Tropical Journal of Nephrology Vol.12 No 2, December, 2017 23 - 30

Evaluation of Urinary Tract Infection and Nephropathy in Adult Nigerians with Sickle Cell Anaemia

Braimoh RW[1], Ale OK[1] and Adewunmi AJ[2]

[1]Department of Medicine, College of Medicine, University of Lagos, Lagos, Nigeria
[2]Department of Medicine, Lagos University Teaching Hospital, Lagos, Nigeria

ABSTRACT

Background: Improved survival of sickle cell anaemia subjects has led to a growing population of adult sicklers. The pattern of urinary tract infections(UTI) and prevalence of nephropathy in adult Nigerians with sickle cell anaemia remains largely speculative as available data are mainly on paediatric population.

Methodology: Bio-data, information on symptoms of UTI/kidney damage and urine specimens were obtained from 100 consecutive stable Hemoglobin-SS subjects and 100 age and sex-matched healthy haemoglobin–AA controls aged ≥ 16 *years* were subjected to urinalysis, microscopy, culture and sensitivity as well as albumin and creatinine estimation.

Results: Significant bacteriuria was more frequent in subjects with HbSS than haemoglobin-A controls: 24(24%) vs 5 (5%), p=0.0002.

Escherichia coli, Staphylococcus aureus and Klebsiella spp. accounted for 45.8%, 37.5% and 16.7% respectively of the isolates in HbSS subjects. Twenty-seven (27%) HbSS subjects had Albumin/ Creatinine ratio >300mg/g out of which 8 (29.6%) of these had UTI.

Antibiotics sensitivities in the HbSS subjects were: ceftazidime (79.1%), ciprofloxacin (58.6%), perfloxacin (58.3%), gentamycin (58.3%), nalidixic acid (37.5%) and nitrofurantoin (45.8%).

Conclusion: Urinary tract infection is commoner in HbSS than HbAA subjects. *E.coli* is the commonest cause. Empirical use of ceftazidime or ciprofloxacin, an oral preparation is suggested while awaiting sensitivity results.

Keywords: *UTI, nephropathy, adults, sickle cell anaemia.*

INTRODUCTION

Urinary tract infection (UTI) is common worldwide and occurs in all age groups [1]. It results from invasion of the genito-urinary tract by pathogenic micro-organism.[1] Urinary tract infection is associated with clinical, histologic or immunologic evidence of host injury [1, 2].

Conditions predisposing to UTI include diabetes mellitus, pregnancy, hypo-proteinaemic states and sickle cell anaemia (HbSS) among others [3]. Sickle cell anaemia (HbSS) is an inherited disease in which normally disc-shaped red blood cells (RBCs) become crescent-shaped and function abnormally due to valine substituting glutamine at position six of the beta-globin chain. This causes the RBCs to clog up

Corresponding author: **Dr. Braimoh Rotimi Williams**, Department of Medicine, College of Medicine, University of Lagos, *E-mail:* rotelbraimoh@yahoo.com

in blood vessels and vital organs. In Nigeria, 25-35% of its over 160 million population carry the haemoglobin S-gene; however the prevalence of HbSS is 2-3%, translating to a population of about 3.5 million Nigerians with HbSS [4].

Sickle cell anaemia patients are prone to infections due to asplenia which makes them susceptible especially to encapsulated organisms such as pneumococcus, salmonella and mycobacterium [5, 6]. Defective alternate complement pathways together with excessive iron deposition in tissues also provide a good milieu for bacteria growth [7]. Common sites of infection are the chest, bone, gall bladder and genito-urinary tract. However, UTI accounts for 75% of all infections in this population [8]. Chronic UTIs in sickle cell anaemia subjects is a cause of kidney damage which may have grave implications in terms of morbidity and mortality [9-12]. Increased survival to adulthood further increases the likelihood of HbSS individuals developing nephropathy [4].

Most studies on UTI in sickle cell anaemia have been conducted in the paediatric age group with only few data on adult subjects. Marked improvement in survival of HbSS individuals in Nigeria to adulthood has created a large pool of adults with increased potential for the development of UTI/nephropathy; these are largely uncharacterised. We studied the prevalence and pattern of UTI (significant bacteriuria) among adult HbSS subjects attending a tertiary care clinic in Lagos, Nigeria.

METHODOLOGY

Patients selection: A hundred sickle cell anaemia (HbSS) subjects (confirmed by low voltage electrophoresis using cellulose acetate paper) in steady state (defined as that period when the subject with sickle cell anaemia is free from infection, pain, or other acute disease processes for at least 3 months) [13], aged 16 – 65 years attending the sickle cell clinic of the Lagos University Teaching Hospital (LUTH) and who were not on immunosuppressive or antimicrobial therapy for ≥ 3 weeks prior to recruitment and sample collection were enrolled for the study. HbSS subjects with recent use of antimicrobial and or immunosuppressive therapy (< three weeks), not in steady state and who did not give their consent were excluded from the study.

One hundred age and sex matched HbAA (confirmed by low voltage electrophoresis using cellulose acetate paper) apparently healthy controls (defined as absence of history/symptoms suggestive of kidney disease or acute medical illness) not on immunosuppressive and or antimicrobial therapy for ≥ three weeks prior to recruitment and sample collection were enrolled. Controls subjects consisted of workers, patients' relatives and students in Lagos University Teaching Hospital, Idi-Araba, Lagos.

Sample collection: Informed consent was obtained from all study subjects prior to commencement of study. All participants were properly educated and carefully instructed by the investigators on how to collect clean catch mid-stream urine into sterile universal bottles and correctly fill the self-administered questionnaire.

All urine samples so collected were sent to microbiology laboratory and processed.

Laboratory methods: Urinalysis was performed by dipstick method using the Bayer® diagnostics 9 point reagent strip (Bayer AG 51368 Leverkusen, Germany). The samples were screened for glucose, protein, nitrite, leucocytes, blood, pH, specific gravity and the strips were read by comparing with the colour charts on the reagent test bottle 30-60seconds after insertion into the urine samples.

Urine microscopy: 5mls of each urine sample was centrifuged at 1500 revolutions per minute (RPM) for 5mins, the supernatant was discarded and the sediment re-suspended with 100ml of the patients urine sample using a micropipette. Fifty microlitre of re-suspended sediment was thereafter placed on a clean glass slide and examined under the microscope. The number of white blood cells and red blood cells were counted under high power field (HPF). Counts less than 5 per HPF were regarded as normal while counts of 5 and above per HPF were regarded as significant.

Culture: A calibrated standardized platinum wire loop was immersed vertically (after flaming and cooling to sterilize) into each thoroughly mixed urine sample. A loopful of urine was then carefully taken out vertically from the specimen bottle, discharged fully

and streaked on the entire surface of cysteine lactose electrolyte deficient (CLED) medium and another loopful of urine into well dried blood agar plate. The two plates were incubated aerobically at 37^0C for twenty four hours. The number of bacterial colonies was counted after 24 hours of incubation. Significant bacteriuria is defined as a minimum of 100,000 colony forming units (CFU) of a single strain per millilitre (ml) in any subject [14]. UTI was therefore defined in this study as presence of significant bacteriuria [15].

Bacterial identification: Identification of bacteria species isolated from urine sample of subject with significant growth of bacteria was performed using analytical profile index (API 20E, bio Merieux inc., USA) for gram-negative bacilli while the morphology on plates and biochemical reactions were used to identify gram-positive organisms.

Sensitivity testing: Three to five colonies of the organism to be tested were picked with a sterilized platinum wire-loop from pure culture plate of the organism and streaked evenly over a well-dried iso-sensed agar plate. A strip containing multiple antibiotics disc was carefully placed on the inoculated iso-sense agar plate, care being taken to ensure that all the antibiotics discs were firmly in contact with the culture medium. Culture plates were thereafter incubated aerobically at 37^0c for twenty four hours. The zone diameters were measured and classified thereafter as sensitive or resistant respectively as follows: ceftazidime (sensitive $\geq$18 and resistant $\leq$14), gentamycin (sensitive $\geq$15 and resistant $\leq$12), cephalexin (sensitive $\geq$23 and resistant $\leq$14), co-amoxiciav (sensitive $\geq$20 and resistant $\leq$19), ciprofloxacin (sensitive $\geq$21 and resistant $\leq$15), perfloxacin (sensitive $\geq$19 and resistant $\leq$15), nalidixic acid (sensitive $\geq$19 and resistant $\leq$13), nitrofurantion (sensitive $\geq$17 and resistant $\leq$14), trimetoprim/ sulfamethoxazole (sensitive $\geq$16 and resistant $\leq$10), amoxicillin (sensitive $\geq$29 and resistant $\leq$28). Only the organisms showing full sensitivity to the antibiotic tested were regarded as being sensitive. Random urine samples were collected from all subjects. Urine albumin was determined in first-morning void specimens by nephelometry (BN II, Dade Behring Diagnostic, Marburg, Germany). Urinary creatinine was assessed by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY, USA). Albumin/ creatinine ratio (ACR, an index of renal damage) was calculated thereafter.

Questionnaire: Biodata of the study population were recorded. These included name, age, gender, level of education and religion. Information on symptoms suggestive of urinary tract infection and kidney damage including dysuria, nocturia, and increased frequency of micturition, loin pain, haematuria and frothiness of urine were elicited for. History of passage of stone in urine as well as sexual history were also elicited and documented.

Data analysis: Data were analyzed using EPI-info statistical package version 6.0 (CDC 1600 Clifton Road, Atlanta, GA30329-4027 USA). The continuous variables were given as means ± standard deviation. The Pearson Chi-squared test was used to test for association between discrete variables. *P* value <0.05 was considered to be statistically significant.

RESULTS

A hundred HbSS subjects attending the Lagos University Teaching Hospital out-patient clinic as well as one hundred HbAA control subjects participated in the study. The HbSS group consisted of 55 females (55.0%) and 45 males (45.0%) whose ages ranged from 16-53 years. The HbAA (control) group consisted of 52 males and 48 females whose age ranged from 17-54 years. The mean age of the HbSS and HbAA subjects were 25.34 ± 7.88 years and 25.95 ± 8.45 years respectively (p=0.6). Table 1 shows the age and gender distribution of the study population.

The frequency of occurrence of symptoms of urinary tract infection in the study population is shown in table 2. Loin pain, the commonest symptom, occurred in 60% of HbSS subjects.

Thirteen HbSS and 5 HbAA subjects had significant pyuria i.e. $\geq$5 pus cell/hpf. Oxalate crystals were present in 4 HbSS subjects while 2 HbAA subjects had oxalate crystals. Yeast cells were found in two HbSS subjects but none of the HbAA subjects had yeast cells in their urine samples.

Out of 27 HbSS subjects with dysuria, 7 had significant bacteriuria, while only one of the 5 HbAA subjects with dysuria had significant bacteriuria (p= 0.78) Out of the six HbSS subjects with haematuria, only one had significant bacteriuria while none of the

Table 1: Age and gender distribution of the study population

Age grp (yrs)	Male HbSS (n/%)	Female HbSS (n/%)	χ2/p-value	Male HbAA (n/%)	Female HbAA (n/%)	χ2/p-value
16-24	28/62.2	32/58.2	0.17/0.68	32/61.5	29/60.4	0.01/0.91
25-33	12/26.7	15/27.3	0.0/0.95	9/17.3	15/31.3	2.66/0.10
34-42	4/8.9	4/7.3	0.09/0.77	7/13.5	1/2.1	4.4/0.04
43-51	1/2.2	3/5.5	0.67/0.41	3/5.8	2/4.2	1.0*
52-65	0/0	1/1.8	1.0*	1/1.9	1/2.1	1.0*
Total	45/100	55/100		52/100	48/100	

**Fisher exact, HbSS: haemoglobin SS, HbAA: heamoglobin AA*

Table 2: Clinical and laboratory features of urinary tract infections in the study population

Symptoms	Response	HbSS subjects (n)	Significant bacteriuria (n)	χ^2/p-value (n)	HbAA subjects	Significant bacteriuria (n)	χ^2/p-value
Dysuria	Yes	27	7	0.08/0.8	5	1	0.23*
	No	73	17		95	4	
Haematuria	Yes	6	1	1.0*	2	0	1.0*
	No	94	23		98	5	
Loin pains	yes	60	13	0.45/0.5	8	2	0.049*
	No	40	11		92	3	
Nocturia	yes	19	6	0.74/0.39	0	0	—
	No	81	18		100	5	
History of UTI	Yes	7	5	0.008*	2	1	0.1*
	No	93	19		98	4	
Urinary frequency	Yes	29	8	0.3/0.6	12	0	1.0*
	No	71	16		88	5	

*UTI- urinary tract infection, *Fisher's exact*

2 HbAA control participants with haematuria had significant bacteriuria (Fisher exact=1.0). Thirteen of the 60 HbSS subjects with loin pain had significant bacteriuria while none of the 8(8%) HbAA control subjects having loin pain had significant bacteriuria (Fisher exact=0.3).

Twelve (30%) of 40 sexually active HbSS subjects had UTI, while only 5 (11%) of 46 sexually active HbAA control subjects had UTI (χ2= 4.94, p=0.026).

A total of 9 (9%) HbSS subjects had sexual contact 3 weeks prior to this study, 2 of which had UTI, while one of the 24 HbAA control subjects who had sexual contact 3 weeks prior to the study had UTI(Fisher exact= 0.7).

Thirty HbSS subjects had leucocyturia out of which 13 (43%) had significant bacteriuria. One of the 2 HbAA subjects with leucocuturia had significant bacteriuria(p=0.0001). Nitrituria was present in 17 HbSS subjects while 2 HbAA subjects had nitrituria.

Urine culture: A total of 24 and 5 cultures were positive in the HbSS and HbAA subjects respectively (p=0.001). *E. coli* was isolated in 11(45.8%), *Staphylococcus aureus* in 9(37.5%) and *Klebsiella spp* in 4(16.7%) urine samples of HbSS subjects. The isolates obtained in the HbAA controls were: E. coli 3(60%), *Staphylococcus aureus* 1 (20%) and *Klebsiella specie* 1 (20%).

TABLE 3: The sensitivity pattern of isolated organisms to anti-microbial agents

Isolated organism	Cipro n(%)	Gent n(%)	Amox n(%)	NA n(%)	Nitro n(%)	Augm n(%)	Cotri n(%)	Pefl n(%)	Ceph n(%)	Cefta n(%)
HbSS										
Combined sensitivity(n=24)	14(58.3)	14(58.3)	9(32.5)	9(37.5)	11(45.8)	11(45.8)	8(33.3)	14(58.3)	8(33.3)	20(79.1)
E.coli only (n=11)	7(63.6)	7(63.6)	3(27.3)	5(45.4)	5(45.5)	4(36.4)	2(18.1)	7(63.6)	3(27.2)	9(81.8)
S. aureus only (n=8)	4(50)	4(50)	5(62.5)	2(25)	4(50)	5(62.5)	4(50)	4(50)	3(37.5)	7(87.5)
Kleb. Spp only (n=5)	3(60)	3(60)	1(20)	2(40)	2(40)	2(40)	2(40)	3(60)	2(40)	4(80)
HbAA										
Combined sensitivity (n=5)	4(80)	4(80)	2(40)	3(60)	3(60)	2(40)	3(60)	4(80)	3(60)	4(80)
E.coli only (n=3)	3(100)	2(67)	1(33.5)	2(67)	2(67)	1(33.3)	2(67)	3(100)	1(33.3)	2(67)
S. aureus only (n=1)	0(0)	1(100)	0(0)	0(0)	0(0)	1(100)	1(100)	1(100)	1(100)	1(100)
Kleb. Spp only (n=1)	1(100)	1(100)	1(100)	1(100)	1(100)	0(0)	0(0)	0(0)	1(100)	1(100)

Cipro=ciprofloxacin, Gent=gentamicin, Amox=amoxicillin, NA=nalidixic acid, Nitro=nitrofurantoin, Augm=augmentin, Cotri=cotrimoxazole, Pefl=perfloxacin, Ceph=cephalexin, Cefta=ceftazidime

Seventeen (71%) of the 24 positive cultures in the HbSS subjects and 2(40%) of the 5 positive cultures in the HbAA subjects had nitrituria. Nineteen (79%) of the 24 culture-positive HbSS subjects had a pH of 5 while five of the positive cultures had pH of 6. Among the HbAA subjects, two each of the positive cultures had pH of 5 and 6 respectively while one positive culture had a pH of 8 ($\chi 2$ =13.5, p-value=0.0002). Table 3 shows the sensitivity pattern of the micro-organisms to antibiotics.

Twenty-seven (27%) of HbSS subjects had Albumin/ Creatinine ratio >300mg/g out of which 8 (29.6%) of these had UTI but one HbAA subject had albumin/creatinine ratio of >300mg/g and none had UTI (χ^2=0.46, P value =0.498).

DISCUSSION

This study evaluated the prevalence of UTI (significant bacteriuria) and nephropathy in adult HbSS subjects, highlighting the clinical and laboratory characteristics of UTI in the study population. It also identified the common aetiologic agents of UTI in the study population and their antimicrobial sensitivity.

The prevalence of UTI among adult sickle cell anaemia subjects from this study was 24% and 5% in the HbAA control subjects. Akinbami *et al.* reported a prevalence of 12.85% while Iwalokun *et al* documented a prevalence of 18.4% in their respectively studies on HbSS population [16, 17]. The higher prevalence in our own study may be due to the fact that Akinbami *et al.* had a younger age group (14-55years) coupled with the fact that some of their subjects were on antibiotic at the time the study was commenced while Iwalokun *et al* included children in their own study population. However, there was a statistically significant relationship between recent sexual activity and UTI (p=0.003). Those exposed to sexual activity prior to the survey had higher prevalence of UTI. This finding, like in the general population is expected as sexual activity increases the risk of UTI [18].

This is similar to the findings of other workers[19-21]. Past history of UTI in HbSS subjects was also found to be a risk factor for another UTI (p=0.008). This finding is not unexpected because sickle cell anaemia subjects are prone to having recurrent UTI due to renal ischaemic damage [3].

There was a high occurrence of history of loin pain in the HbSS population, however this was independent of the presence of significant bacteriuria (p=0.5). Although loin pain is a symptom of upper UTI, it is possible that bone pains from the back were reported as loin pains in HbSS subjects: this may explain the high frequency of loin pain in the HbSS subjects. Renal infarction may also be responsible for some of the loin pain [22].

Haematuria may be the first complaint in HbSS patients [23]. In this study, 6% of the HbSS subjects had hematuria but only one had UTI (Fishers exact=1). This is possibly so because haematuria can

occur in HbSS subjects without UTI as a result of renal medullary vascular obstruction, papillary necrosis and neoplasms [24-26]. This is lower than 25% reported by Akinkugbe et al in an earlier study in Ibadan [27]. Dysuria was found in 27% of HbSS subjects out of which only 7% had UTI. New-onset vaso-occlusive crisis without UTI which may simulate dysuria in HbSS subjects [28]. The lower frequency of UTI in the HbAA subjects compared with the HbSS group may be due to the higher activity of urinary siderocalin which restricted bacterial growth in the HbAA subjects [29]. Also, HbSS subjects are known to have iron overload which encourages bacterial growth [30].

Thirteen (43%) of the thirty HbSS subjects with leucocyturia had significant bacteriuria while one of the two HbAA subjects with leucocyturia had significant bacteriuria (P=0.0001). Leucocyturia has also been documented as a marker of UTI in other studies [2, 31-33]. Interestingly, significant bacteriuria was also found in 16 % (n=11) of HbSS subjects without leucocyturia. This may be due to the poor leucocyte response that may occur in HbSS subjects[33].

Escherichia coli specie was the most common organism isolated from the urine sample of most HbSS subjects with UTI accounting for 45.8%. This was closely followed by Staphylococcus aureus (37.5%) and Klebsiella specie (16.7%). In the HbAA control group, Escherichia coli specie was also found in majority of subjects, constituting 60 % of the positive cultures while Staphylococcus aureus and Klebsiella specie were isolated in 20% each of the HbAA subjects. This finding is similar to those of Akinbami *et al.* and Iwalokun et al. who in two separate studies isolated was E.coli as the most common organism followed by Klesiella specie and Staphylococcus specie [16, 17].

Two HbSS subjects and none of the HbAA controls had yeast cells cultured from their urine. Candiduria occurs in usually in the setting of immunosuppression. However, there has been a non-conclusive debate on whether or not there is immunosuppression in stable sickle cell anaemia subjects [34-37].

The anti-microbial agent to which *E. coli* and *Klebsiella species* were most sensitive were Ceftazidime, ciprofloxacin and perfloxacin while *Staphylococcus species* was sensitive to co-amoxiclav. Ciprofloxacin and Perfloxacin may be preferred in uncomplicated UTI due to the availability of oral preparations and minimal renal side effect profile. This finding is similar to that of Brown *et al.* who found Ciprofloxacin as useful first line drugs in the treatment of UTI [38].

This study shows that 27% of HbSS subjects had evidence of nephropathy (albumin/creatinine ratio >300mg/g) as opposed to 1% in HbAA subjects, although a sizeable number of both study populations had UTI. Sickle cell anaemia is a risk factor for nephropathy because of chronic ischaemic damage[3]. Our finding is similar to that of Abdu A *et al.* in northern Nigeria [39]. Other studies have shown varying values. For instance, Bolarinwa *et al.* [40] found evidence of nephropathy in 50% of their study population while Iwalokun BA, Aleem A *et al.* and Ephraim RK *et al.* reported evidence of nephropathy in 22.3%, 41% and 68.4% respectively [16, 40-42]. This variability might have resulted from different indices used to define nephropathy as well as environmental factors. These studies however show the high prevalence of nephropathy in HbSS study population.

CONCLUSION AND RECOMMENDATION

Urinary tract infection is common in HbSS subjects, with a prevalence of 24% in steady state. The presence of leucocytes and or nitrite on urinalysis is highly suggestive of UTI in adult HbSS subjects.

Ciprofloxacin and Perfloxacin are oral antimicrobial agents which may be used empirically while awaiting culture and sensitivity results. Nephropathy is common in HbSS subjects. Routine urinalysis is recommended in all HbSS subjects for early detection and treatment to delay the progression to end-stage kidney disease.

ACKNOWLEDGEMENTS

We sincerely thank all the staff of microbiology laboratory and sickle cell clinic of the Lagos University Teaching Hospital for their assistance to making this research a uccess.

REFERENCES

1. Stamm WE. Urinary tract infections and pyelonephritis *In*: Harrison's Principles of internal medicine. Editors: Kasper D,

Braunwald E, Fauci A, Longo D, Hauser S, Jameson J, 16th edition 2005, McGrall-Hill; 1715-1718.

2. Stamm WE. Measurement of pyuria and its relation to bacteriuria. Am J Med 1993 July 28; 75 (IB): 53-58.

3. Shinde S, Bakshi AP and Shrikhande AV. Infections in sickle cell disease. IAIM 2015; 2(11): 26-34.

4. Oyedeji G.A. The effects of sickle cell disease on the families of affected children. Central Afr Med J 1995; 45 (10): 333-334

5. Powers D, Overturf G, Weiss J, Lee S and Lhan L. Pneumococcal septicaemia in children with sickle cell anaemia. JAMA 1981; 245: 189-1842.

6. Platt OS, Thorington BD and Brambilla, DJ. Pain in sickle cell disease. Rates and risk factors. N Engl J Med 1991; 325: 11-16.

7. Booth C, Inusa B and Obaro SK. Infection in sickle cell disease: A review. Int J Inf Dis, 2010; 14(1), e2-e12.

8. Zakaria-Abu-Strain HA, El-Bashir AM, A Dabous IS and Al-Khater M. Incidence of major infection in sickle cell paediatric patients at Quatif Central Hospital. Ann Saudi Med 1991; 11: 267-272.

9. Thomas AN, Pattisco C and Serjeant GR. Causes of death in sickle cell disease in Jamaica. Br. Med J 1982; 285: 633-635.

10. Platt, OS, Brambilla, CJ and Rosse, WF. Mortality in sickle cell disease – life expectancy and risk factors for early death. N Engl J Med 1994; 330: 1639-1644.

11. Whalley R. Bacteriuria of pregnancy. Amer J Obstet. Gynaecol, 1967; 97: 723-738.

12. Robinson MG and Halperin C. Infections. Escherichia coli and sickle cell anaemia. J Am Med Ass 1974; 230: 1145-1148.

13. Ballas SK. More definitions in sickle cell disease: steady state vs baseline data. Am J Hematol 2012; 87(3):338.

14. Pfalleer MA and Koontz RP. Laboratory evaluation of Leucocyte esterase and nitrite tests for the detection of bacteriuria. J Clin Microbiol 1985; 21: 840-842.

15. Cumming V, Ali S, Forrester T, Roye-Green K and Reid M. Asymptomatic bacteriuria in sickle cell disease: a cross sectional study. BMC Infec Dis 2006; 6: 46.

16. Akinbami AA, Ajibola S, Bode-Shojobi I, Oshinaike O, Adediran A, Ojelabi O, *et al.* Prevalence of significant bacteriuria among symptomatic and asymptomatic homozygous sickle cell disease patients in a tertiary hospital in Lagos, Nigeria. Niger J Clin Pract. 2014; 2 (17):163-167.

17. Iwalokun BA, Iwalokun SO, Hodonu SO, Aina OA and Agomo PU. Evaluation of microalbuminuria in relation to asymptomatic bacteruria in Nigerian patients with sickle cell anemia. Saudi J Kidney Dis Transpl 2012; 23:1320 30.

18. Foxman B, Geiger AM, Palin K, Gillespie BK and James S. First-Time Urinary Tract Infection and Sexual Behavior. Epidemiology. 1995; 6(2):162-168.

19. Stamm WE, Hooton TM, Johnson JR, Johnson C and Stapleton A. Urinary of tract infections: from pathogenesis to treatment. J infect Dis 1989; 159: 400-406.

20. Hooton TM, Scholes D, Hughes JP, Winter C, Roberts PL *et al.* A prospective study of risk factors for symptomatic urinary tract infection in young women. N Engl J Med 1996; 335: 468-474.

21. Hooton TM, Scholes D, Stapleton AE, Roberts PL, Winter C *et al.* A Prospective study of asymptomatic bacteriuria Sexually Active Young Women. N Engl J Med 2000; 343: 992-997.

22. Granfortuna J, Zamkoff K and Urrutia E. Acute renal infarction in sickle cell disease. Am J Hematol 1986 Sep; 23(1): 59-64.

23. Alebiosu C.O. Renal papillary necrosis as first presentation of a Nigerian sickle cell patient. W Afr J Med 2002; 21 (2): 168-169.

24 McInnes BK. The management of hematuria associated with sickle hemoglobinopathies. J Urol 1980; 124: 171-174.

25. Mostofi FK, Vorder-Bruegge CF and Diggs LW. Lesions in kidneys removed for unilateral hematuria in sickle cell disease. AMA Arch Pathol 1957; 63: 336-351.

26. Osegbe DN. Haematuria and sickle cell disease. A report of 12 cases and review of

the literature. Trop Geogr Med 1990; 42:22-27.

27. Akinkugbe OO. Profuse haematuria in sickle cell trait. W Afr Med J 1996; 15 (4) 151-152.

28. Bolarinwa RA, Akinola NO, Aboderin OA and Durosinmi MA. The role of malaria in vaso-occlusive crisis of adult patients with sickle cell disease. J Med Med Sci 2010; 1(9): 407-411.

29. Shields-Cutter RR, Crowley JR, Hung CS, Stempleton AE, Aldrich CC, Marshall J and Henderson JP. Human urinary composition controls antibacterial activity of siderocalin. J Biol Chem 2015; 290 (25); 159:49-60. Raghupathy R, Manwani D, Little JA. Iron Overload in Sickle Cell Disease. Adv Hematol 2010; 2010: 272940. https://www.ncbi.nlm.nih.gov

30. Raghupathy R, Manwani D, Little JA. Iron Overload in Sickle Cell Disease. *Adv Hematol* 2010; 2010: 272940. *https://www.ncbi.nlm.nih.gov*

31. Musher DM, Thorsteinsson SM and Airola VM. Quantitative urinalysis. Diagnosing urinary tract infection in men. JAMA 1976; 236(18): 2069-2072

32. Morton RE and Lawande R. The diagnosis of urinary tract infection: comparison of urine culture from suprapubic aspiration and midstream collection in a children's outpatient department in Nigeria. Ann Trop Paediatr 1982 Sep; 2 (3): 109-112.

33. Kaplan SS and Nardi M, Impairment of leucocytes function during sickle cell crisis. J Reticulo-endothelial Soc. 1977; 22: 499-506.

34. Ogunye OO, Uy CG, Sheagren JN, Sheagren JN and Strober W. Cellular immune function in sickle cell anaemia. Nig. Med J 1979; 9: 33-38.

35. Winkelstein JA and Drachman RH. Deficiency of pneumococcal serum opsonizing activity in sickle cell disease. N. Engl J Med 1968; 279: 459-466. https://www.ncbi.nlm.nih.gov

36. Johnston RB, Newman SL and Struth AG. An abnormality of the alternate pathway of complement activation in sickle cell disease. N Engl J Med 1973; 288; 803.

37. Hosea SW, Brown EJ, Hamburger MI and Frank MM. Opsonic requirements for intravascular clearance after splenectomy. N Engl J Med 1981; 304: 245-250.

38. Brown BJ, Asinobi AO, Fatunde PK, Osinubi K and Fashina NA. Antimicrobial sensitivity pattern of organism causing urinary tract infection in children with sickle cell anaemia in Ibadan Nigeria. West Afr J Med 2003; 22 (2): 110-113.

39. Abdu A, Emokpae MA, Uadia PO and Kuliya-Gwarzo A. proteinuria among adult sickle cell anemia patients in Nigeria. Ann Afri Med. 2011; 10(1): 34-37.

40. Bolarinwa RA, Akinlade KS, Kuti MA, Olawale OO and Akinola NO. Renal disease in adult Nigerians with sickle cell anemia: a report of prevalence, clinical features and risk factors. Saudi J Kidney Dis Transpl. 2012; 23 (1):171-175. https://www.ncbi.nlm.nih.gov

41. Aleem A. Renal abnormalities in patients with sickle cell disease: a single center report from Saudi Arabia. Saudi J Kidney Dis Transpl. 2008; 19(2): 194-199.

42. Ephraim RKD, Osakunor DNM, Cudjoe O, Oduro EA, Asante-Asamani L, *et al.* Chronic kidney disease is common in sickle cell disease: a cross-sectional study in the Tema metropolis, Ghana. BMC nephrology. 2015; 16 (1):75-81.