JOURNAL OF KENYA ASSOCIATION OF PHYSICIANS

March 2021 Vol. 4 No. 1 ISSN 2663-6484

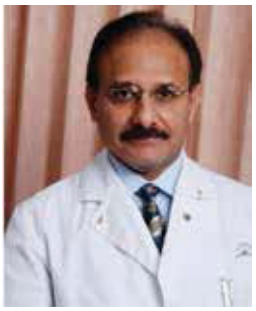
CONTENTS

Editorial Board

Editor-in-Chief

Associate Editors

Members



Published by Kenya Association of Physicians
P.O. Box 48397 Code 00100, Nairobi, Kenya. www.kapkenya.org

Covid-19 vaccination: a personal experience

Quote 01: From a prayer for a vaccine to be manufactured and maybe divine intervention, some people did a complete 360 degrees turn and all of a sudden didn't want the vaccine, peddling all sorts of conspiracy theories against the vaccine.

Quote 02: The other conspiracy was that it was an m-RNA vaccine that could somehow rewrite your DNA. For this to happen the vaccine must enter nucleus of the cell and to do that it would require several enzymes which are released sequentially at relevant times. The vaccine doesn't contain these enzymes and doesn't have signals to release them at specific time. Long and short the vaccine cannot re-write your DNA.

Quote 03: For the few who do get the virus despite being vaccinated they tend to suffer milder forms and don't get severe complications. There was a politician who got Covid a few days after getting the vaccine. I believe he had actually been infected prior to vaccination and even the vaccine takes at least 3 weeks before you mount a proper response and defense from the first dose and most effective after the 2nd dose.

Wonders will never cease!!! This year I am truly privileged to have been a frontline worker and the reason I feel so special is because, I had free access to the Astra Zeneca Vaccine -Covishield. It was on 5th March 2021 when the Ministry of Health rolled out the vaccination campaign. I had volunteered to be one of the first guinea pigs in real life setting for the vaccine.

In usual fashion I got derailed with my activities during the day and completely forgot that the vaccine administration was on-going. I got a call from my sister that some of my friends and colleagues were blasting the internet with their pictures and captions on how they had received the vaccine following 001 - none other than the DG himself Dr. Patrick Amoth.

Seeing as I had registered my interest in getting the vaccine I left the office and dashed to the appointed site at Kenyatta National Hospital (KNH). The place was well arranged and I just made it in the nick of time as they were about to close for the day. The health records were digital and I gave out my details and proceeded to the next step. The nurse was equally digital and had to confirm my registration for vaccination. She entered my ID number and there I was registered to get the vaccine.

I hate jabs but can fake bravery to the highest level (hazard of the trade as you must never look flustered or surprised). I think we have all been immensely entertained by some Far East videos of someone, who I think was a Minister of Health and his antics while receiving the jab and even more hilarious was the soldier who had to be restrained by almost 6 of his colleagues to receive the jab. If you saw Dr. Alfred Mutua, Machakos Governor's grimacing face then the point comes alive. Anyway on a more serious note I feigned bravery and as usual looked away, there was a slight prick and it was done. I had received my first shot of Covishield!

Kudos to the IT team rolling out the vaccine initiative. Before I left the facility I had a congratulatory text from MOH-CHANJO that I had received the first dose of Covishield vaccine Batch No. 41202029. I got a follow up text informing me that my 2nd dose is scheduled for Friday 30th April at Kenyatta National Hospital (facility) Kibra Sub County.

My only regret was that I could not vaccinate my family as the first round was reserved for frontline workers, which included health workers, police and teachers. Fortunately, by the time of writing this article the MOH had opened the space to include people aged 58 years and above. This gave us the opportunity to vaccinate our parents, whom we have been very scared for.

Since November 2019 the whole world had been gripped in fear when the World Health Organization (WHO) announced the presence of this dreaded disease which at that time was named the Novel Coronavirus, Covid-19. We saw lockdowns and as I write the country has embarked on another 30day lockdown. Everyone was petrified at the thought of getting this unknown viral infection and it was on everyone's lips the hope that a cure (normally very difficult for viral infections) could be found or a vaccine.

Several pharmaceutical companies stepped up their act and went on overdrive trying to get us a vaccine. The first to come up with the vaccine was Moderna but the challenge with their vaccine was the storage of the vaccine at very low sub-zero temperatures. In quick succession Pfizer and Astra Zeneca followed suit and even Russia managed to come up with their vaccine Sputnik V.

From a prayer for a vaccine to be manufactured and maybe divine intervention, some people did a complete 360 degrees turn and all of a sudden didn't want the vaccine.

Enter conspiracy theories and the rise of the anti vaxxers. This was quite interesting and the first theory was that never had a vaccine been produced so fast and why hadn't they produced vaccines for other illnesses such as HIV and cancer. On 10th January 2020, the SARS-CoV-2 genetic sequence data was shared through GISAID and what this together with great advances in science allowed, was the rapid development of tests and vaccines unlike some cancers where we still don't know the cause. We hope this can be replicated for other diseases.

The usual other theories came about, of causing infertility, which some groups that include senior medical doctors support. They have tried to insist that vaccines is the West way of trying to engineer population control in developing countries. The biggest evidence to date is the tetanus vaccine. The numbers speak for themselves, billions of women have received the shot including myself and most have had subsequent pregnancies.

Next was the issue that this was an m-RNA vaccine that it could somehow rewrite your DNA. What people forget is that for this to happen the vaccine must enter nucleus of the cell and to do that it would require several enzymes which are released sequentially at relevant times. The vaccine does not contain these enzymes and does not have signals to release them at specific time. Long and short the vaccine cannot re-write your DNA. There are also other vaccines, which are not DNA/RNA based and skeptics can opt for that.

Having debunked some myths, we are cognizant that yes the vaccine has some side effects majority of which are minor such as irritation or pain or swelling at the site of injection, headaches, muscle pain, joint pain, fever being the most common. I unfortunately got majority of these side effects but just took some paracetamol and the next day all had subsided. I only had an issue that I got a nasty wheel (swelling at the injection site) that persisted for 2 weeks but so far I have no record of anyone else getting a similar reaction so I put it down to my delicate skin.

There are some thoughts that people who have recently contracted Covid-19 get a severe immune reaction to the vaccine and this data would have been interesting on the immune status of vaccine naïve people and side effects of the Covid-19 vaccine but don't know anyone who is doing this currently.

The purpose of this article was to encourage people to get the vaccine and clinical trials have proven that all the vaccines are very effective in preventing infection with coronavirus. My family has been fortunate that majority of those who got the virus have recovered though we recently lost a distant aunt. That story is not the same everywhere and if I am to look at the medical fraternity alone we have lost quite a number of colleagues and as we don't want to be statistics for Covid-19 deaths and for this reason alone cannot understand why anyone and more so front line workers would be opposed to the vaccine.

For the few who do get the virus despite being vaccinated they tend to suffer milder forms and don't get severe complications. There was a politician who contracted Covid-19 a few days after getting the vaccine. I strongly believe he had actually been infected prior to vaccination and even the vaccine takes at least three weeks before you mount a proper response and defense from the first dose and most effective after the second dose.

Getting the vaccine yourself may also protect people around you. The reason being, if you don't get the disease you are less likely to spread the virus to those around you. We have also seen many cases of people getting the virus more than once meaning again a portal for infection of people close to them.

This virus is new, aggressive, and mutates like a nonsense. We need to use all available tools of which vaccination is a major game changer. I am personally very tired of having to wear masks all the time though I love the hand hygiene practices inculcated into society and hope this lasts way after we beat this virus. If only for the hope that we will be able to go outside, travel at will and enjoy company of friends and loved ones. Vaccination offers the potential for this to happen but requires that large portions of the community be immunized.

If you've been around someone who has Covid-19, you do not need to stay away from others or get tested unless you have symptoms i.e no need for home self-isolation (does this sound like freedom!!!) For those who have been under home isolation I think you know what I am talking about.

Sometimes one has to be selfish. My children have been actively involved in competitive swimming and since the beginning of the pandemic this activity has been curtailed. Sports as we all know is something that has lifted the lives of many people both directly and indirectly. Sports has several health benefits and societal benefits as we know people involved in sports are less likely to partake in vices such as alcohol and illicit drugs (if only to pass the doping tests).

I would encourage the government to consider people involved in sports for vaccination to enable them not to lose their livelihood. We are a sporting giant as a nation especially athletics and have potential for greatness in other sports. Without proper training at the right time the gains we have made in sport may come to naught. Kindly vaccinate coaches and all athletes to enable them to excel in their endeavors.

I will end by encouraging all the readers to get vaccinated and urge the government not to cease its efforts in vaccinating the entire population. The challenge with the modern world is that we want democracy even in things that are obviously good for us. I hope I am speaking to the converted and hope the government increases its effort to ensure all who are opting to get vaccinated can do so in a more expedited manner.

Acknowledgement

This article is reprinted from the *Marketing Africa Magazine* with permission from the editor.

Owiti M, Obstetrician Gynaecologist and Fertility Consultant, Fortis Suites, First Floor Room No. 10, Nairobi, Kenya.Email: Drmaureenowiti@gmail.com

Original paper

Detection and Molecular Characterization of Antibiotic Resistance Genes in *Pseudomonas* Isolates from Selected Hospitals in Mombasa County, Kenya

Suleiman I[1], Gachara G[2]

[1]The Mombasa Hospital, P.O. Box 90294 - 80100, Mombasa, Kenya
[2]Department of Medical Laboratory Sciences, Kenyatta University, P.O. Box 43844-00100, Nairobi, Kenya

Address for Correspondence: Dr Issa Suleiman, The Mombasa Hospital, P.O. Box 90294 - 80100, Mombasa, Kenya. Email: issasuleimankombo@gmail.com

Abstract

Background: *Pseudomonas* infections are among the most important problems complicating health care provision. Resistance by initially susceptible strains occurs at a relatively high frequency. Information gaps exist on the control of infections caused by *Pseudomonas* species.
Objective: To identify and characterize antibiotic resistance genes in *Pseudomonas* isolates from selected hospitals in Mombasa county.
Methods: One hundred and ninety two clinical samples were collected from admitted patients in each of the two selected hospitals; The Mombasa Hospital and the Coast General Hospital a private and a government hospital respectively. Specimens were inoculated in MacConkey and Blood agar, and later sub cultured in blood agar for purity. Species identification and antimicrobial susceptibility was analyzed by the Vitek® system.
Results: A prevalence of 13% was obtained. The predominant isolate identified was *Pseudomonas aeruginosa* 41(82%), followed by *Pseudomonas fluorescence* 3(6%), *Pseudomonas stutzeri* 3(6%), *Pseudomonas luteola* 2(4%), and *Pseudomonas oleovorans* 1(2%). The relative distribution of the *Pseudomonas* species amongst the two study facilities was not statistically significant (p= 0.955). Twenty *Pseudomonas* positive isolates were screened for the presence of Metallo-beta lactamase and fluoroquinolones resistance conferring genes by conventional PCR. VIM was the prevalent MBL gene observed followed by SPM, SIM, IMP, and GIM. *ParC* and *MexR* genes were detected in all the isolates screened.
Conclusion: Occurrence of *Pseudomonas* species harboring MBL, ParC and MexR genes points to the need to evaluate the trends in antibiotic resistant genes in the region. This will serve as a baseline in identifying suitable antibiogram for the treatment of *Pseudomonas* infections.

Key words: MBL, ParC and MexR genes, *Pseudomonas* species, Clinical samples, *Pseudomonas* infections, Antibiotic resistant genes

Introduction

Pseudomonas species comprise of the major agents of nosocomial and communities acquired infections, widely distributed in hospital environments and are difficult to eradicate (1). Nosocomial infections are localized or systemic conditions resulting in the presence of an infectious agent(s) or its toxin(s) present 48 hours or more after hospital admission (2). Treatment of *Pseudomonas* infections is usually difficult which leads to high mortality and morbidity as well as increased health care costs (3,4). Resistance to antibiotics by these pathogens is mainly because of the diffusion barrier of the bacterial outer membrane, mutations in the target molecules such as, GyrA and/or ParC, as well as antimicrobial inactivating enzymes (5).

Risk factors determining nosocomial infections depends upon the environment in which care is delivered, the susceptibility and condition of the patient, and the lack of awareness of such prevailing infections among staff and health care providers (6). Based on results from most studies, the infection rate and the aetiological agent of nosocomial infections varies between different hospitals and geographical locations (7).

There is often ineffective treatment to acute and chronic *Pseudomonas* infection, alongside biofilm formation where *Pseudomonas* species shows limited susceptibility to antibiotics and disinfectants. The remarkable plasticity of the *Pseudomonas* genome is a result of its members being assumed to be able to attain nearly all known antimicrobial resistance mechanisms with limited treatment options (8).

Infections resulting from antibiotic resistant bacteria are a healthcare problem globally and more so in the developing countries. Studies that show detection and molecular characterization of antibiotic resistant genes in *Pseudomonas* species in Mombasa County hospitals are scanty. The aim of this study was to define the molecular characterization of antibiotic resistance conferring genes in this bacterium at the Mombasa Hospital and Coast Province General

Hospital in patient samples 48 hours after hospital admission.

Materials and methods

Study areas: This study was conducted in two selected Mombasa County hospitals namely The Mombasa Hospital and The Coast Province General Hospital. These hospitals are the major referral hospitals in the region one being a private (The Mombasa Hospital) hospital and the other a government hospital (The Coast Province General Hospital). They provide both in and outpatient services with operating theaters and intensive care facilities. Mombasa Hospital has a bed capacity of 114 beds while Coast General Hospital is the premier public health and reference hospital in the entire coast region with a bed capacity of 700 beds.

Study design: A cross sectional study design utilizing a systematic random sampling technique was adopted. All members of the study population had an equal and independent chance of being selected.

Study population: The study comprised of admitted patients who had stayed for over 48 hours and have volunteered their samples to be collected for this study.

Sampling technique: A systematic random sampling was employed where every third patient was selected and sample taken (12,13). Three hundred and eighty four samples were collected, which included central venous catheter tips, endotracheal tubes, catheter tips and pus swabs. One sample was collected from each patient who had attained the inclusion criteria. Swabs were collected by cleansing the wound or abscess with sterile saline to irrigate any purulent debris. The swab was moistened with sterile saline and using a "zig-zag" motion whilst simultaneously rotating the swab between the fingers, the whole wound surface was sampled. The specimen was placed straight into the transport medium

Before removing the catheter, the skin around insertion site was cleansed with 70% alcohol to reduce contaminating skin flora and remove any residual antimicrobial ointment. The area was then allowed to dry. Aseptically the catheter was removed and clipped, 2 inches of the distal tip of the catheter was directly cut with a sterile scissor into a sterile container. Each sample was preserved in a separate Cary Blair transport media to maintain the organism's viability and transported to the laboratory.

Ethical approval and informed consent: Ethical approval was obtained from Kenyatta University Ethics Review Committee and the study hospitals. Objectives of the study were explained to the patients after whom they were allowed to ask questions. After giving a signed consent, samples were collected.

Laboratory analysis

Bacterial identification: Samples were immediately inoculated into both differential and enriched media (MacConkey agar and blood agar plates), then incubated aerobically at 37°C for 12-48 hours before colonial morphologies were interpreted. Preliminary identification of bacteria was based on colony characteristics of the organisms including beta haemolysis on blood agar, non-lactose fermentation and pigment production (greenish yellow and bluish green pigments) on MacConkey agar. The isolates that showed these characteristics were then sub cultured onto blood agar to obtain a pure culture. Gram staining was performed on colonies from subcultures for the identification of their gram reaction. The stained slides were examined microscopically under oil immersion lens for bacterial morphology.

Species identification and antimicrobial susceptibility: All gram-negative rods were further confirmed by the Vitek system (bioMerieux Vitek) for species identification and antibiotic susceptibility. Suspension of the isolates were prepared, and then adjusted between 0.5 to 0.63 McFarland standards according to manufacturer's instruction for Gram-negative bacteria. Gram-negative identification cards AST-GN83 and AST-N22 were used for Gram-negative *Pseudomonas* organisms. VITEK®2 cards were inoculated following manufacturers instruction then, the isolates ID were introduced into the VITEK®2 system to allow it to choose the correct interpretive criteria. The resulting MIC was translated into clinical categories of susceptible, intermediate, or resistant following the Clinical and Laboratory Standards Institute (CLSI) recommendations (9) .

Antimicrobial agents used were obtained from respective bioMerieux suppliers. Twenty six antibiotics were used in this study. Quality control was done using commercially available sensitive *Pseudomonas* species standard organisms ATCC 27853 as positive controls. All the isolates that showed intermediate reaction to antimicrobial agents were considered as resistant. Based on the clinical breakpoints, (10) an isolate classified as susceptible will be inhibited by the MIC at the site of infection, resistant if it will not be inhibited by the achievable concentration. Intermediate are isolates that have displayed a relative resistance by exhibiting growth at the MIC of an antimicrobial but are in fact susceptible to a concentration above the MIC (11). For isolates classified as intermediate, the therapeutic effect is uncertain (12).

DNA extraction: DNA was obtained from twenty randomly selected *Pseudomonas* positive isolates using the Qiagen DNA extraction kit (Qiagen, Germany), according to manufacturer's instructions. Bacterial colonies were taken from culture plate with an inoculation loop and suspended in 180 µl of buffer ATL (supplied in the QIAamp DNA Mini Kit) by vigorous stirring. The mixture was then centrifuged for 7 minutes at 400-x g with brake. The supernatant was discarded and the bacterial cells suspended with Hank's balanced salt solution, in a total volume of 200 µL. Bacterial cells were lysed by pipetting 20 µL of Qiagen Proteinase K into the bottom of a 1.5 mL micro centrifuge tube, and then 200 µL of bacterial cell suspension added together with 200 µL of buffer AL. The mixture was vortexed for 15 seconds then incubated in a 56˚C water bath for 10 minutes. The mixture was then briefly centrifuged to remove any droplets that may have formed at the top.

To facilitate DNA adsorption to the QIAamp Column, 200 µL of 100% ethanol was added to the mixture, then vortexed for 15 seconds. The entire mixture was then briefly centrifuged and added to a QIAamp spin column, which was centrifuged at 13,200 rpm for 1 minute at room temperature. To remove residual contaminants, the spin column was removed and placed in a clean labeled collection tube, where 500 µL of buffer AW1 was added then centrifuged at 10,000 rpm for 1 minute at room temperature. The spin column was again removed and placed in another clean-labeled collection tube where 500 µL of buffer AW2 was added and centrifuged at 13,200 rpm for 3 minutes at room temperature. DNA was Eluted by removing the spin column and placed in a clean, 1.5 mL micro centrifuge tube. The QIAamp Mini spin column was carefully opened and the 60 µL of buffer AE added. The mixture was incubated at room temperature for 5 minutes then centrifuge at 6,000-x g (8,000 rpm) for 1 minute. The QIAamp mini spin column was then discarded and the micro-centrifuge tube containing the eluted DNA stored at -20˚C to -80°C freezer (13).

Identification of antimicrobial resistant genes: Twenty isolates were screened for the presence of MBL and fluoroquinolones resistance encoding genes using the Polymerase Chain Reaction (PCR). The presence of Metallo-Beta-Lactamase (MBL) drug resistant genes namely IMP-1(Imipenemase), SIM (Seoul imipenemase), VIM-1 (Verona imipenemase), SPM-1 (São Paulo metallo-β-lactamase), and GIM (German imipenemase) was analyzed using published primers (19). Two genes involved in fluoroquinolone drug efflux namely ParC and MexR were amplified in a second PCR using another set of published primers (20). The primers and PCR conditions used in this study are listed in Table 1.

Multiplex PCR: The first conventional multiplex PCR assay was carried out using five sets of primers to detect five families of MBL genes. The second involved two sets of primers to detect two fluoroquinolone resistance genes in single reaction. This was done because the amplicon sizes of the seven genes chosen would not allow their detection in a single multiplex reaction. The MBL genes surveyed included, IMP, VIM, GIM, SPM and SIM. Fluoroquinolone resistance determining region of ParC gene was determined using primers parC-1 and parC-2 to amplify a 267bp region. For the MexR regulatory gene, mexR-1 and mexR-2 primers were used to amplify the whole 503bp region of the gene. Amplification reactions for MBL were prepared in a total volume of 25µl per tube. This was comprised of 2µl genomic DNA, 14 pmol of primers (This was a multiplex of 5 pairs of primers working at a concentration of 10uM. 1ul of each primer (F/R) were added to this master mix), 10X buffer, 2.5µM of each deoxyribonucleotide triphosphate (Invitrogen), 3 mM MgCl2 and 0.5U Taq DNA polymerase (Invitrogen). In each round of amplification, sterile water was used as a negative control. The cycling conditions were 94°C for 5 minutes to activate Taq, followed by 35 cycles of denaturation or unzipping at 94°C for 30 seconds, annealing at 52°C for 40 seconds and extension at 72°C for 50 seconds followed by a final extension for 5 minutes at 72°C.

Amplification reactions for fluoroquinolone resistance-determining genes ParC and MexR genes were prepared in a total volume of 50µl per tube. This comprised of 4µl genomic DNA, 10 pmol of primers (This was a multiplex of 2 pairs of primers working at a concentration of 10uM. 1ul of each primer (F/R) were added to this master mix), 10 x buffer, 0.2 mM of each deoxyribonucleotide triphosphate (Invitrogen), 2.5 mM MgCl2 and 0.5U Taq DNA polymerase (Invitrogen). In each round of amplification, sterile water was used as a negative control. The cycling conditions were 95°C for 15 minutes activating Taq, followed by 35 cycles of denaturation or unzipping at 95°C for 45 seconds, annealing at 51°C for 45 seconds and extension at 71°C for 1 minute and a final extension at 71°C for 7 minutes.

PCR products were mixed with blue-green dye (Promega) and subjected to electrophoresis on a 2% agarose gel in 1X TBE buffer (89 mM Tris borate, 89 mM boric acid, 2 mM EDTA) in which 10ug/ml Ethidium bromide (1ul/100ml agarose) had been added. O'GeneRuler Ultra Low Range DNA Ladder and Sigma's Direct Load™ 1kb Ladder were used as markers to indicate the size of the amplicons. This was run under a constant voltage of 70V for 1 hour. To determine the presence of the amplified gene products, the gel was visualized in a U/V trans-illuminator and the image documented.

Table 1: Primers and PCR conditions used in the study

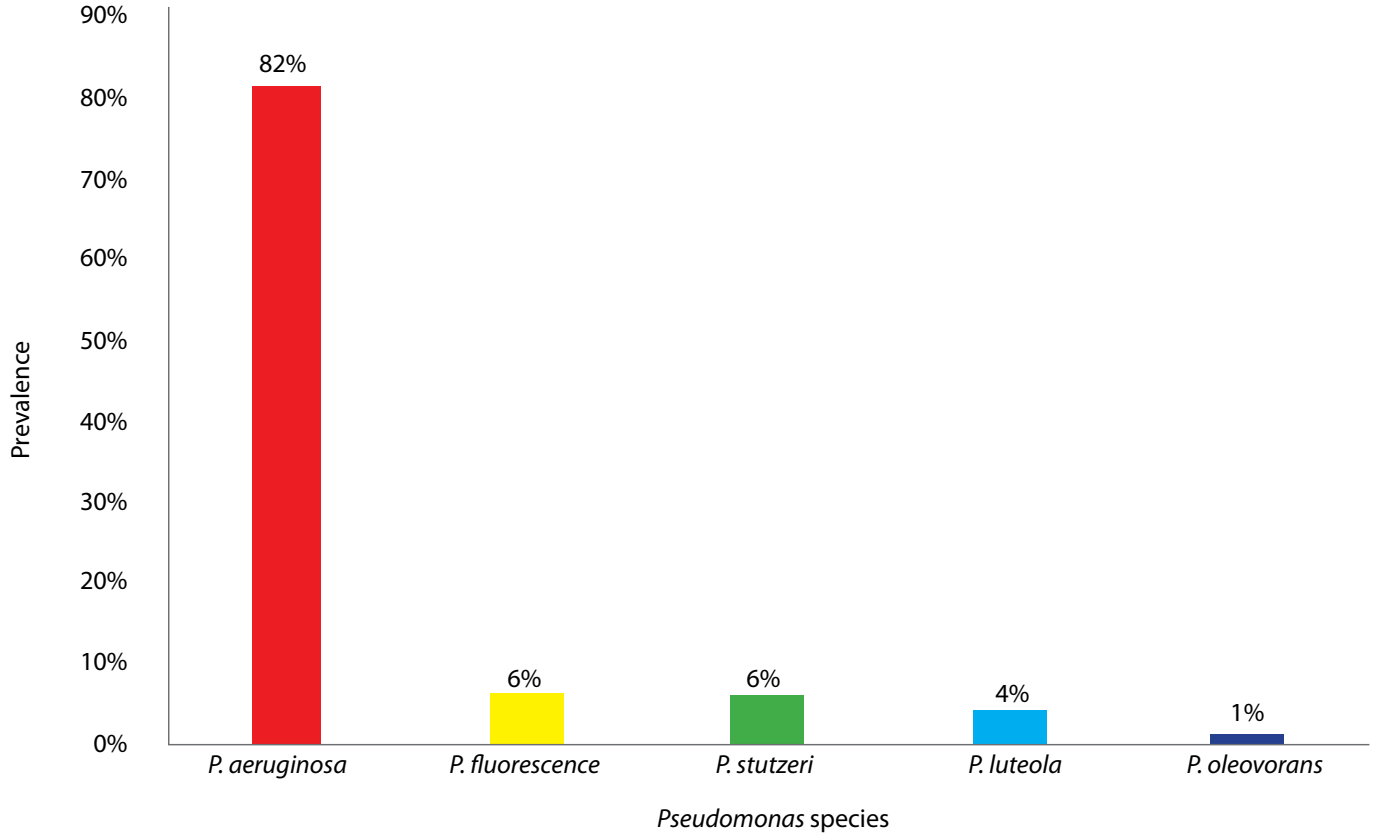
Target	Primer name	Sequence of Primer (5'-3')	Product size (bp)	Reaction conditions
MBL	Imp-F 50	GGA ATA GAG TGG CTTAAY TCTC		Multiplex PCR for the first 5 pairs of primers cycling condition was 94°C for 5min followed by 36 cycles of 94°C for 30 sec, 52°C 40 sec extension 72°C for 50sec and finally 72°C for 5min.
	Imp-R 50	CCA AAC YAC TAS GTT ATC T	188	
	Vim-F 50	GAT GGT GTT TGG TCG CAT A		
	Vim-R 50	CGA ATG CGC AGC ACC AG	373	
	Gim-F 50	TCG ACA CAC CTT GGT CTG AA		
	Gim-R 50	AAC TTCCAA CTT TGC CAT GC	476	
	Spm-F 50	AAA ATCTGG GTA CGC AAA CG		
	Spm-R 50	ACA TTA TCC GCTGGA ACA GG	270	
	Sim-F 50	TAC AAG GGA TTC GGCATC G		
	Sim-F 50	TAA TGG CCT GTT CCC ATG TG	570	
Fluoroquinolones	parC-1	CATCGTCTACGCCATGAG		Multiplex PCR of the last 2 pairs of primers cycling condition was 95°C for 15min, followed by 35 cycles of 95°C for 45 sec, 51°C for 45 sec and 71°C for 1min. Finally 71°C for 7min
	parC-2	AGCAGCACCTCGGAATAG	267	
	mexR-1	CTGGATCAACCACATTTACA		
	mexR-2	CTTCGAAAAGAATGTTCTTAAA	503	

Results

Prevalence of Pseudomonas species in the study hospitals: Out of the 384 samples collected 50 were positive for *Pseudomonas* species. The overall prevalence of *Pseudomonas* species in Mombasa County was 13%. Of the *Pseudomonas* positive samples, 23(46%) were isolated from Mombasa Hospital while 27(54%) were isolated from Coast General Hospital. Overall, the prevalence of *Pseudomonas* at Mombasa Hospital was 12% (23/192) while at Coast General Hospital it was 14.1% (27/192). However the difference in prevalence of the *Pseudomonas* species between the two study hospitals was not statistically significant (p = 0.544).

Pseudomonas species isolated: The predominant isolate from this study was *Pseudomonas aeruginosa* 41(82%), followed by *Pseudomonas fluorescence* 3(6%), *Pseudomonas stutzeri* 3(6%), *Pseudomonas* luteola 2(4%), and *Pseudomonas oleovorans* 1(2%) (Figure 1).

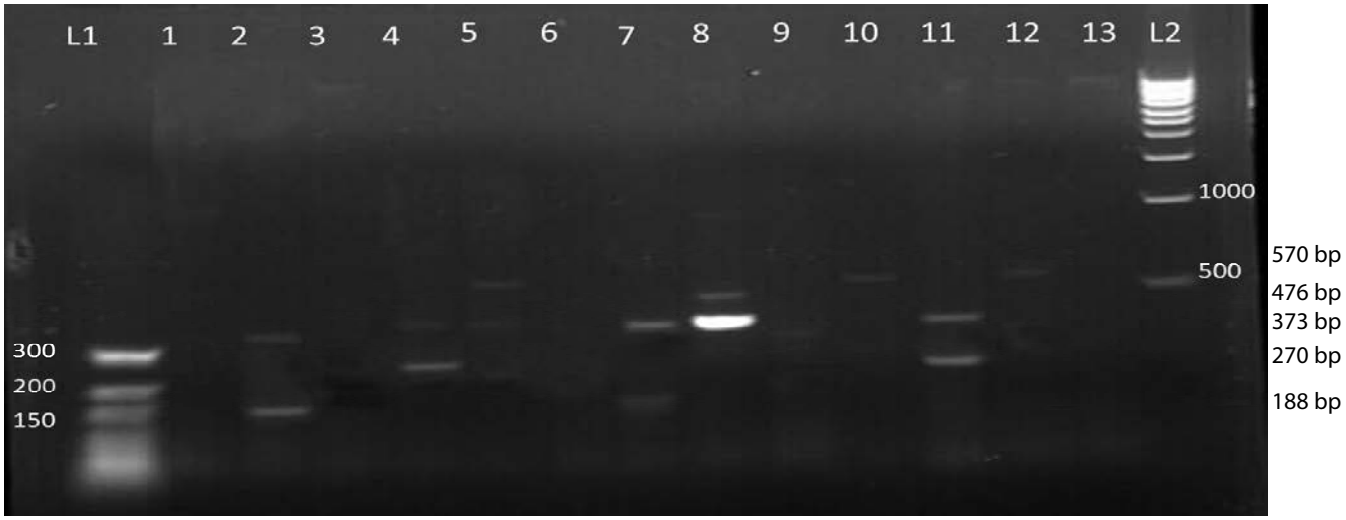
Figure 1: *Pseudomonas* species isolated from the study facilities



Molecular characterization of antibiotic resistance genes in Pseudomonas species: DNA was extracted from twenty randomly selected *Pseudomonas* positive isolates. Two multiplex PCR assays were then conducted to amplify the Metallo-Beta-Lactamase (MBL) and fluoroquinolone resistance conferring genes.

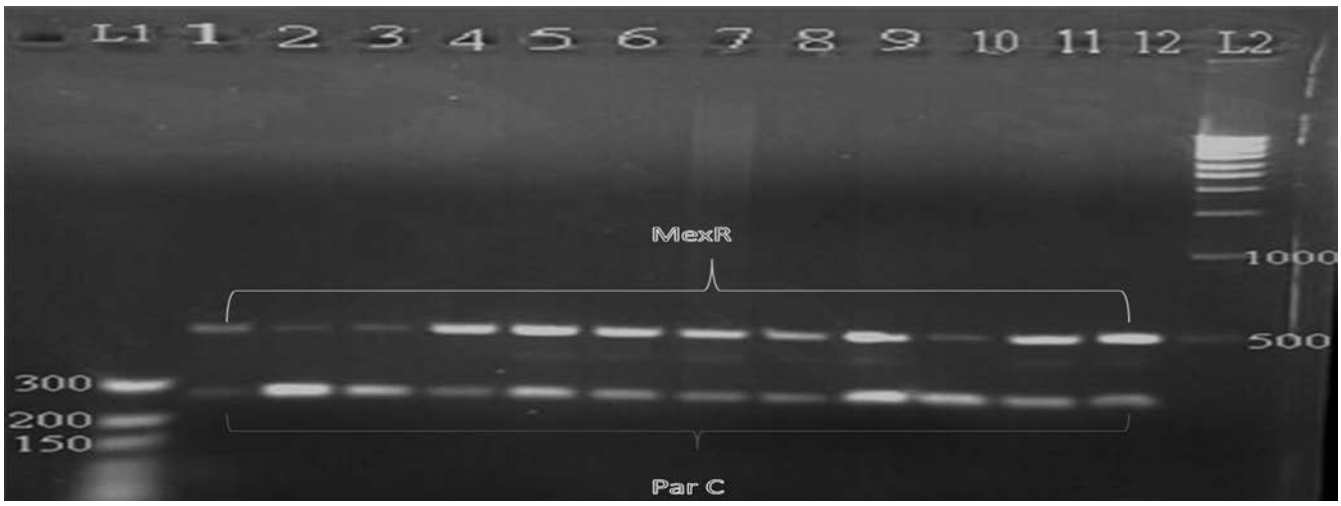
Metallo-betalactamase genes: All the five MBL genes screened were detected in the *Pseudomonas* isolates tested in this study. Out of the twenty antibiotic resistant *Pseudomonas* isolates screened, MBL genes were detected from eight of the isolates (40%). Some of the isolates had more than one gene each. VIM was the predominant MBL gene detected from six *Pseudomonas* isolates (75%). Others were SIM and SPM, which were detected in two different isolates and another isolate having both the SIM and SPM genes. IMP genes were detected in two of the isolates and GIM in one isolate. In general, one isolate had three MBL genes; five isolates had two MBL genes each while the remaining two isolates had one MBL gene each (Figure 2).

Figure 2: Gel image of PCR amplification of the 5 Metallo-betalactamase genes from 13 of the 20 isolates. Lanes 1-13 represent corresponding isolates and are numbered 1-13 while L1 and L2 are O'GeneRuler Ultra Low Range DNA Ladder and Sigma's Direct Load™ 1kb Ladder respectively. Lanes 2,4,5,7,8 and 11 were positive for VIM. Lanes 5,10 and 12 positive for SIM. Lanes 2 and 7 positive for IMP. Lanes 4 and 11 positive for SPM. Lane 8 positive for GIM



Fluoroquinolone resistance genes: Two fluoroquinolone resistance-conferring genes were screened in this study. All the twenty *Pseudomonas* isolates tested positive for the presence of the two-fluoroquinolone resistance conferring genes (MexR and ParC) (Figure 3).

Figure 3: Gel image of PCR amplification of ParC and MexR genes from 12 of the 20 isolates. Lanes 1-12 represent corresponding isolates and are numbered 1-12 while L1 and L2 are O'GeneRuler Ultra Low Range DNA Ladder and Sigma's Direct Load™ 1kb Ladder respectively.



To assess the correlation between the phenotypic and molecular resistance, results from the molecular analysis were compared with the phenotypic antibiotic susceptibility profiles. The phenotypic antibiotic resistant results of most *Pseudomonas* isolates were comparable with the molecular findings obtained. Most *Pseudomonas* isolates showed phenotypic resistance against most of the antibiotic < 50% while 100% of the isolates had the fluoroquinolone resistant conferring genes MexR and ParC (Figure 3).

Discussion

Isolation of Pseudomonas species: This study aimed at isolation, antibiotic susceptibility and molecular characterization of resistance genes in *Pseudomonas* isolates obtained from clinical samples. The prevalence of *Pseudomonas* species observed in this study was 13%. This observation was in line to results obtained in previous studies conducted in, Shaheed Beheshti Medical University Centre for Infectious Diseases Research and Loghman Hakim Hospital in Tehran Iran where they observed a prevalence rate of 13.2%.

This study detected only five *Pseudomonas* species. The predominant species was *Pseudomonas aeruginosa* (82%), followed by *Pseudomonas stutzeri* (6%), *Pseudomonas fluorescence* (6%), *Pseudomonas luteola* (4%), and *Pseudomonas oleovorans* (2%). Similar results were obtained in a study by Singh et al., 2015 (15) at the Dr. Rajendra Prasad Government Medical College in Kangra Tanda, India. In their study the predominant isolates were *Pseudomonas aeruginosa* 337(84.2%), *Pseudomonas stutzeri* 28(7%), *Pseudomonas fluorescence* 17(4.2%), *Pseudomonas putida* 5(1.2%), *Pseudomonas pickettii* 5(1.2%). The smaller variations in prevalence between the two studies might have been due to the different sample sizes used as well as the study design. These results provided evidence of high prevalence of *Pseudomonas aeruginosa,* in the county and the existence of other *Pseudomonas* species.

Molecular characterization of antibiotic resistance genes: A major clinical problem regarding *Pseudomonas* infection is due to their possession of Metallo-Beta-Lactamase (MBL) genes. As a result, this study sought to investigate the distribution of these genes. All the five MBL genes screened in this study were detected in the *Pseudomonas* isolates. This suggests that majority of the *Pseudomonas* isolates were resistant to carbapenems antibiotics, a finding that was corroborated by the phenotypic antibiotic susceptibility results. VIM was the most commonly identified MBL gene in the current study (Figure 2). This finding is in agreement with that of a previous study at the Aga Khan Hospital, Nairobi which identified VIM in all the isolates studied (16). These findings are also in agreement with the findings observed in a study among several hospitals in Zeheden Iran which showed that VIM was the most predominant MBL gene detected (17).

The identification in this study of the MBL genes represents the first documentation of their presence in *Pseudomonas* isolates in the country. However, this is not unexpected phenomenon bearing in mind that bacterium harboring some or all these genes have been detected in other species locally and elsewhere respectively. Factors such as horizontal gene transfer across species, increases in international travel and medical tourism that involves patient transfer between countries raises the possibility of rapid dissemination of these MBL genes in the country.

The two-fluoroquinolone resistance conferring genes were detected in the current study albeit at a higher frequency than the MBL genes. All the isolates tested in this study showed the presence of the two fluoroquinolones resistance-conferring genes under investigation. ParC has been detected previously in *E. coli* and *Shigella* isolates from patients with diarrhoea from Machakos District Hospital (25). With the possibility of horizontal gene transfer, the presence of these genes among the *Pseudomonas* isolates is not unexpected. The presence of MexR gene in the country has not been previously documented. The detection of this gene in the current study may be attributed to the rapid international travel and medical tourism.

In a study conducted by Technologies (18), similar findings as in this study were obtained where all the *Pseudomonas* isolates demonstrated higher frequency of fluoroquinolones resistance conferring genes. These study findings however are in disagreement with those obtained in a study conducted in California, USA where MexR was the most predominant fluoroquinolone resistance conferring gene detected (14). An important observation was also made between the phenotypic results and the genotypic results. While phenotypic results indicate a 34-36% resistance to the fluoroquinolones tested, the genotypic results indicate a 100% resistance. Similar nonconcordance findings were observed in a different study conducted by Binyamin *et al* (27). This finding is not unexpected. It is generally known that genotype is not always predictive of phenotype due to factors including poor gene expression, non-functional expressed gene products, presence of other genes or via other mechanisms that are not known (19).

Conclusion

Pseudomonas species were found prevalent in the two Mombasa County hospitals. A prevalence of 13% was obtained where *Pseudomonas aeruginosa* isolates showed highest incidence followed by *Pseudomonas fluorescence*, *Pseudomonas stutzeri*,

Pseudomonas luteola and *Pseudomonas oleovorans*. Apart from *Pseudomonas aeruginosa*, there are other *Pseudomonas* species isolated from clinical samples that cause infections.

Our study showed the presence of MBL and fluoroquinolones resistance conferring genes in *Pseudomonas* isolates for the first time in Mombasa County. This underscores the necessity of screening all antibiotic-resistant *Pseudomonas* isolates for MBL production as well as fluoroquinolones resistance conferring genes and advocating for the implementation of infection control programs to prevent spread of such organisms. Early and accurate detection of antibiotic resistant genes may control the spread of multi drug resistant pathogens in the future.

References

1. Khan H, Ahmad A, Mehboob R. Nosocomial infections and their control strategies. *Asian Pacific J Trop Biomed*. 2015; **5**:505-509.
2. Cardoso T, Almeida M, Carratalà J, Aragão I, Costa-Pereira A, Sarmento AE, *et al*. Microbiology of healthcare-associated infections and the definition accuracy to predict infection by potentially drug resistant pathogens: A systematic review. *BMC Infect Dis* [Internet]. 2015; **B**(1):1–13. Available from: http://dx.doi.org/10.1186/s12879-015-1304-2.
3. Gomes MZR, Machado CR, De Souza da Conceição M, Ortega JA, Neves SMFM, Da Silva Lourenço MC, *et al*. Outbreaks, persistence, and high mortality rates of multiresistant Pseudomonas aeruginosa infections in a hospital with AIDS-predominant admissions. *Brazilian J Infect Dis*. 2011; **15**(4):312–322.
4. Elzen A, Altayyar I. Prevalence and antibiotic susceptibility pattern of pseudomonas aeruginosa isolated from hospital environment in South Libya. *J Advanced Lab Res Biol*. 2016; **VII**(II): April 2016.
5. Aslam B, Wang W, Arshad MI, Khurshid M, Muzammil S, Rasool MH, *et al*. Antibiotic resistance: a rundown of a global crisis. *Infect Drug Resist*. 2018; **11**:1645-58.
6. Yallew WW, Kumie A, Yehuala FM. Risk factors for hospital-acquired infections in teaching hospitals of Amhara regional state, Ethiopia: A matched-case control study. *PLoS One*. 2017; **12**(7):e0181145.
7. Ghane M, Azimi Z. Isolation, identification and antimicrobial susceptibility of pseudomonas spp. isolated from hospital environment in Tonekabon, North of Iran. *J Appl Environ Microbiol*. 2014; **2**(4):97–101.
8. Li X, Plésiat P, Nikaido H. The challenge of efflux-mediated antibiotic resistance in gram. *Clin Microbiol Reviews*. 2015; **28**(2):337.
9. Schreckenberger P, Binnicker M. Optimizing antimicrobial susceptibility test reporting. *J Clin Microbiol*. 2011; **49**(9):S15-S19.
10. Turnidge J, Paterson DL. Setting and revising antibacterial susceptibility breakpoints. *Clin Microbiol Reviews*. 2007; **20**(3):391.
11. Heil EL, Johnson JK. Impact of CLSI breakpoint changes on microbiology laboratories and antimicrobial stewardship programs. *J Clin Microbiol*. 2016; **54**(4):840-844.
12. Giani T, Morosini MI, D'Andrea MM, García-Castillo M, Rossolini GM, Cantón R. Assessment of the PhoenixTM automated system and EUCAST breakpoints for antimicrobial susceptibility testing against isolates expressing clinically relevant resistance mechanisms. *Clin Microbiol Infect*. 2012; **18**(11):E452-E458.
13. Qiagen. QIAamp® DNA Mini and Blood Mini Handbook, 2012.
14. Gorgani N, Ahlbrand S, Patterson A, Pourmand N. Detection of point mutations associated with antibiotic resistance in Pseudomonas aeruginosa. *Int J Antimicrob Agents*. 2010; **34**(5):414–418.
15. Singh I, Jaryal S, Thakur K, Sood A, Grover PS, Bareja R. Isolation and characterization of various Pseudomonas species from distinct clinical specimens. *Jf Dental Med Sci*. 2015; **14**(6):80-84.
16. Pitout JDD, Revathi G, Chow BL, Kabera B, Kariuki S, Nordmann P, *et al*. Metallo-β-lactamase-producing Pseudomonas aeruginosa isolated from a large tertiary centre in Kenya. *Clin Microbiol Infect*. 2008; **14**(8):755-759.
17. Ghamgosha M, Shahrekizahedani S, Kafilzadeh F, Bameri Z, Taheri RA, Farnoosh G. Metallo-beta-Lactamase VIM-1, SPM-1, and IMP-1 genes among clinical Pseudomonas aeruginosa species isolated in Zahedan, Iran. *Jundishapur J Microbiol*. 2015; **8**(4):e17489-e89.
18. Savov E, Trifonova A, Todorova I, Gergova I, Borisova M, Ananieva M, *et al*. Original contribution assessment of the resistance of clinical isolates pseudomonas aeruginosa to quinolonones. *Trakia J Sciences*. 2014; **12**(3):221–226.
19. Taitt CR, Leski TA, Erwin DP, Odundo EA, Kipkemoi C, Ndonye JN, *et al*. Antimicrobial resistance of Klebsiella pneumoniae stool isolates circulating in Kenya. *PLoS One*. 2017; **12**(6):e0178880.

Original paper

Intradialytic Hypertension: Prevalence,Characteristics and Associated Factors in Chronic Haemodialysis Patients at Kenyatta National Hospital Renal Unit

Kakai E, Kayima J, Ogolla E, Mcligeyo SO, Kamau E

Department of Clinical Medicine and Therapeutics, School of Medicine, University of Nairobi, P.O. Box 19676-00202, Nairobi, Kenya

Address for Correspondence: Dr Elijah Kakai. Email: kakaielijah@gmail.com

Abstract

Background: End Stage Renal Disease (ESRD) is increasingly being diagnosed in our set up with a number of patients being put on haemodialysis. These patients have an age adjusted mortality rate of 3-10 times that of the general population. Cardiovascular causes account for more than 50% of death intra dialysis. Intradialytic Hypertension (IDH), defined as an increase in systolic blood pressure by at least 10 mmHg from pre to post haemodialysis readings in a minimum of four out of six consecutive dialysis sessions is recognized as an independent cardiovascular risk factor. Despite cardiovascular causes accounting for more than 50% of death intra dialysis and IDH being an independent cardiovascular risk factor, there is no local data on its prevalence, patient characteristics and associated factors. This study was meant to provide us with the information that we hope will be used to improve patient outcome on haemodialysis and decrease mortality at the renal unit.

Objectives: The aim of this study was to determine the prevalence of Intradialytic Hypertension (IDH) in End Stage Renal Disease (ESRD) patients undergoing haemodialysis at Kenyatta National Hospital Renal Unit. The secondary objective was to compare selected patients' characteristics and associated factors between those with and without IDH.

Design: This was a cross sectional study done at Kenyatta National Hospital (KNH) Renal Unit over a period of 3 weeks.

Methodology: The study population were adults aged over 18 years on maintenance haemodialysis and who were willing to provide a written consent. All those who met the inclusion criteria were enrolled. Blood pressure was measured using BP machines of the Omron®/Spengler® types for six consecutive dialysis sessions (Pre and Post dialysis) on each of the participants. The fluid status was assessed at the beginning of the study using a Bio Impedance Spectroscopy whose data was analysed using the BC4 software. All those who were recruited had blood samples drawn at the beginning of the study for analysis of serum electrolytes and haemoglobin level at the renal lab in KNH. All data was analysed using SPSS. The prevalence of IDH was calculated, Chi square test was used to test for association between IDH and associated factors with P value and Confidence intervals being calculated where necessary.

Results: Our study involved 512 haemodialysis sessions in 86 Chronic Kidney Disease (CKD) patients with a mean age of 47.3±13.5 years and a sex ratio (M/F) of 1.5:1. The mean duration of dialysis was 6 months to 1 year. The average haemoglobin level was 8.6±1.9g/dl. The mean sodium concentration pre dialysis was 135.6±6.7mmol with a gradient of 4.4±6.7 mmols while that for potassium was 4.7±0.9mmols with a gradient of -2.9±1.1mmols. More than half 45(52.3%) of the study participants had gross fluid overload with an average hydration status pre dialysis of 14.8±7.3%. Most of the study participants were on two antihypertensive medications with CCBS (93.3%) being the drug of choice in our set up. The prevalence of IDH was 51.2%. Factors found to affect IDH in our set up were high pulse pressure and high SBP.

Conclusion: IDH is often neglected despite it being recognized for many years. This study clearly shows that it is common in our cohort of haemodialysis patients with most of them having gross fluid overload. Its management is essential and should possibly incorporate adequate management of fluid status in these patients.

Key words: Intradialytic hypertension, Haemodialysis, End stage renal disease

Introduction

Intradialytic Hypertension (IDH) is defined as systolic blood pressure increase by at least 10 mm Hg from pre to post haemodialysis readings in a minimum of four out of six consecutive haemodialysis sessions (1). It has a general prevalence of 5-15% amongst patients on haemodialysis (2,3). Prevalence figures of 22% and

28% have been reported in Senegal and South Africa respectively (4,5).

Probable pathophysiological mechanisms include; (i) Fluid overload, (ii) Renin Angiotensin Aldosterone System (RAAS) and sympathetic nervous system over activation, (iii) Removal of antihypertensive medications during dialysis, (iv) Endothelial dysfunction, (v) Electrolyte imbalance involving dialysate sodium, calcium or potassium, (vi) Treatment with erythropoietin. Modalities aimed at the various postulated mechanisms causing IDH have been used in treatment with varied levels of success.

There is a 6% increase in mortality over 2 years with every 10mmhg increase in blood pressure during haemodialysis (6). IDH increases cardiovascular burden with resultant more left ventricular hypertrophy in these patients. IDH in End Stage Renal Disease (ESRD) compared to normotensive patients' intra dialysis is associated with more microvascular disease and interstitial fibrosis (7).

Approximately 60-80% of patients are hypertensive at time of diagnosis of ESRD, Up to 75% are reported to have left ventricular hypertrophy pre dialysis (8). Intradialytic blood pressure recordings give a more accurate estimation of biometric load on the arterial tree in haemodialysis compared to inter dialytic blood pressure readings (9). Cardiovascular disease accounts for more than 50% of ESRD deaths intra dialysis. Left ventricular hypertrophy and dilation are associated with increased cardiovascular related mortality hence the need for aggressive identification and treatment of all patients at risk (10).

IDH has been recognized as a marker of fluid overload in Chronic Kidney Disease (CKD) patients on haemodialysis. There are various methods of assessing fluid overload: Invasive and non-invasive. Both do have various limitations. Bio impedance is practical, easy to use, precise, highly reproducible and compares favourably well with other methods in assessing fluid overload in haemodialysis patients (11–14).

Sepsis, fluid overload and inadequate dialysis with electrolyte imbalance are equally important causes of mortality in haemodialysis in the developing countries as opposed to cardiovascular causes and coronary artery disease in the developed ones (15–17).

Materials and methods

This was a cross sectional study conducted at Kenyatta National Hospital Renal Unit. KNH is a teaching and referral hospital located in Nairobi. It also serves as a primary care centre to most residents of the city. It is a referral hospital to the Kenyan health facilities and other countries in Sub-Saharan Africa (SSA). It has a bed capacity of 1800.

Renal services were started at KNH in 1972 with the current renal unit being opened in 1984, approximately a total of 250-300 patients are seen every month with 10-15 patients being reviewed daily as outpatients and 1-3 renal transplants done on a monthly basis. About 110 patients are on maintenance haemodialysis every month with 1-2 new patients joining haemodialysis every week. The renal unit has 35 functional renal machines that are serviced and calibrated regularly. On average, 25 patients are on haemodialysis at any given time between 8 AM to 11 PM daily.

The renal lab is attached to the renal unit and works 24 hours with various machines operated by competent technologists. It contains the Human Analyser Cellydyne 3200 and the Mindray Clinical Chemistry Analyser amongst other machines that are capable of assessing haemoglobin levels, UECS (Urea, Electrolytes and Creatinine), Hepatitis markers, Random Blood Sugar (RBS) and other pre and post dialysis tests required at the renal unit. The renal lab at KNH has the capability to handle the volumes presented from the renal unit with a quick turnaround time. Its machines are serviced regularly.

Study population: All adults aged above 18 years old at Kenyatta National Hospital Renal Unit on maintenance haemodialysis.

Case definition

Maintenance haemodialysis: Was defined as haemodialysis for a minimum of 3 months.

IDH: Was defined as an increase in systolic blood pressure by at least 10mmhg from pre to posthaemodialysis readings in a minimum of four out of six consecutive dialysis sessions.

Fluid overload: Any value greater than 1.1L as measured by bio impedance was defined as fluid overload (18,19).

-< 1.1L (<7% OH) - Normal hydration status.
-1.1-2.5L (7% - 15% OH)-Mild fluid overload.
->2.5L (15 % OH) - Gross fluid overload.

Sodium gradient: The difference between the dialysate sodium concentration and the pre dialysis serum sodium concentration (20).

Potassium gradient: The difference between the dialysate potassium concentration and the predialysis serum potassium concentration.

Inclusion criteria

(i) Haemodialysis for a minimum of 3 months.
(ii) Age above 18 years.
(iii) Informed consent.

Exclusion criteria

(i) Those who changed their mode of dialysis during the study period.
(ii) Patients with contraindications to bio impedance e.g. pacemakers, pregnancy, amputees and those with metal implants.

Sample size estimation

About 110 kidney patients were on maintenance haemodialysis every month at Kenyatta National Hospital Renal Unit. The intended population of study was finite (less than 10,000), therefore, The Daniel,1999 formula that is used to estimate sample size in a finite population was used, based on the Senegal and South African study where prevalence of IDH was 22% and 28%, we used a prevalence of 28% (70).

$n' = NZ^2P\ (1-P)$
$d^2(N-1) + Z^2\ P\ (1-P)$

Where:
n' is the sample size with finite population correction.
N is the population size.
Z is the statistic for level of confidence.
P is the expected proportion (in proportion of one).
d is the desired precision e.g. within +/-5%
110(1.96x1.96)0.28(1-0.28)/ 0.05x0.05 (110-1) + (1.96x1.96)0.28(1-0.28)
Sample size = 86

Consecutive sampling was used to recruit study participants on each day until the sample size was attained.

Recruitment procedure

All patients visiting the renal unit were screened at the renal unit admission desk by the principal investigator at admission. The study, its objectives, involved procedures to be done on the participants including what was to be done with the results was explained verbally in English and Kiswahili and later a written format given to the patients. A written consent form was given to those willing to provide a written consent. All those who met the inclusion criteria and were willing to provide a written consent were recruited into the study.

Clinical and laboratory methods

Clinical methods: The principal investigator with the help of the research assistant (a trained clinical officer), recruited participants, took anthropometric measurements and recorded data. The principal investigator did direct interviews and examination of participants. Socio-demographic data and medical history was obtained from the patient's medical records at Kenyatta National Hospital Renal Unit. Patients' weight was obtained using a digital weighing scale (secar n) in kilograms at initiation of haemodialysis, while height in meters was measured with a standard stadiometer. Body mass index was calculated using the formula kg/m^2 (Kilograms/Meter Squared) where kg was a person's weight in kilograms and m^2 was their height in meters squared. EPO dose / kilograms was obtained from all participants and documented. Blood pressure on each participant was obtained before and after dialysis. This was done for 4-6 consecutive dialysis sessions on each participant.

Blood pressure in patients pre dialysis was done in patients seated quietly for at least 5 minutes with feet on the floor and arms at the heart level, this was done 5 minutes before dialysis (two readings) and later repeated at the end of dialysis (two readings) after restoring the extracorporeal blood circuit. BP machines of the Omron ®/Spengler ® were used (21).

All the involved health care staff were trained on how to take blood pressure and use of appropriate cuffs. Caffeine, exercise and smoking were avoided at least 30 minutes prior to BP measurement.

Bio impedance measurements were done on all those eligible to participate in the study at the beginning of the study with strict adherence to standard operating procedures to ensure we get accurate results. The electrodes were placed on a patient lying supine for at least 10 minutes. A software (BC4) provided by the manufacturer was used to interpret the resistance and reactance values from the bioimpedance machine (Quantum 2 bio impedance analyser manufactured by RJL systems) that gave us fluid volume in both intra and extracellular compartments. Any values >1.1 (greater than 7% OH) was interpreted as FO {Fluid Overload} (1.1-2.5L-mild FO {7 -15%OH}>2.5L {15%OH} –Gross FO).

Laboratory methods: Each patient had 5mls of venous blood drawn aseptically from the antecubital fossa, 3mls was put into the red vacutainer for serum electrolytes (sodium and potassium) analysis and 2mls into the purple vacutainer for a haemoglobin level. All samples were stored at the renal lab at -20 degrees Celsius until the time of analysis. Haemograms were done at the renal lab using the Human Analyser Cellydyne 3200 and haemoglobin levels recorded for the purpose of the study. Serum electrolytes were done at the renal lab using an automated machine (Mindray Clinical Chemistry Analyser). Serum sodium and potassium levels were recorded in a pro-forma sheet that were later analysed. All excess blood samples of blood were discarded into the red bin and later taken to a central place in KNH for incineration. All the lab tests were done at the beginning of the study with competent technologists at KNH. An electrolyte gradient was then determined by getting the

difference between dialysate sodium and potassium and serum sodium and potassium levels.

Patients variables

(i) *Age:* Difference between year of birth and current year documented in years.
(ii) *Gender:* This was taken as self-identity of participants as either male or female.
(iii) *Duration of Chronic Kidney Disease (CKD):* Difference between current year (2019) and year of diagnosis of chronic kidney disease.
(iv) *Duration of dialysis:* Difference between current year and year when dialysis was initiated.
(v) *Blood pressure:* JNC 7 was used to interpret and group various blood pressure findings (22).
(vi) *Pulse pressure:* Average systolic minus diastolic blood pressure readings.
(vii) *Treatment:* All the medications for various conditions the patient was being treated for was recorded, in addition, the number of dialysis sessions per week was also recorded.
(viii) *Body Mass Index:* Was calculated using the aforementioned formula and classified as normal weight, underweight or overweight.

Data management and analysis

All data collected was recorded on a pro-forma sheet and stored by the Principal Investigator until they were analysed. All the data gathered or used in the study; primary, secondary; hard copies were kept confidential and stored by the Principal Investigator in a secure lockable cabinet only accessible to the Principal Investigator. Electronic data was kept in folders accessible by passwords only known to the principal investigator.

The patients' medical records at the renal unit that were used to obtain socio demographic and medical data was not tampered with. They were kept confidential and not shared outside the study. They were all returned to the records department at the renal unit for proper storage and future follow up of the patient. All data was entered and analysed by use of SPSS (Version 21.0, Chicago Illinois). The prevalence of IDH was calculated as a percentage of patients who met the definition criteria. Categorical data was analysed and displayed as proportion and frequencies while Continuous data was analysed and summarized as means and standard deviation.

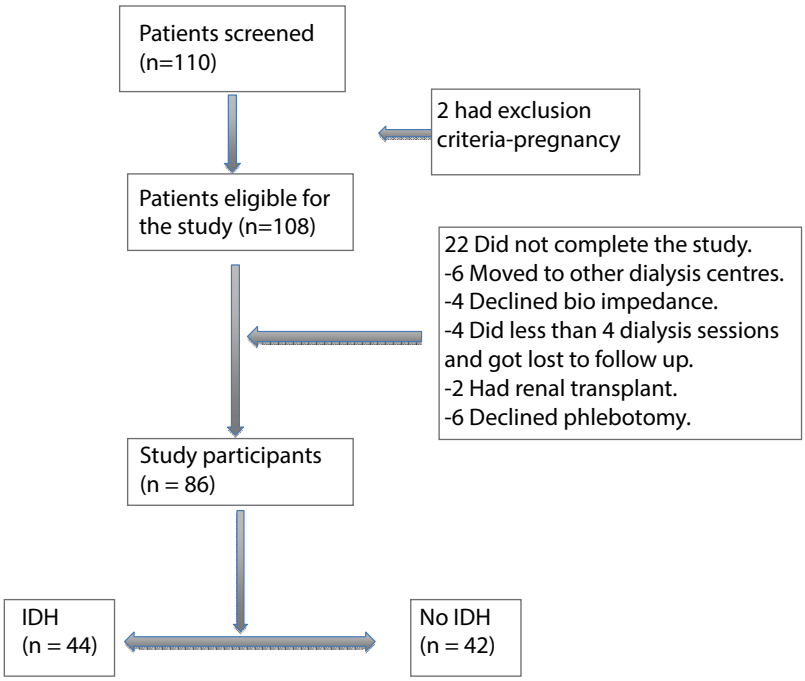
Chi square test was used to test the association between IDH and selected characteristics and associated factors in those patients with intradialytic hypertension at KNH Renal Unit participating in the study. P-value and 95% Confidence Interval were calculated where necessary. A P-value <0.05 was considered to be statistically significant.

Results

The study was carried out between 25th March 2019 and 14th April 2019 at the KNH renal unit. A total of 110 patients were screened for the study, 2 (1.8%) had exclusion criteria while 22 (20%) others did not complete the study.

Eighty six patients, (78 participated in the study to completion). At the beginning of the study, blood samples were drawn for serum electrolytes and haemoglobin analysis, fluid status was assessed by

Figure 1: Flowchart of patient' enrollment



bioimpedance and later on their blood pressures were monitored for 6 consecutive dialysis sessions (Figure 1). *Patients' baseline characteristics:* A total of 86 patients on regular haemodialysis (twice a week haemodialysis) participated in the study, there were 52 (60.5%) males and 34 (39.5%) females. The male to female ratio was 1.5:1. The mean age of participants was 47.3±13.5 years. Majority (66.3%) of study participants were hypertensive with 62.6% of them having a systolic/diastolic hypertension pattern. Our patients had a higher mean post dialysis MAP and SBP compared to pre dialysis readings (109.1±16.8 vs103.6±20.6 and 151.9±25.6 vs 143.5±21.9 respectively). Other baseline characteristics (marital-status, educational level, diabetes, cigarette and alcohol use) of the study population are as demonstrated below (Tables 1A and B, Figures 2, 3, 4 and 5).

Table 1A: Patients' sociodemographic characteristics (N=86)

	All patients
Mean age in years	47.3±13.5
Alcohol use in the last 1 year	23 (26.7%)
Cigarette smoking in the last 1 year	3 (3.5%)
Alcohol/Cigarette use in the last 1 year	7 (8.1%)
Diabetes mellitus	5 (5.8%)
Hypertension	57 (66.3%)

Figure 2: Gender

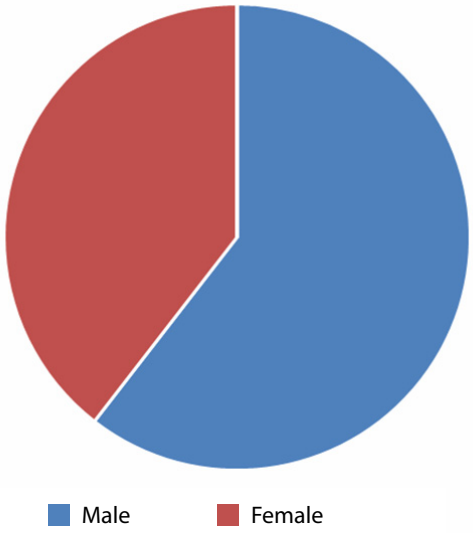


Figure 3: Marital status

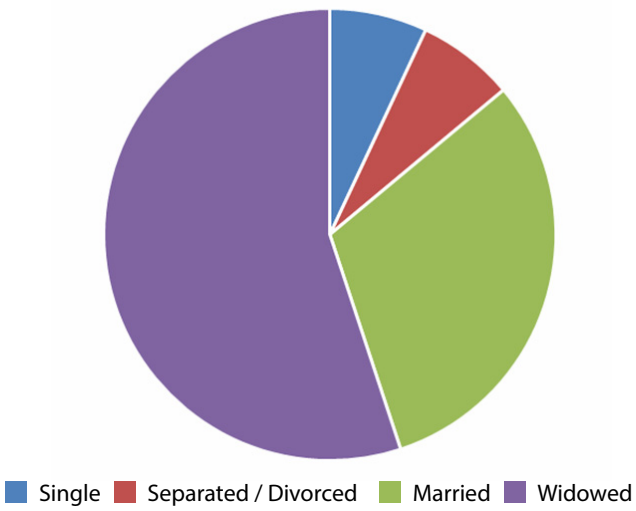


Figure 4: Education level

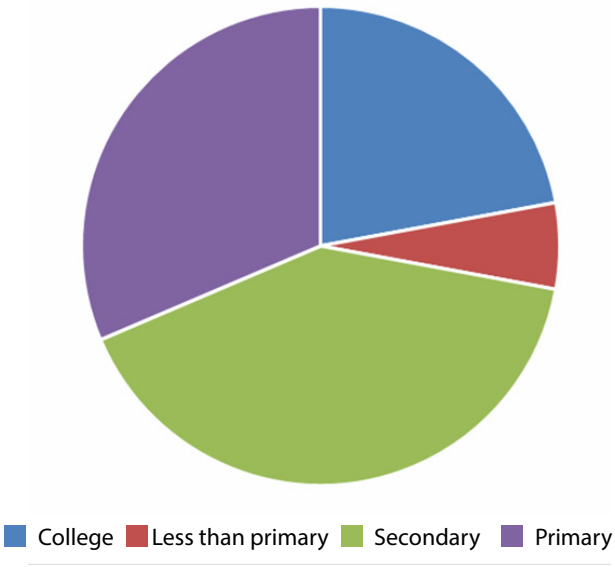
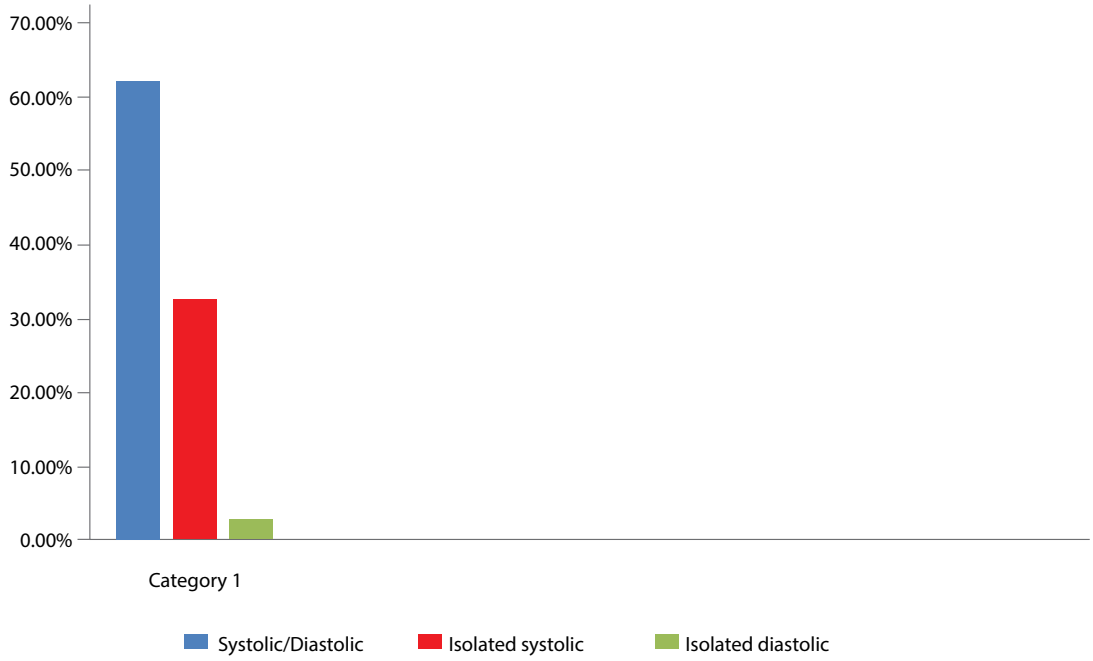


Table 1B: Patients' clinical characteristics

	All patients
Pre dialysis MAP	103.6±20.6
Post dialysis MAP	109.1±16.8
Mean Pre dialysis SBP	143.5±21.9
Mean Post dialysis SBP	151.9±25.6

Figure 5: Hypertension



IDH prevalence: All the 86 patients who participated in the study had their blood pressures recorded for 6 consecutive dialysis sessions. A total of 44 patients out of the 86 patients were found to have IDH resulting in a prevalence of 51.2%.

Associated factors: There was not much difference in age between those with and without IDH. (IDH - 49.2±13.2 years in comparison to No IDH-45.4±13 years). Males constituted most of those with IDH (28 (63.6%)-Males versus 16 (36.4%) - females). We did not have a significant difference in BMI between the two groups. The mean average BMI for all patients was 22.2±3.6 (IDH -22.6±3.9 in comparison to Non IDH- 21.8±3.3). The duration of dialysis was equally distributed between those with and without IDH. Most (65.1%) participants had dialyzed for less than one year. A total of 29 (33.7%) had dialyzed for less than six months [IDH-16 (36.4%) versus No IDH-13 (31.0%)] while 27 (31.4%) had dialyzed between six months to one year. Amongst this cohort 17 (38.6%) had IDH in comparison to 10 (23.8%) with no IDH. The above is demonstrated in Table 2A.

Table 2A: Comparison of socio demographic parameters

	IDH	No IDH	P-value
Overall mean age (years)	49.2±13.2	45.4±13.6	0.198
Male	53.6±12.8	50.8±13.2	0.434
Female	41.3±10.0	38.2±10.8	0.395
Gender			
Male	28 (63.6)	24 (57.1)	0.538
Female	16 (36.4)	18 (42.9)	Ref
BMI			
Overall BMI	22.6±3.9	21.8±3.3	0.284
Underweight (<18.5)	7 (15.9)	6 (14.3)	0.498
Normal (18.5-24.9)	23 (52.3)	30 (71.4)	Ref
Overweight (25.0-29.9)	11 (25)	5 (11.9)	0.075
Obese (>=30.0)	3 (6.8)	1 (2.4)	0.322
Duration of dialysis			
<6 months	16 (36.4)	13 (31.0)	Ref
6 months - 1 year	17 (38.6)	10 (23.8)	0.554
1 - 2 years	4 (9.1)	10 (23.8)	0.101
> 2 years	7 (15.9)	9 (21.4)	0.463

Both sets of groups had a similar profile in terms of haemoglobin level, fluid status and serum electrolyte as demonstrated in Table 2B.

All participants had some degree of fluid overload. The average pre-dialytic relative over hydration was 14.8% ±7.3 (mild fluid overload). IDH patients had a relative over hydration of 15.6%±7.7 (Gross fluid overload) in comparison to 13.9%±6.8 (mild overload) in those without IDH. The mean pulse pressure post dialysis was 63.7±17.8mmHg.IDH participants had a higher post dialysis pulse pressure {IDH - 72.2±16.6mmHg versus Non IDH 54.7±14.3mmHg, P-value < 0.001}. The same trend was seen with pre dialysis pulse pressure.

Table 2B: Comparison of clinical parameters

Fluid status	All patients	IDH	No IDH	P-value
Pre-dialysis OH (%)-Mean	14.8±7.3	15.6±7.7	13.9±6.8	0.273
<7%	13 (15.1)	5 (11.4)	8 (19.0)	Ref
7-15%	28 (32.8)	15 (34.1)	13 (31.0)	0.368
>15%	45 (52.3)	24 (54.5)	21 (50.0)	0.345
Pre-dialysis ECW (%)	16.9±4.5	18.4±4.7	17.4±4.3	0.270
Serum electrolytes				
Serum sodium pre-dialysis	135.6±6.7	134.6±7.2	136.8±6.0	0.128
Sodium gradient	4.4±6.7	5.4±7.2	3.4±6.2	0.169
Serum potassium pre-dialysis	4.7±0.9	4.8±0.9	4.7±0.9	0.614
Potassium gradient	-2.9±1.1	-2.8±0.9	-2.6±1.3	0.334
Haemoglobin	8.6±1.9	8.8±2.1	8.4±1.9	0.250
Pulse pressure				
PP post dialysis	63.7±17.8	72.2±16.6	54.7±14.3	<0.001
PP pre dialysis	57.8±17.9	64.2±17.2	50.8±16.0	<0.001

Sixty (69.8%) of participants were on antihypertensive medications. Slightly more patients with IDH were on antihypertensive drugs (IDH-58.3% versus No IDH-41.7%).The average number of drug molecules used per patient was 1.88±0.8.CCBS, [56 (93.3%)] were the most commonly prescribed medications in those with ESRD at KNH renal unit (Table 3).

Over the last 3 months only 4 patients in the study were on regular EPO with x 2 weekly infusion of 2000IU. None had IDH. There was inadequate data to analyse this factor as a contributing factor to IDH.

Table 3: Types of anti-hypertensive medication

	All patients	IDH	No IDH	P-value
BP Meds				
Total No. of patients on medication	60 (100%)	35 (58.3%)	25 (41.7%)	
ACEI/ARB	1 (1.7%)	0	1 (1.7%)	0.400
α-blocker	3 (5.0%)	2 (3.3%)	1 (1.7%)	1.000
β-blocker	30 (50.0%)	21 (35.0%)	9 (15.0%)	0.197
CCB	56 (93.3%)	33 (55.0%)	23 (38.3%)	0.823
Diuretic	2 (3.3%)	2 (3.3%)	0	0.516
Hydralazine	28 (46.7%)	14 (23.3%)	14 (23.3%)	0.217
Mean No. of drugs	1.88±0.8	1.89±0.8	1.85±0.8	

Discussion

The prevalence of IDH is 51.2%. This is way higher than in most studies done elsewhere where it averages 15-30%. A number of factors might have contributed to this. Moustapha *et al* (4) found a prevalence of 22.6% in a study done to determine the prevalence and associated factors in haemodialysis patients in Senegal in 2017, their study population had a number of significant differences to the one in Kenya; Most of their patients underwent three times haemodialysis sessions per week compared with twice per week at KNH renal unit, 40% of their patients were on ACEI/ ARBS compared to 1% in our setup (4). Similar findings were found in South Africa in 2014 by Chothia *et al.* (5) who had a prevalence of 28.4% in a study done on IDH during chronic haemodialysis and subclinical fluid overload assessed by BIS, In South Africa, 33% of patients were on ACEI compared to 1% in our setup, 48% were on diuretics compared to 2% in our set up. Most patients underwent three sessions of dialysis per week compared to twice at KNH renal unit. The study population in South Africa had better fluid status pre dialysis compared to our study population, ECW; 3.5% vs 18.4% amongst the IDH patients (5).

In Indonesia, two studies done in 2016 and 2019 found a prevalence of 53.1% and 41.4% respectively. In 2016 Adiwanata *et al.* (24) did a study on prevalence and risk factors analysis of IDH among chronic haemodialysis patients at Dr Kanujoso Djatibowo Public Hospital while in 2019, Andryan *et al.* (23) did a study on characteristics of dialysis patients with IDH at the haemodialysis unit at Sumdong Regional Public Hospital. The studies in Indonesia had similar characteristics to ours with patients undergoing two sessions of haemodialysis every week and most patients being on calcium channel blockers for blood pressure control.

Most of the study participants were on CCBs (93% of those on medications). This may partly explain the high prevalence in our study. ACEI, ARBS and BB are thought to decrease IDH. ACEI and ARBS reduce RAAS activity while BB especially carvedilol reduces endothelial dysfunction (25).

In our study, one of the factors that was found to be associated with increase in SBP during dialysis was high post dialysis SBP. Increase in post dialysis SBP is associated with extracellular over hydration and less change in weight post dialysis. This could partly explain the high over hydration status in our cohort of patients. This can be addressed by reviewing and individualizing individual patient target weight and dialysis requirements. These are candidates for increased dialysis duration or frequency (26).

High PP was a predictor of IDH. Several studies have shown that High PP is an independent cardiovascular risk factor of mean arterial pressure. It predicts the probability of getting MI and CVA. Unlike in the Italian study where only pre dialytic PP was more significant, both high pre and post dialytic PP have been found to be statistically significant in our study. More studies are needed on both pre and post dialytic pulse pressures and their impact on mortality (27).

Some studies have reported that IDH is more common in the elderly (>65 years) and that those patients are mostly on multiple drugs. We found no association between those two factors and IDH in our study where most patients were on two drugs and the average age of patients was 47.3±13.5 years.

No correlation was established between the serum electrolyte and gradient with IDH in our study.Higher BMI more than 30 has been found to decrease the incidence of IDH by unknown mechanism (28–30), this was not established in our study. We did not manage to find enough data to assess the effect on EPO on IDH.

Conclusion

IDH is often neglected despite it being recognized for many years, our study clearly shows that it is common in our cohort of haemodialysis patients with most of them having gross fluid overload. Its management is essential and should possibly incorporate adequate management of fluid status in these patients.

Recommendations

(i) Increase the frequency /duration of dialysis in all our patients to attain better fluid status control and decrease or better manage IDH.
(ii) Individualize each patient's dialysis needs and get ideal target weight and strive to achieve it with adequate dialysis and medications.
(iii) Incorporate ACEI and ARBS together with beta blockers especially carvedilol in our blood pressure control in ESRD patients on maintenance haemodialysis.
(iv) Widespread use of bio impedance in assessing volume control in haemodialysis units.

Limitations

Eighty six is a small number, a larger cohort may be needed to establish a statistically significant result that is more representative regarding fluid overload and IDH. Inability to compare frequency of dialysis and impact on IDH as all patients were on twice weekly haemodialysis sessions.

References

1. Siamopoulos K. Treatment of hypertension in patients with chronic renal failure. *Nephrol Dialysis Transplant*. 2001; **16** (Suppl 6):46. DOI - 10.1093/ndt/16.suppl_6.46.
2. Locatelli F, Cavalli A, Tucci B. The growing problem of intradialytic hypertension. *Nat Rev Nephrol*. 2009; **6**:41.
3. Panagiotis IG, Pantelis AS, Carmine Z. Intradialysis hypertension in end-stage renal disease patients. *Hypertension*. 2015; **66**(3):456–463.
4. Moustapha F, Tall LA, Yaya K, Moustapha CM, Mohamed SS, Maria F, *et al*. Intradialytic hypertension: prevalence and associated factors in chronic hemodialysis patients in Senegal. *Open J Nephrol*. 2018; **8**(2):2937.
5. M-Y, Sebastian S, Filmalter C, Harvey J. Intradialytic hypertension during chronic haemodialysis and subclinical fluid overload assessed by bioimpedance spectroscopy. *Clin Kidney J*. 2016; **9**(4):636–643.
6. Inrig JK, Patel UD, Toto RD, Szczech LA. Association of blood pressure increases during hemodialysis with 2-year mortality in incident hemodialysis patients: A secondary analysis of the dialysis morbidity and mortality wave 2 study. *Am J Kidney Dis Off J Natl Kidney Found*. 2009; **54**(5):881–890.
7. Amann K, Rychlík I, Miltenberger-Milteny G, Ritz E. Left ventricular hypertrophy in renal failure. *Kidney Int*. 1998; **54**:S78–S85.
8. London GM, Fabiani F, Marchais SJ, De Vernejoul M, Guerin AP, Safar ME, *et al*. Uremic cardiomyopathy: An inadequate left ventricular hypertrophy. *Kidney Int*. 1987; **31**(4):973–980.
9. Agarwal R, Metiku T, Tegegne GG, Light RP, Bunaye Z, Bekele DM, *et al*. Diagnosing hypertension by intradialytic blood pressure recordings. *Clin J Am Soc Nephrol*. 2008; **3**(5):1364–72.
10. Collins AJ. Cardiovascular mortality in end-stage renal disease. *Am J Med Sci*. 2003; **325**(4):163–167.
11. Azem A, Grabensee B, Steffens F, Schoenicke G, Plum J, Kleophas W, *et al*. Comparison of body fluid distribution between chronic haemodialysis and peritoneal dialysis patients as assessed by biophysical and biochemical methods. *Nephrol Dial Transplant*. 2001; **16**(12):2378–85.
12. Hur E, Usta M, Toz H, Asci G, Wabel P, Kahvecioglu S, *et al*. Effect of fluid management guided by bioimpedance spectroscopy on cardiovascular parameters in hemodialysis patients: A randomized controlled trial. *Am J Kidney Dis*. 2013; **61**(6):957–965.
13. Katzarski K, Charra B, Laurent G, Lopot F, Bergström J, Divino-Filho JC, *et al*. Multifrequency bioimpedance in assessment of dry weight in haemodialysis. *Nephrol Dial Transplant*. 1996; **11**(supp2):20–23.
14. Basso F, Milan Manani S, Cruz DN, Teixeira C, Brendolan A, Nalesso F, *et al*. Comparison and reproducibility of techniques for fluid status assessment in chronic hemodialysis patients. *Cardiorenal Med*. 2013; **3**(2):104–112.
15. Luyckx VA, Tonelli M, Stanifer JW. The global burden of kidney disease and the sustainable development goals. *Bull World Health Organ*. 2018; **96**(6):414-422D.
16. Tamayo Isla RA, Ameh OI, Mapiye D, Swanepoel CR, Bello AK, Ratsela AR, *et al*. Baseline predictors of mortality among predominantly rural-dwelling end-stage renal disease patients on chronic dialysis therapies in Limpopo, South Africa. P*los One*. 2016; **11**(6):e0156642.
17. Kher V. End-stage renal disease in developing countries. *Kidney Int*. 2002; **62**(1):350–362.
18. Dou Y, Zhu F, Kotanko P. Assessment of extracellular fluid volume and fluid status in hemodialysis patients: current status and technical advances. *Semin Dial*. 2012; **25**(4):377–387.
19. Wabel P, Moissl U, Chamney P, Jirka T, Machek P, Ponce P, *et al*. Towards improved cardiovascular management: the necessity of combining blood pressure and fluid overload. *Nephrol Dial Transplant*. 2008; **23**(9):2965–71.
20. Penne EL, Sergeyeva O. Sodium Gradient: A tool to individualize dialysate sodium prescription in chronic hemodialysis patients? *Blood Purif*. 2011; **31**(1–3):86–91.
21. Brook RD, Rajagopalan S. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Soc Hypertens*. 2018; **12**(3):238.
22. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo J Joseph L, *et al*. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure The JNC 7 Report. *JAMA*. 2003; **289**(19):2560–71.
23. Andryan DP, Ariseno, Mulya A. Characteristic of dialysis patient with intradialytic hypertension in hemodialysis unit Sumedang Regional Public Hospital. *J Hypertens* [Internet]. 2019;**37**. Available from: https://journals.lww.com/jhypertension/Fulltext/2019/07002/4_characteristic_of_dialysis_patient_with.4.aspx.
24. Adiwinata R, Hanifiah NA, Rasidi J, Yuliana R, Ratnaningsih R, Ayuningtyas M, *et al*. Prevalence and risk factor analysis of intradialytic hypertension among chronic hemodialysis patients in Dr. Kanujoso Djatiwibowo Public Hospital. *J Hypertens* [Internet]. 2018; **36**. Available from: https://journals.lww.com/jhypertension/

Fulltext/2018/07002/12_prevalence_and_risk_factor_analysis_of.12.aspx.
25. Inrig JK, Van Buren P, Kim C, Vongpatanasin W, Povsic TJ, Toto RD. Intradialytic hypertension and its association with endothelial cell dysfunction. *Clin J Am Soc Nephrol CJASN*. 2011; **6**(8):2016–24.
26. Nongnuch A, Campbell N, Stern E, El-Kateb S, Fuentes L, Davenport A. Increased postdialysis systolic blood pressure is associated with extracellular overhydration in hemodialysis outpatients. *Kidney Int*. 2015; **87**(2):452–457.
27. Losito A, Locatelli F, Del Vecchio L, Del Rosso G. Postdialysis Hypertension: Associated factors, patient profiles, and cardiovascular mortality. *Am J Hypertens*. 2015; **29**(6):684–689.
28. Kalantar-Zadeh K, Kopple J. Obesity paradox in patients on maintenance dialysis. In: contributions to nephrology [Internet]. 2006. p. 57–69. Available from: https://www.karger.com/DOI/10.1159/000095319.
29. Jialin W, Yi Z, Weijie Y. Relationship between body mass index and mortality in hemodialysis patients: A meta-analysis. *Nephron Clin Pract*. 2012; **121**(3–4):c102–11.
30. Park J, Ahmadi S-F, Streja E, Molnar MZ, Flegal KM, Gillen D, *et al*. Obesity paradox in end-stage kidney disease patients. O*bes Obes Paradox Cardiovasc Dis*. 2014; **56**(4):415–425.

Original paper

Patient Dose During Digital Mammography at Kenyatta National Hospital, Nairobi, Kenya

Ger N, Anyenda OE

Department of Diagnostic Imaging, School of Medicine, University of Nairobi, P.O. Box 15167 - 00100, Nairobi, Kenya

Address for Correspondence: Dr Norah Ger. Email: norahger@gmail.com

Abstract

Background: The Government of Kenya, equipped most major public hospitals with digital mammography machines due to their good image quality and reduction of radiation dose. However, few reported studies have been done on digital mammography in developing countries and none so far in Kenya.

Objective: The purpose of this study was to analyze the average glandular dose in symptomatic Kenyan women undergoing diagnostic mammography using the digital mammography machine.

Design: This was a prospective cross sectional study.

Methods: A total of 200 female participants referred by physicians for diagnostic mammography using Senographe Essential (General Electric, USA) at Kenyatta National Hospital (KNH), Kenya, were included during November 2016 – May, 2017 study period. Each participant's age and examination parameters such as type of projection, kilovoltage peak (kVp), milliamperes second (mAs), displayed average glandular dose, anode and filter combinations, and compression breast thickness were recorded on data sheets. Statistical analyses were performed to determine the sample mean doses, dependence of dose on compression breast thickness and type of view using SPSS software.

Results: The average glandular dose values were 1.2 ±0.5 mGy and 1.3±0.6 mGy for Cranio-Caudal (CC) and Medio Lateral Oblique (MLO) views, respectively. There was significant difference in mean radiation dose between the CC and MLO views ($p < 0.001$). The results were similar to those of other studies.

Conclusion: In this study the Average Glandular Dose (AGD) values were found to be within the recommended diagnostic reference levels of between 2 - 3mGy.

Key words: Average glandular dose, Mammography, Patient doses, Craniocaudal, Mediolateral oblique

Introduction

According to WHO statistics, breast and cervical cancers are the leading causes of cancer related mortality in sub-Saharan Africa (SSA) (1). The incidence rate of breast cancer in SSA is 25 per 100,000 (1). Furthermore, it is reported breast cancer is the most common cause of cancer-related mortality in younger women (below 50 years).

In Kenya, breast cancer is reported to be the third most common cause of death after infectious and cardiovascular diseases (1,2). Estimates from patients who seek medical attention in local private Kenyan facilities show that there are 39,000 new cases of cancer per year with about 27,000 deaths annually from cancer (2). Breast cancer constitutes 21% of all these cancer cases and is the third most common cancer (2).

Although breast cancer screening program is not fully established in Kenya, there exists national guidelines that recommends screening to be done via self-breast examinations, clinical breast examination and breast imaging through ultrasound, mammography and Magnetic Resonance Imaging (MRI) (2). The same guidelines recommends screening be done every 2 years among asymptomatic women with age of over 40 years for purposes of cancer management (2).

Mammography has proven to be the gold standard in breast imaging during screening and diagnosis of breast cancer (3). Its capability to detect small non-palpable cancers and suspicious microcalcifications that might be missed on ultrasound and MRI, has been associated with up to 30% reduction in mortality from breast cancer (3). Also, it is widely available and affordable in comparison to MRI.

Even as usage of ionizing radiation is increasing among routine diagnostic procedures (including mammography), there is growing attention towards possible risks of radiation exposure. In its recent publication the International Commission On Radiation Protection (ICRP) classified the breast as one of the highly radiosensitive organs (4). Reduction of patient doses while generating diagnostic quality images is considered crucial in ensuring patient safety. Technological advances have resulted in replacement

of conventional screen film mammography with Full Filed Digital Mammography (FFDM) systems.

In Kenya, mammography studies are used for the examination, diagnosis and monitoring of breast cancer among symptomatic women who are usually referred by the primary physician. Until early 2016, Kenyatta National Hospital (KNH), the largest public referral hospital in Kenya, had one screen film mammography machine. However due to the huge number of patients, in April 2016, the government embarked on a program to equip all government hospitals with various medical equipment through General Electric (GE). This program led to 47 public hospitals being equipped with GE health care digital mammographic machine. The GE Senographe is a FFDM with Automatic Exposure Control (AEC) systems, Molybdeneum/Rhodium(Mo/RH) and Mo/Rh target combinations, two focal spots of 0.3 and 0.1 mm (5).

The basis of the change to digital system was informed by several studies that have shown digital mammography machines provide better quality images with improved tissue contrast. In addition, it is suited for dense breasts and younger females at lower radiation doses compared to screen film mammography (6-8).

Whilst there exists reports from studies done elsewhere (USA, UK, Korea, Japan etc), no report exists for digital mammography in Kenya. One previous study done was related to patient doses during screen film mammography examinations (9). In Ethiopia, a comparative study done reported the AGD to be 1.35 – 1.71 mGy (10). Hence, the present study sought to assess whether the level of patient doses and equipment performance in our own setting conform to the recommended radiation protection standards. Such information is of great significance in the establishment of standards within the country and beyond.

The aim of this study was to compute the mean AGD displayed on GE FFDM unit for the female patients undergoing diagnostic mammographic examination at KNH and its association with breast compression thickness.

Materials and methods

This was a prospective cross sectional study carried out in the mammography unit of the radiology department of Kenyatta National Hospital (KNH) from November 2016 to May 2017. Ethical approval was obtained on 31st October 2016 from the KNH and University of Nairobi Ethical Committee.

The machine used is a Senographe Essential (General Electric, USA) a digital machine with AEC systems, Mo/RH and Mo/Rh target combinations, two focal spots of 0.3 and 0.1mm (dual anode/filter). The machine was installed in April 2016 and the unit is regularly tested during routine Quality Control (QC) checks. AQC check was done a month prior to the study. The maximum kVp and mAs used in this study were 31keV and 335mAs respectively.

The study included 200 female patients who volunteered to participate. These patients were referred by a medical physician for diagnostic mammography at KNH and excluded patients with breast implants, history of mastectomy of one breast and those who did not give consent.

Sample size was calculated using the following formula:

$$n = \frac{Z_{\frac{a}{2}}^{2} \times a^{2}}{d^{2}}$$

Where: n = Sample size.
Zα/2 = Standard normal deviate at 5% level of significance (95% CI) is 1.96
σ = Standard deviation of MGD per exposure 0.61 mGy
d = Margin of error (set at 0.085)

Upon assessment of image quality by the radiologist consultant, each patient's age and radiological examination parameters were recorded by the chief investigator, as provided by the machine. These parameters were automatically selected by the AEC. These parameters included the average glandular dose (mGy), Entrance Skin Exposure (ESE), kVp, mAs, anode and filter material and compression breast thickness.

The Statistic Package for Social Science (SPSS) version 20.0 for Windows® was utilized for statistical analysis of data. Analysis of participants' demographic data was conducted using descriptive statistics. Demographic data were collected as categorical data and analyzed using frequency distribution curves to determine the percentage of participants' with specific demographic traits. The mean AGD was calculated for each of the three imaging modes used: 2D: cranio-caudal and medio-lateral oblique. The mean dose for each imaging mode and view was presented along with a standard deviation to show variation in AGD per exposure. The machine readings for breast thickness were used to calculate a mean Compressed Breast Thickness (CBT) and SD for the sample. Finally, correlations were done between CBT and radiation dose through calculation correlation coefficients.

Results

The mean age of the participants was 50.4 years (SD ± 9.2) with the youngest patient aged 32 years and the oldest patient 77 years. Figure 1 shows the age distribution of participants.

Figure 1: Total number of participants according to age groups during the study period (Nov 2016 – May 2017) at KNH

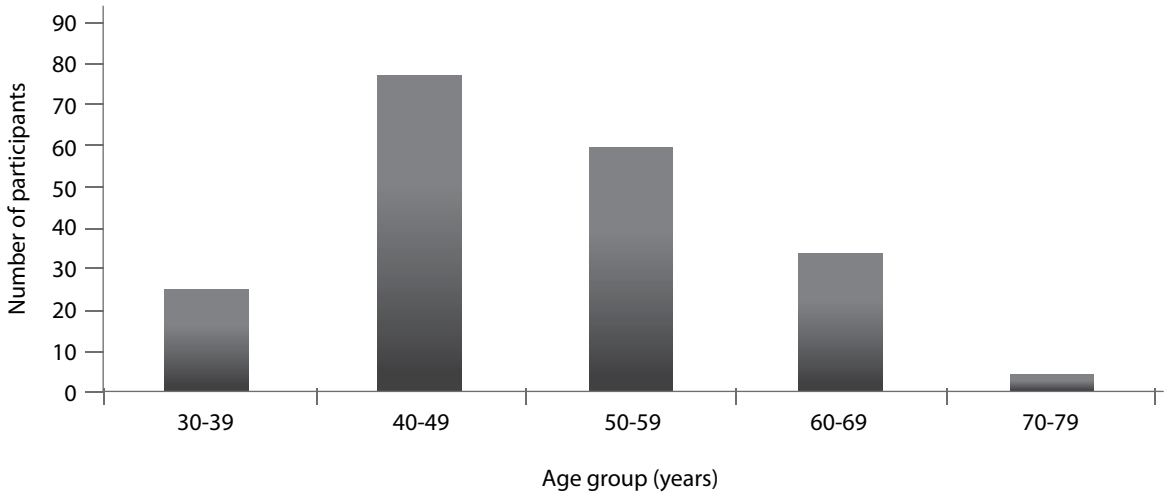


Table 1: Mean kVp values in breast mammography (keV)

View	Mean	SD	Minimum	Maximum
RCC	28.3	1.1	26	31
LCC	28.4	1.1	26	31
RMLO	28.9	1.1	26	31
LMLO	28.8	1.0	26	31

RCC = Right Craniocaudal RMLO = Right Mediolateral Oblique
LCC = Left Craniocaudal LMLO = Left Mediolateral Oblique

The MAS values are as shown in Table 2.

Table 2: Tube Current (mAs) values per view

View	Mean	SD	Minimum	Maximum
RCC	57.8	33.3	27	335
LCC	61.1	44.0	29	335
RMLO	63.8	29.1	29	326
LMLO	69.3	46.5	29	335

RCC = Right Craniocaudal RMLO = Right Mediolateral Oblique
LCC = Left Craniocaudal LMLO = Left Mediolateral Oblique

Age and dose: The doses are slightly higher within the younger age groups but still within international range. Mean glandular dose according to age group is shown in Table 3.

Table 3: Mean glandular dose according to patient age group (mGy)

Age group (years)	No.	AGD	SD
30-39	25	1.3	0.7
40-49	77	1.3	0.6
50-59	60	1.3	0.5
60-69	34	1.1	0.3
70-79	4	1.0	0.1

AGD = Average Glandular Dose

Average CC versus MLO views AGD: The average glandular dose in CC and MLO views for the entire 200 patients are as shown in Table 4. There was a significant difference in mean radiation dose between the CC and MLO views ($p < 0.001$).

Table 4: Comparison of mean CC and MLO AGD in breast mammography (mGy)

Mammography view	Mean dose	SD
CC-AGD	1.2	0.5
MLO-AGD	1.3	0.6

CC =Craniocaudal MLO = Mediolateral Oblique
AGD =Average Glandular Dose

Compressed breast thickness and radiation dose: The mean CBT for various views are given in Table 5 and ranged between 53.1 and 61.5 mm.

Table 5: Mean CBT according to mammography views (mm)

CBT	Mean CBT (in mm)	SD	Minimum	Maximum
RCC	53.1	13.0	17	120
LCC	53.5	14.2	20	115
RMLO	61.5	15.0	18	116
LMLO	61.5	16.0	22	119

RCC = Right Craniocaudal
LCC = Left Craniocaudal
RMLO = Right Mediolateral Oblique
LMLO = Left Mediolateral Oblique
CBT = Compression Breast Thickness

Table 6 shows a positive correlation between CBT and AGD. The results are significant at $p<0.001$.

Table 6: CBT, AGD, Pearson's score and P value per view

View	CBT	AGD	Pearson's score	P-value
RCC	53.1	1.2	0.58	<0.001
LCC	53.5	1.2	0.672	<0.001
RMLO	61.5	1.3	0.567	<0.001
LMLO	61.5	1.4	0.63	<0.001

RCC = Right Craniocaudal
LCC = Left Craniocaudal
RMLO = Right Mediolateral Oblique
LMLO = Left Mediolateral Oblique
CBT = Compression Breast Thickness
AGD = Average Glandular Dose

The results in Table 7 demonstrate the mean compression breast thickness used for the various target/filter combinations in the entire sample population (200) and the AGD. Rh /Rh combination was used for breast with increased thickness.

Table 7: The correlation between dose, CBT and the target/filter combination

A. CC view

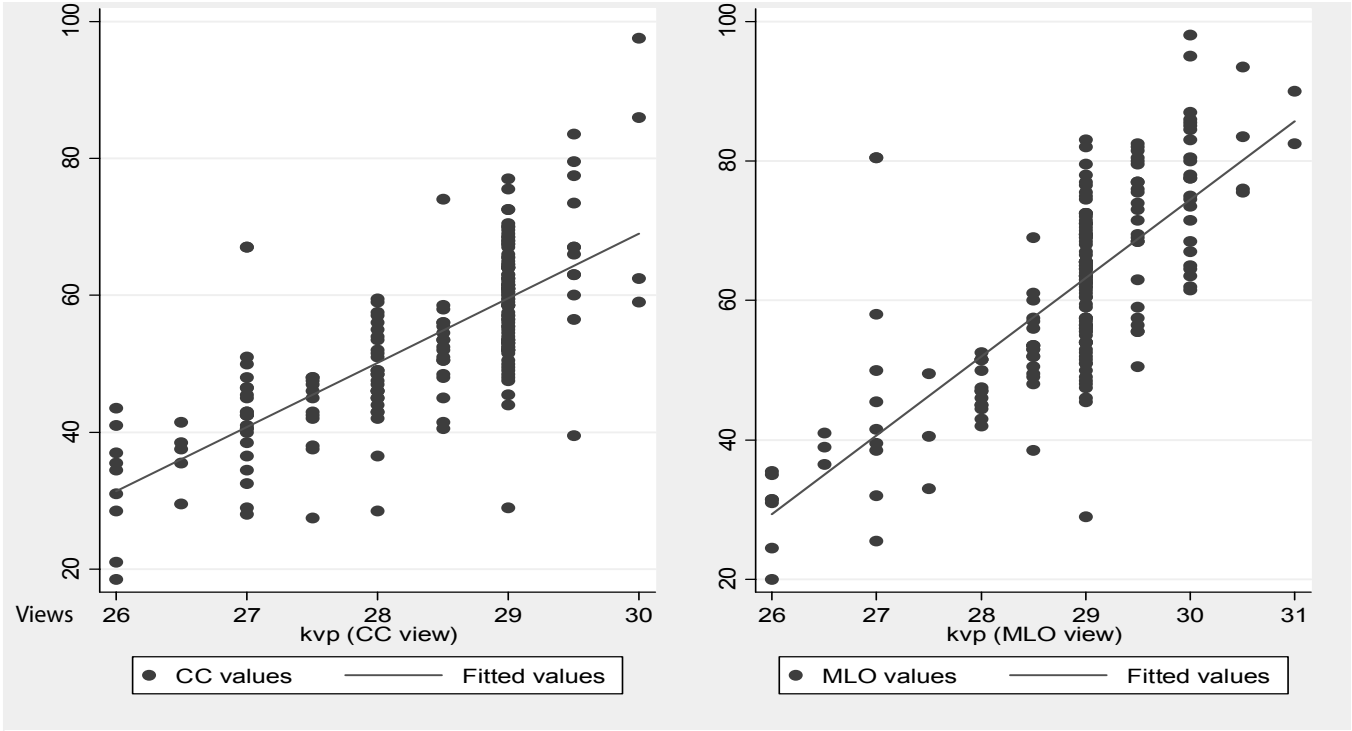
	RCC			LCC			
N	AGD	Mean CBT	Target/Filter	N	AGD	Mean CBT	Target/Filter
150	1.2	58	Rh/Rh	153	1.3	58.1	Rh/Rh
37	0.9	39.4	Mo/Rh	31	1.1	41.2	Mo/Rh
13	1.1	34.5	Mo/Mo	16	1.1	34.1	Mo/Mo

B. MLO view

	RMLO			LMLO			
N	AGD	Mean CBT	Target/Filter	N	AGD	Mean CBT	Target/Filter
172	1.3	65.2	Rh/Rh	173	1.4	65.3	Rh/Rh
19	0.9	39.8	Mo/Rh	18	1.0	38.8	Mo/Rh
9	1.1	34.9	Mo/Mo	9	0.9	33.9	Mo/Mo

AGD= Average Glandular Dose
CBT = Compression Breast Thickness
N =Number of patients
Mo = Molybdenum
Rh = Rhodium

Figure 2: Tube voltage and CBT



There was a strong positive correlation between CBT and kVp values on both CC (Pearson's correlation = 0.74) and MLO (Pearson's correlation = 0.75) (Figure 2).

Discussion

The main objective of this study was to analyze recorded values of the average glandular dose in 2D digital mammography that was found to be 1.2 mGy and 1.3 mGy for CC and MLO views respectively. This result happens to fall within the recommended diagnostic reference levels of between 2 - 3mGy (4,6,11).

Although there are reports of studies done elsewhere, especially in developed countries, there exists scarcity of data on patient dose resulting from digital mammographic examination in Kenya and other developing countries. A previous study in Kenya found the doses to be 2.14 – 2.67 mGy and 2.44 – 3.17 mGy for CC and MLO views respectively using screen-film mammography unit (9). In comparison with the present study doses were found to be lower, this reduction in patient doses could be attributed to the use of FFDM. The results from the current study is similar to those from other studies done elsewhere (6,11-13). Also it was observed that there existed a statistically significant difference between the mean dose for the two views for the entire study population. The difference can be attributed to the high mAs values used in the MLO views and the difference in the compressed breast thickness.

The mean compression breast thickness was found to be 53.1mm in the CC and 61.5mm in the MLO views respectively in the present study. These observations happens to be similar to a previously reported study among British women that found the mean compression breast thickness in CC and MLO views to be 60.5mm and 63mm respectively (7). One possible explanation for the difference in thickness can be attributed to the inclusion of the dense pectoral muscles in the MLO view (14) and hence the increase in patient dose for MLO view. The same study concluded that the difference in compression between the two views resulted in an increase in patient dose in the MLO view. Another study done by Brnić and Hebrang (15) further suggested that the MLO view should be done at an angle of 60 degrees for women with small and pendulous breast. This is because better compression is achieved at this angle as opposed to the 45 degrees and hence a reduction in patient radiation dose.

Whilst the current observation seems to suggest that majority of the women included in this study had thick breasts, it is important to point out that most of the patients who undergo breast mammography at the hospital have existing breast disease. It is known that the breast normally has a tendency of becoming thick and stiff at advanced stage of the disease. This could explain the high kV and mAs values with the most common Rh/Rh target/filter combination used in order to produce a more penetrating beam when imaging thicker and dense breast (14,16). This study found that women who had high CBT values, the machine automatically selected high kV and Rh/Rh

target/filter combinations. This supports the fact that compressed breast thickness as amongst the principal factor that determines the optimum kV and choice of target/filter combination chosen by the AEC.

One of the main limitations of this study was lack of evaluation of the breast density that provides information about breast composition of the asymptomatic Kenyan female population. Breast density correlation would have been helpful to better evaluate the average glandular dose. This is however best conducted during breast screening programs and not during diagnostic mammography examinations. This is among the first studies to present digital mammography dose assessment figures in Kenya. Thus, it provides invaluable information that is useful in the process of setting nationwide standards for quality assurance even as the country prepares to introduce breast screening program. Furthermore, there is also the need of extending the survey to including all mammography facilities across the country.

Conclusion

This study found that the AGD values for patients in the mammography unit in KNH, were within recommended diagnostic reference levels.

Conflict of interest: None to declare.

Funding: The study was self-funded by the principal investigator (NG) and therefore there is no external sources of funding to declare.

Acknowledgments

This work was supported by the Radiology Department of Kenyatta National Hospital. We are grateful to Prof. N.M. Tole for reviewing the manuscript.

References

1. Wild CP, Benard, S. World Cancer Report 2014. WHO, (ISBN: 978-92-832-0429-9). Available at: http://www.who.int/cancer/publications/WRC_2014/en/.
2. Kenya MOH. 2013. Kenya Cancer Statistics & National Strategies, Available at: http://kehpca.org/wp-content/uploads/National-Cancer-Treatment-Guidelines2.
3. Nelson HD, Tyne K, Naik A, Bougatsos C, *et al.* Screening for breast cancer. *Pubmed Central.* 2010;**151**(10). Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2972726/.
4. Vañó E, Miller DL, Martin CJ, Rehani MM, *et al.,* Annals of the ICRP. *ICRP Publication.* 2017; (November), p.151. Available at: http://www.icrp.org/page.asp?id=248.
5. Ghetti, C, Borrini A, Ortenzia O, Rossi R, *et al.* Physical characteristics of GE Senographe Essential and DS digital mammography detectors. *Med Phys.* 2008; **35**(2):456-463. doi:10.1118/1.2828185.
6. Hauge IHR, Bredholt K, Olerud H. New diagnostic reference level for full-field digital mammography units. *Radiation Protection Dosimetry.* 2013; **157**(2): 181–192. Available at: https://academic.oup.com/rpd/article-abstract/157/2/181/1647910?redirectedFrom=fulltext.
7. McCullagh JB, Baldelli P, Phelan N. Clinical dose performance of full field digital mammography in a breast screening programme. *Br J Radiol.* 2011; **84**(1007):1027–33.
8. Riabi HA, Mehnati P, Mesbahi A. Evaluation of mean glandular dose in a full-field digital mammography unit in Tabriz , Iran. *Radiation Protection Dosimetry.* 2010; **142**(2): 222–227.
9. Wambani JS, Korir GK, Shiyanguya Bwonya MN, Korir IK. Assessment of patient doses during mammography practice at Kenyatta National National. *East Afr Med J.* 2011; **88**(11): 368–376.
10. Seife TD, Durga A. Suggested diagnostic reference levels for mammography X- ray examination in Ethiopia. *Indian J Med Sci.* 2016; **68**(1):36–41.
11. Olgar T, Kahn T, Gosch D. Average glandular dose in digital mammography and breast tomosynthesis. *RöFo - Fortschritte auf dem Gebiet der Röntgenstrahlen und der bildgebenden Verfahren.* 2012; **184**(10):911–918.
12. Helvie MA, Chan HP, Adler DD, Boyd PG. 1994. Breast thickness in routine mammograms: effect on image quality and radiation dose. *Amer J Roentgenology.* 1994; **163**(6): 1371–1374.
13. Young KC, Oduko JM. Radiation doses received in the United Kingdom breast screening programme in 2010 to 2012. *Br J Radiol.* 2016; **89**(1058):20150831. doi:10.1259/bjr.20150831.
14. Helvie MA. Digital mammography imaging: Breast tomosynthesis and advanced applications. *Radiologic Clin North Amer.* 2010; **48**(5): 917–929.
15. Brnić Z, Hebrang A. Breast compression and radiation dose in two different mammographic oblique projections: 45 and 60 degrees. *Europ J Radiol.* 2001; **40** (1): 10–15.
16. Dance DR, Thilander AK, Sandborg M, Skinner CL, Castellano IA, *et al.* Influence of anode/filter material and tube potential on contrast, signal-to-noise ratio and average absorbed dose in mammography: a Monte Carlo study. *Br J Radiol.* 2000; **73**(874): 1056–67.

Original paper

Assessment of Guideline Concordant Antibiotic Prescribing for Patients with Community Acquired Pneumonia at the Kenyatta National Hospital Medical Wards

Rintari PN[1], Oyoo GO[1], Amayo EO[1], Achieng L[1], Kagima J[2]

[1]Department of Clinical Medicine and Therapeutics, School of Medicine, University of Nairobi, P.O. Box 19676-00202, Nairobi, Kenya
[2]Kenyatta National Hospital, Nairobi, Kenya

Address for Correspondence: Dr Nkirote Rintari, Department of Clinical Medicine and Therapeutics, School of Medicine, University of Nairobi, P.O. Box 19676-00202, Nairobi, Kenya. Email: pauline.rintari@gmail.com

Abstract

Background: Pneumonia is a major cause of morbidity and mortality globally. Despite the proven benefits of guideline concordant antibiotic prescribing, research has shown that adherence to clinical guideline recommendations is dismal.
Objectives: The study aims to determine utilization of Kenyatta National Hospital (KNH) antibiotic guideline titled 'The KNH guide to empiric antimicrobial therapy 2018' in the management of community acquired pneumonia in the KNH medical wards and the perceived barriers towards the utilization of this guideline.
Design: This was hospital based cross sectional study conducted in six general medical wards at the KNH.
Materials and methods: A check list derived from the KNH guide to empiric antimicrobial therapy 2018 was used to assess guideline concordance based on seven quality indicators: empiric antibiotic, dose and route of administration, switch to oral antibiotics, duration of antibiotics (at least 5 days), collection of microbiological samples before initiating antibiotics, review of antibiotics at 48 hours and once the culture results are out. Online self-administered questionnaires were used to determine attitude and perceived barriers towards utilization of the KNH guideline among the internal medicine registrars and medical officers.
Analysis: Descriptive statistics were applied in the representation of each of the seven quality indicators. These were then compared with the guideline recommendations and adherence to the guideline for each parameter was expressed as a percentage of the total number of patients admitted with community acquired pneumonia. These were then graded into the following categories based on the level of concordance: Good >90%, Intermediate 60-90%, Poor <60%. Questions on the attitude and the perceived barriers towards KNH guideline utilization were answered using a 5 point Likert scale. Perceived barrier statements that were positively formulated were then recorded so that a lower score meant a lower level of the perceived barriers and vice versa. Percentages were then calculated for the total number of doctors that agreed or strongly agreed that the barrier was applicable. An open ended question on the top 3 barriers to the KNH guideline utilization was also included in the questionnaire.
Results: For each of the other quality indicators, adherence to the KNH guideline for patients with community acquired pneumonia was as follows: empiric antibiotic choice 48%, collection of samples for culture prior to antibiotic administration 0%, review of antibiotics at 48hours 26.4%, review of antibiotics with culture results 45.8%, total duration of antibiotics 28.8% and time to switch to oral antibiotics 3.6%. The top three barriers towards guideline utilization among the doctors were: unavailability of drugs (52.7%), inaccessibility of the KNH guideline (45.1%) and lack of or delay of investigations (34.1%).
Conclusion: This study has demonstrated that the level of adherence to the seven quality indicators from the KNH guide is poor with the overall adherence being 35.5%. The recommendation least adhered to was collection of microbiological samples before initiation of empiric antibiotics. The most commonly identified barriers to utilization of the guideline were external and guideline related barriers.

Key words: Community acquired Pneumonia, Adherence, Guideline, Concordance, Antibiotics

Introduction

Pneumonia remains one of the leading causes of hospitalization among adult patients in low and medium income economies despite advancement in the approach to disease prevention and management (1).

The absence of a microbiological aetiology when antibiotics need to be administered, the vast array of available antibiotics and increasing antimicrobial

resistance have led different infectious disease societies to publish antimicrobial guidelines to help in the selection of the appropriate initial antibiotic regimen, taking into account individual patient parameters (2).

Broad-spectrum guideline-concordant empiric therapy increases the possibility of prompt initiation of the appropriate antibiotics and has been shown to be comparable in efficacy to a pathogen-directed approach (3). Adherence to pneumonia treatment guidelines has also been shown to reduce 30 day mortality and length of hospital stay (4). Empiric antimicrobial therapy that is not concordant to pneumonia guidelines has been found to be an independent factor associated with early deaths in patients with severe pneumonia.

Adherence to guidelines for the treatment of pneumonia has been found to be alarmingly low. A study done in Garissa Provincial General Hospital, Kenya, reported 27.7% adherence to the Ministry of Health pneumonia guidelines (5). This is in contrast to studies in other countries that have reported adherence levels of 61- 97% (6).

In line with evidence based practice, the 'Kenyatta National Hospital (KNH) guide to empiric guide to antimicrobial therapy' antibiotic guideline was launched in 2018. Utilization of this guideline in the management of pneumonia is yet to be audited.

Materials and methods

This was hospital based cross sectional study conducted in six general medical wards at the Kenyatta National Hospital (KNH). The study comprised of two population groups: 250 medical records of patients with a diagnosis of community acquired pneumonia and 91 medical doctors (Internal medicine residents, medical officers and medical officer interns at the Kenyatta National Hospital).

All the records of patients aged 18 years and above admitted to the six general medical wards in KNH with a working diagnosis of community acquired pneumonia were included in the study. Community acquired pneumonia was defined as a clinical syndrome with at least one of these "major" clinical features: or temperature > 37.8°C, cough, or sputum production, or at least two of the listed "minor" clinical features: dyspnea, deranged mental status, pleuritic chest pain, consolidation on chest examination, or leukocytosis of >12,000mm with chest X-ray showing features suggestive of pneumonia at admission or within 24 hours (7). The exclusion criteria included patients admitted in the specialized medical wards, those aged 80 years and above with multiple comorbidities (category 2 and above in the KNH antimicrobial guideline) and those who tested positive for pulmonary tuberculosis. Data was extracted from the patients' files using the study pro-forma. Information was obtained concerning their age, sex, length of hospital stay, past or current smoking history, comorbidities and hospitalization in the last 90 days. Concordance to the KNH antimicrobial guideline for community acquired pneumonia was assessed using a checklist derived from the guideline. The check list consisted of 8 statements derived from the antibiotic prescribing algorithm. The domains that were assessed include: documented evidence of pneumonia, collection of microbiological samples before initiation of antibiotics, guideline concordant choice of antibiotics, review of antibiotics after reviewing results of microscopy, culture and sensitivity, time to switch to oral antibiotics and the total duration of antibiotic administration. Documentation of the evidence of pneumonia diagnosis was confirmed by ticking the positive clinical features and a chest radiograph suggestive of pneumonia. Descriptive statistics were used to represent patient demographics, evidence of pneumonia (expressed as at least two positive clinical features and a chest radiograph suggestive of pneumonia), empiric antibiotic regimen chosen, timing of collection of microbiological samples, dose, time to oral antibiotics and the total duration of antibiotic administration as well as the review of antibiotics at 48 hours and upon receiving culture results. These were then compared with the guideline recommendations. Adherence to the guideline for each parameter was expressed as a percentage of the total number of patients admitted with community acquired pneumonia.

In the second study population, the total sample was taken from the internal medicine registrars, medical officers in casualty and medical officer interns. This was done in a ratio of 7:2:1 based on the expected proportions. Enrollment was by consecutive sampling. Informed consent was sought and validated self-administered questionnaires were filled in soft copy had a total of 20 questions. The questions assessing attitude and barriers to guideline utilization were answered using a 5 point Likert scale with the options being strongly agree, agree, neutral, disagree and strongly disagree. One open ended question is also included, where the respondents were expected to list their top 3 barriers to utilizing the KNH guideline 2018 in the management of pneumonia. The questionnaire consists of 2 parts: a general section on the professional characteristics of the doctors which was summarized by descriptive statistics, and a guideline specific part on the attitude towards the guideline and the perceived barriers towards guideline utilization which was answered using a 5 point Likert scale to rate the degree of agreement or vice versa. Perceived barrier statements that were positively formulated were then recorded so that a higher score meant a greater level

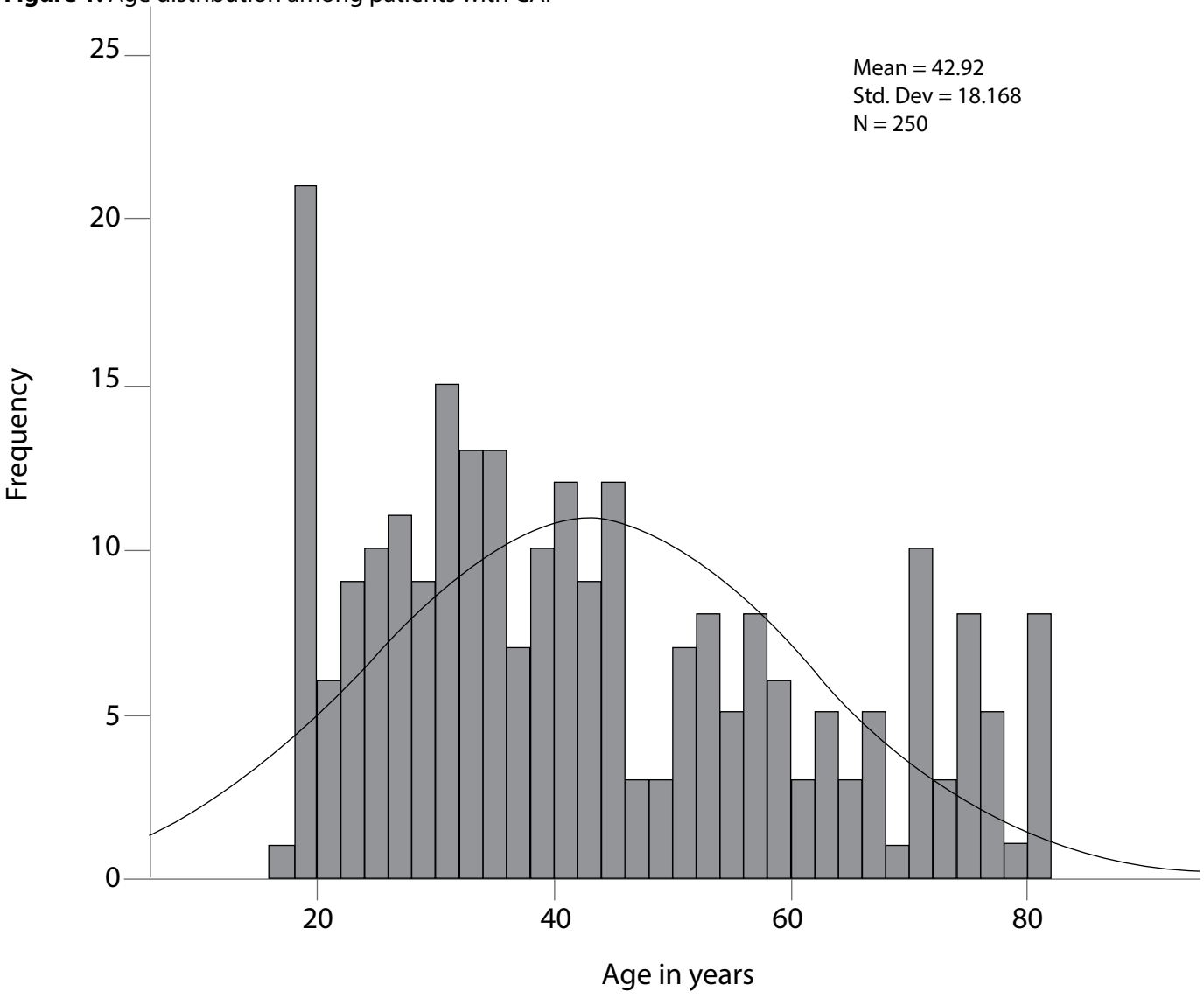
of perceived barriers and the reverse also applied. Percentages were then calculated for the total number of doctors that agreed or strongly agreed that the barrier was applicable.

Results

During the study period, January 2020 to April 2020, a total of 282 patients admitted with pneumonia were screened for eligibility and were considered for the study. Six of these patients did not meet the case definition while 26 patients were excluded from the study due to the following reasons: seven had healthcare associated pneumonia, 2 were treated for aspiration pneumonia, 5 tested positive for pulmonary tuberculosis while 12 patients were over 80 years of age with multiple comorbidities.

The mean age of the study patient population at the time of this study was 42.9 (±18) years. There was a slight male preponderance with male patients being 119 (52.4%). Majority, (78.8%) of the patients, were aged between 18 - 60 years. Extremes of age, represented by patients under 20 years and over 70 years were 21 (8.4%) and 35 (14%) respectively. Notably, patients aged 18 years contributed to the bulk of patients under 20 years at 7.2%.

Figure 1: Age distribution among patients with CAP



Past or current smoking history was reported in 55 (22%) of the study participants, predominantly male. Among the smokers, only 17 (6.8%) had a documented duration of cigarette smoking with the total number of sticks per day, giving an average of 12.29 pack years of smoking. Majority, 177 (70.9%) of the patients had at least one concurrent chronic illness. The two commonly reported comorbidities were heart failure 35(14%) and HIV 30 (12%) (Table 1).

Table 1: Socio-demographic characteristics of patients with CAP (n=250)

Variable	No. (%)
Past or current smoking history	
Yes	57 (22.8)
No	193 (77.2)
Comorbid conditions	
Diabetes	10 (5.9)
HIV	17 (10.1)
Heart failure	20 (11.8)
Asthma	3 (1.8)
COPD	9 (5.3)
Other	56 (33.1)
None	54 (32.0)
Gender	
Male	128 (51.2)
Female	122 (48.8)

The length of hospital stay was defined as the time between admission into the medical ward and documentation of discharge in the patients file. The average length of hospital stays for patients admitted with CAP was 6.5 days. Majority of the patients stayed in hospital for at least 7 days (93.6%) and only 11 patients were discharged within 5 days of hospitalization (Table 2).

Table 2: Length of hospital stay

Length of hospital stay in days	Number of patients (%)
2	1 (0.4)
3	1 (0.4)
4	2 (0.8)
5	6 (2.4)
6	4 (1.6)
≥ 7	236 (94.4)

Assessment of concordance to the KNH guideline was done using 7 quality indicators namely: Empiric antibiotic choice, dose, route and frequency of administration, collection of blood culture samples before starting antibiotics, review of antibiotics in 48 hours after initiation, review of antibiotics after receiving culture results, total duration of antibiotic use and time to switch to oral antibiotics in days. The degree of concordance was then graded into: Good >90%, Intermediate 60 – 90% and Poor <60%. Each of the quality indicators will be discussed below.

Empiric antibiotic concordance

The choice of antibiotic, route, dose and frequency were taken into account to fully assess the full prescribing criteria. The dose, route and frequency of administration was concordant to the KNH guideline in majority of the patients 241 (96.4%). The main reason for lack of adherence in this indicator was the erroneous dosage of ceftriaxone and ceftazidime in nine patients. Two patients received ceftriaxone 1g OD, four received ceftriaxone 2g BD while the remaining three got ceftazidime 2g TDS. There was no documented reason for the dose adjustment in these patients.

The KNH antimicrobial therapy (2018) recommends the use of either ceftriaxone, cefuroxime or amoxicillin-clavulanic acid in combination with a macrolide for the management of hospitalized patients with CAP. The empiric antibiotic choice was guideline concordant in 120 (48%) of the patients. These patients received a combination of amoxicillin- clavulanicacid or ceftriaxone with either clarithromycin or azithromycin.

The most commonly prescribed empiric antibiotics were ceftriaxone (33.2%) and amoxicillin-

clavulanicacid 55.6% either as monotherapy or in combination. Amoxicillin-clavulanic acid and ceftriaxone monotherapy was prescribed in 42.5% and 35.4% respectively, while dual therapy with macrolides was given in 64.4% and 23.3% respectively. Broader spectrum antibiotic use was seen in 9 (3.6%) patients, where ceftazidime, meropenem, and piperacillintazobactam were used. Besides the combination with macrolides, a number of other antimicrobials were used in a small percentage of patients, with metronidazole being the most common in 12 (4.8%) patients (Table 3).

Table 3: Antibiotic prescription patterns

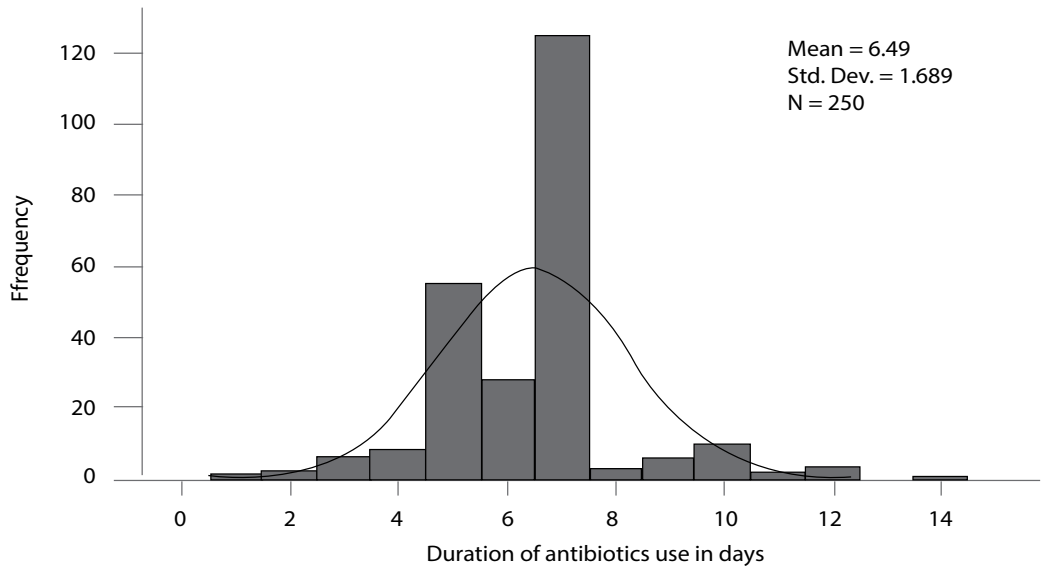
Antibiotics used	No. (%)
Single agent	113 (45.2)
Combination therapy	137 (54.8)
Single agent	
Ceftriaxone	40 (35.4)
Amoxicillin-Clavulanic acid	48 (42.5)
Ceftazidime	16 (14.2)
Cefuroxime	3 (2.7)
Meropenem	2 (1.8)
Piperacillintazobactam	4 (3.6)
Combination therapy	
Augmentin+Clarithromycin	85 (62.0)
Augmentin+Azithromycin	3 (2.2)
Augmentin+ Metronidazole	2 (1.5)
Augmentin+Ciprofloxacin	1 (0.7)
Ceftazidime+Clarithromycin	3 (2.2)
Ceftriaxone+Azithromycin	7 (5.1)
Ceftriaxone + Clarithromycin	25 (18.2)
Ceftriaxone+ Metronidazole	10 (7.3)
Ceftriaxone+Gentamycin	1 (0.7)

Review of antibiotics during the course of admission

Adjustment of antibiotics after 48 hours was done for 66 (26.4%), but only 9 (3.6%) patients were reviewed with the aim of switching to oral antibiotics at 48 hours as recommended by the KNH guideline. Review of antibiotics was done mainly with the aim of adding atypical cover 65 (26.2%), with addition of clarithromycin, azithromycin or metronidazole. Ninety eight (39%) of patients had a complete change of antibiotics, with majority 45 (46%) being changed from ceftriaxone to amoxicillin- clavulanicacid.

During the course of the in-patient stay, 25 (10%) patients received oral antibiotics, with the median time to oral antibiotics being six days. Only 9 (3.6%) of these patients received oral antibiotics within 48 hours of admission, in line with the KNH guideline. The average duration of antibiotic administration was 6.5 (1.7) days, longer than the recommended 5 days of treatment. Guideline concordance for duration of antibiotics was only achieved in 28.8% of the study participants. Two hundred and thirty six (93.6%) of the patients received more than seven days of antibiotics as illustrated in Figure 2 while 118 (47.2%) had comorbidities.

Figure 2: Duration of antibiotics



The KNH antimicrobial guideline recommends the collection of blood culture and sputum for TB analysis (gene Xpert) for all patients admitted with CAP. In the study cohort blood culture and sputum samples for gene Xpert test were collected for 48 (19%) and96 (38.4%) respectively. Eighty one (32.4%) of the admitted patients presented with dry cough. There was no documentation of any attempt to induce sputum therefore no sputum sample collected.

However, none of these microbiological samples were collected before the initiation of antibiotics. These samples were collected from day 2 of admission onwards.

Among the samples collected, over 50% of the results were not available in the patients file by day 7 therefore not reviewed. For the individual samples, blood culture results were reviewed for 21 (43.8%) while sputum gene Xpert results were only reviewed for 45 (46.9%) of the patients by day 7. Overall compliance to this quality indicator was 45.8%.The yield from these cultures was low, with 95.2% blood cultures and 93.3% sputum results being reported as negative for TB.

Assessment of attitude and barriers towards implementation of the KNH guideline

A total of 91 doctors took part in the survey. All the participants gave informed consent and proceeded to fill the online questionnaires. Seventy three internal medicine registrars, 18 medical officers and 1 medical officer intern fulfilled the inclusion criteria and proceeded to fill in the online questionnaires. Majority 59 (64.9%) of the internal medicine registrars who took part in the study were in their second and third year of training while the medical officers worked in the outpatient department. Over half 48 (52.7%) the respondents reported to have worked for more than five years after graduation and only 7 (7.7%) reported to have been in practice for less than 2 years.

Fifty (54.9%) of the respondents reported that they prescribe antibiotics at least once a day while only 1 (1.1%) prescribe antibiotics at least once a week. Table 4 summarizes the socio-demographic characteristics of the doctor.

Table 4: Doctors' socio-demographic characteristics (n=91)

Variable	Frequency (%)
Years worked after school	
1-2	7 (7.7)
3-4	17 (18.7)
4-5	19 (20.9)
> 5	48 (52.7)
Current position held at KNH	
Internal medicine resident	73 (80.2)
Medical officer	17 (18.7)
Medical officer intern	1 (1.1)
Year of training for internal medicine residents	
Year 1	14 (15.4)
Year 2A	20 (22.0)
Year 2B	39 (42.9)
Not applicable	18 (19.8)
Times prescribed antibiotics in work week	Number (%)
More than once a day	50 (54.9)
Once a day	9 (9.9)
3-5 times per week	23 (25.3)
1-2 times per week	8 (8.8)
Less than once a week	1 (1.1)

Attitude toward the KNH guideline

To assess the attitude of the respondents towards the KNH guide to antimicrobial therapy 2018, 4 questions with options ranging from strongly agree to disagree were included in the survey as shown in Table 5. Eighty one (89.1%) of the doctors felt that the guideline is evidence based while 1(1.1%) disagreed with this statement. Seventy four to eighty four percent of the participants find the guideline a useful tool in choosing the initial antibiotic, convenient and easy to find information required. Three (3.3% of the respondents however, felt that the guideline is not useful in improving the quality of treatment given to patients with community acquired pneumonia.

Table 5: Attitude towards the KNH guideline

Question (N=91)	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Guidelines are evidence-based	37 (40.7)	44 (48.4)	9 (9.9)	1 (1.1)	0
Useful and help improve quality of treatment	40 (44.0)	36 (39.6)	11 (12.1)	3 (3.3)	1 (1.1)
Good tool for choosing initial treatment	48 (52.7)	36 (39.6)	7 (7.7)	0	0
Convenient to use and easy to find information	36 (39.6)	38 (41.8)	9 (9.9)	8 (8.8)	0

Barriers towards guideline implementation

The most commonly identified barrier toward implementation of the KNH guideline was lack of medical resources as reported by 56.1% of the respondents. The doctors reported that the guideline is accessible (67.1%), does not reduce their autonomy (61.5%) or limit treatment options (53.9%). Thirty one point nine percent however, felt that the KNH guideline is complicated and difficult to find information (Table 6).

Table 6: Barriers towards guideline implementation

Question	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Hard to implement in daily practice due to lack of medical resources	19 (20.9)	32 (35.2)	13 (14.3)	24 (26.4)	3 (3.3)
Hard to implement in daily practice due to a lack of resources for patients	17 (18.7)	28 (30.8)	14 (15.4)	29 (31.9)	3 (3.3)
There is no time to search for information	3 (3.3)	16 (17.6)	12 (13.2)	45 (49.5)	15 (16.5)
Treatment guidelines are not accessible	4 (4.4)	15 (16.5)	11 (12.1)	42 (46.2)	19 (20.9)
Too complicated and it is difficult to find the information	5 (5.5)	24 (26.4)	20 (22.0)	35 (38.5)	7 (7.7)
Treatment guidelines reduce doctors' autonomy	3 (3.3)	16 (17.6)	16 (17.6)	49 (53.8)	7 (7.7)
Treatment guidelines limit treatment options	2 (2.2)	23 (25.3)	17 (18.7)	43 (47.3)	6 (6.6)
Treatment guidelines limit flexibility and individual approach	1 (1.1)	2 (2.2)	2 (2.2)	40 (44.0)	46 (50.5)
There is no need for treatment guidelines as treatment routines exist	0	1 (1.1)	12 (13.2)	42 (46.2)	36 (39.6)

Barriers towards guideline implementation

The most commonly identified barrier toward implementation of the KNH guideline was lack of medical resources as reported by 56.1% of the respondents. The doctors reported that the guideline is accessible (67.1%), does not reduce their autonomy (61.5%) or limit treatment options (53.9%). Thirty one point nine percent however, felt that the KNH guideline is complicated and difficult to find information (Table 6).

Table 6: Barriers towards guideline implementation

Question	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Hard to implement in daily practice due to lack of medical resources	19 (20.9)	32 (35.2)	13 (14.3)	24 (26.4)	3 (3.3)
Hard to implement in daily practice due to a lack of resources for patients	17 (18.7)	28 (30.8)	14 (15.4)	29 (31.9)	3 (3.3)
There is no time to search for information	3 (3.3)	16 (17.6)	12 (13.2)	45 (49.5)	15 (16.5)
Treatment guidelines are not accessible	4 (4.4)	15 (16.5)	11 (12.1)	42 (46.2)	19 (20.9)
Too complicated and it is difficult to find the information	5 (5.5)	24 (26.4)	20 (22.0)	35 (38.5)	7 (7.7)
Treatment guidelines reduce doctors' autonomy	3 (3.3)	16 (17.6)	16 (17.6)	49 (53.8)	7 (7.7)
Treatment guidelines limit treatment options	2 (2.2)	23 (25.3)	17 (18.7)	43 (47.3)	6 (6.6)
Treatment guidelines limit flexibility and individual approach	1 (1.1)	2 (2.2)	2 (2.2)	40 (44.0)	46 (50.5)
There is no need for treatment guidelines as treatment routines exist	0	1 (1.1)	12 (13.2)	42 (46.2)	36 (39.6)

Responses to the open ended question

The survey utilized an open ended question asking the respondents to list their top three barriers to the utilization of the KNH guideline in treating CAP. The respondents cited unavailability of drugs 48 (52.7%), inaccessibility of the guideline (45.1%) and lack investigations or delay of results 31 (34.1%) as the most common barriers. Time constrains 8 (8.8%) and exposure to antibiotics prior to admission 7 (7.7%) were also listed among the barriers, albeit in a small percentage of respondents as shown in Table 7.

Table 7: Summary of top three barriers (n=91)

Barriers	Frequency (%)
Inaccessibility of guidelines	41 (45.1)
Unavailability of drugs	48 (52.7)
Lack or delay of investigative results	31 (34.1)
Conformity to routine treatment regime	10 (11.0)
Cost to the patients	12 (13.2)
Time constraints	8 (8.8)
Exposure to antibiotics prior to admission	7 (7.7)

Discussion

This audit was looking at the different aspects of adherence to the KNH guide to microbial therapy 2018 in the management of in-patient community acquired pneumonia. The quality indicators studied were: appropriate empiric antibiotic choice taking into account the dose, route, frequency of antibiotic administration, time to change to oral treatment, total duration of antibiotics and the timely collection of microbiological samples. Additionally, the attitude and barriers towards the KNH guideline were investigated. Overall, adherence to the 7 quality indicators was poor at 35.5%, with only the route, dose and frequency of antibiotic administration achieving good adherence (96.3%).

The KNH guideline recommends the use of amoxicillin- clavulanic acid, cefuroxime or ceftriaxone with a macrolide in admitted patients with community acquired pneumonia. The main reason for discordance in the empiric antibiotic choice was the prescription of ceftriaxone or augmentinas monotherapy. Multiple studies are in favor of combination therapy with macrolides for atypical cover as this regimen has been shown to reduce both length of hospital stay and 30day mortality of patients admitted with CAP (8). The use of monotherapy may also contribute to the increasing antimicrobial resistance in Africa, with the resistance of Streptococcus pneumoniae to penicillin reported at 26.7% by 2017(9).

The adherence to the recommended antibiotic in this audit (48%) was higher than the audit done in Garissa County Hospital in 2014 that revealed adherence of 27.7% to the National Pediatric protocols(5). This may be attributed to various factors including: the greater availability of antibiotics in a referral facility like KNH compared to a remote county hospital like Garissa, the adult versus paediatric population, retrospective versus prospective study design as well as the extensive continuous medical education on antibiotic stewardship.

Globally, there is a lot of variation in the level of adherence to empiric antibiotics. Our adherence data are in agreement with other studies that investigated compliance to treatment guidelines in patients admitted with pneumonia and reported adherence rates of between 41% and77%(10). The level of adherence is even lower in African countries with Sudan reporting up to 82% non-adherence to paediatric guidelines (11) while South Africa reported as low as 8%(12).

The study also looked at the full prescribing criteria, and it showed that the route, dose and frequency was appropriate in majority of the patients (96.4%). However, review of intravenous antibiotics at 48 hours with the aim to change to oral treatment was only done for 9 (3.6%)patients. In this audit study, only 10% of the patients received oral antibiotics during their course of hospital admission, with the median time to initiation of oral antibiotics being 6 days. This is despite the fact that the 48-hour review of antimicrobials with the aim to switch to oral treatment is a critical component of antimicrobial stewardship programs to improve judicious antibiotic use and has been shown to reduce both length of hospital stays and health care related costs (13). A study done in Venezuela as part of the CAPO study revealed that switch to oral antibiotics at 48 hours was poorly adhered to at 15%(14). Globally, the recommendation for switch to oral antibiotics is poorly adhered to and some of the reasons that have been cited include: lack of poorly stated recommendations in the clinical practice guidelines, the clinician's perception regarding patient outcome with oral antibiotics and the absence of protocols to monitor switch criteria during daily ward rounds.

The average total duration of antibiotics was 6.5 days (± 1.7) which is above the recommended duration of 5 days. This is likely as a result of the delay in early initiation of oral antibiotics as well as the patients' comorbidities. Studies done globally have shown that patients with CAP are treated with a 10 – 14 day course of antibiotics, inclusive of 6 to

8 days of oral antibiotics (15). Research done has shown that withdrawal of antibiotics after 5 days is not inferior to previously recommended fixed timelines in terms of clinical success (9). Additionally, studies have found that needless prolongation of the duration of antibiotic administration is likely to select for antibiotic resistance (16). With multiple studies favoring short courses of antibiotics for patients with CAP, the thinking is now shifting to "less is more" with regard to in-patient care of pneumonia (17).

In terms of microbiological samples, the KNH guideline recommends that both blood cultures and sputum samples for gene Xpert are taken to rule out tuberculosis due to the high prevalence of mycobacterium tuberculosisin Kenya. Blood cultures were collected for 48 (19.2%) of the patients, while sputum was collected for 96 (38.4%) of the study population. The fact that over one third of the patients with CAP 118 (32.4%) presented with a dry cough contributed to the reduced number of sputum samples collected. There was no documentation of any attempt at sputum induction in the sample population. Studies have shown that sputum induction is safe and increases the yield on sputum specimens by about two fold among HIV infected patients and admitted patients (18).

Despite over half the patients having at least either blood or sputum collected, none of these samples were collected prior to the initiation of empiric antibiotics as recommended by the KNH guideline. A similar finding was reported in a study done between 2013 to 2016 in KNH that found that the median duration of hospital stay before specimen collection for cultures was 4 days (19). The turnaround for culture results was noted to be high with results only (43.8%) and (55.2%) blood culture and sputum gene Xpert respectively available in the file by day 7. This was despite the fact that on average, blood culture results are out in about 48 hours while sputum gene Xpert test takes less than 2 hours. Factors that could explain the delay in getting the results may include a lack of initiative among the staff to follow up results, inertia from many negative blood cultures, large numbers of samples collected in a day in the referral facility leading to a back log of unattended to samples, and logistical factors like lack of reagents to run the tests.

This study also explored the factors affecting the utilization of the KNH guideline, specifically focusing on the attitude and perceived barriers among the doctors who frequently prescribe the antibiotics for patients admitted with CAP in the KNH medical wards. The participants, internal medicine residents (80.2%), medical officers in out-patient (18.7%) and medical officer Interns (1.1%) reported that they routinely prescribe antibiotics for pneumonia patients, with 54.9% prescribing antibiotics at least once a day.

Overall, the attitude towards the KNH guideline is good. This was evidenced by the fact that, 89.1% felt that the KNH guideline is evidence based, a good tool for choosing initial treatment (84%) and it is convenient to use and easy to find information (84%). This is similar to what has been found in other studies, as most studies assessing clinical practice guidelines have reported a good attitude among the users (20). The reasons for the positive attitude include: the portability of the KNH guideline, the fact that it captures the commonly encountered infections not forgetting that each infection is summarized in one page for ease of reference.

In line with the overall good attitude towards the KNH guideline, it was noted that external, rather than individual barriers were cited as the main barriers to utilization of the KNH guideline. The top 3 barriers identified were: unavailability of drugs (52.7%), lack of guideline accessibility (45.1%) and lack or delay of investigations (34.1%). Other factors that featured prominently as hindrances to guideline utilization were: conformity to routine (11%), time constraints (8.8%) and previous use of antibiotics (7.7%). The perceived barriers in our setting were different from those studied in the developed countries as patient and physician factors featured more prominently compared to KNH where external and guideline factors were cited more.

In one study done in the U.S.A, the doctor was likely to disregard the guideline if the patient was severely ill with multi-lobar disease or multiple comorbidities, male, age >65 years. Physician factors that played a key role in non-adherence include: the presence of the primary physician at the emergency department at the time of admission and the physicians level of experience (20). In the study done on adherence to the national paediatric protocols in Garissa County Hospital, it was reported that the presence of comorbidities did not affect adherence to the guidelines while the disease severity led to greater adherence (9).

The choice of empiric antibiotic and time to de-escalation may have been affected by other factors other than non-adherence to the KNH guideline. These include: type of antibiotic available in the hospital pharmacy, the available investigations and their turn-around time as well as comorbidities and exposure to antibiotics prior to hospital admission.

Poor documentation had direct impact on the information abstracted from patients' files and may have affected the quality of data obtained as anything not documented was considered not done.

The Hawthorne effect (observer bias) was likely to have increased the rate of compliance to the empiric antimicrobial guideline and therefore positively skewed the results.

Due to the large number of patients in KNH medical wards who are elderly and have comorbidities, it was not possible to exclude all of them as required under Category 1 of the guideline, we included only patients will one comorbidity and those over 80 years were excluded from the study.

Conclusion

This study has demonstrated that the level of adherence to the 7 quality indicators from the KNH guide is poor with the overall adherence being 35.5%. The recommendation least adhered to was collection of microbiological samples before initiation of empiric antibiotics. The attitude towards the KNH guideline among the doctors was good. The most commonly identified barriers to utilization of the guideline were: unavailability of drugs, inaccessibility of the guideline and lack of or delay of results.

Acknowledgements

I would like to appreciate my supervisors and the entire Department of Clinical Medicine and Therapeutics, University of Nairobi, all the staff at Kenyatta National Hospital general medical wards, my colleagues and all the medical officers who took part in this study, my statistician Mr. Mutai and all the patients who allowed us to use their medical records.

Disclosure

The authors report no conflict of interest in this work.

References

1. Borgatta B, Rello J. How to approach and treat VAP in ICU patients. *BMC Infect Dis.* 2014; **14**(1):4–7.
2. Dambrava PG, Torres A, Vallès X, Mensa J, Marcos MA, Peñarroja G, *et al.* Adherence to guidelines' empirical antibiotic recommendations and community-acquired pneumonia outcome. *Eur Respir J.* 2008; **32**(4):892–901.
3. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, *et al.* Defining community acquired pneumonia severity on presentation to hospital: An international derivation and validation study. *Thorax.* 2003; **58**(5):377–382. doi: 10.1136/thorax.58.5.377. PMID: 12728155; PMCID: PMC1746657.
4. Silveira CD, Ferreira CS, Correa RD. Adherence to guidelines and its impact on outcomes in patients hospitalized with community-acquired pneumonia at a university hospital. *J Bras Pneumol.* 2012; **38**(2):148–157.
5. Mutinda CM, Onyango FE, Maleche-Obimbo E, Kumar R, Wamalwa D, *et al.* Adherence to the National Guidelines for management for children with pneumonia at Grrisa Provisional general. *East Afr Med J.* 2014; **91**(1):13-20. PMID: 26862631.
6. Triantafyllidis C, Kapordelis V, Papaetis GS, Orphanidou D, Apostolidou M, Nikolopoulos I, *et al.* Guidelines adherence for patients with community acquired pneumonia in a Greek Hospital. *Eur Rev Med Pharmacol Sci.* 2012; **16**(1):1–9. PMID: 22338542.
7. Luna HIR, Pankey G. The utility of blood culture in patients with community-acquired pneumonia. *Ochsner J.* 2001; **3**(2):85–93. PMID: 21765724; PMCID: PMC3116772.
8. Caballero J, Rello J. Combination antibiotic therapy for community- acquired pneumonia. *Ann Intensive Care* [Internet]. 2011; **1**(1):48. Available from: http://www.annalsofintensivecare.com/content/1/1/48.
9. Tadesse BT, Ashley EA, Ongarello S, Havumaki J, Wijegoonewardena M, González IJ, *et al.* Antimicrobial resistance in Africa: A systematic review. *BMC Infect Dis.* 2017; **17**(1):1–17.
10. Adler NR, Weber HM, Gunadasa I, Hughes AJ, Friedman ND. Clinical medicine insights: *Circul Resp Pulm Med.* 2014; **8**:17-20. doi: 10.4137/CCRPM.S17978. PMID: 25249765; PMCID: PMC4167314.
11. Salih KEM, Bilal JA, Alfadeel MA, Hamid Y, Eldouch W, Elsammani E, *et al.* Poor adherence to the World Health Organization guidelines of treatment of severe pneumonia in children at Khartoum, Sudan. *BMC Res Notes.* 2014; **7**: 531. https://doi.org/10.1186/1756-0500-7-531.
12. Nyamande K, Lalloo UG. Poor adherence to South African guidelines for the management of community-acquired pneumonia. *South Afr Med J* [Internet]. 2007; **97**(8):601–603. PMID: 17952218.
13. Jenkins C, Pharmacy AC, Health D. Downloaded from https://academic.oup.com/ofid/article-abstract/4/suppl_1/S272/4294658 by guest on 18 April 2020 S272 • *OFID* 2017: **4** (Suppl 1) • *Poster Abstracts Poster Abstracts* • OFID 2017: **4** (Suppl 1) • S273. 2017; **4**(Suppl 1):272–273.
14. Levy G, Perez M, Rodríguez B, Voth H, Perez J, Gnoni M, *et al.* Adherence with national guidelines in hospitalized patients with community-acquired pneumonia: Results from the CAPO study in Venezuela. *Arch Bronconeumol.* 2015; **51**(4):163–168. English, Spanish. doi: 10.1016/j.arbres.2014.03.008. Epub 2014 May 5. PMID: 24809678.
15. Aliberti S, Blasi F, Zanaboni AM, Peyrani P, Tarsia P, Gaito S, *et al.* Duration of antibiotic therapy in hospitalised patients with community-acquired pneumonia Ramirez *Europ Resp J.* 2010; **36** (1): 128-134. DOI: 10.1183/09031936.00130909.
16. Uranga A, España PP, Bilbao A, *et al.* Duration of antibiotic treatment in community-acquired pneumonia: A multicenter randomized clinical trial. *JAMA Intern Med.* 2016; **176**(9):125765. doi:10.1001/jamainternmed. 2016.3633.
17. Pinzone MR, Cacopardo B, Abbo L, Nunnari G. Duration of antimicrobial therapy in community acquired pneumonia: Less is more. *Scientific World J.* 2014; **21**:2014:759138. doi:

10.1155/2014/759138. PMID: 24578660; PMCID: PMC3918712.
18. Khan PY, Yates TA, Osman M, Warren RM, van der Heijden Y, *et al.* Transmission of drug-resistant tuberculosis in HIV-endemic settings. *The Lancet Inf Dis.* 2019; **19**(3): e77e88. https://doi.org/10.1016/S1473-3099(18)30537-1.
19. Wangai FK, Masika MM, Maritim MC, Seaton RA. Methicillin-resistant Staphylococcus aureus (MRSA) in East Africa: red alert or red herring ? *BMC Infect Dis.* 2019; **19**: 596. https://doi.org/10.1186/s12879-019-4245-3.
20. Lugtenberg M, Burgers JS, Besters CF, Han D, Westert GP. Perceived barriers to guideline adherence: A survey among general practitioners. *BMC Fam Pract* [Internet]. 2011; **12**(1):98. Available from: http://www.biomedcentral.com/1471-2296/12/98.

Bleeding in the Gastrointestinal Tract from a not so Typical Site in Typhoid Fever: Case Report

Karanja R[1], Correia M[1], Juma P[2,3], Onyango S[3], Khan M[1]

[1]The Nairobi Hospital, Kenya
[2]Department of Clinical Medicine and Therapeutics, School of Medicine, University of Nairobi, Kenya
[3]Kenyatta National Hospital, Nairobi, Kenya

Address for Correspondence: Dr Becky Karanja, The Nairobi Hospital, Kenya. Email: beckykaranja@yahoo.com

Abstract

Background: Typhoid fever is an acute systemic febrile infection caused by *salmonella typhi.* intestinal perforation and bleeding are the two major complications of small intestinal typhoid infection.
Case presentation: We report a case of a 32 year old patient with typhoid fever who developed massive haematochezia during the hospital stay and was found to have terminal ileal ulcers on colonoscopy. At laparotomy he was found to have a perforated, bleeding duodenal ulcer which was managed as per standard procedure. He died soon after from shock and Adult Respiratory Distress Syndrome (ARDS).
Conclusion: Typhoid is a fatal disease that results in mortality and thus early detection and treatment is important.

Key words: Typhoid, Salmonella typhi, Bleeding, Ulcer, Perforation

Introduction

Typhoid fever is a common vaccine preventable infection in the tropics. It remains a major public health problem in less developed countries, especially in the setting of urban slum dwellings (1). Left unchecked, enteric fever can lead to life threatening complications including intestinal perforations and intestinal bleeding.

Case report

We present a case of a 32 year old African man who presented with constipation, bloating and abdominal pain for 2 weeks. He also reported blood in stool for 3 days. This was associated with decreased appetite, general body malaise and easy fatigability. He had initially self medicated on ciprofloxacin for 2 days. The symptoms persisted and he went to a peripheral facility and was treated for dyspepsia. He was put on an antacid and omeprazole. However, the symptoms persisted and he self medicated on a laxative. He later on passed blood stained stools. His diet consisted of starch and meat with no fibre. He did not have symptoms of diarrhoea and vomiting. There was no family history of a malignancy. He did not have a history of chronic nonsteroidal anti-inflammatory drug use. He had no previous history of the same symptoms.

On examination he was found to be in good general condition, some dehydration with a BP of 139/97 mmHg, heart rate of 114 beats per minute, temperature of 37.2^{0}C, SPO2 of 94% and a respiratory rate of 18 breathes per minute. He had a Body Mass Index (BMI) of 24.7. On his abdominal exam there was no distension, organomegally or tenderness but there were increased bowel sounds. On his respiratory exam he was not in respiratory distress and had bilateral vesicular breath sounds. His pulse was regular with normal heart sounds. His neurological examination was normal. On the rectal examination there was normal external anal anatomy, no obvious fissures, anal tags, external or internal haemorrhoids. There was soft stool in the rectum.

He was started on intravenous fluids and admitted to the ward for investigations. He was also started on medication as shown below. Laboratory investigations were requested and the results are shown on Table 1. The radiological investigations carried out included a plain abdominal X ray and an abdominal ultrasound. The patient was booked for an oesophagoduodenoscopy (OGD).

Table 1: Shows laboratory investigations

Investigation	Results	Normal Reference
FHG		
WBC	10.26*10 ^{9}/L	4-11
Neutrophils	68.3%	40-75
Haemoglobin	9.4 g/dl	13-18
MCV	87.7 fl	77-99
Platelets	254,000mm^{3}	150-450
UEC		
Sodium	144 mmol/l	135-145
Potassium	4 mmol/l	3.5-5.1
Chloride	105 mmol/l	98-118
Urea	6.2 mmol/l	2.5-6.4
Creatinine	227.5 ummol/l	27-119
LFTs		
Total bilirubin	17.7 umol/l	3.4-20.5
Direct bilirubin	11.8 umol/l	0- 8.6
Alanine transaminase	546 iu/l	0-34
Aspartate transaminase	1011 iu/l	5-34
Gamma glutamylT	70 iu/l	9-36
Alkaline phosphatase	101 iu/l	42-98
Total protein	23 g/dl	64-83
Albumin	12 g/dl	34-54
Globulin	11 g/dl	12-39
Calcium	1.8 mmol/l	2.25-2.62
Phosphorus	1.01 mmol/l	1.12-1.45
Magnesium	0.84 mmol/l	0.85-1.10
INR	1.25	0.8-1.1
Stool analysis, ova and cyst	No ova and cyst	No ova and cyst
Urinalysis	Normal	Normal
H. Pylori	Positive	Negative
Malaria antigen	Negative	Negative

Abdominal ultrasound- Hepatic steatosis
Renal and pelvic ultrasound- normal

Treatment: The patient was put on esomeprazole 40mg IV BD, paracetamol 1g IV tds, lactulose 10 mls po bd, hyoscine butylbromide20 mg IV tds and ondansetron 4mg iv bd.

Subsequently on the second day of admission he developed fever with the highest temperature at 39.2^{0}C. He also had vomiting, abdominal bloating and sharp crampy abdominal pain worse with meals. He had another episode of fresh per rectal bleeding with diarrhoea. Intravenous hyoscine butylbromide and ondansetron were added to his treatment. He was reviewed by the gastroenterologist and started on empiric ceftriaxone and metronidazole. Blood cultures and a CT scan of the abdomen were requested. He developed massive frank per rectal bleeding with estimated blood loss of 3700mls and subsequently developed hypotension with a Blood Pressure (BP) of 76/45 mmHg and tachycardia with a pulse rate of 116 beats/minute. Blood group and cross matching for packed cells was ordered. Tranexamic acid 1g iv 8 hourly was given. The patient was transferred to the intensive care unit for close monitoring.

Oesophagoduodenoscopy done was normal. Colonoscopy revealed fresh blood in the ascending, transverse and descending colon. The findings for the colonoscopy are illustrated in Figures 1 and 2.

Figure 1: Endoscopy findings of blood and multiple ulcers in the terminal ileum

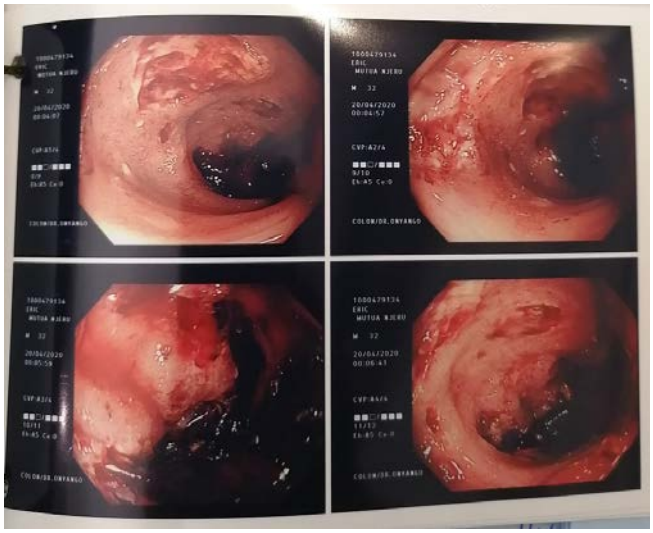
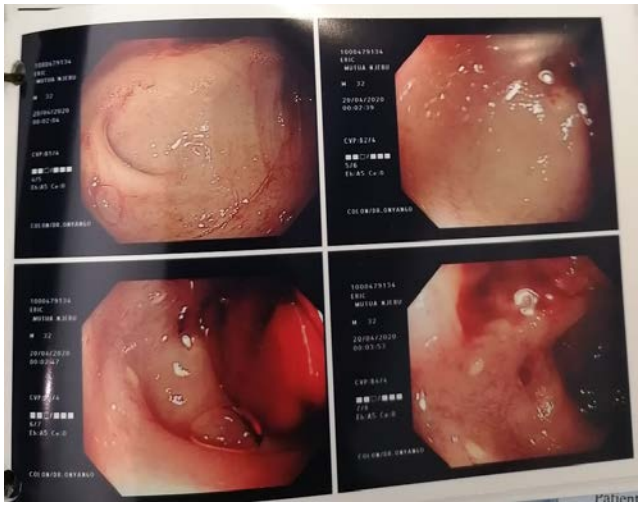


Figure 2: Colonoscopy findings of blood throughout the colon



Multiple large oozing ulcers were seen in the terminal ileum. It was not possible to clip endoscopically. An urgent surgical review was requested. The patient was transfused 3 units of packed cells and IV fluids were given. A central venous catheter was inserted for inotropic support. Surgical review was done and the patient was started on tranexamic acid 1g iv 8 hourly and vitamin K 10mg stat. His haemoglobin level was 6.2 g/dl.

The patient developed haemorrhagic shock and became hypotensive with a BP of 54/24 mmHg on 10 mcg/min of norepinephrine. He was confused and drowsy. His blood gas analysis revealed metabolic acidosis and he was subsequently intubated. He was on esomeprazole 8mg /Kg/hr, norepinephrine 20 mcg/kg/min and epinephrine 5 mcg/kg/min.

Intraoperatively, the small bowel was distended with food from the duodenojejunal flexure terminal ileum. Pyloroduodenotomy was done. The stomach was empty. There was blood in the second and third part of the duodenum with gastric ulcer

Progress: Post operatively, he had a low Glasgow Coma Scale (GCS) of 3 Tube/15 with hypotension and lactate acidemia. Patient was transfused 7 units of packed cells and 6 units of fresh frozen plasma. He was started on Continuous Renal Replacement Therapy (CRRT). Subsequently he improved in terms of the GCS to 10 Tube/15. Blood cultures taken grew Salmonella typhi. He had previously been started on ceftriaxone of which it was sensitive. Unfortunately, the patient developed Acute Respiratory Distress Syndrome (ARDS). On the 5th day post admission, the patient changed condition, he was resuscitated using the Advanced Cardiac Life Support Protocol (ACLS) protocol without success and was pronounced dead.

Diagnosis: The patient was diagnosed to have gastrointestinal perforations secondary to *Salmonella typhi* and duodenal ulcer that resulted in massive gastrointestinal bleeding. He was also managed for ARDS with respiratory failure. His laboratory tests results showed that he had developed acute kidney injury and acute liver injury.

Discussion

The causative agent of typhoid, *Salmonella typhi,* is an enteroinvasive gram negative bacteria. It is ingested orally and proceeds to invade the small bowel mucosa. From here it spreads through the lymphatics and bloodstream to reside in reticuloendothelial cells. It emerges from reticuloendothelial cells in recurrent waves of bacteraemia and infects other organs. In the gastrointestinal tract the terminal ileum is the primary focus of infection due to the presence of abundant lymphoid follicles (Peyer's patches). There is hyperplasia of the follicles which subsequently ulcerate.

Intestinal haemorrhage and perforation are the most dreaded complications of typhoid. These complications were more common in the pre-antibiotic era but they do still occur. Mortality is variable from 5 to 80% depending on the resources available at local facilities as well as patient factors such as late presentation with severe peritoneal contamination, massivehaemorrhage or sepsis (2).

Gastrointestinal bleeding is the most common gastrointestinal complication. The incidence of lower GIT bleeds is 12.5% and that of perforations is 3.3% in typhoid patients. Intestinal haemorrhage usually occurs in the third week from symptom onset when ulcers erode adjacent blood vessels. The most frequent location of bleeds is in the terminal ileum. In a series by Lee *et al* (3) involving seven patients with typhoid bleeds the terminal ileum was involved in all patients 100%. The ileocecal valve in 57%, the ascending colon in 43% and the transverse colon in 20%. Our patient had ulcers in the terminal ileum.

Most typhoid ulcer bleeds are not severe and can be managed conservatively. But occasionally bleeds can be massive requiring interventions such as endoscopic haemostasis or coil embolization of the bleeding vessel or surgical intervention. Our patient had massive bleeding which was contributed to by his concurrent peptic ulcer disease. He was not amenable to endoscopic haemostasis and required surgical intervention.

Our patient tested positive for *H. pylori* antigen in stool and coincidentally had a duodenal ulcer. *H. pylori* affects gastric acid secretion causing hypochlorhydria. The gastric acid barrier is an important defence against infectious agents and it is therefore presumed that *H. pylori* infection would lead to increased gastrointestinal infections. In addition several serological studies have found patients with typhoid

to have a higher incidence of *seropositivity* for *H. pylori* than those without (4). However an association between *H. pylori* and increased risk of typhoid infection has yet to be demonstrated (5). It is thought that similar environmental exposures such as poor hygiene may predispose to both infections occurring concurrently in these patients.

The most dreaded GIT complication is the typhoid perforation and those affected have increased mortality. The incidence of perforation in those with typhoid is 0.8 to 39% (2). This occurrence is higher in sub-Saharan Africa compared to Asian countries and is thought to be due to presence of more virulent strains. In patients with perforation the peritoneal response is delayed. The omentum also does not migrate to cover the defect.

Diagnosis: Laboratory diagnosis is challenging because none of the existing tests including culture, serology and molecular tests has achieved the optimum combination of sensitivity and specificity. For this reason, it is reasonable to treat suspected cases with empiric antibiotic therapy. Enteric fever should be suspected in any person with fever lasting more than three days with an exposure to an endemic area in the preceding 6 weeks.

Our patient had suboptimal antibiotic therapy prior to admission. His blood culture grew *Salmonella typhi* sensitive to ceftriaxone which was then initiated after admission.

Sensitivity of blood cultures is 40 to 80% with an average of 61% (6). Low level bacteraemia and prior antibiotic use limit the sensitivity of blood cultures. Stool cultures are positive in 50% of children and 30% of adults. Bone marrow culture has the highest sensitivity of 80-95%. With 1ml of bone marrow being equivalent to culturing 15mls of blood (7). Culturing of bone marrow is however not routine or practical for most patients except perhaps as part of evaluation for prolonged fever of unknown origin. *Salmonella* can also be cultured from urine, duodenal aspirates and skin biopsy of rose spots (8).

Serologic tests: The widal test is based on detection of agglutinating antibodies to the O and H antigens of *Salmonella typhi.* It remains one of the most widely used test in diagnosis of typhoid. It has serious limitations with regards to sensitivity, specificity and reliability (9). Other rapid serologic tests include IDL tubex and Typhidot assays (10). Data on the *Salmonella* stool antigen test is scanty. A Cochrane analysis on the effectives of these rapid diagnostic tests showed these tests were not sufficiently accurate to replace blood cultures (11).

Treatment of enteric fever: Recently the treatment has become a challenge due to Multidrug Resistance (MDR) to ampicillin, trimethoprim-sulfamethoxazole, and fluoroquinolones. These strains have been responsible for some outbreaks in China, South East Asia and Africa (12). The predominant MDR *S. Typhi* strain in Asia and Africa is H58 (13). There has been documentation of extensively drug-resistant typhoid which shows strains resistant to fluoroquinolones and third generation cephalosporins in addition to antibiotics previously mentioned (14). Currently most *S. Typhi* and *S. Paratyphi* remain susceptible to azithromycin and ceftriaxone as was the case with our patient (15).

The selection of antibiotic medication depends on disease severity, usually one antibacterial drug is required but local resistance patterns, route of administration and duration of therapy also must be considered (16). The current options include fluoroquinolones, third-generation cephalosporins and azithromycin with carbapenems reserved for extensive drug resistant strains (12). Empiric therapy would depend on the local pattern of sensitivity. The trend of susceptibility in Nairobi from isolates of *S. Typhi* has changed over the years from 73.3% of cultures being fully sensitive in 1993 to having 18.4% of isolates being resistant to nalidixic acid and could serve as a warning for fluoroquinolone resistance as has happened in Southeast Asia and parts of West Africa (17). The choice of antibiotic in uncomplicated enteric fever may depend on the susceptibility to fluoroquinolones and ciprofloxacin may be considered first choice. Severe and complicated disease (described when patients have systemic toxicity, prolonged fever, altered level of consciousness or organ system dysfunction necessitating hospitalization) ceftriaxone has been used (12). Intravenous fluoroquinolones are an appropriate alternative and aztreonam when patients are allergic to cephalosporins (18).

In severe systemic disease with delirium, stupor, obtundation, coma or shock adjunctive corticosteroid like dexamethasone for 48 hours should be considered which has been seen to have clinical benefits in observational studies (19,20). In patients who may have ileal perforation, surgical intervention may be required and would involve segmental resection of the involved intestine with use of broad spectrum antibiotics to cover for enteral organisms as per local antibiogram (21).

Patients once treated in uncomplicated cases results in clinical improvement within five days and resolution of fever within a week. Relapse of infection usually occurs within two to three weeks and should be treated with an antibiotics guided by susceptibility pattern (22). If excretion of organisms is seen in stool for more than 12 months after an acute infection confers chronic carriage and this poses a challenge for

public health for food handlers in case of outbreaks in non-endemic areas. Treatment considered would be to use ciprofloxacin twice daily for a month to achieve eradication (23).

Prevention: Transmission of typhoid is faeco-oral. Prevention of infection can be achieved by food and water safety and administration of vaccines. In endemic areas WHO recommends that typhoid vaccination should be carried out as part of national control measures (24).

In non-endemic areas vaccination is only indicated for travellers to endemic areas or intimate contacts of a chronic carriers or occupational exposures for example laboratory workers who handle typhoid cultures (25). Natural infection does not confer lifelong immunity. In fact one study suggested that early treatment blunted the development of humoral immunity to the capsular antigens (26).

Conclusion

Typhoid is still prevalent in low and middle income countries and can lead to mortality in patients who present with complications. Complications tend to occur late in the third week and more effort is needed to develop diagnostic tools which can quickly and accurately pick disease in the early stages. There is also need to consider widening coverage of the populations at risk by regular vaccination against typhoid.

References

1. Breiman RF, Cosmas L, Njuguna H, *et al.* Population-based incidence of typhoid fever in an urban informal settlement and a rural area in Kenya: implications for typhoid vaccine use in Africa. *PloS One.* 2012; **7**(1):e29119.
2. Contini S. Typhoid intestinal perforation in developing countries: Still unavoidable deaths? *World J Gastroenterol.* 2017; **23**(11):1925.
3. Lee JH, Kim JJ, Jung JH, *et al.* Colonoscopic manifestations of typhoid fever with lower gastrointestinal bleeding. *Digest Liver Dis.* 2004; **36**(2):141-146.
4. Vollaard AM, Verspaget HW, Ali S, *et al.* Helicobacter pylori infection and typhoid fever in Jakarta, Indonesia. *Epidem Inf.* 2006; **134**(1):163-170.
5. Salama RI, Emara MH, Mostafa HM, *et al.* Helicobacter pylori infection and risk of salmonella infection. *Medicine.* 2019; **98**(6): e14335.
6. Gilman R, Terminel M, Levine M, *et al.* Relative efficacy of blood, urine, rectal swab, bone-marrow, and rose-spot cultures for recovery of Salmonella typhi in typhoid fever. *The Lancet.* 1975; **305**(7918):1211-13.
7. Wain J, Bay PV, Vinh HA, *et al.* Quantitation of bacteria in bone marrow from patients with typhoid fever: relationship between counts and clinical features. *J Clin Microbiol.* 2001; **39**(4):1571-16.
8. Jason AR, Jason HB, Edward RT. Typhoid fever, paratyphoid fever and typhoidal fevers. In: Mandell, Douglas and Bennett's. Ninth. *Elsevier*; 2020. p. 1365–94.
9. Baker S, Favorov M, Dougan G. Searching for the elusive typhoid diagnostic. *BMC Inf Dis.* 2010; **10**(1):1-8.
10. Keddy KH, Sooka A, Letsoalo ME, *et al.* Sensitivity and specificity of typhoid fever rapid antibody tests for laboratory diagnosis at two sub-Saharan African sites. *Bull World Health Organ.* 2011; **89**:640-647.
11. Wijedoru L, Mallett S, Parry CM. Rapid diagnostic tests for typhoid and paratyphoid (enteric) fever. *Cochrane Database Syst Reviews.* 2017; **5**(5):CD008892.
12. Kariuki S, Gordon MA, Feasey N, Parry CM. Antimicrobial resistance and management of invasive Salmonella disease. *Vaccine.* 2015; **33**:C21-29.
13. Wong VK, Baker S, Pickard DJ, *et al.* Phylogeographical analysis of the dominant multidrug-resistant H58 clade of Salmonella Typhi identifies inter-and intracontinental transmission events. *Nature Genetics.* 2015; **47**(6):632-639.
14. Bayramoğlu G, Özgümüş OB, Kolayli F, *et al.* Molecular epidemiology, antimicrobial resistance and characterization of expanded spectrum beta-lactamases of Salmonella enterica serotype Paratyphi B clinical isolates. *Microbiol Bull.* 2014; **48**(2): 191-200.
15. Parry CM, Thieu NT, Dolecek C, *et al.* Clinically and microbiologically derived azithromycin susceptibility breakpoints for Salmonella enterica serovars Typhi and Paratyphi A. *Antimicrobial Agents Chemotherapy.* 2015; **59**(5):2756-64.
16. Limson BM. Short course quinolone therapy of typhoid fever in developing countries. *Drugs.* 1995; **49**(2):136-138.
17. Kariuki S, Revathi G, Kiiru J, *et al.* Typhoid in Kenya is associated with a dominant multidrug-resistant Salmonella enterica serovar Typhi haplotype that is also widespread in Southeast Asia. *J Clin Microbiol.* 2010; **48**(6):2171-76.
18. Gotuzzo E, Echevarria J, Carrillo C, *et al.* Randomized comparison of aztreonam and chloramphenicol in treatment of typhoid fever. *Antimicrobial Agents Chemotherapy.* 1994; **38**(3):558-562.
19. Punjabi NH, Hoffman SL, Edman DC, *et al.* Treatment of severe typhoid fever in children with high dose dexamethasone. *Pediat Inf Dis J.* 1988; **7**(8):598-599.

20. Chisti MJ, Bardhan PK, Huq S, *et al.* High-dose intravenous dexamethasone in the management of diarrheal patients with enteric fever and encephalopathy. *Southeast Asian J Trop Med Publ Health*. 2009; **40**(5):1065.
21. Nasir AA, Abdur-Rahman LO, Adeniran JO. Predictor of mortality in children with typhoid intestinal perforation in a tertiary hospital in Nigeria. *Pediat Surg intern*. 2011; **27**(12):1317-21.
22. Dolecek C, Phi La TT, Rang NN, *et al.* A multi-center randomised controlled trial of gatifloxacin versus azithromycin for the treatment of uncomplicated typhoid fever in children and adults in Vietnam. *Plos One*. 2008; **3**(5):e2188.
23. Trujillo IZ, Quiroz C, Gutierrez MA, *et al.* Fluoroquinolones in the treatment of typhoid fever and the carrier state. *Europ J Clin Microbiol Inf Dis*. 1991; **10**(4):334-341.
24. Masuet-Aumatell C, Atouguia J. Typhoid fever infection–antibiotic resistance and vaccination strategies: a narrative review. *Travel Med Inf Dis*. 2021; **40**:101946.
25. Jackson BR, Iqbal S, Mahon B. Updated recommendations for the use of typhoid vaccine—Advisory Committee on Immunization Practices, United States, 2015. *Morbidity Mortality Weekly Report*. 2015; **64**(11):305.
26. House D, Ho VA, Diep TS, Chinh NT, *et al.* Antibodies to the Vi capsule of Salmonella Typhi in the serum of typhoid patients and healthy control subjects from a typhoid endemic region. *J Inf Develop Countries*. 2008; **2**(04):308-312.

Taking Another Look at Back Pain: Case Series of Spondyloarthropathies and Literature Review

Genga EK, Gichuru W

Department of Clinical Medicine and Therapeutics, School of Medicine, College of Health Sciences, University of Nairobi, P. O. Box 19676-00202, Nairobi, Kenya

Address for Correspondence: Dr Eugene K Genga. Email:eugenekalman@gmail.com

Abstract

Spondylarthritis (SpA) describes a family of sero-negative arthritis that include ankylosing spondylitis, non-radiographic axial spondylarthritis, and arthritis associated with psoriasis with inflammatory bowel diseases, amongst other conditions. They are characterized by inflammatory back pain in young patients. Studies from Sub-Saharan Africa (SSA) have failed to show the strong association with the human leukocyte antigen (HLA)-B27 as seen in Caucasian populations. Cases are often marked with a delay in diagnosis of up to 8–10 years due to physicians' low index of suspicion, especially in Africa. The mainstay of treatment is biologic DMARDs. We highlight three cases and discuss challenges in the diagnosis and management of spondyloarthropathies. We hope that this may raise awareness of the disease associated with increased morbidity and mortality seen in patients with SpA. They have increased rates of osteoporosis, vertebral fractures, and death from cardiovascular causes.

Key words: Spondyloarthritis (SpA), Ankylosing spondylitis, Kenya, Africa

Introduction

Spondyloarthritis (SpA) is a family of disorders that mainly affects the spine, causing chronic back pain in younger patients, primarily under 45 years (1-3). They are divided into two based on symptoms: axial SpA, in which symptoms are localized mainly in the spine, or peripheral SpA, in which symptoms primarily affect peripheral joints. These groups are distinguished from other arthritis by inflammation of axial joints (in particular sacroiliac). They present as inflammatory back pain (lumbar or buttock/hip pain) lasting longer than three months associated with morning stiffness lasting longer than 30 minutes, which improves with activity in a young person (1-3). Other symptoms include enthesitis (inflammation at the site of insertion of ligament/tendon on the bone), dactylitis (sausage digits), and asymmetrical oligoarthritis, especially at the lower extremities. They are divided into three subtypes. These are Ankylosing Spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), arthritis associated with uveitis, psoriasis, inflammatory bowel diseases, and reactive arthritis. Diagnosis is a challenge due to the disease's rarity and chronic non-specific back pain symptoms; clinicians tend to miss it due to the low index of suspicion (1-3). A common genetic feature across the SpA spectrum is associated with Human Leukocyte Antigen (HLA)-B27 in European populations. This paper looks at a case series of selected SpA cases seen in Kenya. We hope to raise awareness about this rare disease that is often under-diagnosed but has a high morbidity impact as it primarily affects young people.

Case 1

A 20-year-old female referral from Kitui Hospital complained of multiple joint pains for two weeks and back pain for one week. This was associated with right hip pain, which forced her to use elbow crutches for mobility. She was diagnosed with juvenile inflammatory arthritis at 13 years based on a two-year history of generalized joint pain and stiffness. She was put on oral methotrexate 10mg weekly, sulfasalazine 1g twice a day, prednisone 10mg once a day, folic acid 5mg once a day, omeprazole 20mg once a day, ibuprofen, and calcium supplements. However, she was lost to follow-upand sought care of a private physician who stopped her regular medication and started her on oral dexamethasone 0.5mg once a day, calcium supplements, Ginseng and metformin 500mg once a day, which she was started on following episodes of persistent hyperglycemia. On further evaluation during her current admission, she described the back

pain and stiffness as worse in the morning and got better with activities. Her symptoms were associated with heel pain, painful swollen small joints of her hands, and tender bilateral knee and ankle joints. She reported long-standing (approximately two-years) episodes of on and off non-bloody diarrhoea with associated non-severe abdominal pain on systemic inquiry. She reported a subjective decrease in visual acuity over the past two months with a blurring of vision. She had no skin rash or mucosal lesions. An examination of her musculoskeletal system was positive for marked tenderness over the wrists, elbows, ankles, knees, and hips bilaterally, with movement impaired by pain. There was no joint swelling, erythema or warmth noted. The neck was soft, with a standard range of motion. Her spinal curvature was expected, but tenderness was noted on palpation over the lumbar spine with a positive Schober's test. The examination of the precordium was normal. Her inflammatory markers ESR and CRP were reported as within the reference range. Rheumatoid factor, anti-ccp, ANA, anti-DsDNA, serologies for hepatitis B, C, and HIV were negative. Uric acid was within the standard limit. CT spine was reported to have grade 1 sacroiliitis. An earlier MRI of the pelvis done two years earlier had reported the bilateral sacroiliac and hip joint as normal. The diagnosis of possible SpA was made based on the chronic back pain in a patient younger than 45 years, heel pain (enthesitis), painful swollen fingers (dactylitis), right hip pain with possible uveitis (noted worsening vision), and possible Inflammatory Bowel Disease (IBD). The decision was to start on golimumab due to the possibility of radiographic SpA, IBD, possible uveitis symptoms, and a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) the score of 6.2. She was discharged to have OGD, colonoscopy, and review by the ophthalmology teams as an outpatient. The subsequent reviews had BASDAI scores of 5.3, 3.2 in the second and third months. She returned at the fifth month with back pain and a BASDAI score of 6 and was later lost to follow up as she was not able to afford the medication. During the treatment, her symptoms improved but got worse when she wasn't able to afford the medication.

Case 2

A 25-year-old active male athlete referred from physiotherapy with a 5-year history of back pain that was worse in the morning and got better with activity. This was associated with right buttock pain and intermittent painful swelling of the fingers and toes. He reported an intermittent history of bilateral heel pain that alternates worse, especially in the morning when he wakes up. He had normal bowel habits, no red-eye, or recent infections. He, however, noted having an allergic rash over the skin at the back, elbows for which he was on follow up by a dermatologist. He was frustrated at the lack of treatment response despite visiting various dermatologists. On examination he was noted to have swollen sausage digits of the digits 2 and 4 with nail atrophy on the right hand, normal chest expansion, tenderness on rotation at the right hip with reduced spinal motility, a negative tragus to the wall, and Schober's tests. A scaly rash over the back and elbow was observed. The investigations done revealed elevated inflammatory markers ESR, CRP. Other blood tests done were negative for HIV, ANA, and rheumatoid factor. MRI of the sacroiliac joint was reported as normal. A second dermatology review confirmed psoriasis. A decision to start on methotrexate with NSAID was made as he had a BASDAI score of 2. He was dissatisfied with the response after six months of treatment. His back pain and morning stiffness had worsened; the BASDAI score at four months was at 4, at six months, had reached 7. At this point, the decision to start on anti-TNF was made. He was put on infliximab due to the ease of administration. At month 4, his BASDAI score had reduced to 4, and had noted an improvement in his symptoms. At six months, he had a BASDAI score of 2. His symptoms improved from psoriasis to back pain and quality of life.

Case 3

A 28-year-old female lawyer had been referred with a long-term history of back pain. Further evaluation revealed the problem begun at the age of 16 years, and she had attributed it to a sports injury in school. The back pain was worse in the morning, and after prolonged sitting with morning stiffness lasting longer than 30minutes and had affected her quality of life, she was now forced to wake up early to adjust to the stiffness and her profession that requires prolonged standing. She also gave a history of heel pain, which she attributed to the high heels she wore to work. She had no history of suggestive uveitis, dactylitis, or psoriasis. There was an associated history of poor sleep, dyspepsia, and myalgia. She had seen a doctor who had started her on treatment for fibromyalgia due to the negative rheumatoid factor, anti-ccp, ANA, and ENA. The examination had normal chest expansion with negative tragus to wall and Schober's test. She had no improvement in the treatment and sought a second opinion. This was after her primary physician had started her on analgesics based on a normal haemogram, thyroid profile, MRI lumbar spine, and foot X-rays. She was sent for ESR and CRP, which came back elevated. Her BASDAI score was 4. She was diagnosed with undifferentiated SpA with fibromyalgia and put on NSAID, a combination of pregabalin and duloxetine. After a month, her first review reported less pain, better sleep, reduced stiffness, and her

BASDAI score was now at 3. She continued with the medicine and showed improvement for the next six months afterward, and she was lost to follow up. After one year, she returned with worsening back and hip pain associated with morning stiffness and unilateral heel pain. She reported that she had an episode of loose stool the week prior, which had increased in the last five months.

Further evaluation revealed she had experienced loose mucous stools for the last four years and had been treated multiple times for food poisoning. She was shy, not to point it out during earlier reviews. Examination revealed normal chest expansion, negative tragus to wall test, and positive Schober test with a nine BASDAI score. Investigations revealed elevated ESR, CRP, reduced haemoglobin at 10grams per deciliter, and normal MRI sacroiliac joint. Colonoscopy revealed ulcerative colitis. She was diagnosed with IBD-associated SpA and started on anti-TNF therapy. The decision to initiate infliximab (TNF inhibitor) was based on the diagnosis of non-radiographic SpA related to inflammatory bowel disease. Her BASDAI score in response to treatment was 7, 5.9, 3.2, 2.1 at months 2,3,4,5, respectively. Her symptoms of back pain and loose stool had improved.

Discussion

Spondyloarthropathies (SpA) are rarely reported among black Africans. The diseases' epidemiology varies worldwide due to varied genetic backgrounds and diagnostic criteria used by the surveyors. A common genetic feature across the SpA spectrum is associated with Human Leukocyte Antigen (HLA)-B27 in European populations. Studies have demonstrated that populations with HLA-B27 have higher numbers of spondyloarthropathies, contributing up to 20-30% of the total genetic risk (1-3). European studies have shown the prevalence of Ankylosing Spondylitis (AS) ranges between 0.12 and 1.0% depending on the HLA-B27 background (4,5). The prevalence of AS Asia, Latin America, and Africa is 0.17%, 0.1%, and 0.07%, respectively (4,5). Africa has a mixed picture as the prevalence rates in North Africa are similar to those in Europe despite having lower numbers of HLA-B27. The presentation largely mirrors the west in that the age of onset is the young in their early 20s and predominantly in males (80-90%) (3). The picture is different in sub-Saharan Africa as characterized by low numbers of AS partly due to the low prevalence of HLA-B27. Several studies from this region have shown that most patients are HLA-B27 negative (3). An exception was a genetic study from the Gambia, where they found 6% of the participants were HLA-B27 positive though none had symptoms of AS (3). We did not test HLA-B27 status due to its less predictive nature in Africa but primarily due to financial limitations.

The age of onset differs from Europe and the Middle East as evidence points to an older age group in the southern African studies. A North African audit on 518 spondyloarthropathy patients in Tunisia, Algeria, Morocco gave a mean age at onset of 26.6 ± 10.7 years. The female to male ratio was 1:3, with reported inflammatory back pain in 90% of the cohort (6). They reported that 97% of patients reported sacroiliitis symptoms, peripheral oligoarthritis in 42%, and dactylitis in 10%. Extra-articular features were also infrequently reported, with uveitis seen in 13%, psoriasis in 6%, and inflammatory bowel disease in 3%. The three cases we have reported largely mirror these data from age at diagnosis to symptoms. They all had peripheral oligoarthritis and dactylitis; one had sacroiliitis, and another confirmed IBD.

The younger age of onset differs from two studies from Zimbabwe and South Africa reported where they had an age of onset at 36 and 41 years, respectively (7,8). The time to diagnose in our patients was long (for example, case one took about seven years), keeping with literature from the African continent. This could be attributed to the diagnostic challenge of this disease in primary care due to the disease's rarity; the majority of the health care providers have a low index of suspicion. There is also limited access to rheumatology services and Magnetic Resonance Imaging (MRI) facilities. The less predictive nature of the HLA-B27 test in this population also plays a role (3, 9,10). The time to diagnosis is often late, leading to increased morbidity and mortality seen in patients with SpA. They have increased rates of osteoporosis, vertebral fractures, and death from cardiovascular causes (11).

HIV has changed the picture of spondyloarthropathies in SSA (3,9,12,13). The numbers have increased with the onset of the HIV pandemic. Interestingly, most of the SpA cases reported in Africa are in World Health Organization-stage I HIV disease (3, 9). The most common spondyloarthropathy is reactive arthritis. Psoriasis, rare in black Africans, has also recorded increased numbers in HIV-positive patients (3,9). The prevalence rates of SpA are reported to be higher in HIV positive when compared to HIV negative (9). Zambia literature compared HIV positive versus HIV negative reported rates of 180 per 100,000 and 15 per 100,000, respectively (13). None of our patients was HIV positive.

The diagnosis of axial spondyloarthritis (axSpA) should be considered in patients with an onset of chronic inflammatory back pain before 45 years of age. The diagnosis of SpA is often relying on medical history and examination rather than laboratory tests as they are more often non-specific. Inflammatory back pain is defined by Assessment of Spondyloarthritis International Society (ASAS) expert criteria as the onset of back discomfort before the age of 40 years, insidious onset that improves with exercise, no improvement

with rest, and worse in the night/ morning (14). Sieper *et al* (14) demonstrated that having four of the five features listed above had a sensitivity and specificity of 80 and 74%, respectively, in identifying inflammatory aetiology amongst patients with chronic back pain below forty-five years. The three patients in our case series met the above criteria, thus necessitating further evaluation of the inflammatory cause. Other features of SpA include alternating buttock pain, heel pain caused by enthesitis (tendon insertion like ankle and patella), dactylitis (sausage-like swelling of fingers and toes), asymmetric arthritis predominantly of the lower limbs, anterior uveitis (iritis), Crohn's disease or ulcerative colitis, psoriasis, family history of SpA, and good response of pain symptoms to NSAIDs. The examination of the axial spine mobility involves the cervical spine (tragus to wall test greater than 10cm is positive), thoracic spine (chest expansion less than 2cm is positive), and lower spine (Schober test less than 5cm is likely positive and lateral flexion less than 10cm is likely positive). Only cases 1 and 3 had a positive Schober test, probably due to the disease's severity.

Markers of inflammation should be the first choice in any rheumatological case as they distinguish between inflammatory and non-inflammatory causes of the illness. In SpA, the inflammation markers include elevated C reactive protein, erythrocyte sedimentation rate, and normochromic normocytic anaemia (15,16). All our cases had raised CRP, with case 3 having normochromic normocytic anaemia. CRP is more often preferred due to its higher sensitivity and specificity in the diagnosis of SpA, particularly AS, and because it can be used as a component of some composite measures of disease activity (15-16). General laboratory testing may not add value diagnostically, except to the extent that it may suggest an alternative differential diagnosis.

There is a cardinal role of imaging in making the diagnosis of the SpA (17-19). The most characteristic radiographic finding is erosion, ankylosis, and sclerosis of the sacroiliac (SI) joints. All suspected cases of SpA should get an Anterior-Posterior (AP) plain radiograph of the pelvis to visualize the sacroiliac (SI) joints (18-19). Due to its cost-effectiveness, it is advocated due to low radiation compared to CT scans and frequently sufficient to identify sacroiliitis. MRI of the SI joints is usually indicated only in patients without evidence of sacroiliitis on plain radiographs in whom axSpA is suspected based upon other symptoms and findings characteristic of SpA to help establish the diagnosis nr-axSpA.

Early diagnosis is vital as the clinician can identify the appropriate treatment, thus averting the debilitating disease course. Determinants of treatment are dependent on disease activity and clinical manifestations. In cases with persistently high disease activity despite conventional treatment, one should consider using Biologic DMARDs (bDMARDS); the current recommendation is to start with TNFi therapy (20-22). A systematic review and meta-analysis of randomized trials by Callhoff *et al* (22) involving over 2400 patients reported substantial improvements in disease activity, function and halting the disease's radiographic progression in those put on TNFi. The choice of biologic therapy, such as Tumour Necrosis Factor inhibitors (TNFi) and Interleukin 17 (IL-17) inhibitors, is influenced by comorbidities associated with axial SpA, for example, uveitis, psoriasis, and IBD. For example, in case 3, which had IBD associated with SpA, we settled on infliximab, which better fined such cases. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) or the Ankylosing Spondylitis Disease Activity Score (ASDAS) are commonly used to measure disease activity (23). The two tools are very similar in content, except that the ASDAS score incorporates either CRP or ESR. Active disease is defined by BASDAI of at least 4. Clinically significant improvement is defined as either a 50% improvement of the BASDAI score (BASDAI 50) or an absolute change of ≥2 on a scale of 0 to 10 and a clinical "expert" opinion that a particular patient has improved. In all our patients, we performed serial monthly BASDAI scores, and they all showed improvement. Contraindications for the use of biologics include active infection, latent (untreated) tuberculosis (TB), demyelinating disease (e.g., multiple sclerosis, optic neuritis), heart failure, and malignancy. All our patients were screened for tuberculosis, hepatitis B and C, and HIV before the commencement of treatment.

There is low penetration of Biologics generally in Africa, especially SSA. There is no evidence to support using a combination of bDMARDS and CsDMARDS, such as methotrexate. Methotrexate can be used only in the setting of psoriatic arthritis, as was case number 2. Glucocorticoid use is generally discouraged unless for local site injections of musculoskeletal inflammation. Patients with axial disease should not receive long-term treatment with systemic glucocorticoids (20-22). Predictors of poor outcome of AS patients include older age, Human Leukocyte Antigen (HLA)-B27 positivity, presence of other diseases related to SpA (e.g., psoriasis, Inflammatory Bowel Disease (IBD), uveitis, increasing severity of radiographic changes, cigarette smoking, higher disease activity, low functional ability, and elevated C-reactive protein (24).

In conclusion, spondyloarthritis is an important cause of low back pain that is often overlooked. The diagnosis of axial spondyloarthritis (axSpA) should be considered in patients with symptoms of chronic inflammatory back pain in young patients in the background of any of the following; IBD, sacroiliitis, enthesitis, uveitis, psoriasis, dactylitis, and HLA-B27 positivity. The utility of HLA-B27 gene testing in Africa

is still open to debate due to the low numbers of the HLA-B27 gene in Kenya and SSA. There is evidence that biologic therapy reduces disease activity, improves function, and halts the disease's radiographic progression. Biologic penetration is low, primarily due to costs in Africa.

Conflict of interest

The authors declare no conflict of interest.

References

1. Healy PJ, Helliwell PS. Classification of the spondyloarthropathies. *Curr Opin Rheumatol.* 2005; **17**:395.
2. Harper BE, Reveille JD. Spondyloarthritis: clinical suspicion, diagnosis, and sports. *Curr Sports Med Rep.* 2009; **8**(1):29–34.
3. Rachid B, El Zorkany B, Youseif E, *et al.* Early diagnosis and treatment of ankylosing spondylitis in Africa and the Middle East. *Clin Rheumatol.* 2012; **31**: 1633–39.
4. Dean LE, Jones GT, MacDonald AG, *et al.* Global prevalence of ankylosing spondylitis. *Rheumatology* (Oxford). 2014; **53**:650.
5. Bakland G, Nossent HC. Epidemiology of spondyloarthritis: a review. *Curr Rheumatol Rep.* 2013; **15**:351.
6. Claudepierre P, Gueguen A, Ladjouze A, Hajjaj-Hassouni N. Predictive factors of severity of spondyloarthropathy in North Africa. *Br J Rheumatol.* 1995; **34**:1139-45.
7. Stein M, Davis P, Emmanuel J, West G. The spondyloarthropathies in Zimbabwe: a clinical and immunogenetic profile. *J Rheumatol.* 1990; **17**:1337–39.
8. Chalmers IM. Ankylosing spondylitis in African Blacks. *Arthritis Rheum*.1980; **23**:1366–70.
9. Mijiyawa M, Oniankitan O, Khan MA. Spondyloarthropathies in sub-Saharan Africa. *Curr Opin Rheumatol.* 2000; **12**:281–286
10. Genga EK, Moots RJ, Oyoo OG, Otieno FO. Building a rheumatology team for East Africa: a call for action! *Rheumatology* (Oxford). 2017; **56**(9):1441-42. doi: 10.1093/rheumatology/kew432. PMID: 28031440.
11. Moltó A, Nikiphorou E. Comorbidities in spondyloarthritis. *Front Med* (Lausanne). 2018; **5**:62. Published 2018 Mar 12. doi:10.3389/fmed.2018.00062.
12. Ekwom PE, Oyoo GO, Amayo EO, Muriithi IM. Prevalence and characteristics of articular manifestations in human immunodeficiency virus infection. *East Afr Med J.* 2010; **87**(10):408-414.
13. Njobvu P, McGill P, Kerr H, Jellis J, Pobee J. Spondyloarthropathy and human immunodeficiency virus infection in Zambia. *J Rheumatol.* 1998; **25**:1553–59.
14. Sieper J, van der Heijde D, Landewé R, *et al.* New criteria for inflammatory back pain in patients with chronic back pain: A real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). *Ann Rheum Dis.* 2009; **68**:784.
15. Rudwaleit M, Haibel H, Baraliakos X, *et al.* The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis Rheum.* 2009; **60**:717.
16. van Tubergen A. The changing clinical picture and epidemiology of spondyloarthritis. *Nat Rev Rheumatol.* 2015; **11**:110.
17. Harper BE, Reveille JD. Spondyloarthritis: clinical suspicion, diagnosis, and sports. *Curr Sports Med Rep.* 2009; **8**(1):29–34.
18. Weber U, Jurik AG, Lambert RG, Maksymowych WP. Imaging in spondyloarthritis: Controversies in recognition of early disease. *Curr Rheumatol Rep.* 2016; **18**:58.
19. Lambert RG, Bakker PA, van der Heijde D, *et al.* Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. *Ann Rheum Dis.* 2016; **75**:1958.
20. van der Heijde D, Ramiro S, Landewé R, *et al.* 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Annals Rheum Dis.* 2017; **76**:978-991.
21. Ward MM, Deodhar A, Gensler LS, *et al.* 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis Rheumatol.* 2019; **71**:1599.
22. Callhoff J, Sieper J, Weiß A, *et al.* Efficacy of TNFα blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. *Ann Rheum Dis.* 2015; **74**:1241.
23. Machado PM, Landewé R, Heijde DV, Assessment of Spondylo Arthritis international Society (ASAS). Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. *Ann Rheum Dis.* 2018; **77**:1539.
24. Vastesaeger N, van der Heijde D, Inman RD, *et al.* Predicting the outcome of ankylosing spondylitis therapy. *Ann Rheum Dis.* 2011; **70**:973.

Eight Year Follow up of Cardiac Resynchronization Therapy: Case Reports

Gikonyo A[1], Mbili JW[1], Nguchu H[1], Gikonyo D[1], Ponoth P[1], Patel P[2]

[1]The Karen Hospital, Nairobi, Kenya
[2]Park Ridge, IL, United States of America

Address for Correspondence: Dr. Antony Gikonyo, The Karen Hospital, Nairobi, Kenya. Email: gi_konyo@yahoo.co.in

Abstract

Cardiomyopathies are a significant cause of heart failure in Sub-Saharan Africa (SSA). In particular dilated cardiomyopathies often progress over time, with deterioration in myocyte contractile function. Cardiac Resynchronisation Therapy (CRT), that is, simultaneous pacing of both the right and left ventricles to correct the dysynchrony caused by Left Bundle Branch Block (LBBB) is recommended for symptomatic patients with heart failure in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology with left ventricular ejection fraction ≤35% despite optimum medical therapy. This is as per the European Society of Cardiology guidelines which is a class 1 recommendation. This improves symptoms and reduces morbidity and mortality. We present two case reports with a nine year follow up of patients implanted with a CRT device. There was marked reduction in the Left Ventricular Internal Diameter in Diastole (LVIDd), increase in Left Ventricular Ejection Fraction (LVEF) and improvement of New York Heart Association (NYHA) classification. In a selected patient population with symptomatic chronic systolic heart failure, wide QRS, and reduced left ventricular ejection fraction, on guideline directed medical therapy, CRT is efficacious, effective and can slow down or reverse further progression of the disease..

Key words: Dilated cardiomyopathy, Heart failure, Left bundle branch block, Cardiac resynchronization therapy

Introduction

Cardiomyopathies are a significant cause of heart failure in Sub-Saharan Africa (SSA). In particular dilated cardiomyopathies often progress over time, with deterioration in myocyte contractile function, disruption of myocardial architecture, and associated electrophysiological changes (1). In patients with dilated cardiomyopathies characterized by intraventricular conduction delays, biventricular stimulation synchronizes the activation of the intraventricular septum and left ventricular free wall and thus improves left ventricular systolic function (2).

Cardiac Resynchronisation Therapy (CRT) is recommended for symptomatic patients with Heart Failure (HF) in sinus rhythm with a QRS duration ≥150 msec and Left Bundle Branch (LBBB) QRS morphology with LVEF ≤35% despite optimal medical therapy in order to improve symptoms and reduce morbidity and mortality(3).CRT in heart failure therapy in the majority of patients considerably improves cardiac function, in addition to reducing symptoms and hospital stays (4).

Lack of economic resources and facilities, high cost of procedures, deficiency of trained physicians, and non-existent fellowship programs are the main drivers of under-utilization of interventional cardiac arrhythmia care in our setting (5). Several medical decisions appear to be affected by socioeconomic factors. Long-term follow-up data will help evaluate if these variations require adjustments to outcome expectations (6). We present two case reports that illustrate the long-term benefits of CRT.

Case reports

Case 1

A fifty two year-old female, presented with a history of difficulty in breathing over a two month duration. She was in New York Heart Association (NYHA) class II, on the following medication: carvedilol 25mg twice daily, captopril 25mg twice daily, digoxin 0.25mg daily, frusemide 40mg daily and aspirin 75mg daily. Echocardiogram revealed a LVIDd of 7.9cm with an ejection fraction of 35%, severe tricuspid regurgitation and pulmonary artery pressure of 68mmHg.

Cardiac Resynchronisation Therapy and Defibrillator (CRTD) pacemaker insertion was

performed in the year 2010, with subsequent generator change in 2015 complicated by a pocket haematoma. The LVIDd was 5.4cm with an ejection fraction of 54% mild tricuspid regurgitation and pulmonary artery pressure of 40mmHg in 2019, not on fully optimized medical therapy. Electrocardiogram showed a decrease in her QRS length from 174 to 126 msec. NYHA class I, and no history of defibrillation.

Case 2

A sixty six year-old female with history of hypertension and dilated cardiomyopathy, presented with difficulty in breathing, easy fatigability, NYHA class III, on frusemide 80mg daily, losartan 12.5mg daily, carvedilol 3.125mg daily, spironolactone 25mg daily, digoxin 0.125mg daily, warfarin 5mg daily, aspirin 75mg daily, and trimetazadine 35mg daily. The patient was not on fully guideline directed medicine due to low blood pressure. Echocardiogram revealed an LVIDd of 6.88cm with an ejection fraction of 23%.

Cardiac Resynchronisation Therapy Pacemaker (CRTP) insertion was performed in 2010, with subsequent generator change in 2019. The LVIDd was 5.25cm with an ejection fraction of 34% and NYHA I in 2019. Electrocardiogram showed a decrease in her QRS length from 177 to 142 msec.

Figure 1: ECG Pre-CRTD LBBB QRS 174msec

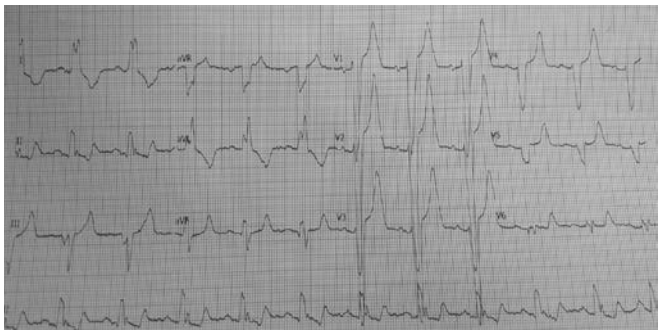
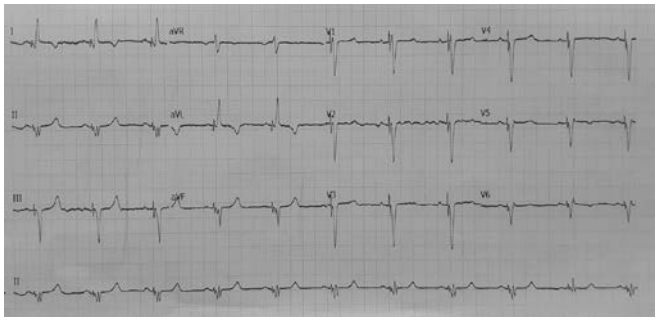


Figure 2: ECG Post- CRTD QRS 126msec



Discussion

Regarding our limited experience, the benefits of CRT in addition to guideline directed medical therapy are remarkable in improving both cardiac function and significantly decreasing patient symptoms. In addition after the implantation there were no further hospitalizations related to heart failure. The initial cost of a CRT device is high; however this is offset by avoiding recurrent hospital admissions which cumulatively will cost more than the device implant.

The 5-year results of REVERSE confirmed that cardiac resynchronisation therapy in mildly symptomatic heart failure and wide QRS reverses remodelling and is associated with low rates of heart failure hospitalization and all-cause mortality over the entire follow-up (7). Our first patient fit into this category of mild symptoms and her course over the 9 years was marked by no admissions except for a generator change. Additionally, the effect of cardiac resynchronisation was able to return the ejection fraction to a normal level.

In a selected patient population with symptomatic chronic systolic heart failure, wide QRS, and reduced left ventricular ejection fraction, cardiac resynchronisation therapy is effective and can slow down or reverse further progression of the disease. As a result of pacing along the latest activated area of the left ventricle, the intra- and interventricular dyssynchrony can be diminished, leading to a better activation pattern with narrower QRS and a more effective contraction with a higher stroke volume (8). Our second patient's ejection fraction did not return to normal, likely due to the chronic nature of the heart failure however symptomatically she progressed to NYHA class I.

It is essential that the general physician remains updated on the common indications for CRT and locally available therapies (9). This is to ensure patients are provided all options regarding management including CRT, when guideline directed medical therapy does not suffice. This is due to the clear benefit of CRT for patients who fit the necessary criteria.

Ensuring that cardiologists are trained and able to perform implantations is a necessary role of national and continental cardiovascular organisations. In turn this will increase access to these therapies and benefit the greater patient population. As the number of implantations increases the cost per implantation will decrease. This is because as the number of devices used increases, then bulk purchasing is possible leading to a decrease of the unit price. This cost saving is then passed on to the patient making the therapy more affordable. This in-turn ensures that there are an adequate number of cases to ensure local training of cardiologists.

Conclusion

The initial cost of implantation of a CRT device is high. In comparison, the cost related to repeat hospitalization, disease progression, morbidity and mortality is much greater. With the increased number of cardiologists able to implant these devices safely in our region, more patients should benefit from this procedure.

Acknowledgments

None

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

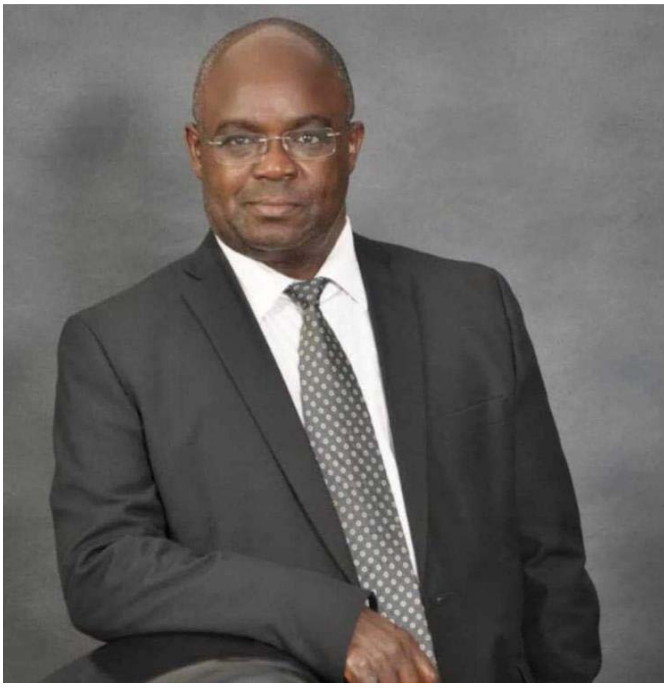
The authors declare no funding was received for this research.

References

1. Lane JD, Whittaker-Axon S, Schilling RJ, Lowe MD. Trends in implantable cardioverter defibrillator and cardiac resynchronisation therapy lead parameters for patients with arrhythmogenic and dilated cardiomyopathies. *Indian Pacing Electrophysiol J*. 2019;**19**(2):49-54.
2. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, *et al,* for the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) investigators cardiac-resynchronization therapy with or without an implantable defibrillatorin advanced chronic heart failure. *N Engl J Med.* 2004; **350**:2140-50.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, *et al.* ESC Scientific Document Group. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016; **37**(27):2129-2200.
4. Goran M,Vera J, Milan P, Žarko C, Dragutin S, *et al.* Resynchronisation therapy in patients with heart failure: Our results. *Srpski Arhiv za Celokupno Lekarstvo.* 2005; **133**(5-6):237-241.
5. Bonny A, Ngantcha M, Jeilan M, Okello E, Kaviraj B, *et al.* Statistics on the use of cardiac electronic devices and interventional electrophysiological procedures in Africa from 2011 to 2016: report of the Pan African Society of Cardiology (PASCAR) Cardiac Arrhythmias and Pacing Task Forces. *Europace.* 2018; **20**(9):1513-26.
6. Bonny A, Ngantcha M, Yuyun M, Karaye KM, Scholtz W, *et al.* Cardiac arrhythmia services in Africa from 2011 to 2018: the second report from the Pan African Society of Cardiology working group on cardiac arrhythmias and pacing. *Europace.* 2020; **22**(3):420-433.
7. ElMaghawry M,Farouk M. REVERSE 5-year follow up: CRT impact persists. *Glob Cardiol Sci Pract*. 2014; **2014**(3): 245–248.
8. Kosztin A, Boros AM, Geller L, Merkely B. Cardiac resynchronisation therapy: current benefits and pitfalls. *Kardiol Pol.* 2018; **76**(10):1420-25.
9. Peal JE, Mathews IG, Runnett C,Thomas HE, David R. An update on cardiac implantable electronic devices for the general physician. *J Royal College Phys Edinburgh.* 2018; **48**(2):141-147.

Tribute to Dr. Antony Jude Omolo Were (AJO)

Oyoo GO, Department of Clinical Medicine and Therapeutics, School of Medicine, University of Nairobi, P.O. Box 19676-00202, Nairobi, Kenya. Email: geomondi@hotmail.com



The curtain of a great hero has fallen. I am glad that through the great legacy he leaves behind, he shall forever live with us even in immortality. My soul is truly torn today from losing a great man.

My first meeting with Dr. Antony Were (AJO), as we referred to him, traces back to the medical wards of Kenyatta National Hospital (KNH) where he partly taught me many years ago when I was an undergraduate medical student and he was a post-graduate student in internal medicine. Through him I learnt a lot. In the early nineties, when I joined the University of Nairobi for my postgraduate programme, *Daktari* was then a member of staff working as a lecturer in internal medicine.

When I finally became a physician, *Daktari* was the secretary of the Kenya Association of Physicians (KAP) where I joined him in the executive committee as the editor of the KAP Newsletter and coordinator of the Continuing Medical Education (CME) for the association. I later succeeded him and became the second secretary of the association. Through this journey of management and coordination of a professional association, I gathered so much from him. I had always admired Dr. Were's determination and his subsequent rise from one level to another which climaxed at his rise to the position of the President of African Association for Nephrologists (AFRAN), a highly coveted and prestigious position.

In the year 2002 when I joined the School of Medicine as a lecturer in the Department of Internal Medicine we became colleagues in the same department, he being my senior. Since I joined the department we have been sharing the same office during which we shared both light and harsh moments. We discussed so many issues such as pertains to medicine, friendship and politics. *Daktari*, being an ardent follower of politics got us engrossed into deep discussions of contemporary political issues. Sometimes we agreed on our views but sometimes we differed completely in some of our political ideologies. However, in this long professional journey, there are real tough moments we went through together with *Daktari*. There were several storms through which we sailed with *Daktari*. Sometimes we stood yonder and wondered how we ever crossed the ocean. Sometimes a man keeps a lot in his heart to be silently told to the world. But that doesn't matter anymore, for such great and low moments are the treasures that I shall hold in memory of *Daktari*.

Dr. Were and I had a few things in common in our practice of medicine. He was a nephrologist while I was a rheumatologist. There are issues of rheumatology that overlapped into nephrology and vice versa. This brought us into frequent discussions on such matters in view of our patients and in view of the future of the two disciplines. However, what baffled me most was how Dr. Were managed to juggle in his seemingly very busy schedule. I wondered how he managed to attend to more than one private clinic and holding three different positions within KNH. As if that is not enough, he even went and contested for a parliamentary seat in Homabay County. Apparently, during the holiday seasons, *Daktari* would shut down all these activities and take his family for holidays. This was indeed a sign that he held his family with such esteem despite all that he had to do. But from these, I learnt my lesson that the purpose of man on earth is all but to serve the nation with all his might and all his strength.

But fate has a way with life. Later on, his son Nick would become my student when he joined Medical School in KNH as an undergraduate student in medicine. My relationship with *Daktari* grew even stronger that he invited me to not only attend his son Nick's graduation party but also to stand as a speaker in the same event.

My last official interaction with *Daktari* pertains to my current role as the postgraduate exam coordinator in the Department of Clinical Medicine and Therapeutics. It was in September last year during the recently concluded postgraduate exams that I had

reached out to him for some official assistance and we were glad to have him carry out the task.

The last three days of Dr. Were's life were to me the most dramatic, memorable and devastating. On Thursday, November 19th 2020, just three days before his demise, I went to the hospital to visit *Daktari* in his ICU room. We talked precisely about a few things and as I was about to leave, he made a special request. He wanted me to get him a pastor from the Seventh Day Adventist church to pray with him. The following day, Friday 20th November 2020, I came with Pastor Paul Owuor from the Lavington Seventh Day Adventist Church who shared the word of God and prayed with him at the ICU. For some reason, I saw a great relief and joy in *Daktari's* face after the prayer. Sometimes relief and satisfaction lies in the face of a man about to rest, only we cannot see. The following day on Saturday 21st November 2020, I received a call early in the morning that *Daktari* has left us. Nonetheless, it would be unwise for me to challenge God who allows a friend to bow. I will forever thank Him for the life we shared and the great insights, ideas and philosophies that I got to acquire from Him.

One cannot help but be saddened by the death of such a great man. I am yet to come to terms with the shock and disbelief that met me on that dark Saturday morning. His death has left a huge gap in the medical profession, not only in Kenya but also in Africa and in the whole world.

Till we meet again *Daktari*.

May your soul rest in Eternal Peace.

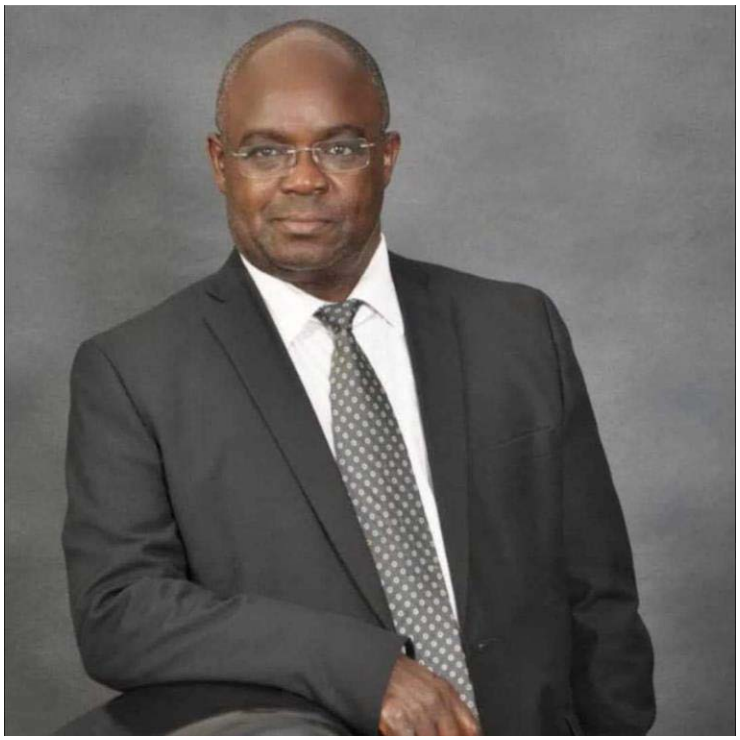
KENYA RENAL ASSOCIATION
P.0.BOX 963 – Sarit Centre
00606
Nairobi
KENYA
TELEPHONE: 3752727 / 3740397
FAX : 3752726
E-mail: info@kenyarenal.org
0714-673305

Tribute

Dr. Anthony Jude Omolo Were (AJO)

(12th September 1956 – 21st November 2020)

MBChB (UoN); MMed (Intern Med) (UoN); Fellowship in Nephrology, Edinburgh; Fellowship in Nephrology, Manchester)



The renal fraternity in Kenya is in mourning. We have lost a gentle giant. Dr. Anthony Were wore many hats and was a titan in the field of nephrology in Kenya and Africa. His many roles included the following;

- President of the African Association of Nephrology (AFRAN)
- Deputy Director, East African Kidney Institute (EAKI)
- Senior Lecturer, Department of Clinical Medicine and Therapeutics, College of Health Sciences, University of Nairobi
- Consultant Physician and Nephrologist in the Renal Unit at Kenyatta National Hospital, Nairobi

He was a member of many professional bodies including: Kenya Renal Association, International Society of Nephrology, European Renal Association, European Dialysis and Transplantation Association, African Association of Nephrology and Southern African Transplantation Society.

When Dr. A.J.O. Were was elected as the President of the African Association of Nephrology (AFRAN) in September 2019, he embraced his new role with focus and vigor. He was determined to excel and put African nephrology in the forefront globally. It was his firm belief that AFRAN had a major role to play in improving access to quality kidney services in Africa. In the short time that he led AFRAN he achieved a lot including establishing secretariat services, forming a guideline committee that released a comprehensive guideline for the nephrology service provision in the era of COVID-19, encouraged the formation of a vibrant young nephrologists committee, arranged the hosting of webinars (including joint sessions with

ISN) to an Africa – wide audience. He was also the brains behind the Africa Nephrologists WhatsApp group where many Nephrologists in Africa exchange ideas and information on issues Nephrology. During his brief stint as President, Dr. Were's foot prints have been boldly printed in the sands of time of AFRAN. He demonstrated commitment to excellence, selfless service and friendship to all across Africa.

Anthony has been a very active member of the Kenya Renal Association (KRA). Indeed, his contribution to KRA activities saw him chair the Annual Scientific conferences of KRA in 2017 and 2019. Both these conferences were very successful in large part due to his able leadership of the organizing committees of these meetings. He has also always made time to attend many other KRA activities including World Kidney Day celebrations.

The role of Dr. Were in the East African Kidney Institute (EAKI) cannot be overstated. As the founding deputy director of the institute, he spent a lot of time encouraging and mentoring trainees in various cadres of renal medicine including nephrology nurses and nephrology fellows. He was instrumental in formulating the curricula for various courses offered by the Institute. He was always available to his students; even in the COVID – era, he always made time to log onto and moderate academic 'zoom' sessions. It was his firm belief that EAKI would grow to be a center of excellence for training nephrologists for Africa and beyond.

It is impossible to capture all that Anthony Were has done for nephrology in Kenya and Africa. He was truly a champion in advancing quality nephrology care whose focus and energy saw him achieve remarkable milestones. He will surely be missed by all.

Condolences go to his family. May the Lord Almighty, grant them the fortitude to bear this devastating loss. May his gentle soul rest in eternal peace.

Twahir A
Chairman, Kenya Renal Association

EAST, CENTRAL AND SOUTHERN AFRICA COLLEGE OF PHYSICIANS (ECSACOP)
CALL FOR APPLICATIONS ACADEMIC YEAR 2021

The East, Central and Southern Africa College of Physicians (ECSACOP) hereby invites applications for full-time specialist training in Internal Medicine, commencing **September 2021** leading to the award of the qualification FCP (ECSA) in Internal Medicine. In Kenya, the College has two training Sites: Moi Teaching and Referral Hospital (MTRH)- Eldoret and Coast General Teaching and Referral Hospital (CGTRH)- Mombasa. Each of these centers have 4 vacancies making a total of 8 for the country.

The duration of training is four years.

ECSACOP is a constituent college under the umbrella of the East, Central and Southern Africa College of Health Sciences (ECSA – CHS).

Applicants must fulfil the following criteria:

- Hold MBChB (or equivalent), as well as have completed all internship training as required by the Medical Council/Relevant Regulatory Body
- Current registration with the Medical Council/ Relevant Regulatory Body
- Valid Annual Practicing License by the Medical Council/Regulatory Body
- Certificate of Good Standing from the Medical Council/Relevant Regulatory Body
- Letter of support from an ECSACOP Council member within the country
- Letter of support from Current employer
- Personal statement

Fees

- Application fee US$50 (This fee is payable to your local Association of Physicians in your country- Kenya Association of Physicians; MPESA pay bill 600100 Acc Number 01000055916). Send the transaction details to Email address:info@kapkenya.org
- **Annual Training fee US$400 (Paid only by successful applicants).** The annual training fees are payable to the East, Central and Southern Africa College of Physicians at the start of each academic year.
- Trainees will be required to pay an additional $500 examinations fee in Year 2 and Year 4 of training

Application Procedure

(Please ensure that you have all the above documents before starting the application)

Visit the ECSACOP website at **www.ecsacop.org** and follow the steps below:

- On the homepage, select the **Training** tab.
- Under the drop down Training menu select **Registration for the 2021 Academic Year**
- Select **Apply now** and fill in the application form
- Upload all the required documents
- Upload the proof of payment of the application fee (Paid to Kenya Association of Physicians)
- Submit your form

Last date of receiving applications: 30th June 2021

For further inquiries, please contact the ECSACOP Secretariat at info@ecsacop.org or the KAP local office at info@kapkenya.org

Instructions to authors

The *Journal of Kenya Association of Physicians (JOKAP)* is a quarterly journal published by the Kenya Association of Physicians.

Authors submitting manuscripts to JOKAP do so on the understanding that if accepted they surrender all copyright to the journal. No part of this journal may be reproduced or transmitted in any form without the written permission of the Editor-in-Chief.

The following categories of manuscripts will be considered for publication;

i. **Original articles:** The article must contribute further to the existing knowledge of the subject. This must follow the IMRAD format with the following sub-headings: Title; Structured abstract with the following sub-titles; background, objective(s), study design, methods, results and conclusion(s); Introduction; Materials and Methods; Results; Discussion; Conclusion(s), Recommendations (if any) and References (not exceeding 25. The article should not exceed 4000 words including text, figures, tables and references.
ii. **Reviews:** This must be a critical analyses of the subject reviewed. Reviews should preferably be written by an expert in that particular area and can be commissioned by the Editor-in-Chief. Reviews should not exceed 6000 words including tables, figures and references. The format should be as follows; title, structured abstract (with the following sub-headings; objective(s); data source, conclusions), Introduction and sub headings where necessary, results and conclusion(s) and references not exceeding 40.
iii. **Case reports:** This should be unique clinical syndromes or presentations. They should not exceed 2500 words. The format should be a Title, Abstract (prose form) not exceeding 200 words, Introduction, Case report, Discussion, Acknowledgement(s) and references not exceeding 15.
iv. **Short communication:** This should possess all the elements of a scientific paper but should be presented in prose form without sub-headings. It should have not more than 1500 words and 10 references.

Note that references should be numbered in order of appearance (Vancouver style) and strictly only those cited in the text should appear in the reference list.

All manuscripts should be submitted to the Editor-in-Chief, Prof. Omondi Oyoo, email: jokapkenya@gmail.com