnoea, and prolonged morning tightness together with $PC_{>20}$ values of 0.5 g/l or less. These symptoms in conjunction with a low $PC_{>20}$ were termed the bronchial irritability syndrome. In the second study bronchial challenge confirmed the close association of these symptoms with bronchial hyper-reactivity, all other subjects being less reactive to histamine. Only 27% of subjects with symptoms of the bronchial irritability syndrome had been diagnosed as asthmatic by their general practitioners.

The bronchial irritability syndrome is a definable entity for epidemiological study and patient care.

Introduction

Despite the frequency with which asthma is diagnosed clinically there is no generally agreed operational definition of the disease. Clear diagnostic criteria would help the clinician to make diagnoses confidently and choose appropriate treatment.

Several definitions have been proposed based on what is widely held to be the characteristic feature of asthma—namely, reversible airways obstruction. For example, "Asthma is a condition characterised by widespread airway narrowing varying in calibre over short periods of time, either spontaneously or in response to treatment."¹ The American Thoracic Society added the important observation that the bronchi also showed "increased responsiveness."² But these definitions are not operational: they do not state how severe the airway narrowing has to be, nor how much and how rapidly it should change; neither is "increased responsiveness" quantified, and with present knowledge any decisions on these aspects would be arbitrary. It may, however, be unreasonable to attempt to define asthma in terms of reversibility, because patients often have no airways obstruction when they are seen. Furthermore, some patients initially have attacks of reversible "asthma" which later become poorly reversible. This state is often referred to as chronic asthma, a contradiction in terms if asthma is to be defined by reversibility. This dilemma was an important factor in the failure to reach agreement on a definition at an international Ciba symposium in 1971.³

In an attempt to identify essential features of asthma and to avoid preconceptions about a basis for its definition we have adopted an approach based on the following: if it were possible to obtain information about every respiratory symptom and every respiratory measurement in a representative population the finding of clusters of symptoms and abnormal measurements would identify people with features in common—that is, with syndromes. If we assume that an entity worthy of the name "asthma" exists, then a cluster should emerge which would include many of those features currently leading to a diagnosis of asthma. The components of such a cluster might then be considered as criteria for an operational definition of asthma. In this paper we report two epidemiological studies based on this approach; of necessity, a restricted number of symptoms were selected and included some thought commonly to be associated with "asthma." Objective measurements were largely limited to spirometry and bronchial reactivity⁴ in selected subgroups.

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Study 1

SUBJECTS AND METHODS

A self administered questionnaire (21 questions) was devised taking some questions from the Medical Research Council's questionnaire on respiratory symptoms⁵ and adding three new questions about symptoms which we had previously noted to be common in patients with "asthma" and which we suspected might reflect increased bronchial reactivity or responsiveness. These three questions were: (a) When you get up in the morning how does your chest usually feel? [free, tight, very tight?]. If tight or very tight, how long [in minutes or hours] does it usually take to become free? (b) Are you ever woken at night with shortness of breath? (c) Do any of the following [12 environments] affect your chest?—the list included cold air, smoky atmospheres, traffic fumes, and common household chemicals (hair sprays, perfumes, bleach, etc) and there were five possible responses: shortness of breath, wheezing, cough, phlegm, and "other." Other questions asked about chest illnesses and treatments.

A one in 30 systematic sample (2145 subjects) from the 1980 electoral register of the Test parliamentary constituency of Southampton was posted the questionnaire and a reminder sent four weeks later if it was not returned. The results of the completed questionnaire were transferred on to computer punch cards and tabulation carried out on Southampton University's ICL 2970 computer using the statistical package for the social sciences. Four subsamples, each of 50 subjects, were randomly selected from respondents aged below 70 who had either shortness of breath on exertion (group 1), wheezing (group 2), shortness of breath and wheezing (group 3), or neither shortness of breath nor wheezing (group 4). They were invited by letter (with a reminder if required) to attend for spirometry and bronchial challenge and if possible to refrain from taking any treatment for their chests on the day of attendance.

Baseline forced expiratory volume in one second (FEV₁) and forced vital

TABLE 1—Prevalence of common symptoms elicited by questionnaire. Figures are numbers (percentages) of subjects giving positive answers to questions completed

	Study 1	Study 2
Shortness of breath on exertion	446 (30.1)	410 (28.5)
Wheezing	380 (26.9)	372 (25.8)
Morning tightness (any duration)	152 (10.8)	123 (8.5)
Nocturnal dyspnoea	77 (5.8)	76 (5.3)
Sputum for three months each year	195 (11.7)	202 (13.8)
Admitted to current or past asthma	89 (6.1)	105 (7.5)

TABLE 2—Response to atmospheric "irritants" (study 1). Figures are numbers of subjects

	Cold air	Smoke	Traffic fumes	Household chemicals
Cough only	104	245	187	155
Shortness of breath + cough	28	29	39	55
Wheezing + cough	8	8	14	21
Shortness of breath + wheezing + cough	10	24	2	6

TABLE 3—Sample sizes and results in subgroups 1-8

	Study 1 (No sampled 2145; No (%) of respondents 1474 (74.0*))				Study 2 (No sampled 1998; No (%) of respondents 1474 (80.2*))			
	1 (shortness of breath)	2 (wheezing)	3 (shortness of breath + wheezing)	4 (No shortness of breath or wheezing)	5 (bronchial irritability syndrome symptoms)	6 (morning tightness <1 h)	7 (shortness of breath/ wheezing)	8 (No shortness of breath or wheezing)
No invited for tests	50	50	50	50	63	47	63	63
No attended for tests	22	24	26	30	30	19	29	27
Mean (SE) age (years)	48.3 (3.8)	43.0 (3.8)	48.6 (3.0)	43.7 (2.5)	48.0 (2.5)	41.0 (3.6)	44.0 (2.5)	47.0 (2.6)
Mean (SE) FEV ₁ (l)	2.9 (0.2)	3.1 (0.2)	2.3 (0.2)	3.3 (0.1)	2.4 (0.2)	3.1 (0.1)	3.0 (0.2)	3.3 (0.1)
Mean (SE) FEV ₁ (% predicted)	96.0 (4.2)	91.0 (3.8)	80.0 (5.4)	104.0 (2.2)	74.0 (3.8)	82.0 (4.1)	97.0 (3.3)	101.0 (3.3)
No of smokers	5	18	19	8	9	19	14	7
No of ex-smokers	10	12	4	12	7	0	15	7
No with morning tightness	2	3	15	0	16	19	0	0
No with nocturnal dyspnoea	1	2	11	0	24	0	0	0
No with bronchial irritability	2	3	4	0	26	0	0	0
No with asthma at any time	0	3	9	4	20	0	0	0
No given bronchial challenge	18	18	14	25	22	16	27	25

*Percentage calculated after allowing for subjects reported as dead or having left area.

capacity (FVC) were measured with a Vitalograph dry wedge spirometer as the mean of three readings. Histamine aerosol was generated using a portable de Vilbiss Pulmasonic nebuliser model 2511 and histamine acid phosphate in 0.9% wt/vol saline solution in doubling concentrations ranging from 0.03 to 8.0 g/l (of histamine salt). Subjects were excluded if the FEV₁ was less than 1.5 l or less than 50% of their predicted value⁶ or their consent was withheld. The procedure was modified from that of Cockcroft *et al* to reduce the time needed for completion.⁴ After basal measurements the rested, seated subject, wearing a noseclip, inhaled an aerosol of isotonic saline from a mouthpiece with tidal breathing for 30 seconds, and 30 seconds later a single FEV₁ was measured. If the FEV₁ did not fall by more than 20% histamine challenge began with a concentration of 0.03 g/l inhaled for 30 seconds; 30 seconds later FEV₁ was measured, and after a further 30 seconds the next doubling concentration of histamine solution was given. Challenge was stopped when the FEV₁ fell by more than 20% of the value after saline. This concentration of histamine was referred to as the PC_{>20}.

RESULTS

After allowing for subjects reported as dead or having left the area, the overall response rate to the questionnaire was 74.0% (1474 subjects). Completion rates for individual questions varied from 99.4% to 89.4%. The unsuccessful use of a raffle to improve response rate has been reported.⁷ Table I shows the prevalence of common symptoms and a history of "asthma" and table II lists the responses to atmospheric irritants. Cough was the most common response, especially to smoky atmospheres; shortness of breath or wheezing, or both, was much less common and was most often caused by chemicals such as aerosols and perfumes. There was considerable overlap among these responses, which were often induced by more than one, and sometimes several, of these irritants.

The overall response rate for attendance for spirometry and bronchial challenge was 51% (102/200), with no significant differences among the groups in terms of response rate, age, or sex distribution. Table III gives the mean and standard error of age and baseline spirometric results of the subjects attending in the four groups. One way analysis of variance showed a significant difference in mean FEV₁ values (both absolute and percentage predicted) among the four groups ($p < 0.001$); values in group 3 were substantially lower than in the other groups. Before exclusions 20 subjects reported morning tightness, 12 having tightness for less than 30 minutes and eight for one hour or longer. Table III also shows the number of subjects with nocturnal dyspnoea and a history of smoking and asthma in those who attended for spirometry.

Of the 102 subjects who attended for objective measurements, 27 were not tested: three refused, 18 were not challenged because the FEV₁ was less than 1.5 l or less than 50% predicted, one reacted with a greater than 20% fall in FEV₁ after inhaling saline, and five had to discontinue the test because of coughing; hence 75 subjects completed the bronchial challenge test. Figure 1 shows the relation of symptoms and bronchial reactivity in these subjects. No subject in group 4 (neither shortness of breath nor wheezing) had a PC_{>20} below 0.5 g/l. The PC_{>20} showed a wide distribution, extending from 8 g/l or above to 0.125 g/l in groups 1 and 2 and to 0.03 g/l in group 3. Morning tightness of any duration occurred in 14 of the subjects tested in groups 1-3 and was associated with the whole range of PC_{>20} values, but all five subjects with morning tightness lasting longer than one hour had a PC_{>20} of 0.5 g/l or lower. Nocturnal dyspnoea was reported by seven of the subjects tested, who all had a PC_{>20} of 0.5 g/l or lower. When the symptoms

FIG 1—Study 1. Distribution of bronchial reactivity and associated symptoms in groups 1-4. (Group 1, shortness of breath; group 2, wheeze; group 3, shortness of breath + wheeze; group 4, no shortness of breath or wheeze.)

provoked by the wide range of atmospheric irritants were analysed there was little correlation between $PC_{>20}$ and the response of cough or sputum. By contrast, all nine subjects responding with shortness of breath or wheezing, or both, had a $PC_{>20}$ of 0.5 g/l or lower, and these responses were termed "bronchial irritability."

Discussion

Three subgroups with shortness of breath or wheezing, or both, were selected for spirometry and bronchial challenge in order to concentrate the numbers likely to be abnormal. Nine subjects had one or more of the three symptoms of bronchial irritability, nocturnal dyspnoea, and morning tightness for longer than one hour and high levels of bronchial reactivity—that is, a $PC_{>20}$ of 0.5 g/l or less. Defining bronchial irritability as the response of shortness of breath or wheezing, or both, to inhaled irritants requires explanation. Whereas the response of cough to these irritants was very common and occurred in all four groups, it bore no relation to the level of bronchial reactivity. By contrast, the response of shortness of breath or wheezing, or both, to these irritants was reported only by those subjects in whom a high level of bronchial reactivity was found. Because of its unique association with one or more of these three symptoms (bronchial irritability, nocturnal dyspnoea, morning tightness for longer than one hour) we have defined this high level of reactivity—that is, a $PC_{>20}$ of 0.5 g/l histamine or less—as "bronchial hyper-reactivity."

The term bronchial hyper-reactivity has been widely used in the past without having been defined operationally. Several studies have shown that reactivity in "asthmatics" is increased compared with normal subjects but with an overlap among the ranges.¹⁸ No unique range which would characterise asthmatics or any other diagnostic group has been identified. We have defined bronchial hyper-reactivity operationally by its association with characteristic symptoms. Other protocols might have given different results but bronchial reactivity measurements by two other methods have been similar.⁹

The presence of the three symptoms only in subjects with bronchial hyper-reactivity strongly suggested that the grouping constituted a clinical entity. There was insufficient information about respiratory illnesses to draw confident conclusions about the relevance of this entity to the diagnosis of asthma, though five of the

nine subjects with bronchial hyper-reactivity said that they had asthma as compared with only four of the remaining 66. We therefore gave this cluster of one or more of the three symptoms bronchial irritability, nocturnal dyspnoea, and morning tightness for longer than one hour, plus bronchial hyper-reactivity, the name "bronchial irritability syndrome." Hence based on symptoms alone the prevalence of the bronchial irritability syndrome in this adult population was 6.7%.

The second study sought to test the existence of the proposed bronchial irritability syndrome and to gain more information about its relation to the diagnosis of asthma.

Study 2

SUBJECTS AND METHODS

A simplified questionnaire was constructed of 11 questions from study 1 and including questions (a), (b), and (c). Question (c) was simplified as follows: Do any of the following affect your chest: going from a warm room into a cold one; going into a room where people are/were smoking; traffic fumes; chemicals such as hair spray, bleach, perfumes, etc? Subjects replied by putting a tick in boxes labelled: short of breath, wheezing, cough, or "none of the above affect my chest."

A one in 30 systematic sample (1998 subjects) from the 1982 electoral register of the Test constituency was posted the questionnaire and a reminder sent to non-respondents. The data were processed as in study 1. After excluding subjects over 70 four groups totalling 236 subjects were selected: group 5, all 63 subjects who had one or more of the three symptoms identified in study 1 as characterising the bronchial irritability syndrome; group 6, all 47 subjects with morning tightness for less than one hour and not in group 5; group 7, a random sample of 63 subjects with shortness of breath or wheezing, or both, not in group 5 or 6; group 8, a random sample of 63 subjects with neither shortness of breath nor wheezing (normal group).

Invitations to attend for spirometry and histamine bronchial challenge were by letter. Non-respondents received a second letter and then a visit from a trained interviewer.

The general practitioners of subjects in groups 5-8 were invited to complete a simple postal questionnaire asking if their patients had a chronic or recurrent chest illness and, if so, its nature, severity, and treatment.

Spirometry was performed as in study 1. To align with practice for correlation with baseline FEV_1 bronchial reactivity was also expressed as the histamine concentration that produced a 20% fall in FEV_1 —the PC_{20} , determined by linear interpolation of the FEV_1 -log histamine concentration plot—rather than as $PC_{>20}$.⁴ In practice the differences between PC_{20} and $PC_{>20}$ were small and unimportant.

RESULTS

The response rate to the simplified questionnaire was 80.2% (1474 subjects—by chance the same number as in study 1). The prevalences of respiratory symptoms were similar to those in the first study (table I). Seventy four subjects (5.0%) had one or more of the symptoms characterising the bronchial irritability syndrome. After excluding subjects over 70 and five whose general practitioners requested that we did not approach them there were 63 in group 5 and 47 in group 6. The response rate from those invited to attend for spirometry and bronchial challenge was 44.5% (105/236), with no significant difference among the groups. Table III gives details of the four groups.

Of the 30 subjects with symptoms of the bronchial irritability syndrome who attended, 26 had bronchial irritability, five of whom had this alone. Nocturnal dyspnoea occurred in 24 subjects, one of whom had this alone. Morning tightness for longer than one hour occurred in 16 subjects, and none had this alone. Eight subjects had both bronchial irritability and nocturnal dyspnoea and 12 had all three symptoms. There were 15 subjects admitting to current and five to past asthma in the group with symptoms of the bronchial irritability syndrome. No subject reported current or past asthma in the other three groups.

Of all 105 subjects who attended for spirometry and bronchial challenge, one refused to be tested and 14 were excluded because of low FEV_1 values. Mean FEV_1 values (both absolute and percentage predicted) were significantly lower in group 5 ($p < 0.01$). Ninety subjects underwent histamine challenge (table III).

All 22 subjects tested in group 5 had a $PC_{>20}$ of 0.5 g/l or less, while none of the normal subjects (group 8) had a $PC_{>20}$ below 2 g/l. Subjects in groups 6 and 7 had $PC_{>20}$ values ranging upwards from 1 g/l (fig 2). Those tested in the group with morning tightness for less than one hour did not include any

FIG 2—Study 2. Distribution of bronchial reactivity in groups 5-8. (Group 5, symptoms of bronchial irritability syndrome; group 6, morning tightness for less than one hour; group 7, shortness of breath or wheezing, or both; group 8, no shortness of breath or wheezing).

FIG 3—Study 2. Relation between histamine PC_{20} and baseline FEV_1 (% predicted) in subjects with bronchial irritability syndrome (group 5) and subjects with morning tightness for less than one hour (group 6).

of the few subjects who admitted on the questionnaire to morning tightness for between half and one hour. Figure 3 shows the positive correlations between baseline FEV_1 (percentage predicted) and PC_{20} for groups 5 ($r=0.75$; $p<0.01$) and 6 ($r=0.57$; $p<0.05$).

The response rate to the general practitioners' questionnaire (table IV) was 95%. Seventeen subjects confined to group 5 had either been diagnosed as having or were being treated for asthma.

Discussion

The second study sought to test the reproducibility of the proposed bronchial irritability syndrome and to gain more information about its relation to the diagnosis of asthma. The existence of the syndrome was confirmed when bronchial challenge showed that all subjects who had at least one of the symptoms of the syndrome had bronchial hyper-reactivity. Another aim was to study those subjects with morning tightness lasting less than one hour. None of those who were tested had bronchial hyper-reactivity, but no subject with morning tightness lasting between half and one hour presented for testing. We must therefore question whether the clear separation between the ranges of bronchial reactivity of these groups would have been found had all been tested. Furthermore, subjects with severe airflow obstruction were excluded from

bronchial challenge, and we do not know whether the close association of the symptoms of the bronchial irritability syndrome and bronchial hyper-reactivity would have applied to them.

MECHANISM OF SYMPTOMS

The mechanism of the three symptoms of the bronchial irritability syndrome is uncertain. In the presence of bronchial hyper-reactivity many non-specific stimuli, such as dusts and cold air, may induce airflow obstruction.¹⁰ Hence bronchial irritability symptoms are probably associated with bronchoconstriction. Similarly, nocturnal dyspnoea may reflect the bronchoconstrictor response of hyper-reactive airways to events during sleep.¹¹ Morning tightness for longer than one hour is less easily explained; the sensation itself

TABLE IV—General practitioners' assessments of chest illnesses and treatment of subjects in study 2

	Group			
	5 (bronchial irritability syndrome symptoms)	6 (morning tightness <1 h)	7 (shortness of breath/wheezing)	8 (No shortness of breath or wheezing)
No for whom questionnaires sent	63	47	63	63
No with current/past asthma	13/0	0	0/1	0
No with chronic obstructive lung disease:				
(a) Treated with steroids/cromoglycate	4	0	0	0
(b) Not treated with steroids/cromoglycate	1	5	0	1
No with bronchiectasis	2	0	0	0
No with bronchitis	1	1	4	3

appears to be qualitatively indistinguishable to an inquirer from that lasting less than one hour. This shorter duration of tightness usually disappears when the subject coughs up the night's accumulation of sputum and may have its origin in increased loading of breathing.¹² Interestingly, all subjects in group 6 who were given bronchial challenge were smokers, only two of whom did not have chronic bronchitis. By contrast, within the 30 subjects in group 5 who attended for spirometry there was no significant association between chronic bronchitis and morning tightness for longer than one hour, which suggests that prolonged tightness has either a different or an additional mechanism. This is consistent with our clinical observation that tightness in this group tended to recur later in the day when sputum should not have accumulated. Morning tightness lasting more than one hour was not observed in the absence of bronchial irritability or nocturnal dyspnoea, suggesting that in the subjects tested this symptom was of lower discriminating power in identifying bronchial hyper-reactivity. Regardless of mechanisms these three symptoms were so closely associated with bronchial hyper-reactivity that the bronchial irritability syndrome may be regarded as a collection of features that have a common basic abnormality—namely, bronchial hyper-reactivity, as defined.

MECHANISM OF BRONCHIAL HYPER-REACTIVITY

The mechanism of increased bronchial reactivity is obscure; increased vagal activity,¹³ atopy,¹⁴ damage to bronchial epithelium due to inflammation,¹⁵ and reduced initial airway calibre⁴ have been implicated. The positive correlations between baseline FEV_1 and PC_{20} in groups 5 and 6 (fig 3) suggest an association between PC_{20} and the mechanical state of the airways, but whether this is with initial airway calibre, lung elastic recoil, or other factors is unknown. The clear separation between the two groups suggests an additional mechanism in the subjects with the bronchial irritability syndrome. This mechanism must ultimately affect bronchial smooth muscle, and might be as simple as increased resting tone.¹⁶

RELATION OF BRONCHIAL IRRITABILITY SYNDROME TO "ASTHMA"

The relation between clinical asthma and the operationally defined bronchial irritability syndrome is not immediately clear. Seventeen of the 63 subjects in group 5 (27%) had been diagnosed by their general practitioners as currently having asthma, or were being treated as such, while only one subject in group 7 had been diagnosed in the past as having asthma. The self administered questionnaire showed similar results in group 5, current asthma being reported by 31% of subjects. Despite this close association, on this evidence the bronchial irritability syndrome and asthma cannot be considered synonymous; most subjects in group 5 had not been diagnosed as having asthma, and their clinical state remains uncertain. Some had not consulted their doctors and others had not been recognised as having an illness worthy of a specific diagnosis, despite having severely reactive bronchi (bronchial hyper-reactivity) and symptoms. It is important to note that we have defined the term bronchial hyper-reactivity operationally as the range of bronchial reactivity associated with the specific symptoms of the bronchial irritability syndrome. The term bronchial hyper-reactivity as used by others has been less precisely defined and has included higher values of PC₂₀. Hence not surprisingly bronchial hyper-reactivity has been reported both in patients with "asthma" and in non-asthmatic chronic obstructive lung disease.^{7,8}

While a correlation between bronchial irritability and bronchial hyper-reactivity was to be expected, the closeness of this relation was surprising. Probably with larger numbers some overlap between the bronchial irritability syndrome and other groups would emerge, but in comparison with "asthma" the bronchial irritability syndrome is a clear diagnostic category identifiable operationally either by symptoms or by bronchial hyper-reactivity. By contrast, "asthma" denotes an ill defined disorder based largely on clinical judgment. The paradox of the term "chronic asthma," with its implications of both reversibility and irreversibility, disappears if it is thought of as bronchial hyper-reactivity coexisting with irreversible airflow obstruction. No subject in these studies had asymptomatic bronchial hyper-reactivity, but only 50 normal subjects were tested.

RELATION OF BRONCHIAL IRRITABILITY SYNDROME TO OTHER RESPIRATORY DIAGNOSES

In the group with symptoms of the bronchial irritability syndrome (group 5) five subjects had been diagnosed by their general practitioners as having "chronic obstructive lung disease," two as having bronchiectasis, and one as having bronchitis. It is common experience that some patients presenting with "chronic bronchitis and emphysema" respond, at least subjectively, to corticosteroids despite never having had an attack of "asthma."¹⁷ Since completing

this study we have seen several such patients, all of whom had one or more of the symptoms of the bronchial irritability syndrome, which we believe should alert practitioners to the likely benefit from treatment with corticosteroids or cromoglycate, or both.

In conclusion, recognising the bronchial irritability syndrome should help in both research and patient care. It provides an operationally definable entity for clinical research and population studies. It should alert the clinician to the presence of highly reactive bronchi and to the possible benefits of a therapeutic trial of corticosteroids or cromoglycate, or both, regardless of whether the patient presents with "asthma," "chronic bronchitis and emphysema," or other diagnoses. Further studies are needed, however, to clarify the nature of the bronchial irritability syndrome, its clinical course, and the place of treatment in patients with less severe symptoms.

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