CEFTRIAXONE RESISTANCE IN TERTIARY HOSPITAL SOUTH EASTERN NIGERIA: A RETROSPECTIVE STUDY

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Abstract

Background: Amid the global crisis of antibiotic resistance, including ceftriaxone resistance, physicians continue to prescribe ceftriaxone as an empiric first line treatment for both community acquired and hospital acquired infections. The study aimed at detecting the rate of ceftriaxone resistance to isolated bacteria in Nnamdi Azikiwe University Teaching Hospital, Nnewi.

Methods: A check list was used to extract information from the Antimicrobial Susceptibility testing records in the Medical Microbiology and Parasitology Laboratory of the hospital, over a period of one year. Information including patient's sex, ward, specimen type, bacteria isolated, and their ceftriaxone susceptibility profile were documented on a proforma. Statistical analysis of the data was done using STATA version 13 statistical package.

Results: A total of 225 isolates were subjected to ceftriaxone sensitivity testing. The prevalence of ceftriaxone resistance in the total bacteria population was 110/225(48.89%), while resistance rates for *Staphylococcus aureus, Klebsiella species, Escherichia coli* and *Pseudomonas aeruginosa,* the commonest pathogens implicated in health-care associated infections were 12/19(63.2%), 19/35(54.3%), 43/81(53.1%), and 13/25(52.0%) respectively. The specimen from which isolated organisms showed the most resistance was wound swabs 33/44(75.0%). There were statistically significant relationships between isolated bacteria and ceftriaxone resistance (*P*= 0.034), as well as cultured specimen and ceftriaxone resistance (*P*= 0.001).

Conclusion: The rate of ceftriaxone resistance in this setting is high, hence, there is a need to review the antibiogram of several pathogens in the hospital and come up with a new antibiotic for empirical use.

Key words: ceftriaxone, resistance, cephalosporin, Nigeria

INTRODUCTION

Ceftriaxone is an extended spectrum cephalosporin belonging to the beta-lactam group of antibiotics.[1][2] Although ceftriaxone was developed mainly for the treatment of invasive and probably severe life threatening infections, its inappropriate and irrational use as well as that of most other beta lactam agents in developing countries remain the major factors that promote the spread of antimicrobial resistance.[3][4][5]

Resistance to extended-spectrum cephalosporins requires sequential and multiple mutations of target genes, but the commonest mechanisms of resistance to ceftriaxone are by enzymatic degradation with extended-spectrum ß-lactamases (ESBLs) and AmpC ß-lactamases.[1][2][3] Furthermore, genes responsible for the development of these resistance enzymes are transmitted horizontally between bacteria, hence when these antibiotics are used empirically in frequent proportions in the treatment of non-specific infections or other disease states, the spread of resistance is facilitated.[1][6]

Globally, there has been an increase in the prevalence of antimicrobial resistance (AMR), especially among the *Enterobacteriaceae*,[6] with ceftriaxone resistance almost reaching the limits. This has resulted in increased patient morbidity and mortality, increased health-care costs, and increased use of last-line antibiotics[3][6]. It is these deleterious effects that ceftriaxone resistance poses on the society that has made major health organizations to label ceftriaxone resistant *Enterobacteriaceae* as priority pathogens of critical importance.[7]

In Nigeria, ceftriaxone is notably one of the commonest drugs used as first line empirical parenteral therapy for most infectious disease conditions as well as surgical prophylaxis, hence, strengthening regulatory bodies with information on its resistance profile will go a long way in restructuring antibiotic prescribing patterns as well as curbing further antibiotics resistance in the country. This audit was a surveillance on ceftriaxone resistance in Nnamdi Azikiwe University Teaching Hospital over a period of one year.

METHODS

Study Design: It was a retrospective study which assessed the antimicrobial susceptibility testing records in the Medical Microbiology laboratory of Nnamdi Azikiwe University Teaching Hospital, Nnewi, to determine the ceftriaxone resistance patterns of different bacterial isolates over a period of one year spanning from 1st January, 2019 to 31st December, 2021. The work was conducted as part of the routine antimicrobial resistance surveillance of the Infection Prevention and Control Committee (IPC), in collaboration with the Infectious Diseases Group of Nnamdi Azikiwe University Teaching Hospital Research Society of the institution. A check list was used to extract information from the Antimicrobial Susceptibility testing records, wherein information including patient's sex, ward, specimen type, bacteria isolated, and their susceptibility profile to ceftriaxone were documented.

Ethical Consideration

All information for this study were obtained from the record books in the Medical Microbiology laboratory of the institution, by the Infectious Disease Research Group of Nnamdi Azikiwe University Research Society and the Infection Prevention and Control Committee of the institution. Hence, ethical approval was waived.

Statistical Analysis

Data obtained in the course of the research, was summarized and presented using Frequency distribution tables, while chi square was used to test for associations between categorical variables at level of significance <0.05.

RESULTS

A total of 225 test records were retrieved with ceftriaxone antibiogram documented, and these records revealed that specimens were collected from individuals with a female:male ratio of 1.05:1. Also, majority of the tests done were referred from the general out patient department 52(23.1%), followed by the accident and emergency ward 33(14.7%). The most frequently requested investigation yielding the isolates was urine culture and sensitivity 74/225(32.9%), while the most frequently isolated organism was *Escherichia coli* 81/225(36.0%) (Table 1).

The prevalence of ceftriaxone resistance in the total bacteria population was 110/225(48.9%), while resistance rates for *Staphylococcus aureus, Klebsiella species, Escherichia coli* and *Pseudomonas aeruginosa,* the commonest pathogens implicated in health-care associated infections were 12/19(63.2%), 19/35(54.3%), 43/81(53.1%), and 13/25(52.0%) respectively. There was statistically significant relationships between isolated bacteria and ceftriaxone resistance (P= 0.034) (Table 2).

The specimen from which isolated organisms showed the most resistance was wound swab 33/44(75.0%), and there was a statistically significant relationship between specimen type and ceftriaxone resistance (P= 0.001) (Table 3).

The relationship between ward/clinics and ceftriaxone resistance was not statistically significant (P= 0.250). (Table 4).

Table 1: Distribution of several socio-demographic parameters

Parameter	Frequency (n)	Percent
Gender		
Female	115	51.1
Male	110	48.9
Total	225	100.0
Ward/Clinic		
General Out Patient Department	52	23.1
Accident and Emergency	33	14.7
Surgical Out Patient	21	9.3
Gynaecology	21	9.3
Medical Out Patient	18	8.0
Female Medical Ward	14	6.2
Retro viral Disease	9	4.0
Paediatrics Medical Ward	7	3.1
Male Surgical Ward	6	2.7
Female Surgical Ward	5	2.2
Paediatrics Surgical Out Patient	5	2.2
Ear/Nose/Throat	5	2.2
National Health Insurance Scheme	5	2.2
Lying in Ward	4	1.8
Male Medical Ward	3	1.3
Antenatal Care	3	1.3
Paediartics Surgical Ward	3	1.3
Children Emergency Room	2	0.9
Children Out Patient	2	0.9
Special Care Baby Unit	2	0.9
Intensive Care Unit	2	0.9
Respiratory	2	0.9
Orthopaedics	1	0.4
Total	225	100.0
Specimen		
Urine	74	32.9
Sputum	49	21.8
HVS	16	7.1
Semen	12	5.3
Ear Swab	7	3.1
Throat Swab	6	2.7
Blood	6	2.7
Stool	4	1.8
Pus Aspirates	3	1.3
Catheter Tip	2	0.9
Wound Swab	2	0.9
Pleural Fluid	1	0.4
ECS	1	0.4
Total	225	100.0

Isolated Organisms		
Escherichia coli	81	36.0
Klebsiella species	35	15.6
Coagulase negative Staphylococcus	33	14.7
Pseudomonas aeruginosa	25	11.1
Staphylococcus aureus	19	8.4
β- haemolytic Streptococcus	17	7.6
α- haemolytic Streptococcus	7	3.1
Proteus species	3	1.3
γ- haemolytic Streptococcus	2	0.9
Enterococcus species	1	0.4
Citrobacter species	1	0.4
Salmonella species	1	0.4
Total	225	100.0

n= Frequency; %= Percentage; *P*-value= Probability

Table 2: Relationship between isolated bacteria and ceftriaxone resistance

	Ceftriaxone Resistance		
Isolate (n)	**Yes, n(%)**	**No, n(%)**	***P*-value**
Escherichia coli (81)	43(53.1)	38(46.9)	0.034
Klebsiella species (35)	19(54.3)	16(45.7)	
Coagulase negative *Staphylococci (33)*	15(45.5)	18(54.6)	
Pseudomonas aeruginosa (25)	13(52.0)	12(48.0)	
Staphylococcus aureus (19)	12(63.2)	7(36.8)	
β- haemolytic Streptococci (17)	2(11.7)	15(88.2)	
α- haemolytic Streptococci (7)	1(14.3)	6(85.7)	
Proteus species (3)	1(33.3)	2(66.7)	
γ- haemolytic Streptococci (2)	2(100.0)	0(0.0)	
Citrobacter species (1)	1(100.0)	0(0.0)	
Enterococcus species (1)	1(100.0)	0(0.0)	
Salmonella species (1)	0(0.0)	1(100.0)	
Total (225)	110(48.9)	115(51.1)	

n= Frequency; %= Percentage; *P*-value= Probability

Table 3: Relationship between cultured specimen and ceftriaxone resistance

	Ceftriaxone Resistance		
Specimen	**Yes, n(%)**	**No, n(%)**	***P*-value**
Urine (74)	45(60.8)	29(39.2)	0.001
Sputum (49)	15(30.6)	34(69.4)	
Wound Swab (44)	33(75.0)	11(25.0)	
HVS (16)	4(25.0)	12(75.0)	
Semen (12)	3(25.0)	9(75.0)	
Ear Swab (7)	2(28.6)	5(71.4)	
Blood (6)	3(50.0)	3(50.0)	
Throat Swab (6)	1(16.7)	5(83.3)	
Stool (4)	1(25.0)	3(75.0)	
Pus Aspirates (3)	1(33.3)`	2(66.7)	
Catheter Tip (2)	1(50.0)	1(50.0)	
Pleural Fluid (1)	0(0.0)	1(100.0)	
ECS (1)	1(100.0)	0(0.0)	
Total (225)	110(48.9)	115(51.1)	

n= Frequency; %= Percentage; *P*-value= Probability

Table 4: Relationship between ward/clinic and ceftriaxone resistance

	Ceftriaxone Resistance		
Ward Clinic (n)	**Yes, n(%)**	**No, n(%)**	***P*-value**
General Out Patient Department (52)	20(38.46)	32(61.54)	0.250
Accident and Emergency (33)	15(45.45)	18(54.55)	
Surgical Out Patient (21)	14(66.67)	7(33.33)	
Gynaecology (21)	7(33.33)	14(66.67)	
Medical Out Patient (18)	9(50.00)	9(50.00)	
Female Medical Ward (14)	8(57.14)	6(42.86)	
Retro-viral Disease (9)	4(44.44)	5(55.56)	
Paediatrics Medical Ward (7)	5(71.43)	2(28.57)	
Male Surgical Ward (6)	4(66.67)	2(33.33)	
Female Surgical Ward (5)	5(100.00)	0(0.00)	
Paediatric Surgery Out Patient (5)	2(40.00)	3(60.00)	
Ear Nose and Throat (5)	1(20.00)	4(80.00)	
National Health Insurance (5)	1(20.00)	4(80.00	
Lying in Ward (4)	2(50.00)	2(50.00)	
Male Medical Ward (3)	2(66.67)	1(33.33)	
Antenatal Care (3)	2(66.67)	1(33.33)	
Paediatric Surgical Ward (3)	1(33.33)	2(66.67)	
Special Care Baby Unit (2)	2(100.00)	0(0.00)	
Intensive Care Unit (2)	2(100.00)	0(0.00)	
Children Emergency Room (2)	1(50.00)	1(50.00)	
Children Out Patient (2)	1(50.00)	1(50.00)	
Respiratory (2)	1(50.00)	1(50.00)	
Orthopaedics (1)	1(100.00)	0(0.00)	
Total (225)	110(48.89)	115(51.11)	

n= Frequency; %= Percentage; *P*-value= Probability

DISCUSSION

Ceftriaxone, a third-generation cephalosporin antibiotic frequently used to treat invasive infections caused by *Enterobacteriaceae*, as well as other bacterial pathogens has increasingly been abused in most countries of the world.[8][9][10] This has resulted to bacterial pathogens developing high level resistance to this antibiotic, thus leading to increased morbidity, mortality, prolonged hospital stay, increased health-care costs, and increased use of last-line antibiotics in patients who would have otherwise recovered from their illnessses without much difficulties or complications.[8][9][11] Till date, most African health-care institutions use ceftriaxone as first-line empiric antibiotic for invasive infections.[12][13]

In this study, a large proportion of the requested investigations were referred from the general out patient department 52(23.1%), thus, implying that in addition to the health-care settings, ceftriaxone resistance is also present in the community. The situation could be explained by the fact that in Nigeria antibiotics are sold as over the counter medication which are easily accessible to the community.[14]

The prevalence of ceftriaxone resistance in the total bacteria population was 110/225(48.9%). Similar findings were observed in studies done in Ethiopia 140/248(56.5%)[15] and Yemen 107/172(62.2%).[16] The observation also agrees with statements by the WHO that ceftriaxone and other 3rd generation cephalosporin resistance in common bacterial populations have reached the 50% mark.[17]

Staphylococcus aureus had the highest resistance rate 12/19(63.2%), followed by *Klebsiella species* 19/35(54.3%), *Escherichia coli* 43/81(53.1%), and *Pseudomonas aeruginosa* 13/25(52.0%), which was consistent with a previous study in which most of the strains of *Staphylococcus aureus* were resistant.[18] These observations also agree with the 2014 WHO global antibiotic resistance reports.[17] In contrast, other research finding reported that *Escherichia coli* exhibited the highest resistance to the 3rd generation cephalosporins.[19][20] Varying observations were also seen in Ethiopia with 73% resistance to ceftriaxone in *Escherichia coli* and 23.4% in *Staphylococcus aureus*.[15]

These variations may be as a result of different antibiotic prescribing patterns in the different regions as well as different levels of implementation of antimicrobial stewardship. It could also be as a result of different proportions of the sample populations used in the different studies. The fact that these bacteria are commonest pathogens implicated in health-care associated infections is worrisome, because it will further limit treatment options of these infections.

The specimen from which isolated organisms showed the most resistance was wound swab 33/44(75.0%). This was similar to a study done in Zambia with 60% of the bacteria isolates from wounds being resistant to a 3rd generation cephalosporin,[21] but a lower rate (47.4%) was observed in Ethiopia.[15] The discovery of a high ceftriaxone resistance rate in this study could be attributed to the empirical use of the drug for most wounds treatment, as well as surgical prophylaxis.

There were significant relationships between isolated bacteria (P= 0.034) and specimen type (P= 0.001) with ceftriaxone resistance. This was similar to previous studies in Ethiopia where significant differences were observed in specimen types from which the strains were isolated.[15]

CONCLUSION

Observations from this study has revealed a high prevalence of ceftriaxone resistant bacteria in Nnamdi Azikiwe University Teaching Hospital and its surrounding community, which will ultimately result in treatment failure and higher cost of eradicating these resistant pathogens. An extensive effort to decrease inappropriate use of antibiotic and to raise awareness of health-care providers through implementation of antimicrobial stewardship programs is recommended. Other options for empiric antibiotics should be sort through proper antimicrobial surveillance and testing in each locality.

Limitations

This study was limited by the fact that the specific genes responsible for resistance to ceftriaxone and other 3rd generation cephalosporins were not determined, thus, the work would have benefited from a more robust prospective determination of specific genes responsible for the observed resistance. Also, a larger sample size may have given a clearer representation of the ceftriaxone resistance profile in the study location.

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