# Emergence of Cross- Resistance to Fluoroquinolones in Gram-Negative Isolates from Cancer Infections in a Tertiary Hospital in Nigeria

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**ABSTRACT: Background:** This study determined the gram-negative bacilli associated with various cancer infections and defined fluoroquinolone (Ciprofloxacin, Pefloxacin and Ofloxacin) susceptibility of isolated strains. **Methods:** Materials for research were blood culture, urine, aspirates, fluids and swabs from cancer wounds. Samples were cultured and organisms isolated were determined using API system (Bio-Merieux). Antimicrobial resistance was estimated by the disc diffusion method according to NCCLS/CLSI recommendations and ESBL detection was carried out using the Double Disk Synergy Test method. **Result**: Of the 103 strains isolated 22 (21.4%) were found to be resistant to only ciprofloxacin. Only 1 of these resistances to ciprofloxacin was observed to have an accompanying production of ESBL. Of the 7 isolates that had resistance to a combination of two fluoroquinolones, 2 (28.6%) were found to be ESBL-producers. Cross resistance to the 3 quinolones tested, occurred in 40 (38.8%) of the strains isolated. The strains in this group were observed to be associated in most of the cases with MDR [35 (37.5%)] and production of ESBL [16(41%)]. This group was observed to be predominant amongst strains of *E.coli*, *Pseudomonas* spp and *Klebsiella* spp. **Conclusion:** Cross-resistance to fluoroquinolones has emerged amongst our clinical isolates and more worrisome is its association with ESBL-Production and Multidrug Resistance. Antibiotic resistance surveillance is thus of utmost importance for prompt intervention in the spread of emerging resistance. [The Journal of American Science. 2008;4(4):14-20]. (ISSN: 1545-1003).

**Keywords:** fluoroquinolone resistance, multidrug resistance, ESBL, Cancer, Gram-negative organisms

## INTRODUCTION

The introduction of the fluoroquinolones (FQs) in the 1980s provided clinicians with a class of broad-spectrum agents applicable to a range of gram-negative infections (Ball, 1998, Hooper, 1998). The fluoroquinolones were a major therapeutic advance because they have 100-fold greater activity than their parent compound, nalidixic acid (Bauernfeind and Petermuller, 1983). Unlike nalidixic acid, which is used only for urinary infections and occasionally shigellosis, the fluoroquinolones have a broad range of therapeutic indications and are given as prophylaxis, e.g., for neutropenic patients. (Livermore *et al*. 2002).

Early researchers had thought that fluoroquinolone resistance was unlikely to evolve, largely because resistant *Escherichia coli* mutants are exceptionally difficult to select in vitro (Smith, 1986) and because plasmid-mediated quinolone resistance remained unknown even after 30 years of nalidixic acid usage. Nevertheless, mutational fluoroquinolone resistance emerged readily in staphylococci and pseudomonads, and more recently, fluoroquinolone resistance has emerged in *E. coli* and other Enterobacteriaceae, and these are attributable to multiple mutations that diminish the affinity of its topoisomerase II and IV targets in various ways, reduce permeability, and upregulate efflux (Everett *et al*., 1996). Plasmid-mediated quinolone resistance now has also been reported (Paterson, 2006; Martinez-Martinez *et al*., 1998).

Bacterial infections remain an extremely frequent complication of neutropenia caused by cytotoxic chemotherapy and are a major cause of complications and death in patients with hematologic cancers and chemotherapy-induced neutropenia. (Bucaneve *et al*. 2005). Worldwide, the reported mortality rate due to bacterial infection in patients with cancer and neutropenia has been estimated to be approximately 5% (Cometta *et al*., 1996, Del Favero *et al*., 2001). Neutropenic patients are at high risk for various infectious diseases even if cultures of clinical specimens are not positive. However, the choice of empirical antimicrobial therapy should be evaluated periodically to prevent treatment failure due to antimicrobial resistance. (Siu *et al*., 1999) as the emergence of new groups of antibiotic-resistant bacteria is once again threatening the ability to manage these bacterial infections in cancer patients.

Agents such as ciprofloxacin, norfloxacin and ofloxacin are used in most large cancer treatment centres for antimicrobial prophylaxis in high-risk patients with prolonged neutropenia, including patients with acute leukaemia undergoing remission induction chemotherapy, and recipients of bone marrow transplantation.(Dekker *et al*., 1987; Winston *et al*., 1987). Ciprofloxacin and ofloxacin have also been used for the treatment of febrile episodes in neutropenic patients (generally in combination with agents such as the aminoglycosides, beta-lactams, and vancomycin) both in the hospital and in ambulatory settings (Flaherty *et al*., 1989; Rolston *et al*., 1989; Rubenstein *et al*., 1993). The rise in resistance to many antimicrobials has led to the growth of the fluoroquinolones for use in various forms of infection. But since the early 1990s, Rybak (2004) reported that the resistance to this type of drug has increased by as much as 21%, corresponding to a 2.5-fold increase.

This study thus sets out to investigate the current status of FQ activity against prominent Gram-negative species associated with cancer infection and also to determine phenotypically any association between fluoroquinolone resistance and resistance to the broad spectrum antibiotics, ESBL production and multidrug resistance. This is because a decline in the activity of FQs would lead to many clinical therapy failures in view of the ability of gram-negative bacilli to easily acquire resistance to all these other classes of antimicrobials.

## MATERIALS AND METHODS

### Isolation and Identification

One hundred and three bacteria isolates from 256 patients who attended the Radiotherapy & Radio diagnosis Unit of Lagos University Teaching Hospital, Nigeria between January 2006 and November, 2006 have been included in this study. The identity of the organisms were confirmed with API 20E and API 20NE systems (Bio Merieux, France). These strains were from various clinical sources including blood culture, urine, fluids, aspirates and wounds.

### Susceptibility Testing

Susceptibility testing was performed using antibiotic disk testing to 9 antimicrobials: cefotaxime (30µg), ceftriaxone (30µg), ceftazidime (30µg), imipenem (30µg), gentamicin (10µg), amikacin (30µg), ciprofloxacin (30µg), ofloxacin (30µg) (Oxoid, UK), and pefloxacin (30µg) (May and Baker, Nigeria). Testing was performed on Mueller-Hinton II agar (Oxoid, Basingstoke, United Kingdom) according to NCCLS guidelines (NCCLS, 2000). The control strains *E. coli* ATCC 25922, *E. coli* ATCC 35218, *Proteus vulgaris* ATCC 13315 and *Pseudomonas aeruginosa* ATCC 27853, obtained from the Research laboratory of the Department of Medical Microbiology and Parasitology, College of Medicine, University of Lagos, were run simultaneously with the test organisms. Results were interpreted with the National Committee for Clinical Laboratory Standards now known as Clinical and Laboratory standard Institute (CLSI) criteria for disk diffusion (NCCLS, 2000). Strains with intermediate susceptibility have been included in the 'resistant' category.

### Double-Disk Synergy Test (DDST)

All isolates resistant to at least one of the extended-spectrum cephalosporins (ESCs) namely ceftazidime, ceftriaxone and cefotaxime were subjected to Double-disk synergy tests (DDST) as described by Jarlier *et al*. (1988) with modifications suggested by Thomson and Sanders (1992) to detect the presence of ESBL enzyme.

## RESULT

One hundred and three non-duplicate gram-negative organisms belonging to 12 different species were isolated from clinical samples of various cancer infections of 256 patients, who attended the Radiotherapy & Radio diagnosis unit of Lagos University Teaching Hospital, Nigeria between January 2006 and November, 2006.

Table 1 shows the list of various cancer infections from which the organisms were isolated. Tables 2 and 3 show the antibiotic resistance patterns of the isolates. The strains were classified into 3 groups based on resistant pattern to the FQs. Group 1 showed strains found to be resistant to only ciprofloxacin amongst the 3 FQs tested. This occurred in 22 (21.4%) of the 103 strains. Only 1 of those resistant to ciprofloxacin was observed to have an accompanying production of ESBL. This occurred in a strain of *Acinetobacter calco iwoffii.* Group 2 showed strains with resistance to a combination of any two of the

fluoroquinolones tested. There were 3 combination types of resistance to 2 fluoroquinolones observed in this study ( 1.Pefloxacin and Ciprofloxacin resistance; 2.Ofloxacin and Ciprofloxacin resistance and 3. Pefloxacin and Ofloxacin resistance). Of the 7 isolates that had these types of resistance to a combination of two fluoroquinolones, 2 (28.6%) were found to be ESBL-producers (*E. coli* and *K. planticola*) and both of these ESBL-producers had ciprofloxacin resistance. Group 3 highlights strains resistant to all of the 3 quinolones tested. This occurred in 40 (38.8%) of the strains isolated. This group 3 resistance phenotype was found to be associated in most of the cases with multidrug resistance [35 (87.5%)] and production of ESBL [16(41%)] and was observed to be predominant amongst strains of *E.coli* 13(59%), *Pseudomonas* spp 11(64.7%) and *Klebsiella* spp 7(25%) particularly *K. planticola* 5 (45.5%). Other species in which this resistance phenotype was found were *Providencia* spp, *Enterobacter* spp, *Citrobacter freundii*, *Yersinia enterocolitica* and *Stenotrophomonas maltophilia* (Table 2).

**Table 1: List Of Various Cancer Infections From Which Organisms Were Isolated**

| |
|---|
| Cancer of the Breast |
| Cancer of the Cervix |
| Sigmoid Colon Cancer |
| Cancer of the Lungs |
| Cancer of the Oesophagus |
| Squamous Cell Carcinoma |
| Basal Cell Carcinoma |
| Oropharyngeal Cancer |
| Fibrosarcoma |
| Histiocytoma |
| Nasal Cancer |
| Renal Cell Carcinoma |
| Cancer of Larynx |
| Rhabdomyosarcoma |
| Retinoblastoma |

**Table 2. Antimicrobial Resistance Pattern of Clinical Isolates To The Three Fluoroquinolones Tested and the Strains in the 3 Different Groups**

| Organisms | Total No and % isolated | Cip | Ofl | Pef | Grp 1 | Grp 2 | Grp 3 |
|---|---|---|---|---|---|---|---|
| *K. ozaenae* (4) | | 1 (25%) | 1 (25%) | 1 (25%) | | | |
| *K.pneumoniae*(6) | | 4(66.7%) | 2 33.3%) | 2 (33.3%) | | | |
| *K.planticola* (11) | | 8(72.7%) | 5 45.5%) | 6 (54.5%) | | | |
| *K. oxytoca* (5) | | 2 (40%) | 0 (0%) | 0 (0%) | | | |
| *K.rhinoscleromatis(2)* | | 2 (100%) | 0 (0%) | 0 (0%) | | | |
| ***Klebsiella* spp** | **28(27.2%)** | **17(60.7%)** | **8 8.6%)** | **9 (32.1%)** | **8(28.6%)** | **2(7.1%)** | **7(25%)** |
| ***Escherichia coli*** | **22 21.4%)** | **16 72.7%)** | **16(72.7%)** | **16(72.7%)** | **3(13.6%)** | **3(13.6%)** | **13(59.1%)** |
| *P. alcalifaciens* (1) | | 0 (0%) | 0 (0%) | 0 (0%) | | | |
| *P. stuartii* (2) | | 1 (50%) | 1 (50%) | 1 (50%) | | | |
| ***Providencia* spp** | **3 (2.9%)** | **1 (33.3%)** | **1 (33.3%)** | **1 (33.3%)** | **0 (0%)** | **0 (0%)** | **1 (33.3%)** |
| *A. baumanii* (4) | | 2 (50%) | 0**(0%)** | 1 (25%) | | | |
| *A. calco iwofii* (1) | | 1 (100%) | 0**(0%)** | 0**(0%)** | | | |
| ***Acinetobacter* spp** | **5 (4.9%)** | **3 (60%)** | **0(0%)** | **1 (20%)** | **4 (80%)** | **0 (0%)** | **0 (0%)** |
| *S. amnigenus* (1) | | 0**(0%)** | 0**(0%)** | 1 (100%) | | | |
| *S.liquefaciens*(1) | | 1 (100%) | 0**(0%)** | 0**(0%)** | | | |
| ***Serratia* spp** | **2 (1.9%)** | **1 (50%)** | 0**(0%)** | **1 (50%)** | **2 (100%)** | **0 (0%)** | **0 (0%)** |
| *E. agglomerans* (2) | | 0**(0%)** | 0**(0%)** | 1 (50%) | | | |
| *E. aerogenes* (2) | | 2 (100%) | 1 (50%) | 2 (100%) | | | |
| *E. cloacae* (5) | | 2 (40%) | 2 (40%) | 2 (40%) | | | |
| ***Enterobacter* spp** | **9 (8.7%)** | **4 (44.4%)** | **3 (33.3%)** | **4 (44.4%)** | **1(11.1%)** | **1(11.1%)** | **3 (33.3%)** |
| *C. freundii* (4) | | 2 (50%) | 2 (50%) | 2 (50%) | | | |
| *C. amaloniticus* (3) | | 1 (33.3%) | 0 | 1 (33.3%) | | | |
| ***Citrobacter* spp** | **7 (6.8%)** | **3 (42.9%)** | **2 (28.6%)** | **3 (42.9%)** | **0 (0%)** | **0 (0%)** | **3 (42.9%)** |
| *A. caviae* (1) | | 0 | 0 | 0 | | | |
| *A. fluvialis* (1) | | 0 | 0 | 0 | | | |
| ***Aeromonas* spp (2)** | **2 (1.9%)** | **0** | **0** | **0** | **0 (0%)** | **0 (0%)** | **0 (0%)** |
| ***Proteus mirabilis*** | **5 (4.9%)** | **1 (20%)** | **0** | **1 (20%)** | **0 (0%)** | **1 (20%)** | **0 (0%)** |
| ***Yersinia enterocolitica*** | **1 (0.97%)** | **1 (100%)** | **1 (100%)** | **1 (100%)** | **0 (0%)** | **0 (0%)** | **1 (100%)** |
| ***Stenotrophomonas maltophilia*** | **2 (1.9%)** | **1 (50%)** | **1 (50%)** | **1 (50%)** | **0 (0%)** | **0 (0%)** | **1 (50%)** |
| *P. fluorescens* (3) | | 2 (66.7%) | 2(66.7%) | 2(66.7%) | | | |
| *P. aeruginosa* (14) | | 9 (64.3%) | 10(71.4%) | 12(85.7%) | | | |
| ***Pseudomonas* spp** | **17(16.5%)** | **11(64.7%)** | **12(70.6%)** | **14(82.4%)** | **4(23.5%)** | **0 (0%)** | **11(64.7%)** |

Key:
Cip=Ciprofloxacin, Ofl=Ofloxacin, Pef=Pefloxacin, No=Number

**Table 3. Resistance Pattern to Other Antimicrobials and ESBL-Production**

| Organisms | Imipenem | Amikacin | Gentamicin | Ceftazidime | Cefotaxime | Ceftriaxone | ESBL-Producers |
|---|---|---|---|---|---|---|---|
| *Klebsiella spp (28)* | 2 (7.1%) | 8 (28.6%) | 15 (53.6%) | 11(39.3%) | 16 (57.1%) | 11 (39.3%) | 4 (57.1%) |
| *E.coli (22)* | 1(4.6%) | 5 (22.7%) | 15 (68.2%) | 13 (59.1%) | 15 (68.2%) | 14 (63.6%) | 8 (61.5%) |
| *Providencia spp (3)* | 0 (0%) | 0 (0%) | 1 (33.3%) | 3 (100%) | 3 (33.3%) | 2 (66.7%) | 0 (0%) |
| *Acinetobacter spp (5)* | 0 (0%) | 0 (0%) | 3 (60%) | 3 (60%) | 1 (20%) | 1 (20%) | 0 (0%) |
| *Serratia spp (2)* | 0 (0%) | 1 (50%) | 2 (100%) | 1 (50%) | 1 (50%) | 2 (100%) | 0 (0%) |
| *Enterobacter spp (9)* | 0 (0%) | 2 (22.2%) | 4 (44.4%) | 1 (11.1%) | 3 (33.3%) | 4 (44.4%) | 0 (0%) |
| *Proteus spp (5)* | 0 (0%) | 1 (20%) | 3 (60%) | 2 (40%) | 3 (60%) | 2 (40%) | 0 (0%) |
| *Citrobacter spp (7)* | 0 (0%) | 2 (28.6%) | 3 (42.9%) | 2 (28.6%) | 3 (42.9%) | 2 (28.6%) | 2 (66.7%) |
| *Stenotrophomonas maltophilia (2)* | 0 (0%) | 1 (50%) | 1 (50%) | 0 (0%) | 1 (50%) | 1 (50%) | 0 (0%) |
| *Yersinia spp (1)* | 0 (0%) | 0 (0%) | 1 (100%) | 1 (100%) | 1 (100%) | 1 (100%) | 1 (100%) |
| *Aeromonas spp (2)* | 1 (50%) | 1 (50%) | 0 (0%) | 0 (0%) | 2 (100%) | 0 (0%) | 0 (0%) |
| *Pseudomonas spp (17)* | 6 (35.3%) | 6 (35.3%) | 14 (82.4%) | 8 (47.1%) | 15 (88.2%) | 16 (94.1%) | 1 (9.1%) |

**DISCUSSION**

We determined the activities of three fluoroquinolones (ciprofloxacin, ofloxacin and pefloxacin), and six comparative agents against aerobic gram-negative organisms isolated from cancer patients attending the Radiotherapy & Radiodiagnosis unit of Lagos University Teaching Hospital, Nigeria. Ciprofloxacin and other FQs resistance has been focused on in this study, because of the increasingly frequent use of fluoroquinolones for treatment in most large cancer treatment centres for antimicrobial prophylaxis (Rubenstein et al., 1993, Flaherty et al., 1989, Rolston et al., 1989, Dekker et al., 1987).

Notable findings in this study include the presence of a number of gram-negative pathogens not commonly encountered in clinical samples of patients from this environment. These organisms included *Stenotrophomonas maltophilia*, *Aeromonas caviae, Aeromonas fluvialis, Yersinia enterocolitica, Providencia alcalifaciens* and *Providencia stuartii*. This finding is in agreement with the report by Oppeinheim [1998] who reported that cancer patients and more particularly the neutropenic host is extremely vulnerable to a range of bacterial infections. Indeed, for some of the rarer opportunistic organisms, this is sometimes the only setting in which infection occurs.

Secondly, resistance to ciprofloxacin which is known to be one of the most potent FQs (Habib Babay, 2007), and which is also widely used in this environment, was observed to be high amongst the Gram-negative organisms identified in this study except for *Aeromonas* spp. This may be due to the fact that it is one of the commonest FQ used in this environment for therapeutic purposes. The rise in resistance to many antimicrobials has led to the growth of fluoroquinolones use in various forms of infection. Incidence of FQ resistance has now been reported to have increased markedly in recent years due to increase in use in human, agricultural and veterinary sector (Paterson, 2006, Aibinu *et al*., 2004). The most notable resistance to ciprofloxacin in this study occurred in *Yersinia enterocolitica* (100%), *E.coli* (72.7%), *Pseudomonas* spp (64.7%), *Klebsiella* spp (60.7%) and *Acinetobacte*r spp (60%).

Thirdly, there was cross-resistance to other FQs amongst the ciprofloxacin-resistant organisms. 40 (38.8%), of the strains isolated, had resistance to ciprofloxacin and the other 2 FQs used in this study. This development is rather a worrisome trend in this environment. Though cross-resistance had been observed with other newer fluoroquinolones against ciprofloxacin-resistant gram-negative bacteria in other regions of the world (Tankovic et al., 1999) few data exist on such report here in Nigeria.

Fourthly, the most disturbing finding of this work is the occurrence of extended-spectrum beta-lactamase (ESBL)-production and multi-drug resistance amongst the group 3 strains. Of the 40 strains that

had resistance to the 3 FQs tested, 16 (41%) were found to be ESBL-producers and 35 (87.5%) were multi-drug resistant. Production of ESBL enzymes confers resistance on organisms producing this enzyme against the third generation cephalosporins which are amongst the last line drugs available in this environment for treatment of serious infections. Existence of resistance to a combination of 3 FQs in association with ESBL-production and MDR, particularly in cancer patients is a great cause for concern. This may be one of the underlying or contributing factors to the high mortality and morbidity rate observed amongst cancer patients in this environment as therapeutic options available due to these resistances is grossly limited. More investigation needs to be carried out to ascertain this.

The global public health implication of the findings of this work is the potential mobility of these MDR strains and the plasmids that may harbor them, as plasmid-mediated quinolone resistance is being reported now (Paterson, 2006; Martinez-Martinez et al., 1998). Patients move from one health care centre to the other, interchangeably; in both developed and developing countries where adequate and qualitative treatment can be obtained; particularly when it is related to cancer treatment. In essence it is imperative to carefully continue to monitor trends in infection and modify our guidelines for treatment accordingly. This can be achieved by routinely screening patients to be admitted into health-care institutions for possible colonization or infection with a cross-resistant and MDR organism. This will guide the clinicians in the appropriate treatment to be given to such patients and also in the implementation of adequate infection control practices that should be followed for a timely intervention and prevention of spread of such resistance in health-care institutions and amongst health-care workers.

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