



RISK FACTORS FOR NEAR-FATAL ASTHMA — A CASE-CONTROL STUDY IN A WESTERN CAPE TEACHING HOSPITAL

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Background and objectives. To evaluate risk factors for asthma death such as access to health care, over-use of β_2 -agonists or under-use of inhaled corticosteroids in the Western Cape (WC) population, using near-fatal asthma (NFA) as a surrogate marker.

Subjects and methods. Patients with NFA (cases) admitted to a WC teaching hospital were compared with patients with acute asthma in a case-control study using a structured questionnaire, clinical examination, arterial blood gas measurements, chest radiograph and pulmonary function measurements.

Results. Sixteen patients with NFA (cases) and 55 with acute asthma (controls) were prospectively enrolled. Duration of asthma, gender, smoking status and ethnicity were similar. Cases had significantly more previous mechanical ventilation ($P < 0.05$) and a trend towards more previous intensive care unit (ICU) admissions. No significant differences were found in primary health care variables.

Conclusion. Our study demonstrates that patients with NFA constitute a significant number of emergency room (ER) admissions for acute asthma (30%) in our population. Similar to other studies, there was a trend for NFA toward more previous ICU admissions and mechanical ventilation. Relative under-use of β_2 -agonists the day before admission and fewer ER visits during the previous year in the NFA group, suggests an impaired perception of the severity of disease or a more rapid onset of symptoms. Negative factors such as inability to access health care or lack of medication supply were similar in both groups. The challenge remains to identify and manage high-risk patients effectively.

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Rising asthma morbidity and mortality rates are experienced internationally despite increased understanding of the pathogenesis of asthma and the development of new treatment modalities.¹⁻⁴ Over the past 3 years admission rates for patients with severe life-threatening asthma to the Tygerberg Hospital Respiratory Intensive Care Unit have increased substantially (P Bardin — personal communication).

Near-fatal asthma (NFA) is used as a validated surrogate marker for patients at risk of fatal asthma on the assumption that they share similar pathophysiological mechanisms.^{1,5-8} This assumption provides physiological and biochemical data that can provide clues to the pathophysiology of asthma deaths. To reduce the incidence of NFA and asthma deaths it is essential to identify fatality-prone subjects, recognise life-threatening features (e.g. respiratory arrest or coma, or severe dyspnoea with a silent chest) and to understand the pathophysiology (e.g. severe airway obstruction and alteration of the acid-base status). NFA is defined as respiratory arrest caused by acute asthma, or acute asthma with an arterial carbon dioxide tension (PaCO_2) greater than 6 kPa and/or an altered state of consciousness.⁹⁻¹⁴

Several risk and precipitating factors for NFA have been identified in previous studies. They include marked diurnal variations in peak expiratory flow (PEF),¹⁵⁻¹⁸ worsening of asthma over 2 - 7 days before admission,¹⁹ young people,^{20,21} smoking,^{22,23} allergens,²⁴ respiratory infections, atopy²⁵ and chronic use of β_2 -agonists.²⁶⁻³⁴ Other factors may also be important, in particular geographical location, but this has not been assessed in the Western Cape.

Previous studies on risk factors for NFA were mostly done in developed countries. Only one study addressing some of these risks in patients in South Africa has previously been published, by Kallenbach *et al.*³⁴ They identified attack duration and under-treatment as risk factors in the 81 Johannesburg-based patients they studied. In the present study we planned to identify the risk factors for NFA in our Western Cape population. Primary risk factors evaluated were access to health care, relative over-use of β_2 -agonists, under-use of inhaled corticosteroids, previous history of mechanical ventilation and admission to the intensive care unit (ICU) for severe acute asthma. Our results show that up to 30% of admissions meet criteria for NFA. Risk factors for NFA in our population are similar to those identified in other countries.

METHODS

All patients admitted to Tygerberg Hospital with the diagnosis of acute asthma were prospectively identified for 12 months from September 1999 to August 2000. Patients who met our *a priori* case definition for NFA ($\text{PaCO}_2 > 6$ kPa or intubation and ventilation before or during admission) were classified as subjects with NFA. Hospitalised patients with acute severe



asthma were used as the control group. Patients between 18 and 45 years old with a confirmed diagnosis of asthma were eligible and diagnosis was based on criteria used by the American Thoracic Society.³⁵

Clinical and demographic data were obtained through the use of a structured questionnaire during a personal interview. Data obtained included duration of asthma, previous history of NFA, duration of current attack, prescribed therapy and access to health care. Smoking status, occupational history and precipitating factors were also noted, as well as arterial blood gas measurements, chest radiograph reports and electrocardiogram (ECG) results. Peak expiratory flow rates were measured on admission. Skin-prick testing was done employing a panel of common allergens. A reaction of > 3 mm to one or more allergens was defined as a positive result. All patients gave informed consent for a study protocol approved by the University of Stellenbosch-Tygerberg Hospital Ethical Committee.

Analysis of data

Data were analysed using MS Office-based spreadsheets and statistical tools. Subjects were grouped and analysed as NFA cases and controls. Risk factor analyses were based on sample sizes comparable to published studies.^{19,36,37} Descriptive statistics were calculated using pivot (contingency) tables. Means and standard deviations (where appropriate, otherwise ranges) were calculated for continuous variables. Trends were examined using percentages. Where suggested by the data, comparisons between groups were made using the Mann-Whitney U-test (continuous data) and chi-square test (categorical data). Statistical significance was accepted at a level of $P < 0.05$.

RESULTS

Approximately 230 patients between 18 and 45 years old were admitted to the emergency room (ER) with the diagnosis of acute asthma in the 12-month period from 1 September 1999 to 31 August 2000. For logistical reasons (availability of staff, weekends and holidays excluded, etc.) we enrolled 71 patients into our study during this period, 16 as cases of NFA and 55 in the control group with acute severe asthma. There was no clear seasonal pattern observed (Fig. 1). There were 3 deaths in the NFA group. Two deaths were as a result of ICU-related sepsis and 1 death followed a spontaneous pneumothorax. There was no significant difference between the case and control groups with regard to demographic variables, smoking status, employment or duration of asthma (Table I). Cases were more likely than controls to have had a history of previous pulmonary tuberculosis (PTB) according to the patient (not diagnosed on chest radiograph (CXR)) ($P < 0.05$). Cases had significantly more mechanical ventilation compared with

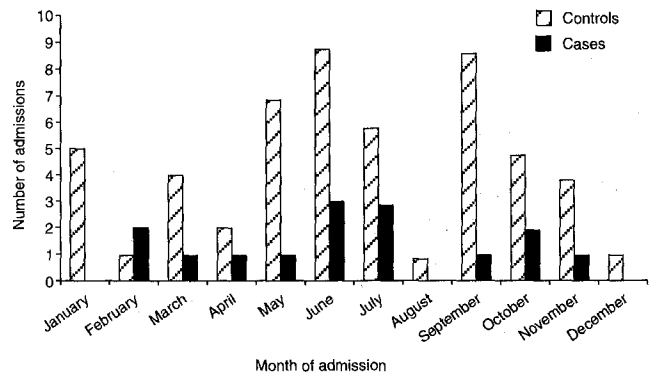


Fig. 1. Month of admission.

Table I. Clinical and demographic characteristics

	Cases (N = 16)	Controls (N = 55)
Age (years)	33.75 ± 7.64	31.67 ± 9.70
Gender (N (%))		
Male	1 (6.25)	12 (21.82)
Female	15 (93.75)	42 (76.36)
Race (N (%))		
White	0	6 (11.11)
Coloured	13 (86.67)	41 (75.93)
Black	2 (13.33)	5 (9.26)
Indian	0	2 (3.70)
Smoking status (N (%))		
Non-smokers	6 (37.5)	22 (40.0)
Ex-smokers	7 (43.75)	27 (49.09)
Current smokers	3 (18.75)	6 (10.91)
Pack-years (SD)	2.3 (3.64)	4.21 (8.07)
Occupational status: employed (N (%))	10 (62.5)	39 (70.90)
Duration of asthma (years)	18.91 ± 14.29	16.13 ± 11.22
Previous PTB (N (%))	4 (26.67)*	3 (5.56)
History of severe asthma (N (%))		
ER visits†	11 (73)	47 (81)
Hospital admissionst	8 (53)	38 (70.4)
ICU admissions	8 (53)	13 (24)
Mechanical ventilation	8 (53)*	10 (18.5)

Data presented as means ± standard deviation (SD) unless stated otherwise.
 * $P < 0.05$.
 † = Previous 12 months.
 PTB = pulmonary tuberculosis; ER = emergency room; ICU = intensive care unit.

controls (53% versus 18.5%, $P = 0.02$). There was a trend for cases towards more prior ICU admissions (53% versus 24%, $P = 0.062$). ER visits (73% versus 81%, $P = 0.38$) and hospital admissions (53% versus 70.4%, $P = 0.35$) did not differ significantly.

Clinical characteristics, CXR findings, arterial blood gas measurements and medication use by the study subjects are presented in Table II. Cases were more likely than controls to



Table II. Admission characteristics (data presented as means ± standard deviation unless stated otherwise)

	Cases (N = 16)	Controls (N = 55)
Heart rate (beats/min)	109.5 ± 26.2	102.1 ± 18.8
Respiratory rate (breaths/min)	26.35 ± 4.4	26.7 ± 4.1
Accessory muscle use (N (%))	10 (62.5)	22 (40)
Altered level of consciousness (N (%))	5 (31.25)*	2 (3)
Chest radiograph (N (%))		
Normal	7 (43.75)	31 (56.36)
Abnormal†	3 (18.75)	3 (5.45)
Arterial blood gases		
pH	7.29 ± 0.15	7.37 ± 0.07
PaCO ₂ (kPa)	7.34 ± 4.19	4.5 ± 0.92
Medication use		
β ₂ -agonists (µg/day)		
Usually	257.14 ± 217.37	312.96 ± 293.99
24 hours before admission	761.53 ± 531.56*	1 315.21 ± 1 881.01
Inhaled corticosteroids (µg/day)		
Prescribed	546.66 ± 551.44	495.83 ± 414.60
Taken past 2 weeks	485.71 ± 598.93	582.60 ± 659.73
Oral corticosteroids (mg/day)	20 ± 18.25	22.25 ± 18.55
Theophyllin (N (%))	9 (56.25)	39 (70.09)

* P < 0.05.

† Abnormalities consistent with fibrosis and other mild structural abnormalities.

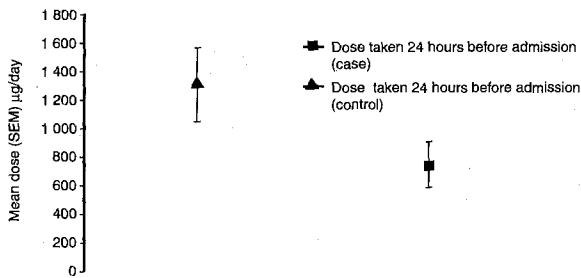


Fig. 2. Mean dose of inhaled β₂-agonist taken 24 hours before admission (P < 0.05).

present with an altered level of consciousness (P = 0.015). The mean daily dose of inhaled β₂-agonist taken in response to exacerbations is shown in Fig. 2. Controls used significantly larger doses of β₂-agonists in the 24 hours before admission (761.53 µg versus 1 315.2 µg, P = 0.027). Peak flow measurements done during admission to the ER did not differ between cases and controls (Table III).

Table III. Peak flow measurements during emergency room admission (means ± standard deviation)

	Cases (N = 10)	Controls (N = 55)
Initial		
% Predicted	33.3 ± 19.8	40.15 ± 127.6
After nebulisation		
% Predicted	54.21 ± 37.0	59.08 ± 92.0

There were no significant differences in primary health care variables between cases and controls (Table IV). In the NFA group, however, 3 of 16 patients (18.75%) waited more than 2 hours before they were seen by a doctor, compared with 4 of 55 (7.27%) in the control group.

Table IV. Primary health care variables

	Cases (N = 16)	Controls (N = 55)
Primary care facility (N (%))		
Tygerberg Hospital	3 (18.75)	9 (16.36)
Day hospital/regional hospital	8 (50.0)	26 (47.27)
Medication (N (%))		
Supply exhausted	12 (75.0)	33 (60.0)
Adequate supply given at facility	4 (25.0)	23 (41.8)
Time before medical attention sought > 24 hours (N (%))	5 (31.25)	7 (12.75)
Transport to medical facility (N (%))		
Self	9 (56.25)	33 (60.0)
Other	7 (43.75)	22 (40.0)
Time before seen by doctor (N (%))		
Immediately	10 (62.5)	36 (65.45)
After > 2 hours	3 (18.75)	4 (7.27)

DISCUSSION

We used a case-control study of hospitalised patients with asthma to identify risk factors for NFA. Our findings confirmed



the results of previous work, suggesting that a history of prior ICU admissions and mechanical ventilation are predictors of life-threatening asthma. Moreover, we identified a relative under-use of β_2 -agonists as well as fewer ER visits in the 12 months before admission in patients with NFA. No difference was noted for access to health care and other primary health care evaluations.

The final pathway leading to death in patients with acute severe asthma has not been clarified. It is clear that several risk factors may be important in this process and that this may vary in different areas and populations. We assessed the importance of risk factors for asthma death using a validated surrogate marker, NFA, in the Western Cape, with a different population to that found in westernised, First-World countries and environments. In general, our observations were similar to those found in studies in Canada and other countries.^{19,38,39} We assessed age, gender, smoking habits, social factors, environmental conditions and use of medication in the control and NFA groups. There were no significant differences, although a number of variations were observed. This included lower doses of inhaled β_2 -agonists in the day before admission in the NFA group.

Several studies have reported an association between the use of inhaled β_2 -agonists and asthma death,^{39,40} especially in the absence of inhaled corticosteroids.⁴¹⁻⁴³ The risk was particularly high in subjects who reported a rapid increase in β_2 -agonist use. In this study the NFA group used less bronchodilator treatment for 24 hours before admission, suggesting that they had either exhausted their supply or required less medication. This in turn implies that their perception of dyspnoea may be impaired, or a more rapid onset of symptoms in this group given the severity of the asthma attack as judged on admission. Good evidence exists to show a reduced ability to perceive life-threatening airway obstruction in some asthmatics, particularly males.⁴⁴⁻⁴⁶ Our observations are similar to those reported by Turner and co-workers,⁹ who found a similar difference. Furthermore, there was a lower rate of ER admissions compared with the prior 12 months in the NFA group, also suggesting an inability to judge the severity of acute asthma in this group.

Because of social instability, poverty and a perceived lack of access to health care, we analysed social and other factors as possible risk factors. Surprisingly, there was no indication that NFA was associated with an inability to access health care or a lack of supply of medication. However, it is likely that such negative factors had an influence across both groups and future studies must assess differences in asthmatics seen in other hospitals, areas and situations. There was also no difference in the use of various treatments, particularly inhaled and oral corticosteroids, risk factors identified in other studies.^{47,48}

The absence of external factors that appear to predispose asthmatics to severe asthma is not entirely surprising. Recent

evidence has suggested that a primary determinant of severity is likely to be related to the asthmatic phenotype itself. Coupled with genetic influences, asthmatics may have an inability to control and repair allergic inflammatory responses that may be independent of outside factors.⁴⁹ In acute asthma there may be an important exception — the cause of the exacerbation — and in this situation, certain viruses may be the trigger for very severe asthma as a result of their inflammatory actions and consequences.

The finding of a history of previous PTB in the NFA group might be important. Although the diagnosis was subjective, this might indicate the detrimental effects of previous structural lung damage.

A potential criticism of any study such as this one is always in the selection of a control group. We selected hospitalised patients with asthma as a control group to isolate variables of interest: risk factors for NFA in severely asthmatic individuals. Because most community asthma patients would never be hospitalised, their inclusion could increase the magnitude of association for NFA risk factors. However, a three-way comparison between groups would enhance the ability to discern the effect of hospitalisation itself as a factor.

In conclusion, our study in the Western Cape, the first in South Africa to evaluate NFA risk factors prospectively, suggests that the NFA group contributes a significant number of ER admissions for acute asthma. NFA was associated with significantly more mechanical ventilation and a trend towards more ICU admissions. Patients with NFA also used significantly less β_2 -agonists before admission. Although guidelines designed to improve asthma management have been published,^{42,50,51} the challenge remains to identify high-risk patients and to implement these recommendations. In order to realise this goal an effective asthma education strategy, aimed at patients and physicians, will be crucial in future.

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WHAT IS WRONG WITH MY PATIENT? HOW TO READ AN ARTICLE CONCERNING DIAGNOSIS

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Two critically important questions arise from the doctor-patient encounter. Firstly, given the patient's profile (demography, signs and symptoms), what is the most likely diagnosis, and secondly given the diagnosis what is the most effective intervention?

Diagnostic reasoning skills are vital for effective patient care. The basis of these skills should be sound diagnostic research on the appropriate signs, symptoms and tests regarding a particular disease. Diagnostic research has undergone significant developments during the last number of years. Some of these principles are common knowledge while others are poorly understood. Given that diagnostic knowledge is vital for patient care it is imperative that the practising physician should be able to appraise articles on diagnostic research critically.

The development of diagnostic research has been a stepwise refinement of concepts (Fig.1).

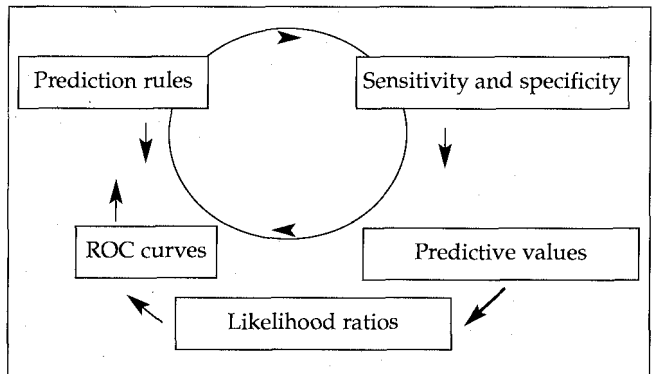


Fig. 1. Progressive steps in diagnostic research.

STEPS IN DIAGNOSTIC RESEARCH

Sensitivity and specificity

	Disease + (D ⁺)	Disease - (D ⁻)
Test + (T ⁺)	a	b
Test - (T ⁻)	c	d

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