

Risk factors for asthma exacerbation in patients presenting to an emergency unit of a national referral hospital in Kampala, Uganda.

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Abstract

Background: Asthma exacerbations are caused by a variety of risk factors. Reducing exposure to these risk factors improves the control of asthma and reduces medication needs. Knowledge of the particular risk factors is essential in formulating controlling and treatment protocols. This study set out to determine the risk factors for asthma exacerbations in patients presenting to the emergency unit of Mulago Hospital.

Methods: An unmatched case-control study involving 43 cases and 43 controls was conducted from November 2011 through February 2012. Asthma patients with exacerbations presenting to Mulago hospital's emergency unit were chosen as cases. The controls were asthma patients recruited from the hospital's outpatient department who had not had an exacerbation in the past 7 days. The study variables were age, sex, level of education, adherence to treatment, exercise, upper respiratory tract infections, household pets, smoking, strong emotions, exposure to in house wood or charcoal burning, weather, use of corticosteroids, beta-blockers and non-steroidal anti-inflammatory drugs. Univariate and multivariate statistical analysis was done using SPSS version 16 to identify independent risk factors for exacerbations.

Results: Lack of corticosteroid use (OR =22.109; 95% Confidence interval 6.952 to 70.315; $p<0.001$) and presence of upper respiratory tract infections (OR 4.516; CI 1.258-16.213; $p=0.018$) were significantly associated with exacerbations.

Conclusion: Lack of corticosteroid use and upper respiratory tract infections are associated with exacerbations in asthma patients presenting to the Emergency unit of Mulago Hospital

Key words: Asthma, asthma exacerbations, risk factors, corticosteroids

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Introduction

Asthma is a worldwide problem with an estimated 300 million people currently affected, 38.9 million from sub-Saharan Africa and a global prevalence ranging from 1% to 18% (1). The global prevalence of asthma is continuing to rise with increases in asthma symptom prevalence in Africa (2).

Asthma exacerbations can be associated with a variety of risk factors. Notably asthma exacerbations are associated with exposure to irritants such as cigarette smoke exposure and diesel exhaust fumes (3, 4), inhaled allergens such as house dust mites (5), drugs known to worsen asthma (6), poor adherence/non-compliance to therapy (5), extremes in weather or temperatures (7),

exercise, respiratory infections (8) and strong emotions (9) to date we are unaware of studies investigating risk factors of asthma exacerbations in Mulago Hospital in particular and Uganda in general. A case control study in Canada found symptomatic colds as the most common trigger of asthma exacerbations in the winter and spring, while a transient increase in dust exposure was also identified as a significant trigger (10). However, this is a different environment compared to Uganda in terms of weather and affluence.

Noncompliance to treatment was found as a strong predictor of exacerbations in adult patients in a South African hospital (11).

A study in a university hospital serving developing communities in the Western Cape province, South Africa found the risk factors for severe life threatening asthma to be rural residence, poverty and lack of use of inhaled corticosteroids (12).

The main risk factors for wheeze in urban children in Ethiopia are environmental tobacco smoke, use of kerosene and a longer duration of breastfeeding (13).

No study looking at reasons for exacerbations in asthma patients has been done in Mulago Hospital. Knowledge of the particular risk factors precipitating asthma exacerbations in our patients is essential in formulating

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controlling and treatment protocols. The objective of this study was to determine the risk factors for asthma exacerbations in patients presenting to Mulago Hospital.

Methods

Design and setting:

This was an unmatched case-control study to investigate the risk factors causing exacerbations in patients with asthma attending the Emergency Unit of Mulago Hospital.

The study was carried out in the Emergency Unit and the Medical Outpatient Department Chest Clinic of Mulago National referral Hospital. The Emergency unit is the portal for all emergencies in the hospital. The medical wing of the emergency unit receives about 80 patients per day. The majority of these are self-referred patients from the surrounding communities. Asthma exacerbations constitute 2.5% of emergency visits in Mulago Hospital. Sixty five percent of all asthma visits in Mulago Hospital are due to exacerbations. More than 90% of these patients are treated as outpatients with some being frequently readmitted and having no clear documentation of the risk factors triggering these exacerbations (14).

The chest clinic is a specialist outpatient clinic that provides care to patients with respiratory diseases. About 800 patients are seen in this clinic annually and 16.9% of them are patients with asthma. The chest clinic operates for one day in a week. The hospital doubles as the teaching hospital for Makerere University College of Health Sciences. (14)

Study eligibility: Patients were included in this study if they were 13 years and older and had asthma. In this study, a patient with asthma was defined as a person with a history of recurrent episodes of wheezing and cough that is often reversible either spontaneously or with treatment and any one of the following: Personal/family history of asthma and a physician/doctor diagnosis of asthma

The cases were asthma patients who had developed an acute asthma exacerbation. An acute asthma exacerbation was defined in this study as having all four of the following:

1. An emergency room visit because of asthma
2. Forced Expiratory Volume in one second (FEV₁) of less than 80% of the predicted value for age, sex and height.

3. Reduced ratio of FEV₁ to Forced Vital Capacity (FEV₁/FVC) of less than 70%.

4. Reversibility demonstrated by an increase in FEV₁ of 12% or 200mls after the administration of a short acting bronchodilator (salbutamol).

The controls were asthma patients who had had no exacerbations requiring emergency visits during the preceding 7 days but with history of wheezing in the past twelve months.

Patients with any history of pulmonary embolism, active pulmonary TB, chronic obstructive pulmonary disease, known congestive heart failure, known mechanical obstruction (e.g. tumor) were excluded. Prior participation in the study constituted an exclusion criterion. A record of the study participants was kept by the principal investigator and research assistants. Any potential participant's particulars were verified to ensure that they had not participated in the study.

Cases and controls were recruited from the emergency unit and the medical outpatient chest clinic respectively.

Study Variables and definitions:

The study variables were age, sex, level of formal education, occupation, non-adherence to asthma medication use of corticosteroids, exercise/sport, upper respiratory tract infections, household pets, smoking (active and passive), stoves (exposure to in house wood or charcoal burning), weather and use of drugs known to worsen asthma.

Non-adherence to asthma medication was measured by the 4-item self-report scale developed by Morisky et al (15). Exercise was considered a risk factor if the participant was involved in any formal or informal sports activities including walking distances of at least 1km. Upper respiratory tract infections (URTI) were seen as a risk factor when at least three of the following five components are marked positive: sore throat, fever, runny/blocked nose, muscle aches and exposure to other people with a cold. The Household pets considered were cats or birds in the house or in the direct work place.

The strong emotions considered were anger, excitement and anxiety. Anger was seen as a risk factor when a participant had any loss of temper during the exposure assessment period. Excitement was seen as a risk factor when a participant was extremely excited or happy about something e.g. sports, finances, or relationships. Anxiety was seen as a risk factor when a participant was anxious for reasons related to death of a relative, work etc.

Weather was considered as a risk factor for all participants who experienced rainy weather conditions during their exposure assessment period.

The drugs known to worsen asthma are any orally ingested, rectally inserted or injected Non-steroidal anti-inflammatory drug and any Any beta blocker-containing medication.

Sample size calculation:

The following formulae by James Schlesselman (1974) were used to calculate the sample size.

$$n = \frac{(1+1/c)pq(Z_{\alpha} + Z_{\beta})^2}{(P_1 - P_0)^2}$$

$$P_1 = \frac{P_0 R}{(1 + cP_0)}$$

$$P = \frac{[1 + P_0(R-1)]}{(1+C)}$$

Where:

C= number of controls per case which is 1

R (Relative Risk) – estimated relative risk (odds ratio) = 2.18 Derived from a South African study of asthma risk factors which found non-adherence to treatment as a risk factor for asthma exacerbation.

P_0 = Expected proportion of controls (asthma patients without exacerbations) = 0.5 (since we do not know the figures for our setting)

Calculated $P_1 = 0.69$

Calculated $p = 0.59$

n = Number of cases i.e. patients with asthma exacerbations

$Z_{\alpha} = 1.96$ for α of 0.05 (where α is the significance)

$Z_{\beta} = 0.84$ for β of 0.2 (where $1-\beta$ is the power)

Substitution of the above values into the formula gives Cases – 38

Assuming 10% non-responders (NR) will increase the number of cases to 43 and the controls to 43 giving a total sample size of 86.

Measurements and data Collection:

Patients with asthma who met the inclusion criteria (both cases and controls) were requested to participate in the study. Their demographic and clinical data were recorded. The procedure and purpose of doing spirometry was explained to the study patients. With the patients seated, spirometry was done using an electronic spirometer (NDD EasyOne, Massachusetts, USA) and the FEV_1 and FEV_1/FVC ratio were measured. Emphasis was made about the essential elements of the test like filling lungs completely, sealing lips around the

spirette so that there are no leaks, taking care not to block its opening with teeth or tongue, blowing out as hard and fast as possible and continuing to blow out until the lungs are completely empty. Three acceptable readings were considered.

For the cases (patients in asthma exacerbation), 5 puffs of salbutamol metered dose inhaler were administered using a spacer. Spirometry was repeated after 15 minutes to demonstrate reversibility (increase in FEV_1 of 12% or 200mls). Patient care was by the attending physicians. In summary patients received parenteral steroid (intravenous hydrocortisone or oral prednisolone), inhalational bronchodilators by either nebulization or frequent administration of bronchodilators by the metered dose inhaler every 15 minutes and oxygen depending on the severity of the exacerbation. Patients were monitored in the emergency room until stable before transfer to the admitting wards. A structured questionnaire was used as a basis for interviewing the participants. Information obtained about the risk factors included adherence to treatment, upper respiratory tract infections, exercise, smoking, in-house charcoal fires, drugs known to worsen asthma (like beta blockers, NSAIDS), use of corticosteroids, strong emotions and exposure to household pets. Exposure to the risk factors was noted for the previous week (7 days) in both cases and controls.

Data management and analysis:

Data was entered into Epidata version 3.1 and exported to SPSS version 16.0 for analysis. Continuous data were summarized into means, while categorical variables were summarized into percentages and proportions. A p-value of less than 0.05 was considered significant. We compared baseline characteristics of the cases and controls using Student's t test for when continuous variable and chi-square test when they were proportions. Risk factors for asthma exacerbations were evaluated by logistic regression in univariate and multivariate analyses. Asthma exacerbation was the dependent variable. Following univariate analysis, factors that had association with p-value less 0.20 were entered into a multivariable logistic regression model to assess for independence of association.

Ethics:

Approval was obtained from the department of Medicine, Mulago Hospital and the Research and Ethics Committee of Makerere University College of Health

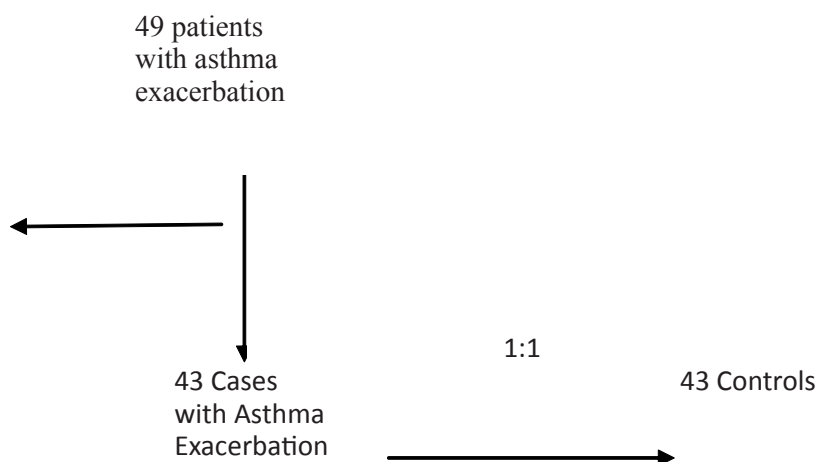
Sciences. Informed consent/assent was obtained from all patients. Confidentiality was ensured throughout the study.

Results

During the study period (November 2011 through February 2012) 49 patients with suspected asthma exacerbation were approached and 43 were recruited.

Figure 1: patient flow diagram

2 could not perform spirometry, 2 had no reversibility on spirometry, 1 had normal spirometry and 1 patient declined to participate



Of the 6 who were excluded, 2 could not perform spirometry, 2 had no reversibility on spirometry after administration of inhaled salbutamol, 1 had normal spirometry and 1 patient declined to participate in the

study. For each of the 43 cases 1 control was selected in the chest clinic. A total of 43 controls were selected. The demographic characteristics of the study patients are shown in Table1.

Table 1: Demographic characteristics of the study population (N=86)

Variables	Cases(n=43) n (%)	Controls(n=43) n (%)	Total(n=86) n (%)
Sex			
Male	15 (34.9)	19 (44.2)	34(39.5)
Female	28 (65.1)	24 (55.8)	52(60.5)
Age			
Mean age	32.9	39.0	36.0
Std deviation	14.3	18.5	16.7
Employment			
Unemployed	7 (16.3)	12 (27.9)	19(22.1)
Self employed	12 (27.9)	9 (20.9)	21(24.4)
Civil servant	2 (4.7)	4 (9.3)	6(7.0)
Peasant	4 (9.3)	5 (11.6)	9(10.5)
Others	18 (41.9)	13 (30.2)	31(36.0)
Education level			
No formal education	1 (2.3)	2 (4.7)	3(3.5)
Primary education	20 (46.5)	15 (34.9)	35(40.7)
O'level	17 (39.5)	17 (39.5)	34(39.5)
A'level	0	3 (7.3)	3(3.5)
Tertiary	5 (11.6)	6 (14.0)	11(12.8)
Marital status			
Single	16 (37.2)	13 (30.2)	29(33.7)
Married	16 (37.2)	21 (48.8)	37(43.0)
Separated	7 (16.3)	5 (11.6)	12(14.0)
Widowed	4 (9.3)	4 (9.3)	8(9.3)

Among the 43 cases the mean age was 32.86 years (standard deviation (SD) 14.3) whereas among the 43 controls selected the mean age was 39 (SD 18.48). The

majority of the study participants were in the 12-39 year age group (cases 67%, controls 51.2%)
The clinical characteristics of the study patients are shown in Table 2.

Table2: Clinical characteristics of the study population

	Cases (N=43) n(%)	Controls (N=43) n(%)
Wheezing after exercise	39(90.7)	38(88.4)
Limitation of physical activity by asthma	37(86)	33(76.7)
Troublesome cough at night	39 (90.7)	36(87.7)
Pre-bronchodilator FEV1		
≥80% (Normal)	0	19 (44.2)
60-79% (Mild Obstruction)	5 (11.6)	11 (25.6)
40-59% (Mod. Obstruction)	14 (32.6)	7 (16.3)
<40% (Severe Obstruction)	24 (55.8)	6 (14.0)
Mean BMI ± SD	22.6 ± 6.0	22.1 ± 4.8
Mean number of attacks in the past 7 days ± SD	5.2 ± 6.1	2.1 ± 2.8
Mean number of nights with troublesome cough in the past 4 weeks ± SD	14.5 ± 10.9	7.5 ± 7.2
Mean Pre-bronchodilator FEV1± SD	38.5 ± 16.2	69.3 ± 23.2

The cases had five attacks of wheezing in the past seven days while the controls reported two attacks. Of the cases, 39 (90.7%) reported troublesome cough at night over the past one month with a mean of 14.51 nights (SD 10.85) with troublesome cough. Thirty six (87.7%) controls reported troublesome cough at night over the past one month with a mean of 7.51(SD 7.23) nights of troublesome cough.

Risk factors for asthma exacerbations

Patients with asthma exacerbations were younger (Mean

age 32.86years SD 14.334) than the controls (Mean age 39.0 years SD 18.480) and the difference was statistically significant ($p= 0.044$). Lack of corticosteroid use in the past 7 day was strongly associated with asthma exacerbations (OR 22.101, CI 6.952-70.315, $P<0.001$). Thirty two of the patients with asthma exacerbation (74.4%) had not used corticosteroids (oral or inhaled) compared to 5 of the controls (11.6%). We also found that presence of upper respiratory tract infections showed a trend towards significance as a risk factor for exacerbations on bivariate analysis (OR 2.1332 CI 0.899-5.052, $P=0.08$) (table 3).

Table 3: Bivariate analysis of the risk factors for asthma exacerbations in the study patients

Variables	Cases(N=43) n(%)	Controls(N=43) n(%)	Odds ratio	CI	P Value
Age (Mean±SD)	32.9±14.3	39.0±18.48			0.044
Education					0.354
No formal education	1(2.3)	2(4.7)			
Primary education	20(46.5)	15 (34.9)	3.286	0.025-424.749	0.632
O'level	17 (39.5)	17 (39.5)	0.894	0.007-116.252	0.964
A'level	0	3 (7.3)	0.000	0.000	0.999
Tertiary	5 (11.6)	6 (14.0)	4.986	0.026-958.217	0.549

URTI	yes	24 (55.8)	16 (37.2)	2.132	0.899-5.053	0.086
	No	19(44.2)	27(62.8)			
Living with pets	Yes	17 (39.5)	15 (34.9)	0.819	0.341-1.967	0.656
	No	26(60.5)	28(65.1)			
Smoking						
<i>Active Smoking</i>	Yes	4 (9.3)	2 (4.7)	0.476	0.082-2.745	0.406
	No	39(90.7)	41(95.3)			
<i>Passive smoking</i>	Yes	17 (39.5)	9(20.9)	0.405	0.156-1.053	0.064
	No	26(60.5)	34(79.1)			
Strong emotions						
<i>Anger</i>	Yes	16 (37.2)	11 (25.6)	0.580	0.231-1.460	0.247
	No	27(62.8)	32(74.4)			
<i>Excitement</i>	Yes	11 (25.6)	4 (9.3)	0.298	0.087-1.027	0.055
	No	32(74.4)	39(90.7)			
<i>Anxiety</i>	Yes	7 (16.3)	5 (11.6)	0.677	0.197-2.326	0.535
	No	36(83.7)	38(88.4)			
In-house wood burning or charcoal stoves	Yes	32 (74.4)	33 (76.7)	0.882	0.329-2.360	0.802
	No	11(25.6)	10(23.3)			

Variables		Cases(N=43)	Controls(N=43)	O d d s ratio	CI	P Value
Rainy Weather	Yes	29 (67.4)	30 (69.8)	0.898	0.361-2.233	0.816
	No	14(32.6)	13(69.8)			
Exercise	Yes	14 (32.6)	10 (23.3)	1.593	0.615-4.130	0.338
	No	29(67.4)	33(76.7)			
NSAIDS	Yes	5 (10.5)	4 (9.3)	1.283	0.320-5.143	0.725
	No	38(88.4)	39(90.7)			
Beta-blockers	Yes	0	2 (4.7)	0.000	0.000	0.999
	No	43(100)	41(95.3)			
Used corticosteroids	Yes	11(25.6)	38 (88.4)	0.019	0.011-0.144	<0.001
	No	32(74.4)	5(11.6)	22.109	6.952-70.315	<0.001
Used inhaled corticosteroids	Yes	4(9.3)	22(51.2)			
	No	39(90.7)	21(48.8)	10.214	3.107-33.579	<0.001
Used oral corticosteroids	Yes	9(20.9)	32(74.4)			
	No	32(79.1)	11(25.6)	10.990	4.025-30.009	<0.001
Adherent to medication	Yes	17(39.5)	19(44.2)	0.826	0.350-1.948	0.662
	No	26(60.5)	24(55.8)			

As can be seen in table 3, sex, level of education, non-adherence to medication, exercise/sport, household pets, smoking, strong emotions, exposure to in house

wood or charcoal burning, rainy weather, non-steroidal anti- inflammatory drugs and beta blockers were not found to be statistically significant risk factors.

At multivariate level analysis the only factors found to be independently associated with asthma exacerbation were

lack of corticosteroid use in the past 7 days ($P<0.001$) and upper respiratory tract infections ($P=0.018$) (table 4)

Table 4: Factors associated with asthma exacerbation at multivariate analysis

Variable	Odds Ratio	CI	P Value
Age	0.755	0.523-1.090	0.710
URTI	4.516	1.258-16.213	0.018
Used Corticosteroids	0.031	0.08-0.118	<0.001

Discussion

This study has established that lack of use of corticosteroids (oral or inhaled) in the past 7 days is associated with asthma exacerbations in Mulago hospital. Inhaled corticosteroids (ICSs) are essential medicines for all but the mildest asthma. Corticosteroids reduce the production of pro-inflammatory cytokines, particularly the Th2 cytokines IL-4, 5 and 13; airway spasmogens like leukotriene LTB4 and LTC4 and thromboxane; and the influx and survival of inflammatory cells specifically eosinophils, lymphocytes, macrophages and mast cells (16, 17). The START trial (18), the largest trial of ICSs to date, which established the role of ICSs in reducing exacerbations and improving lung function showed nearly a 50% reduction in time to first exacerbations in the treatment arm with a significantly reduced (2 vs 0.4%) number of severe/life threatening events compared to placebo.

The reasons for failure to use ICSs were not established in this study but could be due to cost, lack of awareness about ICSs among health care providers or patient ignorance. Watson et al in a study to assess the therapeutic aspects of published international asthma management guidelines in developing countries found that many asthma patients in developing countries are not receiving adequate treatment because the required drugs are not available in their area or are prohibitively expensive (19). Regular use of steroid inhalers was correctly prescribed by only 1.8% surveyed doctors in an Indian study (20). A survey of Nigerian doctors showed that that inhaled corticosteroids were infrequently prescribed (21). A retrospective chart review by Kirenga et al found that only 2.4% of asthma patients received a prescription of

an inhaled corticosteroid from the emergency unit of Mulago Hospital (14). More than half of the controls in this study were on inhaled corticosteroids. This is higher than that found in an earlier study by Kirenga and others where 24.2% of asthma patients in the chest clinic were on inhaled corticosteroids (14).

Upper respiratory tract infections were significant as a risk factor for exacerbations in this study. This is consistent with a study by Nicholson et al which found that URTI/Viral infections are the cause of an exacerbation in about 65% of adults with asthma (22). A study in Nigeria of microbial inciters of asthma exacerbation in urban children identified viral agents (RSV, Parainfluenza and influenza viruses) in 53% of patients and bacterial isolates in only 3.5% (throat swabs). This emphasizes the importance of viral upper respiratory tract infections in asthma exacerbation (23).

Exercise/sport, household pets, smoking, strong emotions, exposure to in house wood or charcoal burning, rainy weather, NSAIDs and beta blockers were not found to be statistically significant risk factors for asthma exacerbation in this study. This is similar to findings by Geiser and colleagues in a South African hospital (11).

A study by Emerman et al found no relationship between asthma relapse and cigarette smoking or pets in the home (24). None of the patients with asthma exacerbation in this study had received a beta blocker in the preceding week. This is likely due to awareness of the adverse effects.

Although not found to be a risk factor, non-adherence to medication was high in both the cases and controls

(60.5% vs. 55.8%). Gamble and others found poor adherence to be as high as 88% in patients with severe asthma (25).

Majority of study participants reported limitation of physical activity by asthma, attacks of wheeze in the past 7 days and troublesome cough at night in the past 4 weeks. This shows that most of the asthma patients studied had poorly controlled asthma.

This study had limitations. It may not be generalized beyond the study population, as it involves patients at a single center. The diagnosis of respiratory tract infections was clinical. This being a case control study, recall bias may be a limitation. Only patients with an obstructive picture on spirometry were included as cases. Age and gender were not controlled for in the analysis.

Conclusion

Lack of corticosteroid use (oral or inhaled) and upper respiratory tract infections are risk factors for exacerbations in asthma patients presenting to the emergency unit of Mulago Hospital. The need to use inhaled corticosteroids as controller therapy for patients with asthma should be emphasized among patients and health care providers

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