Rates of asthma exacerbations and mortality and associated factors in Uganda: a 2-year prospective cohort study

Bruce J Kirenga,[1,2] Corina de Jong,[3,4] Levicatus Mugenyi,[1,5] Winceslaus Katagira,[2] Abdallah Muhofa,[2] Moses R Kamya,[1] H Marike Boezen,[6] Thys van der Molen[3,4]

ABSTRACT

Data on asthma treatment outcomes in Africa are limited. 449 patients with asthma (age 5–93 years) in Uganda were followed up for 2 years to determine rates of exacerbations and mortality and associated factors. During follow-up the median number of exacerbations per patient was 1 (IQR 0–5) and 17 patients died (3.7%, 27.3 deaths per 1000 person years). Considering only the first year of follow-up, 59.6% of the patients experienced at least one exacerbation, 32.4% experienced three or more exacerbations. A multivariable model showed that the likelihood of experiencing at least one exacerbation in the first year of follow-up was lower with better baseline asthma control (higher asthma control test (ACT) score), with OR 0.87 (95% CI: 0.82 to 0.93, P=0.000), and was higher with more exacerbations in the year prior to enrolment (OR for log number of exacerbations 1.28, 95% CI: 1.04 to 1.57, P=0.018). Better asthma control (OR 0.93, 95% CI: 0.88 to 0.99, P=0.021) and number of baseline exacerbations (OR 1.35,95% CI: 1.11 to 1.66, P=0.005) were also the only factors that were independently associated with experiencing three or more exacerbations during the first year of follow-up. The only factor found to be associated with all-cause mortality was FEV_1, with higher recent FEV_1 associated with lower all-cause mortality (OR 0.30, 95% CI: 0.14 to 0.65; P=0.002). Rates of asthma exacerbations and mortality are high in Uganda and are associated with poor asthma control. Health systems should be strengthened to care for asthma patients.

BACKGROUND

Asthma exacerbations and mortality are the worst asthma treatment outcomes.[1] Asthma exacerbations are responsible for most asthma morbidity, healthcare utilisation, poor quality of life and precede most asthma deaths.[2] Some patients experience frequent asthma exacerbations (defined usually as experiencing at least three exacerbations in a year). These patients have been described as having an exacerbation-prone asthma phenotype in some literature[3] and are at the greatest risk of adverse asthma outcomes, including death. The risk factors for exacerbations include low use of inhaled corticosteroids, allergic rhinitis, seasonal changes, gastro-oesophageal disease, psychosocial factors, recurrent chest infections, aspirin intolerance, cigarette smoking, non-adherence to medications, obesity and higher number of exacerbations in the past year.[3]

Globally, asthma mortality is estimated at 0.19/100 000 population.[4] According to a recent analysis of asthma mortality in 46 countries, asthma mortality rates were observed to be decreasing in the 1990s through the 2000s but have recently stagnated.[4] Asthma mortality rate was 0·44 deaths per 100 000 people in 1993 and reduced to 0·19 deaths per 100 000 people in 2006 but no significant change was observed between 2006 and 2012.[4]There are significant disparities in asthma mortality between countries, with low and middle income countries having the highest number of asthma deaths. Risk factors for asthma mortality include older age, gender, African race, low use of inhaled corticosteroids (ICS), inappropriate use of long-acting β agonists (LABAs), fixed airway obstruction (lack of reversibility), previous exacerbation, low FEV_1 and psychological and psychosocial factors.[5]

Data on asthma exacerbations and mortality and their predictors in Africa are severely limited. We therefore set up this prospective cohort study called the Uganda Registry for Asthma and Chronic Obstructive Pulmonary Disease (URAC) to document the rates of asthma exacerbations and mortality, and their predictors in Uganda.

METHODS

URAC is conducted in the chest clinics of six tertiary hospitals in Uganda, namely Mulago Hospital, Mbarara Hospital, Mbale Hospital, Hoima Hospital, Arua Hospital and Gulu Hospital. For the current analysis, only patients enrolled at Mulago Hospital are included. The Mulago Hospital Research and Ethics Committee and the Uganda National Council for Science and Technology approved this study. All patients with asthma who were 5 years and older for whom consent was provided were enrolled and followed up every 6 months for 2 years. Using a standardised clinical record form (CRF), data on patients' socio-demographics, clinical and lung function were collected. Asthma control was measured at each visit using the Asthma Control Test (ACT). All patients underwent spirometry according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines using a Pneumotrac spirometer with Spirotrac V software (Vitalograph Ltd, Buckingham, UK). Predicted parameters were based on NHANES III models for African Americans. Asthma medication prescriptions were based on GINA guidelines.

Median number of exacerbations per patient over the entire 2-year follow-up period was

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[1]Makerere University Lung Institute, Makerere University College of Health Sciences, Kampala, Uganda
[2]Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda
[3]GRIAC-Primary Care, Department of General Practice and Elderly Care, University of Groningen, University Medical Center Groningen (UMCG), Groningen, The Netherlands
[4]Groningen Research Institute for Asthma and COPD (GRIAC), University of Groningen, University Medical Center Groningen (UMCG), Groningen, The Netherlands
[5]Center for Statistics, Interuniversity Institute for Biostatistics, and Statistical Bioinformatics, Hasselt University (UHasselt), Groningen, The Netherlands
[6]Department of Epidemiology, University of Groningen, Groningen, The Netherlands

Correspondence to
Dr Bruce J Kirenga, Makerere University Lung Institute, Mulago Hospital, Kampala 7072, Uganda;
brucekirenga@yahoo.co.uk

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calculated. The proportions of patients experiencing at least one exacerbation and at least three exacerbations during the first year of follow-up were calculated. First data on exacerbations were considered to avoid recall bias and because of the high attrition rate (32.5%) and the fact that less than 50% of the cohort could be followed up by this time. Exacerbations were defined according to the ATS/ERS definitions. Death was by postmortem reports and verbal autopsy, and all-cause mortality was considered. Incidence of death was calculated as the number of deaths during the total follow-up period divided by the total follow-up time in years. Factors associated with all-cause mortality were analysed using the Cox proportional hazards model with age at death used as the survival time variable while factors associated with exacerbations (at least one and at least three exacerbations per year were determined using logistic regression.

RESULTS

From 13 August 2013 to 24 April 2016, 449 patients with asthma (28.3% male, median age 33 years (IQR 20–48)) were enrolled into the URAC Registry at Mulago Hospital. Patients' socio-demographic characteristics are presented in table 1. At baseline, 32.2% of the patients had controlled asthma and 33.0% had evidence of airflow obstruction on spirometry (ie, had FEV_1/FVC ratio <0.70). Smoking was reported by 12% of the patients, HIV by 6%, history of tuberculosis treatment by 6.2%, nasal congestion by 88.2% and heartburn by 60.6%. A total of 147 (32.7%) patients were on either ICS alone or ICS/LABA at baseline.

Exacerbations

The proportion of patients who experienced at least one exacerbation during the first year was 59.6% (268) while 32.4% (133) experienced at least three exacerbations in the first year. At the bivariate level, experiencing at least one exacerbation in the first year was associated with respiratory rate (OR 2.58, 95% CI: 1.01 to 6.57, P=0.047), having used ICS prior to the clinic visit (OR 2.93, 95% CI:1.56 to 5.48, P=0.001), number of baseline exacerbations (OR 1.47, 95% CI: 1.21 to 1.79, P≤0.001), asthma control test (ACT) scores (OR 0.89, 95% CI: 0.85 to 0.94, P≤0.001) and FEV_1(OR 0.56, 95% CI: 0.35 to 0.89, P=0.014); while experiencing three or more exacerbations was associated with age (OR 1.71, 95% CI: 1.17 to 2.50, P=0.006), number of baseline exacerbations (OR 1.48, 95% CI: 1.22 to 1.79, P<0.001), having used ICS prior to the clinic visit (OR 1.96, 95% CI: 1.14 to 3.35, P=0.014), respiratory rate (OR 2.14, 95% CI: 1.04 to 4.40, P=0.039), ACT scores (OR 0.84, 95% CI: 0.79–0.89, P<0.001), FEV_1(OR 0.64, 95% CI: 0.41 to 0.99, P=0.044), FEV_1/FVC ratio (OR 0.11, 95% CI: 0.03 to 0.46, P=0.011) and exposure to biomass smoke exposure (OR 0.54, 95% CI: 0.30 to 0.99, P=0.048).

At multivariate analysis the only factors independently associated with experiencing at least one exacerbation in the first year of follow-up were ACT score (OR 0.87, 95% CI: 0.82 to 0.93, P=0.000) and number of baseline exacerbations (OR 1.28, 95% CI: 1.04 to 1.57, P=0.018). ACT score (OR 0.93, 95% CI: 0.88 to 0.99, P=0.021) and number of baseline exacerbations (OR 1.35, 95% CI: 1.11 to 1.66, P=0.005) were also the only factors independently associated with experiencing three or more exacerbations during the first year of follow-up.

Table 1 Baseline patients' characteristics

Characteristic	Number	Percentage
Male gender	127	28.3
Age groups		
<15	54	12.0
15–24	87	19.4
25–34	91	20.3
35–44	83	18.5
45–54	60	13.4
55–64	38	8.5
65+	36	8.0
Respiratory symptoms		
Cough	379	84.4
Sputum	214	47.7
Wheezing	434	96.7
Shortness of breath	436	97.0
Lung function abnormalities		
FEV_1/FVC ratio<0.70	148	33.0
FEV_1≥80% predicted	211	47.0
FEV_1%, 50–79% predicted	163	36.3
FEV_1%, 30–49% predicted	58	12.9
FEV_1%, <30% predicted	17	3.8
Asthma control		
Uncontrolled, ACT<15	126	28.1
Partially controlled, 15≤ACT≤19	174	38.8
Controlled, ACT>19	149	33.2
Medications		
Salbutamol inhaler	318	70.8
Inhaled corticosteroids	83	18.5
Combination inhalers (steroid, LABA)	64	14.3
Leukotriene modifiers	66	14.7
Risk factors and comorbid conditions		
History of smoking	54	12.0
Exposure to bio-mass*	390	86.9
Ever been treated for TB	28	6.2
HIV positive	27	6.0
Nasal congestion or rhinorrhea	396	88.2
Heart burn/acid irritation	272	60.6

*Including use of wood, charcoal and kerosene for cooking or lighting.
ACT, Asthma Control Test; LABA, long-acting β agonist; TB, tuberculosis.

Mortality

Overall 17 patients died (3.7%), 11 (64.7%) from circumstances judged to be asthma related (online supplementary table 2). The incidence of all-cause mortality was 27.3 per 1000-person years, male vs female, 34.2 vs 24.6, incidence death rate ratio 1.39 (0.42–4.09) and increased with age (online supplementary table 1). At bivariate analysis, all-cause mortality was associated with FEV_1 and FVC (adjusted hazard ratio 0.30, 0.14–0.65, P=0.002; and 0.28, 0.12–0.68, P=0.005) respectively while history of tuberculosis treatment (adjusted HR 3.10, 1.00–9.65, P=0.051) and use of herbs (adjusted HR 3.86, 0.99–15.04, P=0.052) were associated with higher mortality but only as a trend (table 2). At multivariate analysis only FEV_1 remained independently associated with

Table 2 Factors associated with exacerbations and all-cause mortality at multivariate analysis

Factor	OR (95% CI)	P values
At least one exacerbation/year		
ACT score	0.87 (0.82 to 0.93)	0.000
Number of baseline exacerbations*	1.28 (1.04 to 1.57)	0.018
At least three exacerbations/year		
ACT score	0.93 (0.88 to 0.99)	0.021
Number of baseline exacerbations*	1.35 (1.11 to 1.66)	0.005
All-cause mortality		
Recent FEV_1*	0.30 (0.14 to 0.65)	0.002

*Log transformed because of skewness, interpretation should be done at the log scale. Note: analysis considers only the first year of follow-up.
ACT, Asthma Control Test.

all-cause mortality (HR 0.30, 95% CI: 0.14 to 0.65, P=0.002).

DISCUSSION

Our study has shown that 59.6% of patients with asthma experience at least one exacerbation in a year, 32.4% experience at least three exacerbations in a year, and the all-cause mortality rate is 3.7% (27.3 per 1000 person years). Exacerbations were less likely with better baseline asthma control and more likely with higher number of baseline exacerbations. Mortality was lower with higher recent FEV_1.

The rates of exacerbations and mortality observed in this study are much higher than the rates observed in developed settings and higher than the 1% asthma mortality rate for Uganda reported in the Global Burden of Disease report.[4–8] For example, De Marco *et al* reported a mortality incidence rate of only 1.1/1000 person years in a cohort of Italian young adults (20–44 years) followed up for 7 years.[7] Although the 27.3/1000 person years found in our cohort could be because we reported all-cause mortality while the De Marco study reported asthma-specific mortality, the 27-fold higher mortality rate we observed in this study indicates that asthma mortality rates in Uganda are very high. The associations between exacerbations and mortality with asthma control, number of baseline exacerbations and FEV_1 have been previously reported.[5 7] Both the ACT and FEV_1 are measures of asthma control; ACT uses symptoms, medication use and work impairment to assess asthma control, while FEV_1 is an objective measure of the severity of airflow obstruction, a component of asthma control. Therefore, the grim asthma treatment outcomes in this study are most likely a reflection of uncontrolled asthma due to limited access to asthma treatment in our setting. The higher rates may also be race related, since the African race has been found to be associated with more severe asthma.[9] The lack of use of recommended asthma medications, particularly ICS in this cohort, calls for efforts to increase availability and affordability of asthma medication. Increased access to medicines has been reported to result in better asthma treatment outcomes in some settings, such as the case of Brazil where hospitalisations were significantly reduced with increased access to medications.[10] In conclusion, the rates of asthma exacerbations and mortality observed in this study are very high and require strengthening of the health systems to improve asthma care in Uganda.

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Contributors BJK conceived the idea of the project and wrote the initial proposal. TvdM, MRK and HMB critically advised the writing of the proposal. CdJ and LM supported data analysis. WK and AM performed patients' clinical reviews. All authors critically reviewed and contributed to manuscript writing.

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