

## Antibiotics Sensitivity and Resistance Patterns of Uropathogens to Nitrofurantoin and Nalidixic Acid in Pregnant Women with Urinary Tract Infections in Ibadan, Nigeria

<sup>1</sup>I.O. Okonko, <sup>2</sup>O.B. Donbraye-Emmanuel, <sup>3</sup>L.A. Ijandipe,  
<sup>4</sup>A.A. Ogun, <sup>5</sup>A.O. Adedeji and <sup>6</sup>A.O. Udeze

<sup>1</sup>Department of Virology, Faculty of Basic Medical Sciences, University of Ibadan College of Medicine,  
University college Hospital (UCH), Ibadan, University of Ibadan, Ibadan,  
Nigeria. WHO Regional Reference Polio Laboratory,  
WHO Collaborative Centre for Arbovirus Reference and Research,  
WHO National Reference Centre for Influenza

<sup>2</sup>Department of Medical Microbiology and Parasitology, University College Hospital (UCH), Ibadan, Nigeria

<sup>3</sup>Department of Microbiology, Olabisi Onabanjo University, Ago-Iwoye, Ogun State, Nigeria

<sup>4</sup>Department of Epidemiology, Medical Statistics and Environmental Health,  
Faculty of Public Health, College of Medicine, University of Ibadan, Ibadan, Nigeria

<sup>5</sup>Department of Veterinary Microbiology and Parasitology, Faculty of Veterinary Medicine,  
University of Ibadan, Ibadan, Nigeria

<sup>6</sup>Department of Microbiology, Faculty of Sciences, University of Ilorin, Ilorin, Nigeria

**Abstract:** This study reports on antibiotic sensitivity and resistance patterns of uropathogens to nitrofurantoin and nalidixic acid in Ibadan, Nigeria. The susceptibility and resistance patterns of 38 bacterial pathogens were determined using standard procedures. Based on the standard zones of inhibition ranging from 17mm-37mm in diameter exhibited by the pathogens, most of the isolates were highly sensitive to Nitrofurantoin and Nalidixic acid with lethal effects. The antibiogram studies also showed that *E. coli* in most clinical samples was highly sensitive to Nitrofurantoin, which were found to be 100% effective in-vitro against the *E. coli*, followed by and *Klebsiella sp.* (85.7%) and *S. aureus* (72.7%) study while sensitivity to Nalidixic acid were higher for *E. coli* (75%), followed by and *Klebsiella sp.* (71.4%) and *Pseudomonas aeruginosa* (50%). The resistance pattern showed that *S. aureus* was highly resistance to Nalidixic acid (63.6%), followed by *P. aeruginosa* (50%), *Klebsiella sp.* (28.6%) and *E. coli* (25%) while resistance pattern to Nitrofurantoin was higher for *P. aeruginosa* (50%), then followed by *S. aureus* (27.3%). The study showed a high sensitivity of most of the pathogens to the two antibiotics used. It also indicates that Nitrofurantoin and Nalidixic acid remains the effective drug of choice, judicious use of these drugs is essential to preserve their efficacies. It is therefore recommended that routine microbiological analysis and antibiotic sensitivity test of mid-stream urine samples of pregnant women and other patients be carried out before the administration of the drugs for the treatment of UTIs. In so doing, development of unusual resistance among such strains could easily be detected, and thus, helped in better treatment and management of those infected by these pathogens.

**Key words:** Bacteria pathogens • Antibiotics sensitivity • Resistance pattern • UTI

### INTRODUCTION

Drug resistance is a large and growing problem in infections that account for most of Africa's disease burden, including malaria, tuberculosis (TB), HIV infection, and respiratory and diarrheal diseases [1]. The proportion

of malaria infections resulting in death has increased in Africa, largely due to resistance, and the cost of effective antimalarial agents is higher than the health budgets of malaria-endemic countries can accommodate [2]. Similarly, a recent outbreak of extensively drug-resistant TB in rural South Africa illustrated that resistant organisms pose an

enormous and costly threat to HIV-infected persons and their HIV-negative contacts [3].

Much of the current discourse on infectious disease and drug resistance as it affects sub-Saharan Africa is limited to the pressing problems associated with HIV, TB, malaria and other emerging- and re-emerging resistant organisms. Resistance, however, equally compromises the management of acute respiratory infections, sexually transmitted diseases, and diseases spread by the fecal-oral route, such as typhoid fever, cholera, dysentery, and other diarrheal diseases [1]. Moreover, young children are especially likely to acquire resistant enteric infections, from which they can experience less obvious, but long-term adverse effects [1].

The prevalent pathogens of UTIs have been found to be resistant to most chemotherapeutic agents [4], though the antimicrobial susceptibilities of these pathogens are highly predictable. Development of resistance to these antimicrobial agents in UTI cases will therefore affect future treatment and management of the infection with these drugs. Adequate treatment and control of these conditions need a good knowledge of the bacteria species involved and their susceptibility to antimicrobial agents [5]. Majority of the treatments begins or is done completely empirically, the knowledge of the organisms, their epidemiological characteristics and their antibacterial susceptibility is therefore mandatory [3]. Data obtained are essential to optimize the treatment and avoid the emergence of bacterial resistance, which is responsible for the increasing number of therapeutic failure [3]. In view of the limited spectrum of causative organisms and their predictable susceptibility, urine cultures and susceptibility testing add little to the choice of antibiotic for the treatment of UTIs. This current study therefore, reports on antibiotic sensitivity and resistance of bacteria pathogens of UTIs in pregnant women in Ibadan, Nigeria and to determine the extent of resistance of these bacteria pathogens to these drugs in the community.

## MATERIALS AND METHODS

**Study Area:** The study area is the municipal area of Ibadan, which is made up of five local government areas. Ibadan city lies on the longitude 3°5' East of Greenwich meridian and latitude 7°23' North of the Equator. Besides being the largest indigenous city in Africa south of Sahara, the city is an important trade and educational centre. It also houses one of the largest and foremost teaching hospitals in Africa. However, the city is characterized by low level of environmental sanitation, poor housing, and lack of potable water and improper

management of wastes especially in the indigenous core areas characterized by high density and low income populations.

**Selection of Isolates:** Thirty-eight bacterial pathogens were selected for this study. These isolates were recovered from our previous study on pregnant women with UTIs [4] and analyzed at the Medical Microbiology and Parasitology laboratory of University College Hospital (UCH), Ibadan according to the standard bacteriological methods described by Baur *et al.* [7] and Ebie *et al.* [8]. The agar diffusion method described by Baur *et al.* [7] and Ebie *et al.* [8] was employed in this study. Five discrete colonies were inoculated into 5 ml of sterile nutrient broth and incubated at 37°C over night. The broth culture was then diluted 1:10 with a freshly prepared nutrient broth to give a count of approximately  $10^5$  colonies per millimeter. A sterile cotton wool was allowed to soak in the broth culture, squeezed by the side of the bottle before streaking over the sensitivity plates and incubated at 37°C for 18 h. interpretation of results was done using the zone of inhibition sizes. Zones of inhibition of > 18 mm were considered sensitive, 13-17 mm intermediate and < 13 mm resistant. Nitrofurantoin (50 mcg) and Nalidixic acid (30 mcg) anti-microbial discs were used.

## RESULTS

Thirty-eight bacterial pathogens were examined in this study (Table 1 & 2). Of the 38 bacterial isolates obtained, *Escherichia coli* [13 (42.1%)] was the most predominant, followed by *Staphylococcus aureus* [11 (28.9%)], *Klebsiella sp.* [7 (18.4%)] and *Pseudomonas aeruginosa* [2 (5.3%)] and a mixed culture of *Klebsiella* and *Staphylococcus spp.* [2 (5.3%)] (Table 1 and 2). These bacterial isolates were tested against Nitrofurantoin and Nalidixic acid to determine their sensitivity and resistance pattern. The in-vitro antibiotic sensitivity pattern of the isolates to these two (2) common anti-microbial agents is shown in Table 1. Nitrofurantoin and Nalidixic acid were drugs of choice for *Escherichia coli* with sensitivity rates of 100% and 75% respectively. The sensitivity of *Klebsiella pneumoniae* was Nitrofurantoin (85.7%) and Nalidixic acid (71.4%). The sensitivity of *Pseudomonas aeruginosa* to the two drugs was 50.0%. The sensitivity rates of *Staphylococcus aureus* to the two antibiotics were Nitrofurantoin (72.7%) and Nalidixic acid (36.4%). The mixed culture of *Klebsiella spp.* and *Staphylococcus spp.* were 50% sensitive to these drugs.

Table 1: Antibiotics Sensitivity Pattern of Bacterial Pathogen to Nitrofurantoin and Nalidixic Acid

Isolates	No. (%)	No. of strains sensitive to Antibiotics (%)	
		Nitrofurantoin (%)	Nalidixic Acid (%)
<i>Escherichia coli</i>	16(42.1)	16(100.0)	12(75.0)
<i>Klebsiella sp.</i>	11(28.9)	6(85.7)	5 (71.4)
<i>Pseudomonas aeruginosa</i>	7(18.4)	1(50.0)	1(50.0)
<i>Staphylococcus auerus</i>	2 (5.3)	8 (72.7)	4 (36.4)
Mixed cultures	2 (5.3)	1(50.0)	1 (50.0)
Total	38(100.0)	32(84.2)	23(60.5)

Table 2: Antibiotic Resistance Pattern of Some Selected Bacterial Pathogen to Nitrofurantoin and Nalidixic Acid

Isolates	No. (%)	No. of strains resistant to Antibiotics (%)	
		Nitrofurantoin	Nalidixic Acid
<i>Escherichia coli</i>	16(42.1)	0	4(25.0)
<i>Klebsiella sp.</i>	11(28.9)	1(14.3)	2 (28.6)
<i>Pseudomonas aeruginosa</i>	7(18.4)	1(50.0)	1(50.0)
<i>Staphylococcus auerus</i>	2 (5.3)	3 (27.3)	7 (63.6)
Mixed cultures	2 (5.3)	0	0
Total	38(100.0)	5(13.2)	14(36.8)

The *in-vitro* antibiotic resistance pattern of the isolates to Nitrofurantoin and Nalidixic acid is shown in Table 2. The resistance pattern to the two antibiotics was higher for *Staphylococcus auerus* with 63.6% resistance to Nitrofurantoin and 27.3% resistance to Nalidixic acid. *Pseudomonas aeruginosa* showed 50.0% resistance to the two drugs. *Klebsiella sp.* showed 28.6% and 14.3% resistance to Nalidixic acid and Nitrofurantoin respectively while *E. coli* showed 25% resistance to Nalidixic acid (Table 2).

## DISCUSSION

Acquired resistance to antimicrobial drugs is becoming more prevalent among *Vibrio cholerae*, *Salmonella enteritidis*, *diarrheagenic Escherichia coli*, and other pathogens in this region. The poor, who experience most of the infections caused by these organisms, bear the brunt of extended illness and exacerbated proportion of deaths brought about by resistance [1]. The findings of this study have shown that most Gram-negative and Gram-positive bacteria are sensitive to the two antibiotics used. The antibiotics used in this study were Nitrofurantoin and Nalidixic acid because they inhibited commonly isolated Gram-negative bacteria which constituted 66% of the total bacterial pathogens. This is similar to other reports where Nitrofurantoin and Nalidixic acid remain the drug of choice for treatment and management of asymptomatic bacteriuria in pregnant women and symptomatic UTIs in general [8-13]. Nalidixic

acid has been recommended as drug of choice for the treatment of uncomplicated UTIs [5, 11, 14] because of its activity against several different types of Gram-negative bacteria such as *E. coli*, *Klebsiella aerogenes* etc.

The findings of this study compared favorably to Akortha and Ibadin [15] who found that *S. aureus* strains were sensitive to nitrofurantoin (63.5%) and highly resistant to naladixic acid (79.3%). Shittu and Mandara [16] in slight contrast to this study, reported *S. aureus* as 100% sensitive to genta-mycin and cephalosporin and resistant to augmentin and nitrofurantoin. Moreover, these differences in sensitivity pattern of the isolates could be attributed to time difference between the two studies or environmental factors such as practices of self medication, the drug abuse and indiscriminate misuse of antibiotics among the general population, which has favoured the emergence of resistance strains just as it could be the case in other organisms in any particular region or community in Nigeria which hassled to the emergence of bacterial strains that are resistant to these relatively safe antibiotics [8, 10, 15].

Several studies have confirmed that single-dose therapy is highly effective in the treatment of UTIs, with cure rates ranging from 80-99% [17]. Nevertheless, single-dose antibiotic therapy fell into disfavor when it was observed that women had a high risk of recurrence within six weeks of the initial treatment [18]. The risk was attributed to the failure of single-dose antibiotics to eradicate gram-negative bacteria from the rectum, the source or reservoir for ascending uropathogens.

However, a large proportion of the isolates were sensitive to nitrofurantoin and nalidixic acid and should be considered as first line drugs for treating cases of urinary tract infection in this environment. The result of this finding is comparable with Onifade *et al.* [12] and Aiyegoro *et al.* [13] in a similar study on UTIs. This study highlights the presence of multi-resistance *P. aeruginosa* to the two antibiotics used in this study and the poor compliance of the pathogens *in vitro* to antibiotics commonly used in treating UTI [19]. Drug resistance is now of serious concern in Hospitals. Drug resistance is one of nature's never ending process whereby organisms develop a tolerance for new environmental condition. These may be due to a pre-existing factor in the organisms or it may result from the acquired factor(s). Some naturally susceptible strains of bacteria may acquire resistance [11].

These antibiotics such as nitrofurantoin and nalidixic acid may be recommended for the treatment of urinary tract infection when treatment is necessary. Although amoxicillin is frequently suggested as the agent of choice, *E. coli* is now commonly resistant to ampicillin, amoxicillin and cephalexin [17]. Thus, treatment should be based on the results of susceptibility tests. Nitrofurantoin or nalidixic acid may also be used; however, caution should be exercised in the third trimester because the sulfonamides compete with bilirubin binding in the newborn.

The susceptibility patterns seen in this study tend to suggest that it is absolutely necessary to obtain sensitivity reports before initiation of antibiotic therapy in cases of suspected UTIs. Nevertheless, it should be noted that in-vitro antibiotic sensitivity is only a guide and that the conditions may be quite different from those obtained in-vivo. Hence, the ultimate decision to use a particular antibiotic depends on such as factors as its selective toxicity, cost, drug absorption and metabolism, drug clearance rate, bioavailability and serum attainable level. It is therefore suggested that appropriate antimicrobials be administered to reduce the risk of multiply resistance organisms developing and avert ineffectiveness of antibiotics. On the other hand, proper adherence and compliance to drug prescription and dosage on the part of the patients also plays a role in the efficacy of the antibiotics in use.

The adverse effects of infectious diseases in many developing countries, in particular, in sub-Saharan Africa is considerable and, within those countries, economically disadvantaged persons are most likely to contract communicable diseases and least likely to access

appropriate treatment [1, 20-21]. Many bacterial and parasitic diseases could, until recently, be treated with inexpensive antimicrobial agents, but treatment has recently been made more expensive and less successful by the emergence and spread of resistant organisms [1]. Therefore, the findings of this current study have in no doubt highlighted the need for constant monitoring of susceptibility of specific pathogens in different populations to commonly used antibiotics. Prompt therapeutic intervention is therefore advocated in this current study as it is essential to prevent cases of asymptomatic UTI from becoming symptomatic with resultant damage. Though, improved antimicrobial drug stewardship and intervention for resistance control is an often cited in this part of the world, they are inadequately implemented [1]. However, resistance containment also requires improvements in infectious disease control, access to and quality assurance of antimicrobial agents, as well as diagnostic facilities. Structural improvements along these lines will also enhance disease prevention and control as well as rational antimicrobial drug use [1].

It is therefore recommended that routine microbiological analysis and antibiotic sensitivity test of mid stream urine samples of pregnant women and other patients be carried out before the administration of the drugs for the treatment and management of UTIs since resistance to these drugs are developing in the community. Additionally, more research is needed to identify low-cost, high-impact interventions for resistance control. In so doing, development of unusual resistance among such strains could easily be detected, and thus, will help in better treatment and management of those infected.

## REFERENCES

1. Okeke, I.N., O.A. Aboderin, D.K. Byarugaba, K.K. Ojo and J.A. Opintan, 2007. Growing problem of multidrug-resistant enteric pathogens in Africa. *Emerging Infectious Diseases*, 2007 Nov. [cited 2009 August 18]. Available from <http://www.cdc.gov/EID/content/13/11/1640.htm>
2. Arrow, K., C. Panosian and H. Gelband, 2004. Saving lives, buying time. Economics of malaria drugs in an age of resistance. Washington: National Academies Press.
3. Singh, J.A., R. Upshur and N. Padayatchi, 2007. XDR-TB in South Africa: no time for denial or complacency. *PLoS Med.*, 4: e50.

4. Okonko, I.O., L.A. Ijandipe, A.O. Ilusanya, O.B. Donbraye-Emmanuel, A.A. Ogun, O.A. Akanbi, J. Ejembi and T.O.C. Faleye, 2009. Detection of Urinary Tract Infection (UTI) among Pregnant Women in Oluyoro Catholic Hospital, Ibadan, South-Western Nigeria. *Malaysian J. Microbiol.*, (in press).
5. Elhag, K.M. and T.D. Chug, 1982. Bacteriuria in the Arabian Gulf. *Arab. J. Med.*, 1:5-10.
6. Baur, A.W., W.M. Kirby, J.C. Sherris and M. Jurek, 1996. Antibiotic susceptibility testing by a standard single disc method. *American J. Clin. Pathol.*, 451: 493-496.
7. Ebie, M.Y., Y.T. Kandakai-Olukemi, J. Ayanbadejo and K.B. Tanyigna, 2001. Urinary Tract Infections in a Nigerian Military Hospital. *Nigerian J. Microbiol.*, 15 (1): 31-37.
8. Okonofua, E.E.A. and B.N. Okonofua, 1989. Incidence and Pattern of Asymptomatic Bacteriuria of Pregnancy in Nigerian Women. *Nigerian Med. Pract.* 17: 354-358.
9. Akinyemi, K.O., S.A. Alabi, M.A. Taiwo and E.A. Omonigbehin, 1997. Anti-microbial susceptibility pattern and plasmid profiles of pathogenic Bacteria isolated from subjects with urinary tract infections in Lagos, Nigeria. *Nigeria Quarterly J. Hosp. Med.*, 1: 7-11.
10. Omonigho, S.E., E.E. Obasi and R.N. Akukalia, 2001. In-vitro Resistance of Urinary Isolates of *Escherichia coli* and *Klebsiella* species to Nalidixic Acid. *Nigeria J. Microbiol.*, 15(1):25-29.
11. Onifade, A.K., F.O. Omoya and D.V. Adegunloye, 2005. Incidence and control of urinary tract infections among pregnant women attending antenatal clinics in government hospitals in Ondo State, Nigeria. *J. Food, Agric. Environ.*, Vol.3 (1): 37-38.
12. Aiyegoro, O.A., O.O. Igbinosa, I.N. Ogunmwonyi, E.E. Odjadjare, O.E. Igbinosa and A.I. Okoh, 2007. Incidence of urinary tract infections (UTI) among children and adolescents in Ile-Ife, Nigeria. *African J. Microbiol. Res.*, pp: 013-019.
13. Oren, B., R. Raz, H. Hefter, Y. Kennes and T. Potasman, 1991. Antimicrobial Susceptibility of Organisms Infecting the Tract in Northern Israel. *Harefuah*, 120 (20): 60-62.
14. Akortha, E.E. and O.K. Ibadin, 2008. Incidence and antibiotic susceptibility pattern of *Staphylococcus aureus* amongst patients with urinary tract infection (UTI) in UBTH Benin City, Nigeria. *African J. Biotechnol.*, 7 (11):1637-1640.
15. Shittu, S.O. and M.U. Mandere, 1999. Asymptomatic bacteriuria in antenatal patients in A.U.TH Zaria, Trop. J. Obst. Gynea., 16(1): 41.
16. Stamm, W.E. and T.M. Hooton, 1993. Management of urinary tract infections in adults. *N. Engl. J. Med.*, 329:1328-34.
17. Kunin, C.M., 1994. Urinary tract infections in females. *Clin. Infect Dis.*, 18:1-12.
18. Olowu, W.A. and T.G. Oyetunji, 2003. Nosocomial significant bacteriuria prevalence and pattern of bacterial pathogens among children hospitalized for non-infective urinary tract disorders. *West Afr. J. Med.*, 22 (1): 72-75.
20. Schellenberg, J.A., C.G. Victora, A. Mushi, D. de Savigny, D. Schellenberg and H. Mshinda *et al.*, 2003. Inequities among the very poor: health care for children in rural southern Tanzania. *Lancet*. 361: 561-566.
21. Bates, I., C. Fenton, J. Gruber, D. Laloo, A. Medina Lara, S.B. Squire and S. Theobald, 2004. Vulnerability to malaria, tuberculosis, and HIV/AIDS infection and disease. Part 1: determinants operating at individual and household level. *Lancet Infect. Dis.*, 4: 267-77.