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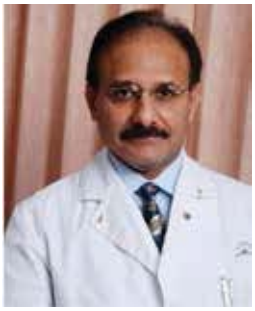

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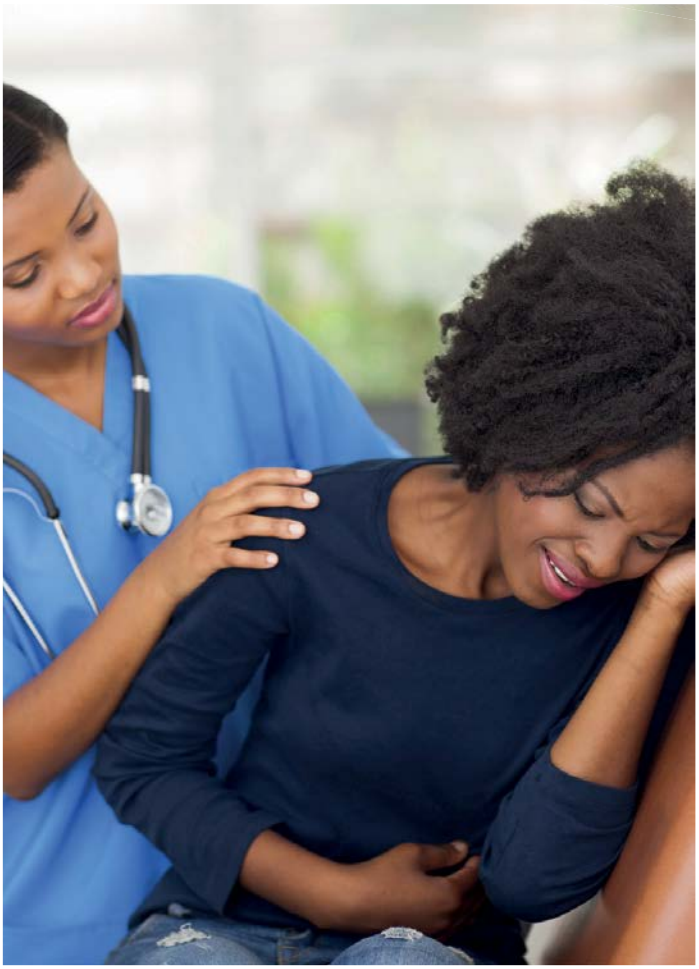
TAVANIC®
(levofloxacin 500 mg)

Clinical efficacy for treatment of the following indications caused by Gram negative, Gram positive & Anaerobic microbes [1]



Do it right first time

- Complicated UTI and pyelonephritis
- Community Acquired Pneumonia
- Intra abdominal infections
- Skin and Soft tissue infections
- Septicemia

	Indications[2]	Dosage	Duration
RTIs	**Sinusitis**	**500mg OD**	**10 - 14 days**
	Acute exacerbation of chronic bronchitis	500mg OD	7 - 10 days
	Community acquired pneumonia	**500mg OD or BD**	**7 - 14 days**
UTIs	Uncomplicated Urinary Tract Infection	250mg OD	3 days
	Acute pyelonephritis	250mg OD	7 - 10 days
	Complicated Urinary tract Infection	250mg OD	10 days
	Chronic Bacterial Prostatitis	**500mg OD**	**28 days**
Other Infections	Septicaemia	500mg OD	10 - 14 days
	Skin & Soft Tissue Infections	250 - 500mg OD	7 - 10 days
	Intra-Abdominal Infections	**500mg OD**	**10 - 14 days appropriate antibiotic with anaerobic activity**

1. Hurst M. et al. Levofloxacin: An Updated Review of its use in Treatment of Bacterial Infections; Drugs 2002; 62 (14) : 2127-2167
2. Tavanic [levofloxacin] Summary of Product Characteristics - last updated March 2016

TAVANIC® 500 mg film-coated tablets, box of 5 tablets; Tavanic® 5 mg/ml solution for infusion, 100ml. Tavanic 500mg film coated tablet contains 500mg levofloxacin as levofloxacin hemihydrate; 100ml solution for infusion contains 500mg levofloxacin as levofloxacin hemihydrate **THERAPEUTIC INDICATIONS** Tavanic is indicated in adults for the treatment of the following infections: acute bacterial sinusitis, acute exacerbation of chronic bronchitis, community-acquired pneumonia, complicated skin and soft-tissue infections. (For the above-mentioned infections, Tavanic should be used only when antibiotics usually recommended for the initial treatment of these infections are not considered to be indicated); Pyelonephritis and complicated urinary tract infections, chronic bacterial prostatitis,, uncomplicated cystitis, inhalation anthrax: for post-exposure prophylaxis and as curative treatment. Tablets can be used to continue a course of treatment in patients who have shown improvement during initial treatment with intravenous levofloxacin. Consideration should be given to the official recommendations on the appropriate use of antibiotics. **POSOLOGY AND METHOD OF ADMINISTRATION:** Tavanic film-coated tablets are administered once or twice daily. The dosage depends on the type and severity of the infection and the susceptibility of the presumed causative pathogen. Tavanic tablets can also be used to continue a course of treatment in patients who have shown improvement during initial treatment with intravenous levofloxacin. Given the bioequivalence of the parenteral and oral forms, the same dose can be used. Tavanic solution for infusion is slowly infused once or twice daily via the intravenous route. The dosage depends on the type and severity of the infection and the susceptibility of the presumed causative pathogen. Given the bioequivalence of the parenteral and oral forms, the same dose can be used. Acute bacterial sinusitis: 500 mg once daily 10 - 14 days; Acute bacterial exacerbation of chronic bronchitis: 500 mg once daily 7 - 10 days; Community-acquired pneumonia: 500 mg once or twice daily 7 - 14 days; Pyelonephritis 500 mg once daily 7 - 10 days; Complicated urinary tract infections 500 mg once daily 7 - 14 days; Uncomplicated cystitis 250 mg once daily 3 days; Chronic bacterial prostatitis 500 mg once daily 28 days; Complicated skin and soft tissue infections 500 mg once or twice daily 7 - 14 days; Inhalation anthrax 500 mg once daily 8 weeks **CONTRA-INDICATIONS:** Levofloxacin film-coated tablets must not be used in patients with hypersensitivity to levofloxacin or other quinolones, or to any of the excipients; in patients with epilepsy,In patients with a known history of tendon disorders after previous fluoroquinolone use, in children and growing adolescents, during pregnancy, in breast-feeding women. **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**: See full prescribing information **INTERACTIONS:** Iron salts, zinc salts, magnesium- or aluminium-containing antacids, didanosine; Sucralfate; Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs; Probenecid and cimetidine; Ciclosporin; Vitamin K antagonists; Medicinal products known to prolong the QT interval. See full prescribing information **UNDESIRABLE EFFECTS:** Insomnia, Headache, light-headedness, (after IV administration only): Phlebitis, Diarrhoea, vomiting. Nausea, Elevated liver enzyme values (ALT/AST, alkaline phosphatase, GGT), (After IV administration only): Infusion site reactions (pain, reddening) For uncommon, rare and very rare side effects see full prescribing information **OVERDOSE:** According to toxicity studies in animals or clinical pharmacology studies with supratherapeutic doses, the most important symptoms to be expected following acute overdose of Tavanic film-coated tablets are central nervous disturbances (confusion, light-headedness, impairment of consciousness and seizures), prolongation of the QT interval and gastrointestinal disturbances such as nausea and mucosal erosions. CNS effects (including confusion, seizures, hallucinations and tremor) have been observed in post-marketing experience. In the event of an overdose, symptomatic treatment should be instituted. ECG monitoring should be undertaken due to the possible occurrence of QT interval prolongation. Antacids may be used for protection of the gastric mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are unable to eliminate levofloxacin effectively. No specific antidote exists. **PHARMACODYNAMIC PROPERTIES:** Pharmacotherapeutic group: quinolone antibacterials, fluoroquinolones, ATC code: J01MA12Levofloxacin is a synthetic antibiotic of the fluoroquinolone group. It is the S (-) enantiomer of the racemate ofloxacin. Orally administered levofloxacin is rapidly and almost completely absorbed, with peak plasma concentrations being achieved within about 1 to 2 hours. The absolute bioavailability is 99 to 100%. Date of SPC abbreviation: 19th June 2017. Date of SPC text revision: March 2016.

For more details please refer to the full prescribing information, date of last revision 29 July 2016.
For additional information and for reporting of adverse events please use the following email address: esa.pv@sanofi.com
Sanofi Aventis Kenya Limited, Crowne Plaza Hotel Annex, 13th Floor, Longonot Road, Upperhill. P.O Box 20337 - 00200, Nairobi, Kenya (+254) 20 2051396
(+254) 733-825000/725-801128.
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SANOFI

Law and Ethics in Clinical Practice: Medical Negligence

Medical practice represents one of most noble and reputable occupations in the world epitomized by the practitioner's duty to preserve life. Medical practice is guided by one simple logic that life in all its preciousness is a gift from God and the doctor has the duty to utilize their God-given talent to protect it (1). Doctors and other professionals in the field of medicine are morally obligated to be providing quality care to their patients. Care as defined in medical practice refers to one's ability to use a combination of personal skills and knowledge to diagnose, treat and provide healthcare information. The focus of this editorial is to give an insight on medical negligence as a detrimental practice to society.

Normally, a patient visits a doctor with two expectations namely that the attending doctor has the requisite knowledge and skills to treat the ailment and that no harm shall befall him or her during the course of the treatment occasioned by a doctor's reckless attitude, carelessness or negligence (2). In essence, medical attention provided to any patient by a doctor bears all the characteristics of a legal contract (3). This legally binding contract typified by traits such as fee payments, informed consent, and provision of the required treatment bears all the characteristics of tort (4). By definition, a tort refers to *right in rem* which essentially protects any person from any form of harm meted by another party (5). A patient by law is entitled to *in personam* which allows the patient to seek judicial mediation in the wake of any contractual infringement by a doctor.

According to the Law of Torts articulated by Salmon, medical negligence represents any failure by a doctor to carry out actions that any rational medicine professional is expected to (6). Doctors violate their duty to provide care anytime they provide a diagnosis or treatment below the expected standard. Any patient who experiences any injury or harm as a result of this contractual breach may bring forward an allegation of negligence with aim of obtaining compensation (7).

Types of medical negligence

(i) Active negligence is occasioned by inadequate training and medical know-how (8). Active negligence is exemplified by the administration of an injection at the incorrect site.

(ii) Passive negligence arises whenever there is no omission or action during the care giving act (9). For example, a doctor prescribing medicine without appropriate knowledge on the patient's allergy history.

(iii) In contrast contributory negligence results from failure by a patient to follow doctor's instructions occasioned by a lack of understanding of the medical terminology used by the doctor when issuing the said instructions which leads to injury or harm (10).

(iv) Concurrent negligence is brought about by more than one act of omission during the course of treatment (11). For example, the doctor initially fails to identify the patient's allergy history the same patient is taken into surgery where the anaesthetist administers a drug that the patient is allergic to without first counter checking the patient's allergy history.

(v) Continued negligence refers to the intentional abandonment of a patient by his doctor.

(vi) Gross negligence occurs when the doctor accidentally leaves behind a foreign body after conducting a medical procedure (12). For example, a doctor leaves behind a tourniquet when fixing a branula, and to compound the problem the nurses continue administering medication without any knowledge of the tourniquets existence giving rise to gangrene.

(vii) Hazardous negligence happens when the doctor intentionally or unintentionally utilizes an unsterile instrument which results in harm to the patient (13).

(viii) Willful negligence manifests itself when a doctor knowingly administers harmful medication doses or intentionally holds back treatment (14).

(ix) Reckless negligence occurs when doctors fond of risky practices during operations end up causing harm to the patient as a result of taking the risk.

(x) Negligence per se occurs when a doctor goes against the ethical standards and rules.

(xi) Criminal negligence arises when a doctor knowingly conducts controlled medical procedures outside the confines of a hospital resulting to bodily harm (1). An infamous example of criminal negligence is the case where Propofol was given to a well-liked musician ultimately leading to his demise.

(xii) Comparative negligence happens when a practitioner is held accountable for adding onto damages levied by a court based on the level of negligence.

Unbearable conditions within the healthcare sector occur as a result of lack of accountability coupled with medical negligence. An inadequacy of the required medical appliances, limited resources and medicines as well as an alarmingly disparate ratio of medical

practitioners to patients has become the norm (15). Therefore, the government is legally mandated to enforce and preserve every citizen's right to healthcare.

Despite the fact that medical practitioners operate in unfavorable working environments negligence can never be accepted as an excuse for the hostile conditions that they are forced to work in. In truth, a doctor's shortcomings cannot be forgiven during cases of misconduct, illegal activities, or negligence. It is of utmost importance to note that all shortcomings during the dispensation of a doctor's duty to their patient are ultimately associated to some form of medical negligence. Therefore, professionals should hold accountability in the healthcare sector as a way of rebuilding public trust within healthcare system. Amendment of existing laws can go a long way in re-enforcing accountability. Measures such as the establishment of health tribunal, development of local health guidelines and the re-training of medical professionals should be undertaken with an aim of promoting information symmetry in the healthcare sector. Lastly, for a medical practitioner it's the ability to possess firm commitment to evidence-based medicine, medical guidelines and ethical guidelines to protect themselves from medical malpractice.

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Original paper

Burden of Cardiac Disease among Patients Undergoing Chronic Haemodialysis at Moi Teaching and Referral Hospital, Eldoret, Kenya

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Abstract

Background: Cardiovascular Disease (CVD) is the leading cause of mortality in patients with End Stage Renal Disease (ESRD) globally. Renal replacement therapy improves the quality of life of these patients but CVD remains a threat to their survival. Whereas atherosclerotic coronary artery disease is the leading culprit in high income countries, this has not been characterized in Kenya.
Objective: To determine the prevalence and spectrum of cardiac disease in patients with ESRD undergoing haemodialysis at Moi Teaching and Referral Hospital (MTRH), a tertiary medical centre in Western Kenya.
Methods: This was a cross sectional study conducted at MTRH renal unit. Consenting consecutive adults with ESRD undergoing chronic heamodialysis were enrolled into the study after obtaining ethical approval from the institution's review board. Data on socio demographics, medical and drug history was collected using a structured questionnaire followed by a focused cardiovascular examination. A standard trans-thoracic echocardiogram was done by a study dedicated sonographer and interpreted by a cardiologist using American Society of Echocardiography guidelines. A standard 12 lead resting ECG was also done and read by the same cardiologist. Outcomes of interest included Left Ventricular Hypertrophy (LVH), Left Ventricular Ejection Fraction (LVEF), pathological valve disease, pathological Q waves and arrhythmias. The prevalence estimates were reported with the corresponding 95% confidence intervals.
Results: Seventy two participants were included in the final analysis. Their median age was 41 (29.8, 60) years and 51.3% were male. Majority (93%) were on two sessions of dialysis per week, with 97.2% being known hypertensives. Almost three quarters of them (72.2%) had some form of cardiac disease as follows; left ventricular hypertrophy 58%, left ventricular systolic dysfunction 49%, pathological valvular disease 15.3%, arrhythmias 9.7% and pathological Q waves 6.9%.
Conclusion: There is a high burden of cardiac disease in patients with ESRD on heamodialysis at MTRH with the predominant lesions being LVH and left ventricular systolic dysfunction.

Key words: End stage renal disease, Haemodialysis, Cardiac disease, Sub-Saharan Africa

Introduction

Patients with End-Stage Renal Disease (ESRD) are exposed to haemodynamic stress and metabolic perturbations, which could predispose them to myocardial dysfunction, valve disease, arrhythmias and atherosclerosis (1). It is known that Cardiovascular Disease (CVD) is the leading cause of morbidity and mortality in patients with Chronic Kidney Disease (CKD). Nearly half of these deaths are secondary to myocardial infarction, cardiac arrest, malignant arrhythmias and other cardiac causes. The high prevalence of diabetes, anaemia, hyperparathyroidism and hypertension among these patients fosters structural heart diseases. Moreover, fluid overload and metabolic abnormalities such as metabolic acidosis, dyskalemia and dysmagnesemia lead to an increased risk of clinically significant arrhythmias and sudden cardiac death. ESRD is often characterized by the presence of sympathetic hyperactivity and activation of the Renin-Angiotensin-Aldosterone System (RAAS) that further compound the picture (2,3).

The prevalence of ESRD is increasing globally with great societal economic impact (3). In sub-Saharan Africa (SSA), the prevalence of CKD is also increasing especially among young adults in their economically productive years and the majority of these patients are referred to nephrologists late due to poor referral systems and inadequate skilled personnel. Poverty and lack of access to modern specialized care make them not undergo renal replacement therapy at all or only manage inadequate dialysis. Besides, management

of other modifiable cardiovascular risks is usually not optimized and this explains the increase in CVD and cardiovascular risk factors in patients on maintenance dialysis (4).

Left Ventricular Hypertrophy (LVH) is the most common cardiac lesion in patients with CKD in High Income Countries (HIC) and is present in more than 75% of patients on chronic heamodialysis (5,6). The occurrence of LVH and its progression to (uremic) cardiomyopathy and later cardiac failure are influenced by high prevalence of traditional and uremia-related cardiovascular risk factors in haemodialysis patients (1,6). In CKD, there is also an increased risk for atherosclerosis, which is the main cause of ischemic heart disease in such patients. This may be due to accelerated progression of coronary plaque; greater thickening and vascular calcification preceded by dyslipidemia and mineral bone disease (1,6). In the mix of all these events, arteriosclerosis occurs due to large vessel remodeling and loss of elasticity and compliance that causes increased pulse pressure and hypertension (6).

LVH attended by secondary hypertension, LV systolic dysfunction, metabolic derangements and the uremic milieu constitute a fertile ground for arrhythmias. Further, during dialysis patients show a non-homogeneous repolarization through an increase in Q-T duration and Q-T dispersion, a phenomenon that can be highly arrythromogenic. The dialysis-related sudden variation in extra-cellular potassium, calcium and pH levels may further enhance the genesis of an electrical disequilibrium in myocardial cells thus predisposing to more arrythromogenesis (7). Various rhythm abnormalities have been described in this population ranging from benign to malignant with atrial fibrillation being the commonest (8).

Valvular heart disease is common in patients undergoing chronic dialysis. Abnormalities include valvular and annular thickening and calcification of any of the heart valves but commonly the aortic and mitral valves, with the subsequent development of valvular regurgitation and/or stenosis (9). The single most risk factor for development of valve disease is presence of secondary hyperparathyroidism with attended adynamic bone disease (9,10). Additional factors that may further enhance this pathology include the presence of hypertension, diabetes mellitus, hyperlipidemia, LVH, mitral valve prolapse, high cardiac output states, anaemia, infective endocarditis and Arteriovenous Fistulae (AV) (10 -12).

Chronic dialysis services are increasingly becoming available in Kenya with the support of the national public insurer – National Health Insurance Fund (NHIF). In middle income economies like India, approximately 9-13% of patients on haemodialysis die within the first one year, mainly attributed to CVD (13). sub-Saharan Africa and Kenya in particular is grossly under-represented in this data and we therefore sought to fill this gap by describing the spectrum of structural cardiac disease and arrhythmias in this patient population. The study was approved by Moi Teaching and Referral Hospital (MTRH)/Moi University ethics committee.

Materials and methods

This was a descriptive cross sectional study that was conducted on patients with ESRD undergoing chronic haemodialysis at the renal unit of MTRH, a tertiary medical centre in Western Kenya with a catchment population of over 16 million. A structured questionnaire was used to collect data on socio-demographics and medical history from consenting adult participants who were attending the renal unit for their routine scheduled haemodialysis. A physical exam with a bias towards cardiovascular system exam was conducted by one of the authors (MH). A standard 12 lead electrocardiogram (ECG) was then done using Philips equipment (Page writer TC20 (Andover MA, USA) by a qualified technician followed by a standard trans-thoracic echocardiogram (SE) by a qualified sonographer using a Siemens equipment (Siemens ACUSON X700TM Erlangen, Germany). These two were interpreted by a cardiologist with the latter being based on American Society of Echocardiography guidelines.

Outcome measures: From the SE we sought to obtain LVH, Left Ventricular Ejection Fraction (LVEF) as a measure of LV function, and pathological valve disease. From the ECG, we sought for presence of pathological Q waves as a marker of ischemia, arrhythmias and LVH.

Statistics: The sample size was calculated using a formula by Cohen *et al* for calculation of a sample size for a small population with 80% power based on a prevalence study by Kaze *et al* (Francois Folefack) in Yaounde Cameroon. Prevalence estimates were reported with the corresponding 95% confidence intervals. Analysis was done using software for statistical computing known as R (R core Team, 2016). Continuous variables were summarized using mean and standard deviation. Categorical variables were summarized as frequencies and the corresponding percentages. Continuous variables that did not follow the Gaussian distribution were summarized using median and interquartile range.

Results

Between January and July 2016, 95 patients were screened for inclusion into the study of which 72 were recruited. Majority of them (42, 58%) were male and

their mean age was 41 years. Hypertension (97.2%) and diabetes (18%) were major co-morbidities. Almost all (90%) of the hypertensive patients were on medication with most of them being uncontrolled. Majority were on twice weekly haemodialysis sessions funded by NHIF and their mean duration of dialysis was 8 weeks. Human Immunodeficiency Virus (HIV) infection was low reflecting the national prevalence in the general population (Table 1).

Table 1: Socio-demographic and clinical characteristics

	No.	(%)
Gender		
Male	42	58.3%
Female	30	41.7%
Occupation		
Farmer	36	52.0%
Business	9	12.5%
Housewife	9	12.5%
Student	12	16.7%
Retired	6	10.3%
Known hypertensive	70	97.2%
On anti hypertensive drugs	63	90.0%
Diuretics	23	36.5%
Calcium Channel Blockers	51	81%
Angiotensin Receptor Blockers	11	7.5%
Beta blockers	17	27%
Hydralazine	7	11.1%
Known diabetics	13	18.1%
On insulin	10	76.9%
On oral hypoglycemic agents	2	16.7%
HIV positive	4	5.7%
Systolic blood pressure	72	148.0 (139.8,158.0)
Range (Min.-Max.)		90.0-201.0
Diastolic blood pressure	72	93.0 (84.0,100.0)
Range (Min.-Max.)		50.0-132.0
SBP>140mmhg/DBP>90mmhg	72	59(81.8%)
BMI (Kg/m2)	72	21.2 (18.3,23.0)
Range (Min-Max)		(14.0-31.2)
<18.5		21 (29.6%)
18.5-25.0		38 (53.5%)
25.0-30.0		10 (14.1%)
>30		2 (2.8%)
Variable	N	Mean (SD) or Median (IQR) or n (%)

The prevalence of cardiac disease in this population was high at 72% with LVH being the predominant lesion. Valvular heart disease (15%) was of low prevalence despite the region being rheumatic heart disease bedrock. Equally, ischemic heart disease/ pathological Q waves burden was surprisingly low unlike the picture in HICs (Figure 1). Of the valve pathologies, mitral regurgitation was the predominant lesion followed by tricuspid regurgitation and aortic regurgitation (Table 2). About a half of the participants had depressed LV systolic function though in the vast majority, this tended to be in the mild to moderate ranges (LVEF 30-54%). Rhythm abnormalities were uncommon and were mostly benign (Table 2).

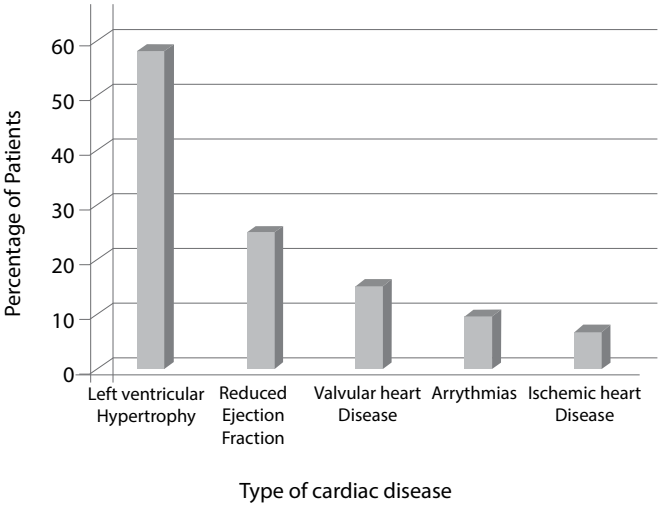

Figure 1: Spectrum of cardiac disease in patients with ESRD on haemodialysis

Table 2: Stratification of type of cardiac disease and severity in patients with ESRD

Rhythm anomalies		
Ventricular arrythmias	Premature ventricular complexes	3 (33%)
Brady-arrhythmias	1°Atrio-ventricular block	2 (22%)
	Sinus Bradycardia	1 (11%)
Bundle branch blocks	Left bundle branch block	1 (11%)
	Right bundle branch block	2 (22%)
Systolic dysfunction		
Mild	45-54%	23
Moderate	30-44%	5
Severe	<30%	7
Valvular disease		
Pathological mitral regurgitation	9	42.9%
Mitral stenosis	1	4.8%
Pathological aortic regurgitation	3	14.3%
Aortic stenosis	1	4.8%
Pathological tricuspid regurgitation	7	33.3%

Discussion

This cross sectional prospective study reveals a very high prevalence of cardiac disease among patients with ESRD on chronic haemodialysis in Western Kenya. LVH, perhaps a component of poorly controlled hypertension or uremic cardiomyopathy, was the predominant lesion. LV systolic dysfunction is also

common, affecting almost half of the participants, perhaps as part of the disease progression (from LVH) towards end stage process. An additional contributory factor is the presence of fluid overload due to inadequate dialysis amongst the participants, as it was noted that 66 (93%) of them were on two sessions of dialysis per week. This is inadequate as the Kidney Disease In Improving Global Outcomes (KDIQO) guidelines, recommend a minimum of 3 sessions per week (14). This inadequate dialysis is likely to be as a result of the NHIF policy to cover the cost of only two dialysis sessions per week. A majority of the patients depend on NHIF to meet the costs of dialysis. Valvular heart disease was surprisingly uncommon in this population, even with rheumatic heart disease being highly prevalent in the region. Given that this was relatively a young population with a mean age of 41 years, the implications of this twin co-morbidities (renal and cardiac) to the economy and family structures are disastrous.

Very few contemporary studies on a similar topic have been conducted in sub-Sahara Africa. A small old (1997) prospective study in Dakar, Senegal looking at 14 patients and a more recent one in Yaunde, Cameroon in 2014 that studied 45 patients (5,15). Despite the small numbers, the Senegal study had almost similar findings with all of the patients being hypertensive and 13 (of the 14) having cardiac abnormalities: all with LVH and a quarter with LV systolic dysfunction. The Cameroonian study on the other hand was a cross sectional study that looked at 45 ESRD patients undergoing chronic haemodialysis at one of the four government funded dialysis centers. Cardiac disease was also highly prevalent at 84%; a rate slightly higher than what we observed (72%) in our study. The longer mean dialysis duration (36.5 months) as compared to 2 months in our study as well as the relatively older mean age (52.7 years as compared to 41 years) of the study participants could possibly explain the higher cardiac disease prevalence that was observed in Cameroon.

The prevalence of LVH in our study population at 58.3% is comparable to the Cameroonian study that revealed a slightly higher prevalence at 60%. The similarity can be attributed to similar methodology and patient characteristics. The slightly higher prevalence can be attributed to a longer duration on dialysis (36.5 months) that results in a longer duration of exposure of the myocardium to both preload and uremia hence development of LVH as a compensatory mechanism. The higher mean age in the Cameroonian study (52.2 years as compared to 41 years), could also explain the higher prevalence of LVH as this increases with age (16). On the other hand, the higher prevalence of LVH in the Senegalese study could be explained by the small sample size and the fact that modern guidelines are more stringent on quantification of echocardiographic parameters unlike the past.

About a half of the participants were noted to have left ventricular systolic dysfunction. Of these, 23 (31.94%) had mild, 5 (5.94%) moderate and 7 (9.7%) severe systolic dysfunction. This is a crucial finding as LVEF is a powerful predictor of CVD outcomes in heart failure patients across a broad spectrum of ventricular function with hazard ratio for all cause mortality increasing by 39% for every 10% reduction in systolic function (16). This implies that about 10% of the participants were at a high risk of mortality based on the systolic dysfunction alone. In the Cameroonian study, prevalence of LV systolic function was not well characterized as the authors dealt more with the clinical syndrome of heart failure and diastolic filling (5). In Senegalese study, the prevalence of LV systolic function was lower at 28.5% (4 patients) and this could be due to the small sample size and use of older echocardiographic technology that was less sensitive (15).

The proportion of participants with pathological valve disease was 11/72 (15.3%). Only three of these valve pathologies were found to be of rheumatic origin. Nine participants (45%) were found to have mitral valve regurgitation (one severe, four moderate and four mild severity). One participant (4.8%) had mild mitral stenosis. Three (14.5%) had aortic regurgitation with one having a severe and two, a mild forms. One participant had aortic stenosis (4.8%). Seven participants (33.3%) had tricuspid regurgitation with two having severe disease, three having moderate and two with mild forms. In the Cameroonian study, aortic stenosis was highly prevalent at 40% in contrast to this study where the prevalence was 4.8%. This can be explained by the higher mean age (thus older) Cameroonian population (52.7 years) compared to this study (5). Mitral regurgitation was prevalent at 43% in this study, comparable to the Cameroonian study where it was prevalent at 50%, whilst tricuspid regurgitation was prevalent at 33.3% in this study also comparable to the Cameroonian study at 20%. This similarity can be explained by the similar patient characteristics, environmental factors and similarities in the methodology. The Senegalese study did not document any valve disease perhaps due to the small sample size.

Our study revealed the proportion of participants with pathological Q waves (ischemic heart disease) to be at 6.9%. This was a significantly low rate as compared to the proportion of other cardiac lesions. Not withstanding this, our study populations were fairly high risk for Coronary Artery Disease (CAD) with 97.2% being hypertensives and 18.1% with diabetics (17). The Cameroonian study showed an even lower prevalence of IHD at 2.22%, despite the fact that more than a fifth (22.2%) of their study population were smokers (another significant risk factor for CAD), a risk that was absent in all our study population (17). The differences between the two studies can be explained

by a study by Herzog *et al* (18) who showed that very adverse long term survival of such patients after acute myocardial infarction. Thus extremely low prevalence of IHD in the Cameroonian study could be due to the longer duration of dialysis of 36.5 months (3 years 4 months), which may have resulted in mortality within the first, second and third years whilst on dialysis thus significantly reducing the overall prevalence. In HICs the prevalence of IHD is extremely high perhaps due to the advanced age of their patients attended by other traditional risk factors (19). The Senegalese study did not report on ischemic burden because they did not do ECGs (15).

Our study found a prevalence of rhythm anomalies at 9.7%. These were all benign arrhythmias and this is comparable to the Cameroonian study where predominantly mild atrioventricular blocks 10 (67%) and bundle branch blocks 5 (33%) were described. The similarities could be attributed to similar patient characteristics and study methodology. This is in sharp contrast to what is seen in the HIC countries where sudden cardiac death, mainly caused by malignant arrhythmias is responsible for more than 40% of all-cause mortality in patients with ESRD. This difference could be due to the high prevalence of CAD in the HIC which predisposes them to the malignant rythms due to chronic myocardial and conduction system ischemia (19,20).

Limitations

Firstly, we did not do invasive evaluation (coronary angiography) thus we were likely to have missed less severe forms of coronary artery disease. Secondly, we also probably missed paroxysmal variants of arrhythmias as we did not do 24-hour holter monitoring.

Finally, there could have been some degree of intra-operator variability as the echocardiograms were done by one sonographer and interpretation of the archived images were only done by one cardiologist.

Conclusion and recommendations

Patients with ESRD undergoing chronic haemodialysis have a high burden of cardiac disease. The predominant lesions are LVH and depressed LV systolic dysfunction. Based on these findings, we recommend that cardiac evaluation should be part of care for patients with ESRD on chronic haemodialysis. The economic and survival benefits of such a strategy should be further interrogated in future prospective studies.

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Original paper

A Seven-Day Mortality Profile of Medical Inpatients at Kenyatta National Referral Hospital

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Abstract

Background: Morbidity and mortality statistics are an important resource for research and informing policy in any country as it reflects on the public health status. Majority of the mortality in the medical wards occur within the first few days following admission. Factors such as age, sex, diagnosis, comorbidities, social-economic factors and duration of hospital stay have been shown to affect mortality. There is a paucity of such studies in Kenya.
Objective: To describe the causes and circumstances around early mortality among inpatients in the KNH medical wards.
Design: An observational cohort study comprising of a retrospective and prospective arm.
Methodology: The study was conducted from 7th April to 18th June 2014. Retrospective arm: files of patients who died within the first 7 days of admission 6 months prior to study start date were reviewed. Prospective arm: Admitted patients were followed up for 7-day outcomes.
Results: Six hundred and ninety five files were reviewed in the retrospective arm while 193 patients were recruited into the prospective arm. The mean age of the participants in the retrospective and prospective arms were 46.7 years (Range 15-107 years) and 44.5 years (Range 15-100 years) respectively. The overall mortality rate was 29.6%. The seven-day mortality rate was 17.6%. Malignant neoplasms at 12.5% were the leading cause of death followed by congestive heart failure at 10.5%. The leading co-morbidity was HIV at 42%, followed by hypertension at 18.8% and diabetes at 8.7%. The median Karnofsky's score at admission and the mean duration of hospital stay in days were the two variables strongly associated with risk of dying.
Conclusion: The 7-day mortality rate was high. Malignancies were the commonest cause of death. Most of the deaths were preventable.

Key words: Early mortality, Medical in-patients, Mortality profile, Knowledge of morbidity and mortality patterns

Introduction

Morbidity and mortality statistics are an important resource for research and informing policy in any country as it reflects on the public health status (1). Awareness of common causes of death is part of the basic steps to extend life and promote healthy communities. However, in many developing countries including Kenya, there is paucity of this vital data at the national level to reliably inform policy. Unavailability of population-based statistics makes hospital-based studies a suitable alternative to provide correlates (2).

In Kenya the estimated adult mortality rate is 7.26 deaths /1,000 of the population (3). Most of these deaths occur in adults in sub-Saharan Africa and are preventable (4). They account for about 21% of all the avoidable years of life lost. Recent studies demonstrate a trend of early mortality among admitted patients. A study by Elias *et al* (5) in Ethiopia showed that 53% of patients who died in the medical wards died within five days of admission and 75% of all mortalities died within ten days of admission. Einterz and Bates (6) in a study done in northern Cameroon reported that 43.7% of all adult deaths admitted with medical conditions occurred within forty-eight hours of admission in one hospital. There is paucity of data to explain the reasons and circumstances around early in-patient mortality.

The WHO predicts that by 2020, the causes of morbidity and mortality will have undergone

a significant shift towards endemic non-communicable diseases away from infectious diseases (7). This shift will necessitate changes in the deployment of resources to deal with new health challenges. However, health policy change will need to be informed based on local findings from local research due to variations in morbidity and mortality patterns even within the same country. The pattern of illnesses responsible for the high mortality rates in sub-Saharan Africa has not been well characterized due to deficient data to make this evaluation (3, 8). Locally, there are no studies that have been recently done to facilitate this characterization.

Knowledge of morbidity and mortality patterns are essential not only for planning interventions and setting health priorities but also for assessing the quality of health delivery systems. At the moment, few countries in the developing world rely on research evidence for guiding policy interventions (9). Community based studies provide an accurate picture of the profile of the illnesses of adults because they minimize the bias inherent on hospital-based studies occasioned by variable access to health care (10). However, these surveys are expensive undertakings and useful information could be obtained from an analysis of well-conducted clinical surveillance activities (11). Although in-hospital mortality may not give a true reflection of deaths from all causes in the general population, it may give insight into the burden of disease in the community and may be valuable in evaluating the quality of care and health delivery systems at the KNH.

This study aimed to provide information on the current trends of mortality at the medical wards at KNH and the factors that contribute therein and explore ways in which these could be mitigated.

Materials and Methods

Study subjects: We conducted a cohort study running from 7th April to 18th June 2014 on inpatient admissions in the medical wards at Kenyatta National Hospital (KNH). KNH is a state owned National referral and teaching hospital, situated in Nairobi, Kenya. It has a capacity of 1800 beds and has over 6000 staff members, hosting in its wards between 2500 and 3000 patients (12).The Department of Medicine has seven admitting wards. Only patients admitted through specialty clinics go straight to their specialty wards. Each ward has one admitting day per week through which patients diagnosed with medical conditions at the emergency department will be admitted. On average, each ward admits fifteen to thirty medical patients on their admission days through the emergency department. The cohort study included two arms;

A retrospective arm: Involved consecutive sampling and review of all the files of the patients who died in the medical wards in the preceding six months prior to the onset of the study. A total of 695 files were reviewed. For files to be eligible they had to belong to patients aged 15 years and above, admitted 6 months prior to study start and died within 7 days of admission. Incomplete, mutilated and files with missing records were excluded.

Prospective arm: All adult medical patients admitted to the medical wards, 15 years and above and willing to participate after signing a consent form were eligible. Simple random sampling method was used to select participants. A total of 193 patients were enrolled in the study and followed up to a maximum of 7 days in the ward.

A standard case report form was used to collect specific data on sex, age, time patient was seen at emergency department/specialty clinic, date and time of admission to the medical ward, primary diagnosis at admission, co-morbidities, duration of hospital stay, time of death and primary cause of death. Data on post-mortem results was collected from the copies of the original post-mortem results. Diagnoses were standardized using the ICD 10.

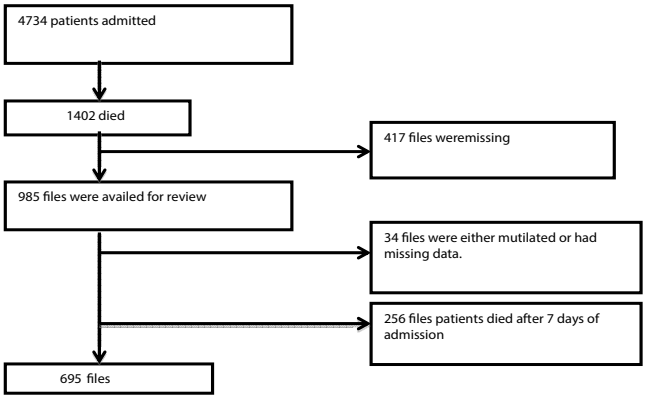

Figure 1b: Prospective arm patient recruitment flow chart

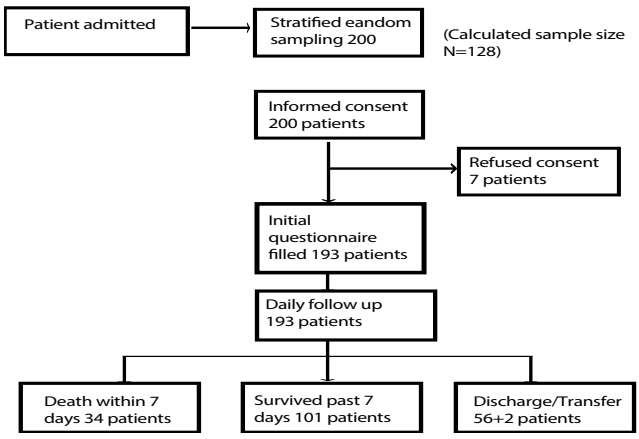

Figure 1a: Retrospective arm: File review flow chart

Statistical analysis: Data analysis was done using SPSS version 20. The seven-day mortality rate, which was the primary variable, was calculated as the number of deaths that occurred within seven days of admission divided by the total number of patients recruited into the prospective arm of the study. Frequency distribution of secondary categorical variables was computed where appropriate. Means and Standard deviations was computed for normally distributed continuous variables and compared for significance using the Student t-test. Multiple logistic regressions were used to assess for the differences in mortality rates (early= <forty-eight hours following admission and overall mortality=seven days after admission) between these two groups after adjusting for age and sex. The results of logistic regression were reported as Odds Ratio. Length of stay in hospital (LOS) was calculated as the number of midnights that the patient observed in the ward between admission and primary outcome. All reported p-values were two-tailed. A panel of experts from the Department of Clinical Medicine and Therapeutics analyzed the study. It received ethical approval from the KNH/University of Nairobi Research and Ethics Committee (KNH/UON – REC).

Results

Study patient characteristics in the retrospective arm the mean age for patients was 46.7 years with an age range of 15-107 years. There were more males 53.7% than females. Majority of the patients 66.8% were referred from other facilities. The median length of stay in days was 3 days. This information is depicted in Table 1.

Table 1: Demographic and admission characteristics of patients in the retrospective arm (N-695)

Variable	Frequency (%)
Age in years, mean (SD)	46.7 (20.0)
Min-Max	15-107
Sex	
Female	311 (44.7)
Male	373 (53.7)
Missing	11 (1.6)
Referral pattern	
Hospital	464 (66.8)
Self	221 (31.8)
Missing	10 (1.4)
Length of stay in days, median (IQR)	3.0 (2.0-6.0)

Prospective arm study patient characteristics: In this arm a total of 193 patients were included. One hundred and three (53.4%) were female. The average age was 44.5 years with an age range from 15-100 years. Most of the patients were referrals 54.9%. 67.9% of the patients spent more than eight hours in ED. The median duration of symptoms before admission in days was 7 days with a range of 1-6 months. The Karnofskys score at admission ranged from 20 to 90. The average ward occupancy at admission was 95.7%. The baseline characteristics at admission are presented in Table 2.

Table 2: Demographic and admission characteristics of patients in the prospective arm (N-193)

Variable	Frequency (%)
Age in years	
Mean (SD)	44.5 (18.9)
Min-Max	15-100
Sex	
Female	103 (53.4)
Male	90 (46.6)
Referral pattern	
Hospital	106 (54.9)
Self	86 (44.6)
Not specified	1 (0.5)
Casualty overcrowding	
Yes	131 (67.9)
No	62 (32.1)
Median duration of symptoms before admission in days (IQR)	7.0 (3.0-14.0)
Min-Max	1 day – 6 months
Karnofskys score at admission	20-90
Min-Max	
Average ward occupancy at admission (%)	95.7 (17.4)
Min-Max	68-129

Mortality rate: The overall mortality rate was 29.6 % using data from the retrospective arm. The seven-day mortality rate was 17.6% using data from the prospective arm

Table 3: The overall and seven-day mortality

	N=4734 n (%)	95% Confidence Interval
Overall mortality	1402 (29.6 %)	28.3-30.9
	N=193	95% CI
7-day mortality	34 (17.6%)	(12.4 – 23.3)

Case specific mortality rate: Malignant neoplasm at 12.5% was the leading cause of death followed by congestive heart failure at 10.5%. Chronic kidney disease was third at 9.6%. Stroke and pulmonary tuberculosis were fourth and fifth while acute renal failure was sixth at 5.11%. However, if both chronic kidney disease and acute renal failure were combined then kidney disease as a whole was the leading cause of death. Other causes were meningitis, pneumonia, anaemia and gastroenteritis in descending order.

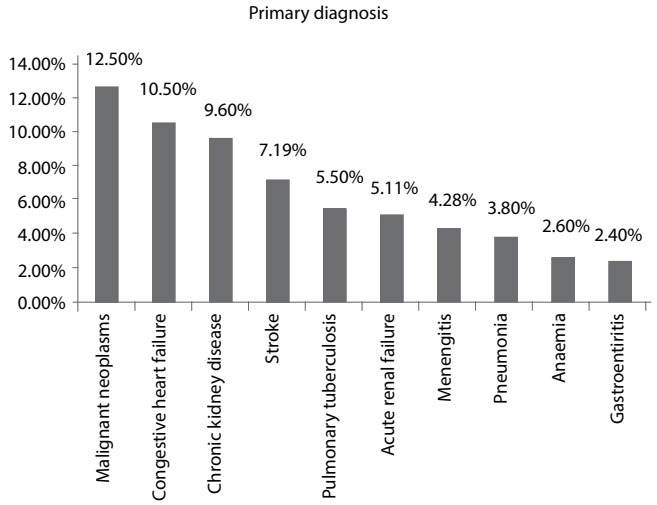

Figure 2: Case specific mortality rate according to primary diagnosis

Co-morbidities at admission: Majority of the patients had one or more co-morbidity at admission. HIV at 42% was the leading co-morbidity followed by hypertension at 18.8% and diabetes at 8.7%. Other diseases that were not the primary cause of death were chronic kidney disease, acute renal failure, pulmonary tuberculosis, anaemia, sepsis and rheumatic heart disease.

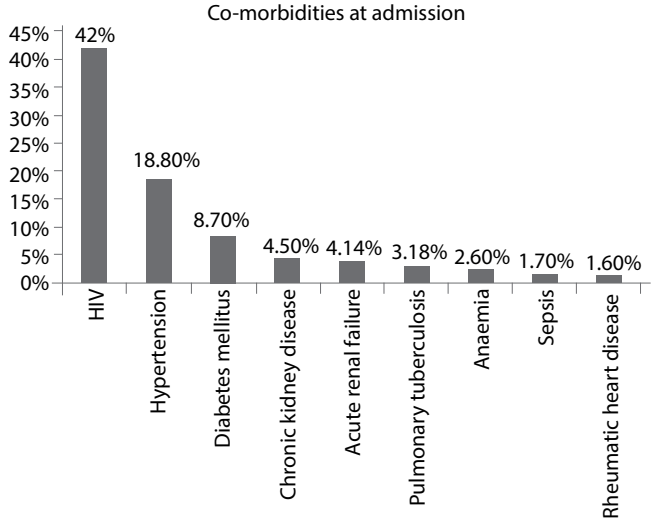

Figure 3: Co-morbidities by disease categories associated with primary diagnosis

Disease categorisation according to ICD 10: We further subcategorized the top causes of death according to the ICD 10 coding and infectious and parasitic diseases were the most common at 53.6% followed by diseases of the circulatory system and genitourinary in that order (Table 5).

Table 5: Top 5 diseases among the patients who died (n=729)

ICD coding	No.	(%)
Infectious and parasitic diseases	391	53.6
Disease of circulatory system	309	42.4
Disease of genitourinary system	185	25.4
Malignant neoplasm	115	15.8
Endocrine, nutritional and metabolic diseases	92	12.6

Seven day outcomes in the prospective arm: There were thirty-four (17.6%) deaths recorded during period of the study. The mean duration of stay in the wards was four days. One hundred and fifty-nine (82.4%) of the patients recruited into the study survived past seven days of admission.

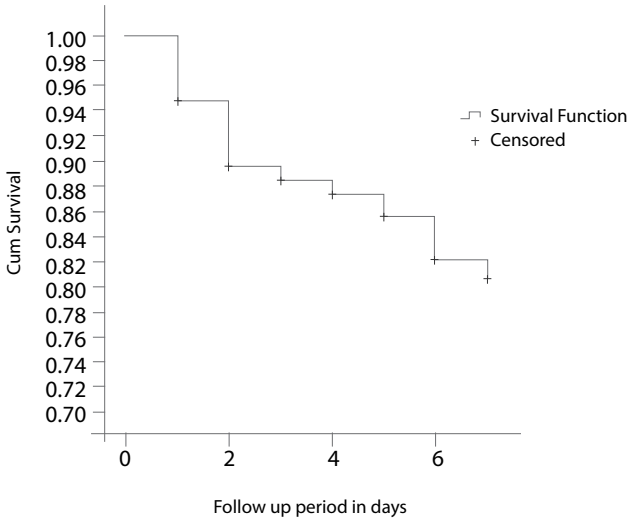

Figure 4: Kaplan Meier curve showing survival of patients admitted in medical wards during the study period

Determinants of mortality: The only patient factor that demonstrated a strong association with mortality was the median Karnofsky's score at admission (score (IQR), dead 40 (14.6) versus alive 60 (14.4), p <0.001). No strong association was observed with the other patient factors. The other factor, which was found to be significant, was the mean duration of stay in hospital in days.

Post-mortem results: Post-mortems were done for the patients who had died, and their relatives had consented to the procedure. Ten (29.45%) of the relatives consented to having a post mortem done, while 24 (70.6%) declined. Most of the relatives declined consent because they did not view it as important. Majority of the ward diagnosis were found to be keeping with the post mortem diagnosis. The results of post-mortem diagnosis are shown in Table 6.

Table 5: Factors associated with mortality in the wards

Variable	Dead (n=34)	Alive (n=159)	OR (95% CI)	P value
Age, mean (SD)	44.3 (19.1)	44.6 (19.0)	-	0.930
Sex				
Female	18 (17.5%)	85 (82.5%)	1.0 (0.5-2.1)	0.956
Male	16 (17.8%)	74 (82.2%)	1.0	
Admission day of the week				
Mon	6 (12.2%)	43 (87.8%)	0.6 (0.2-1.5)	0.905
Tue	7 (17.5%)	33 (82.5%)	1.0 (0.4-2.5)	
Wed	4 (19.0%)	17 (81.0%)	1.1 (0.3-3.5)	
Thur	4 (23.5%)	13 (76.5%)	1.5 (0.5-4.9)	
Fri	7 (19.4%)	29 (80.6%)	1.2 (0.5-2.9)	
Sat	2 (16.7%)	10 (83.3%)	0.9 (0.2-4.5)	
Sun	4 (22.2%)	14 (77.8%)	1.4 (0.4-4.5)	
> 8hrs in casualty overcrowding				
Yes	26 (19.8%)	105 (80.2%)	1.3 (0.5-3.4)	0.334
No	8 (13.5%)	51 (86.4%)	1.0	
Median duration of symptoms before admission in days (IQR)	7.0 (2.0-14.0)	7.0 (3.0-14.0)	-	0.448
Median Kanofskys Score at admission (IQR)	40 (30-50)	60 (50-70)	-	<0.001
Range	20-70	30-90		
Ward Occupancy at admission (%)	97.4 (17.3)	95.3 (17.4)		0.529
Duration of stay in casualty (Mean SD) Range 2 hr. – 28 hrs.	12.2(4.7)	12.1(5.4)		0.853
Referral pattern				
Hospital	20 (18.9%)	86 (81.1%)	1.2(0.6-2.5)	0.640
Self	14 (16.3%)	72 (83.7%)	1.0	
Mean hospital stay in days (SD)	3.0 (2.1)	6.1 (1.4)	-	<0.001
Categories				
≤1 day	10 (90.9%)	1 (9.1%)	1.0	<0.001
2 Days	10 (76.9%)	3 (23.07%)	0.1 (0.0-0.8)	
3 Days	2 (16.6%)	10 (83.3%)	0.0 (0.0-0.2)	
4 Days	2 (15.3%)	11 (84.6%)	0.0 (0.0-0.1	
5 Days	3 (15%)	17 (85%)		
6 Days	5 (35.7%)	9 (64.2%)		
7 Days	2 (1.8%)	108 (98.1%)		

Table 6: Post-mortem diagnosis

Ward diagnosis	Post-mortem diagnosis	Misdiagnosis
DKA	ARDS, cerebral oedema	No
Gastroenteritis	Aortic dissection sec to HTN	Yes
CHF	PE # femur	Yes
CAP	Lobar pneumonia	No
Stroke	Massive ICH	No
AML	AML	No
GE	TB disseminated	Yes
Encephalopathy	Pulmonary oedema + ^ ICP	No
CKD	ESRD (HIVAN)	No
CKD	HIVAN, PTB	No

Post mortem acceptance rate: Our post-mortem acceptance rate was found to be modest at 29.4%. We only performed 10 of the 34 patients who died. Majority of the patient's relatives declined to give consent for post mortems with reasons for decline being: The relatives did not find it important to do a post-mortem, some relatives transferred the bodies out of the hospital morgue immediately and others declined due to religious and cultural beliefs concerning death.

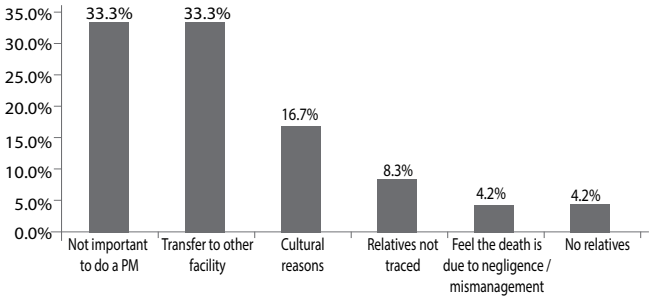

Figure 5: Reasons for deceased's relative refusal for a post-mortem

Discussion

The overall 7-day mortality rate of 29.6% for the medical wards in KNH was higher than that of other hospitals in the region. Mortality rates of 12.6% and 11.2% were reported at Jimma University Specialized Hospital in Ethiopia and Ahmadu Bello University Teaching Hospital, Kaduna respectively (5, 13). This

difference in overall mortality could be explained by the difference in patient characteristics at admission.

While majority of the patients at KNH on admission were diagnosed with malignant-neoplasm with poor prognosis, most of the patients in Ethiopia and Nigeria were diagnosed with community acquired severe pneumonia and other infections, which were mostly treatable (5,13). However, the seven-day in-patient mortality was similar for KNH (17.6%) compared to that of the studies done in Ethiopia, Nigeria and Cameroon (5, 6,13). Most common causes of mortality among the admitted patients were malignant neoplasm, congestive cardiac failure, chronic kidney disease, stroke and pulmonary tuberculosis. This could be attributed to changing urban lifestyles and increased westernization (14, 15). This finding is important since it suggests that the significant shift from infectious diseases to endemic non-communicable diseases (NCDs) in developing countries predicted by the WHO by 2020 (7) is already taking shape in the country.

The local evidence from this study implies that the government should begin to shift their policy focus from infectious diseases to NCDs to address this new health challenge. Similar results were reported by studies done in medical wards of two different South African hospitals in an urban setting, which showed a shift in morbidity and mortality from communicable to NCDs (14, 15).

While chronological age and gender has been identified as the most important risk factor for death in acute illness independent of severity of disease, in this study age and gender were found to have no effect on the risk of dying among admitted patients in the medical wards. The distribution of the gender at admission and among the mortalities in this study was even and the difference in proportions observed showed a slight preponderance towards the female gender though not statistically significant. These results were however, different from those reported by Garko *et al* (13) in a study in Nigeria that observed elderly males above 70 years to constitute a larger proportion (65%) of the admitted patients. This was mainly attributed to their cultural practices of burying their dead almost immediately with associated low funeral costs which favored their seeking medical attention. The patients admitted at KNH however, came from a cosmopolitan geographical area and the role of culture could not be determined.

Health seeking behaviors of the patients was studied to determine what role it plays in the overall mortality. Delays in seeking medical attention by patients and late hospital referrals of patients from lower hospitals to tertiary hospitals have been attributed to contribute to increased inpatient mortality (13). In our study the mean duration of symptoms in patients before seeking medical attention was seven days while the proportion of patients who self-referred versus hospital referred was even. These results pointed to a more health conscious population that sought medical treatment early during the disease process. This contrasted with findings reported by Einterz and Bates (6) in a study done in rural Cameroon, which reported the mean duration of symptoms among the patients to be 68.5 days before presenting to hospital. These findings were strongly linked to the socio-economic status of the patients interviewed and the costs of seeking treatment which resulted in coping strategies employed that had negative implications for the future survival of these patients (16, 17). Conversely in KNH, it could be argued that due to the relatively higher socio-economic status of the urban patient population, access to medical care was faster improving their survival once admitted in hospital. These findings are like that of a survey done in coastal Kenya (18) which reported that households in the urban areas were more likely to report illness than their rural counterparts (19.5% versus 16.9%) and more likely to visit a health provider (81.5% versus 75.9% respectively). Karnofsk'y Performance Scale at admission was found to be the strongest determinant of mortality of death among patients admitted in KNH medical wards. Patients who died had a median score of 40 compared to a median score of 60 among those who survived. While no studies could be identified that directly used Karnofsky's Performance Scale as a determinant of inpatient mortality, Convisky *et al* (19) in a study in the US reported that in-patient mortality increased from 0.9% in the patients dependent in no Activity of Daily Living (ADL) on admission, to17.4% in patients dependent on all 6 ADLs. This finding is important as it underscores the importance of assessing the functional status of the patients during admission as predictor of the outcomes (20). While the use of Karnofsky's Performance Score may not be adopted in routine care, its use may be considered in the acute care of the patients especially in the first 48 hours following admission when the risk of death is highest and patients with poor scores may be considered for transfer to high dependency unit or intensive care unit to improve patient outcomes.

Access block refers to the situation where patients requiring emergency admission spend more than eight hours in an Emergency Department (ED) because they are unable to gain access to appropriate hospital in-patient beds (21). Access block generally leads to overcrowding at the ED and delays in instituting appropriate medical care to acutely ill patients. While only 19.8% of the patients who died within 7 days of admission reported overcrowding at casualty, the mean duration of their stay at casualty was 12.2 hours, which means all of them, experienced access block phenomenon. While this study could not replicate the results of the study done in Western Australia which reported that there was a positive relationship between level of hospital occupancy and death by day

two after the index ED attendance (22), more studies may need to be conducted to fully understand how this phenomenon impacts on the quality of care at KNH since even among the survivors at day 7 of admission, access block was observed.

The findings of this study demonstrated a strong association between the length of hospital stay and mortality. Majority of the deaths occurred within the first 48 hours of admission. Similar results were reported by Garko *et al* (13) in a study done in Nigeria, which reported 55% of all mortalities occurring within 48 hours of admission. The similarity of these findings could be as a result of similar structural factors since both studies were conducted in university teaching hospitals. However, the higher day 2 mortality rates for the Nigerian study were attributed mainly to late referrals from other hospitals and to infectious diseases as the major reason for mortality compared to KNH where non-communicable diseases were the main reasons for admission. However, different results were reported in Spain where day two-in-patient mortality was reported to be 2.5% (23). This low in-patient mortality was attributed to the stratification of patients based on their performance status and patients with poor scores were admitted to the intensive care units or high dependency units. These findings are significant since it indicates that the most important time to change patient outcomes are within the first 48 hours of care.

The results of this study did not demonstrate the "weekend effect" (24) as the number of mortalities was evenly distributed throughout the days of the week and time of day. Kevat *et al* (25) in a study in Australia reported that that patients admitted on weekends had a greater risk of dying than those admitted on week days. This was attributed to the number of physicians working on internal medicine wards on weekends and holidays being below compared to the mean number working on weekdays which could result in less intense medical care during the weekend. Another attributed factor was that performance of diagnostic and therapeutic studies, as well as consultations with other specialists, was limited during weekends. In addition, weekend staff were mainly on call physicians, who had less experience and knowledge about patients than the regular ward physicians, who know their patients best. While the same factors apply in our set up, the failure to demonstrate this phenomenon could be attributed to the small sample of our study and limited period of follow up, since the Spain study examined 400,000 consecutive admissions over a period of 1 year. A well-powered study with adequate sample size may need to be performed locally to conclusively rule out this phenomenon.

Our study had the following limitations; this was a referral hospital-based study and therefore the results we got might not accurately reflect those in the community. There was a low post mortem acceptance rate among the relatives of the deceased patients, which limited the analysis of post-mortem data. It was beyond the scope of this study to establish whether treatment modalities influenced the mortality.

Conclusions

The seven-day mortality rate was found to be high at 17.6%. Most of these deaths were preventable deaths if early measures were put in place. Malignant neoplasm was the commonest cause of death followed by congestive cardiac failure and chronic kidney disease. HIV infection was the commonest co-morbidity associated with primary diagnosis. Majority of the admitted patients died within the first 48 hours of admission. The important predictors of early mortality in this study were Karnosfsky's Performance Scale and length of stay in the ward. An association between early mortality and access block phenomenon, "weekend effect", poor health seeking behavior and late patient referrals were not demonstrated. However, continued disease surveillance and well powered studies may need to be done to conclusively exclude these factors as impacting early mortality at KNH.

Recommendations

The government should allocate resources to tackle non-communicable diseases with malignant neoplasm and kidney disease being of special mention since they are the leading causes of mortality. This should include provision of adequate treatment facilities and training of personnel to handle these cases.

KNH management should institute long-term disease surveillance activities and regular mortality audits to characterize disease patterns and any intra-institutional variations that may exist and continually evaluate the quality of care that the patients are receiving. An operational research should also be done to assess the treatment modalities that patients receive viz a viz the causes of mortality to optimize patient management within the department.

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Original paper

Epidemiology and Risk Factors for Asthma in Kenya

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Abstract

Background: Asthma is a common disease affecting up to 18% of the world's population. Although declining in some parts of the world, the prevalence is increasing in most low and medium income countries. In addition to reducing quality of life among sufferers, asthma is burdensome to health systems. The epidemiology of asthma in Kenya has not been comprehensively described to date. The aim of this study was to describe the prevalence and risk factors for asthma in Kenya.
Methods: Between May-July 2015, we systematically searched published literature on chronic respiratory diseases in Kenya by applying a customized search string on six databases to identify articles on the epidemiology of asthma in Kenya. Additionally, we systematically screened abstracts presented at key respiratory scientific conferences and conducted a review of unpublished dissertations at the two largest medical schools in Kenya. Critical appraisal of retrieved papers was carried out using the 'Critical Appraisal Skills Program tools'.
Results: The prevalence of asthma ranged from 3% to 28.6%. The International study of asthma and allergy in children reported an urban 'rate' of 17.1% in 1995 increasing to 18% in 2001. The corresponding prevalence 'rates' in rural areas were 10.4% and 13.8%. Risk factors for asthma included urban residence, home environment and exposure to cigarette smoke. Breastfeeding was protective against asthma.
Conclusion: Despite its high prevalence in Kenya, the burden of asthma on health systems, society and individuals has not been adequately quantified to support policy and practice. This is especially true for phenotypes such as occupational and severe asthma.

Keywords: Asthma, Epidemiology, Risk-factors, Prevalence, Kenya

Introduction

Asthma is a common disease affecting up to 18% of the world's population (1). The Global Initiative for Asthma (GINA) defines asthma as a 'heterogeneous disease, usually characterized by chronic airway inflammation and defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation'(1). It is remarkable that asthma has been defined variously throughout history, including as a 'neurotic affection' by none other than Sir William Osler, the father of modern medicine(2,3). There now exists a greater understanding of 'behind-the-scenes' intrigues underlying the recognizable clinical syndrome and the need for a unifying definition to standardize clinical and epidemiological diagnosis (4). Revised estimates from the Global burden of disease studies suggest that as many as 334 million persons, most living in Low and Medium Income Countries (LMIC), have asthma (5). Asthma is the most frequent chronic disease of childhood, affecting one out of seven 13-14 year-olds, where it exacts a heavy toll in terms of morbidity and disability (1, 5, 6). Though stabilizing in Western Europe and Australia, the prevalence of asthma is increasing in many parts of the world by as much as 50% every decade (7-9). This asthma related morbidity - especially in children aged 10-14 and adults between 75-79 years old -remains unmitigated, despite 'better recognition and increased prescriptions for anti-asthma therapy' (5, 7, 10). The high burden of disease, notwithstanding,less than 1% of patients die of asthma, translating to an estimated 250,000 deaths annually (5, 11). In the United Kingdom, it has been estimated that up to 65% of asthma deaths may be preventable, through strengthening chronic care, improving adherence to therapy and mitigating tobacco use amongst patients (12, 13). Global economic costs arising from asthma are

enormous, exceeding those of tuberculosis and HIV/AIDS combined. (14) Moreover, asthma is responsible for 15 million Disability-Adjusted Life Years (DALYs) lost annually, similar to diabetes and schizophrenia, whose impacts are more widely recognized (15). The mean cost per patient per year due to asthma is estimated at US $1,900 in Europe and US $3100 in the United States (USA)(16). Alarmingly, severe disease which occurs in 10-20% of patients with asthma, disproportionately contributes to 50% of these costs (17). In a one year prospective economic analysis of asthma-related expenditure, worsening disease severity was significantly associated with increased overall costs (18).

To begin to turn the tide against the rising burden of asthma in Kenya, it is important to understand what is known about asthma from the local perspective in order to guide policy formulation, develop standards of care and highlight research priorities (19, 20).

The aim of this study was to undertake a literature review of the epidemiology and risk factors for asthma in Kenya, using a systematic approach.

Methods

Between May and July 2015, and as part of a wider review, we systematically searched published literature on chronic respiratory diseases in Kenya. We applied a customized search string on six databases (Africa Wide Information, Ovid Medline, Embase, Global Health, Scopus and the Cochrane Library) to identify articles on the epidemiology of asthma. Additionally, we systematically screened abstracts presented at key respiratory scientific conferences - European Respiratory Society (ERS) Congress, American Thoracic Society (ATS) Conference, International Union against TB and Lung Diseases (IUATLD) and Kenya International Scientific Lung Health Conference (KISLHC) - and conducted a review of unpublished dissertations at the two largest medical schools in Kenya. Critical appraisal of retrieved papers was carried out using CASP (Critical Appraisal Skills Program) tools (21). These methods have been published elsewhere (22).

Results

Twenty of 446 articles from online databases, 7 of 24 dissertations and 2 of 5 conference abstracts were included in the final review. Of these 12 (38.7%) were focussed on asthma prevalence and risk factors. Identified studies (Table 1) spanned three decades from 1970 to 2007.

Table 1: Critical Appraisal of Studies on Asthma Epidemiology in Kenya

Study	Authors	Journal	Year	Focused?	Appropriate Method?	Sampling?	Measurements?	Power?	Clear Analysis?	Findings
Exercise induced bronchospasm: a pilot survey in Nairobi school children	Ng'ang'a, Odhiambo, Omwega *et al.*	East Afr Med J	1997	Yes	Yes. CSS*	Stratified random	Standardised objective assessments done. Standard definitions for EIB used as validated in other studies. Calibration of spirometers done.	No	Yes	Prevalence of EIB of 10.5%. EIB fell with age especially with low socioeconomic status.
Prevalence of exercise induced bronchospasm in Kenyan school children: an urban-rural comparison	Ng'ang'a, Odhiambo, Mungai *et al.*	Thorax	1997	Yes	Yes. CSS	Stratified random	Standardised objective assessments done. Standard definitions for EIB used as validated in other studies. Calibration of spirometers done.	Yes	Yes	Urban children had 96% greater odds of EIB. AOR 21% (95% CI 0.69-2.11).
Urban–rural differences in questionnaire-derived markers of asthma in Kenyan school children	Odhiambo, Ng'ang'a, Mungai *et al.*	Eur Respir J	1993	Yes	Yes. CSS	Stratified random	Subjective (Self-reports) as elicited by a questionnaire administered to parent/guardian	No	Yes	Higher odds of asthma in urban children. AOR 1.59 (95% CI 0.70-3.55).

Study	Authors	Journal	Year	Focused?	Appropriate Method?	Sampling?	Measurements?	Power?	Clear Analysis?	Findings
Prevalence of asthma, allergic rhinitis and dermatitis in primary school children in Uasin Gishu district, Kenya ISAAC Phase 1 study	Esamai, F. Anabwani, G. M.	East Afr Med J	1995	Yes	Yes. CSS	Random	Subjective (Self-report) as elicited by a written and video questionnaire	Yes	Yes	1 year prevalence wheeze 10.2% on written questionnaire
Prevalence of asthma, allergic rhinitis and dermatitis in primary school children in Uasin Gishu district, Kenya ISAAC Phase 3 study	Esamai, F Ayaya, S Nyandiko, W	East Afr Med J	2001	Yes	Yes. CSS	Random	Subjective (Self-report) as elicited by a written questionnaire	Yes	No	1 year prevalence wheeze 13.8 % (2001) and 10.2% (1995), p=0001.
Prevalence of symptoms of asthma, rhinitis and eczema in 13 to 14-year-old children in Africa: The International Study of Asthma and Allergies in Childhood Phase III	Ait-Khaled, N. Odhiambo, J. Pearce, N. *et al.*	Allergy	2007	Yes	Yes. CSS	Random	Validated written questionnaire, Video questionnaire	Yes	Yes	Prevalence of wheeze in the past one year in Nairobi was 18.0% compared to 13.8% in rural Eldoret.
Home environment and asthma in Kenyan school children: a case-control study	Mohamed, N. Ng'ang'a, L. Odhiambo, J	Thorax	1995	Yes	Yes. CCS	Matched controls	Cooking fuel use, housing type (walls and floor), presence of rugs, damp damage, indoor air pollution, cigarette smoking and salt intake estimated in both cases and controls	Yes	Yes	Asthma associated with dampness (AOR 4.9), presence of rugs and carpets (OR 3 6) and furniture in child's sleeping area, and indoor air pollution (OR 2.5). Salt intake was higher amongst cases (mean 817 vs 483mg) than controls.
Atopy, asthma, and antibodies to Ascaris among rural and urban children in Kenya	Perzanowski, M. S. Ng'ang'a, L. W. Carter, M. C. *et al.*	J Pediatr	2002	Yes	Yes. CSS	Stratified random	Anthropometric, Body fat, skin tests, serum IgE and IgG, exercise challenge test, history of asthma	No	Yes	Association between atopy and asthma among school children
Some aspects of the aetiology of asthma in Nairobi with special reference to parasites and the house dust mite	Rees, P. H. Gitoho, F. Mitchell, H. S. Rees, C.	East Afr Med J	1974	Yes	Yes. MMS	Consecutive	Physical examination, chest xray, stool examination, blood film and serological testing done	No	Yes	House dust mite was an important precipitating factor for asthmatic attacks.

Study	Authors	Journal	Year	Focused?	Appropriate Method?	Sampling?	Measurements?	Power?	Clear Analysis?	Findings
Effects of passive smoking and breastfeeding on childhood bronchial asthma	Wafula, E. M. Limbe, M. S. Onyango, F. E. Nduati, R.	East Afr Med J	1999	Yes	Yes. CSS	Not clear	Number of attacks, age of onset, breastfeeding history, household smoking exposure (reported)	No	Yes	Passive smoking association with early onset of asthma (OR 2.44 95%CI 1.2-5.0). Breastfeeding protective against severe asthma (OR 0.4 95% CI 0.14-0.98)
Allergic conditions in a general practice in Nairobi: A pilot study	De Souza, M	East Afr Med J	1992	Yes	Yes. Series	Random	Data collected on sex, age, residence, history, clinical findings, causative factors, laboratory tests, diagnosis and management	N/A	Yes	Asthma had highest prevalence among allergic conditions at 28.9%. Total prev. of allergic conditions was 18.8%.
Bronchial Asthma in Kenya.	Mitchell, HS	East Afr Med J	1970	Yes	Yes. Series	None	Clinical examination, eosinophil levels, stool examination for parasites, skin testing for animal dander. Post mortem examination for 2 patients who died	N/A	Yes	Youthful patients with asthma, rarity of parasitic infestation, sensitization to animal dander, lack of deaths from asthma

KEY: *CSS- Cross sectional study, MMS-Mixed methods study, EIB – Exercise Induced Bronchoconstriction

Discussion

Of the eight studies reporting on prevalence (Figure 1), four were part of the International Study of Asthma and Allergies in Childhood (ISAAC) conducted at 306 centres in 105 countries (23-31). Two studies evaluated the prevalence of Exercised-Induced Bronchospasm (EIB) in children (aged 8-17 years) using standard definitions and performed quality spirometry (25, 30). In their study on urban-rural differences in asthma markers, Odhiambo *et al.* (29) recorded parental-reported asthma while D'Souza (31) quantified the number of patients with physician-diagnosed asthma in a general practice setting. Evidence suggests that 'definitions used in current epidemiological studies are inconsistent' resulting in wide estimates of asthma prevalence. In their review of 117 commonly cited studies, Sá-Sousa *et al.* (32) reported that operational definitions such as 'lifetime asthma, diagnosed asthma, and current asthma were defined in 8, 12 and 29 different ways respectively' - yielding prevalence rates of 5.3-24.4% and 1.1-17.2%, when applied to the national Portuguese and National Health and Nutrition Examination Survey (NHANES 2005-6) datasets respectively (32). The reported Kenyan prevalence of asthma reflects this variation, with the highest estimate (28.6%) found amongst the subset of patients with allergic conditions attending a GP clinic. Asthma clusters with allergic diseases, and is present in up to 48% of patients with allergic rhinitis (33). Several reports corroborate associations between allergy, atopy and asthma - with allergic rhinitis further identified as a risk factor for asthma in a 23-year cohort study (34-36). Recent observations that the two developmental phenotypes: bronchial hyper-responsiveness and the abnormal T helper 2 (Th2) response are present at birth point to a role of prenatal influences (37).

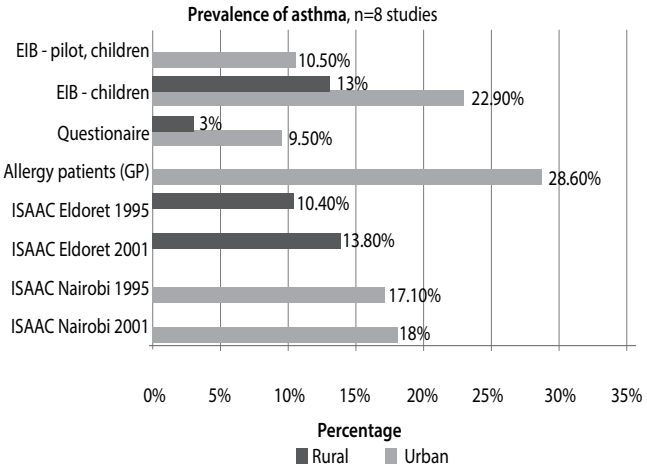

Figure 1: Asthma prevalence in Kenya

In Kenya, asthma is more common in urban than rural areas and its prevalence may be increasing over time. A systematic analysis from Africa showed that the prevalence of asthma had increased over the past two decades with estimates consistently higher in urban areas (38).

In the earliest published description from Kenya, dating back five decades, the 'youthful nature of patients, rarity of parasitic infestation or sensitization to animal dander, and lack of deaths from asthma' was remarked upon (39). Perzanowski *et al.* (34) highlight a possible protective role of helminthic infestation with the finding that rural children with lower rates of asthma and atopy harbored more antibodies to ascaris. This protection may be mediated through helminth-induced immune hypo-responsiveness, a mechanism employed by the parasite to evade host defenses (40). In spite of these observations and the protective effect observed in a murine model, a 2012 Cochrane review of five published studies found no clinical benefit of helminth therapy (40, 41).

Further explanation for the observed rural-urban differences in asthma prevalence might be provided by the home environment. In the study by Mohammed *et al.* (42), home dampness, presence of rugs, and Indoor Air Pollution (IAP), increased the odds of developing asthma by between two and five-fold (42). Furthermore, asystematic review of 69 papers published between 2000 and 2013, concluded that indoor dampness was associated with exacerbations of asthma - with sufficient evidence of a causal relationship between House Dust Mite (HDM) allergen and asthma exacerbations in children (43). These findings complement those of Rees *et al.* (44) who found more asthmatics to be sensitized to HDM as compared to non-asthmatics. Despite this established link between HDM and asthma exacerbations, strategies to control dust mites have so far not proved beneficial in asthma control (45). The Global Initiative for Asthma recommends remediation of home dampness and mould to reduce symptoms and medication use in adults, and multicomponent avoidance strategies for children sensitized to HDM or pets (1).

Wafula *et al.* (46) provide local evidence that modifiable early life exposures are important risk factors for asthma. In their study, passive exposure to cigarette smoke was associated with more than twice increased odds of early onset of asthma. In contrast, breastfeeding was associated with variable protection against severe asthma (OR O.4 95% CI 0.14-0.98). Larger studies have established the detrimental effects of tobacco exposure on children. In an analysis of data on 22,712 children from nine countries in Europe and North America, parental smoking during pregnancy was associated with a 40% higher risk of clinically abnormal lung function amongst children (47). A recent meta-analysis further reported that breastfeeding was protective against asthma (OR 0.76-0.81), and that this effect was strongest at ages 0-2 years (48).

The influence of dietary salt on the asthma has been the subject of much speculation (49-52). In Kenya, using a case-control design, Mohamed *et al.* (53) found a higher mean salt intake amongst cases with asthma (817mg) than controls (483 mg). Although no causal association has been established between salt intake and asthma to date, a low salt diet over 2-5 weeks has been shown to improve lung function and reduce bronchial hyper-reactivity amongst adults with asthma (52). Moreover, a 2011 Cochrane review did not find evidence of a beneficial effect of salt restriction on asthma control (54).

Conclusion

The reported prevalence of asthma in Kenya varies widely by case definition and population. The ISAAC studies are notable for their use of standardized methodology across multiple centres and countries. The Kenya ISAAC studies suggest that asthma is more prevalent in urban areas and increasing with time. Other risk factors for asthma and asthma exacerbation locally are: exposure to cigarette smoke, indoor air pollution, home dampness, mould and sensitization to HDM. Helminthic infection, though possibly protective, is yet to demonstrate therapeutic efficacy. Breastfeeding is protective against severe asthma and is recommended by the Kenya national asthma guidelines (55).Though differences in mean salt intake have been highlighted by one study, these findings require further elucidation (53).

Recommendations

There is need to further quantify the burden of asthma through economic evaluations, quality of life assessments and audits of clinical care pathways, including health services research. The short and long term consequences of local efforts aimed at improving Indoor Air Quality (IAQ)on asthma exacerbations have not been widely documented and the broader impact of breastfeeding on asthma severity in children remains unexplored. More than a decade ago in 2007, Kenya enacted the tobacco control ACT (56). The impact of this bold public health initiative on asthma burden has not been studied to date, and warrants scientific scrutiny. As up to 15% of cases of adult onset asthma might be occupational and thus preventable, data to establish the local prevalence of this entity are required (55, 57). Finally, reliable Kenyan prevalence estimates of severe asthma, which accounts for 50% of total global asthma costs, will help prioritize allocation of resources (17).

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Original paper

Hypomagnesaemia among ambulatory patients with type 2 diabetes at Kenyatta National Hospital diabetes outpatient clinic

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Abstract

Background: Type 2 diabetes mellitus is a recognized independent risk factor for hypomagnesaemia with a reported global prevalence of 13.5-47.7%. There is an established association between hypomagnesaemia, poor glycaemic control and diabetes complications.
Objective: To determine the prevalence of hypomagnesaemia among ambulatory type 2 diabetes mellitus patients at Kenyatta National Hospital and to document their glycaemic control, renal function reserve and their clinical characteristics (duration of disease and treatment therapy).
Methods: A descriptive cross-sectional study was conducted at the Kenyatta National Hospital diabetes outpatient clinic between August and September 2016. One hundred and ninety patients were recruited, socio-demographic and clinical details including blood pressure and body mass index were obtained from the study subjects and their medical records. Blood samples for measuring serum magnesium, creatinine and glycated haemoglobin were obtained and analyzed.
Results: The prevalence of hypomagnesaemia was 12.1% (IQR 7.9 – 16.8%). Of the 190 patients recruited, 23 (12.1%, IQR: 7.9 – 16.8%) had hypomagnesaemia [mean age: 58.3 years; male: 65.2%; overweight and obese: 82.6%]. 60.9% had poor glycaemic control; 82.6% had diabetes for more than 5 years; 56.5% were on an insulin-based therapy (as monotherapy or in combination with oral hypoglycaemic agents); 73.9% were hypertensive; 30.4% were on diuretic therapy and 39.1% were in chronic kidney disease stage 3 and beyond.
Conclusion: Although the prevalence recorded appears to be low compared to studies done in other regions, there is still a significant burden of hypomagnesaemia among our diabetic patients. Patients with hypomagnesaemia were noted to have poorer glycaemic control and a longer mean duration of diabetes.

Key words: Hypomagnesaemia, Renal function reserve, Quality of glycaemic control

Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both (1). Type 2 diabetes mellitus accounts for approximately 90% of all diabetes cases worldwide and is a global public health concern since it is on the rise due to change in lifestyle and dietary habits (2). According to the International Diabetes Federation 2015 statistics, 415million people globally are currently living with diabetes and this number is expected to rise to 642million by 2040. The federation also revealed that 80% of diabetic people live in the low- and middle income countries and most are aged between 40-59 years. It also reported 478,000 cases of diabetes in Kenya in 2015 and predicted that by 2040 this number will rise to 1.1 million.

The hallmark of type 2 diabetes mellitus is chronic hyperglycaemia which is associated with long-term complications including electrolyte imbalances (1). Magnesium is the most under diagnosed electrolyte deficiency and is referred to as 'the essential forgotten electrolyte'(3). Type 2 diabetes mellitus is a recognized independent risk factor for hypomagnesaemia with a reported prevalence of 13.5-47.7% (4). The principal causes of magnesium loss being gastrointestinal and renal losses (5). Notably, the kidney is the principal site for magnesium homeostasis. There is an established association between hypomagnesaemia, poor glycaemic control and the diabetes-related complications (6). Hypomagnesaemia in critically ill diabetic patients has been shown to be associated with high mortality (7).

Oral magnesium supplementation restores magnesium levels, improves insulin sensitivity and glycaemic metabolic control eventually slowing down the rapid progression into the diabetes-related complications (8). It is therefore necessary to regularly monitor serum magnesium levels ideally in all type

2 diabetes patients but more so amongst those with poor metabolic control and those with diabetes-related complications.

Significance of the study: Hypomagnesaemia is a serious yet forgotten electrolyte deficiency which has been implicated in type 2 diabetes mellitus. It is associated with poor glycaemic control and diabetes-related complications including retinopathy, foot ulcers and deterioration in renal function (3,6). There is paucity of data on the prevalence of hypomagnesaemia amongst patients with type 2 diabetes mellitus in Kenya.

Objective: To determine the burden of hypomagnesaemia among ambulatory type 2 diabetes mellitus patients at Kenyatta National Hospital and to document their glycaemic control, renal function reserve and their clinical characteristics (duration of disease and treatment therapy).

Materials and methods

This was a descriptive cross-sectional study conducted in the diabetes out-patient clinics at Kenyatta National Hospital. We included patients aged 30 years and above with a documented diagnosis of type 2 diabetes mellitus, on follow up at the Kenyatta National Hospital diabetes clinic for at least 1 year who gave written informed consent. We excluded patients with diabetes ketoacidosis or any acute illness requiring in-patient care 3 months prior to assessment. The sample size was calculated using the Daniel's formula (1999) for finite population as shown below (9).

$$n \geq \frac{N Z^2_{\alpha/2} P(1-P)}{d^2(N-1) + Z^2_{\alpha/2} P(1-P)}$$

Where:
n = minimum sample size required
N = Total estimated accessible population (N=400)
$Z^2_{\alpha/2} Z^2_{\alpha/2} Z_{\alpha/2} Z_{\alpha/2}$ = Critical value for standard normal distribution at α-level of significance (α = 0.05, $Z_{\alpha/2} Z_{\alpha/2}$ = 1.96)
P = Estimated prevalence of hypomagnesemia in type 2 diabetes mellitus patients (p=0.65 based on a study in Ethiopia (10)
d = Margin of error (d = 0.05)
The minimum sample size required was; n = 187 patients.

One hundred and ninety patients were recruited. Data collection was done using a structured data collection tool and anthropometric measurements taken. Blood samples for serum magnesium, creatinine and glycated haemoglobin levels were drawn and analysed in the Kenyatta National Hospital Biochemistry Laboratory.

Flow chart of study participant's recruitment

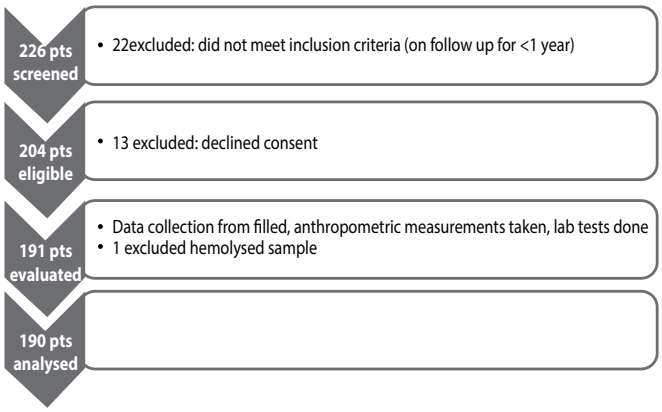

Figure 1: Recruitment Process

Study variables

- ✓ Serum Magnesium levels
  - o Hypomagnesaemia was defined as magnesium levels less than 0.66 mmol/L
  - o Normomagnesaemia defined as magnesium levels between 0.66 and 1.07 mmol/L
  - o Hypermagnesaemia was defined as magnesium levels greater than 1.07 mmol/L
- ✓ Glycaemic control - This was assessed by measuring glycated hemoglobin (HbA_1c). HbA_1c less than or equal to 7% was considered as good control and HbA_1c greater than 7% as poor control (ADA 2015 Recommendations)
- ✓ Renal function reserve - Serum creatinine was measured and an estimated Glomerular Filtration Rate (eGFR) calculated. Based on the calculated eGFR patients were categorized in stages of chronic kidney disease as follows:
  - o Stage 1 - eGFR equal to or more than 90 ml/min/1.73m^2
  - o Stage 2 - eGFR 60-89 ml/min/1.73m^2
  - o Stage 3a - eGFR 45-59 ml/min/1.73m^2
  - o Stage 3b - eGFR 30-44 ml/min/1.73m^2
  - o Stage 4 - eGFR 15-29 ml/min/1.73m^2
  - o Stage 5 - eGFR less than 15ml/min/1.73m^2

Data analysis: Descriptive statistics were used to summarize the data. For continuous variables, histograms were plotted to show the distribution and means (SD) or medians (IQR) were reported. For categorical variables, bar/pie-charts were plotted to show the distribution; frequencies and proportions were reported in tables.

Ethical considerations: The study was undertaken after approval by the Department of Clinical Medicine and Therapeutics, University of Nairobi and the Kenyatta National Hospital / University of Nairobi Ethics and Research Committee, Research Approval number P335/04/2016. Only patients who gave informed

written consent were recruited and confidentiality was maintained.

Results

Table 1 is a summary of the various characteristics of the 190 diabetic patients recruited into the study.

Table 1: Socio-demographic and clinical characteristics

Variable	Category	Frequency (n=190)	Proportion (%)
Age groups	<45	29	15.3
	45-59	65	34.2
	60-74	75	39.5
	≥75	21	11.1
Gender	Male	81	42.6
	Female	109	57.4
Employment status	Employed	127	66.8
	Unemployed	63	33.2
Highest level of education	None	15	7.9
	Primary	74	38.9
	Secondary	76	40.0
	Tertiary	25	13.2
Marital status	Single	5	2.6
	Married	164	87.4
	Divorced/ Widowed/ Separated	21	10.0
BMI (Kg/M^2)	Underweight (<18.5)	3	1.6
	Normal weight (18.5-24.9)	34	17.9
	Overweight (25-29.9)	78	41.1
	Obese (≥30)	75	39.4
Blood pressure (mmHg)	Normal (≤140/90)	89	46.8
	Elevated (>140/90)	101	53.2
Duration of diabetes illness	<5	52	27.4
	5-10	49	25.8
	>10	89	46.8
Any medication for sugar control?	Yes	186	97.9
	No	4	2.1
Type of medication for sugar control	OHA	87	46.8
(n=186)	Insulin	22	11.8
	OHA & Insulin	77	41.4

Table 2: Summary of laboratory findings

Variable	Category	Frequency (n=190)	Proportion (%)
Serum magnesium levels (mmol/L)	Hypomagnesaemia (<0.66)	23	12.1
	Normomagnesaemia (0.66-1.07)	154	81.1
	Hypermagnesaemia (>1.07)	13	6.8
Glycated haemoglobin (%)	Good (≤7%)	41	21.6
	Poor (>7%)	149	78.4
Estimated glomerular filtration rate (ml/ min/1.73m2)	Stage 1 (≥90)	28	14.7
	Stage 2 (60-89)	91	47.9
	Stage 3a (45-59)	44	23.2
	Stage 3b (30-44)	19	10.0
	Stage 4 (15-29)	8	4.2

In summary, we recruited 190 type 2 diabetes patients; 57.4% were female, the mean (SD) age was 59.2 (12.3) years; duration of diabetes was 11.5 years, 53.2% were on insulin based therapies (as monotherapy or in combination) yet only 21.6% patients had achieved good glycaemic control (HbA_1c <7%). 78.4% were hypertensive with 38.9% of them on diuretics. 37.4% had poor renal function reserve with stage 3 chronic kidney disease and beyond. The overall prevalence of hypomagnesaemia was 12.1% (95% CI 7.9 – 16.8%). We then did Pearson chi-square tests of association to evaluate for any relationship between hypomagnesaemia and the different patient characteristics. Serum magnesium levels had significant negative correlation with glycaemic control (p-value=0.029) and mean duration of diabetes (p-value=0.014).

Table 3: Association between serum magnesium and patients' profile

Variable	Category	Hypo-magnesaemia	Normo/hyper magnesaemia	Pearson Chi-sq	P-value
Glycaemic control	Good	9	32	4.764	0.029
	Poor	14	135		
Diuretic therapy	Loop	5	5	16.382	<0.001
	Thiazide	2	46		
Gender	Male	15	66	5.458	0.019
	Female	8	101		
Mean duration of diabetes		15.0 ± 11.0	11.0 ± 8.1		0.014
eGFR	Stage 1	2	26	2.555	0.645
	Stage 2	12	79		
	Stage 3a	4	40		
	Stage 3b	4	15		
	Stage 4	1	7		
BMI	Underweight	-	3	*	*
	Normal	4	30		
	Overweight	7	71		
	Obese	12	63		
Blood pressure	Normal	12	77	0.299	0.585
	Elevated	11	90		
Age group	<45	1	28	4.210	0.240
	45-59	7	58		
	60-74	13	62		
	≥75	2	19		
DM treatment	OHA	7	70	0.462	0.794
	Insulin	3	19		
	Both	10	77		

** Test of association not done due to one empty cell*

Discussion

The study population was predominantly mature adults; with a female preponderance at 57.4%, the mean (SD) age was 59.2 (12.3) years and the duration of diabetes was 11.5 years on average. 21.6% had achieved good glycaemic control (glycated haemoglobin, HbA_1c of less than 7%) and 37.4% had poor renal function reserve with stage 3 chronic kidney disease and beyond. 78.4% of the patients were hypertensive and 38.9% of them were on diuretic therapy.

This study evaluated 190 patients overall. The prevalence of hypomagnesaemia defined as serum

magnesium levels below 0.66mmol/L was found to be 12.1% with a mean (SD) serum magnesium concentration of 0.83mmol/L (0.15mmol/L). Serum magnesium concentration is closely regulated within the range of 0.7 - 1.0mmol/L (1.5 - 2mEq/L; 1.7 - 2.4mg/dL) but in our study, we used the magnesium colorimetric assay kit (Xylidyl Blue-I Method) which had a kit-dependent reference range of 0.66 - 1.07mmol/L. Studies have shown a significant fall in serum magnesium levels among diabetes patients compared with non-diabetic controls; the reasons for this are multi-factorial including inadequate magnesium intake, reduced magnesium intestinal absorption or hypermagnesuria (5). The recorded prevalence rates of hypomagnesaemia range from 11-47.7% among patients with type 2 diabetes compared to 2.5 – 15% in the general population (4, 6).

Studies done in different African countries give varying prevalence. The Ethiopian study by Seyoum *et al* (10), recorded an overall prevalence of 65% with mean (SD) serum magnesium of 0.86mmol/L (0.02mmol/L). In this specific study they included both type 1 and 2 diabetes patients; type 1 diabetes patients were found to have significantly lower magnesium levels compared to patients with type 2 diabetes. Insulin stimulates magnesium conservation in the loop of Henle and distal convoluted tubule therefore with insulin deficiency which is characteristic of type 1 diabetes there is increased urinary magnesium excretion. This could have contributed to the high prevalence recorded, although the mean serum magnesium levels were comparable to what we obtained in our study. Dietary differences could also explain this observation, at that time there was widespread famine and drought in Ethiopia rendering a large portion of the population to a magnesium-deficient diet.

Eighty two point six percent of the study participants with hypomagnesaemia had lived with diabetes for a period of at least 5 years. On further analysis, the mean (SD) duration of diabetes among patients with hypomagnesaemia was 15 years (11.0 years) and 11.0 years (8.1 years) in patients with normal or high magnesium levels ($p = 0.014$). This implies that duration of diabetes could have an indirect relationship with serum magnesium levels especially if the diabetes is poorly controlled. Patients who have had diabetes for long periods are likely to have an element of diabetes nephropathy hence are more prone to excess urinary magnesium loss. In 2015, Arpaci *et al* (11) in Turkey showed a similar pattern with hypomagnesaemic patients having a longer mean (SD) duration of illness; 8.58 years (7.92 years) compared to 6.5 years (7.08 years) among patients with normal magnesium levels; albeit the longer duration of diabetes in both patient groups in our study compared to the Turkey study.

Serum magnesium level was found to be significantly associated with diuretic therapy (p-value <0.001); 30.4% of the patients with hypomagnesaemia were on diuretic therapy. Rampant use of diuretics promotes urinary magnesium wasting. Loop diuretics inhibit the electrical gradient necessary for magnesium re-absorption in the thick ascending loop of Henle hence causing magnesium depletion especially with chronic use. Long term use of thiazide diuretics can cause substantial magnesium depletion due to secondary hyperaldosteronism, increased sodium load and interaction with calcium metabolism as well as causing reduced renal expression levels of the epithelial magnesium channel TRPM6 (12).

The glycaemic control in our study population was relatively poor with only 21.6% of the patients achieving HbA_1c of 7% and below. This reflects the challenges that exist in management of diabetes where achieving glycaemic control requires a multi-disciplinary approach involving nutritional and social support among others.

Sixty point nine percent of our patients with hypomagnesaemia had HbA_1c of 7% and above; with a mean of HbA_1c 8.5%. This was comparable to a mean of 8.3% recorded by Xu *et al* (13) in a study done among type 2 diabetes patients in China. We also found that patients with poor glycaemic control were more likely to have hypomagnesaemia compared to those with good glycaemic control ($p = 0.029$). This could be explained by the fact that poor glycaemic control and glycosuria increase magnesium excretion via osmotic diuresis. In addition, glycosuria also impairs renal tubular magnesium reabsorption. There is an established inverse relationship between serum magnesium levels and glycaemic control (6). However, it is important to note that the poor glycaemic control can also be attributed to poor compliance to drugs as well.

The mean estimated glomerular filtration rate (eGFR) among the hypomagnesaemic patients was 72.7 (20.3) ml/min/1.73m^2 compared to 77.9 (26.8) ml/min/1.73m^2 among the patients who had normal magnesium levels. These findings differed with those of a study done in Turkey by Arpici *et al*(11). In this Turkish study, they found a mean eGFR of 115.3 ± 3.70 ml/min/1.73m^2 among the hypomagnesaemic patients compared to 118.0 ± 1.3 ml/min/1.73m^2 in normomagnesaemic patients. This could mean that their study population was still in the 'early' hyperfiltration stage of diabetic nephropathy.

In a study done among the Chinese with type 2 diabetes, Xu *et al* (13) found a mean eGFR of 85.7 ml/min/1.73m^2 in those with hypomagnesemia compared to 94.0 ml/min/1.73m^2 among those with normal serum magnesium levels. This difference could be due to the poor glycaemic control with increased likelihood of developing diabetes kidney disease.

Hypomagnesaemia is associated with accelerated loss of kidney function among diabetics (14).

There have been controversial views regarding the relationship between microalbuminuria and magnesium deficiency. Some studies demonstrated a significant reduction in serum magnesium levels among diabetic cases with microalbuminuria (15); while others revealed that microalbuminuria and overt proteinuria did not affect serum magnesium levels (16). Although we were unable to assess for microalbunimuria; the eGFR trends obtained indicate that hypomagnesaemia was actually associated with a decline in eGFR.

Conclusion

Although the prevalence recorded appears to be low compared to studies done in other regions, there is still a significant burden of hypomagnesaemia among our diabetic patients. Patients with hypomagnesaemia were noted to have poorer glycaemic control and a longer mean duration of diabetes; although there could still be other unexplored confounding factors.

Recommendations

Larger and longitudinal studies to determine the direction of association between hypomagnesaemia and: glycaemic control and renal function reserve.

Limitations

This was a cross-sectional study hence no causal inference or temporal association could be drawn. It would have been ideal to compare the serum magnesium levels obtained in our study with those generated from the local population; however there is lack of locally generated data on serum magnesium. We were unable to investigate for causes of hypomagnesaemia such as dietary intake and drugs like proton pump inhibitors. It was also difficult to establish other causes of poor glycaemic control and renal function reserve among our diabetic patients due to limited resources. This was a single centre study with a relatively small sample size so these results may not be generalisable to the entire population of patients with type 2 diabetes in Kenya.

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Original paper

The profile of patients seen at the Kenyatta National Hospital with chronic lymphocytic leukemia between 2008-2015

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Abstract

Background: At Kenyatta National Hospital despite Chronic Lymphocytic Leukemia (CLL) being frequently seen we have no data with regards to the demographic characteristics, the clinical features, stage at diagnosis, treatment and outcomes of patients.
Objective: To profile patients seen at the Kenyatta National Hospital with CLL, in terms of demographic and clinical characteristics.
Setting: Kenyatta National Hospital, Nairobi, Kenya.
Methods: A retrospective cohort study analysed hospital case notes for 82 patients diagnosed with CLL. Demographic, clinico-pathologic and haematological characteristics were recorded. Treatment regimens given were recorded. Outcomes in terms of death, loss to follow up or still attending the haemato-oncology clinic were recorded.
Results: Male: female ratio was 1:0.9. Median age at diagnosis was 59.5 years. The commonest presenting complaint was generalised weakness or easy fatigability 40 (60%), followed by swelling of glands 47 (57%). The commonest physical finding at presentation was palpable lymphadenopathy (79.3%), followed by splenomegaly (76.8%). The median WBC count was $52x10^9$/L. The haemoglobin level at presentation was a median of 9g/dl. The platelet count was a median of 121 $x10^9$/L. Sixty patients (73.2%) were diagnosed to be at Binet C stage of disease. Followed by 14 (17.1%) at Binet B and 8 (9.8%) at Binet A. The commonest treatment regimen given was chlorambucil and prednisolone 64 (86.4%). At the time of analysis 40 (48.8%) patients had died, 32 (39%) were still alive and the status of 10 patients was unknown.
Conclusion: There is no male preponderance. CLL is diagnosed at a younger median age than that documented in literature from Caucasian populations. The physical findings in patients do not differ from literature. The presenting complaints however are more frequently weakness and fatigue. The commonest treatment regimen irrespective of age/fitness, given is chlorambucil prednisolone. A significant number of CLL patients seen at the KNH died.

Key words: Chronic lymphocytic leukemia, KNH

INTRODUCTION

There was paucity of data regarding the prevalence and incidence of CLL in Africa in general and Kenya in particular. At Kenyatta National Hospital (KNH) despite CLL pathology being frequently seen we had no data with regards to the demographic characteristics, the clinical features, stage at diagnosis, treatment regimens and outcomes of patients.

This study is the only study carried out in the past 35 years at the KNH to describe our patient data. It has enabled us to better characterise the cohort of patients with CLL seen at the KNH. The study provided an insight into what the current practice with regards to the evaluation and clinical care of patients with CLL is at the KNH. From this information recommendations can be made to better patient care, as well as make an early diagnosis. It also forms the basis on which future studies on CLL can be carried out in order to improve the clinical care of patients with CLL.The aim of the study was to profile patients seen at the KNH with CLL in terms of demographic and clinical characteristics. The specific objectives of the study were;

(i) To determine the demographic characteristics of patients diagnosed as CLL in terms of age, sex, and occupation.
(ii) To determine the clinico-pathologic and haematologic characteristics at presentation.
(iii) To determine what treatment regime, if any, the patients diagnosed as CLL were put on.
(iv) To determine the outcomes of patients diagnosed as CLL.

Materials and methods

Study design: Retrospective cohort study.

Setting: Patients in this study were seen or were still on follow up at the Kenyatta National Hospital, Nairobi. (Kenya's major teaching and tertiary referral centre). Hospital case notes from the medical records department at KNH were used. Records for the duration of 2008 to 2015 (inclusive) were analysed.

Study population and sampling strategy: The study population comprised all the patients already diagnosed with CLL at the KNH, using the diagnostic criteria of absolute persistent lymphocytosis of $\geq 5x10^9$/L in association with a BMA showing ≥30% small mature lymphocytes. In the absence of a BMA, absolute lymphocytosis of $\geq 5x10^9$/L with appropriate immunophenotyping (CD19, 20, 23 and 5) was diagnostic.

Inclusion criteria: Any file of a patient with a diagnosis of CLL seen at the KNH.

Sampling procedure and sample size: The sampling procedure was by consecutive sampling. Medical files from the medical records department at the KNH were sampled consecutively until the sample size was achieved.

Sample size: An estimated number of 120 CLL patients had been seen in KNH between 2008 and 2015. A representative sample was drawn from this fixed population and the sample size calculation was obtained using the Daniel formula for finite population (less than 10,000). The sample size was 82.

Data collection: Patient medical files that met the inclusion criteria were identified and data from each file was recorded in a data collection sheet. Demographic, clinico-pathologic (signs and symptoms at presentation, Binet stage at diagnosis) and haematologic characteristics (white blood cell, haemoglobin, and platelet count at presentation) were recorded from the hospital case notes. Treatment regimens given to patients were recorded. The outcomes that were recorded were loss to follow up, still attending the Haemato-oncology clinic, death, complete remission, progressive disease and stable disease. If a patient was lost to follow up a call was made to the patients next of kin (telephone number was available in the hospital medical file) to find out if the patient was dead or alive. Among patients who received treatment, complete remission, stable disease and disease progression where applicable were documented.

Data analysis: Demographic and clinical factors associated with attrition (death/loss to follow up) were tested using chi square test of associations for categorical data analysis and Student's t test for comparison of means.

Time to progression among patients who completed chemotherapy and developed disease progression was analysed and presented using Kaplan Meier Curve. The survival curves were generated by sex of the patients, as well as age at diagnosis and statistical differences tested using log-rank test. Also overall survival time to death was presented in a Kaplan Meier curve and compared between sexes, age at diagnosis, by stage at diagnosis and treatment regimen using log-rank test. All statistical tests were performed at 5% level of significance. All the study findings were presented in form of tables and graphs.

Results

Patient demographic characteristics: The files of 82 patients were studied for the period 2008-2015. All the patients were black Africans. Thirty nine (47.6%) were female and 43 (52.4%) were male. The male: female ratio found was 1:0.9. Forty two patients were aged less than 60 years. (males-22, females-20) (M:F ratio 1:0.9). Forty were aged 60 years or above (males-21, females-19) (M:F ratio 1: 0.9).

The median age at diagnosis was 59.5 years, with a mean of 58.5 ±11.09 (SD). Patients ranged from between 34-79 years, with the youngest being 34 years, and the oldest 79 years. The most prevalent age group was 50-59 years (Table 1).

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Table 1: Gender distribution in age groups

		Age groups			
		< 60 years		≥60 years	
	No.	(%)	No.	(%)	
Gender	Female	20	51.3	19	48.7
	Male	22	51.2	21	48.8

Patient clinico-pathologic and haematologic characteristics: The commonest presenting complaint was generalised weakness or easy fatigability which occurred in 40 (60%) of the patients, followed by swelling of glands in 47 (57%) and abdominal pain/ discomfort/distension among 30 (37%). Weight loss was a presenting complaint among 13% of patients, fever 13% and night sweats 12% of patients. The median duration of symptoms was 3 months with the shortest duration being 1 week and the longest 36 months. The commonest physical finding at presentation was palpable lymphadenopathy (79.3%; n=65), followed by splenomegaly (76.8%; n=63) and

pallor (62.2%; n=51). Hepatomegaly was only picked in 27 (32.9%) patients. The median WBC count at presentation was 52x10^9/L. The median ALC was 32.9x10^9/L.

The haemoglobin level at presentation ranged from between 3 to 16g/dl with a median of 9g/dl. Forty seven patients out of 82 (57.3%) had HB below 10g/dl. The median platelet count was 121 x 10^9/L. Thirty three patients (40.3%) had platelets below 100 x10^9/L. Twenty patients (24.4%) had platelets less than 100 x109 /L and HB below 10g/dl. Sixty patients (73.2%) had Hb below 10g/dl or platelet counts below 100 x10^9/L or both.

In terms of diagnostic testing 65 (79.3%) out of 82 patients had a bone marrow aspirate done while 2 (2.4%) had immunophenotyping done and 15 (18.3%) had both tests done. Irrespective of bone marrow aspirate, 17(20.7%) had immunophenotyping done. Sixty patients (73.2%) were diagnosed to be at a Binet C stage of disease. This was followed by 14 (17.1%) at Binet B and 8 (9.8%) at Binet A.

Table 2: Hematologic characteristics at presentation

	Mean	Median	Minimum	Maximum	Standard Deviation
WBC (x10^9/L)	119	52	6	960	188
ALC (x10^9/L)	95144	32913	5040	785700	156602
HB (g/dl)	9	9	3	16	3
Platelets (x10^9/l)	148	121	20	787	110

		Platelets (x10^9/L)					
		<100		≥100		Total	
		No.	(%)	No.	(%)	No.	(%)
HB (g/dl)	<10g/dl	20	60.6	27	55.1	47	57.3
	≥10g/dl	13	39.4	22	44.9	35	42.7
	Total	33	100.0	49	100.0	82	100.0

Treatment characteristics: The median duration between diagnosis and treatment initiation was 20 days, with a mean of 52 ±98 (SD) days. Patients who had presented with Binet stage C disease had the shortest median time from diagnosis to treatment initiation (18 days). This was followed by a median of 36 days to initiate treatment in patients diagnosed with Binet stage B disease and a median of 50 days to initiate treatment among patients who had presented in Binet stage A.

The most common treatment regimen offered to the 74 patients was chlorambucil and prednisolone. This regimen was given to 64 patients (86.4%). The remaining patients were put on cyclophosphamide + doxorubicin + vincristine + prednisolone (CHOP) in 5 (6.75%), cyclophosphamide + vincristine + prednisolone (CVP) in 4 (5.4%), fludarabine + cyclophosphamide in 1 (1.35%).

Disease outcomes among those who received treatment: At the time of analysis, among the 74 patients who received treatment, 23(31.1%) had stable disease, 23(31.1%) had disease progression, 12(16.2%) achieved complete haematologic remission but then relapsed and only 4(5.4%) remained in complete haematologic remission at the time of analysis. The outcome of 12(16.2%) patients among the 74 who received treatment was unknown. The median follow up time was 20 months.

The median duration from treatment initiation to achieving complete remission among the 16 patients who achieved complete remission was 360 days. The median duration from treatment initiation to disease progression (time to progression)among the 35 patients who developed disease progression was 826 days (27 months). Among the 35 patients who were treated and developed disease progression, the median time to progression among males was 27 months and females was 24 months. The median time to progression among patients aged 60 years or below was 17 months, while it was 38 months among patients older than 60 years. The median time to progression of patients on chlorambucil and prednisolone was 32 months, 17 months for CHOP, and 10 months for CVP.

Table 3: Number of patients treated and their outcomes

	No.	(%)
Treatment given	74	90.0
Disease Outcome		
Stable disease	23	31.1
Complete haematologic remission	4	5.4
Disease progression	23	31.1
Complete remission then relapse	12	16.2
Unknown	12	16.2
Disease progression based on		
New lymph nodes	13	37.1
Increase in LN by 50% or more	10	28.5
New hepato/splenomegaly	5	14.3
Increase in liver/spleen by 50 % or more	9	25.7
Alc- more than 5x10^9/l	17	48.6
Alc increase by 50% or more	18	51.4
Cytopenia	9	25.7

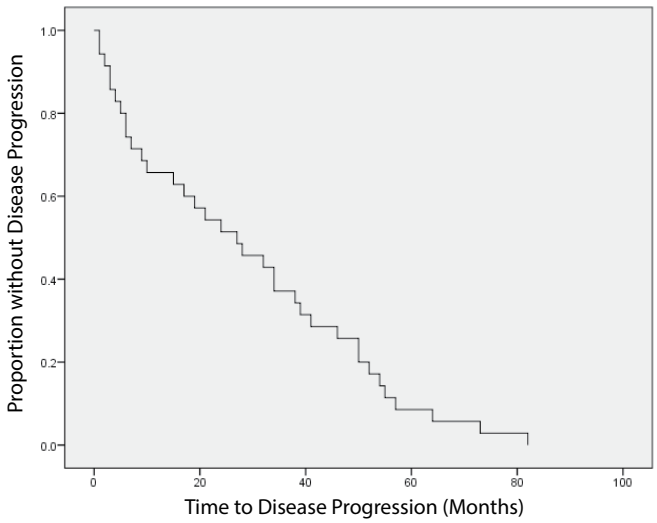

Figure 1: kaplan meiercurve depicting time to progression among patients who developed disease progression (n=35)

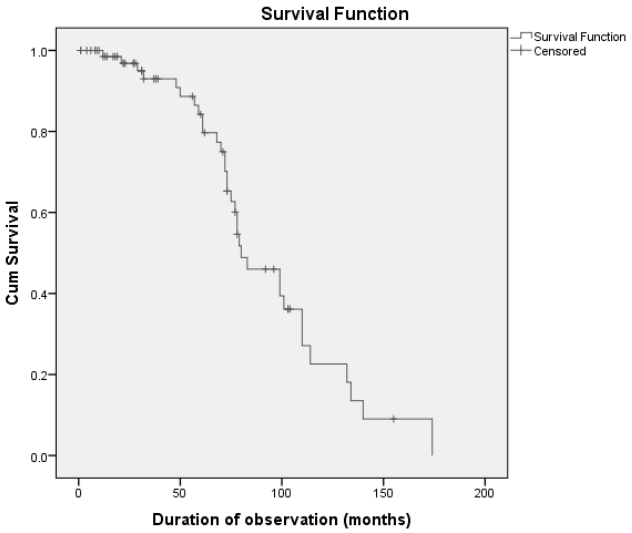

Figure 2: kaplan meier curve depicting overall survival of the entire sample

Overall patient outcomes (loss to follow-up and survival): Twenty six (31.7%) out of 82 patients were still on follow-up, 16 (19.5%) were lost to follow up. Nine (11%) had died in the ward at the time of their diagnosis and 31(37.8%) died after discontinuing attendance at the clinic as reported when the next of kin was called. Among the 16 patients lost to follow-up, 6 (7.4%) were called and found to still be alive, while 10 (12.1%) patients could not be traced by phone. The median follow up duration was 20 months, with the longest follow up for a patient being 143 months. Overall, at the time of analysis 40 (48.8%) patients had died, 32 (39%) were still alive and the status of 10 patients was unknown. The overall survival time of the entire sample at the time of analysis was a median of 80 months (6.6 years) and a mean of 93.5±6.43 (SE).

Among patients aged 60 years or below the overall survival was a median of 99 months (8.25 years), while patients aged above 60 years had an overall survival median of 75 months (6.25 years). Females had a median overall survival of 99 months (8.25 years) while males had a median overall survival of 78 months (6.5 years). The median overall survival among patients diagnosed with Binet A disease was 110 months (9.16 years). Patients diagnosed with Binet B disease had a median overall survival of 73 months (6.1 years), while those with Binet C disease had a median overall survival of 80 months (6.67 years).

Discussion

Chronic Lymphocytic Leukemia (CLL) is considered to be mainly a disease of the elderly, with a median age at diagnosis of 70 years (2,3). The incidence increases rapidly with increasing age. In this study the median age at diagnosis was 59.5 years, and this is lower than the median of 70 years seen in developed countries (2,3). This may be explained by the life expectancy of the population. The life expectancy in Africa is lower than that in Europe or North America, and this may create a selection bias that could explain the clustering of diseases at an earlier age. In a local study done by Patel (1) at the KNH in 2013 the median age at diagnosis was 62 years which is comparable to this study. In a study by Mulwa - Babu *et al* (5) in 2013 at the Aga Khan University Hospital the median age at diagnosis was 62 years which is again, comparable to this study.

The age range in this study was 34-79 years with the youngest patient being 34 years of age. CLL is uncommon among young patients and in this study had only 18 patients (21.9%) who were younger than 50 years. In a similar study done at the KNH in 1982 by Oloo (7) the age range was 17-78 years with the youngest patient being 17 years. CLL at that age is unusual and the case may represent a rare case or may reflect misdiagnosis due to unavailability of immunophenotyping facilities. In the study done by Mulwa - Babu *et al* (5)the youngest patient was 45 years.

The male: female ratio in this study was 1:0.9, for both patients above 60 years of age and those aged 60 years and below. There was no male predominance. In the Caucasian population the disorder is more common in men with a male to female ratio of approximately 1.7:1(2). In the local study by Mulwa - Babu *et al* (5)the male: female ratio was 1.3:1, and in another local study by Patel (1) the male to female ratio was 1:1; which is in agreement with the review conducted by Fleming (4) in CLL patients in Africa. The male: female ratio in this study conforms with other local studies.

The most common presenting symptom in CLL is lymph node enlargement, while smaller numbers of patients report "B" symptoms (fever, weight loss, or night sweats), and 25% of patients are asymptomatic. In this study the commonest symptom was generalised weakness or easy fatigability (60%), followed by swelling of glands (57%). The easy fatigability/generalised weakness may be due to cytopenias, as pallor was picked in 62.2% patients. Oloo (7) had found abdominal pain and discomfort to be the commonest presenting symptom and this may be due to the fact that the commonest physical finding was splenomegaly.

The commonest physical finding at presentation was palpable lymphadenopathy (79.3%), followed by splenomegaly (76.8%) and pallor (62.2%). In view of the commonest presenting complaint being easy fatigability, it is possible that a number of patients are unaware that they have developed any swellings. In certain regions of Kenya glandular swellings commonly occur due to tropical infections. This may be the reason patients who developed body swellings did not consider them a cause for concern. In local studies by Patel (1) and Mulwa - Babu *et al* (5), lymphadenopathy was the commonest physical finding. Both studies showed that splenomegaly was the second commonest physical finding. In agreement with this study, literature from the Caucasian population also states that lymphadenopathy is the commonest physical finding followed by splenomegaly (6). In this study there was a wide range of white blood cell and absolute lymphocyte counts at presentation. The very wide range of counts at presentation maybe the reason why many patients are diagnosed at a late stage. Perhaps patients with counts in the lower range are overlooked and are not investigated early enough for CLL.

The haemoglobin at presentation ranged from between 3 to 16g/dl with a median of 9g/dl. More than half of the patients (57.3%) had HB below 10g/dl. This is likely due to the fact that the majority of patients presented in late stages of the disease. The anaemia maybe due to hypersplenism, autoimmune haemolytic anaemia, bone marrow involvement or even prior treatment. It is difficult to determine the exact cause of the anaemia. In the study by Oloo (7) at the KNH, similar results to our study were found where more than half the patients had HB below 12g/dl. At a private institution, the AKUH a study showed that only 36.7% of patients had an HB below 11, and this maybe due to early presentation of patients (5).

The platelet count at presentation ranged from 20 to 787 $x10^9$/L with a median platelet count of 121 $x10^9$/L. Thirty three (40.3%) patients had platelets below 100. The thrombocytopenia can be due to all the same causes of anaemia however it is difficult to determine the exact cause. In the study by Mulwa-Babu *et al* (5) a very small percentage of patients had platelet counts below 100 (18.4%). Again this may be due to earlier presentation of their patients compared to the patients in this study who presented with advanced disease. Sixty (73.2%) patients had HB below 10 or platelets below 100 or both. This represents a late stage of disease (Binet C) that patients are presenting in.

The commonest Binet stage at diagnosis in this study was stage C (73.2% of patients), followed by Binet B 17.1% and Binet A 9.8%. The local study by Patel (1) which was also conducted at KNH found Binet stage C (51%), to be the commonest stage of diagnosis. In the study by Mulwa-Babu *et al* (5) the commonest stage was Binet A. This likely represents the delayed presentation of patients to the KNH as opposed to a private hospital, possibly due to the socioeconomic status of patients at the KNH as well as level of education. Another explanation for this scenario maybe the delayed diagnosis in peripheral facilities as well as the delayed referral of patients to appropriate cancer centres. Since the WBC range at diagnosis is so wide, it may be possible that patients with lower WBC counts are not being diagnosed as early as should be.

In a similar study carried out among 60 patients in Nigeria over a period of 10 years it was found that 53 (88.3%) patients presented as Binet stage B and C while only 7 (11.7%) patients were seen in Binet A(10). Late presentation in West Africa is similar to our study. In this study diagnostic testing was conducted in all patients. However majority of the patients had a bone marrow aspirate (79.3%), while only 2 (2.4%) patients had immunophenotyping done and 15 (18.3%) patients had both tests done. Irrespective of whether a bone marrow aspirate was done, only 17(20.7%) patients had immunophenotyping done. At the KNH the low numbers of patients undergoing immunophenotyping (20.7%) maybe due to the cost of the test as well as lack of availability of the test at government institutions like the KNH. This is because of high costs of instruments and reagents, specialised skills and experience required to perform the tests and even interpret results. Currently bone marrow aspirates remain the mainstay of diagnosis at the KNH. Treatment was given to 74 (90%) out of the 82 patients.

Eight patients did not receive treatment and this is possibly because they could not afford treatment or the patient died in the admission during which the diagnosis of CLL was made. The commonest regime offered to patients in this study was chlorambucil and prednisolone. This regimen was given to 64 (86.4%) patients. The reason for this is that chlorambucil and prednisolone as a regimen is cheaper than fludarabine, cyclophosphamide and rituximab, hence regardless of age chlorambucil and prednisolone was used even among younger patients.

The median time from diagnosis to treatment initiation was shortest among patients who had presented with Binet stage C disease (18 days). This was followed by a median of 36 days to initiate treatment in patients diagnosed with Binet stage B disease and a median of 50 days to initiate treatment among patients who had presented in Binet stage A. Patients in Binet B and C represent more advanced disease and fulfil the criteria for initiation of therapy hence the shorter duration between diagnosis and treatment initiation(11). It took the longest time to initiate therapy among Binet A patients because at the time of diagnosis a lot of them do not fulfil the criteria for therapy institution and so a 'wait and watch' approach is used. With time and disease progression, therapy is initiated when the patient fulfils any of the criteria for therapy.

Disease outcomes: At the time of analysis, among the 74 patients who received treatment 23 (31%) had stable disease, 23 (31%) developed disease progression, 12 (16.2%) achieved complete remission but then relapsed and 4 (4.9%) remained in complete remission. In this study a large proportion of patients remained in stable disease and a large proportion developed disease progression. A small number achieved complete remission. The reason for this is possibly poor compliance to medication, irregular follow-up as well as late disease presentation and the use of an inferior treatment regimen in all age groups even younger/fitter patients. Irrespective of age, patients in this study were treated with chlorambucil and prednisolone due to the high cost of regimens such as fludarabine and cyclophosphamide. Three large randomised Phase III trials have previously demonstrated that the combination of fludarabine plus cyclophosphamide (FC) is superior to single agent therapy with fludarabine or chlorambucil. The patients in these trials were either young and/or were considered fit enough to tolerate fludarabine-based combination therapy (9).

Time to progression: The median duration from treatment initiation to disease progression (TTP) among the 35 patients who developed disease progression was 826 days (27 months). Among the patients who were treated and developed disease progression (n=35), the median TTP among patients aged 60 years or below was 17 months, while it was 38 months among patients older than 60 years. The fact that TTP is shorter among the younger age group may be due to a number of clinical (stage of diagnosis) and biological factors (cytogenetic mutations, IGVH mutational status, CD38 expression).

In a retrospective study analysing data from the Mayo clinic it was found that patients aged less than 55 years had a shorter time to treatment initiation (4 years) than patients older than 55 years (5.2 years). Differences in disease stage and biological characteristics (rather than age) were thought to be responsible for this difference. Young patients were more likely to present with intermediate Rai risk disease, have unmutated IGHV gene mutation status and express ZAP-70. This study suggested that young CLL patients are more likely than older patients to have biologically aggressive disease (12). The same may be applicable to our study but IGVH mutational status and genetic testing by FISH would be the only way to tell. The shorter time to progression among younger patients, may be driven by differences in disease biology rather than age.

Overall survival: In this study, at the time of analysis 40 (48.8%) out of 82 patients had died, 32 (39%) were still alive and the status of 10 (12.2%) patients was unknown. The median overall survival time at the time of analysis was 80 months (6.67 years). Among patients of ≤ 60 years the median overall survival was 99 months (8.25 years), while patients aged> 60 years had a median overall survival of 75 months (6.25 years). This is in keeping with literature that clearly states, older age has consistently been shown to confer a poor prognosis in CLL. A study by Lee *et al* (13) in 1987 looked at the prognostic indicators among 325 patients with CLL. They found that advanced age was a poor prognostic indicator. Overall survival had been significantly lower in patients of advanced age.

In the study conducted from records at the Mayo clinic it was found that patients ≤55 years old also had a longer overall survival compared to 968 patients between 56–65 years of age (12.5 years versus 11.0 years, P=0.001). This was despite younger patients having a shorter time to progression and what was thought to be biologically more aggressive disease (12). Our study shows similar data, whereby the time to progression in the younger age groups is shorter but the overall survival is longer than older age groups. The overall survival may be shorter in older patients due to advanced age and multiple co- morbidities, as well as poor response to treatment. Younger patients may have more aggressive disease but they respond better to treatment and have less comorbidities hence they have a longer overall survival. Females had a median

overall survival of 99 months (8.25 years) while males had a median overall survival of 78 months (6.5 years). In literature it is known that females survive longer than males even if other variables like disease stage are matched, however according to this study there was no statistically significant difference between the overall survival among females and males.

The median overall survival among patients diagnosed with Binet A disease was 110 months (9.16 years). Patients diagnosed with Binet B disease had a median overall survival of 73 months (6.1 years). Patients diagnosed with Binet C disease had a median overall survival of 80 months (6.67 years). However it is important to note that at diagnosis many more patients were at Binet stage C (n=60) compared to Binet stage B (n=14).

From literature, patients with early stage disease (Binet stage A) have a median survival that is close to 15 years, those with intermediate-stage disease (Binet stage B) have a median survival of 5–7 years, and most patients with advanced stage disease (Binet stage C) have a life expectancy less than 3–4 years (8).

In this study, at Binet stage A the overall survival rates are much lower than what is reported in literature however we must take into consideration clinical factors (age, sex, lymphocyte doubling time, bone marrow infiltration patterns) and biological factors (cytogenetic abnormalities, IGVH mutation status, CD38 expression ZAP-70 expression) may have influenced the overall survival figures. Overall survival among patients in Binet stage B was comparable with data from the Caucasian population. However patients at Binet stage C appear to have a longer overall survival compared to the Caucasian population. It is possible that racial differences influenced these results but no conclusions can be drawn as the sample size of this study is small.

Study limitations

Immunophenotyping is expensive and not widely available hence the diagnosis of CLL relied on full blood counts and bone marrow aspirates. Not all patients were immunophenotypically characterised.

Recommendations

Immunophenotyping should be routinely done as part of the diagnostic workup for patients suspected of having a haematological malignancy. This ensures accurate diagnosis and favourable outcomes.

At the KNH complete remission is defined by resolution of clinical signs and symptoms and normalisation of complete blood counts, however it is important that peripheral blood immunophenotyping, to confirm the absence of clonal lymphocytes be incorporated, to make an accurate diagnosis of complete remission.

Superior treatment regimens should be made available to younger/fitter patients. Large prospective comparative studies should be undertaken at the KNH looking at the outcomes of patients on different treatment regimens, to determine what the population responds best to.

Conclusions

(i) There is no male predominance and the disease affects males and females equally.
(ii) The disease is diagnosed at a younger median age than what is documented in literature from the Caucasian population. There is no doubt that CLL is mainly a disease of the elderly but it is not unusual to make this diagnosis in younger individuals.
(iii) The physical findings in patients do not differ from literature based on Caucasian populations. The presenting complaints however are more frequently weakness and fatigue.
(iv) A significant proportion of patients present with anaemia and/or thrombocytopenia.
(v) Diagnostic testing for CLL is confined to bone marrow aspirates, full blood counts and peripheral blood films. Immunophenotyping is not frequently done due to the cost and availability of the test.
(vi) Most patients are diagnosed at advanced stages of the disease and not all patients return to the clinic for initiation of therapy, or survive long enough for treatment to be given to them.
(vii) The commonest treatment regimen irrespective of age/fitness, given to patients at the KNH is chlorambucil prednisolone, because it is an affordable treatment choice.
(viii) Among the patients who are treated, most remain in stable disease or develop disease progression. Complete remission is only achieved in a minority of patients.
(ix) A significant number of CLL patients seen at the KNH died or were lost to follow up.

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Review article

The psychological effects on patients with chronic renal failure on haemodialysis

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Abstract

Background: Chronic Renal Failure (CRF) has serious impact on quality of patient's life and most of the patients feel sense of hopeless, loss of indecency, anxious with fear of death and family burden. Depression is one of the widely recognized psychosocial factors seen in patients with chronic kidney disease on dialysis. Several co-morbidities are associated with low level score of Quality of Life (QOL), these include poor nutritional status, anaemia, increased hospitalization and decreased immune defenses. Rapid and early recognition of the problems through patient's education, social support groups will reduce the psychological impact. The interrelationship between psychological factors, socioeconomic status and clinical outcomes require further research.

Objective: The aim of the literature review is to address the psychological problems in CKD patients on dialysis, clinician support, pharmacological and non- pharmacological interventions to address this problem.

Data source: The literature review uses social science based literature published locally and internationally on psychological aspects and support for patients with Chronic Kidney Disease (CKD) on dialysis

Conclusions: Patients undergoing haemodialysis are at a great risk of psychological issues including depression, anxiety, fatigue and decreased quality of life. It is important to identify these factors among patients as early as possible to prevent further psychological effects. Treatment plan with comprehensive management plan for the patients is critical so as to improve outcome either through pharmacological treatment and or non-pharmacological aspects.

Key words: Dialysis, Chronic renal failure, Quality of life, Psychological factors, Depression

Introduction

Chronic Kidney Disease (CKD) is a major health problem in the world with mortality due to CKD increasing by 32% between 2005 to 2015. The mortality increased to 1.2 million deaths worldwide. Most of the patients with advanced kidney failure will require long term dialysis or transplant (1,2).

Lifelong dialysis has an impact on the patient's physical and mental capacity leading to psychological effects which include decreased quality of life, depression, fatigue, anxiety and risk of suicide due to perception of loss of control as a family member and change of roles (3,4). These thoughts can even instill fear of death as a consequence of the psychological impact in these patients, it is important to identify the pattern and recognizing these factors early among patients who are undergoing treatment (5,6).

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Depression

One of the most common psychological symptoms which occur as a result of kidney diseases is regarded as depression in those individuals suffering from this disorder, and furthermore anxiety is also the associated symptom of depression (3,5).

Different studies have investigated the relationship between depression and cytokines (7,8). The inflammatory cytokines are produced during dialysis when the dialyzer membrane interacts with blood leading to activation of the mononuclear and dentritic cells (9,10). The pro inflammatory cytokines which several studies have associated with depression include, interleukin (IL)-1, interleukin-6, tumour necrosis factor apha (TNF-α), and C-reactive protein (7,11,12).

Majority of the patients undergoing dialysis have low Body Mass Index (BMI) due to malnutrition which is related to the chronic inflammatory state (13,14). Many researchers have noted that malnutrition, inflammation and atherosclerosis (MIA syndrome) leads to depression in the End Stage Renal Disease (ESRD) patients (12).

The different dialysis modalities have been compared between peritoneal dialysis and haemodialysis on the effect on depression. Patients

undergoing peritoneal dialysis have less psychological effects like insomnia, anxiety and depression than haemodialysis patients (12,14,15).

It has been observed that patients with kidney failures and all the individuals who are going through dialysis may rarely return to their full time job or work activity (13,16). It is a fact that the job or a work of a person along with the source of financial support and income is mostly linked with self-esteem, a sense of accomplishment and self-identity in number of patients with this disorder or any other ailment. As depression is now associated with this physical disorder, now medical professionals provide some accepted and credible treatment and management of depression. This treatment or management include some antidepressants along with psychotherapy. Special attention and considerations are required while putting an individual with ESRD on therapy dealing with depression or on some antidepressants. Currently, a variety of antidepressants are available for managing depression. Though most of the antidepressants are safe but still each and every antidepressant has some varied impact and effect on renal function (2).

Table 1: Prevalence of depression

Study	Number of patients	Assessment tools	Prevalence	Additional outcomes
Cukor *et al.* (2008)	70	SCID, HADS, KDQOL-SF	Depression: 29% Anxiety: 45.7%	Patients with persistent depression showed marked decrease in QOL and self-reported health status, compared with non depressed and intermittently depressed patients
Hedayati *et al.* (2008)	98	SCID, BDI, CDI, CESD	Depression: 26'7% Major depression: 17.3%	There were no difference between reasons for hospitalization for the depressed vs non-depressed. Patients with depression had increased risk of death or hospitalization
Ibrahim & Salamony (2008)	60	BDI, SF-36, DSI, MIS	Depression 33.3%	Depression was affected by employment and marital status. DSI and MIS showed positive correlation with BDI scores and negative correlation with SF-36 scores
Kao *et al* (2009)	861	SF-36, BDI	Depression: 60% Insomnia: 31% Fatigue: 30.6%	Depression scores were negatively correlated with QOL. Higher monthly income and increased social activities were associated with better health related QOL.
Chen *et al* (2010)	200	MINI, HADS, CFS, SF-36	Depression: 35% Anxiety: 21%	In the previous months, 21.5% patients had suicidal idealation. Depressed patients had higher rates of fatifue, and lower QOL,. Suicide risk was strongly related to depression and anxiety
Keskin & Engin (2011)	92	BDI,SBQ,COPE	Depression: 40.2%	Suicidal ideation increased as the severity of depression increased. Depression and suicide ideation were increasing with age and lower educational status
Araujo *et al.* (2011)	400	BDI	Depression: 19.3%	Depression was associated with female gender , poor sleep quality , unemployment, diabetes hypoalbuminaemia and low education.

Key: BDI: Beck Depression Inventory; CCI: Charlson Comorbidity Index; CESD: Center of Epidemiology studies Depression Scale; CFS: Chalder Fatigue Scale; CKD: Chronic Kidney Disease; COPE: Coping Orientation to Problem Experienced Inventory; CRP: C-reactive protein; DSI: Dialysis Symptom Index; HADS: Hospital Anxiety and Depression Rating Scale; ESRD: End stage renal disease; HARS; Hamilton Anxiety Rating Scale; HDRS: Hamilton Depression rating scale; KDQol; Kidney Disease quality of life ; KDQoL-SF; Kidney Disease and Quality of life ; MMSE; Mini Mental State Examination; PHQ-9; Patient Health Questionnaire; SCID; Structured Clinical Interview for DSM; SCL-90-R: Hopkin symptoms checklist 90 revised: SF-36: The short-form Health related quality of life.

Suicidal behaviour

The risk of suicide in haemodialysis patients was 0.24% per 1000 dialysis patients/year as was reported by Kurella *et al* (10). A number of observational studies has verified that patients on dialysis seem to have a higher rate for attempting suicides as compared to the normal population who are physically healthy. It is notable that when patients experience depression, they start to miss dialysis sessions or they start to go for potassium food binge with increase in fluid intake which ultimately can cause death (5,6,17-20).

There are several independent factors which are predictors of suicidal ideation which include old age, male gender, drug dependence or alcoholic, low educational status, pre-existing depression and previous history of mental illness (10,21,22).

Anxiety and panic symptoms

People suffering from renal failure or chronic kidney diseases may result in an extreme level of anxiety and some somatic symptoms associated with that extreme anxiety e.g. chest pain, palpitation, breathlessness; fear of dying and sweating. Sometimes, somatic symptoms are not linked with any kind of triggers and may arise unexpectedly. However, there are a number of reasons

related to the incidence of anxiety. The procedure for dialysis and a massive amount of potential medical complications ultimately give the person with CKD a lot of worry and anxiety. Pharmacological treatment and management is obviously paramount in the treatment and management of panic disorder and anxiety. Benzodiazepines, for example alprazolam and clonazepam, would be helpful in order to reduce anxiety in patients with renal failure or kidney diseases. A number of patients who also suffer from anxiety also tend to experience sleep disorders like insomnia. Medicines or drugs such as zaleplon or zolpidem are helpful in the management and treatment of these disorders like insomnia with no residual kind of drowsiness and sometimes minimal sort of side effects (23,24).

Fatigue

Fatigue is one of the symptoms which is subjectively categorised as weakness, tiredness, and lack of energy. Sixty per cent to 97% of the patients who went through haemodialysis suffer from fatigue, as it is said to be one of the most excruciating symptoms during the whole process. Patients with chronic kidney failure or renal disease who are either receiving haemodialysis or peritoneal dialysis, are observed to have high levels of fatigue and later they usually seem unable to engage in all the normal daily functionalities and activities of life (6,19,25). Furthermore, fatigue is referred as one of the positively correlated factors with psychiatric symptoms (14,26) and it has a negative correlation with life quality (15).

There are a number of aspects which contribute to fatigue level in patients that have undergone dialysis which include; inflammation, malnutrition, anaemia, sleep disorder and depression (11,28,29). Anaemia which results from lower level of erythropoietin production and it has been mentioned as one of the important causes of fatigue, especially in those CKD patients on dialysis (11). In addition, chronic haemodialysis patients show high level of protein catabolism, and it may be because of the major loss of amino acids which are prompted by the dialysis (14,28). Therefore, it is realistic to assume that there might be a significant correlation between reduced level of albumin and higher levels of fatigue. Another problem is malnutrition in patients with dialysis might also show a link with poor intake, or may be the outcome of some chronic infections and irritation (11). Therefore, chronic malnutrition and inflammation might end up in fatigue by either directly or indirectly triggering multisystem deregulation or through central nervous system activation via adrenal axis (6,21).

Quality of Life (QoL)

Quality of life is assessed by different domains which include social functioning, physical state, psychological state of mind and satisfaction in life (7,19,30). The nutritional status which involves the malnutrition and inflammatory state results in poor tolerance to exercise and prolonged weakness in the muscles limiting the daily activities resulting in poor quality of life (31,32).

Most of the biological factors including tumour necrosis factor alpha, interleukin -1, interleukin-8, low haemoglobin, low albumin, ferritin, CRP have been associated with decreased quality of life.

Social support for ESRD

Social support is a notion of identifying patients which facilitates them to receive aid, and in which they can easily involve in exchanges. Social support easily can be gained from a group of friends and family, divine counsellors, co-workers, a member of one's neighbourhood or community or health care personnel. Numerous researches have verified that social support is connected with enhanced survival and better outcomes in numerous prolonged disorders, including ESRD of end stage and cancer. The method of application of this social support and its favourable effects are still unidentified, but it practically aids in order to achieve defiance, enhanced access to health care, and upgraded nutritional and psychosocial status and also immune function, and a reduction in level of stress. Significant data exists about social support in patients whose renal disease is at end stage and some chronic renal insufficiencies that show high connection between social support and quality life standard. Management that develop elaborate social support in renal disease patients who are at last stage must be examined and evaluated (13,33).

Table 2: Pharmacological intervention

	Symptoms	Side effects	Clinical consideration
Selective serotonin re-uptake inhibitors (fluoxetine, citalopram, paraxetine, sertaline)	Depression Anxiety	Gastrointestinal symptoms, sexual dysfunction, risk of bleeding , suicidal idealation	Fluoxitine: long half life Citalopram: use causiously in several renal impairment patients Paroxetine: use lower dose
Serotonin-non-repinephrine reuptake inhibitors (venlafaxine, duloxetine)	Depression	Accumulation of toxic metabolites, sexual dysfunction, hypertension	Decrease total daily dose by 50% in mild-to-moderate renal impairment

	Symptoms	Side effects	Clinical consideration
Dopamine-norepinephrine reuptake inhibitor (Bupropion)	Depression Fatigue	Insomnia, agitation , seizure, accumulation of toxic metabolites	Use with caution and consider a reduction for dose in the renal impairment
Noradrenergic and specific serotonergics (Mirtazapine)	Depression	Sedation , somnolence, weight gain	Reduce dose, give before sleep
Tricyclics and tetracyclics (amitriptyline, desipramine doxepin nortriptyline)	Depression	Anticholinergic effects, sedation, QTc prolongation, cardiac arrhythmias, orthostatic hypotension	Avoid if possible given cardiac effects
Serotonin modulators (netazodone, trazodone)	Depression	Accumulation of toxic metabolites, liver failure (for nefazodone), sedation , hypotension, cardiac arrhythmias	Avoid use in patients with cardiac disease or hypotension
Erythropoietin	Fatigue Quality of life	Seizure, increased clotting, and influenza-like syndrome	No significant differences between once- weekly versus thrice weekly subcutaneous administration

Table 3: Non- Pharmacological interventions

	Symptoms	Side effects	Clinical consideration
Cognitive Behavior Therapy (CBT)	Depression Quality of life	Takes longer time to reach effects than pharmacological treatment	Group therapy weekly sessions need well trained therapist
Exercise training	Depression Quality of life	No serious adverse effects were reported	10 months to 1 year training program. also improves the Heart Rate Variability (HRV) indices
Acupuncture	Quality of life	No serious adverse effects were reported	Individualized acupuncture treatment provided twice a week for 6 consecutive weeks
Social support , marital , family counseling	Depression	No serious adverse effects were reported	Treatment programs need to be comprehensive

Table1 and Table2 Liang-Jen Wang and Chih-Ken Chen (2012). The psychological impact of hemodialysis on patients with chronic renal failure, Renal Failure - The Facts, Dr. Momir Polenakovic (Ed.), ISBN: 978-953-51-0630-2, InTech, Available from: http://www.intechopen.com/books/renal-failure-the-facts/the-psychological-impact-of- hemodialysis-on-patients-with-chronic-renal-failure

Conclusions

Patients undergoing haemodialyses are at a great risk of psychological issues including depression, anxiety, fatigue and decreased quality of life. It is important to identify these factors among patients as early as possible to prevent further psychological effects. Treatment plan with comprehensive management plan for the patients is critical so as to improve outcome either through pharmacological treatment and or non-pharmacological aspects.

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Disseminated tuberculosis: a case report

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Abstract

Background: Disseminated tuberculosis is a mycobacterial infection in which the mycobacteria has spread to the rest of the body through the blood stream. The most common site is the lungs, though other organs may be involved.
Case presentation: We describe a case of disseminated tuberculosis in a 25 year old female patient who presented with chronic back pain, headache and bilateral lower limb weakness. Investigations revealed spinal, lung and brain tuberculosis. She was started on antituberculous medication.
Conclusion: Disseminated tuberculosis is a fatal disease in which early detection and treatment is important for effective treatment of a patient.

Key words: Disseminated tuberculosis, Pulmonary, Meningitis, Spine

Introduction

Disseminated tuberculosis is defined as presence of tuberculosis in two or more sites that arise from haematogenous or lymphatic spread of mycobacterium tuberculosis (1). Extrapulmonary tuberculosis occurs in 20% of immunocompetent tuberculosis cases (2). There may be no pulmonary involvement. Spinal tuberculosis is more common in young children and young adults (3). A high index of suspicion is required as many cases go undiagnosed due to nonspecific nature of presentation. Empirical treatment increases the chances of survival for these patients. We describe a case of chronic back pain that was treated with analgesics and only after the symptoms persisted and worsened was medical attention sort by the patient.

Case report

A 25 year old African female who presented with back pain for 7 months, headache for 3 weeks and bilateral lower limb weakness for 1 week. She had been managed at a peripheral hospital for bilateral lower limbs for 2 days. The lower back pain was on and off. She reported that her back gave way while lifting a heavy load. She developed bilateral lower limb weakness subsequently which worsened one week prior to the admission. The weakness was associated with numbness. There was a history of urinary and stool incontinence. The headache was global and throbbing and was relieved by analgesics. There was no history of cough or fever. She had no history of chronic disease e.g. diabetes mellitus or hypertension. There was no history of previous tuberculosis contact or treatment. Her past medical and family social history were non contributory.

On physical examination she was sick looking, was pale, there was no jaundice, lymphadenopathy or cyanosis. She was not dehydrated. Her blood pressure was 119/71 mmHg, heart rate of 115, respiratory rate of 14, temperature of 35^0C and saturations of 96%. Her neurological exam revealed a GCS of 14/15, she was confused, her neck was soft and kerning's was negative. She had right eye ptosis. She had anisocoria with the right pupil measuring 4mm and the left was 3mm. Both pupils were sluggishly reactive to light. Bulk was normal on all limbs. The tone was reduced, power was 0 and reflexes were reduced on the right upper and lower limbs. She had a sensory level at T11-T12. The cardiovascular, respiratory and abdominal exam were normal. One hour later her condition deteriorated, she had a low GCS of 3/15. She was intubated and transferred to ICU.

His initial workup revealed a normal total blood count with WBC $7.1*10^9$, neutrophils-67.5%, lymphocytes 18%, Hb-13.2, MCV 76, platelet 194. The procalcitonin was elevated at 8.25 and CRP of 144.3. The kidney function was normal, Na 132, K 4.1, urea 68 and creatinine of 64.9. The transaminases were elevated AST 146, ALT 274, direct bilirubin 35.6, albumin 29. A blood gas analysis done was normal. A connective tissue screen was normal (Anti DsDNA, SSA, SSB, SM/RNP, SCL 70, JO-1). Complement C3 and C4 were normal. Blood, urine, stool cultures done were normal. Tracheal aspirate grew *staphylococcus aureus.* Lumbar puncture was done and on CSF TB PCR, Mycobacteria tuberculosis was detected. The CSF

protein was elevated at 246 and CSF sugar 1.5 mmol/l. CSF CRAG was negative.

Radiological examination done included chest X-ray, CT scan head and MRI head. The chest X-ray revealed features of pneumonia. CT Scan of the head without contrast showed no obvious intracranial abnormalities detected. MRI cervical scan showed muscular spasms. MRI thoracic spine concluded T12 and L1 vertebral bodies marrow lesions suggestive of TB spine and moderate cord edema myelitis. MRI brain revealed nodular parenchymal T2 hyperintensities resolving tuberculomas, early communicating hydrocephalus and right maxillary and sphenoidal sinusitis. We made a diagnosis of disseminated tuberculosis consisting of spine tuberculous meningitis and pulmonary tuberculosis. The patient was treated with antituberculous drugs, steroids dexamethasone, levofloxacin and was put on DVT prophylaxis enoxaparin.

While in ICU the patients developed a fever and tachycardia. She had copious secretions from the chest. The anisocoria increased on the right pupil at 8mm and the left 4mm. She was also treated for pneumonia and started on levofloxacin. Total blood count revealed a neutrophilia WBC $11.89*10^9$, neutrophils 93.9%, Hb 11.4g/dl, MCV 78, ESR-73. She was ventilator dependent. She was started on inotropic support due to low blood pressure with norepinephrine. She suffered a cardiac arrest on the 6th day after admission but was successfully resuscitated. A tracheostomy was fashioned on the 6th day, she was still febrile with a temperature of 38.1^0C. She also had a low GCS of 3T/15. She was still on inotropic support. She also had tachypnea at 40 breathes per minute. The inflammatory markers were declining CRP-9 (19.5) Procalcitonin 2.86 (8.25). She subsequently developed upper limb weakness. The tachycardia and tachypnea persisted. She also developed thrombocytopenia with platelets of 86, anaemia Hb 7.6 g/dl. A month later her relatives requested for a transfer to another hospital due to the rising hospital bills. She passed away after a month.

Discussion

Disseminated tuberculosis is an important cause of morbidity and mortality in developing countries. The rate is increased in patients with Human Immunodeficiency Virus (HIV) (4). Tuberculosis is estimated to affect more than two billion people. There were 9 million cases and 1.5 million deaths in 2013. The incidence is increasing in some parts of the world such as Africa (5). Disseminated tuberculosis mostly occurs in people with weakened immune systems and in children (6). Risk factors for disseminated tuberculosis include, young age, female sex, Asians and Africans and HIV (7).

HIV has increased the incidence of TB, especially in sub-Saharan Africa, where the two diseases coexist. HIV increases the risk of infection and severity of TB with an increased rate of mortality. The presence of the two diseases makes diagnosis difficult due to the atypical presentation in both clinical and radiological presentation. This is especially more so in disseminated disease. The coinfection of the two diseases makes treatment complicated due to drug to drug interactions, adherence, toxicities and immune reconstitution syndrome. The initiation of antiretroviral therapy is important during the course of treatment of tuberculosis (8).

The lungs are the most common site for the development of tuberculosis, with 85% of patients presenting with pulmonary complaints (9). Extrapulmonary TB occurs when tuberculosis develops in other organs such as the pleura, brain, spine, lymph nodes (6). Infection occurs as a result of exposure of lungs or mucous membrane by infected aerosols. Extrapulmonary tuberculosis is a result of haematogenous spread from the lungs and via the lymphogenic pathway through para-aortic lymph nodes (10).

The most common presentation is cough, weight loss, fever, night sweats, hemoptysis, chest pain and fatigue (11). Patients with tuberculous meningitis may present with symptoms of meningoencephalitis such as persistent or intermittent headache lasting for 2-3 weeks. They may have subtle mental changes and progress to coma if not treated (12). Spinal tuberculosis present with back pain, leg weakness, gibbus and stiffness. Paralysis may occur in patients who are undiagnosed (13).

Diagnosis of extrapulmonary tuberculosis may be difficult. Radiologic features of extrapulmonary disease may mimic those of other diseases. Diagnosis is made using sputum culture for acid fast bacilli, CSF examination, bronchoscopy, chest X-ray and Ct scan and MRI (11).

Other investigations that can be carried out include quantiferon gold test, gene Xpert MTB/RIF assay, urine lipoarabinomannan (LAM) and adenine deaminase (ADA). GeneXpert is an automated molecular platform used to detect M. tuberculosis and rifampicin resistance testing. It is a rapid test that is user friendly. Results are obtained within 2 hours (14). Urine LAM detects antigens present in urine. LAM is a component of mycobacterial outer cell wall that is shed by degrading cells or metabolically active cells. It is cleared by the kidneys and can be detected in urine. The sensitivity in HIV infected patients is good especially those with a low CD4 count (15). Adenine deaminase (ADA) is an enzyme found in most cells in the body. It is usually elevated in tuberculosis effusions. It can be used to confirm the aetiology of an effusion (16). Quantiferon TB Gold is a simple blood test that detects mycobacterium tuberculosis. It is an interferon gamma release assay and is a modern alternative to tuberculin skin test. It is highly specific and sensitive in the diagnosis of tuberculosis however it is not able to distinguish active and latent tuberculosis infection (17).

Treatment of disseminated tuberculosis is by first line antituberculous drugs consisting of two

months initial phase of treatment consisting of rifampicin, isoniazid, pyrazinamide and ethambutol. This is then followed by a continuation phase of rifampicin and isoniazid for 4 months. The doses for the drugs are as follows: isoniazid 5mg /kg maximum dose 300 mg, rifampicin 10mg/kg maximum dose 600mg, pyrazinamide 25mg/kg maximum dose of 2g and ethambutol 15mg/kg. The use of fixed dose combinations is recommended over separate drug formulations. Daily dosing of the drug is also recommended. The approach to treatment is similar to that of pulmonary tuberculosis, where treatment is carried on for 6 months. For the tuberculous meningitis treatment should be carried out for at least 9 months. The treatment may require a longer duration up to 12 months for spinal TB (18). Early treatment of suspected patients decreases mortality and improves outcome. Surgical intervention may be needed in case a patient develops hydrocephalus. Spinal tuberculosis responds to antituberculous drugs. Surgery is unnecessary in most patients (19). In tuberculous meningitis there is a role for corticosteroids and patients in early stages of the disease respond well to antiberculous medication (19). Patients with TB who are diagnosed to have HIV should be initiated on antiretroviral therapy 8 weeks after starting antituberculous drugs. For those with CD4 counts of less than 50 cell/mm^3 should be initiated after 2 weeks of starting on anti TB medication.

Corticosteroids are generally recommended in tuberculous meningitis and pericarditis. They are used to prevent complications. Corticosteroids decrease the risk of pleural thickening in tubercular pleural effusion. They also improve morbidity in HIV coinfected patients who have developed IRIS. Evidence for use of corticosteroids in other forms of TB are few and lacking (16). When patients with disseminated tuberculosis are not treated the mortality is 100%. Non-specific symptoms results in a high mortality rate (20). Most cases of disseminated tuberculosis are treatable, the mortality rate is 25-30% for adults (21).

Conclusion

Disseminated tuberculosis is a common presentation in our setting. It is difficult to diagnose due to non-specific presentation, therefore one should have a high index of suspicion.

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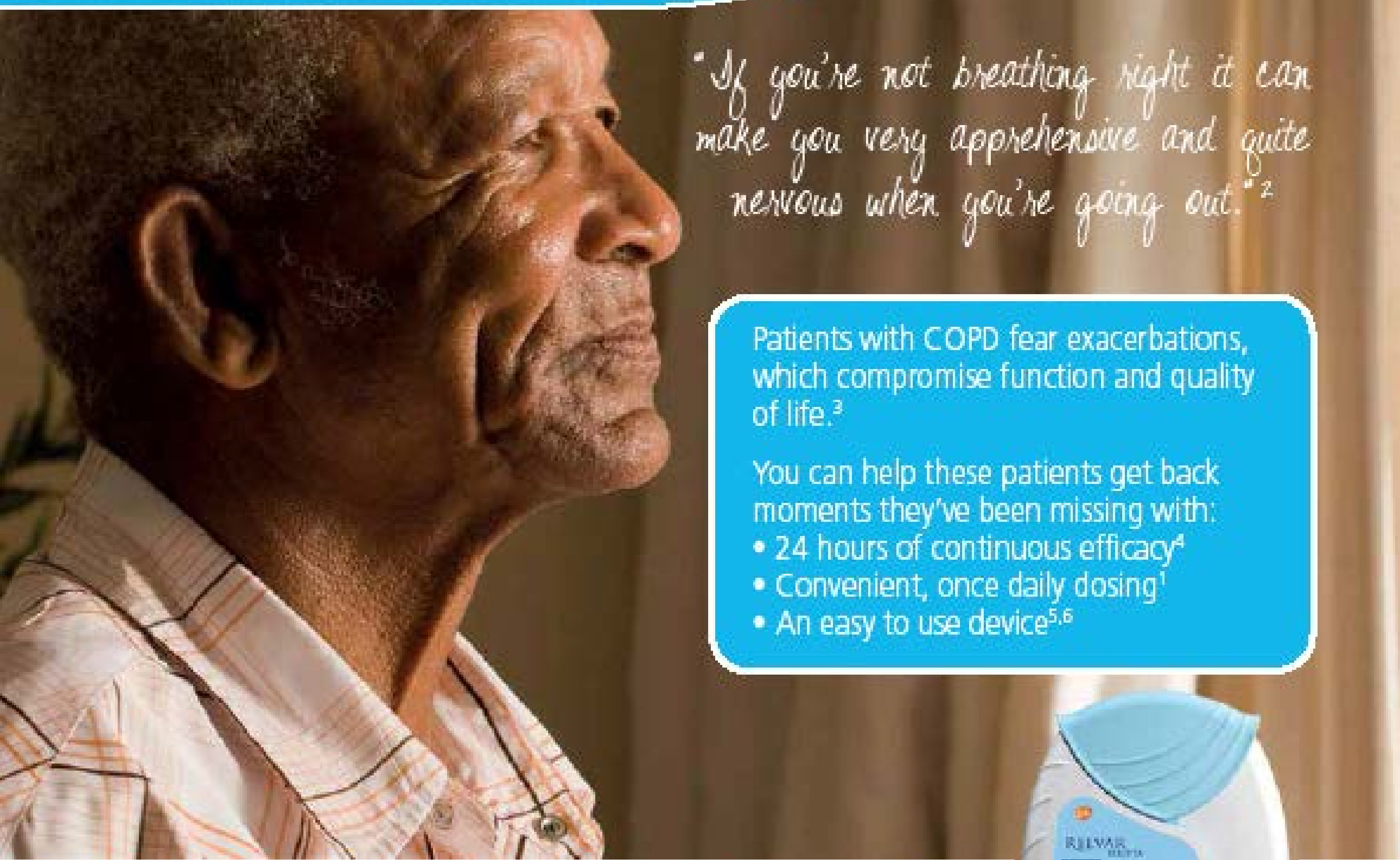

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COPD = Chronic Obstructive Pulmonary Disease
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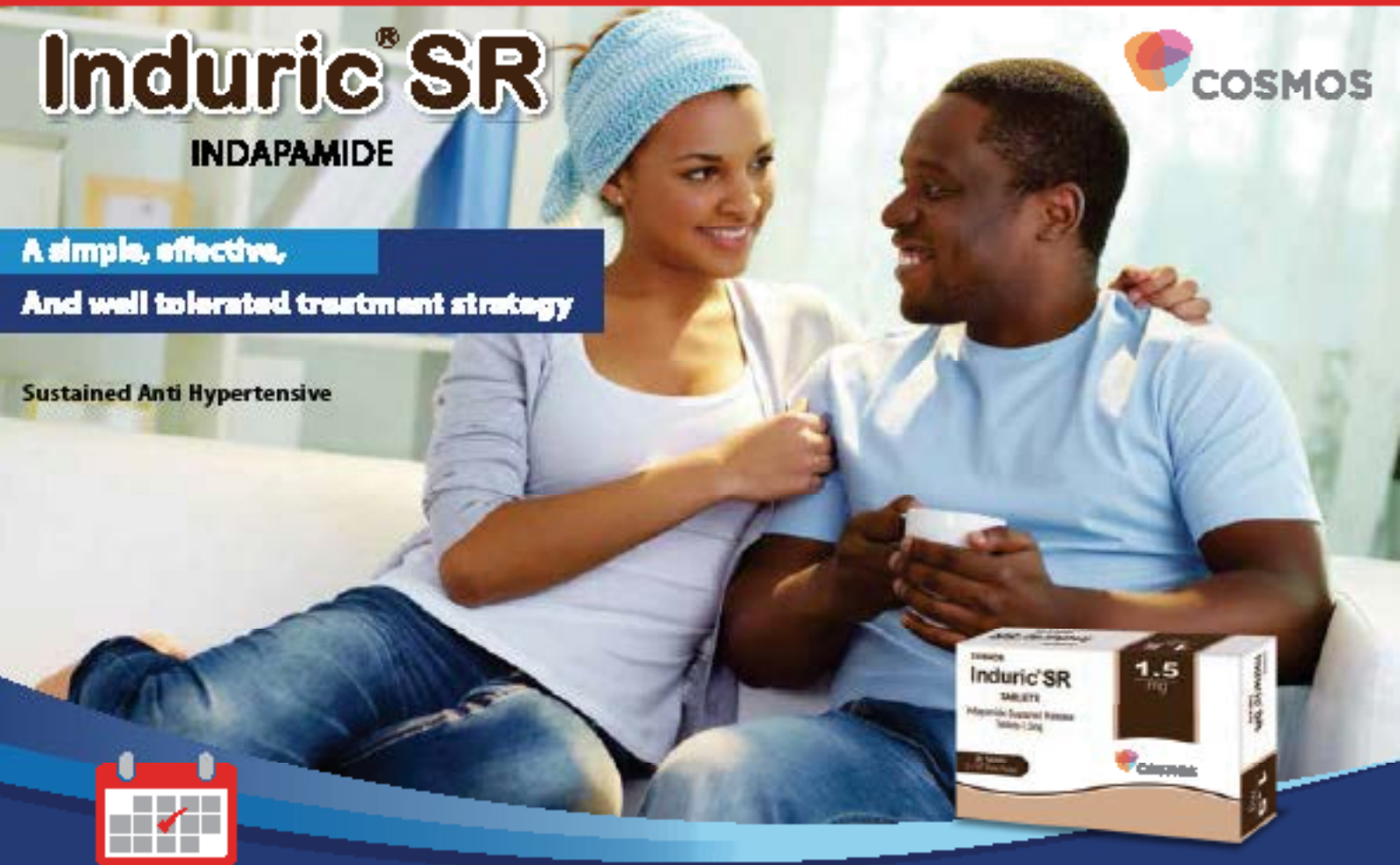

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