Determinants of Empirical Antibiotics Candidates for Ear, Nose and Throat Infections in a West African Tertiary Hospital

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Abstract: Ear, nose, and throat (ENT) are usual sites of infection because of their direct contact with the physical environment and are always exposed to air borne microorganisms. Therefore, misuse of antimicrobial agents in the treatment of ENT bacterial infections can only be avoided by evaluating the culture and sensitivity pattern of pathogens towards specific drugs, since resistance against antibiotics is directly linked to clinical practice. Hence, this study is aimed at the identification and pattern of susceptibility/resistance of pathogens causing ENT infections. The study was a hospital based prospective cross-sectional study. Informed consent was obtained and One hundred and fifty (150) samples of either ear, nose or throat infectious material were collected. Each sample was transported in thioglycolate media to the microbiology laboratory for isolation, identification of bacteria and antibiotic susceptibility profile determination. Samples of the ear 88 (58.7%), nose 46 (30.6%) and throat 16 (10.7%) infections were collected from 150 participants. A total of 17 different bacterial species were identified from 192 bacteria isolated and 113 (58.9%) bacterial isolates were cultured. *Staphylococcus* species 62 (32.3%) especially *Staphylococcus aureus* (21.1%) and *Proteus* mirabilis 29 (15.1%) were the most prevalent Gram-positive and Gram-negative bacteria respectively. The isolates were more susceptible to vancomycin, meropenem, ofloxacin and ciprofloxacin, and most resistant to tetracycline, cotrimoxazole, cefuroxime, augmentin and ceftazidime. Meropenem, vancomycin and ofloxacin are the most active antibiotics for effective treatment of *Staphylococcus aureus* and *Proteus spp*. who has been identified as the most common bacteria cultured from ENT infectious samples in our region.

Key word: Ear, Nose, and Throat; Bacterial infection; Antibiotic susceptibility; Empirical Antibiotics.

INTRODUCTION

Upper respiratory infections are among the most widespread and serious infections affecting people of all ages (Ahmed *et al*., 2018; Ullah *et al*., 2022). These infections are one of the leading causes of morbidity and mortality in critically ill patients. The ear, nose, and throat are the frequent sites of infection, because they come in direct contact with the physical environment and are constantly exposed to air borne microorganisms. Studies have identified different bacterial as an aetiology agent causing ear, nose and throat infections. The most common organisms that have been reported to be responsible for bacterial infections around ENT region includes *Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus* spp., *Proteus* spp., *Haemophilus* spp., Coliforms, *Candida* spp., and *Aspergillus* spp (Obiajuru and Chukuezi, 2013).

The most common treatment given to patients suffering from ENT infection are antibiotics (Vasileiou *et al.,* 2009; Ullah *et al*., 2022). Abuse (misuse/overuse) of these antibiotics is the major cause of antibiotic resistance (Bhattacharyya and Shapiro, 2002; Ullah *et al*., 2022). Antibiotic-resistant bacteria have remained a major public health challenge. As of 2019, over 2 million people were infected with antibiotic resistance bacteria and about 35,000 people die from their infections annually (CDC, 2019). Antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas* species, penicillin-resistant *S. pneumonia* and so on, have been reported (CDC, 2019). However, antibiotic resistance does not only results in severe infections leading to increased mortality but can also contribute towards undue financial burden (Lönnroth *et al*., 2015; Ullah *et al*., 2022). In UK, 25,000 patients die every year

due to hospital-acquired infections caused by multi-drug resistant microorganisms (Prestinaci *et al*., 2015; Ullah *et al*., 2022).

However, ear infections such as otitis media have been the second most important cause of hearing loss affecting 1.23 billion of people, therefore ranked fifth global burden of disease (Hailegiyorgis *et al.*, 2018). In the United States, 24 and 31 million cases of rhinosinusitis occur annually (Anon, 2010; Dykewicz and Hamilos, 2010). Also Sadoh *et al*. (2008) reported GAS pharyngitis in 48% of the population of children aged 3 months to 16 years.

In this regard, the misuse of antibiotics can only be avoided by evaluating the culture sensitivity pattern of pathogens towards specific drugs, since resistance against anti-microbial drugs is directly linked with clinical practice. However, very few literature evidences from Nigeria are available that evaluated the susceptibility patterns of various routinely used antibiotics in upper respiratory tract infections among patients reporting to specialized tertiary care hospitals in Ile-Ife, Nigeria. Hence the present study is concerned about the identification of common pathogens causing respiratory infections in Ile-Ife, Nigeria and their pattern of susceptibility and resistance to antimicrobial agents.

MATERIALS AND METHODS

Study design and ethical clearance: This study was a prospective cross-sectional hospital-based study conducted in the Department of Microbiology, Obafemi Awolowo University (OAU) and the Department of Otorhinolaryngology-Head and Neck Surgery of the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC) Ile-Ife, Nigeria. Ethical clearance with protocol number (ERC/2018/06/14) was duly obtained from the Ethical and Research Committee of the OAUTHC, Ile-Ife, Nigeria. Furthermore, informed consent was acquired from patients or their caregivers, after a clear and satisfactory explanation of the objectives, nature and processes of the study.

Sample collection: Samples of ear discharge, nasal discharge throat swab, and ENT surgical sample (aspirate and tissue) were collected at the Otorhinolaryngology clinic and Operating theatre of the hospital respectively. Each sample was collected aseptically using sterile swab sticks or bottles as appropriate and according to the study protocol.The samples properly labelled (with patient's number, date, sex, age and time) and immediately transported in thioglycolate media to the laboratory for bacteriological analysis. Sample collection was carried out till the sample size was met between the periods of 24th of June, 2018 to 14th of December, 2018.

Isolation and identification of bacteria from the samples: The sample collected in the transport media was incubated for 24 hours at 37ºC. The incubated culture was then inoculated separately on a sterile nutrient agar, blood agar, Mannitol salt agar and MacConkey agar (lab M ltd, UK) by streak plate method for discrete colonies. Pure culture organism was obtained by sub-culturing on nutrient agar plate and incubated at 37°C for 24 hours. Morphological and physiological characteristics identification of the isolates was line with the Bergey's Manual of Determinative (Holt *et al.,* 1994). The isolates were further identified using MICROBACT ™ identification kits 24E (Oxoid Ltd, Uk) for Gram-negative and 16rna for *Staphylococcus aureus*.

Antibiotic susceptibility profile of the bacterial isolates: The antibiotic susceptibility profile of the isolates was determined on Mueller-Hinton agar (LAB-M, UK) following Kirby-Bauer's disc diffusion technique (Bauer *et al.,* 1966). The commercially available antibiotic discs (Oxoid, UK) such as, gentamycin (10 µg), augmentin (30 µg), ceftriaxone (30 µg, cotrimoxazole (25 µg), ofloxacin (5 µg), amoxicillin (25 µg), ciprofloxacin (10 µg), tetracycline (30 gµ), cefotaxime (30 µg), cefoxitin (30 µg), ceftazidime (30 µg), cefuroxime (30 µg), and meropenem (10 µg) were used for the susceptibility test. The

diameter of the zones of inhibition was measured and interpreted according to Clinical and Laboratory Standard Institutes Guidelines (CLSI, 2017).

***Data analysis*:** Prior to statistical analysis, which was performed using SPSS (Statistical Product and Service Solutions) version 22, the obtained data were logged, sorted, and error-checked. Tables and basic charts were used to display the findings. By aligning the findings with the study's purpose, discussions and conclusions were derived from the data.

RESULTS

One hundred and fifty (150) patients made up of 73 (48.7%) males and 77 (51.3%) females, were diagnosed with ear 88 (58.7%), nose 46 (30.6%) and throat 16 (10.7%) infections and recruited in the study as outlined on Table 1. A total of 17 different bacterial species were identified from 192 bacteria isolated from 150 samples. One hundred and thirteen (58.9%) bacterial isolates were cultured from ear, nose 56 (29.2%) and throat 23 (12.0%) infections. *Proteus* mirabilis 29 (15.1%) had the highest occurrences among Gram-negative bacteria cultured from ear, nose and throat infections, followed by *Pseudomonas aeruginosa* 20 (10.4%), while *Acinetobacter* baumannni 1 (0.5%) was the least (Figure 1). However, *Staphylococcus* species 62 (32.3%) especially *Staphylococcus aureus* (21.1%) was the most prevalent Gram-positive bacteria culture from ear, nose and throat infection, followed by *Corynebacterium* spp. 20 (10.4%), *Bacillus* spp. 17 (8.9%), *Staphylococcus saprophytic* 12(6.3%), *Streptococcus* spp. 10 (5.2%) and *Staphylococcus epidermis* 9(4.7%), while both *Micrococcus* spp. and *Enterococcus* spp. 3 (1.6%) were the least (Figure 2).

Table 1: Nature of samples collected in relation to their site of infection

Nature of the Sample	Site of infection Ear infection n=88 (58.7%)	Nose Infection n=46(30.6%)	Throat infection n=16(30.6%)	Total n=150(100%)
Sex				
Male	42(47.7%)	25(54.3%)	6 (37.5%)	73(48.7%)
Female	46 (52.3%)	21(45.7%)	10(62.5%)	77(51.3%)

Table 2: Age related prevalence of bacteria isolated in ear, nose and throat infection

Bacterial isolates	Age group									
	0-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40	41-45	≥46
Staphylococcus aureus (n=41)	11	4	1	1	1	5	2	5	3	8
Proteus mirabilis (n=29)	4	1	4	6	2	2	2	3	0	5
Staphylococcus saprophytic (n=12)	3	2	1	1	1	0	2	1	0	1
Staphylococcus epidermis (n=9)	4	1	2	0	0	0	1	0	0	1
Pseudomonas aeruginosa (n=20)	5	0	4	0	1	1	1	0	2	6
Corynebacterium diphtheriae (n=20)	2	3	3	1	2	1	2	2	0	4
Bacillus spp. (n= 17)	5	2	3	2	1	0	0	1	1	2
Streptococcus spp. (n= 10)	3	0	1	0	2	2	0	1	0	1
Escherichia coli (n=7)	2	1	0	0	0	0	1	1	0	2
Citrobacter freundii (n= 5)	2	0	0	1	0	0	0	2	0	0
Enterobacter cloacae (n=4)	2	0	1	0	0	0	0	0	0	1
Serratia marcescens (n= 4)	2	0	0	0	1	0	0	0	1	0
Micrococcus spp. (n=3)	1	1	0	0	0	1	0	0	0	0
Enterococcus spp. (n= 3)	2	0	0	0	0	0	0	0	0	1
Salmonella spp. (n= 2)	0	0	1	0	1	0	0	0	0	0
Acinetobacter baumannii (n= 1)	1	0	0	0	0	0	0	0	0	0
Total	50	15	22	12	14	12	11	16	7	33
Total in %	26	7.8	11.5	6.3	7.3	6.3	5.7	8.3	3.6	17.2

Table 3: Antibiotics susceptibility pattern of Gram-negative bacteria isolates cultured from ENT infectious samples

Bacterial isolates	GEN			AMK			OFL			CIP			MER			AUG			CAZ			CRX			CXM			CTX			TET			COT			CHL		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Proteus mirabilis (n=29)	66	0	34	45	10	45	79	0	21	69	10	21	100	0	0	41	38	21	41	45	14	25	38	52	90	7	3	45	55	0	17	3	79	66	7	27	62	17
Pseudomonas aeruginosa (n=20)	65	20	15	60	10	30	90	5	5	100	0	0	100	0	0	155	155	70	150	10	75	10	5	85	155	8	80	155	10	75	50	25	25	15	5	80	30	155
Escherichia coli (n=7)	43	0	57	43	14	43	100	0	0	86	14	0	100	0	0	29	147	57	42	29	29	42	29	29	86	14	0	29	71	0	57	0	43	57	0	43	57	14	29
Klebsiella pneumonia (n=5)	40	20	40	60	20	20	100	0	0	80	0	20	100	0	0	20	60	20	20	40	40	20	40	40	60	0	40	60	20	20	20	0	80	20	40	40	60	0	40
Citrobacter freundii (n=5)	60	40	0	100	0	0	100	0	0	80	20	0	100	0	0	0	60	40	80	20	0	80	20	0	60	40	0	40	40	20	20	0	80	0	20	80	40	40	20
Enterobacter cloacae (n=4)	75	0	25	75	25	0	100	0	0	100	0	0	100	0	0	50	25	25	0	75	25	0	25	75	75	0	25	50	50	0	50	0	50	25	25	50	75	25	0
Serratia marcescens (n= 4)	100	0	0	75	25	0	100	0	0	100	0	0	100	0	0	25	50	25	50	25	25	0	0	100	75	25	0	25	50	25	25	75	0	75	25	0	75	25	0
Salmonella spp. (n= 2)	50	50	0	50	50	0	100	0	0	0	100	0	100	0	0	0	50	0	0	100	0	0	0	100	100	0	0	100	0	0	50	0	50	100	0	0	100	0	0
Acinetobacter baumannii (n= 1)	0	100	0	0	100	0	100	0	0	100	0	0	100	0	0	0	100	0	100	0	0	100	0	0	0	100	0	100	0	0	0	0	100	0	100	0	0	0	100

Keys: CAZ- Ceftazidime 30 µg, CRX- Cefuroxime 30 µg, GEN –Gentamycin 10 µg, CXM- Cefixime 5 µg, OFL –Ofloxacin 5 µg, AUG –Augmentin 30 µg, NIT Nitrofurantoin 300 µg, CPR –Ciprofloxacin 5 µg TET –Tetracycline 30 µg, CHL-Chloramphenico 30 µg l, MEM-Meropenem 10 µg, FOX- Cefoxitin 30 µg, COT –Cotrimoxazole 25 µg, CTX-Cefotaxime 30 µg, CTR-Ceftriaxone 30 µg, AMK- Amikacin 30 µg, ERY- Erythromycin, VAN-Vancomycin, AMP-Ampicillin 10 µg

Table 4: Antibiotics susceptibility pattern of Gram-Positive bacteria isolates cultured from ENT infectious samples

Bacterial isolates	GEN			OFL			MER			AUG			AMP			CAZ			CRX			FOX			VAN			ERY			TET			COT		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Staphylococcus aureus (n=41)	49	22	29	93	5	2	98	2	0	76	0	24	46	10	24	32	24	44	71	12	17	63	0	37	100	0	0	34	32	34	47	22	51	11	0	59
Staphylococcus saprophytic (n=12)	50	17	33	92	8	0	100	0	0	75	0	25	75	0	25	33	25	42	66	17	17	92	0	8	100	0	0	25	33	42	50	8	42	67	0	33
Staphylococcus epidermis(n=9)	45	23	33	100	0	0	100	0	0	78	0	22	78	0	22	44	0	56	56	22	22	100	0	0	100	0	0	22	67	11	45	33	22	67	0	33
Corynebacterium diphtheria (n=20)	70	20	10	85	15	0	100	0	0	15	0	85	20	0	80	45	0	55	40	0	60	-	-	-	100	0	0	45	35	20	60	30	10	80	0	20
Bacillus spp. (n= 17)	82	12	6	88	12	0	100	0	0	0	0	100	0	0	100	6	0	94	0	0	100	-	-	-	100	0	0	59	35	6	53	18	29	59	12	29
Streptococcus spp. (n= 10)	50	0	0	100	0	0	100	0	0	80	0	20	30	0	70	0	0	20	20	0	60	-	-	-	100	0	0	60	40	0	50	30	20	50	0	50
Micrococcus spp. (n=3)	0	33	67	100	0	0	100	0	0	33	0	67	67	0	33	100	0	0	33	0	67	-	-	-	100	0	0	67	0	33	33	0	67	33	0	67
Enterococcus spp. (n= 3)	67	0	33	100	0	0	100	0	0	100	0	0	100	0	0	300	0	0	100	0	0	-	-	-	100	0	0	67	0	33	0	67	33	67	0	33

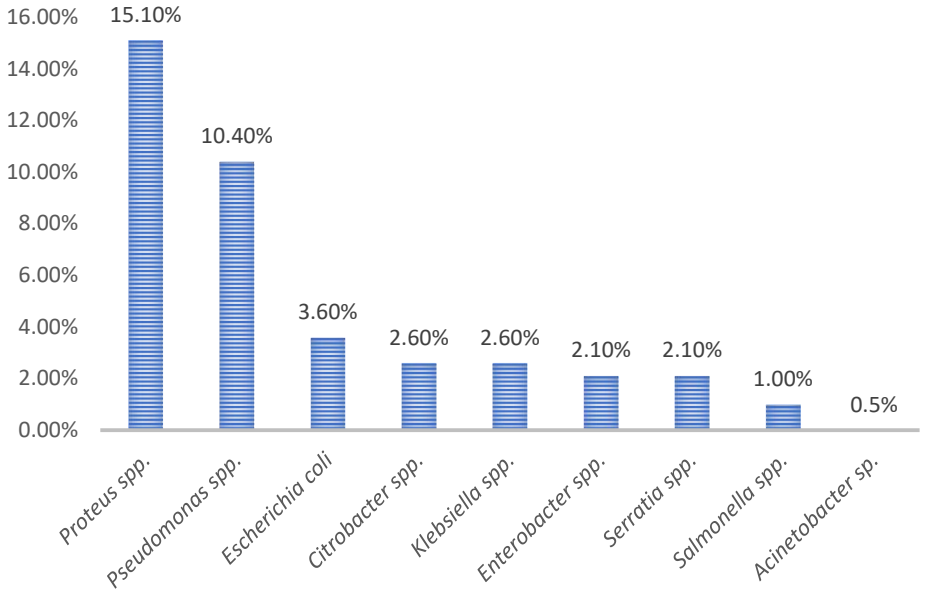

Figure 1: Prevalence of Gram-negative bacteria isolated from ENT infectious samples

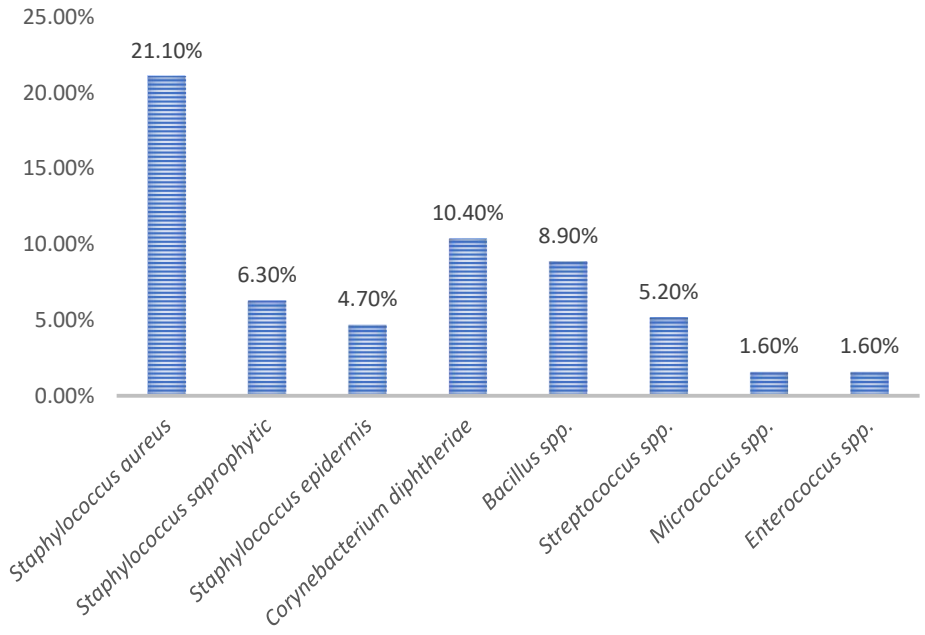

Figure 2: Prevalence of Gram-positive bacteria isolated from ENT infectious samples

According to Table 2, age related prevalence of ENT infection in the study area showed that the highest prevalence of bacterial infection 26% was amongst those aged 0-5 years, 17.2% was amongst the aged greater than 45 years, 11.5% was amongst the aged 11-15 years, 8.3% was amongst 36-40 years while the least (3.6%) was amongst 41-45 years. Table 2 also indicated that *Staphylococcus aureus*, *Staphylococcus saprophytic Pseudomonas aeruginosa* were the most prevalence isolate in children below 5 year while, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Proteus mirabilis* and *Corynebacterium diphtheriae* are most prevalence in adult.

Table 3 displayed the bacterial isolates' profiles of antibiotic susceptibility to the different antibiotics that were tested. The Gram-negative bacteria were mostly

susceptible to meropenem, followed by ofloxacin and ciprofloxacin. However, the isolates were most resistant to tetracycline, followed by cotrimoxazole, cefuroxime, augmentin and ceftazidime. Table 4 presented the Gram-positive bacteria's profile of antibiotic susceptibility to the different antibiotics that were tested. All the Gram-positive bacteria were susceptible to vancomycin antibiotics, followed by meropenem and ofloxacin. Moreover, the isolates were most resistant to cotrimoxazole, augmentin and ceftazidime.

DISCUSSION

Ear, nose and throat infections have been the most commonly encountered infections of upper respiratory tract infections causing significant morbidity and mortality in children who are more vulnerable and adult suffering chronic ENT infection if not properly treated in appropriate time. In this study, ear infection had the highest prevalence, followed by nasal and throat infections. This corroborates the findings of Sharma *et al.* (2014) in Guwahati, India and Otoghile *et al.* (2019) in River State, Nigeria. Study has reported highest prevalence of ENT infections (85%) amongst those ages 41 – 50 years, while the least (75%) was amongst those aged 11 – 20 years (Obiajuru and Chukuezi, 2013). However, in this study the children were more prone to ENT infections than the adults, especially children between ages 0-5 years.

The ear, nose, and throat have been reported as frequent sites of infection, because of their direct contact with the physical environment and are exposed to air borne microorganisms (Ahmad *et al*., 2016). As a matter of fact, studies have identified different bacteria as etiologic agent causing ear, nose and throat infections (Obiajuru and Chukuezi, 2013; Kumar *et al.,* 2013; Ahmad *et al*., 2016; Phukan and Das, 2020). In this study, the leading isolated bacteria was *S. aureus* (21.4%), followed by *Proteus* spp. (15.1%), *Staphylococcus* spp. (10.9%), *Corynebacterium* spp. and *Pseudomonas aeruginosa* with 10.4%. Similar to reports of other investigators, Obiajuru and Chukuezi (2013) and Ahmad *et al*. (2016) separately implicated *Staphylococcus aureus* as the most prevalence organism in Imo and Kano states of Nigeria, respectively. These observations were in contrary to Kumar *et al.* (2013) reporting *Pseudomonas, Staphylococcus aureus, Proteus* and *Klebsiella* as the common bacteria that cause ENT infections in Japura India. However, E-Mahmood *et al.* (2010) has also reported that *Streptococcus pyogens, S. aureus, Klebsiella pneumoniae, Proteus mirabilis* and *P. aeruginosa* as the bacteria isolated in the ENT among patients visiting different hospitals in Yola city, Nigeria. The possible reasons for such variation in the bacteria profile might be attributed to the difference in climatic and geographic factors linked to the study sites (Muluye *et al.,* 2013). In addition, *Staphylococcus aureus, Staphylococcus saprophytic Pseudomonas aeruginosa* were the most prevalent isolate in children below 5 years, while *Staphylococcus aureus, Pseudomonas aeruginosa, Proteus mirabilis* and *Corynebacterium diphtheriae* were most prevalent in adult. This finding is contradicted to the report of Ahamd *et al* (2016).

The susceptibility pattern of bacterial isolates in this study indicated meropenem antibiotics as the most sensitive antibiotics to Gram negative bacteria, while both vancomycin and meropenem antibiotics were most sensitive to Gram-positive bacteria. Vancomycin-resistance has been reported to be more common with *Enterococcus* spp. Sader *et al.* (2014), in contrary to this study in which *Enterococcus* spp. isolates was 100% sensitive to vancomycin antibiotic. Susceptibility of *S. aureus* to vancomycin in this study is also similar to the study of Olowe *et al.* (2013) where authors isolated and characterized *S. aureus* obtained from clinical specimens in Ekiti State, Nigeria. In addition, Worku and Bekele (2014) work on bacterial isolate and antibacterial resistance pattern of ear

infection in Hawassa, Ethiopia showed that *S. aureus* are susceptible to vancomycin. The susceptibility of meropenem and vancomycin could be attributed to the fact that the antibiotics are not commonly used, being expensive and not easily accessible, thereby prevent irrational use of drugs, self-medication and misuse of drugs in the study area.

Studies have shown that resistance to fluoroquinolones often have a class distribution with bacteria resistant to ofloxacin usually being also resistant to ciprofloxacin (Pribu *et al.,* 2016). In spite of the foregoing, there are several studies that have shown that organisms resistant to one floroquinolone may be sensitive to another floroquinolone (Oluremi *et al.,* 2011; Pribu *et al.,* 2016). In this study, sensitivity to ofloxacin was found to be above 90% across all bacterial isolates. This is in spite of the widespread resistance to ciprofloxacin observed in this study. Ofloxacin is a relatively cheap floroquinolone with a good safety profile in addition to it availability for oral administration (Oluremi *et al.,* 2011), unlike meropenem and vancomycin, the two drugs with better sensitivity profiles in this study. Traditionally, meropenem and to a lesser extent have been reserved for in hospital usage in severe life threatening infections. This study is in support of the use of ofloxacin as an empiric choice in the management of ear, nose and throat infections, while keeping meropenem and vancomycin for the treatment of severe or life-threatening infections or patients with documented resistant organisms to ofloxacin.

CONCLUSION

Staphylococcus aureus and *Proteus* spp. are the most likely culprits in patients presenting with ENT infections in the study area. Previous usage of antibiotics before presentation to the hospital for proper assessment has significantly contributed to the multiple antibiotic resistance bacteria isolated in this study. This has resulted into an increasing rate of resistance to commonly used empirical antibiotics such as augmentin and ampicillin. Therefore, meropenem, vancomycin and ofloxacin, being the most active antimicrobial agents isolated in this study, should be the drugs of choice for empirical and effective treatment of ear, nose and throat bacterial infections in Otorhinolaryngology clinics in West Africa.

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