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Antibiotic Potential of Cefuroxime (a Second-Generation Cephalosporin Antibiotic) on Nasal *Staphylococcus aureus* Isolates

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Abstract

Bacterial resistance to several antibiotics has become an increasing issue in the treatment of bacterial infections including *Staphylococcus aureus* (*S. aureus*); the most common cause of bacterial infections. The problem has resulted to drug discovery and development and consequently, drug classification into generations. This study therefore investigates the antibiotic potential of Cefuroxine (a second generation Cephalosporin's known to have a broader spectrum than the first-generation) on nasal *S. aureus* isolates. In a bid to achieve this objective, nasal swab were collected from undergraduate students in Ambrose Alli University, Ekpoma. Following standard laboratory procedures, the minimum inhibitory concentration (MIC) of Cefuroxime was determined and recorded and results presented in simple descriptive statistics and tables. The results showed that *S. aureus* is a β-Lactamase producing bacterial and that Cefuroxime has antibiotic potential to β-Lactamase producing bacterial. The mean MIC of Cefuroxime was 0.38±0.32µg/ml and ranges from 0.02µg/ml (minimum) to 0.64µg/ml (maximunm). Although the different between the minimum and maximum MICs was statistically significantly ($p<0.05$), the very low MICs indicated that Cefuroxime is a powerful antibiotic against nasal isolates of *S. aureus*.

Keywords

Cefuroxine, Antibiotics, *Staphylococcus aureus,* Nasal Isolates, Apparently Healthy Students

1. Introduction

Cephalosporins are ß-lactam antibiotics *Cephalosporium acremonium;* the first source of the Cephalosporins was isolated in 1948 by Brotzu from the sea near a sewer outlet off the Sardinian coast. Cefuroxime is a second-generation cephalosporin antibiotic (Calderon and Sabundayo, 2007) that has been widely available in the USA as Ceftin since 1977 and in many other countries as Zinnat. Cefuroxime is given by mouth to treat infections of ears, nose, throat, skin, soft tissue and the upper and lower airways (Kucers and Benelt, 2004). When drugs cannot be taken by mouth, injection is administered either intramuscularly or intravenously (Karchmer, 2000) for certain sexually transmitted infections and urinary tract infections. Considering the about 3 decades between the discovery of Cephalosporins; which is believed to be the first generation drug of the class, and the availability of a second generation class, drug discovery is fast growing with age. Cefuroxime development is no doubt due to reasons of drug resistance to first-generation cephalosporin antibiotics. This assertion is based on the emergence of drug resistant strains isolated from pathogenic processes and has been attributed to the increasing introduction of various antibiotics into general use as documented by Hanan*et al*. (2005). In accordance with this assertion, penicillin which was the first antibiotic used for *Staphylococcus* infections became resistance shortly after its introduction and this was followed by resistance to methicillin, amoxillin, tetracycline and to a lesser extent, erythromycin, gentamycin and other antibiotics (Mostafizur*et al*., 2005).

Worrisome is the documentation and scientific findings that *Staphylococcus aureus* is a normal human pathogen capable of living a benign lifestyle in the nasal passage and skin (Highet*et al*., 1992). This is in the light of literatures that *Staphylococcus aureus* is responsible for a great variety of pyogenic infection in man and animals, infecting about one-

third of the world population (Todar, 2008). Its manifestations are countless and include asymptomatic diseases and syndromes with low morbidity and mortality such as folliculitis, food poisoning and fatal systemic illness such as endocarditis and toxic shock (Lowry, 1998). A number of literatures have indicated it as the main causal agent of many infections in Nigeria (Adeleke and Asani, 2009; Bekibele et al., 2009; Onipede et al., 2009; Anah et al., 2008; Odetoyin et al., 2008).

Previous study showed that Cefazolin; a first generation cephalosporin, presented a 17% resistant to *Staphylococcus aureus* isolates (Livorsi et al., 2012). Another study indicated that the activities of Cefuroxime; a second generation cephalosporin, was highly active against oxacillin-susceptible *Staphylococcus aureus* but with minimum inhibitory concentration greater than 16 ug/ml (Washington et al., 1993). However, cefotaxime; a third generation cephalosporin, was highly effective against Gram positive and Gram negative bacteria including *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa* (Masroor et al., 2002). These studies point toward phenomenal evolution and increase of generational drug-resistance within class of antibiotic. For this reason, there is need for periodic drug screening investigations to monitor the already emergent antibiotics resistance. While an early detection of this growing multi-drugs resistance can help in preventing treatment failure, selection of antibiotics for the management of bacterial infections should be based on findings of the susceptibility patterns of the agent.

This study therefore investigates the antimicrobial potential of Cefuroxine (a second generation Cephalosporin's known to have a broader spectrum than the first-generation) on nasal S. *aureus* isolates via determining the minimum inhibitory concentration (MIC). The study was conducted among apparently health undergraduate students of the Department of Microbiology, Faculty of Natural Sciences, Ambrose Alli University, Ekpoma in Edo State, Nigeria. Students were chosen as the target populations because they are believe to practice good hygiene and as such examine the fact that *S .aureus* can be a normal human commensal and maybe asymptomatic.

2. Materials and Methods

Materials: The materials used in this research work include, measuring cylinder, distilled water, Pasteur pipette, hot air oven, oil immersion, test tube racks, glass slides, masking tape, gloves, markers, detergent, cover slips, microscope, spatula, conical flask, test tubes, autoclave, cotton wool, incubator, aluminum foil, bijoux bottle, inoculating wire loop, Bunsen burner, Petri dishes, disinfectant and weigh balance. The media used were MacConkey agar, Nutrient agar and Peptone water.

Sample source and storage of isolates: Pure culture of twelve (12) gram positive bacteria of *staphylococcus aureus* gotten from the nasal region of healthy susceptible students in Ambrose Alli University, Ekpoma, Edo State, Nigeria, were used for the test. Test isolates were kept on nutrient agar slope and stored at 40^0c before use.

Cleaning and sterilization of equipments used: The glassware used were washed with detergent, water and rinsed in distilled water. All glassware were sterilized using the hot air oven at 160^0c for 1hour, wire loops were sterilized by passing them through a Bunsen burner until red hot before use, other equipment used were also sterilized thoroughly to achieve maximum sterility.

Preparation and sterilization of media: The media were available in the commercially prepared powder forms. Media were reconstituted with water according to manufacturer's guide. Specifically, 28g of nutrient agar powder was weighed and dispensed in 1litre of distilled water and allowed to soak for 10minutes, swirl to mix and them sterilized by autoclaving at 121^0c for 15 minutes. On the other hand, 48.5 grams of MacConkay agar powder was weighed and dispersed in 1 litre of distilled water and was allowed to soak for 10minutes, swirled to mix and then sterilized by autodialing for 15minutes at 121^0c. It was allowed to cool to 47^0c, prior to inoculation, the surface of the agar was dried by parts exposure at 37^0c. Media were dispersed into sterilize Petridis and allowed to solidify at room temperature before use. 15g of peptone water powder were added a litre of distilled water. It was then vigorously mixed and distributed into bijoux bottles, their steadied by autoclaving at 121^0c for 15minute.

Sample Collection: After giving their written/informed consent, nasal swab specimens were collected from the volunteers. The samples collected were then transported to the microbiology laboratory of Ambrose Alli University and analyzed within 24 hours of collection.

Culture and Isolation: The swab samples were streaked unto mannitol salt agar plates and incubated for 18 – 24 hours at 370C. Characteristically golden yellow colour colonies observed after incubation were identified as *S. aureus* and confirmed with coagulase test (Cruickshank *et. al* 1975).

Identification of test isolates: Confirmatory test was done on test isolate, test strain were inoculated into peptone water and allowed to stay for 2hours on the bench before inoculating onto MacConkey agar. Culture plates were examined and preliminary identification of the isolate was done using their colonial morphology. Biochemical test was then performed.

Morphological characteristics: Isolated colonies from the agar medium were subjected to gram staining using the gram staining technique as described by Christian Gram (1883).

Gram Staining: Differences in gram reaction between bacteria is thought to be due to differences in the permeability of the cell wall of gram positive and gram negative organisms during the standing process. Smear of isolates was made on a clean glass slide and fixed by passing the slide through a flame for about 3 times and allowed to cool. The fixed smear is covered with crystal violet stain for 60 seconds. Rapidly wash the stain off with clean water tip off all the water, and then flushed with lugol's iodine for 30-

60 seconds, again wash off iodine with clean water. The smear was differentiated briefly with acetone and washed off immediately. It was then counter stained with neutral red and this was allowed to act for 2 minutes and flushed with water. The back of the slide was wiped clean and placed in a draining rack for the smear to air dry, the slides were then examined under the microscope using the oil immersion objective (X100) lens, but was first viewed with the 40X objective to check the staining. The 100X objective showed the morphology and gram reaction of cells gram positive bacterial were recorded as those retaining the colour of the primary stain (crystal violet), while gram negative bacterial were recorded as those retaining the colour of the counter stain (Neutral red).

2.1. Biochemical Tests

Catalase test: This test is used to differentiate those bacteria that produce the enzyme catalase such as staphylococci, from non-catalase producing bacteria such as streptococci. Catalase acts as a catalyst in the breakdown of hydrogen peroxide to oxygen and water. Procedure was as follows; a colony from the pure culture of the organism was emulsified in a drop of normal solution on a slip and a drop or of 3% solution of hydrogen peroxide (H_2O_2) was added to the suspension of the organism. Catalase production from grain positive bacterial was indicated by the production of effervescence or bubbles whereas a negative result showed no gas bubbles or effervescence.

Coagulase test: This test is used to identify *S. aureus* which produces the enzyme coagulase. The procedure was as follows; an inoculum was taken from a pure culture and emulsified in a loopful of normal saline on a clean slide until a homogenous suspension is obtained. A drop of human plasma was added and stirred for 5 seconds. The production of coagulase enzyme was indicated by clotting or coagulation of plasma, which is seen by granule formation while the absence of granules, indicates a negative result.

Sugar fermentation: The sugars used were lactose, glucose, maltose, sucrose and mannitol. In brief, 19% solution of the series of sugars were prepared in peptone water to which neutral red indicator had been added and was sterilized in bijoux bottles containing Durham's tubes. Inoculums was taken from a pure culture and inoculated into peptone water and incubated at 37^0c for 3-4 and after incubation a sterile wire loop was used to inoculate the peptone water culture into sterile sugar solution and the inoculated sugars were incubated at 37^0 for 24 hours. Utilization of sugar was indicated by change in color from red to pink or yellow due to acid production, while gas production was indicated by a space in the Durham's tube. No colour change or gas formation indicates a negative result.

2.2. Determination of Minimum Inhibitory Concentration (MIC)

Tube Dilution Method was use to determine MIC. The stock solutions of Cefuroxime antibiotic were prepared. A row of 10 sterile test tubes were set up on test tube rack. 1ml of sterile peptone water was dispensed into each test tube. Dispense 1ml aliquot from standard solution to the 1st test tube. A drop of in 100 dilution of an overnight broth culture of the test organism was added into each test tube. Test tubes were incubated at 37^0c for 18-24 hours. At the end of the incubation period, the test tubes were observed for turbidity. The last test from the left without visible turbidity was regarded as the one with the concentration of the MIC and this was recorded and repeated three times and the average documented and simple descriptive statistical analysis was performed.

3. Results and Discussion

The identification of *Staphylococcus aureus* isolates in the nasal region of apparently healthy students in this study has further justified the popular fact that *Staphylococcus aureus* is a human commensal and can be asymptomatic. This finding is not surprising because studies by various researchers have clearly indicated that the spreading of *Staphylococcus aureus* infection between health workers and patients and vice versa and among medical students (Shanmugam et al., 2009; Adesida et al., 2007; Santhosh et al., 2007) and in population of healthy students (Baliga et al., 2007; Lamikanra et al., 2006). Thus, the identification of *Staphylococcus aureus* infection in the nasal region of students in this study is in line with other studies.

Table 1. *Biochemical characteristic of the nasal isolates of Staphylococcus aureus.*

Bacterial spp.	Biochemical test									
	Coagulase	Mannitol*	Sucrose*	Lactose*	Glucose*	Maltose*	Indole	Urease	Oxidase	Catalase
S. aureus	+	+	+	NA	NA	NA	-	-	-	+

Key: * = Fermentation test; + = Positive; - = Negative, NA = Not available. Note: cultural characteristic of *S. aureus* is Golden Yellow characteristic

Table 1 presents the biochemical characteristics of the nasal *Staphylococcus aureus* isolated from the students that participated in the study. It was observed that the nasal isolates of *Staphylococcus aureus* were positive to coagulase, mannitol, sucrose and catalase tests but negative to indole, urease and oxidase tests, while tests were not available for lactose, glucose and maltose tests (see table 1). The biochemical characteristics of the *Staphylococcus aureus* isolated from the students agrees with the study conducted among apparently healthy female at the Irrua Specialist Teaching Hospital, Edo state, Nigeria (Orhue and Momoh, 2012). It can be observed that nasal *Staphylococcus aureus* was positive for β- Lactamase indicated by the biochemical test but negative to iodometric biochemical tests. It can therefore be concluded that the enzymes produced were β-Lactamase and not acylase, which according to Plested et al.

(1983) gives positive result in microbiological and acidimetric methods and negative result in iodometric methods. In line with the biochemical findings of this study, the study of Kolawole et al. (1992), has previously reported that 100.0% of hospital isolated *Staphylococcus aureus* was β-Lactamase producing. Biochemical cultural characteristic of *Staphylococcus aureus* in this study showed a golden yellow characteristic.

Table 2 shows the MICs of the nasal *Staphylococcus aureus* isolates to Cefuroxime antibiotic (a second-generation ß-lactam cephalosporin antibiotic). The results showed that the minimum concentration capable of inhibiting the growth of nasal *Staphylococcus aureus* activity was 0.02µg/ml and the maximum recorded minimum concentration capable of inhibiting the growth of nasal *Staphylococcus aureus* activity was 0.64µg/ml. This gives a narrow different of 0.62µg/ml and thus indicates that Cefuroxime is a potent antibiotic against nasal *Staphylococcus aureus*. Comparatively, a study has reported MICs ranges between 0.5-2µg/ml for Cefuroxime (Turnidge et al., 2002; Suhail and Sulieman, 2014) and between 0.25 to 4 for classes of Cephalosporins (Suhail and Sulieman, 2014). Thus, the antibiotic potential of Cefuroxime reported in this study is high compared to that reported by Turnidge et al. (2002) and Suhail and Sulieman (2014). In addition, this study showed that Cefuroxime is a better antibiotic in the cephalosporin class judging by the findings reported by Suhail and Sulieman (2014) that places MICs ranges for classes of Cephalosporins as 0.25 to 4µg/ml. Indeed, the drug has been reported to be a broad spectrum antibiotic of the cephalosporin class and an alternate drug of choice when patients are allergic to the penicillins or when there is a need to overcome ß-lactamase inactivation (Agbonlahor and Adegbola, 1996).

Table 2. *Minimum Inhibitory Concentration (MIC) of nasal Staphylococcus aureus isolates to Cefuroxime; a second-generation cephalosporin antibiotic.*

Variables	MIC of Cefuroxime (µg/ml)
Min MIC	0.02
Max MIC	0.64
Difference in Min and Max MICs	0.62
Mean±SD	0.38±0.32
t value	4.141
Sig. (2-tailed)	0.002
Remark	P<0.05
Interpretation	There is a statistically significant different

Values are mean ± SD. CI= 95% and error of 5%.

Recall that the first generation cephalosporin; cefazolin, has display some degree of resistance to *Staphylococcus aureus* isolates (Livorsi et al., 2012) and that the activities of Cefuroxime was highly active against Oxacillin-susceptible *Staphylococcus aureus* (Washington et al., 1993) couple with the third generation cephalosporins; cefotaxime, been highly effective against Gram positive and negative bacteria (Masroor et al., 2002), the findings in this study support the generation potency of Cephalosporins. On the other hand, a study has reported *Staphylococcus aureus* obtained from cases of sinusitis to be resistance to cephalosporin antibiotic and this was reported to be 50% for cefuroxime, 41% for cefaperazone and 50% for cefotaxime (Sasikala et al., 2011). When First-generation cephalosoprins (eg-cephalexin) have failed or there is a high prevalence of β–lactamase resistance, second or third-generation cephalosporins (e.g., cefuroxime, cefpodoxime, cefprozil) provide broader coverage.

In this regards, Cephalosporins have been reported to demonstrate variable stability to staphylococcal beta-lactamase, depending on their chemical structure and composition. To the degradation staphylococcal beta-lactamase, cefazolin is reported to be sensitive while Cephalothin is reported to be relatively resistant (Fong et al., 1976; Regamey et al., 1975). Although this is an *in vitro* phenomenon, it has not been clearly demonstrated to be clinically significant as some prefer cephalothin for the treatment of life-threatening *Staphylococcus aureus* infections (Quinn et al., 1973). Data from animal studies however suggest that cephalosporins are probably less effective than the penicillinase-resistant penicillins against serious staphylococcal infections. Specifically, in a rabbit model of endocarditis, it was shown that Cefazolin and cephalothin were less effective than nafcillin (Carrizosa et al., 1979; Steckelberg et al., 1993). Compared with first-generation cephalosporins, the second-and third-generation cephalosporins in general have inferior *in vitro* activity against *Staphylococcus aureus*. This is not in agreement with the finding of this study considering the low MIC observed. Although the different in MICs (0.62µg/ml) was significantly different ($p<0.05$); it is very low and this indicates the potential of Cefuroxime. Indeed, it has been shown that with the exception of cefamandole, cefuroxime, and possibly cefaclor, cephalosporins of later generations generally have lower activity against *staphylococci* and offer no advantages over first-generation cephalosporins when they need to be used in the management of staphylococcal infection.

Despite the fact that some strains may appear susceptible in routine laboratory tests, it is said that almost all cephalosporins have sufficient activity to provide initial coverage pending the results of laboratory investigations but Cephalosporins are not active against methicillin-resistant *Staphylococcus aureus* (MRSA) strains *in vivo*. Exceptions to this rule have been found in new cephalosporin molecules under development, such as ceftobiprole, LB11058 and RWJ-33341 (Glinka et al., 2003; Vouillamoz et al., 2004, Chambers, 2005), thus indicating broader spectrum for newer generation cephalosporins.

4. Conclusion

The low different between the minimum and maximum MICs of Cefuroxime (0.62µg/ml) to nasal isolates of *Staphylococcus aureus*in this study indicated that Cefuroxime has a high antibiotic potential to nasal isolates of *Staphylococcus aureus*. Hence, Cefuroxime antibiotic may be considered as the antibiotic of choice for *Staphylococcus*

aureus infections of the respiratory system. However, it is recommended that periodic monitoring be conducted to monitors changes in antibiotics susceptibility and prevalence of isolates resistant to classes of antibiotic.

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