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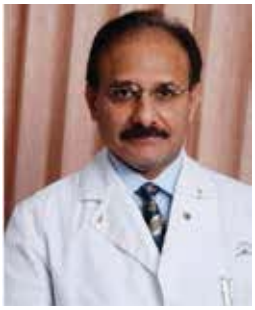

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Chairman's Message

Dear Colleagues,
It is with a great sense of pride and pleasure that I present to you the 3rd issue of our Journal of Kenya Association of Physicians, fondly named as JOKAP! It is once again a remarkable milestone for our Association on our road to establish JOKAP as a peer-reviewed, respected scientific medical journal in the fraternity of other national and international medical journals, published regularly and on time!

You will recall that we launched the first issue at our last Annual Scientific Conference and AGM in March 2018 at Pride Inn Paradise Beach Resort in Mombasa. At that time we had the intention and ambition to publish a new issue every 3 months. But, unfortunately, due to various constraints we have not been able to achieve our goal. However, once again with hard work from our Chief Editor Professor Omondi Oyoo and our Publisher Mr. David Ngethe, we produced the second issue to coincide with the 3rd Annual ECSACOP Conference which we were proudly hosting in Mombasa in September 2018. And it was our Chief Editor who presented the first copy of our second issue of JOKAP to the President of ECSACOP, Professor Evarist Njelesani, at a special ceremony during the ECSACOP Conference.

I sincerely hope that you will find this third issue of JOKAP both informative and interesting. My fond hope is that JOKAP should not only remain an organ of Kenya Association of Physicians but should also become the umbrella journal of all the well-established, and also not so well-established, sub-specialities of general medicine in Kenya, at least until such time when each sub-specialty is able to establish its own sub-specialty journal. Thus we should aspire for more review papers on selected subjects to encompass the depth and breadth of general medicine. And towards that end, I feel, we should invite the heads of various sub-specialties to contribute review articles on topics of interest in their own specialty. For I feel that one of the aims of JOKAP should be to keep informed and updated the growing number of physician sub-specialists in Kenya about developments in other sub-specialities of general medicine, so that our physicians are well-read and well-informed all-round physicians!

If you have any suggestions on how we can make JOKAP more relevant and more interesting then please do write to our Chief Editor or myself. Also, if you have any comments or queries on any article in JOKAP then please do write to us and it will be published under "Letters to the Editor" column.

JOKAP is your Journal! Please read it and comment on it! And, please, please, contribute articles, letters to the editor, whatever, to keep our Journal alive! We have started this Journal after talking about it for many years, with a lot of hopes and aspirations, and many of us have put in a lot of work into it. If this Journal dies then it will be very difficult to revive or replace it. I am sure you will not let this Journal down!

In the meantime I wish you happy reading of JOKAP, as we look forward to the fourth issue, hopefully, by September 2019!

Dr. Yusuf Karim, MBBS (London); FRCP (London); FCP (ECSA)
National Chairman, Kenya Association of Physicians

Pneumonia: Is it Still an Opportunity to Die

Sir William Osler called pneumonia "the captain of the men of death" because in his era having a pneumonia in Canada was so fatal to a point that to die of pneumonia was almost a natural end for the aged thus Sir William Oslerand his colleagues considered suffering a pneumonia as *"an opportunity to die!"*(1).

The basics of pneumonia have largely remained the same right from the definition that pneumonia is an inflammation of the lung parenchyma from an infectious cause viz: bacterial, fungal, viral or parasitic. The stages of a pneumonia viz: consolidation, red hepatization, gray hepatization and finally resolution are still the same. There has been an increase in the use of the term pneumonitis to differentiate lung inflammation from non- infectious causes such as autoimmunity, hypersensitivity etc. (2).

Traditionally bacteria were the most common causes of pneumonia accounting for over 60% of the primary infectious agent. They were classically been categorized into two divisions on the basis of aetiology, "typical" and "atypical" organisms. Typical organisms can be cultured on standard media or seen on Gram stain, but "atypical" organisms do not have such properties (3).

(i) Typical pneumonia refers to pneumonia caused by *Streptococcus pneumoniae*, *haemophilus influenzae, S. aureus,* Group A *streptococci, Moraxella catarrhalis, anaerobes* and aerobic gram-negative bacteria.
(ii) Atypical pneumonia is mostly caused by *Legionella spp, Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *C. psittaci.*

Recent studies show that viral causes such as human rhinovirus and influenza have overtaken *strep pneumonia* as causal organisms for severe community acquired pneumonia (4,5). This is further worsened by emergency of new infections especially novel viruses such as Middle East Respiratory Corona virus that have resulted in pandemic rapidly progressing pneumonias with high mortality, luckily such agents have not affected our region (6,7). Perhaps the most frightening is the emergency of pan-resistant (resistant to all antibiotic classes), extensive resistant (resistant to most antibiotic classes except 1 or 2) and multidrug resistance (resistant to 2 – 3 antibiotic classes) bacteria that have rendered previous active drugs useless in the treatment of pneumonia (8-10). Many theories have been advanced to explain the emergency and spread of these drug resistant strains with the most plausible being antibiotic misuse in both human and veterinary medicine sectors. This is actually the basis of the new classification of pneumonias in the various international guidelines (11-15) into:

(i) *CAP (Community Acquired Pneumonia):* The acute infection of lung tissue in a patient who has acquired it from the community which is likely to be caused by drug sensitive strains.
(ii) *HAP (Hospital Acquired Pneumonia):* The acute infection of lung tissue that develops 48 hours or longer after the hospitalization of a non-intubated patient.
(iii) *VAP (Ventilator Acquired Pneumonia):* A type of nosocomial infection of lung tissue that usually develops 48 hours or longer after intubation for mechanical ventilation. This pneumonia has a high propensity for drug resistant causal agents.
(iv) *HCAP (Health Care Associated Pneumonia):* The acute infection of lung tissue acquired from healthcare facilities such as nursing homes, dialysis centers, and outpatient clinics or a patient with hospitalization within the past 3 months (previously included in HAP but becomes a separate category after some cases presenting as outpatients with pneumonia have been found to be infected with multidrug-resistant (MDR) pathogens previously associated with HAP).

The most notorious are the gram negative bacteria christened the 'ESCAPE' bugs which is a mnemonic for; *Enterococcus, Staph aureus, Clostridium difficile/Candida, Acinetobacter, Pseudomonas, Enterobacteriaceae.* This has lead to the need for tests that have a quick turnaround time and carry resistance information in diagnosis of the pneumonia causal agent such as urinary streptococcal antigen test, rapid influenza serology, polymerase chain reaction based platforms etc. (16). Since new antibiotics are hard to come by the solution has been to use the remaining in new prudent ways to change dosing regimens to achieve favorable pharmacokinetics and pharmacodynamics that ensure killing of these bacteria (17-20). Also the re-entrry of old drugs previously deem very toxic such as colistin have made a notable comeback.

Severe pneumonia still has very high mortality rate ranging between 12% to 40% in ICU patients and this rises to 55% for ventilated patients aged >65 years. Current pneumonia is the leading infectious cause of death in USA and the 6th cause of death generally (11). We also know that delay to administer appropriate treatment timely increases mortality by 7.6% for each hour delayed (21). Pre- existing cormobid conditions also impact the mortality and morbidity of pneumonia, for example diabetic patients after a pneumonia bout have a higher mortality than the general population (22). The high mortality and difficulty in diagnosis making has been compounded by the HIV pandemic

(23). It is also known that HIV positive patients are more likely to suffer complications such as sepsis, multi-organ failure, coagulopathy, metastatic infections, lung abscess, and complicated pleural effusion more than HIV negative patients.

While it is note worthy that massive vaccination has reduced the incidence of pneumonia in vulnerable populations the mortality rates have largely remained stable for the last 20 years (24). In an effort to standardize the treatment of pneumonia numerous guidelines have been written from international, regional, national and even hospital based ones (11-15). These have been credited with a trend towards reducing mortality. They guide on how to make the pneumonia diagnosis, tests to carryout and empiric treatment to consider. These will need regular refreshing to keep up with the changing terrain of antibiotic resistance.

In summary the management of pneumonia is multidisciplinary (25). Besides the administration of antibiotics, these patients often require chest physical therapy, a dietary consult, physical therapy to help regain muscle mass and a dental consult. The key is to educate the patient on discontinuation of smoking and abstaining from alcohol. Further, patients should be encouraged to get the appropriate influenza and pneumococcal vaccines. It is important to educate the patient on compliance with antibiotics and need to complete the full dose of prescribed drugs to forestall the emergency of resistant strains. Ultimately it is following guidelines combined with early aggressive treatment using efficacious drugs will lead to a lower mortality otherwise a bout of pneumonia will continue being an opportunity to die for your patient!

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Original paper

Burden of Respiratory Disease Symptoms and Prevalence of Spirometric Pulmonary Function Abnormalities in Patients with Type 2 Diabetes Mellitus at the Kenyatta National Hospital

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Abstract

Background: World Health Organization's statistics estimates that more than 180 million people worldwide have diabetes; by 2030 it is expected that this number will have doubled. Non-communicable diseases such as cardiovascular diseases, diabetes, cancers, obesity and respiratory diseases, account for about 60% of the 56.5 million deaths each year and almost half of the global burden of disease. The prevalence of DM in Kenya is reported at 2.7% (rural) and 10.7 % (urban), with over 3.3% of the population affected and an additional 7% of Kenyans undiagnosed.

Patients with Type 2 diabetes tend to have 3% to 10% lower lung volumes than controls. Pulmonary function testing non-invasively quantifies physiological reserves in diabetes. Sub-clinical loss of pulmonary reserves becomes overtly debilitating under conditions of stress, such as aging, chronic hypoxia due to lung disease or high-altitude exposure, or volume overload secondary to cardiac and renal failure.

Inhaled insulin may affect long-term pulmonary function, while preexisting pulmonary dysfunction may alter the absorption and bio-availability of inhaled insulin.

Objectives: The study evaluated the burden of respiratory symptoms in patients with Type 2 DM and determined the prevalence of spirometric pulmonary function abnormalities in patients with Type 2 DM.

Design: This was a descriptive cross-sectional study.

Methods: The study was done at the KNH Outpatient Diabetic Clinic between January and March 2018. The study population was ambulatory Type 2 DM on routine follow–up at KNH Diabetic Clinic. A total of 417 patients were evaluated and simple random sampling was used. Respiratory symptoms obtained by an interviewer administered ATS-DLD 78 questionnaire. Spirometry was done on eligible participants, according to ERS guidelines.

Results: Four hundred and seventeen diabetics were interviewed. Females were 270 (64.8%) and males were 147 (35.2%). Mean age was 56.4 years (SD=12.2 years) and ranged from 18 to 90 years: mean age was 55.6 years (SD=12.3 years) in females and 57.8 years (SD=12.0 years) in males. Ninety-five point two per cent (397/417) of the respondents had spirometric abnormalities. Ninety-five per cent (377/397) had restrictive spirometric abnormality, 4.3% (17/397) had obstructive spirometric abnormality and 0.7% (3/397) had mixed spirometric abnormality. Twenty-five point nine per cent (108/417) of the respondents reported to have experienced respiratory symptoms. Sixty-nine point five per cent (75/108) reported cough, 12.0% (13/108) reported wheezing whereas breathlessness was reported by 18.5% (20/108).

Conclusion: A high prevalence of respiratory symptoms and restrictive spirometric abnormalities was found in individuals with Type 2 diabetes, thus suggesting that diabetes may contribute to the respiratory symptoms seen in patients with Type 2 DM.

Key words: Diabetes mellitus, Kenyatta National Hospital, American Thoracic Society Division of Lung Disease questionnaire, European Respiratory Society, forced expiratory volume in 1 second, Forced vital capacity

Introduction

There is an increasing burden of NCDs mostly being born by developing countries Kenya included, it is predicted that, by 2020, NCDs will account for about 70% of the global burden of disease, causing seven out of every 10 deaths in developing countries (1).

The WHO estimates that more than 180 million people worldwide have diabetes, and by 2030 it is expected that this number will have doubled (2). Kenya has recently seen a remarkable rise in DM with over 3.3% of the population affected and an additional 7% of undiagnosed (2,3).

Diabetes is a micro-macrovascular disorder with debilitating effects on many organs. Pulmonary complications of DM have been poorly characterized with conflicting results. Because of its large reserve, substantial loss of the microvascular bed can be tolerated without developing dyspnea(4).

Davis *et al* (5) suggested that the lung is a target organ in DM and that glycemic exposure is a strong determinant of reduced pulmonary function in Type 2 patients. Respiratory function in diabetics have been investigated in several countries, while in Kenya there are no studies regarding these abnormalities.

Diminished elastic recoil, declining lung volume, and decreased respiratory muscle function due to polyneuropathy, chronic inflammation, decrease in pulmonary diffusion capacity for carbon monoxide, autonomic neuropathy are some of the important changes occurring in patients with diabetes mellitus (4).

Materials and methods

This study was a descriptive cross-sectional study carried out at the Kenyatta National Hospital Diabetic Clinic; one of the National referral hospitals situated in the Capital City of Kenya, Nairobi. It serves as the teaching hospital for University of Nairobi Medical School. There are about 5000 Type 2 DM patients on follow up at the KNH-Diabetic Clinic. The clinic runs every day from 8am to 2pm with the main clinic running every Friday. The study population included ambulatory Type 2 DM patients presenting at the KNH-Diabetic Clinic for routine follow-up with a documented diagnosis of Type 2 DM. Simple random sampling procedure was used to select patients into the study.

A written informed consent and demographic data were collected using a study proforma, and respiratory symptoms obtained by an interviewer administered ATS-DLD 78 questionnaire. Spirometry was done on eligible participants, according to European Respiratory Society guidelines. A total of 417 spirometries were done. The primary spirometry measurements used for analysis was Forced Expiratory Volume in one second (FEV1), Forced Vital Capacity (FVC) and FEV1/FVC ratio.

(i) An obstructive spirometry defect was defined by an FEV1 below 80% predicted and FEV1/FVC ratio below 0.7. with a normal or reduced FVC
(ii) A restrictive spirometry defect was defined by an FVC below 80% predicted and FEV1/FVC ratio above 0.7 with a normal or mildly reduced FEV1
(iii) A mixed spirometric defect was defined by an FVC below 80% with FEV1/FVC ratio of < 0.7

Results

A total of 440 patients comprising of ambulatory Type 2 DM patients presenting at the KNH-Diabetic Clinic for routine follow up and met the inclusion criteria for the study were screened. Four hundred and seventeen participants were recruited and interviewed between January 2018 and March 2018. Nineteen patients were excluded from the study as they were not fit for spirometry. Four patients declined to give consent for the study.

Table 1: Socio-demographic characteristics of the study respondents

Variable	Frequency	(%)
Age groups (years)		
18 – 24	6	1.4
25 – 39	30	7.2
40 – 59	212	50.8
≥60	169	40.5
Sex		
Female	270	64.8
Males	147	35.7
Marital status		
Married	318	76.2
Single/separated	99	23.8
Education		
Primary	118	28.3
Secondary	211	50.6
Tertiary	66	15.8
None	22	5.3

Spirometry findings: 397/417 (95.2%) participants had abnormal spirometric findings as shown in Table 2.

Table 2: Spirometry findings

Findings	Frequency n (%)
Normal	20(4.8)
Abnormal	397(95.2)
Total	417(100)

Type of spirometric abnormalities: Participants with spirometric abnormalities were distributed as follows; 377 (95%) had restrictive spirometric abnormality;17 (4.3%) had obstructive spirometric abnormality and 3(0.75%) had mixed spirometric abnormality (Table 3).

Table 3: Types of spirometric abnormalities

Type of spirometric abnormality	Frequency	(%)
Restrictive	377	95
Obstructive	17	4.3
Mixed	3	0.7
Total	397	100

Mean FEV1/FVC ratio was 0.89 (SD=0.10). Mean FEV1/FVC ratio was 0.91 (SD=0.09) in females and 0.87 (SD=0.09) in males. Mean FEV1/FVC ratio was 0.89 (SD=0.1) in married and 0.88 (SD=0.09) in those who were single. With regards to education level, mean FEV1/FVC was 0.91 (SD=0.26) in those with no education, 0.90 (SD=0.08) in those with primary education, secondary education 0.90 (SD=0.08) and 0.89 (SD=0.08) for tertiary education.

The participants were asked about presence of respiratory disease symptoms and 108/417(25.9%) reported respiratory symptoms. The respondents were further asked about their specific respiratory symptoms, and the findings are as shown in Table 4.

Table 5: Specific respiratory symptoms

Symptom	Percentage of cases (N=108)
Cough	75 (69.5%)
Wheezing	13 (12.0%)
Breathlessness	20 (18.5%)

Thirty four out of seventy-five (45.3%) of patients who experienced cough reported to have phlegm production. Among them, 8/34 (23.5%) produced phlegm during day/night for three consecutive months or more during the year and 38.2% (13/34) reported they had episodes of cough with phlegm lasting ≥ 3 weeks in a year.

Thirteen out of one hundred and eight (12.0%) respondents reported wheezing with shortness of breath and mean age of first episode of wheezing with shortness of breaths was 42.6 years. Five of them had ≥2 episodes of wheezing with shortness of breath. Among the thirteen, 7 had been on medication for the wheezing and SOB. Breathlessness was reported by 20/108 (18.5%) respondents, 12/20 (60%) were slower than their age mates while walking on level ground due to SOB.

Factors associated with spirometric abnormalities: At univariate analysis, being female was associated with two and half times odds of developing restrictive spirometric abnormality (OR 2.46, CI=1.28-4.76) compared to being male, those who had attained secondary education had twice higher odds of developing restrictive spirometric abnormality (OR 2.17, CI=0.94-5.06) compared to tertiary education, although this was not statistically and clinically significant.

Those who had reported breathlessness as a symptom had 29% less chance of developing restrictive spirometric abnormality (OR 0.04, CI=0.10-0.85) compared to those who did not report breathlessness (Table 6).

Table 6: Univariate analysis of factors associated with restrictive spirometric abnormality

Variable	Frequency	COR (95% CI)	p-value
Age groups (years)		Ref	
18 – 24	29 (96.7)	1.5 (0.05 – 405.1)	0.67
25 – 39	194 (91.5)	1.8 (0.04 – 16.1)	0.95
40 – 59	148 (85.6)	1.2 (0.05 – 8.5)	0.83
≥60			
Sex			
Female	252 (93.3)	2.46 (1.28 – 4.76)	0.006
Male	125 (85.0)		
Marital status			
Married	292 (91.8)	1.85 (0.90 – 3.67)	0.12
Others	85 (85.9)		
Education			
Secondary	195 (94.2)	2.17 (0.94 -5.06)	0.11
Primary	108 (91.5)	1.93 (0.76 – 4.91)	0.25
None	18 (81.8)	0.80 (0.22 – 2.88)	0.97
Tertiary	56 (84.9)	Ref	
Cough			
Yes	66 (88.0)	0.73 (0.34 – 1.69)	0.43
No	311 (90.9)		
Sputum production			
Yes	3 (75.0)	0.31 (0.03 – 3.08)	0.30
No	374 (90.6)		
Wheezing			
Yes	11 (84.2)	0.57 (0.12 – 2.67)	0.81
No	366 (90.6)		
Breathlessness			
Yes	15 (75.0)	0.29 (0.10 – 0.85)	0.04
No	362 (91.2)		

Variable	Frequency	COR (95% CI)	p-value
Type of previous severe respiratory infection			
Pulmonary tuberculosis	14 (73.1)	0.47 (0.13 – 1.61)	0.30
Pneumocystis pneumonia	3 (75.0)	1.22 (0.06 – 25.56)	0.55
Asthma	2 (66.7)	0.33 (0.03 – 4.07)	0.94
Bacterial pneumonia	54 (85.7)	Ref	
Smoking status			
Current smoker	2 (66.7)	0.20 (0.02 – 2.32)	0.52
Ever smoked	62 (89.7)	0.91 (0.38 – 2.14)	0.82
Never smoked	313 (90.7)	Ref	
Biomas exposure			
Yes	222 (90.2)	0.95 (0.49 – 1.86)	0.97
No	155 (90.6)		
BMI			
<18.5	3 (60.0)	0.24 (0.04 – 1.63)	0.36
18.5 – 24.9	Ref		
25.0 – 30	163 (92.1)	1.91 (0.84 – 4.34)	0.18
>30	138 (92.0)	1.9 (0.81 – 4.42)	0.14
Duration since diagnosis (years)			
<1	Ref		
1 – 5	111 (91.7)	0.82 (0.11 – 3.62)	0.43
>5	239 (89.5)	0.63 (0.07 – 2.76)	0.75

Discussion

Our study found that diabetic patients had an increased burden of respiratory disease symptoms presenting with cough and phlegm production, wheezing and breathlessness. The most remarkable finding was significant spirometric abnormalities in Type 2 diabetics, with restrictive pattern being the most predominant as shown by FEV1/FVC ratio of >0.8.

These findings are in keeping with findings from previous studies that corroborated that patients with Type 2 diabetes more frequently reported chronic cough and phlegm production, and grade 2 dyspnoea as compared to the general population of the same age, although presenting with similar smoking habits (6,7). Available literature supports the notion that the lung is a possible end target organ for diabetic injury and that Type 2 diabetes is associated with notable reduced lung volumes and airflow limitation (5).

A meta-analysis by van den Borst, *et al.* (8) showed that DM is associated with statistically significant, impaired pulmonary function predominantly of the restrictive pattern. A few patients were found with obstructive spirometric abnormalities. A small number of studies have linked obstructive diseases, in particular COPD, to metabolic syndrome or impaired glucose tolerance. Meo *et al.* (9) and Davis *et al.* (5) found that there was a combined obstructive and restrictive pattern of spirometric abnormalities in patients with diabetes but restrictive pattern was more predominate.

Most of our participants had a high BMI. Females increased the risk, possibly explaining the higher prevalence of restrictive spirometric abnormalities amongst females in our study population. The effect of BMI in reducing lung function may be due to reduced chest wall compliance and increased airway resistance (10).

The participants in this study self-reported a higher level of biomass and dust exposure. This exposure could partly explain the higher prevalence of dyspnoea and chronic cough/phlegm among people with Type 2 diabetes.

Smoking habits were not significantly different amongst individuals with Type 2 diabetes. Moreover, univariate analysis was adjusted for self-reported smoking history, as well as for dust and biomass exposure and there was no association with spirometric abnormalities.

Thomas Brack *et al* (11) reported that, patients with restrictive lung disease are typically dyspnoeic and tend to have an increase in overall respiratory center drive, which appears to result from an increased lung elasticity. When lung elasticity is decreased, as in patients with restrictive lung disease, a deep breath will necessarily involve a large effort. Contrary to this, we found that there was a lower incidence of restrictive lung disease in participants who presented with breathlessness.

Restrictive lung spirometric abnormalities in previous population-based studies suggest increased risk of restrictive pattern among females, which is consistent with our study. Kurth *et al* (12) observed a decline in restrictive pattern among those aged 50–59 years, females, Whites, those with less than a high school education, those with diabetes, those with a non-obese waist circumference, and never smokers. The decline in moderate to more severe restrictive pattern was observed among those with a non-obese waist circumference and never smokers.

Inhaled insulin can be used to achieve better metabolic control in diabetes and increased compliance and adherence to treatment by the patient, impaired lung function could result in a reduced effect of such a therapy (13,14).

Whether inhaled insulin could contribute to lung injury, and thus increase the accelerated decline in lung function in diabetic patients is a question that has not been answered adequately to date.

Conclusions

Our data confirmed the evidence of an increased prevalence of respiratory symptoms and spirometric abnormalities in individuals with Type 2 diabetes. The impairment in PFTs can lower the threshold for clinical manifestations of acute or chronic respiratory disease in patients with Type 2 DM and therefore pulmonary dysfunction should be regarded as a specific complication induced by DM.

Usefulness of spirometry and its utility in patients with diabetics has been highlighted as inhaled insulin is anticipated to be introduced as a novel mode of drug delivery. Therefore, our results may be relevant to the practicing physicians as they highlight the possible clinical value of spirometry as an early screening tool for respiratory diseases in patients with Type 2 diabetes.

The strength of this study was the use of a standardized internationally-validated questionnaire to assess respiratory health in Type 2 DM patients.

Information on respiratory health was collected by an interviewer-administered questionnaire with direct assessment of spirometric pulmonary function.

The study has a few limitations that need to be considered. Individuals with respiratory disorders tend to have symptoms that are subjective to the interviewer-administered questionnaires, a reduction or increase in response percentage may have led to overestimate or underestimate the prevalence of respiratory symptoms in our study population.

Additionally, the prevalence of type 2 diabetes in the study population consisted mostly of patients above 50 years old and thus creating a bias on the findings due to the possible existence of age associated lung disease.

This was a cross sectional study and therefore we were not able to look at the effect of Type 2 DM and the associated risk factors on progression of pulmonary function parameters.

Recommendations

We recommend that spirometry should be in-cooperated as a scheduled evaluation tool for patients with Type 2 DM.

We also recommend a follow up study to assess the relationship between glycemic control and severity of respiratory symptoms and pulmonary function abnormalities in patients with Type 2 DM.

Acknowledgments

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Original paper

The Prevalence of Asthma Phenotypes in Patients attending The Chest Clinic at Kenyatta National Hospital

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Abstract

Background: Asthma is a heterogeneous disease characterized by distinct inflammatory and clinical phenotypes. Knowledge of these phenotypes enables individual patient targeted treatment resulting in better control leading to a reduction in treatment costs.
Objective: To determine the prevalence of asthma phenotypes among adult asthmatics attending the chest out-patient clinic at Kenyatta National Hospital.
Methodology: The study was a cross-sectional, descriptive study carried out on asthma patients attending the chest clinic at KNH. The inclusion criteria included patients who met the case definition for asthma, aged 13 years and above and had provided an informed consent/assent. The clinical phenotypes were associated comorbidities which were determined from the case notes. Sputum samples were collected to determine the inflammatory phenotypes.
Data was analyzed using SPSS 21.0 software. Continuous data was analyzed into means and medians. Categorical data which included the asthma phenotypes and spirometry findings was presented as percentages. The prevalence of asthma phenotypes was analyzed as proportions using 95% CI. The results from spirometry were graded as mild, moderate, severe and very severe obstruction based on the spirometry findings of FEV1 and were presented as percentages.
Results: Eighty one asthma patients with an average age of 50.1 years and female predominance of 76.5% were studied. The prevalence of inflammatory phenotypes was paucigranulocytic (84%), mixed granulocytic (8.6%), neutrophilic (7.4%) and eosinophilic (0%). The prevalence of clinical phenotypes was allergic rhinitis (76.5%), atopy (67.9%) and gastroesophageal disease (54.3%).
Conclusion: There is very little benefit in phenotyping all asthma patients. Instead following GINA treatment steps is recommended. We accept most of our study patients had mild to moderate asthma and that these findings may be different in a severe asthma population.

Key words: Asthma, Phenotypes, Inflammatory, Clinical, Paucigranulocytic, Mixed granulocytic, Neutrophilic, Eosinophilic

Introduction

It is estimated that there are 300 million asthma cases worldwide affecting all age groups and this figure is postulated to increase to 100 million in 2025 (1). There are approximately 250,000 asthma deaths every year and this is mostly in the low and middle income countries. It has been estimated that the prevalence of asthma in Kenya is 10% with 4 million having asthma (2).

Asthma manifestations are as a result of interaction between genetic, epigenetic and environmental factors. There may be different asthma genotypes based on the differences in genes and phenotypes based on epigenetics and environmental factors (3). There is now increased evidence that suggests that phenotyping asthma according to airway inflammation may be a direct measure of the basic asthma inflammatory nature and allows identification of subgroups of patients who are most likely to respond to targeted therapy (4) The eosinophilic phenotype responds to inhaled corticosteroids resulting in better asthma control, reduced exacerbations and hospital admissions (5).

Establishing asthma genotypes and phenotypes may be the next frontier in targeted asthma therapy for better treatment. Thus, treatment aimed at

normalizing eosinophils in the airway results in better outcomes. Neutrophilic asthma has been associated with poor short term response to inhaled corticosteroids (6)

It has been noted that not all asthma patients show similar response to all drugs. These variations in response to therapy have put into question the current uniform treatment. Prescription of futile treatments can be minimized and response variability maximized by use of phenotypic patterns that predict response to certain medication.

There are no studies done on asthma phenotypes in Kenya and very few in Africa. We currently do not know the phenotypes of our asthma patients, and whether these fit the global described phenotypes and there is no local data on asthma phenotypes. This study will serve as a baseline survey of the phenotypes present in asthma patients. Phenotyping asthma will enable individualized treatment of patients resulting in better outcomes and a reduction in cost.

This was a cross sectional study to determine the prevalence of the inflammatory and clinical phenotype in the asthma patients who attended the chest clinic. We also described the spirometry findings in the different phenotypes. The most common inflammatory phenotype was the paucigranulocytic phenotype with allergic rhinitis being the predominant clinical phenotype.

Materials and methods

Design: This was across-sectional study conducted at the chest clinic at Kenyatta National Hospital. Ethical approval was obtained from the hospital ethics committee. Eighty one patients were consecutively sampled on each Tuesday clinic. The inclusion criteria were a written informed consent/assent, patients who were 13 years and above and had a chest physician's diagnosis of asthma and or cough, chest congestion, dyspnoea and wheezing. The patients excluded had contraindications to spirometry and were unable to follow spirometry instructions.

Results

Participants description

Table 1: Patients characteristics at the chest clinic

Variable	Categories	Frequency (n=81)	(%)
Age (years)	Mean age (SD) Min-Max	50.1 (15.1) 17-80	
Gender	Male Female	19 62	23.5 76.5
Level of education	None Primary Secondary Tertiary	9 24 39 9	11.1 29.6 48.1 11.1
Occupation	Student Formal employment Business Unemployed	2 12 27 40	2.5 14.8 33.3 49.4
Residence	Urban Rural	48 33	59 41
Duration of asthma in years	<1 1-5 5-10 >10	11 22 25 23	13.6 27.1 30.9 28.4
Asthma treatment	SABAprn ICS+ SABA prn LABA+ICS+SABA prn	17 50 14	21 62 17
BMI kg/m^3	Obese (>25) None obese (< 24.9)	21 60	25.9 74.1

Table 2: Clinical characteristics of the asthma patients

Variable	Frequency (n=81)	(%)
Smoking	5	6.2
Drug adherence	61	75.3
Severity of symptoms with menses (n=62)	7	11.3
Asthma exacerbation during exercise	57	70.4
Obtaining medication		
Self	47	58
Employer/Insurance	4	4.9
Parent	5	6.2
Child	10	12.3
Others	15	18.5

SABA-Short Acting Beta Agonist; ICS-Inhaled Corticosteroids; LABA- Long Acting Beta Agonist; BMI-Body Mass Index

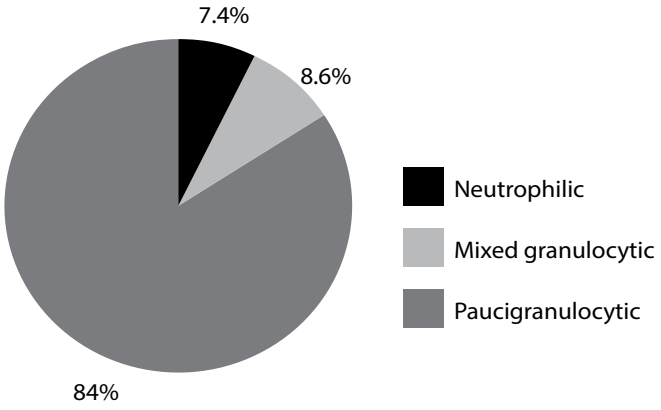
Table 3: Spirometry findings of the study participants

Spirometry FEV1	BD (n=81) No. (%)	Post-BD (n=81) No. (%)
Mild (>80%)	27(33.3)	33(40.7)
Moderate (50-80%)	40(49.4)	43(53.1)
Severe (30-50%)	12(14.8)	5(6.2)
Very severe (<30%)	2(2.5)	0(0.0)

FEV1-Forced Expiratory Volume; Pre-BD- Pre bronchodilation; Post-BD- Post bronchodilation

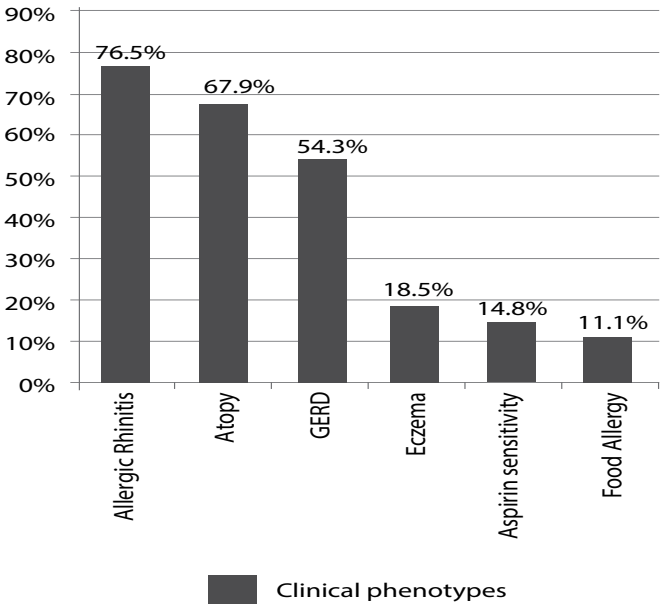
Prevalence of inflammatory and clinical phenotypes: Majority (84%) of asthma patients had paucigranulocytic phenotype. The other inflammatory phenotypes were mixed granulocytic (8.6%) and neutrophilic (7.4%). However, eosinophilic phenotype was not identified in this population of patients. The most common clinical phenotypes identified in this study included allergic rhinitis and gastroesophageal disease in 76.5% and 54.3% of the patients respectively. Food allergy was the least clinical phenotype at 11.1%.

Figure 2: Prevalence of inflammatory phenotypes



The subjects in the study population had more than one comorbid condition and this resulted in an overlap of the clinical phenotypes (Figure 3).

Figure 3: Prevalence of clinical phenotypes



Discussion

The prevalence of paucigranulocytic phenotypes was high at 84% among the asthmatic patients. Paucigranulocytic phenotype has been found to be the most common phenotype in stable patients (7). Wang *et al* (8) in a case control study carried out in Australia in 2011 reported the prevalence of paucigranulocytic phenotype at 51.7%. Mixed granulocytic phenotype in our study was in 8.6% of the patients; findings which were similar to the 10% prevalence reported

in a cross-sectional study by Murthy *et al* (9) in 2012. The study also used a lower cut off to determine the inflammatory phenotype with neutrophilic at or greater than 61% and eosinophilic greater than 1% (9).

Neutrophilic phenotype was identified in 7.4% of the patients we studied. Similar findings were reported in a case control study carried out by Romagnoli *et al* (10) in 2002 where 5.7% of the patients had neutrophilic phenotype. We did not report any eosinophilic phenotype. A low prevalence of 2.5% of eosinophilic phenotype was also reported in a case control study by Romagnoli *et al* (10) in 2002.

The study by Mohamed *et al* (11) reported that asthma patients who have been on ICS had reduced eosinophil counts compared with patients receiving other forms of treatment. Our study cohort had been on ICS and this may have attenuated airway inflammation thus decreasing eosinophils. In addition, eosinophils may have decreased due to the fact that our patients had well controlled asthma. Eosinophilic phenotype, patients tend to have more symptoms, exacerbations and lower FEV1(7). In this study, we analyzed spontaneous sputum compared to the other studies which analyzed induced sputum. The viability and quality of cells has been found to be higher in induced sputum samples. The presence of mucus secretion along the airways for a long duration of time may result in fewer viable cells and the inability to distinguish the different types of cells in spontaneous sputum(8). This may explain why majority of the patients were found to have paucigranulocytic phenotype and the lack of eosinophilic phenotype.

About three quarters (76.5%) of the asthma patients had allergic rhinitis. This high prevalence was comparable to 70% reported in a study carried out by Saha *et al* (12) in 2013 in India. Controlling of allergic rhinitis results in better control of asthma and relieves patients' discomfort(13).The prevalence of atopy in our study was 67.9%. This was similar to a study by Murthy et al (9) in 2012 in United Kingdom in which 62% of their study population had atopy. Exposure to allergens such as house dust mites, cats and dogs may result in development of atopy (14). The prevalence of gastroesophageal reflux disease was reported to be 54.3%. Our findings were similar to a study by Saha *et al* (12) in 2013 with a prevalence of 55%.

Conclusion

Inflammatory and clinical phenotypes were not significantly associated with spirometry findings or the GINA treatment step the patients were on/or the level of their control.

Acknowledgments

To the management of Kenyatta National Hospital for allowing us to carry out the study in the facility and to all the asthma patients attending the chest clinic who participated in the study.

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Original paper

Quality of Sleep and Sleep Disorders in Patients Undergoing Haemodialysis at a National Referral Hospital

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Abstract

Background: The burden of poor sleep quality and sleep disorders is higher amongst patients with End-Stage Renal Disease (ESRD) on haemodialysis compared to the general population and is associated with increased morbidity and mortality. The quality of sleep and burden of sleep disorders amongst Kenyan patients with ESRD on haemodialysis is not known.
Objective: To assess the quality of sleep and the prevalence of insomnia and high risk for Obstructive Sleep Apnea (OSA) in patients with ESRD on haemodialysis and to determine the associated socio-demographic, clinical and biochemical parameters.
Methodology: This was a hospital based cross sectional study carried out at the renal unit of Kenyatta National Hospital (KNH) over a period of three months. Patients with ESRD on haemodialysis for more than three months were eligible for the study. All patients who met the inclusion criteria were recruited, after giving written consent, based on consecutive sampling. Targeted history was taken and anthropometric measurements done. Blood was drawn for biochemical parameters (haemoglobin and phosphate). Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), high risk for OSA using Berlins Questionnaire (BQ) and insomnia using the Athens Insomnia Scale (AIS). Associations between poor sleep quality, high risk for OSA, insomnia and various socio-demographic, clinical and biochemical factors were explored.
Results: The study was conducted between August 2016 to October 2016. Out of the 115 patients analyzed mean age was 44.7(±16.1) years, 59.1% were males and the mean BMI was 23.1(±5.1) kg/m^2. Of the 115 patients with ESRD on haemodialysis assessed, 80 (69.6%) had poor sleep quality, 54 (47%) had insomnia and 40(34.8%) had high risk for Obstructive Sleep Apnea (OSA).
Conclusion: We obtained a high prevalence of poor sleep quality and sleep disorders (insomnia and high risk for OSA), similar to that reported in other populations. Assessment for and management of quality of sleep and sleep disorders in ESRD patients on haemodialysis should be an important component of care.

Key word: Quality of sleep, sleep disorders, Haemodialysis.

Introduction

The prevalence of sleep abnormalities is greater in ESRD than the general population (1). Poor quality of sleep contributes to poor health related quality of life in haemodialysis patients (2). Sleep disorders are common in ESRD patients and it is one of the most common symptoms with a mean prevalence of 44% (3). Sleep disorders contribute to poor sleep quality in ESRD patients (2). They affect African Americans more than Caucasians (4). The most common sleep disorders in haemodialysis patients are insomnia and OSA.

The burden of ESRD is high in sub Saharan Africa. The World Health Organization (WHO) estimates one in every five men and one in every four women in Kenya aged between 65 and 74 years suffer from Chronic Kidney Disease (CKD). The Kenyan Ministry of Health estimates that 10000 cases of kidney disease are diagnosed annually (5). Anaemia and hyperphosphatemia are two biochemical parameters associated with various sleep disorders.

With this increasing burden of ESRD, attention should be given to all aspects of patients wellbeing. However sleep complaints are under recognized by health care providers (6). Improving the quality of sleep and treating sleep disorders may improve quality of life in these patients.

Materials and methods

One hundred and fifteen patients with ESRD undergoing haemodialysis at the renal unit of KNH were screened for quality of sleep and sleep disorders

between August 2016 and October 2016. Patients on haemodialysis for more than three months and above the age of eighteen years were enrolled consecutively after informed consent. A targeted history was then taken and questionnaires administered (PSQI, BQ and AIS). This was followed by measurement of anthropometric measurements (Body Mass Index and Neck circumference). Blood was then drawn for haemoglobin and phosphate levels.

Statistics: Data analysis was carried out using the statistical package for the Social Sciences Software version 21. Means (±SD) were calculated for continuous data and proportions for categorical data. The chi square test was used for comparison of categorical variables and Mann Whitney U test for continuous variables; p-values<0.05 were considered significant.

Ethics: Ethical Approval was obtained from the KNH/ University of Nairobi Research and Ethics committee and consent was obtained from each patient before the start of the study.

Results

One hundred and fifteen patients were enrolled and the mean age was 44.7(±16.1) years. The male to female ratio was 1.4:1. The median duration on haemodialysis was one year (range of 0.25-10 years). Table 1 summarizes the anthropometric and clinical characteristics of patients.

Eighty (69.6%) patients had poor sleep quality, 54 (47%) had insomnia and 40(34.8%) had a high risk for OSA. Figure 1 shows the prevalence figures of poor sleep quality, insomnia and high risk for OSA.

At univariate analysis hypertension was found to be a risk factor for insomnia (p=0.039). However no associations were noted between poor quality of sleep and high risk for OSA with socio-demographic, anthropometric and clinical parameter (Table 1).

Figure 1: Prevalence of poor sleep quality, insomnia and high risk for OSA

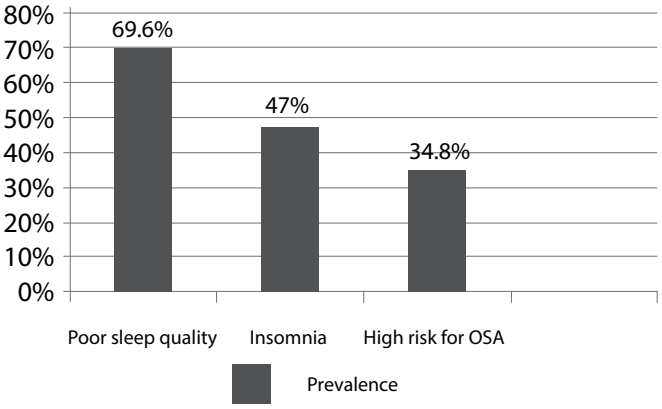

Table 1: Anthropometric and clinical characteristics

Variable	Frequency (%)
Mean age (years)	44.7(±16.1)
Median duration on haemodialysis (years)	1.0(0.5-2.0)
Current smokers	3(2.6)
BMI	
Underweight	16 (13.9)
Normal	69 (60)
Overweight	15(13)
Obese	15(13)
Increased neck circumference	31 (27)
Haemoglobin	
Normal	6(5.2)
Mild	16(13.9)
Moderate	82(71.3)
Severe	11(9.6)
Phosphate (mmol/L)	1.64 (±0.5)

Haemoglobin: Normal > 13 g/dl or > 12 g/dl in men and women respectively, mild 11-12.9 g/dl and 11-11.9 g/dl in men and women respectively, moderate 8-10.9 g/dl, severe <8 g/dl

Table 2: Univariate analysis of factors associated with poor sleep quality and sleep disorders

Variables	Poor sleep quality (p-value)	Insomnia (p-value)	High risk for OSA (p-value)
Age	0.554	0.970	0.544
Male gender	0.900	0.724	0.146
Hypertension	0.708	0.039	0.269
Diabetes	0.306	0.764	0.621
Glomerulonephritis	0.130	0.750	0.478
Current smoking	0.246	0.062	0.240
Underweight	1.000	0.054	0.712
Overweight	1.000	0.424	0.913
Obese	0.226	0.885	0.913
Neck circumference	0.300	0.416	0.170
Haemoglobin	0.163	0.432	0.247
Phosphate	0.367	0.713	0.609

Discussion

This study shows that there is a high burden of poor sleep quality, insomnia and high risk for OSA in Kenyan patients undergoing haemodialysis.

We obtained a high prevalence of poor sleep quality of 69.6%, and this is consistent with the range found in previous studies (49%-75%) (2,7-9). Elder *et al* (2), conducted a populous (11351 patients) multicenter study and found a prevalence of poor sleep quality of 49%. However they used a self-reported sleep quality scale as compared to the PSQI (2). Our prevalence of 69.6% was in keeping with that of Iliescu *et al* (7) and Chen *et al* (8), who found a prevalence of 66% and 71% respectively. This high prevalence of poor sleep quality may be explained by the presence of other sleep disorders and overall poor quality of life as eluded to by Elder *et al* (2). We found a high prevalence of insomnia and high risk of OSA and these can contribute to poor sleep quality. Kamau *et al* found that health related quality of life in hemodialysis patients is reduced at the KNH, and studies have shown that health related quality of life is linked to sleep quality.

Prevalence of insomnia using the AIS, in chronic haemodialysis patients ranges from 28-57.4% (10-12). We found a prevalence of 47%, this is much higher than that obtained by Nena *et al* (12) and Bornivelli *et al* (11) (prevalence of 28.3% and 29% respectively) who used a higher cut off of 9 (instead of 6) for insomnia on the AIS. Ebrahim *et al* (10), found a prevalence of insomnia in ESRD patients of 57.4% using the AIS. This was higher than the prevalence we obtained (47%). This maybe because Ebrahim *et al* (10) had a much larger sample size than ours, was a multicenter study with a mean age much higher than ours.

In keeping with other studies, we found insomnia to be the most prevalent sleep disorder in dialysis patients (10,13,14). This high burden of insomnia in ESRD may be because of the presence of other sleep disorders such as restless leg syndrome and OSA which contribute to insomnia (14).

The prevalence of high risk for OSA ranges from 20%-49.1% (8,13,14-16). We obtained 34.8% prevalence, this was comparable to another African study done in Egypt by Sabry *et al* (16) who found a prevalence of 31.8%. The differences in prevalence between the various studies may be explained by different patient characteristics.

Hypertension was found to be a risk factor for insomnia (p=0.039). No previous study has noted such an association. This may be explained by the use of antihypertensive medications such as beta blockers and Angiotensin Converting Enzyme inhibitors. Beta blockers cause inhibition of the night time secretion of melatonin and Angiotensin converting enzyme inhibitors cause a dry hacking cough which may keep patients up at night. Also hypertension has been noted to be a risk factor for OSA, and OSA may contribute to insomnia.

African studies have noted an association between anaemia and insomnia (10,13) however we did not find such an association. In the general population age, male sex, obesity and smoking have been found to be risk factors for OSA. In our study, age, sex, hypertension, anthropometric measures and laboratory parameters were not associated with high risk of OSA. Previous studies that used the BQ have shown mixed results on the association between age, male sex and obesity with high risk for OSA. BMI was not associated with high risk for OSA in Chinese and Italian populations (8,14). However both Wali *et al* (15) and Ibrahim *et al* (10) noted associations with obesity and sleep apnea. This may implicate that other factors apart from obesity contribute to risk of OSA in the haemodialysis cohort.

This study was the first of its kind studying sleep quality and sleep disorders in our dialysis cohort. This was a questionnaire based study however we used validated questionnaires translated to Kiswahili for ease of understanding. The study was carried out in a public referral hospital in a center that receives the largest number of dialysis patients daily. However it was not a multicenter study and the data presented may not be generalizable to all patients with ESRD on chronic haemodialysis in Kenya.

Due to the very high prevalence of poor sleep quality obtained in this study, all patients undergoing chronic haemodialysis should routinely be administered the PSQI to assess their sleep quality. The dialysis unit team (nephrologists, renal nurses, internal medicine residents) involved in the care of patients on chronic haemodialysis should enquire about sleep complaints in these patients and where appropriate screen patients for sleep disturbances (insomnia and high risk for OSA), those at high risk may be referred for polysomnography studies and medications initiated where appropriate. Further studies are needed to further elucidate the relationship between hypertension and insomnia. Since questionnaires assess sleep subjectively, studies using polysomnography are warranted in the same cohort.

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Original paper

Baseline Patient Profile, Rhythm Abnormalities and Outcomes for Patients with Pacemakers Inserted at The Kenyatta National Hospital

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Abstract

Background: Permanent pacemakers are the only treatment for high degree atrioventricular block or symptomatic bradycardia. Quadrennial surveys by the World Society of Arrhythmias have demonstrated a rise in the uptake of device therapy worldwide. However there is limited data on pacemaker use in sub-Saharan Africa including Kenya.
Objectives: The aim of this study was to determine the baseline clinical characteristics, rhythm abnormalities at presentation and the outcomes for patients who underwent pacemaker insertion at the KNH between 1st January 2011 and 31st December 2015.
Methodology: This study was a retrospective chart audit based at the records department of the KNH. Patient details were retrieved from a register in the cardiac catheterization laboratory and the matching record searched for. Patients whose records were retrieved and who met the inclusion criteria constituted our study population. The vital status for each patient was then established via a phone call placed to the contacts in their record.
Results: Between 2011 and 2015, 359 patients underwent pacemaker insertion at KNH. We retrieved records for 214 patients. We were able to contact 165(77.1%) by phone. Most patients were elderly (median age of 71years) and female (65.4%). The most frequent presentation was dyspnoea (41.6%) and dizziness (29.9%). The commonest co-morbidity was hypertension (64%). The leading indication for pacemaker insertion was complete heartblock in 78%. The pacemaker mode most employed was DDD in 54.2%. Majority of the patients (92.1%) had presented for an index pacemaker insertion. Complications were recorded for 8.9% of patients. The median duration lived with a pacemaker in situ was 3 years and 69.2% of the 214 patients were alive at the time of the study. We confirmed that 7.9% were deceased while the vital status for 22.9% could not be established.
Conclusion: The commonest indication for pacemaker insertion at KNH is complete heart block. Most of the patients undergoing the procedure are elderly and hypertensive. Complication rates were comparable to those of developed countries with low infection rates and no mortalities during the procedure.

Key words: Pacemaker, Rhythm abnormalities, Indications, Complications, Kenyatta National Hospital

Introduction

Pacemakers are the only treatment for advanced atrioventricular block or symptomatic bradycardia. In the 2009 survey by the World Society of Arrhythmias, bradycardia constitutes 95% of the indications for pacemaker insertion (1). The same survey indicates a rise in the uptake of pacemaker therapy worldwide even in the developing countries. However while the developed world showed increased use of dual chamber devices in the developing world single chamber device use still predominates. Data from most African countries was lacking in this survey.

Pacemaker insertion in Africa: In 2014 PASCAR (The Pan African Society of Cardiology) carried out a survey on pacing and electrophysiology in Africa (2). This involved fourteen countries: South Africa, Tunisia, Morocco, Sudan, Kenya, Nigeria, Senegal, Cameroon, Libya, Ghana, Benin, Mali, Niger, Sierra Leone and Uganda. It was found that there were severe shortages of pacemakers in all countries surveyed. There was also a severe shortage of expertise required for device insertion. Most African centers were low volume implanters with pacemaker implantation rates being generally low in the countries surveyed.

Pacemaker insertion in Kenya and Kenyatta National Hospital: There is limited data on pacemaker insertion in Kenya. According to a 2014 survey, Kenya had 6 pacemaker insertion centers and between 20-30 doctors trained in pacemaker insertion (2). Kenyatta National Hospital, the largest referral hospital in Kenya is one of these centers. Pacemaker insertion at this institution is carried out by local cardiologists. Since 2011 a local non-governmental organization has sponsored annual pacemaker insertion projects boosting the numbers of patients able to receive this therapy (3). We chose to limit the study period to between 1st January 2011 and 31st December 2015 as the cardiac catheterization laboratory register had only listed patients who had pacemakers inserted during this period.

Materials and methods

We carried out a retrospective chart audit at the records department of Kenyatta National Hospital. We included records for adults who had a pacemaker inserted at Kenyatta National Hospital during the period between 2011 to 2015. Patient details were retrieved from a register in the cardiology unit and a search was made for the matching patient record. A pre-designed proforma was used to collect data from the patient records retrieved. We then placed a phone call to each patient or next of kin to establish their vital status.

Results

Between the period 1st January 2011 and 31st December 2015, 359 patients are listed as having undergone pacemaker insertion at the Kenyatta National Hospital. The number of pacemakers inserted each year is summarized in Figure 1. We managed to retrieve records for 224 patient records but we could not establish why the other records were missing (Figure 2). We then placed a phone call to each patient by the number available in the patient record to establish their vital status.

Figure 1: Number of pacemaker insertions per year from 2011-2015

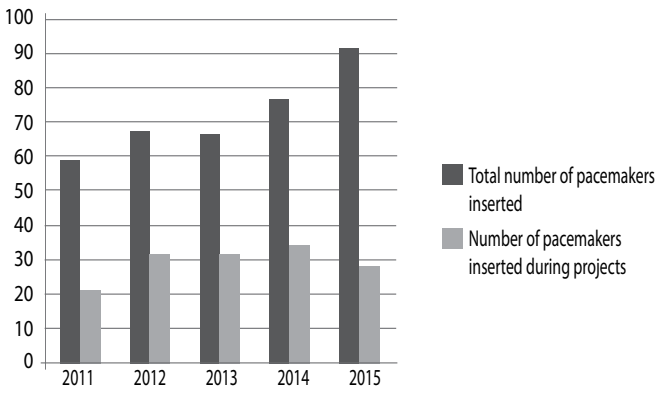
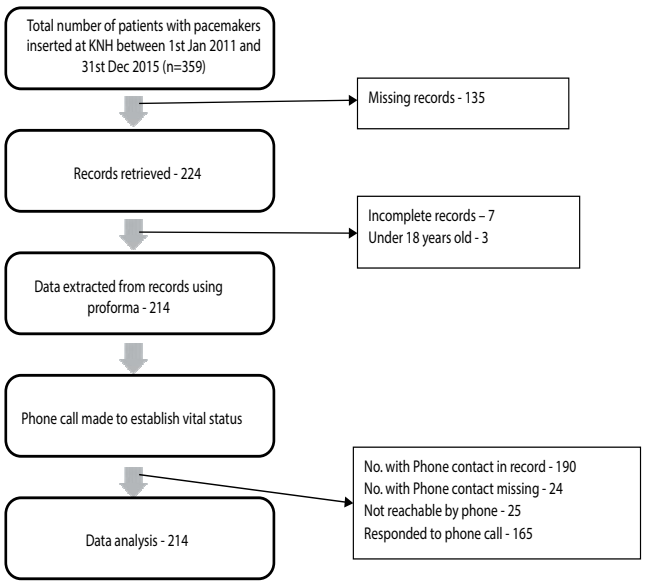


Figure 2: Recruitment flow chart



The median age of our study participants was 71 years with an age range of 26 to 98 years. Females accounted for 65% of the patients. The average age for females was 71.5 years and males 70.2 years. Forty three point five per cent of patients were resident in a rural setting. Thirty seven point nine per cent were unemployed or retired. With regards to level of education 55.6% of patients had achieved at least a minimum of primary school education.

The main indications for pacemaker insertion as derived from procedure notes included complete heart block in 73.3% and second degree atrioventricular block in 9.8%. The mean pulse rate was 43.8 beats per minute with a range of 21 to 117 beats per minute. Other indications were sick sinus syndrome in 4.7% and cardiac resynchronisation therapy in 1.9%.

The symptoms at presentation included dyspnoea in 41.6%, dizziness in 29.9%, syncope in 17.3%, palpitations in 12.1%, presyncope in 6.1%, convulsions in 4.2%, 6.1% of the patients were asymptomatic. The co-morbidities recorded included hypertension in 64%, congestive cardiac failure in 22.9%, diabetes in 15.9%, chronic kidney disease in 4.2%, dilated cardiomyopathy in 3.7%, valvular heart disease in 1.4%, hyperthyroidism in 1.4% and chronic lung disease in 2.8%. More than half the patients (54%) were on medication.

Most of the patients who underwent pacemaker insertion had come for a first time insertion (92.1%). The commonest pacemaker type inserted was the dual chamber device in 54.1% while 41.2% received a single chamber device. The commonest access route used during insertion was the left subclavian vein in 70.6%. Most patients (93.9%) received prophylactic antibiotics. Most patients (93.9%) had the procedure done under local anaesthesia. Most patients (68%) were discharged on the day of the procedure i.e. were not admitted for observation.

Table 1: Socio-demographic characteristics

Variable (study population N= 214)	n (%)
Age (years)	
Mean age (SD)	70.6(11.8)
Median age	71
Range (min -max)	29-98
Mean age by sex	
Females	71.5 years (12.2)
Males	70.2 years (11.8)
Sex	
Male	74 (34.6)
Female	140 (65.4)
Usual residence	
Urban	56 (26.6)
Rural	94 (43.5)
Unknown	64 (29.9)
Education level	
None	33 (15.9)
Primary	57 (26.6)
Secondary	33 (15.4)
College	29 (13.6)
Missing	62 (28.6)
Occupation	
Employed	73 (35.0)
Unemployed/retired	84 (37.9)
Missing	57 (27.1)

Figure 3: Indications for pacemaker implantation

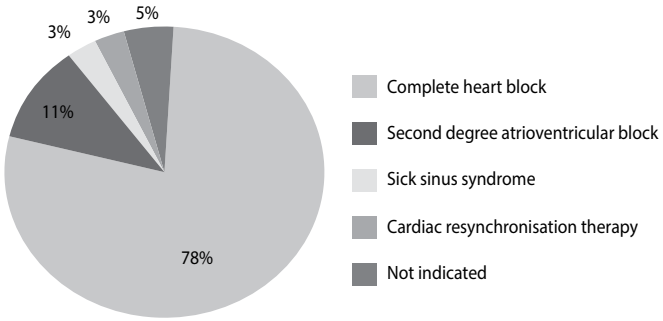
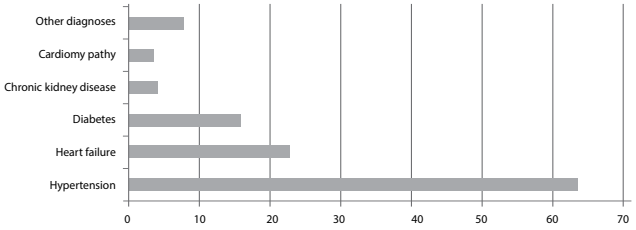


Figure 4: Concurrent diagnoses present at baseline (%) n=214



Other includes valvular heart disease 1.4%, hyperthyroidism 1.4%, chronic lung disease 2%

Table 2: Pacemaker insertion procedure details

Variable		n (%)
Pacing mode	VVI	88 (41.2)
	AAI	0
	VVD	0
	DDD	116 (54.2)
	Biventricular	8 (3.7)
Pacemaker status	New	197 (92.1)
	Replacement	5 (2.3)
	Missing	12 (5.6)
Access	RSCV	7 (3.3)
	LSCV	151 (70.6)
	LCV	28 (13.1)
Antibiotic prophylaxis	Yes	201 (93.9)
	No	1 (0.5)
	Missing	12 (5.6)
Type of anaesthesia used	Local	201 (93.9)
	Missing	13 (6.1)
Duration of admission	Discharged same day	147 (68)
	Number admitted	62 (28)
	Mean duration of admission (days) range	5 days 1-60

RSCV = Right subclavian vein, RFV = right femoral vein, LSCV = Left subclavian vein, LCV = Left cephalic vein, LFV= Left femoral vein

Overall complications were reported in 19 patients (8.9%). The complications included lead dehiscence in 7 patients, pocket infections in 3 patients, pacemaker syndrome in 2 patients, one pneumothorax, 3 haematomas at the incision site, angina in one patient, asystole in 2 patients and sustained ventricular tachycardia in one patient. Nine patients had immediate/procedure-related complications. However there were no mortalities during the procedure (Table 3).

Table 3: Complications

Variable N=214	n (%)
Complications	
Number with complications	19(8.9)
Procedure- related	9(4.2)
Pneumothorax	1(0.5)
Haematoma	3(1.4)
Haemothorax	1(0.5)
Asystole	2(0.9)
Angina	1(0.5)
Ventricular tachycardia	1(0.5)
Other:	10(4.7)
Pocket infection	3(1.4)
Pacemaker syndrome	2(0.9)
Lead dehiscence	7(3.3)
Failure of capture	4(1.9)
Timing of complication	
Procedure related	9(4.2)
Short-term	13(6.1)
Long-term	7(3.3)
Mortalities during insertion	None

Table 4: Outcomes after pacemaker implantation

Variable		Frequency (%)
Outcome	Alive	148 (69.2)
	Dead	17 (7.9)
	Missing	49 (22.9)
Current follow up	KNH	92 (43.0)
	Other private hospitals	29 (13.6)
	Other public hospitals	25 (11.7)
	Missing	68 (31.8)
Mean duration lived pacemaker (years)	Median (IQR)	3.0 (2.0-4.0)
	Min-Max	1.0-16.0

Sixty nine point two per cent of patients were alive by the time of the study, with 7.9% confirmed dead. Twenty two point nine per cent of patients' vital status was unknown. For those who are alive 42% are on follow up at KNH while 13.7 % are on follow-up at private clinics. A large number are lost to follow-up i.e. 22.9%. The average duration of survival from time of pacemaker insertion was 3 years with a range of 1 to 16 years (Table 4).

Discussion

This study was a retrospective chart audit carried out between 1st of June 2015 and 31st of July 2015. From our analysis of the available records we found that majority of the patients undergoing pacemaker insertion were elderly females (65.4%) with a median age of 70.6 years and a range of 29-98 years. This is well within the range of 65 to 75 years reported in the 11th worldwide survey of cardiac pacing (4). Although cardiovascular disease is considered to be more prevalent in the male sex, majority of the patients who underwent PM insertion were females at 65%. The reason for female predominance is unclear. One factor may be increased health seeking behavior of females and longevity of females compared to their male counterparts (7).

The commonest indications for pacemaker insertion was complete heart block (78%), sick sinus syndrome in 3%, second degree atrioventricular block in 11% and cardiac resynchronization therapy in 3%. However in Europe and North America the proportion of PM insertions for sick sinus syndrome is greater than in African or Asian countries (4). Jensen *et al.* carried out a prospective study to describe the epidemiology of SSS in the participants of the Atherosclerosis Risk in Communities (ARIC) study and the Cardiovascular Health Study (CHS) in the USA. They found that blacks had a 41% lower risk of developing SSS than whites. This may explain the lower numbers of patients undergoing PM insertion for SSS in our setup.

Left ventricular hypertrophy was present in 21.6%. Majority of the patients were hypertensive and this may explain the presence of LVH. Ten patients were in atrial fibrillation while 6 had atrial flutter. Q waves were present in ECGs of 12 patients while 20 patients had a Left Bundle Branch Block (LBBB.) This could be indicative of presence of ischaemic heart disease as an aetiology of the heart block.

The mean heart rate i.e. ventricular rate was 43.6 beats per minute. The mean sinus rate was 84 beats per minute for our patients. This implies normal sympathetic nervous system tone. Increased sympathetic tone puts the patient at increased risk of sudden cardiac death.

The QRS complex was narrow in the majority of our patients (55.6%). In those with complete heart block 63.4% had a narrow QRS. In a study done at a Cameroonian hospital to assess the incidence and survival of patients with complete heart block it was found that 35.2% had a narrow QRS while 64.8% had a wide QRS (5). A wide QRS has been shown to be an independent predictor of increased morbidity and mortality in other cardiac arrhythmias such as atrial fibrillation. The significance of this finding in the setting of heartblock is unknown.

The commonest co-morbidity was hypertension in 64%. Ekpe *et al* (8) in Nigeria had similar findings in their study whereby 67% of the patients were hypertensive. Bradycardia is thought to cause elevated blood pressure by increasing ventricular filling time in diastole. The commonest symptoms recorded at presentation were dizziness in 29.9% and dyspnoea in 41.6%. In other studies the commonest symptom for which pacemakers were inserted was syncope in 45% (9). In our study population 17.3% had syncope.

Relative to other African studies more pacemaker insertions are carried out at our center annually. For example Tantchou *et al* (5) carried out a prospective study involving patients with complete heartblock in Cameroon. Over a 2 year period 15 patients underwent pacemaker insertion at this center. Ekpe *et al* (8) in a retrospective study at a Nigerian teaching hospital recorded a figure of 23 patients undergoing pacemaker insertion over a 5 year period. Thiam *et al* (10) in Dakar found that 92 implants were carried out over 3 years. But compared to centers in Europe our numbers are considerably small. For example Bond *et al* (11) carried out a study on pacemaker complications at a District hospital in the UK. Here the number of procedures at a single center over a 3 year period was 1286. KNH recorded 357 insertions over 5 years.

The pacing mode most commonly employed was DDD as opposed to VVI. In other developing countries the commonest mode used was VVI. This is because single chamber pacemakers are more affordable. In a study by Thomas *et al* (12) in Nigeria 89% of pacemakers inserted were single chamber devices. Thiam *et al* (10) in Dakar in 2003 found that 87% of pacemakers inserted were single chamber devices.

Worldwide there is a trend towards use of DDD pacemakers. This was informed by data from earlier studies such as a prospective randomised trial by Andersen *et al* (13) where comparison of AAI and VVI modes was done in a cohort of 225 patients with a mean follow-up of 3.3 years. The frequency of atrial fibrillation and thromboembolic events was higher in the ventricular pacing group. However three subsequent large prospective randomised control trials have failed to show the same effect. These include the CTOPP-Canadian Trial of Physiological Pacing trial (DDDR vs. AAI(R) or VVI (R)) which enrolled 2568 patients, the MOST Mode selection Trial (DDDR versus VVIR) which enrolled 2010 patients and the UKPACE

United Kingdom Pacing and Cardiovascular event trial (DDDR vs. VVI(R) which enrolled 2021 patients (6,15,16). These trials showed that the outcome with regards to mortality, cardiovascular events, stroke, hospital admissions and rates of development of pacemaker syndrome were similar in all pacing modes i.e. AAI, VVI or DDD. The only area where benefit was demonstrated with physiological pacing was in the reduction in the incidence of chronic atrial fibrillation. Current guidelines however still recommend DDD over VVI despite there being no survival benefit (17,18). In the study by Thomas *et al* (12) where 89% received a single chamber device none had complications while in the study by Thiam *et al* (10) in Dakar where 87% received single chamber implants only 1 had pacemaker syndrome.

Majority of our patients came for an index pacemaker insertion i.e. 92.7% while 2.1% had a replacement. In the 2009 worldwide survey 75% of pacemakers inserted were index insertions with 25% being replacements. The reason for the low rate of replacements may be explained by the fact that device therapy has become more accessible during the last five years due to presence of donated pacemakers. Donations form a significant proportion of devices inserted. This indicates an unmet demand. It may be worthwhile therefore to explore strategies such as recycling of devices to increase availability and affordability. Reuse has been practiced since the 1970s. The commonest access route used was the left subclavian vein (70.6%) with the left cephalic vein used in 13.1% of cases. The left cephalic vein is associated with fewer complications such as pneumothorax and haemothorax.

In our study population complications were recorded for 19 patients (8.9%). Most complications (68.4%) occurred within 6 months of device insertion. According to a European registry most complications occur within 6 months (17). Falase *et al* (9) reported complications in 19.6% of their patients. Five point nine per cent had lead displacements, 5.9% had pacemaker infections, 3.9% had pocket erosions and there was one pacemaker related death. Thiam *et al* (10) in Dakar reported complications in 9 patients out of 92 who had undergone pacemaker insertion (9.9%). infection was encountered in 5, 3 had lead displacements, one had pacemaker syndrome. Our figures are lower which could be explained by the fact that this was a retrospective study and as we were not able to retrieve the full complement of records there may have been selection bias. In addition not all the patients who received pacemakers at KNH continued their follow-up here and therefore complications may have been recorded at another facility.

The most common complication was lead dehiscence. Lead related complications are the commonest complications encountered in the USA (21). The estimated risk of infection from studies done in the USA is 1-2% (21). Our infection rate was comparable at 1.4%. Antibiotic prophylaxis was used routinely in 93.9% in our setup. This may explain the low infection rates. Most patients had the procedure done under local anaesthesia which may explain the low rates of hospitalisation. Most patients were admitted and discharged home the same day (68%). Use of local anaesthesia may also increase ability to tolerate the procedure by even the extremely elderly patients. The oldest patient to undergo the procedure was 98 years old. Three patients developed haematomas at the site of incision. Two of them had a history of prior anticoagulant use. All bleeds resolved with conservative management. Two patients had asystole during insertion, one had ventricular tachycardia and one experienced angina. Resuscitation was successful for all. There were no mortalities during the insertion procedure.

Verbal confirmation was used to establish vital status in this study. Mutuga *et al* (22) applied the same method in his study on the outcomes for patients with ambulatory heart failure. Through phone calls we were able to confirm that at the time of the study 69.2% of the patients whose records were retrieved were alive. The mean duration lived with a pacemaker after insertion was 3 years with a range of 1 year to 16 years. Prior to the age of pacemakers 75 to 90% of patients were dead within 5 years (23). We confirmed that 7.9% of the patients were deceased at the time of the study. We could not establish the vital status for 22.9% of the patients because of missing phone contacts in the record (11.2%) as well as no response to calls (11.7%).

Conclusion

The uptake of pacemaker therapy has been increasing from year to year over the period from 2010 to 2015 at KNH. Majority of the patients who underwent the procedure were elderly with co-morbidities. Our complication rates are low compared to other developing countries with low infection rates and no mortalities during the procedure. The commonest indication for pacemaker insertion is complete heart block and most patients received dual chamber devices.

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Original paper

Prevalence of Systemic Hypertension in Kenya: A Multicentre Analysis of the Karen Hospital Database

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Abstract

Background: Systemic hypertension is the leading cause of morbidity and mortality also known as a silent killer among non-communicable diseases. The World Health Organization (WHO) estimates that 36 million of the 57 million deaths that occurred worldwide in 2008 were due to Non Communicable Diseases (NCD) making this the leading cause of death with a 63% mortality rate.
Objective: To evaluate the prevalence of systemic hypertension in Kenya.
Design: This was a retrospective and descriptive study covering a one week database from 16th to 23rd July 2017 making a sample size of 1718 in 12 clinics.
Methods: The database analyzed was from 12 outpatient clinics of the Karen Hospital located in different areas of Kenya namely; The main Karen Hospital located at Langata road, Karen, Nairobi with two clinics (Nairobi Heart Clinic and Accident & Emergency), Town clinic Nairobi, Nakuru, Nyeri, Thika, Karatina, Meru, Ngong, Kitengela, Rongai and Naivasha. Variables extracted from the hospital information system, Insta 12.0 of the Karen Hospital were transferred to Microsoft excel and Spss for analysis.
Results: The normal blood pressure counts for 31% while optimal reach 21%. High normal blood pressure was 18%. The total prevalence of hypertension was 30% subdivided in grade1 hypertension 10%, grade 25%, grade 2 2% and 13% with isolated hypertension. Male clients were nearly twice more likely to be hypertensive compared to their female counterparts (p-value=0.000) and age as well as site location. Additionally, prevalence and likelihood of hypertension increased with age of patients (p-value=0.000 from 41 to 80 years and p-value = 0.008 for age>80). Furthermore, the risk of hypertension was more than twice likely to be reported among overweight and obese patients compared to those who had normal weight after adjusting for Body Mass Index (BMI) with respectively P-value=0.001 and 0.000. More than half of patients in Kitengela and Nairobi Heart Clinic had hypertension. On the Contrary, very few cases of hypertension were reported in Karatina and Naivasha. As the overall hypertension prevalence was 30%, this is alarming to the nation and emergency policies need to be in place.
Conclusion: The prevalence of hypertension was 30% with hypertension likelihood increases with age from 41 to 80 years old. It depicts a necessity of a comprehensive health care management policy which can incorporate prevention measures (diet, physical activity, weight loss, avoid smoking), clear management guidelines and policy formulation.

Key words: Hypertension, Kenya, Prevalence, High blood pressure, NCD

Introduction

Systemic hypertension is the leading cause of morbidity and mortality also known as a silent killer among Non-Communicable Diseases (NCD) (1). Normal blood pressure is considered 120/80 mmHg. Pre-hypertension is characterized by 120-139 systolic and 80-89 diastolic blood pressures. Stage 1 hypertension is characterized by 140-159 systolic and 90-99 diastolic pressures. Levels above the stage 1 range qualify as Stage 2 hypertension, and medications are required to avoid a cardiac emergency (2). Individuals with pre-hypertension have a higher risk of developing hypertension compared with those with ideal blood pressure levels; also, they have an increased risk of cardiovascular morbidity and mortality (3). Hypertension is the leading contributor to cardio-vascular diseases burden and is the primary cause of coronary artery disease, atherothrombotic and haemorrhagic stroke, hypertensive heart disease, heart failure and kidney failure (4). Hypertension is mainly associated with environmental and lifestyle factors and has a stronger association and causal link with some particular behaviors: tobacco use, excessive

use of alcohol, physical inactivity, high salt intake and, insufficient fruit and vegetable consumption and obesity (5). More than 1.5 billion individuals are estimated to currently have hypertension worldwide and this is a major public health problem that affects approximately 26% of adult population (6). The World Health Organization (WHO) estimates that 36 million of the 57 million deaths that occurred worldwide in 2008 were due to Non-Communicable Diseases (NCD) making this the leading cause of death with a 63% mortality rate (7). It is estimated that in 10 years global NCD deaths will increase by 17%. This number will even be greater in developing African nations where estimations reach 27% increase, among them, Kenya (8). Fortunately, according to WHO data, 80% of deaths due to NCD such as Cardiovascular Disease (CVD), stroke, and diabetes are preventable by controlling the risk factors (9). The condition is emerging in Low and Middle-Income Countries (LMICs) where health resources are scarce and stretched by other non-communicable and communicable diseases burden (10). Currently, the burden of hypertension is greatest in LMICs and it affects about 1 in every 5 of the adult population and it is projected that by 2025, almost 3 out of every 4 people with hypertension will be living in LMICs (11). It is currently estimated that in some settings, high blood pressure accounts for more than 40% of adults. The prevalence of hypertension has increased significantly over the past two to three decades. There were approximately 80 million adults with hypertension in sub-Saharan Africa in 2000 and projections based on current epidemiological data suggest that this figure will rise to 150 million by 2025 (12). The levels of hypertension are estimated higher in urban than in rural areas simply because of contextual and behavioral factors linked to urban environments such as dietary changes and sedentary lifestyle which form a complex system conducive for developing hypertension. As Africa becomes more urbanized, the prevalence of hypertension will continue to increase (13). A prevalence of range from 19.3% in Eritrea to 39.6% in Seychelles was reported in 20 African countries between 2003 and 2009 using a WHO STEPS survey (14). In studies done in South Africa and Democratic Republic of Congo reported 10% high prevalence in urban than the rural area. In sub-Saharan Africa, the disease prevalence ranges from 6 to 48% (15). In Kenya, the initial survey in 1986 done in a regional centre, both rural and urban population reported a non-standardized hypertension prevalence of 6.4% (16). In 2008, another study restricted to the population aged over 50 years in Nakuru in the year 2008 reported a prevalence of 50.1%. Similarly, a survey done in rural Kenya which included a sample of a specific target group composed of members of dairy farmer cooperatives and their families in the Nandi district, showed age-standardized prevalence of hypertension of 21.4% (17). Data from Nairobi collected from the adult population in two slum settlements show a prevalence of hypertension at 19% (18). Beside WHO STEPS survey, no study in Kenya has been done covering more than one clinical centre in different cities of Kenya. This study comes as an evidence-based with a multi centre study of prevalence of hypertension. The objective of this study is to evaluate the prevalence of hypertension in Kenya.

Materials and methods

Setting: The Karen Hospital opened its doors in 2006 in Karen, an urban and high income residence area located at 15 km from Nairobi Central Business District (CBD), Kenya. A 102 bed capacity hospital offering different health care services but more specialized in cardio-vascular diseases and holding a high standard leading cardiothoracic surgery specialty department in the region. The hospital is ISO 9001:2015 certified by Kenya Bureau of Standards (KEBS) and ranked among three top health care tourism destinations in Kenya. The Karen Hospital management team runs the main hospital and ten outpatients satellites clinics with top quality health services across Kenya, namely; Main hospital (with two different clinics: Nairobi Heart Clinic and the Karen Hospital accidents & Emergencies), Town clinic, Nakuru, Nyeri, Thika, Karatina, Meru, Ngong, Kitengela, Rongai and Naivasha making a total of 12 clinics (Referred as research centres in this study). The Karen Hospital (main) and satellites conduct weekly cardiovascular outreaches by different cardiologists under the supervision of a senior cardiologist with more than 40 years of experience in cardiology. Cases which need interventions are transferred to the main hospital for further investigations and management.

Study design: This is a retrospective and descriptive study covering a one week database from 16th to 23rd July 2017 making a sample size of one thousand seven hundreds and eighteen in twelve clinics after data cleaning. This study focuses on the prevalence and does not include factors affecting hypertension

Study area: The database analyzed was from 12 outpatient clinics of the Karen Hospital located in different towns of Kenya namely The main Karen Hospital located at Langata road, Karen, Nairobi with two clinics (Nairobi Heart Clinic and Accidents & Emergencies), Town clinic Nairobi Central Business District (CBD), Nakuru, Nyeri, Thika, Karatina, Meru, Ngong, Kitengela, Rongai and Naivasha. These areas were chosen because of the locations of the clinics and secondary data were available for analysis after extracting it from insta 12.0 database.

Inclusion and exclusion criteria: The data for all clients aged between 2 and 99 years who visited the Karen Hospital in the following outpatient clinics for general consultation, general check-up or cardiology (Main hospital, Town clinic, Rongai, Ngong, Thika, Nakuru, Meru, Nyeri and Kintengela) during the period of 16th to 23rd July 2017 were included in the study. Inpatient clients were excluded.

Data collection technique: This study used secondary data from the Karen Hospital database stored in the health information system known as INSTA version 12.0. The data of clients who met the inclusion criteria were reviewed and extracted from the Karen Hospital insta 12.0 database by the researcher helped by a data manager using an excel sheet. After data cleaning, the database was transferred to SPSS for further analysis.

Data management and analysis: Variables extracted from hospital information system (Insta 12.0 of the Karen Hospital) were transferred to Microsoft excel, missing data were identified, cleaned and transferred to SPSS for analysis. Descriptive data were analyzed using Microsoft excel by summarizing the categorical data into proportions and continuous data into means and median. Correlations and associations were analyzed using SPSS version 16.0 and multiple regression analysis was performed at confidence interval of 95% and the level of significance at 5%. Odds ratio was used to show the likelihood of association between variables.

Ethical consideration: An approval of the Karen Hospital ethics committee was obtained and the confidentiality of the medical records was guaranteed. Data collected were for the purpose of this study only and no client identity was exposed during data manipulation and analysis.

Results

Demographic characteristics: This section presents the descriptive results of this study where 1718 clients (after data cleaning) seen in outpatient consultations from 12 health facilities managed by the Karen Hospital within a period of one week covering from 16th to 23rd July 2017. Sex ratio female to male was 14:10. The mean age was 42.6 years ranging from 2 years to 99 years. Twenty eight per cent of the client had normal body mass index, 5% were underweight, 34% were overweight and 34% were obese. The Karen Hospital (main) was leading in numbers of clients with

Table 1: Demographic characteristics

		Frequency	Percent
Gender	Female	1,006	58.6
	Male	712	41.4
Age (years)	≤ 20	153	8.9
	21 – 40	716	41.7
	41 – 60	603	35.1
	61 – 80	196	11.4
	> 80	50	2.9
BMI	Underweight	47	4.9
	Normal	265	27.6
	Overweight	325	33.9
	Obese	323	33.7
Centre	Karatina	76	4.4
	Kitengela	77	4.5
	Meru	284	16.5
	Nairobi Heart Clinic	80	4.7
	Naivasha	19	1.1
	Nakuru	225	13.1
	Ngong	45	2.6
	Nyeri	190	11.1
	Rongai	76	4.4
	The Karen Hospital	439	25.6
	Thika	91	5.3
	Town Clinic	116	6.8

26% followed by Meru with 17%. The lowest number of clients was registered in Naivasha clinic 1%.

Prevalence of hypertension: The normal blood pressure counts for 31% while optimal reach 21%. High normal blood pressure was 18%. The total prevalence of hypertension was 30% subdivided in grade1 hypertension 10%, grade2 5%, grade3 2% and 13% with isolated hypertension (either high systolic or diastolic alone). This means that one client out of three (1/3) who consults in the mentioned facilities was hypertensive regardless of the grade of the hypertension (Figure 1).

Figure 1: Prevalence of hypertension

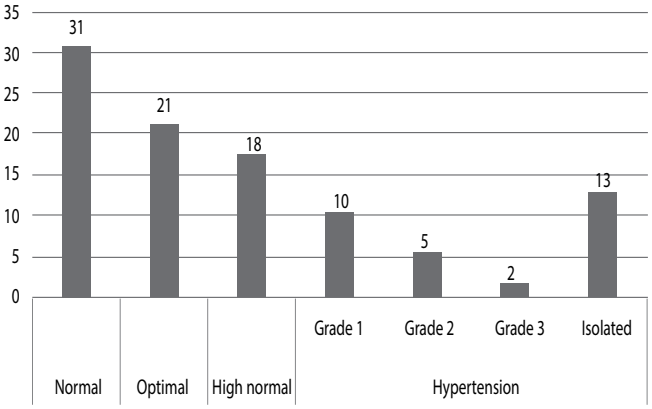

Table 2: Hypertension and its correlates

		Hypertension		OR CI [95%]			
	No	Yes	OR	Lower	Upper		P-value
Gender	Female	73.6	26.5	Ref	Ref	Ref	Ref
	Male	64.7	35.4	1.97	1.42	2.72	0.000
Age (years)	<=20	92.8	7.2	0.49	0.20	1.23	0.128
	21 - 40	82.4	17.7	Ref	Ref	Ref	Ref
	41 - 60	58.1	41.9	2.65	1.81	3.89	0.000
	61 - 80	47.2	52.8	3.83	2.29	6.41	0.000
	>80	52.0	48.0	3.25	1.36	7.73	0.008
BMI	Underweight	93.5	6.5	0.63	0.17	2.28	0.480
	Normal	85.2	14.8	Ref	Ref	Ref	Ref
	Overweight	70.7	29.3	2.17	1.36	3.46	0.001
	Obese	61.2	38.8	2.79	1.74	4.46	0.000
Centre	Karatina	44.0	56.0	Ref	Ref	Ref	Ref
	Kitengela	92.2	7.8	0.08	0.03	0.27	0.000
	Meru	60.8	39.2	0.16	0.04	0.59	0.006
	NairobiHeart Clinic	44.3	55.7	0.60	0.25	1.42	0.243
	Naivasha	94.7	5.3	0.09	0.01	0.77	0.028
	Nakuru	71.1	28.9	0.34	0.16	0.73	0.005
	Ngong	62.2	37.8	Ref	Ref	Ref	Ref
	Nyeri	66.8	33.2	0.30	0.13	0.70	0.005
	Rongai	76.3	23.7	0.36	0.12	1.07	0.066
	The Karen Hospital	75.5	24.5	0.29	0.14	0.61	0.001
	Thika	74.7	25.3	0.35	0.15	0.83	0.017
	Town Clinic	83.6	16.4	Ref	Ref	Ref	Ref

OR – Odds Ratio; CI – 95% Confidence interval

Hypertension and its correlates: Male clients were nearly twice more likely to be hypertensive compared to their female counterparts (p-value=0.000) and age as well as site location. Additionally, prevalence and likelihood of hypertension increased with age of patients (p-value=0.000 from 41 to 80 years and p=value = 0.008 for age>80). Furthermore, the risk of hypertension was more than twice likely to be reported among overweight and obese patients compared to those who had normal weight after adjusting for Body Mass Index (BMI) with respectively P-value=0.001 and 0.000. More than half of patients in Kitengela and Nairobi Heart Clinic had hypertension. On the contrary, very few cases of hypertension were reported in Karatina and Naivasha (this may be linked to the low sample size in Karatina and Naivasha) (Table 2).

Discussion

Sex ratio female to male was 14:10. The mean age was 42.6 years ranging from 2 years to 99 years. Twenty eight per cent of the clients had normal body mass index, 5% were underweight, 34% were overweight and 34% were obese. This means that 68% of the population sampled is on high risk of developing high blood pressure if no preventive measures is taken. Male clients were nearly twice more likely to be hypertensive compared to their female counterparts (p-value=0.000). This gap can be explained by the fact that males are more involved in lifestyle behaviors than females and they are also rarely screened if they are not sick. On the contrary, females are more screened during special clinics like antenatal and the raise of hypertension can be captured early enough. The results of this study correlate well with those of Olack *et al* (19). in 2015. Hypertension likelihood increased with age of patients (p-value=0.000 from 41 to 80 years and p=value = 0.008 for age>80). With current literature, the likelihood of high blood pressure increases at age of 40 years. The results correlate with the study by Senthil and Krishnadasa (20) in 2016. The main Karen Hospital was leading in numbers of clients with 26% followed by Meru with 17%. The lowest number of clients was registered in Naivasha clinic 1% because the clinic was new and the flow of patients was still low at the time of the study. The total prevalence of hypertension was 30% subdivided in grade1 hypertension 10%, grade2 5%, grade3 2% and 13% with isolated hypertension. This prevalence compares well with that of Bonita *et al.* with World Health Organization (WHO) steps survey conducted between 2003-2009 in 20 African countries which reported by then a prevalence rate ranging from 19.3% and 39.6%. In Dhaka (Pakistan), in 2015, the age-adjusted hypertension prevalence and pre-hypertension in 730 participants was 23.7 and 19%. A study done in an urban slum of Nairobi and published in 2014 showed a prevalence of hypertension of 23% and 60% pre-hypertension. High blood pressure was also correlated with the location of the clinic, Kitengela (P=0.000), Nakuru (p=0.005), Nyeri (p=0.005) and the Karen Hospital (p=0.001). High blood pressure and Kitengela correlate and the reason is not well known but the area is a dry and scarcity of water is high compared to other studied areas. The same study gives correlation between hypertension and the Karen Hospital. This area is an urban area with high income earning within Nairobi city. This links to the argument that the population in urban area is more likely to have hypertension than rural reasons being that urban population is more exposed to lifestyles behaviors and lack of physical activity, and a probable more pollution than rural. An Indian study showed that the prevalence of hypertension increased around 30 times in urban populations over 25 years, and by 10 times in rural populations over 36 years (21).

Conclusion

The normal blood pressure counts only for 31% while optimal reach 21%. High normal blood pressure was 18%. The total prevalence of hypertension was 30% with hypertension likelihood increases with age from 41 to 80 years old. This means that one client out of three (1/3) was hypertensive. This prevalence raises an alarm for a said silent killer in Kenya and beyond. It depicts a necessity of a comprehensive health care management system which can incorporate prevention measures (diet, physical activity, weight loss, avoid smoking), clear management guidelines and policy formulation. Kenyan health care system policy-makers should focus on NCDs especially hypertension if the country has to reach universal health coverage.

Policy implications

As a multicenter study in Kenya, this paper will contribute to shade more light on prevalence of hypertension in Kenya and therefore, policy makers will use this information to design appropriate policies for prevention and management of hypertension in the Country.

Conflict of interest

Authors declared no conflict of interest.

Limitations

This study has some limitations that can be considered while interpreting the results. Analyzed data were meant for other purpose; therefore some data were missing therefore not representative of the diverse

group of people living in Kenya. Thus, the results might not represent other parts of Kenya. Larger studies collecting population data from both urban and rural areas may provide a better estimate of the prevalence.

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Review article

Bronchiectasis in Adults: A review

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Abstract

Background: Bronchiectasis is a common lung disease that has for long been neglected. It is frequently a complication of previous infections of the lung, including bacterial pneumonia, chemical injury to the airways, or is due to underlying systemic illness. Patients may have a predisposing congenital disease, immune disorder, or inflammatory disease. In almost half of cases no cause is identified. Clinically significant bronchiectasis is characterized by the presence of cough and sputum production and demonstrable bronchial dilatation on imaging studies of the lung. The diagnosis is confirmed by high-resolution CT scans. Management is multimodal, and includes physiotherapy and antibiotics. Surgery is occasionally required for limited disease with frequent exacerbations and troubling symptoms. The prognosis for patients with bronchiectasis is variable given the heterogeneous nature of the disease

Objective: The aim of this paper is to provide an up to date review of bronchiectasis in adults. This will encompass all aspects of the disease but with special emphasis on recent research findings and guideline recommendations on management.

Data source: Material for this review is obtained from a perusal of recent published literature on bronchiectasis among adult patients.

Conclusions: A tailored, patient-focused approach is needed to optimally evaluate and treat individuals with bronchiectasis. Acute exacerbations should be treated with antibiotics for 14- 21 days. A new isolate of *pseudomonas aeruginosa* warrants bacterial eradication therapy. Those who suffer more than 2 exacerbations in a year should be offered long term antibiotic therapy. Regular physiotherapy and pulmonary rehabilitation remain the backbone of management. Mucoactive agents are used as add-ons among those with persistent mucus problems despite optimal physiotherapy. There is little role for long term bronchodilators nor anti-inflammmatory agents.

Key words: Bronchiectasis, adults, lungs

Introduction

Bronchiectasis is a lung condition characterized radiologically by abnormal and permanent dilatation of bronchi that manifests clinically with a syndrome of cough, sputum production and recurrent bacterial infections (1). Hitherto a neglected disease recent years have seen a resurgence of interest with new research and development of new therapies.

Bronchiectasis was first described by René Laennec in 1819 (2). In 1922 Jean Sicard introduced contrast bronchography into medical practice which made possible accurate imaging of the destructive changes in the airway. This remained the diagnostic modality of choice until it was superseded by High Resolution Computerized Tomography (HRCT) scanning. Lynne Reid in the 1950s meticulously compared bronchography with the gross pathology of resected lobes and classified bronchiectasis into cylindrical, varicose and cystic forms (3).

Patients with bronchiectasis have daily cough with production of mucopurulent sputum. Those with severe disease expectorate copious amounts of sputum, and may have hemoptysis. They may also have foul smelling breath. If the disease is advanced with extensive lung damage dyspnoea sets in as a result of respiratory failure.

Numerous conditions may give rise to bronchiectasis. These include infections, allergic, genetic, anatomic, and autoimmune disorders. In a large number of patients a predisposing condition cannot be identified.

The prevalence of bronchiectasis in Kenya is not known. Globally prevalence is not precisely known and has been historically underestimated. Recent data shows that prevalence is on the rise worldwide. The disease has been estimated to be present in 52 persons per 100 000 inhabitants in the USA (4).

The impact of bronchiectasis on healthcare systems is significant. Recent European data demonstrate an

annual exacerbation rate of 1.8 to 3% per patient, with a hospitalization rate of 26.6 to 31.4% (5). In the largest cohort of patients reported so far, 50% of patients died from respiratory causes while a quarter died from cardiovascular causes (6).

Pathophysiology

The pathophysiology of bronchiectasis is still not fully understood, partly because there are no animal models. Infection or other insult triggers inflammation of bronchi. This is the initiating event according to Cole's vicious cycle hypothesis (7). The inflammation is neutrophilic, driven by a high concentration of neutrophil chemo-attractants such as interleukin 8 and leukotriene B4. Biopsies show transmural inflammation with cratering of the mucosa and neovascularization of medium sized bronchi. Loss of structural integrity results in bronchial dilatation.

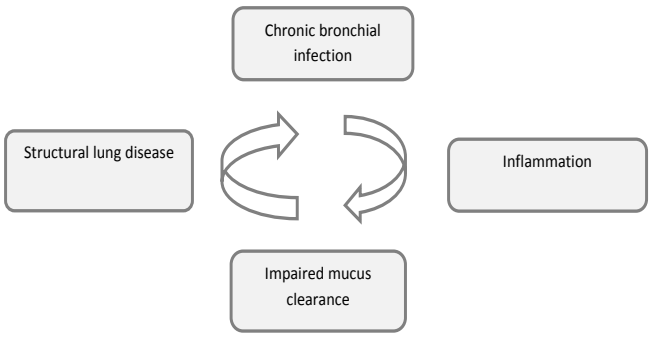
The muco-ciliary apparatus becomes dysfunctional with resultant accumulation of mucus in bronchi. Muco-ciliary clearance is impaired by the structural changes in bronchi, airway dehydration, excess mucus volume and viscosity. Neutrophil elastase plays a role in this by its effects on epithelial cells which include slowing of ciliary beat frequency, and inducing mucus hypersecretion (8).

Bacterial colonization occurs because of impaired mucus clearance and failure of neutrophil opsonophagocytic killing. Elastase impairs opsonophagocytosis through cleavage of opsonins from the bacterial surface as well as cleavage of neutrophil surface receptors FcγRIIIb and CD35. Alpha defensins released from neutrophil granules also impair phagocytic activity. Other mechanisms of immune dysfunction include failure of clearance of apoptotic cells and T cell (Th17) infiltration (9).

Recently 16S rRNA sequencing techniques have shown that the airways, even in normal people, are colonized by polymicrobial communities of bacteria (10). The colonizers in bronchiectasis include common organisms like *Pseudomonas aeruginosa, Haemophillus influenza* and *Moraxella catarrhalis*. Moreover, organisms previously not recognized by culture-based studies like Veilonella, Prevotella and Neisseria species have been identified. Loss of diversity, with dominance of one or two species, is associated with more severe disease and exacerbations (11).

In addition colonizing bacteria have developed mechanisms of evading airway clearance. *Pseudomonas aeruginosa* for instance is able to induce formation of O antigen specific immunoglobulin G (G2 class) antibodies that protect it from complement mediated killing (12). Additional defects in the complement system have also been demonstrated such as mannose-binding lecithin deficiency associated with severe bronchiectasis.

Figure 1: The vicious cycle of bronchiectasis



Aetiology

Bronchiectasis is best viewed as a consequence of insult to the bronchial tree. The insults follow infections, toxic inhalations, congenital heritable conditions, immunological and systemic disorders (Table 1).

Childhood infections such as pertussis and recurrent bacterial pneumonias may damage the bronchial tree leading to bronchiectasis. Chicken pox, measles, and other viruses, may cause bronchopneumonia that similarly damages the bronchi. Childhood infections have been found in one USA series to account for 11% of bronchiectasis. In this series 35% of adults were found to have a history of remote pneumonia predating the symptoms of bronchiectasis (13).

Pulmonary tuberculosis is a leading attributable cause of bronchiectasis in Kenya. Mycobacteria cause necrotizing inflammation of the bronchi which causes structural damage and bronchial dilatation. Non tuberculous mycobacteria may cause a form of the disease called nodular bronchiectasis and may be problematic colonizers in established disease (14).

The human immunodeficiency virus has been reported as a predisposing condition to the development of bronchiectasis (15). This is most likely attributable to the markedly increased incidence of bacterial and mycobacterial infections in this condition. Immunoglobulin disorders such as primary hypogammaglobulinemia and immunoglobulin G subclass dysfunction have also been implicated (16, 17).

Inhalation of irritant substances may ultimately lead to bronchiectasis. Chronic aspiration of gastric contents has been found in an English series to account for 4% of cases of bronchiectasis (18).

Auto-immune related causes of bronchiectasis include the connective tissue diseases rheumatoid arthritis, Sjogrens syndrome (19), systemic lupus erythematosus and relapsing polychondritis. Inflammatory bowel diseases especially ulcerative colitis and to a lesser degree Crohn's disease are associated with bronchiectasis among other thoracic manifestations (20). Bronchiectasis may antedate the onset of bowel symptoms in ulcerative colitis.

The pathogenesis of bronchiectasis in auto-immune conditions is poorly understood.

Long standing poorly controlled Chronic Obstructive Pulmonary Disease (COPD), may lead to the development of bronchiectasis. Fifty per cent of chronic stable patients with COPD were found on high resolution CT scanning to have bronchiectasis (21). Three per cent of patients with severe persistent asthma have been found to have bronchiectasis (22). The mechanism in these two conditions is thought to be similar to that in allergic bronchopulmonary aspergillosis.

Congenital causes of bronchiectasis include ciliary dyskinesia, α-1 antitrypsin deficiency and cystic fibrosis. Cystic fibrosis usually manifests in infancy but adult presentations may occur and should be considered especially among Caucasians below 40 years of age.

The cause of bronchiectasis remains unknown in 50% to 80% of cases even after extensive testing. This large category of idiopathic bronchiectasis represents a poorly understood subtype. This group may represent those who have currently unrecognized or undetectable immunological or autoimmune disorders.

Table 1: Predisposing conditions

Post infectious conditions	Bacteria: Bordetella, Pseudomonas, Heamophilus, Mycobacteria Viruses; Measles, Varicella, Adenovirus, Other viral pneumonias Aspergillus
Congenital conditions	Cystic fibrosis, Primary ciliary dyskinesia Alpha-1 antitrypsin deficiency, Marfan's syndrome, Cartilage deficiency (Williams Campbell syndrome) Tracheobronchomegaly (Mournier- Kuhn syndrome), Pulmonary sequestration, Young's syndrome, Yellow nail syndrome
Immunodeficiency disorders	Human immunodeficiency virus infection Immunoglobulin deficiencies
Inhalation sequelae	Chlorine, Heroine Aspiration pneumonia
Systemic inflammatory conditions	Ulcerative colitis, Crohn's disease, Systemic lupus erythematosus, Rheumatoid arthritis Sjogren's syndrome, Relapsing polychondritis
Pulmonary conditions	Asthma Allergic bronchopulmonary aspergillosis Chronic obstructive pulmonary disease
Airway abnormalities	Endobronchialtumours Foreign bodies

Clinical presentation

Cough is the clinical hallmark of bronchiectasis. More than 70% of patients expectorate sputum daily with highly variable sputum volumes (23).Sputum may be copious and foul smelling. Usually it is muco-purulent, with the colour varying from clear, through yellow to green. Patients often report coughing immediately they enter their beds at night, reflecting the effect of postural change on the cough.

Haemoptysis is a common presentation, usually mild but can be massive. Patients may have weight loss and shortness of breath. Dyspnoea sets in when sufficient lung has been damaged. Once corpulmonale and right heart failure set in, fluid retention with oedema may be found. Ascites and anasarca are, however, rare.

On examination there is usually a paucity of signs. Wasting and finger clubbing may be evident. Digital clubbing is found in a minority of patients. This sign was found in only 3% of patients in one series (13). On auscultation there will usually be found course crackles, and sometimes wheezes as well as rhonchi.

Natural history

Bronchiectasis exhibits a variable clinical course. Most patients have disease with symptom intensity that does not vary much over time and are said to have chronic stable disease. A minority experience acute exacerbations.

Some patients have daily symptoms and suffer progressive decline in lung function (24). Studies have shown an annual decline in forced expiratory volume in the first second (FEV1) of 50ml. An accelerated decline in lung function is associated with chronic colonization by *Pseudomonas aeruginosa,* a history of severe exacerbations, and evidence of systemic inflammation (25).

Acute exacerbations are characterized by marked worsening of symptom intensity with development of new respiratory symptoms and signs as well as imaging findings. Frequent exacerbations are associated with poor prognosis.

Mortality due to bronchiectasis is highest in patients with chronic hypoxemia, hypercapnia, and extensive radiographic disease (26). Bronchiectasis is also associated with cardiac abnormalities, including right ventricular and left ventricular systolic and diastolic dysfunction.

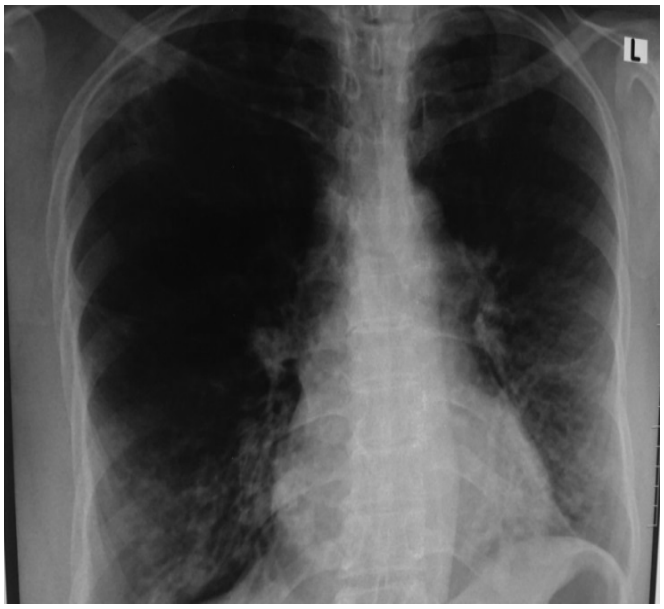
Diagnostic approach

Thorough history and careful physical examination are necessary. Sputum tests to exclude active tuberculosis are mandatory.

Radiology

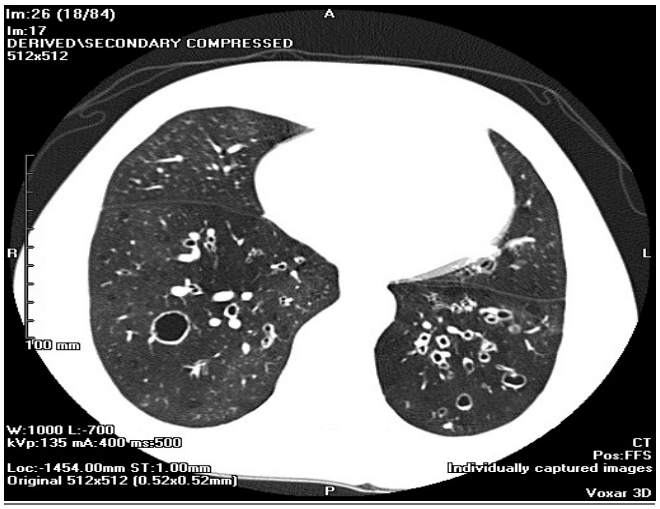
Chest radiography is an essential starting point. Classic features are tram lines, ring shadows, and peri-bronchial infiltrates. Suggestive chest radiographs with a compatible history are sufficient for diagnosis.

Figure 2: Chest radiograph showing ring shadows and tram lines at the bases



If bronchiectasis is suspected but the radiograph is non-diagnostic a high resolution CT scan is indicated. This shows dilated, thickened, non-tapering bronchi and demonstrates the various subtypes of bronchiectasis. CT scan is also needed if surgery is contemplated to confirm extent of disease.

Figure 3: High resolution CT scan of the chest showing dilated thickened bronchi, signet ring sign and air -fluid levels



Laboratory tests

A minimum bundle of tests to elucidate aetiology comprises of full blood count, serum immunoglobulin levels (IgA, IgM and IgG), and testing for allergic bronchopulmonary aspergillosis. These tests have meaning in terms of interventions that will have an impact on the disease. Sputum bacterial cultures should be done at each patient encounter for tracking purposes (1).

Acute exacerbation

Acute exacerbations are not always easy to diagnose. A combination of clinical and radiological signs is required. In a large series of bronchiectasis cases O'Donnel *et al* (23) used the presence of any four of the nine criteria in Table 2 to define an acute exacerbation of bronchiectasis.

Table 2: Criteria for diagnosing acute exacerbation of bronchiectasis

Increased cough
Change in sputum production
Increased dyspnoea
Increased wheezing
Malaise, lethargy, fatigue
Decreased effort tolerance
Fever
Changes in chest sounds
New infiltrates on chest X-ray

Management

The goals of management in bronchiectasis are to reduce symptoms, improve quality of life, prevent exacerbations, and stop disease progression.

Acute exacerbation

Acute exacerbations of bronchiectasis are attributed to infection. The most frequently isolated organisms are *Haemophilus influenza* and *Pseudomonas aeruginosa. Moraxella catarrhalis, Staphylococcus aureus* and *Enterobacteriaceae* are found less frequently (1).

Persistent isolation of these organisms in sputum or broncho-alveolar lavage fluid is associated with an increased frequency of exacerbations, worse quality of life and increased mortality (27). This is particularly the case with *Pseudomonas aeruginosa* infection, an organism that may be very difficult to eradicate.

Suitable empiric antibiotics should be those that are active against these organisms. The recommended duration of treatment is 14 to 21 days. Sputum specimens should be taken for culture and antibiotic sensitivity testing.

It may be possible to use shorter courses of antibiotics in mild exacerbations, those due to bacteria more sensitive to antibiotics such as *Streptococccus pneumoniae,* or patients with a rapid return to baseline state. However, there is no evidence to support shorter course treatment. Lack of recovery by 14 days of antibiotic therapy should prompt re-evaluation of the patient's clinical condition and a new microbiological investigation. Taking a sputum sample, at the start of an exacerbation, for culture and sensitivity testing is

helpful in guiding choice of antibiotics initial therapy fail (1).

Adequate hydration should be ensured. Muco-active agents are recommended if the sputum is difficult to expectorate. Chest physiotherapy should be enhanced during exacerbations typically being required more than two times a day. The only contraindication for this is significant haemoptysis.

Nebulization with bronchodilators is helpful before physiotherapy. It may also be employed if the patient has shortness of breath and is wheezing. Supplementary oxygen should also be administered as required.

Chronic stable disease

Chronic stable bronchiectasis is managed with regular physiotherapy, with the addition of muco-active agents in selected cases. Antibiotics are used for bacterial eradication therapy of specific troublesome organisms and on a long-term basis for patients with frequent exacerbations. Long term bronchodilators may be used in some cases whereas long term anti-inflammatory agents have been shown to have no role. Surgical intervention has a role in some patients.

1. Regular physiotherapy

This consists of airway clearance techniques and pulmonary rehabilitation. It deals with mucus problems, exercise intolerance and respiratory muscle weakness.

Airway clearance

This is the cornerstone of therapy. The patient is positioned such that the affected part of the lung is lower than the rest of the body. A method of loosening the secretions such as chest percussion is then deployed. The freed secretions are hence able to flow up the airways with the aid of gravity. This, done for ten to fifteen minutes, twice a day is sufficient for most patients. Breathing techniques such as active cycle of breathing are also useful.

Chest percussion may sometimes be combined with an instrument, such as the Acapella (Smiths Medical, London, UK), an oscillatory positive expiratory pressure device that modifies expiratory flow and volumes, in order to increase mucus clearance (28).

Airway clearance is recommended for patients with chronic productive cough or difficulty to expectorate sputum. Patients should be taught an airway clearance technique by a trained respiratory physiotherapist.

The principal effect obtained by airway clearance is an increase in sputum volume and a reduced impact of cough on quality of life (29). Other benefits of airway clearance may include reduced peripheral airways obstruction, fewer inflammatory cells in sputum and improved exercise capacity.

Pulmonary rehabilitation

Pulmonary rehabilitation, including respiratory muscle training, has been shown to be useful in patients with bronchiectasis (30). The aim of a pulmonary rehabilitation program is to improve exercise tolerance and quality of life through a tailored standardized exercise protocol.

Patients with bronchiectasis and impaired exercise capacity should participate in a pulmonary rehabilitation program and take regular exercise. All interventions should be tailored to the patient's symptoms, physical capability and disease characteristics. Pulmonary rehabilitation has been shown to have a clear beneficial impact on exercise capacity soon after the program. Studies have also shown a non-significant trend to improved quality of life. Improvements in exercise capacity and quality of life may be maintained far beyond the period of training.

Pulmonary rehabilitation, 8 weeks of supervised exercise training and review of airway clearance techniques, has been shown in one study to decrease the frequency of exacerbations over 12-month follow-up and lengthen time to first exacerbation (8 versus 6 months; p=0.047) (31).

Airway clearance techniques and pulmonary rehabilitation have been reported to have a beneficial effect on pulmonary function but this is not clinically significant.

2. Muco-active agents

Long-term muco-active treatment, for a minimum of three months, is advised in patients who have difficulty in expectorating sputum and poor quality of life, in whom standard airway clearance techniques have failed to control symptoms (1). Muco-active agents serve as airway clearance adjuncts. Their purpose is to alter mucus viscosity and, or, enhance mucociliary clearance.

Agents that have been shown to be beneficial in bronchiectasis are nebulized dry powder mannitol (320mg or 400 mg), and hypertonic saline (7%). There is little literature on oral mucolytics such as carbocisteine.

Mannitol in patients with two or more exacerbations in the preceding year and a baseline minimum St George's Respiratory Questionnaire (SGRQ) score of 30 was shown in one study to significantly improve total SGRQ score compared to controls (low dose mannitol). Whereas none of the muco-active agents have been shown to significantly reduce the number of exacerbations, in patients with two or more exacerbations in a year, mannitol has been shown to increase the time to first exacerbation. Mannitol has also been found to significantly increase twenty four hour sputum weight after treatment compared to control, consistent with improved muco-ciliary

clearance. No change in lung function has however been observed in studies with mannitol (32, 33).

Hypertonic saline 7% use has been demonstrated to reduce health care utilization when compared with isotonic saline. It has also been shown to significantly improve FEV1 and Forced Vital Capacity (FVC) at 3 months (34).

Overall inhaled long-term muco-active agents slightly prolong the time to first exacerbation and improve quality of life. They have a slightly elevated but acceptable adverse event rate of bronchospasm and dyspnoea. The indication and type of treatment given should, therefore, be tailored to each individual patient according to their baseline symptom profile, baseline lung function and patient preferences. Testing for tolerance is advisable prior to starting therapy and beta-agonist premedication should be considered (1).

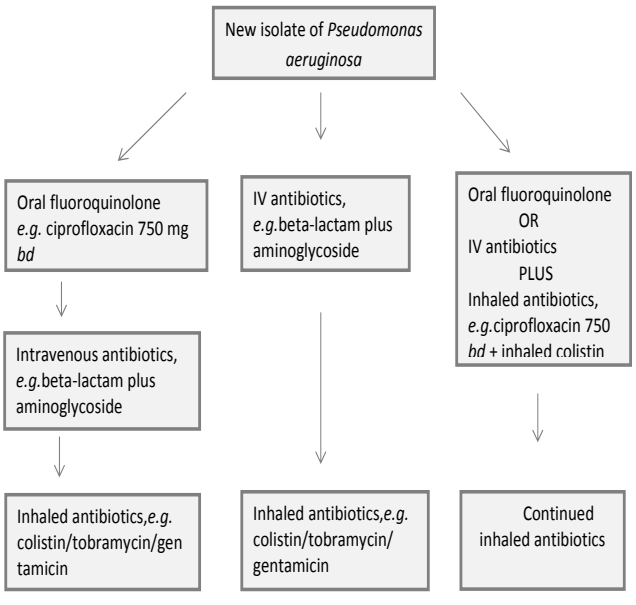
3. Bacterial eradication therapy

Antibiotic therapy, with the express purpose of achieving eradication of bacteria from the airways, is recommended among those who have a new isolate of a potentially pathogenic organism. This is especially so for *Pseudomonas aeruginosa* which has the propensity to establish chronic airway infection with deleterious effects (1).

Chronic airway infection is frequent in bronchiectasis and is usually associated with worse outcomes such as more exacerbations and poorer quality of life. The most frequent definition of chronic airway infection used in studies is two or more isolates of the same organism at least 3 months apart in one year (35).

Aerosolized antibiotics alone or in combination with oral or parenteral antibiotics should be used over a three month period with the aim of eradication. Suggested regimens are shown in Figure 4.

Figure 4: Suggested eradication combinations (1)



4. Long term antibiotics

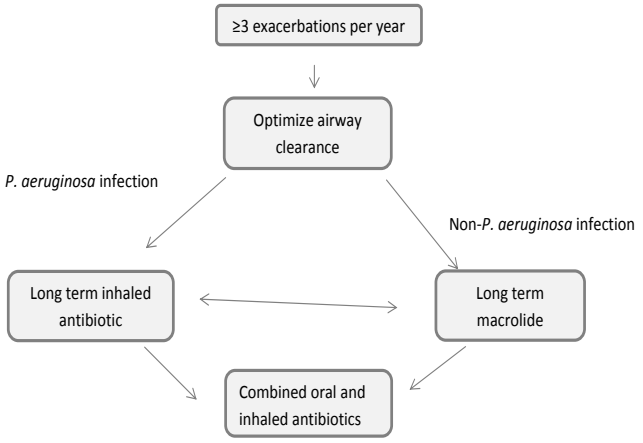
Patients with bronchiectasis who suffer more than two exacerbations in a year should be offered long term antibiotic therapy. However, before prescribing long-term antibiotics, airway clearance should be optimized and any underlying causes treated. Careful characterization of sputum pathogens (bacteria, mycobacteria and fungi) before and after implementation of long-term antibiotics is essential to direct antibiotic choices, monitor resistance patterns and identify treatment emergent organisms. Drug toxicity monitoring is also required, most notably with macrolides and inhaled aminoglycosides.

Chronic *Pseudomonas aeruginosa* infection is treated with inhaled antibiotics, such as tobramycin. Macrolides are an alternative if aerosolized antibiotics are not available. Macrolides should also be added to, or replace an inhaled antibiotic, for those who have a high exacerbation frequency despite taking an inhaled antibiotic.

Patients who are not infected with *Pseudomonas aeruginosa* should get macrolides. Besides their antimicrobial effects, macrolides have anti-inflammatory effects including inhibition of inflammatory cell migration, cytokine secretion and possible attenuation of the production of reactive oxygen species. They have also been proposed to cause reduction of biofilms surrounding virulent Gram-negative organisms such as *P. aeruginosa*. Other oral antibiotics, with the choice based on antibiotic susceptibility and patient tolerance, may be used in this category of patients if macrolides are contraindicated, not tolerated or ineffective. These include ß-lactams and tetracyclines. Inhaled antibiotics are advised in this category of patients if oral antibiotic prophylaxis is contraindicated, not tolerated or ineffective.

Long term antibiotic therapy reduces the number of exacerbations, time to first exacerbation, sputum purulence and breathlessness in patients with bronchiectasis. However, they are also associated with more adverse events and bacterial resistance (1).

Figure 5: Suggested long term antibiotic regimens (1)



5. Other measures

Long term bronchodilators: Routine use of long-acting bronchodilators, ß2 agonist or anti-muscarinic agents,among patients with bronchiectasis is not recommended. However, these agents may be considered for those with significant dyspnoea on a case by case basis. Quick onset bronchodilators are also useful before physiotherapy, or before administering inhaled muco-active drugs or inhaled antibiotics (1).

Long term anti-inflammatory treatment: Inhaled corticosteroids have not been found in studies to add any value to adults with bronchiectasis.

A study of inhaled budesonide 400µg twice a day or placebo with a primary outcome of lung function showed no benefit. There was also no benefit in the secondary outcome of reducing exacerbations (36).

Inhaled fluticasone versus placebo over 12 months in 86 patients with the co-primary end-points of twenty four hour sputum volume and annual exacerbation frequency also failed to show any benefit in the two end points (37).

Vaccination: All patients with bronchiectasis should be offered pneumococcal vaccination. Either of the two types of vaccine available may be used. However there is some evidence that the conjugate vaccine offers better protection. A vaccine against influenza A is also available. This should be given annually at the beginning of the long rain season which marks the influenza season in Kenya

Haemoptysis: Most patients with bronchiectasis who suffer from haemoptysis get the non-massive bleeding. Tranexamic acid and antitussive agents suffice to get this under control. Massive haemoptysis is life threatening and should be treated with percutaneous catheter based embolization or surgery.

Smoking cessation: Seven to eighteen per cent of patients with bronchiectasis in a large European cohort study were found to be active smokers (5). Smoking is an independent risk factor for mortality in bronchiectasis. Patients should therefore be encouraged to stop smoking.

Nutrition

Nutrition is also important, with lower body mass index being an independent risk factor for mortality. Vitamin D deficiency has been found to be common in bronchiectasis. This is associated with worse symptoms and chronic airway infection. Adequate intake of this vitamin should be ensured.

Surgery and transplant

Surgery is reserved for patients with localized disease and a high exacerbation frequency despite optimization of all other aspects of management. The rationale for surgery is to break the vicious cycle, removing lung segments that are no longer functional, and preventing the contamination of adjacent lung zones. The most frequent indication for operation is recurrent infections with chronic symptoms such as productive cough, purulent sputum and haemoptysis (38).

Lobectomy is the most frequently performed operation, but numerous options have been described including segmentectomy and pneumonectomy (39). The Video-Assisted Thoracoscopic Surgery (VATS) is often preferred to better preserve lung function or reduce scarring. In comparison with open surgery, VATS has been reported to produce comparable symptomatic improvement but with shorter hospital stay, fewer complications and less pain.

Patients with bronchiectasis and advanced lung disease despite compliance with maximal medical management should be considered for lung transplant if available. Indications for this are an FEV1 $\leq$ 30% predicted or an FEV1 > 30% predicted but with rapid decline, frequent hospital admissions, worsening cachexia, massive haemoptysis, resting hypoxemia or hypercapnia.

The future

This has been declared the age of bronchiectasis (40). New treatments are being developed focused on modulating inflammatory processes,including targeting neutrophil, macrophage, T-cell, and epithelial function to reverse underlying disease processes. There have been many trials of antibiotic treatment. A lot of the antibiotic trials have not been successful in reaching their endpoints, calling for a reassessment of how therapies in patients with bronchiectasis are tested.

Bronchiectasis is a heterogeneous disease that has numerous causes, with various radiological, microbiological, inflammatory, and physiological subgroups, referred to as phenotypes and endotypes. It is therefore unlikely that a one-size-fits-all approach to clinical trials and clinical practice will be successful. Instead the so-called treatable traits approach to airways disease, used in treatment of asthma and chronic obstructive pulmonary disease, could be applied to bronchiectasis, to improve therapeutic targeting both in clinical trials and clinical practice

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Successful Thrombolytic Management for Prosthetic Mitral Valve Thrombosis: An Analysis of Case Reports

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Abstract

Obstruction of a mechanical heart valve by a thrombus is a serious complication. Clinically, valve thrombosis presentation is usually not conclusive, as symptoms will vary based on the degree of obstruction of the prosthetic valve. Most patients however will present in heart failure. We present the management of three patients with mitral valve thrombosis which we managed at our institution successfully.

Key words: Heart valve prosthesis, Thrombolytic therapy, Thrombosis

Introduction

While a patient's clinical presentation may suggest a possible prosthetic valve complication, diagnosis requires direct visualization of the valve by various imaging modalities. Valvular obstruction should be considered when an unexpected rise in trans-valvular gradient is observed on Doppler echocardiography (1).

The differential diagnoses for prosthetic valve obstruction include pannus formation, prosthetic valve dehiscence, prosthetic valve endocarditis, chordae entrapment, patient-prosthesis mismatch and primary device failure. Development of a thrombus is usually dependent on factors such as valve design, location (mitral >aortic position) and sub-therapeutic anticoagulation. The presence of atrial fibrillation, or severe left ventricular dysfunction will also be influential (2).

Intravenous streptokinase may be life-saving in critically ill NYHA class III/IV patients with left-sided prosthetic valve thrombosis. Thrombolytic therapy is much cheaper and easier to administer than surgical replacement of the thrombosed prosthetic valve (3).

Case report 1

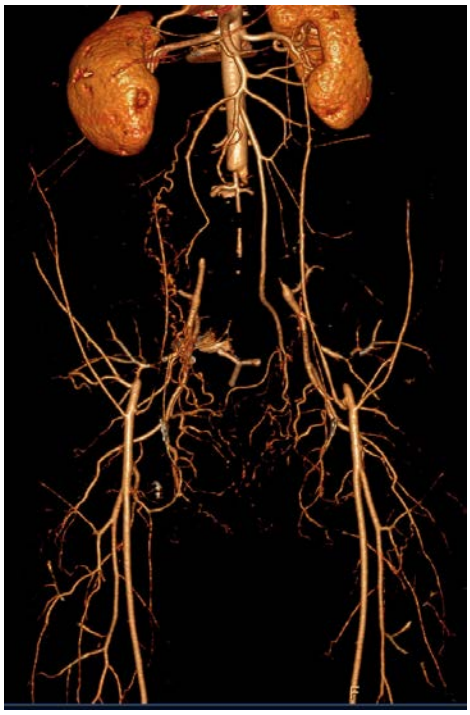
A 43-year-old female, known to have rheumatic heart disease for over twenty years, with a history of percutaneous valvuloplasty in 1997 and 2004. Mitral valve replacement for moderate to severe mitral stenosis, in November 2017. Surgery was successful with a good recovery and was discharged on warfarin and anti-failure therapy.

Three weeks later, on her second review, she presented with shortness of breath on exertion, inability to perform her usual daily activities, and orthopnea. On physical examination there was a reduced mitral valve click. ECG confirmed atrial fibrillation. Transthoracic echocardiography showed, mitral valve flow restriction, with a mass associated with the valve and an ejection fraction of 50%. International normalized ratio was 1.7.

She was administered 80mg of subcutaneous enoxaparin and thrombolysis with an infusion of 1.5million units of streptokinase over one hour. She remained clinically and haemodynamically stable. Repeat echocardiogram revealed normal prosthetic leaflet movements and valve gradient.

Post thrombolytic therapy, she was noted to have bilateral leg pain and decreased pulses in her feet. CT aortogram revealed a chronic total occlusion of her aortic aorta with multiple collaterals to the iliac vessels.

Figure 1: Complete occlusion of abdominal aorta



Case report 2

A 41-year-old female known to have HIV on HAART, underwent hysterectomy due to a uterine cancer in 2009 and had aortic valve and mitral valve replacement in March 2017 secondary to rheumatic heart disease.

She presented to our emergency department nine months later with complaints of difficulty in breathing on exertion. Blood pressure was 90/55mmhg, tender hepatomegaly and S1 and S2 valve clicks were present. INR was sub-therapeutic at 1.6. Transthoracic echocardiography revealed a severely reduced ejection fraction of 18.9%, with limited prosthetic mitral valve leaflet motion with a mass.

She was put on streptokinase 1.5 million units over one hour. The following morning transthoracic echocardiogram showed impaired movement of the posterior leaflet of the prosthetic mitral valve. A further 1.5 million units of streptokinase was repeated with intravenous steroid and antihistamine. She had markedly clinical improvement and the ejection fraction rose to 42.3% and normal prosthetic valve movement. She was discharged home ambulant and an INR of 2.8

Case report 3

A 55-year-old female was on treatment for epilepsy, had rheumatic heart disease diagnosed in 2007 and had severe mitral stenosis. Pre-operatively she had left atrial mass and atrial fibrillation. Mitral valve replacement was done in January 2017.

She presented one year seven months later with severe vomiting and seizures. Physical examination was significant for reduced valve click. Transthoracic echo revealed increased gradient across mitral valve and mitral valve area of 0.4cm^2 and normal ejection fraction. Transesophageal echocardiogram showed mass on posterior leaflet with no movement. This was confirmed on fluoroscopy.

She was put on streptokinase 1.5million units over 24 hours. Repeat transesophageal echocardiogram revealed normal valve movement. She was discharged on warfarin and aspirin.

Discussion

Thrombolysis is recommended as the first-line treatment for all patients with left-sided prosthetic valve thrombosis by the Society for Heart Valve Disease (4). Recently, several meta-analyses and systematic reviews have been published. Karthikeyan and colleagues evaluated seven studies with 690 episodes of PVT (446 treated with surgery and 244 with thrombolytic therapy) and found no significant differences in the main outcome (restoration of valve functions) between patients treated surgically and thrombolytic therapy (5). Intravenous streptokinase may be life-saving in critically ill NYHA class III/IV patients with left-sided prosthetic valve thrombosis. Thrombolytic therapy is much cheaper and easier to administer than surgical replacement of the thrombosed prosthetic valve (3). The TROIA and PROMETREE trials have both confirmed low dose slow infusion thrombolytic therapy is efficacious with fewer side effects (6). Long term management post thrombolysis, 2014 ACC/AHA valvular heart disease guidelines recommend a new INR goal of 3.5–4.5 and low dose aspirin in patients with prosthetic valve thrombosis (7). Furthermore, heparin should be continued with warfarin until INR reaches a level of 2.5, rather than only 48 hours after successful thrombolytic therapy (8).

Conclusion

In line with the above experience and evidence slow streptokinase infusion provides a more efficacious method for thrombolysis for valve thrombosis. Long term therapy should target an INR of 2.5-3.5 with the addition of aspirin. Diagnosis should incorporate transthoracic, transoesophageal and cine fluoroscopy. In addition, valve thrombosis may present with other evidence of thromboembolic disease.

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Epstein Barr Virus Meningoencephalitis in a HIV-Positive African Man on HAART for 15 Years: A Case Report

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Summary

Over 95% of the world's population has a history of Epstein Barr Virus (EBV) infection. Most people have self-limiting infections. However, 1-18% develop chronic cerebral complications such as meningitis and encephalitis due to immuno suppression. We report the case of a deceased HIV-positive African male(48-years) on Highly Active Antiretroviral Therapy (HAART) who complained of fever, changes in behavior or confusion, chronic dizziness and headaches. A gross external examination found no lesions or injuries on the body. A gross internal examination of the heart, major blood vessels, the kidneys, and the gastrointestinal system yielded unremarkable results. However, pathological signs of high intracranial pressure and military tuberculosis were evident in the brain and the lungs respectively. Histological analysis of brain and lung tissue revealed a chronic inflammation of the meninges and interstitia. Microbiological analysis of blood and Cerebro-spinal Fluid (CSF) detected an EBV infection. EBV meningoencephalitis was confirmed as the cause of death. Screening for EBV should be done if HIV patients complain of headaches and dizziness.

Introduction

The Epstein Bar Virus (EBV) is a member of the herpesviridae family of viruses. Discovered in 1964 in tissues of Burkitt's lymphoma, EBV infects B lymphocytes and induces an uncontrolled proliferation of cells with both acute and chronic pathological outcomes (1). In immuno competent patients, EBV is a self-limiting infection, which is also asymptomatic. However, in immuno compromised patients, it leads to the development of life-threatening neurological complications such as aseptic meningitis, encephalitis, and cerebral ataxia (2). These complications occur in 1-18% of patients and are associated with suffering and death (3). In Kenya, EBV infections are prevalent in malaria holoendemic zones and are associated with a high incidence of Burkitt's lymphoma. Diagnosis of EBV in rural or peri-urban hospitals is difficult due to the inaccessibility of imaging, serological, and molecular diagnostic tools for EBV (4). EBV infections are not detected early. As such, many patients often develop chronic end-stage complications, which are hard to treat and manage (5). Children are most at risk. In Black adults or Native Africans, EBV complications are poorly documented. We report a case of a deceased 48-year-old African male with EBV meningoencephalitis who was a known HIV patient on HAART from 2003.

Case report

Case history: We present a case of a HIV positive 48-year-old male on HAART from 2003 with a history of dizziness and headaches. Six months prior to his demise, the deceased had complained of chronic dizziness and headaches also had occasional changes in behavior or confusion. He was a moderately built African man with a good nutritional status.

Autopsy results: Gross external examination of the body did not reveal injuries/lesions. During internal gross examination, an extended mid line incision was made to open the body and the lettules method used to eviscerate the organs.

Central nervous system: The Brain weighed 1200 grams. An increased intracranial pressure was evident. This was demonstrated by the flattening of the gyri, shallowing of the sulci, and increased CSF pressures. The spinal cord was not exposed. The skull and meninges of the case were grossly unremarkable.

Cardiovascular system: The heart of the deceased was of a normal weight (300 grams).The major blood vessels were grossly unremarkable.

Respiratory system: Upon examination, the right and left lung of the diseases weighed 400 grams and 380 grams respectively. Both lungs had multiple tiny tubercles in the parenchyma, characteristic of miliary tuberculosis. The trachea, pulmonary vessels, mouth, and nasopharynx were all grossly unremarkable.

Genitourinary system: The right and left kidneys weighed 200g and 210g respectively. Kidneys were grossly unremarkable. Capsules peeled off easily, while both the ureters and the bladder of the case had a grossly remarkable outlook.

Gastrointestinal system: The mouth, tongue, and oesophagus of the case were grossly remarkable. The stomach, ileum, colon, liver, and pancreas were grossly remarkable.

Histopathological and microbiological analysis: Samples of the brain, lungs, kidneys, meninges, and the liver were collected for histological analysis. Samples of blood and cerebrospinal fluid (CSF) of the victim were aspirated for microbiological assessment.

Tissues of the brain and meninges had chronic inflammation. Lungs showed marked interstitial inflammation. However, liver and kidneys biopsies were unremarkable. The CSF tested positive for EBV. After post-mortem analysis, EBV meningoencephalitis was confirmed as the cause of death.

Discussion

Meningoencephalitis is an inflammation of the parenchyma of the brain and the meninges. Acute bacterial meningoencephalitis due to isolates of *Pseudomonas putida* and *Neisseria meningitides* are among the commonest forms of the disease in humans (6). Reports and case studies have also described EBV-induced encephalitis in children. Jang and Lee (8) presented the case of a 2-year-old child with asymptomatic lesions on the white matter of the brain following EBV encephalitis. Hashemian *et al.* (7) reported localized lesions on the basal ganglia of a 10-year-old with EBV encephalitis. However, reports of adult cases in Africa are few.

Residents of developing countries such as Kenya and Indonesia are most at risk of EBV infections (4,8). Children acquire EBV at a young age and live with the infection to adulthood. Viral infections such as HIV compromise the immunity of the body of adults, which reactivates latent EBV infections in the body. Our case was a resident of Kisumu County, a malaria holoendemic region in Kenya with a high incidence of Burkitt's lymphoma(9). Furthermore, due to his immuno-compromised state,he had a higher risk of contracting EBV and developing chronic complications. In a study by Oladipo *et al.,* one out of every 10 HIV positive adults had an active EBV infection. The incidence was highest among males aged 41-50 years old. As a preventive measure, screening for EBV infections should be a standard protocol for immuno-compromised adults in Kenya.

The deceased patient in this report had clinical features of a chronic EBV infection. Constitutional symptoms such as a headache and dizziness were reported six months prior to his demise. In malaria holoendemic areas, constitutional symptoms such as fever and headache are often misdiagnosed as malaria during clinical examination. They are indicative of acute EBV infection as well (7). Left untreated, complications such as encephalitis ensue and lower the quality of life of victims. As in case studies by Jang and Lee (10) and Widayanti *et al*.(8), this was the case for the deceased. He was of good nutritional status. Gross external examination was unremarkable. However, gross internal examination revealed few pathological signs of high intracranial pressure (flattened gyri and shallow sulci) (11). Co-infection of EBV and respiratory microbes is also a common occurrence in adults(12). We corroborated this finding. Signs of miliary tuberculosis in the lungs (tiny tubercles in parenchyma) were evident after a histopathological analysis of biopsies. This case report identifies the importance of standardized routine diagnosis of infection with well standardized platform such as the Taq Man Array Card (TAC) in detection of multiple pathogens simultaneously from the cerebro-spinal fluid (13).

Conclusion

Immuno-compromised adults have a high risk of developing chronic EBV infections and neurological complications such as meningoencephalitis. Coinfections with bacteria of the genus mycobacterium are also common. Regular screening for EBV infections is essential in at-risk populations such as HIV infected adults. Early detection and treatment of EBV in HIV patients can lower its viral load to the level of an immuno-competent individual(14). Unfortunately, because of negligence of constitutional symptoms and late diagnosis, many People Living with HIV/AIDs (PLWHA) develop complications such as EBV meningoencephalitis, which leads to death. It is therefore, important to do routine diagnosis of infections to detect multiple pathogens simultaneously from the cerebro-spinal fluid in immuno-compromised patients such as HIV/AIDS.

Acknowledgment

Dr. Benjamin Ndibile, a Kenyan pathologist who performed the autopsy.

Ethical considerations

Consent to do an autopsy was obtained from the family of the deceased.

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Short Communication

Growth Hormone Replacement in Patients with Hypopituitarism

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Abstract

Growth hormone has been in use for little over half a century and although its therapeutic indication in children with short stature is widely accepted, its use in adults remains controversial.

The aim of this short communication is to explore the various arguments for and against the use of recombinant growth hormone in adults with hypopituitarism in the light of recommendations from Professional Endocrine Societies.

Growth hormone replacement in patients with hypopituitarism

According to the Full Prescribing Information (FPI) from Eli Lilly, Humatrope® (Somatotropin r DNA), one of several preparations of recombinant growth hormone, is indicated for the treatment of children with short stature or growth failure associated with Growth Hormone (GH) deficiency, Turner syndrome, idiopathic short stature, SHOX (short stature homeobox) deficiency and failure to catch up in height by 2-4 years of age after Small for Gestational Age (SGA) birth. Additionally, Humatrope® is approved for treatment of adults with either childhood onset or adult onset GH deficiency (1).

Although there is general consensus on the paediatric indications of GH, controversy still surrounds the use of GH in adults (2). The basis of this discordance is perhaps best understood from a historical context. In the 1940's, the effects of GH were quickly observed to be species specific by Li and Evans at UCLA (University of California Los Angeles) Berkeley (3); and Fishman at Yale (4), through their work on purified bovine GH extracts. It was thus clear that GH would have to be sourced from the human pituitary gland, if its metabolic and biochemical activities were to be harnessed therapeutically. In 1956, GH was first isolated from the human pituitary gland by Li and Papkoff at Berkeley (5). In 1958, Raben (6) documented an increase in height of 2.6 inches per year (more than 5 times that during the pre-treatment period) in a 'pituitary dwarf' following administration of GH. These developments led to the formation of the National Pituitary Agency (NPA), the forerunner of the US National Hormone and Pituitary Program (7), and similar programs in Canada and Europe, to 'coordinate efficient collection and distribution' of scarce GH resource 'in a logical and sensible manner' to maximize availability for research and clinical use (8). By 1985, when the use of pituitary GH was suspended by the US FDA following reports of Creutzfeld-Jacob Disease (CJD) amongst four young adults who had received pituitary GH prior to adoption of more effective purification methods in 1978 (9), development of recombinant forms of GH (rhGH) was fairly advanced, the first having been developed by Genentech in 1981 (10). Approval of Genentech's synthetic Methionyl GH in October 1985 (11), ushered in the era of unlimited supply of GH, whose scarcity in the preceding 25 years had restricted its use to children with the most severe cases of growth hormone deficiency (12). In 1996, rhGH was licensed for use in adults with GH deficiency (13) an indication that was soon marred in controversy (14). The recent introduction of long acting rhGH preparations is likely to further expand clinical indications and use (15). Proponents of GH use in adults with hypopituitarism allude to the existence of a distinct adult Growth Hormone Deficiency (AGHD) syndrome defined as a "condition associated with weight gain, abnormal body composition (increased fat mass and decreased lean body mass), decreased bone mass, an atherogenic lipid profile, and increased cardiovascular risk in patients with documented growth hormone deficiency (16)". Isley (17) points out the lack of unambiguous evidence that AGHD phenotype is a result of isolated GH Deficiency (GHD) and notes that it might very well be related to pan-hypopituitarism. Indeed several components of AGHD resemble those of the metabolic syndrome (18) and are frequently seen in persons that are not GH deficient (2).

Second, earlier reports of increased mortality from excess cardiac and cerebral vascular risk amongst patients with hypopituitarism including a Swedish

cohort(19) suggested a possible pathological role for GHD, as these patients had received replacements of other anterior pituitary hormones. However, these studies were retrospective and observational; did not employ standardized measures of GHD, and had often included subjects who had received cranial irradiation (17), a treatment known to increase the risk of cerebrovascular disease. Further, the adequacy of replacement of other pituitary hormones remained undetermined (17), despite the fact that gonadotropin deficiency had been tied to increased mortality in a prospective study (20). Assuming that GHD was responsible for the excess mortality risk (Standardized mortality ratio, SMR 1.2-2.17) (20), GH therapy would be expected to reduce mortality in patients with hypopituitarism, an observation yet to be made. In another Swedish cohort, Svenson *et al* (21) concluded that GH therapy did appear protective against fatal myocardial infarctions but that there was a trend towards more cerebrovascular events. Interestingly, data from the Dutch National Registry of Growth Hormone Treatment in Adults (22) demonstrated an 'increased mortality rate for all-cause mortality in GH-treated GHD adults, especially in women, with a high mortality due to CVD.' Although it is not yet proven that GH replacement reduces mortality in patients with hypopituitarism, there is some consensus, though inconsistent, for beneficial effects on HDL and triglycerides (17), body composition, skeletal integrity, exercise capacity, Health Related Quality of Life (HRQoL) and cardiovascular risk factors (15,23).

Third, and closely tied to the second point, it remains unclear to what extent the abnormalities in AGHD are better off treated with highly efficacious, easier to use, and less expensive agents - statins, hypoglycemic, bisphosphonates, antiplatelet agents and other well established cardiovascular therapies - than with GH replacement (2,17). Illustratively, the annual cost of GH is estimated at 3000-10000 USD as compared to USD 1499, USD 131, and USD 711 for Simvastatin, Ramipril and Alendronate respectively (17). This cost-effectiveness argument is an important one from a health economic and resource allocation perspective. A recent simulation from Sweden found GH (Genotropin®) replacement in adults to be cost-effective (at the €55,371 per Quality adjusted life year, QALY, threshold) over a 20 year period with the effect being driven by improvements in Quality of Life (QoL), and reductions in mortality and intervention costs (24).

Fourth, long term GH replacement is not without risks such as increased BMI, increased waist-hip ratio, increased abdominal circumference, reduced insulin sensitivity, increased fasting glucose, increased lipoprotein (23), a trend towards more cerebrovascular events and persistence of higher mortality especially among women (21). Although GH therapy has been associated, with an increased risk of second malignancy in patients treated in childhood, this in itself does not imply causality (25) despite the recognized anabolic and anti-apoptic effects of IGF-1 in animal studies and studies involving human cancer cell lines (26). Furthermore a recent meta-analysis by Li *et al* (27), reported that GH therapy reduced the incidence of cancer (RR=0.69, 95%CI: 0.59-0.82) in adults with GH deficiency.

The current National Institute for Health and Care Excellence (NICE) guidelines last reviewed in 2014, recommends GH replacement in adults with hypopituitarism who meet three criterias (28);

(i) Severe GH deficiency defined by a peak response of less than 3ng/ml (9Mu/l) during an insulin tolerance test or cross validated GH threshold in an equivalent test.
(ii) Perceived quality of life impairment as demonstrated by a score of at least 11 in the QoL-AGHDA questionnaire (with discontinuation of therapy if score does not improve by 7 or more points after 9 months).
(iii) Already receiving treatment for other pituitary hormone deficiencies as required

Moreover young adults should be treated until final bone mass has been achieved (age 25 years) and the decision to proceed or stop treatment based upon adult criteria above.

According to the American Association of Clinical Endocrinologists (29), GH 'should only be prescribed to patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD.' The Endocrine society clinical practice guidelines (30) recommend GH in adults with hypopituitarism confirmed to have GH deficiency for its body composition, exercise capacity, skeletal maturity, quality of life and cardiovascular benefits; and that the dose be individualized.

Growth hormone is contraindicated in patients with active malignancy, active proliferative or severe non-proliferative diabetic retinopathy, hypersensitivity and acute critical illness (1).

In conclusion, there seem to be two paradigms at play, one which is to treat the most severe spectrum of AGHD where benefits of therapy outweigh risks; and two, to offer treatment to anyone with documented GH deficiency. Whether therapy should be lifelong or interrupted in old age (when GH requirements are few) is still unclear, but it is generally agreed that lack of response after 12 months of therapy is a good reason for discontinuation (15).

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