

***Kocuria*: A Potential Problem in Patients with Complicated Urinary Tract Infections**Imanyikwa O. E. E.¹ Ezeonu I. M.² and Agbo M. C.^{3*}

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Abstract: *Kocuria* species are Gram-positive, catalase positive and coagulase-negative cocci that were not previously associated with human infections; but have recently emerged as human pathogens. These organisms have been implicated in different infections including urinary tract infections (UTIs), mostly in patients with underlying diseases. The aim of this study was to investigate the possible involvement of *Kocuria* species in UTIs in patients attending different clinics at Enugu State University of Science and Technology Teaching Hospital, Enugu, southeastern Nigeria. In this cross-sectional study, urine specimens from 867 patients were analyzed by standard microbiological and biochemical techniques. Polymerase chain reaction (PCR) was used to confirm *Kocuria* species and *mecA* gene. Antibiotic resistance profile (ARP) of *Kocuria* was determined using Kirby-Bauer disc diffusion method. Of the participants, 26.2% had UTI. The highest prevalence was observed among out-patients (52.4%), followed by male patients having bladder outlet obstruction (22.5%), diabetics (15.4%), Human Immunodeficiency Virus (HIV) Patients (9.7%). *Kocuria* was identified as the etiologic agent in 4 cases (1.8% prevalence); one was a male patient with supra-pubic cystostomy due to urethral strictures, while 3 were out-patients suspected of UTIs. Antibiotic resistance profile showed the *Kocuria* spp. to have a high degree of antibiotic resistance to various antibiotics including methicillin. This study suggests that *Kocuria* spp. are a potential problem for patients with complicated and uncomplicated UTI, more so as antibiotic resistance already exists among these organisms. It also highlights the need to investigate every case of suspected coagulase-negative *Staphylococcus* with more sensitive diagnostic techniques, such as PCR

Key word: Antibiotic resistance, Coagulase-negative, *Kocuria* species, *Staphylococcus*, UTIs

INTRODUCTION

Kocuria species are Gram-positive cocci arranged in pairs, short chains, tetrads, cubical packets of eight and irregular clusters. *Kocuria* belongs to the phylum Actinobacteria, class Actinobacteria, order Actinomycetales, and family Micrococcaceae (Kandi et al., 2016, Dave et al., 2018). The organism owes its name to Miroslav Kocur, a Slovakian microbiologist, who first named them (Purty et al., 2013). More than 18 species of *Kocuria* have been identified based on 16S rRNA phylogeny. However, only about three species (*K. rosea*, *K. kristinae* and *K. varians*) have been implicated in human disease, although other species may be found in animals. Most *Kocuria* spp are strict aerobes, except *K. kristinae*, which is a facultative anaerobe, *Kocuria marina*, which may grow in 5 % CO₂, and *Kocuria rhizophila* strain DC2201, which can proliferate anaerobically (Savini et al., 2010, Kandi et al., 2016, Dave et al., 2018, Ali et al., 2020). They are also catalase positive and coagulase negative.

Kocuria has been known to be a part of the normal microbiota, inhabiting the skin and mucous membrane of humans and animals (Kandi et al., 2016). *Kocuria* species were not previously associated with human infections, but in recent times the organism has emerged as a human pathogen, especially in compromised hosts with severe underlying disease. *Kocuria kristinae*, in particular, has been reported in cases of urinary tract infections, cholecystitis, catheter-associated bacteremia, dacryocystitis, canaliculitis, keratitis, native valve endocarditis, peritonitis, descending necrotizing mediastinitis, brain abscess and meningitis (Purty et al., 2013, Bernshteyn et al., 2013, Kandi et al., 2016, Dave et al., 2018, Napolitani et al., 2019; Ali et al., 2020). Despite the increasing recognition and identification of *Kocuria* in different infections, it is believed that their involvement in disease situations may still be grossly underestimated. This is due to their close resemblance and biochemical similarity to the coagulase-negative

staphylococci, which would lead to their misdiagnosis in disease situations. In fact, it has been suggested that a number of clinical cases which were hitherto attributed to coagulase negative staphylococci, could possibly have been due to *Kocuria* spp., particularly in cases where diagnosis was based only on morphological and biochemical characterization (Lee *et al.*, 2009, Purty *et al.*, 2013, Napolitani *et al.*, 2019).

Antibiotics susceptibility testing of *Kocuria* species had shown the organism to be very susceptible to drugs in various classes of antibiotics; however recently, there are increasing reports on their resistance to some of these antibiotic classes (Ma *et al.*, 2005, Savini *et al.*, 2010, Tewari *et al.*, 2013, Lakshmikantha *et al.*, 2015, Abdulla and Barzani, 2017). Despite observation of antibiotics resistance in these agents, there is paucity of reports showing investigation on possible presence of resistant genes in them. Notably is the report on oxacillin resistance in which the researchers did not consequently screen for the presence of methicillin resistant gene (*mecA*) in the isolates. Probably because of the popular believe that *mecA* gene is usually conserved in the genus *Staphylococcus* (Lai *et al.*, 2011, Tewari *et al.*, 2013). Infections caused by methicillin-resistant organisms are of special concern due to few therapeutic options, increase in duration of hospital stay, hospital costs, increased morbidity and mortality in patients as compared with those associated with methicillin sensitive organisms (Abdulla and Barzani, 2017).

Although, there are increasing reports of involvement of *Kocuria* spp. in clinical manifestations in different parts of the world, there are dearth of report of involvement of *Kocuria* in any infections in Nigeria. This study was therefore, undertaken to investigate the possible involvement of *Kocuria* spp. in urinary tract infections in patients attending different consultant's clinics at Enugu State University of Science and Technology

Teaching Hospital (Parklane), Enugu, southeastern Nigeria.

MATERIALS AND METHODS

Study area: The study was carried out at Enugu State University of Science and Technology Teaching Hospital (ESUTTH), Parklane, Enugu, located in southeastern Nigeria. The hospital is strategically located centrally at Government Reserved Area (GRA), Enugu metropolis where patients from all the Local Government Areas of Enugu State have easy access to the hospital. The hospital was selected based on high patients' influx in all the Consultants' Clinics.

Ethical consideration: Ethical approval was obtained from the Ethical Committee on Research of ESUTTH Parklane, before the commencement of the research. Informed consent was also obtained from the participants before the collection of specimens. The research protocol was carried out in accordance with the ethical standards of committees on human experimentation laid down in the Helsinki declaration of 1964 revised in 2000.

Sample size determination: A minimum sample size of 476 participants was estimated using modified Cochran formula

$$n_o = \frac{Z^2 pq}{e^2}$$

Where $z = Z$ score for 95% confidence interval (1.96), e = desired level of precision (4.5%), p = the (estimated) proportion of the population which has the attribute in the study (43.6% prevalence of UTIs in a tertiary hospital in South West Nigeria was used (Oluwafemi *et al.*, 2018), $q = 1 - p$; a 10% attrition was added. However, 867 participants were included in the study.

Study design and sampling strategy: The study was a descriptive cross-sectional study conducted from November 2018 to December 2019. Patients within different risk groups, attending different Consultants' Clinics at Enugu State University of Science and Technology Teaching Hospital Parklane, Enugu, were recruited into the study. The participants included: 220 male patients having bladder outlet obstruction

(BOO) visiting urology clinic; 212 diabetic patients visiting diabetics clinic; 210 Human Immunodeficiency Virus (HIV) patients visiting HIV clinic; and 225 out-patients suspected of having urinary tract infections at the general out-patients (GOP) clinic. Participants who met the selection criteria from each risk group were selected using simple random sampling technique. There was no pre-selection of participants based on suspicion of UTIs except for out-patients who were sent for urine culture on presentation or suspicion of UTIs. Participants who did not give consent, female participants who were menstruating and patients with a history of antibiotics administration for past two weeks were excluded from the study. Before collection of specimens, a well-structured questionnaire was used to elicit the following information among others from the participants: age, gender, antibiotics use, catheterization status, reason for catheterization, underlying disease condition and symptoms of UTI. Information was collected using the patients' preferred language (English or Ibo). Questionnaire items were coded to be anonymous such that it is not possible to identify individual patients. The code on the questionnaire was made to tally with the corresponding sample bottle.

Urine specimen collection was scheduled for the clinic days of each study group; Tuesdays for patients having BOO, Wednesdays for diabetic patients, Thursdays for HIV patients and Monday was conveniently chosen for out-patients. Sample collection for each group was done weekly for convenience and to give enough time for specimen analysis. Sample collection was done between November 2018 and December 2019, until the sample size of 867 was obtained. Patients were educated on how to collect freshly voided, clean-catch mid-stream urine (MSU) specimen aseptically, in sterile screw capped well labeled universal bottles. After the collection, the specimens were transported immediately to the Microbiology laboratory,

Department of Medical Microbiology, College of Medicine ESUT Parklane in a cold box for analysis. The samples were analyzed within 2 hours of collection.

Sample processing, culture and characterization of isolates: The media used (Chromogenic agar, blood agar and MacConkey agar) were prepared aseptically according to manufacturers' instructions. The chromogenic agar (Uriselect Bio-Rad, UK) used is a selective and differential media for the rapid isolation and identification of clinically important uropathogens. A loopful of each urine specimen was inoculated on the surface of chromogenic agar, blood agar and MacConkey agar plates, respectively, using a standard wire loop (1/500 ml loop) and incubated aerobically at 37°C for 24 h. The plates were examined macroscopically for bacterial growth. Urinary tract infection was determined if the number of colonies are $\geq 10^5$ cfu/ml or $\geq 10^4$ cfu/ml of a single species for catheter urine. Colonial appearance, colour and morphological characters of bacteria on the agar plates were observed, and isolates were stored in 20% glycerol at -80°C. Other conventional microbiological test such as Gram-staining, and biochemical tests such as catalase, coagulase and mannitol fermentation test previously described (Cheesbrough, 2006) were carried out. The isolates which showed similar morphological and biochemical characteristics as coagulase-negative staphylococci (CoNS), that is Gram-positive cocci, arranged in pairs or clusters, coagulase-negative and catalase positive were further screened for possible presence of *Kocuria* spp. *Kocuria* spp. were confirmed using polymerase chain reaction.

PCR for confirmation of *Kocuria* species: The genomic DNA of presumed CoNS isolates were extracted using the Zymo Research Mini Quick-DNA™ Fungal/Bacterial Miniprep Purification Kit (Zymo Research Corp, CA, USA). Then, 16S rRNA primer sequences of the genus *Kocuria* as reported by Purty *et al.* (2013) were used for the PCR. The conserved

primers sequences purchased from Inqaba, Biotech, South Africa are as follows; PKRF (5'-ATC CTG GCT CAG AGC GAA CG-3') and PKRR (5'-CCC TAC GGC TAC CTT GTT ACG-3'). The PCR for detection of *Kocuria* spp. was carried out using the New England Biolabs one Taq 2X Master-mix with standard buffer. Amplification was carried out in a 25 µl total volume of PCR mixture containing 12.5 µl of 1x Master mix (New England Biolabs) with standard buffer, 0.5 µl of 10 µM each of forward and reverse primers; 3 µl of the extracted DNA and 8.5 µl of nuclease free water in a DNA thermal cycler. The amplification program was as follows at 40 cycles; pre-heat lid 105°C, initial denaturation was at 94°C for 5 min, while denaturation was at 94°C for 45 s, annealing was at 58°C for 45 s, extension at 72°C for 45 s. And a final extension step was set at 72°C for 5 min.

Antibiotic sensitivity testing for *Kocuria* species: Routine antibiotic sensitivity testing was carried out on Mueller-Hinton agar by Kirby-Bauer disc diffusion method according to Clinical and Laboratory Standards Institute (CLSI) guidelines for *Staphylococcus*, using the following antibiotic discs from Rapid Labs, UK: Ciprofloxacin 5 µg, erythromycin 10 µg, ceftriaxone 30 µg, ampicillin 10 µg, cloxacillin 10 µg, levofloxacin 5 µg, cephalixin 30 µg, gentamicin 10 µg, ofloxacin 5 µg, clindamycin 2 µg, and oxacillin 1 µg as previously described (Brown *et al.*, 2005).

PCR for detection of *mecA* gene: Isolates showing resistance to oxacillin were analysed using PCR for possible detection of *mecA* gene from the extracted DNA. The primer sequences for *mecA* (Inqaba Biotec, South Africa) and are as follows; F5'-GTTGTAGTTGTCGGGTTTGG-3' and R5'-CCTCCACATACCATCTTCTTAAC-3'. The PCR for detection of *mecA* gene was carried out using the new England BIO Labs one Taq 2X Master mix with standard buffer. Amplification was carried out in a 25 µl total volume of PCR mixture containing 12.5 µl of 1X Master mix (England BIO

Labs) with standard buffer, 0.5 µl of 10 µM each of primers; 3 µl of the extracted DNA and 8.5 µl of Nuclease free water in a DNA thermal cycler. The amplification program was as follows at 40 cycles: initial denaturation was at 94°C for 5 mins, while denaturation was at 94°C for 30 seconds, annealing was at 55°C for 30 seconds, extension at 72°C for 60 seconds, and a final extension step was set at 72°C for 5 min. After PCR amplification, the samples were subjected to electrophoresis in 1.5% agarose gel stained with 5 µl ethidium bromide at 90 volts. The gel was removed and visualized in ultraviolet trans-illuminator in a dark room.

Data analysis: Data collected were analyzed using percentage frequency distribution.

RESULTS

Out of the 867 urine samples examined, 227 (26.2%) had UTI. The highest prevalence of urinary tract infections was observed among the out-patients (52.4%), followed by male patients having bladder outlet obstruction (22.5%), Diabetic patients (15.4%), and then HIV patients (9.7%) (Table 1). Bacteria identified from the cases of UTI by cultural and biochemical characterizations were *Escherichia coli* (67; 29.5%), *K. pneumoniae* (46; 20.3%), *Enterococcus* spp. (38; 16.7%), CoNS (31; 13.7%), *Staphylococcus aureus* (25; 11.0%) and *P. aeruginosa* (20; 8.8%). Out of the 31 presumptive CoNS, PCR screening identified 4 to be *Kocuria* (Figure 1 and 2); thus, changing the prevalence of CoNS to 11.9%, and giving a prevalence of 1.8% for *Kocuria* spp. (Table 2).

The antibiotic susceptibility testing of the *Kocuria* isolates showed that there was high rate of resistance to all the antibiotics used (75 - 100%) (Table 3). Furthermore, all the *Kocuria* isolates were multidrug resistant, exhibiting resistance to at least three antibiotics. PCR screening for *mecA* gene, responsible for methicillin resistance, confirmed the presence of *mecA* in two isolates (Figure 3).

Table 1: Prevalence of UTIs in Different Study Groups

Study Groups	Number of Samples Examined	Number Positive for UTI (%)
BOO	220	51 (22.5)
Outpatients	225	119 (52.4)
HIV Patients	210	22 (9.7)
Diabetics	212	35 (15.4)
Total	867	227 (26.2)

Keys: BOO= bladder outlet obstruction, UTIs = urinary tract infections

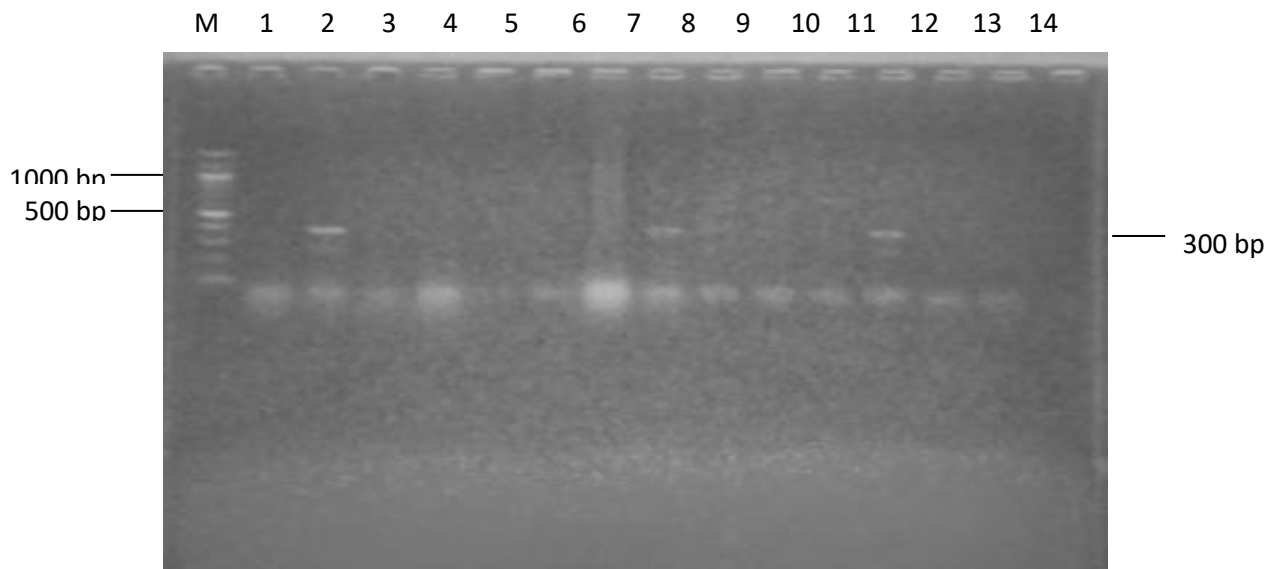


Figure 1: Gel Image for PCR Identification of *Kocuria* spp. Lane M Represents 100 bp Molecular Weight Standard, while Lanes 2, 8 and 12 Show Positive Amplification for *Kocuria* spp. *PKR* Gene (390 bp).

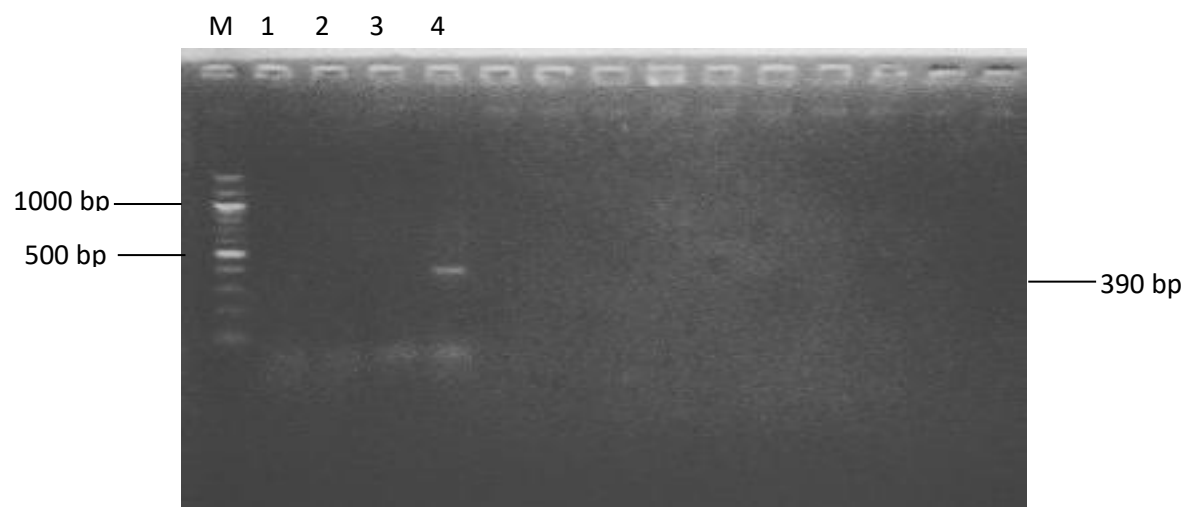


Figure 2: Gel Image for PCR Identification of *Kocuria* spp. Lane M Represents 100 bp Standard, while Lane 4 Shows Positive Amplification for *Kocuria* spp. *PKR* Gene (390 bp).

Table 2. Prevalence of Bacterial Isolates among the Study Groups

Isolates	Study groups				Total N (%)
	BOO N (%)	Out-patients N (%)	Diabetics N (%)	HIV/AIDS patients N (%)	
<i>E. coli</i>	13 (5.7)	37 (16.3)	11 (4.8)	6 (2.6)	67 (29.5)
<i>K. pneumoniae</i>	4 (1.8)	33 (14.5)	7 (3.1)	2 (0.9)	46 (20.3)
<i>Enterococcus</i> spp.	6 (2.6)	18 (7.9)	6 (2.6)	8 (3.5)	38 (16.7)
<i>P. aeruginosa</i>	12 (5.3)	6 (2.6)	1 (0.4)	1 (0.4)	20 (8.8)
<i>Staphylococcus aureus</i>	6 (2.6)	13 (5.7)	4 (1.8)	2 (0.9)	25 (11.0)
CoNS	9 (4.0)	9 (4.0)	6 (2.6)	3 (1.3)	27 (11.9)
<i>Kocuria</i> spp.	1 (0.4)	3 (1.3)	0 (0.0)	0 (0.0)	4 (1.8)
Total	51 (22.5)	119 (52.4)	35 (15.4)	22 (9.7)	227 (100)

Keys: N (%) = number (percent), BOO= bladder outlet obstruction

Table 3. Antibiotics Susceptibility Patterns of *Kocuria* Isolates

Antibiotic	Concentration	Number (%) of Isolates exhibiting trait (n=4)		
		R	I	S
OX	1 µg	03 (75.0)	0 (0.0)	01 (25.0)
E	10 µg	04 (100)	0 (0.0)	0 (0.0)
CT	30 µg	03 (75.0)	0 (0.0)	01 (25.0)
AM	30 µg	04 (100)	0 (0.0)	0 (0.0)
CL	10 µg	03 (75.0)	0 (0.0)	01 (25.0)
LV	5 µg	03 (75.0)	0 (0.0)	01 (25.0)
CX	30 µg	03 (75.0)	0 (0.0)	01 (25.0)
CIP	5 µg	04 (100)	0 (0.0)	0 (0.0)
GN	10 mg	03 (75.0)	0 (0.0)	01 (25.0)
OF	10 mg	03 (75.0)	0 (0.0)	01 (25.0)
CD	10 mg	03 (75.0)	0 (0.0)	01 (25.0)

Keys: OX= Oxacillin, E=Erythromycin, CT= Ceftriaxone, AM= Ampicillin, CL=Cloxacillin, LV= Levofloxacin, CX= Cephalexin, CIP= Ciprofloxacin, GN= Gentamicin, OF= Ofloxacin, CD=Clindamycin, R-resistant, I-intermediate, S-susceptible. Values are expressed as Number (%)

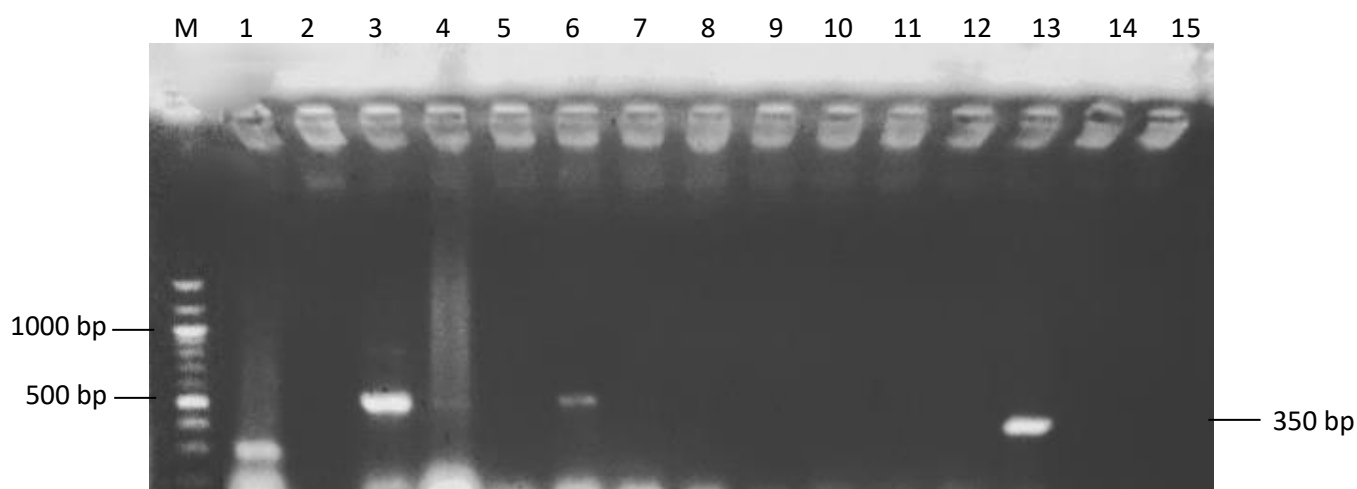


Figure 3. Gel Electrophoresis of PCR Detection of *mecA* Gene in *Staphylococcus* and *Kocuria* Isolates. Lane M- 100 bp DNA Marker; Lanes 3 and 4, Positive *Staphylococcus* Isolates; Lanes 6 and 13, Positive *Kocuria* Isolates

DISCUSSION

The findings from this study showed bacterial identification of the commonest causes of UTIs by cultural and biochemical characterizations to be *E. coli*, *K. pneumoniae*, *Staphylococcus* spp., and *P. aeruginosa*; this result is consistent with results from other similar studies (Simkhada *et al.*, 2013, Srinivas *et al.*, 2014, Sewify *et al.*, 2016, Oluwafemi *et al.*, 2018). However, out of the 31 presumptive CoNS, PCR screening identified 4 to be *Kocuria*. This result agrees with the suggestions previously made that some infections hitherto attributed to CoNS could actually be due to *Kocuria* species (Purty *et al.*, 2013, Napolitani *et al.*, 2019). The finding of *Kocuria* spp. in this study is most likely due to the adoption of a gene-based method (PCR) in identification. There are various reports of bacterial isolates being misidentified in clinical laboratories due to reliance on phenotypic assays. Typically, the misidentification of *Kocuria* isolates as coagulase-negative staphylococci using only phenotypic typing are well documented (Savini *et al.*, 2010, Napolitani *et al.*, 2019). However, in recent times, there are increasing reports of different infections caused by *Kocuria* spp. due to the use of molecular methods of identification (Lai *et al.*, 2011, Dunn *et al.*, 2011, Tewari *et al.*, 2013, Lakshmikantha *et al.*, 2015, Abdulla and Barzani, 2017).

Out of the four identified cases of *Kocuria*, in this study, one was from a male patient with supra-pubic cystotomy due to urethral strictures, while 3 were isolated from out-patients suspected of UTI. It was not possible in this study to ascertain the underlying disease condition of the out-patients. This study represents possibly the first report of *Kocuria* spp. from any clinical case in Nigeria.

The findings of the antibiotic susceptibility of the *Kocuria* isolates showed that there was high rate of resistance to all the antibiotics used (75 - 100%). Furthermore, all the *Kocuria* isolates were multidrug resistant, exhibiting resistance to at least three antibiotics. Currently, there are no

recommended guidelines of antibiotic susceptibility of *Kocuria* spp, and researchers have relied on guidelines for CoNS. However, existing reports have indicated a favourable response to most broad-spectrum antibiotics for *Kocuria* spp. (Savini *et al.*, 2010, Dave *et al.*, 2018, Ali *et al.*, 2020). It is therefore, of significance that the *Kocuria* isolates in this study exhibited high rates of resistance to most of the tested antibiotics, including oxacillin. The PCR screening for *mecA* gene, responsible for methicillin resistance, confirmed the presence of *mecA* in two isolates. These findings suggest that *Kocuria* spp. may also be methicillin resistant. A similar study had reported *mecA* gene in one *Kocuria* isolate (Abdulla and Barzani, 2017).

The findings from this study are of great significance for several reasons: the study highlights the need for use of molecular techniques in laboratory diagnosis, in order to reduce the rate of misdiagnosis due to reliance on phenotypic characterization. Also, the findings showed that contrary to the belief that *Kocuria* may only be significant in immunocompromised individuals; the organism could also present a problem in healthier individuals, as three out of the four cases were from out-patients and not hospitalized patients. Furthermore, the degree of resistance recorded among the *Kocuria* isolates raises alarm that an antibiotic resistance crisis could already be developing in Nigeria, for an organism that is yet to be recognized as an etiologic agent of disease. There is therefore, need for creation of awareness of this organism and more judicious application of broad-spectrum and commonly used antibiotics, to check the spread of resistance.

CONCLUSION

This study suggests that *Kocuria* spp. are a potential problem for patients with complicated and uncomplicated UTIs, more so as antibiotic resistance already exists among these organisms. This study clearly documents *Kocuria* spp. associated with UTI in Nigeria. It also highlighted the need

to investigate every case of suspected coagulase-negative *Staphylococcus* with

more sensitive diagnostic techniques, such as PCR.

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