

## MULTIDRUG RESISTANT (MDR) UROPATHOGENS PROFILE IN HIV-POSITIVE INDIVIDUALS WITH ASYMPTOMATIC BACTERIURIA IN PORT-HARCOURT, NIGERIA

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Article Received on 14/08/2019

Article Revised on 04/09/2019

Article Accepted on 25/09/2019

### ABSTRACT

Asymptomatic bacteriuria (ASB) refers to the quantitative growth of same species of bacteria in mid-stream urine to the tune of  $10^5$  CFU/ml or above with no presence of any signs and symptoms of urinary tract infections. Asymptomatic bacteriuria is a common occurrence in healthy individuals with HIV sero-positive individuals at greater risk. The study aimed to determine the prevalence of asymptomatic bacteriuria and the sensitivity patterns of the isolates among HIV-positive individuals assessing medical care in Port-Harcourt. Early morning urine samples were collected from HIV positive persons attending University of Port-Harcourt Teaching Hospital (UPTH) and analyzed using standard procedures. Statistical analysis was carried out using SPSS version 20.0 (USA). Of the four hundred (400) urine samples, asymptomatic bacteriuria was diagnosed in 203 (50.75%). *Escherichia coli*, 50 (24.63%) were the highest uropathogens isolated followed by *Klebsiella* species 42 (20.96%), *Pseudomonas* species 34 (16.75%), *Enterobacter* species 26 (12.81%), *Proteus* species 22 (10.84%), *Providencia* species 16 (7.88%), *Staphylococcus aureus* 5 (2.46%), *Alcaligenes* species 2 (0.99%), *Enterococcus* species 2 (0.99%) and *Candida albicans* 4 (1.97%) in that order. Antibiotic susceptibility patterns showed 66% and above resistance rates by all the isolates except *Staphylococcus aureus* which had 49% resistivity to all the 7 classes of antibiotics used. *Alcaligenes* species and *Enterococcus* species were 100% resistant to the antibiotics. In this study, *Escherichia coli* was the most prevalent organism. Multiple antibiotic resistance is high among sero-positive individuals attending UPTH in Port-Harcourt. Regulation of antibiotic use is lacking in Nigeria and Government needs to tackle it.

**KEYWORDS:** Asymptomatic bacteriuria, prevalence, HIV.

### INTRODUCTION

Urinary tract infection (UTI) is usually characterized by symptoms ranging from flank pain, lower back pain, frequent micturition, sepsis and even death. The diagnosis is made only when two successive urine samples are obtained aseptically (Rubin, *et al.*, 1992). Vulnerable populations who are at risk of UTIs are mostly women, especially in pregnancy, children and aged patients (Nicolle, 2008; Jackson, *et al.*, 2004; Nelson, 2015). Certain circumstances such as spinal cord injuries, urinary catheters, diabetes, multiple sclerosis, immunodeficiency as well as primary urologic anomalies might also predispose some people to infections (Mladenovic, *et al.*, 2015; Foxman, 2003). Both asymptomatic and symptomatic urinary tract infections cause grave illnesses that decrease the living standards and economy of the family. (Olowe, *et al.*, 2015).

According to the prevalence estimate of 2013 in Nigeria, HIV infection burden was as high as 3.2% and when the large population size is taken into consideration, it means a very large number of individuals are already living with the dreaded disease and invariably at risk of coming down with urinary tract infections and other complications as a result of ASB. The prevalence of asymptomatic bacteriuria which is a common occurrence varies from 1% in healthy pre-menopausal women to as high as 100% among patients with long term indwelling catheters (Nicolle, 2008). In healthy individuals, it is of no clinical implication and seemingly benign, but it is associated with significant adverse outcomes in some individuals especially pregnant women; 40% of who may come down with UTI and acute pyelonephritis if left untreated (Guberman, *et al.*, 2007). It is based on this fact that screening for asymptomatic bacteriuria is recommended for this group (Nicolle, *et al.*, 2005). Nevertheless, the occurrence of asymptomatic bacteriuria

depends on the populace considered (Widmer, *et al.*, 2010; Banu & Jyothi, 2013).

## MATERIALS AND METHODS

This study was carried out of HIV clinic at the University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria located at Obio/Akpor Local Government Areas (OBALGA) of Rivers State. Four hundred (400) consented individuals enrolled for this cross-sectional study which was conducted for a period of one year. These included HIV-sero positive persons of both genders irrespective of their exposure to antiretroviral drugs.

### Ethical Approval

Ethical approvals were obtained from the Ethical Committees of the hospital where specimens were collected and processed. Written consents were also obtained from all the participants.

### Sample collection

Early morning, mid-stream urine samples were collected from HIV-positive individuals. At the end of each collection day, the samples after properly labeled were transported within one hour to the Microbiology Laboratory Department of the University of Port-Harcourt Teaching Hospital for analyses. If processing was delayed, the samples were preserved in the Refrigerator at 4°C.

### Sample size determination

Sample size was determined using the formula;  $n = Z^2pq/e^2$  (Araoye, 2004).

## RESULTS

The study diagnosed asymptomatic bacteriuria in 203/400 (50.75%) among HIV sero-positive individuals in Port-Harcourt. *Escherichia coli*, 50 (24.63%) were the highest uropathogens isolated followed closely by *Klebsiella* species 42 (20.96%), *Pseudomonas* species 34 (16.75%), *Enterobacter* species 26 (12.81%), *Proteus* species 22 (10.84%), *Providencia* species 16 (7.88%), *Staphylococcus aureus* 5 (2.46%), *Alcaligenes* species 2 (0.99%), *Enterococcus* species 2 (0.99%) and *Candida*

*albicans* 4 (1.97%) (Table 1). Distribution was highest in age group 31-40 years 83(40.89%) and lowest in age group 71-80 years 9(4.43%) (Table 2). Female subjects 135(53.57%) had higher infections of asymptomatic bacteriuria than male subjects 68(45.95%) although, the difference was statistically insignificant ( $P > 0.05$ ). (Table 3). There was no significant difference in bacteriuria between HAART-users 180/365 (49.32%) and non-users 23/35 (65.71%) ( $p > 0.05$ ) (Table 4). Antibiotic susceptibility testing pattern revealed high degree of multiple resistance. Resistance rates of 66% and above were observed with all the (13) antibiotics (Cephalexin, Cefuroxime, Cefotaxime, Ceftriaxone, Ceftazidime, Cefpodoxime, Cefepime, Meropenem, Gentamycin, Ciprofloxacin, Nitrofurantoin, Cotrimoxazole and Augmentin) used. These antibiotics belonged to 7 broad drug classes, namely; Cephalosporins, Carbapenems, Aminoglycosides, Fluoroquinolones, Nitrofurans, Sulphamethoxazole/Trimethoprim and  $\beta$ -lactam- $\beta$ -lactamase inhibitor. The highest resistance rates were observed in Cephalexin and Cotrimoxazole while the lowest resistance rates testing with Meropenem. *Enterococcus faecalis* and *Alcaligenes* species had 100% resistance rates to all the antibiotics used. Only *Staphylococcus aureus* had 80% sensitivity to Cephalexin, Cefuroxime and Cotrimoxazole (Figures 1 & 2).

**Table 1: Distribution of Isolated Uropathogens.**

Isolate	Frequency (%)
<i>Enterococcus faecalis</i>	2 (0.99)
<i>Alcaligenes</i> species	2 (0.99)
<i>Candida albicans</i>	4 (1.97)
<i>Staphylococcus aureus</i>	5 (2.46)
<i>Providencia</i> species	16 (7.88)
<i>Proteus</i> species	22 (10.84)
<i>Enterobacter</i> species	26 (12.81)
<i>Pseudomonas</i> species	34 (16.75)
<i>Klebsiella</i> species	42 (20.69)
<i>Escherichia coli</i>	<i>Escherichia coli</i>
<b>Total</b>	<b>203 (100.0)</b>

OR: Odds Ratio, CI: confidence interval,  
Likelihood of bacteriuria increases if OR is  $> 1$

\*OR is statistically significant ( $p < 0.05$ )

**Table 2: Association of Age Group and Bacteriuria in HIV Subjects.**

GROUP (years)	UROPATHOGEN		Chi-Square (p-value)
	YES	NO	
20 -30	36 (17.73)	54 (27.41)	5.36 (0.0204)*
31 - 40	83 (40.89)	84 (42.64)	0.12 (0.7222)**
41 - 50	58 (28.57)	34 (17.26)	7.22 (0.0071)*
51 -60	17 (8.37)	16 (8.12)	0.01 (0.9268)**
61 - 70	9 (4.43)	7 (3.55)	0.20 (0.6533)**
71 - 80	0 (0.0)	2 (1.02)	102.4 (0.0002)f
<b>Total</b>	<b>203 (100.0)</b>	<b>197 (100.0)</b>	

\*Distribution is statistically significant ( $p < 0.05$ )

\*\*Distribution is not statistically significant ( $p > 0.05$ )

**Table 3: Bacteriuria in HIV subjects by Gender.**

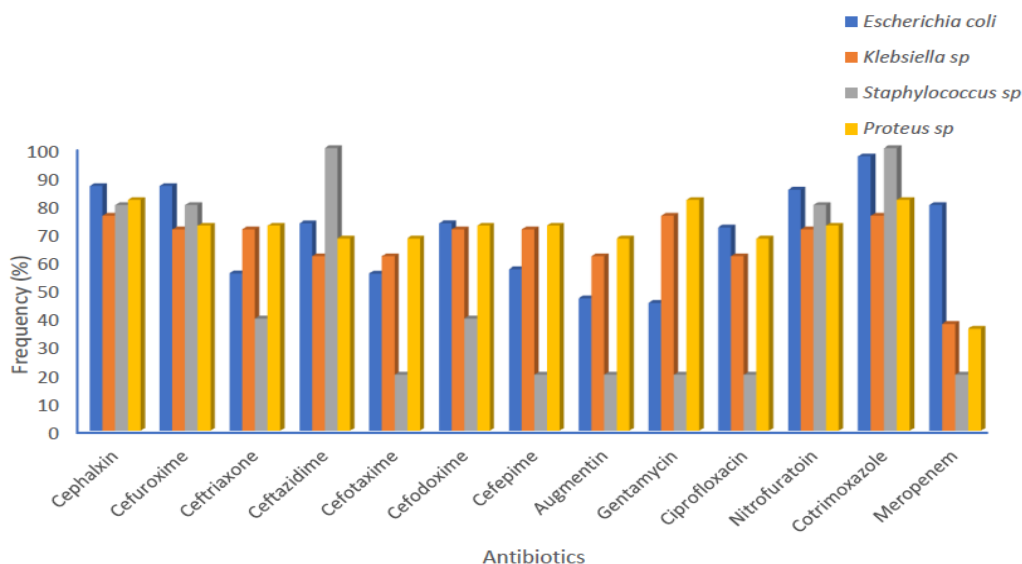
Bacteriuria	Male	Female	Chi-square (p-value)
No	80 (54.05)	117 (46.43)	2.16 (0.1408)**
Yes	68 (45.95)	135 (53.57)	
Total	148 (100.0)	252 (100.0)	

\*\*Difference is not statistically significant

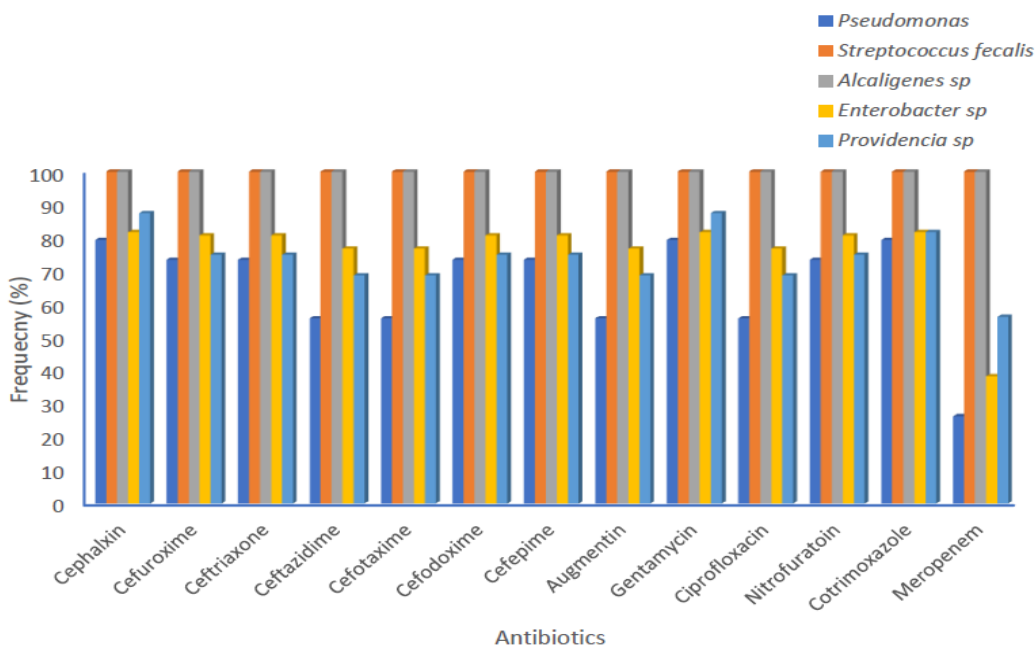
**Table 4: Association of Uropathogen and HAART Exposure.**

Uropathogen	HAART-Unexposed	HAART- Exposed	Total
No	12 (34.29%)	185 (50.68%)	3.43 (0.0637)**
Yes	23 (65.71%)	180 (49.32%)	
Total	35 (100.0%)	365 (100.0%)	

\*\*There is no significant difference in bacteriuria between HAART-users and non-users (p > 0.05).



**Figure 1: Resistance Pattern of Selected isolates in HIV-positive Subjects.**



**Figure 2: Resistance Pattern of Selected isolates in HIV-positive Subjects.**

## DISCUSSION

This study showed high incidence of asymptomatic bacteriuria in HIV-positive individuals 203 (50.75%) in Port-Harcourt. These results were in consistent with other studies whereby people living with HIV (PLHIV) were reported to be highly disposed to urinary tract infections due to the suppression of their immunity (Inyang-Etoh, *et al.*, 2009; Frank-Peterside & Wokoma, 2009; Okafor, *et al.*, 2005). About 90% of all the isolates belonged to gram-negative bacteria, just as recorded in numerous studies that implicated enteric Gram-negative organisms in urinary tract infections (Iweriebor, *et al.*, 2012; Raheem, *et al.*, 2013). The preponderance of *Escherichia coli* followed closely by *Klebsiella* species in this study also agreed with numerous recent studies in other regions that reported that the commonest causative agents for uncomplicated (simple) as well as complex urinary tract infections were *Escherichia coli* (uropathogenic) and *Klebsiella pneumoniae* (Foxman, 2014; Kline, *et al.*, 2011; Omoregie & Eghafona, 2009; Mucheye, *et al.*, 2013) in HIV sero-negative individuals as well as HIV infected persons (Skrzat-Klapaczynska, *et al.*, 2018). The infecting organisms identified in this study were in agreement with commonly isolated bacteria in other populations studied in Nigeria (Okonko, *et al.*, 2009) and in Ethiopia (Assefa, *et al.*, 2008; Teshager, *et al.*, 2008).

The distribution was significantly higher ( $P < 0.05$ ) among the ages between 31-40 years (40.8%) and 41-50 years (28.57%). This was line with other findings which stated that the elderly and the younger age groups were found to be more at risk of Asymptomatic bacteriuria with the prevalence doubling in older age group. High sexual activity was implicated as the reason behind this high occurrence in younger age group (Olowe, *et al.*, 2015).

Generally, prevalence of bacteriuria was higher in females (53.57%) than in males (45.95%) in this study but statistical analysis showed that the difference was not significant ( $P > 0.05$ ) Similar results were obtained in an Indian study where women (28%) and men (22%) were diagnosed of urinary tract infections (Vignesh, *et al.*, 2008). Many recent studies reported same, attributing the cause to the short urethra in women and same being in close proximity to the anus (Salvatore, *et al.*, 2011; Demilie, *et al.*, 2012; Herrmann, *et al.*, 2002; Iduoriyekemwen, *et al.*, 2012)

However, few studies disagreed with our results, Litwin, *et al.*, (2005) reported that men between the ages of 16-64 years were significantly more likely to have UTI than women in that category.

Another reason also proffered by other studies was the brief urethra which harbors normal flora and pushes them into the bladder during sexual activity (Kumamoto, *et al.*, 2002, Ugbogu & Nworie, 2010).

There was no statistically significant difference regarding the prevalence of significant bacterial growth between subjects under highly active antiretroviral therapy (HAART) and non-users in the studied population. Subjects who had not been exposed to Highly active antiretroviral therapy (non-HAART users) were not more infected with asymptomatic bacteriuria than those under treatment.

These findings were in line with a study in Nigeria that published a higher incidence among HAART users (25.3%) in comparison to non-users (13%) (Inyang-Etoh, *et al.*, 2009). A similar work also showed HAART- users having more infections than the control group, though the control group were non-HIV subjects (Amiri, *et al.*, 2009). Some works that evaluated the efficacy of HAART on urinary tract infections of bacterial origin among People living with HIV found out that the drug had a major role to play (de Gaetano, *et al.*, 2003). However, additional researches are needed to better understand this condition.

An analysis of the antibiotic susceptibility testing profile of the isolates revealed an extreme degree of resistance to antibacterial agents which were broadly grouped into seven (7) classes, namely; first to fourth generation Cephalosporins (Cephalexin, Cefuroxime, Ceftriaxone, Ceftazidime, Cefpodoxime and Cefepime), Carbapenems (Meropenem), Aminoglycosides (Gentamycin), Fluoroquinolones (Ciprofloxacin), Nitrofurans (Nitrofurantoin), Sulphamethoxazole/Trimethoprim (Septrin) and  $\beta$ -lactam- $\beta$ -lactamase inhibitor (Augumentin). Data showed 89% of the test organisms had resistance rates of 66-100% to all the antibacterial drugs. *Enterococcus faecalis* *Alcaligenes* species and *Escherichia coli* had the highest resistance rate of 100%, 100% and 76% respectively while *Staphylococcus aureus* had the lowest resistance rate of 20% to the antibiotics. The most susceptible bacteria were *Staphylococcus aureus* being sensitive to 8 out of 13 (62%) antibiotics employed. Generally, all the isolates except *Staphylococcus aureus* showed resistance rates of 56% and above to all the antibiotics (Figures 1 & 2). This trend was reflected in several studies globally. The highest resistance rates were observed in Cephalexin and Cotrimoxazole while the lowest resistance rates were seen in Meropenem. It is noteworthy that the isolates were highly resistant to the major first-line antibiotics; Penicillins and Cephalosporins which were the preferred antibiotics of choice for routine treatment of infections caused by Enterobacteriaceae. (Delgado-Valverde, *et al.*, 2013). Numerous studies had published high resistance rates to these antibiotics across the globe. Resistance resulted in the organisms being able to withstand the harmful effect of the drugs thereby continue to thrive and prolong the therapy period. This trend was reflected in may studies in which resistance rates of greater than 80% were noted with the two first line drugs ((Liu, *et al.*, 2017; Tadesse, *et al.*, 2017).

Multiple drug resistance (MDR) rates of 62-100% were seen in all the bacteria isolated except *Pseudomonas* species and *Staphylococcus aureus* having rates of 56% and 40% respectively. The study was in agreement with current studies that reported MDR rates ranging from 55.7% - 78% (Monira, *et al.*, 2017; Moolchandani, *et al.*, 2017; Adenipekun, *et al.*, 2016). Conversely, the resistance rates were very high in comparison to some earlier studies on clinical isolates with values ranging from 21.4% to 29.7% (Okonko, *et al.*, 2009; Motayo, *et al.*, 2012; Khawaja, *et al.*, 2017). It is very worrisome that high resistance rates were also recorded in antibiotics such as Gentamycin and Meropenem that currently serve as the last hope for the treatment of highly resistant organisms. This study showed that HIV sero-positive individuals assessing medical care in Port-Harcourt were highly infected with multidrug resistant uropathogens which harbour multiple resistant mechanisms

## CONCLUSION

Multidrug resistant uropathogens were highly predominant in HIV positive individuals attending University of Port Harcourt Teaching Hospital, Port-Harcourt, Nigeria. *Escherichia coli* and *Klebsiella* species have continued to evolve in their epidemiology leading to an increase in colonization and infection of HIV sero-positive population. The isolates obtained from this group of individuals revealed high levels of multidrug resistance patterns. The presence of multiple drug resistant bacteria in these immunocompromised subjects would greatly increase the risk of superimposed opportunistic infections which are resistant to antibiotic therapy. The high incidence of multidrug resistance among these regularly isolated uropathogens could be linked to lack of regulatory policy on the use of antibiotics especially in many developing nations like Nigeria which aids abuse.

## Conflict of Interest

The authors declared no competing interests.

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