Antimicrobial Resistance in Nigeria: An Overview

F. T. Ogunsola, C. N. Kesah, and Tolu Odugbemi
Department of Medical Microbiology and Parasitology
College of Medicine, University of Lagos
Idi–Araba, Lagos.

Correspondence: **F. T. Ogunsola**

SUMMARY

The resistance patterns of common pathogen like *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Neisseria gonorrhoear, Neisseria meningitidis* amongst others have been reviewed in the period between 1979 and 1994. The studies in general have given limited information but show a general increase in resistance to commonly used antibiotics like penicillin, cotrimoxazole, ampicillin, tetracycline, chloramphenicol, streptomycin and erythromycin. Sensitively rates to third generation cephalosporins, and quinolones are still high, thus, in life threatening infections, e. g. meningitis and septicaemia, treatment with these agents is advocated for empiric therapy. This review emphasizes the urgent need for a good antibiotic policy to guide the therapy of infectious diseases.

Key Words: Antibiotics, Resistance, Nigeria

INTRODUCTION

Antimicrobial agents, and in particular beta–lactam drugs, are widely used in most parts of the world. The widespread and indiscriminate use of antimicrobial agents in developing countries have adversely influenced the antibiotic resistance rates. Antibiotics are easily purchased without prescription both from legal sources like pharmacies and chemists and from illegal sources like flea markets and street hawkers[1, 2].

In Nigeria, most classes of antibiotics can be bought. The most common being, the beta–lactams, tetracyclines, aminoglycosides, cotrimoxazole and chloramphenicol. Table I, is a list of the different classes of antibiotics, with locally available examples, their modes of action and mechanisms of resistance. There may exist more than one mechanism of resistance to each antibiotic. Some organisms may possess more than one mechanism for evading the effect of a particular antibiotic or may be resistant to more than one type or class of antibiotic (multiple–antibiotic resistance). The presence of de–activating enzymes (e. g. beta–lactamase resistance) is probably the most common mechanism of resistance. There abound many anecdotal reports on resistance to virtually every antibiotic in Nigeria. Unfortunately very little work has been carried out in Nigeria to study the mechanisms of resistance to the different antibiotics. Most of the work has been on the production of beta–lactamases by clinical isolates[3–7,10]. Some work has also been carried out on plasmids responsible for tetracycline resistance[23].

Antimicrobial susceptibility testing is essential for the rational therapy of most bacterial infection. Information on antimicrobial susceptibility testing in Nigeria is inadequate[9–17] and the information obtained from these have been limited. This study was carried out to review the existing literature on antibiotic susceptibility testing, highlight the problems and stress the need for a continuous surveillance of the susceptibility profiles of bacteria because of the impact on therapy and control of infectious diseases.

Resistance to beta–lactam antibiotics

The prevalence of organisms resistant to beta–lactam antibiotics has probably been the most studied in Nigeria[3–9] and even these do not give the overall picture in the country. A lot of these studies were carried out in Lagos, while a few were reported from Jos and Ilorin[3–9,21]. The studies show widespread production of beta–lactamase by many of the commonly encountered pathogens.

Table II shows the prevalence of bela–lactamase producers amongst some clinical isolates. These studies were carried out belween 1979 and 1996. The beta–lactamase profiles of *Neisseria gonorrhoeae, Neisseria Meningitdis, Moraxella catarrhalis, Streptococcus pyogenes, Staphylococcus aureus, Yersinia enterocolitica, Salmonella spp, Enterococcus faecalis, Klebsiella pneumoniae, Escherichia coli* and *Proteus spp* have been studied.

Resistance of *N. gonorrhoeae* to beta–lactams has been well documented (24, 25) and this was borne out by two studies carried out 5 years apart in 1988 in Lagos[5] and 1993 Ilorin[4] which showed 81.8% and 81.2% of beta–lactamase producers respectively. On the other hand a study in 1993[4] of 68 isolates of *N. meningitidis* confirmed the continued susceptibility of this organism to penicillin. No beta–lactamase producer was identified. This confirmed the report of Njoku–Obi and Agbo[6] who in 1976, reported a 95% sensitivily of *N. meningitidis* to penicillin.

Obi *et al* in 1995 reported that 20 (33%) of 60 isolates of *N. catarrhalis* were beta–lactamase producers. Unfortunately, a trend cannot be commented upon because in the study in 1994[15] only one clinical isolates of *M. catarrhalis* was tested.

The rates of beta–lactamase production amongst enterobacteria in Lagos is high. Over 94% and 93% of *E. coli* and *K. pneumoniae* respectively were found to be beta–lactamase producers by Odugbemi *et al* in 1995[15]. In 1992 all of the 15 isolates of *Y. enterocolitica* tested for beta–lactamase production were producers[19] while only 21 (36%) of 58 isolates of *Salmonella spp.*[9] produced the enzyme.

In 1994, a comprehensive study was carried out involving 460 clinical isolates[15]. Approximately 80% of all isolates were positive for beta lactamase production. Interestingly none of the 30 isolates of *E. faecalis* was beta–lactamase positive. (Table III) suggesting that ampicillin may still be adequate for treatment of enterococci in this environment. Another study involving a larger number of isolates, preferably, from all over the country will confirm this. A high proportion (68.42%) of clinical isolates of *P.*

mirabilis were found to be beta–lactmase producers[15] while most strains of *K. pneumoniae* (Table IV) were resistant to amoxyclav (augmentin), cephalothin, piperacillin, gentamicin (65.6%), chloramphenicol and cotrimoxazole (septrin). *Pseudomonas aeruginosa* is reknowned for being multiply – antibiotic resistant, Odugbemi *et al.* in 1994[15] tested a small number of clinical isolates against antibiotics believed to have good activity against *P. aeruginosa* (Table V). There was 100% sensitivity to Piperacillin, Imipenem, Amikacin and Ciprofloxacin, 85% sensitivity to aztreonam, 78.5% to gentamicin and less than 65% to cefotaxime and ticarcillin. All strains were resistant to amoxyclav. This gives food for thought because the antibiotics with 100% activity to this organism are all prohibitively expensive and most are not easily available in the Nigerian market. In 1984, Amiebenom *et al.*[22] showed 83% of *Staph. aureus* isolated from neonates in Zaria were still sensitive to cloxacillin though they were resistant to penicillin and ampicillin.

The susceptibility pattern of *Staph. aureus* in 1994, on the other hand, is grim (Table IV) Commonly used antibiotics against this organism, I. e. penicillin, oxacillin (representing cloxacillin and flucloxaciilin) gentamicin and tetracycline show less than 50% activity against all the strains tested. Erythromycin is slightly better with 64% activity while fusidic acid still has good activity. All strains of *Staph. aureus* tested were sensitive to Vancomycin.

Resistance to other antibiotics

Very few studies have been carried out to determine the basis for resistance of clinical isolates to antibiotics other than beta–lactams. Most studies show susceptibility patterns of different organisms to various antibiotics Including beta–lactmase antibiotics[9, 12, 17, 18] Kandakai–Olukemi, Bello and Olukemi in 1996[21] showed that *Staph. aureus* strains isolated from nurses at Jos showed that 10 (20%) of 50 isolates were resistant to cloxacillin, erythromuycin and azithromycin only. All resistant isolates were found to be beta–lactamase positive.

In 1986, Onile *et al*[12] showed the susceptibility patterns of bacteria causing septicaemia in Ilorin (Table VII), most isolates were resistant to ampicillin, tetracycline, chloramphenical and streptomycin. In particular, most isolates of *Streptococcus pneumoniae* showed resistance to tetracyciine, chloramphenicol, septrin. Unfortunately no isolate was tested against oxaciilin to screen for penicillin – resistance. In 1993, Olukoya, Daini and Niemogha[23] identified the plasmids in enteric bacteria coding for resistance to tetracycline. Twelve types of piasmids were isolated with molecular weights ranging between 3 to 180 kilo bases. These plasmids also coded for resistance to ampicillin, cotrimaxazole and streptomycin. There is still a need to determine the mechanism of resistance of the various organisms to chloramphenicol, gentamicin, tetracycline, the microiides and other groups of antibiotics.

Sensitivity to the quinolones is still very high. Using Ofloxacin as a prototype, all isolates of *K. pneumoniae*, *B. cepacia*, *E. coli*, *Staph. aureus* and Enterococci isolated in 1996 from 250 septicaemic neonates in Lagos were found to be 100% sensitive [20]. This mimics the pattern observed with the cephalosporins (2nd and 3rd generations) in 1994[15].

Susceptibility may remain high for a few more years because these drugs are expensive and beyond the reach of most individuals. But their use is increasing and resistance may become more problematic in the years to come.

CONCLUSION

Antibiotic resistance is a real problem in Nigeria because of the easy accessibility of antibiotics[2] and the presence in the market of many substandard drugs. The trend as can be seen is for increasing resistance to all antibiotics. Many of the common organisms are already resistant to many of the common (and cheaper) antibiotics with negative implications for therapy. Many Nigerians self medicate[2]. There is need for a continuous surveiilance of antimicrobial resistance trends in the country. In addition studies to determine the basis for resistance, whether they are due to transmissible plasmids or are chromosomall y mediated are needed so as to be able to predict trends and hopefully develop a comprehensive and practical antibiotic policy which if properly implemented may reverse the trend.

Table I

Classes of Antibiotics with the Mechanisms of Antimicrobial Resistance

Class of Antibitic	Example	Mode of Action	Mechanism of Resistance
1. Beta–lactams			
a) Penicillin – natural	Penicillin G Penicillin V.		B-lactamase* (plasmid)
– Broad spectrum	Ampicillin Bacampicillin Amoxycillin	Inhibition of cell wall synthesis	– B–lactamase (plasmid)
– Isoxazolyl Penicillin i. e. B–lactamase resistant	Methicillin Cloxacillin Flucloxacillin		Alteration of* Penicillin Binding proteins (PBP) (Chromosomal)
b) B-lactamase Inhibitors	Sulbactam Clavulanic acid		
c) Cephalosporins	Cefuroxime, Cephalothin, Celoxitin, Ceftazidime		B–lactamase*/ PBP changes
2. Aminogly–cosides	Gentamicin Streptomycin	Inhibition of protein synthesis	– *Deactivating enzymes – Alteration of ribosomal binding sites
3. Aminocycli–tols	Spectinomycin		
4. Tetracy–cline	Oxytetracycline Doxycycline	* Efflux	* Altered target
5. Chloramphe–nicol	Chloramphe–nicol		–Enzyme deactivation – Impermeability
6. Sulphonamides	Sulphadiazine Trimethoprim Cotrimoxazole	Inhibition of folate metabolism	*Altered metabolic pathway
7. Macrolides	Erythromycin Azithromycin	Protein synthesis	Altered targets – Enzyme modification

Table I (Contd.)

Class of Antibiotics	Example	Mode of Action	Mechanism of Resistance
8. Lincosamides	Lincomycin Clindamycin		
9. Quinolones	Nalidixic acid Norfloxacin Ofloxacin Ciprofloxacin	DNA replication	*Altered DNA gyrase Reduced Permeability
10. Glycopeptides	Vancomycin Teicoplanin	cell wall	Blocking of drug access to binding sites
11. Carbapenems	Imipenem	Inhibition of cell wall synthesis	
12. Polymycins	Polymixin E (colistin)	Cell membrane destruction	
13. Metronidazole		DNA replication	–Reduced uptake * Reflux – impermeability.
14. Rifampicin		DNA replication	

KEY: * = Major resistance pathway.

Table II

Beta–lactamase production amongst local isolates

Isolates	No. of Strains tested	No.% Positive	Authors/Year/ Locality
Neisseria gonorrhoeae	133	108(81.2)	Agbabiaka *et al*[4] (1993), Lagos
Neisseria gonorrhoeae	22	18(81.8)	Odugbemi & Onile (1988), Ilorin[5]
Neisseria meningitidis	68	0(0)	Agbabiaka *et al*[4] (1993), Lagos
Moraxella (Branhamella) catarrhalis	60	20(33)	Obi, Animashaun & Odugbemi (1990)[7]
Moraxella catarrhalis	1	1(100)	Odugbemi *et al.* (1995)[15]
Yersinia enterocolitica	15	15(100)	Agbonlahor & Odugbemi (1982)[19] Lagos
Staphylococcus aureus	202	143(70.8)	Rotimi *et al*(1979)Lagos
Staphylococcus aureus	117	98(83.76)	Odugbemi et al. (1995)[15] Lagos.
Staphylococcus aureus	50	49(98%)	Kandakai–Olukemi et al (1996), Jos[21]
Enterococcus faecalis	30	0(0)	Odugbemi et al. (1995) Lagos[15].
Klebsiella pneumoniae	103	96(93.20)	Odugbemi et al. (1995) Lagos[15].
Escherichia coli	105	09(94.29)	Odugbemi et al. (1995) Lagos[15].
Proteus mirabilis	38	26(68.42)	Odugbemi et al. (1995) Lagos[15].

Table III

Comparison of Susceptibility of *Enterococcus faecalis* Isolates to various Antibiotics in 1994

Antimicrobial agents	MIC break Point (ug/ml)	1994 Number of Strains tested	1994 % Susceptibility
Penicillin G	8	8	100
Amoxycillin	8	8	100
Cephalothin	8	8	12.5
Chloramphenicol	8	8	57.5
Tetracycline	4	8	0
Erythromycin	0.5	8	0
Clindamycin	0.5	8	50
Vancomycin	4	8	100

(From Odugbemi *et al.* 1995)[15]

Table IV

Comparison of Susceptibility of *Klebsiella pneumoniae* Isolates to various Antibiotics in 1994

Antimicrobial agents	MIC break point (ug/ml)	1994 Number of strains tested	1994 % Susceptibility
Amoxycillin–Clavulanic acid	8/4	29	27.6
Amoxycillin	8	4	0
Mecillinam	16	28	42.8
Piperacillin	16	28	17.8
Cephalothin	8	34	38.2
Cefoxitin	8	28	92.8
Cefotaxime	8	33	90
Gentamicin	4	32	34.4
Amikacin	16	30	100
Chloramphenicol	8	33	27.3
Tetracycline	4	33	27.3
Nalidixic acid	16	14	92.8
Trimethoprim–Sulphamethoxazole	2/38	33	42.4

(From Odugbemi et al., 1995)[15]

Table V

Comparison of Susceptibility of *Pseudomonas aeruginosa* Isolates to various Antibiotics in 1994

Antimicrobial agents	MIC break point (ug/ml)	1994 Number of strains tested	1994 % Susceptibility
Amoxycillin–Clavulanic acid	8/4	10	0
Ticarcillin	64	14	60
Piperacillin	64	11	100
Cefotaxime	8	12	50
Aztreonam	8	13	85
Imipenem	4	14	100
Gentamicin	4	14	78.5
Amikacin	16	14	100
Ciproloxacin	1	8	100

(From Odugbemi *et al.*, 1995)[15]

Table VI

Comparison of Susceptibility of *Staphylococcus aureus* Isolates to various Antibiotics in 1994

Antimicrobial agent	MIC break point (ug/ml)	1994	
		Number of strains tested	% Susceptibility
Penicillin G	0.12	39	5
Oxacillin	2	37	43
Amoxycillin–Clavulanic acid	4/2	31	71
Gentamicin	4	39	33
Tetracycline	4	39	23
Erythromycin	0.5	39	64
Clindamycin	0.5	21	71
Rifampicin	1	28	89
Fusidic acid	16	24	87.5
Vancomycin	4	38	100
Trimethoprim–Sulphamethoxazole	2/38	39	64

(From Odugbemi *et al.*, 1995)[15]

Table VII

Antimicrobial Susceptibility of Bacteria Causing Septicaemia in Ilorin

Percentage Sensitive Strains (No. of Strains tested)

	PENICILLIN G	AMPICILLIN	TETRACYCLINE	CHLORAMPHENICOL	SEPTRIN	CEFOTAXIME	STREPTOMYCIN	CEFOXITIN	GENTAMICIN	AUGMENTIN
Salmonella spp.		84.7 (72)	94.7 (76)	95.1 (41)	79.1 (86)	97.3 (74)	47.7 (67)	96.4 (28)	100 (19)	100 (16)
Atypical bacterium	0 (1)	7.7 (26)	10.3 (29)	7.7 (13)	18.2 (22)	58.9 (26)	16 (25)	63.6 (11)	61.5 (13)	58.8 (17)
Klebsiella spp.	NT	0 (30)	29.4 (34)	50 (18)	51.6 (31)	100 (31)	24 (33)	100 (18)	83.3 (12)	82.4 (17)
Esch. coli	NT	17.4 (23)	17.4 (23)	20 (5)	60.9 (23)	95.3 (21)	13.3 (15)	75 (12)	63.6 (11)	80 (5)
Staphylococcus aureus	11.3 (29)	28.7 (59)	14.3 (63)	79.1 (19)	84.2 (57)	45.2 (45)	38.3 (47)	92.6 (27)	100 (3)	100 (3)
Strept. pneumoniae	100 (9)	100 (11)	8.3 (12)	35.7 (7)	33.3 (12)	100 (4)	4 (11)	100 (12)	NT	100 (9)
Beta–haemolytic Streptocci	100 (4)	100 (9)	60 (5)	100 (1)	0 (5)	66.7 (3)	20 (4)	66.7 (11)	100 (5)	NT

NT = Not tested (From Onile et al., 1995)[15].

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