RESEARCH ARTICLE

Oral Cavity Microbiome as Infectious Agents: Iraqi Kocuria Rosea

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ABSTRACT

Oral microbiota has a significant effect on human health, representing an indicator of oral and systematic health problems. *Kocuria spp.* are gram-positive bacteria isolated from healthy people as oral flora; the main species of this study were to enlighten variation in bacterial attitude in Iraqi people from nonpathogenic in healthy samples to pathogenic in patients samples mostly with chronic disease. Oral swabs were collected from the oral cavity 25% of third-grade students, cultivated under aerobic conditions, isolates have been identified, and susceptibility to different antibiotics was determined using Vitek 2 system GP version 08.01. Data of the experiment samples were collected and analyzed. *Kocuria rosea* (*K. rosea*) VITEK results declared Antibiotic susceptibility as resistance to Polymixin B, Bacitracin, Novobiocin, Optochin, and O/129 (comp.vibrio.) also proved it's D-mannose negative, which attributes to bacterial adherence ability. In addition to previously known biofilm formation ability and "Kocuran" production, all these facts indicate the capability of *Kocuria* to initiate infection (particularly in immunocompromised, immunosuppressed, and immunocomplete patients) and medical complications of irreversible damage which required argent protocols, these varied virulence factors within species encouraging studies on a genetic level, pathogenicity, and treatments. Iraqi records highly frequent site of infection was kidney compering to international records, were bloodstream, kidney 37% and 24% respectively (χ^2) = 11.262**, While developed disease varies, CRB and CAPD-related peritonitis were the highest frequent 25% (χ^2) = 8.910**, Comorbidity disease was Kidney diseases 28%, Diabetes mellitus 14%, (χ^2) = 8.263 **, an effective treatment used was Vancomycin 24% and Amikacine 10%. (χ^2) = 11.947 **.

Keywords: *Kocuria rosea*, Vitek 2 system GP version 08.01, oral microbiota, bacteremia, immunosuppressed, Peritoneal dialysis.

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INTRODUCTION

Micro-organisms inhabit the human body surface, cavities, and many organs, included pathogenic, opportunistic, and commensal. This variation considers one of the most impressive ecosystems where these micro-organisms perform synergic and antagonistic activities together and with the immune system. The oral cavity ecosystem has a substantial effect on human health. Through years scientists illustrated numerous micro-organisms and their relation to tooth status odontogenic, including dental caries, periapical infection, gingivitis, periodontal infection and abscesses, and deep fascial space infections[1,2] also transporting infection through the body system. Oral microbiota is important as an indicator of many health problems orally and systematically, like pancreatic cancer,[3] endocarditis,[4] respiratory infection[5,6], and many other diseases.

In this research, oral swabs of Iraqi samples were examined for bacterial species and their relation to patients' health status. One of these bacterial species was identified as *Kocuria rosea,* normal flora of (skin, oropharynx, and mucosa membrane) in human and other mammals,[7] some isolates were collected from water sources and different kinds of fermented food.

Kocuria belongs to the phylum *Actinobacteria*, Class *Actinobacteria*, order *Actinomycetales*, sub order *Micrococcinae* and family *Micrococcaceae.*[7] Currently, there are more than 17 species of *Kocuria* identified based on the 16S rRNA phylogenetic studies. *Micrococcus kristinae* was the earlier name of *Kocuria.*[8] The genus *Kocuria* are gram-positive cocci arranged in pairs, tetrads and irregular clusters, non-motile, non-capsulated, non-spore forming, and colonies appeared round, raised, convex and non-hemolytic colonies on blood agar, *Kocuria* spp. are obligate aerobes, catalase-positive, coagulase-negative, and nitrate reductase negative, non-acid fast and positive for Voges-Proskauer test (VP).[9,10]

MATERIALS AND METHODS

Isolation and Identification of Bacteria

The experiment samples were oral swabs of 25% third-grade

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students (21–23) years, collected using cotton swabs and applied immediately on nutrient and MacConkey agar, incubated for 24 hours at 37°C under aerobic condition. Colonies developed, and their shape, color, size were observed; then, they were identified by Gram's staining and VITEK-2 system GP Version 08.01 (BioMérieux Inc., Durham, NC, USA), of 43 biochemical tests measuring carbon source utilization, enzymatic activities, and antibiotic resistance.

Statistical Analysis

The Statistical Analysis System or SAS (2012) program was used to detect different factors in study parameters.[11] Chi-square test was used to compare between percentage in this study significantly.

RESULTS

Data of the experiment samples were collected and organized as shown in Table 1. Colonies developed on nutrient agar after an incubation period of 24 hours; macroscopical characteristics were recorded, colonies of the selected genus *Kocuria rosea*, whitish, round, and convex, while no bacterial growth appeared MacConkey agar. Bacterial cells on slides with Gram's stain showed large-sized cocci arranged in pairs, short chains, tetrads, irregular clusters, Figure 1. All experiment samples were diagnosed using VITEK -2 compact system (bioMérieux), giving us a certain diagnosis for different bacterial species.

For *Kocuria rosea* Vitek-2 system ID-GP card panel tested negative for all the tests, as shown in Table 2.

DISCUSSION

The results showed that the examined samples could be classified as normal oral microbiota, including bacteria and yeast (*candida* spp.) except *Pseudomonas aeruginosa*. Normal flora mainly diagnosed within the samples as the experiment performed on healthy people's teeth status is shown in Table 1. No chronic diseases have been recorded, and an acceptable diet has been applied. *Candida* spp. has been diagnosed in

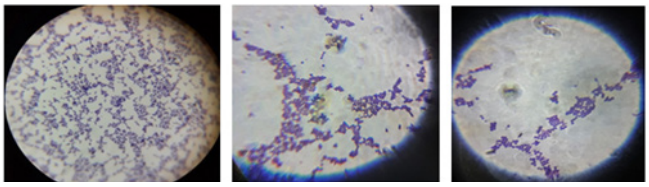

Figure 1: *Kocuria rosea* under Microscope 40X, 100X, and 100X, respectively

Table 1: Bacterial species from oral cavity swabs of healthy people in Baghdad

	Diet							
Code	*varied*	*vegan*	*Teeth status*	*Health status*	*Antibiotic course*	*Chronic Disease*	*Smoking*	*VITEK*
1	1	0	orthodontic / filling 8 teeth	slight Mouth ulcers (caused by ortho)	Azithromycin	Non	0	*Candida spp.*
2	1	0	canine caries	Healthy	Non	Non	0	*Kocuria rosea*
3	1	0	Moderate oral hygiene (extraction, endo)	Healthy	Non	Non	0	*Staph. lentus*
4	1	0	fair oral hygiene/amalgam filling/root filling	Healthy	Non	Non	0	low reactive
5	1	0	Good	Healthy	Non	Non	0	*Leuconostoc pseudomesenteroides*
6	1	0	Good oral hygiene / filling	Healthy	Non	Non	0	*Staph. lentus*
7	1	0	One extraction/ three filling	Healthy	Non	Non	0	*Lactobacillus salivarius*
8	1	0	Two filling / sound	Tonsillitis (fever)	Azithromycin	Non	0	*Candida spp.*
9	1	0	one filling	Healthy	Augmentin	Non	0	*Candida spp.*
10	1	0	Three filling	Healthy	Non	Non	0	no growth
11	1	0	Good oral hygine / filling	Healthy	Non	Non	1	*Dermacoccus nishinomiyaensis / Kytococcus sedentarius*
12	0	1	Good oral hygiene	Healthy	Non	Non	0	*Lactobacillus salivarius*
13	1	0	Good oral hygiene	Healthy	Non	Non	1	*Staph. lentus*
14	1	0	Good oral hygiene	Healthy	Non	Non	0	*Pseudomonas aeruginosa*
15	0	1	Good oral hygiene	Healthy	Non	Non	0	*Kocuria rosea*
16	1	0	Good oral hygiene	Healthy	Non	Non	0	*Staph. aureus*
17	1	0	Good oral hygiene	Healthy	Non	Non	1	*candida spp.*
18	1	0	Good oral hygiene	Healthy	Non	Non	0	*Staph. lentus*
19	1	0	Good oral hygiene	Healthy	Non	Non	1	low reactive
20	1	0	Good oral hygiene	Healthy	Non	Non	0	*Dermacoccus nishinomiyaensis / Kytococcus sedentarius*

people used antibiotic within 7 days after completing the antibiotic course.

Kocuria rosea was one of the experiment samples, confirmed to be gram-positive, opportunistic bacteria isolated from a healthy person not diagnosed with health issues within the sampling period and after. It's known to be a nonpathogenic low virulence microorganism[12] though low medical importance. In the seventieth, it was diagnosed in urinary tract infection patient,[7] lately many cases with immunity disorder (immunocompromised, immunosuppressed, and immunocompetent patients) have been diagnosed with complication rooted to this species, causing a wide range of local infections and systematic diseases that lead to death in some cases.

Referring to findings during researches on the oral experiment, bacteria *K. rosea* was chosen for this study. Emphasizing this bacteria's neglection in scientific research and illustrating that, Table 3 has been derived. The data collected from Iraqi papers shows the variation in this bacteria attitude from nonpathogenic bacteria in healthy Iraqi samples to pathogenic bacteria in patients Iraqi samples, mostly with chronic disease.

Numbers of *K. rosea* isolates have been recorded in the previous table; kidney infections in most cases plus the usual location were listed as infection site. Though these infections, researchers did not inspect *k. rosea* as infectious agents, and nonspecific treatment has been used mostly. Many researchers worldwide react to this species reassembly as it's known to be common virulence bacteria.

The establishment of infection required possessing virulence factors. Opportunistic as pathogenic bacteria have at least a single (rare) virulence determinant, causing variable types of diseases that may refer to the particular complement of virulence determinants.[19] VITEK results

Table 2: *Kocuria rosea* VITEK-2 compact system ID-GP card Version 08.01 results.

Biochemical Details											
AMY	-	PIPLC	-	dXYL	-	ADH1	-	BGAL	-	AGLU	-
APPA	-	CDEX	-	AspA	-	BGAR	-	AMAN	-	PHOS	-
LeuA	-	ProA	-	BGURr	-	AGAL	-	PyrA	-	BGUR	-
AIaA	(-)	TyrA	-	dSOR	-	URE	-	POLYB	-	dGAL	-
dRIB	-	ILATk	-	LAC	-	NAG	-	dMAL	-	BACI	-
NOVO	-	NC6.5	-	dMAN	-	dMNE	-	MBdG	-	PUL	-
dRAF	-	O129R	-	SAL	-	SAC	-	dTRE	-	ADH2s	-
OPTO	-										

+ = 95% to 100% positive; v = 6% to 94% positive; – = 0% to 5% positive
Susceptibility to antibiotic: Antibiotic susceptibility according to VITEK-2 compact system results was Polymixin B resistance, Bacitracin resistance, Novobiocin resistance, Optochin resistance and O/129 resistance (comp.vibrio.)

Table 3: Records of infections with *Kocuria rosea* and associated comorbidities in Iraqi governorates.

Reference (s)	*Specimens*	*Site of infection*	*Type of infection & associated comorbidities*	*Antibiotics susceptibility test*	*City*
Assafi et al., 2015[13]	2/141	kidney	Urinary tract infection (UTI)	*Vancomycin, linezolid, tigecycline, and nitrofurans*	Duhok
Abdullah & Barzani,2016[14]	6/225	Oral cavity, Ear, and kidney	Thalassemia	Vancomycin, Azithromycin, Erythromycin, Imipenem. Resistant for Amoxicillin/ Clavulanic, Bacitracin, Ciprofloxacin, Clindamycin, Doxycycline, Methicillin, Meropenem, Nitrofurantoin, Penicillin G.	Erbil
AL-Ghizawi &Jomaa,2017[15]	3/100	Urogenital tract	*Mycoplasma*	_____	Basrah
Abdullah & Barzani, 2017[16]	5/96	Oral cavity and kidney	Thalassemia	Amoxicillinclavulanate	Erbil
Al-Douri & Maaroof, 2018[17]	1/135	kidney (urine)	UTI	Levofloxacin، Norfloxacin ، Ofloxacin، Doxycycline ، Meropenem, Oxytetracycline Rifampin and. Imipenem resistant for Ampicillin/Cloxacillicn ، Cephalothin, Lincomycin ، Netilmicin,	Samarra
Al-Jebouri & Al-Mahmood,2019[18]	4/200	Skin	Acute-phase of wound infections	_____	Baghdad
This study	1/20	Oral cavity	Normal flora	polymixin b resistance, bacitracin resistance, novobiocin resistance, optochin resistance and o/129 resistance (comp.vibrio.)	Baghdad

shown in the present study (as presented in table 2) that *k. rosea* doesn't have virulence enzymes such as urease, catalase (potential virulence factors in many pathogenic bacteria), and others. But in reverse to all these results, this bacteria is proved as an infectious agent causing nosocomial infections, aided by their adherence to surfaces like prosthetic devices and catheters.[1,20-22] Hence, catheter removal is one of the first treatment protocol steps.

VITEK results also proved that *K. rosea* is a D-mannose negative (mannose-resistant fimbriae) one of the bacterial attachment tools. It's correlation to infection is a matter of high expectation as it acts as virulence factors in a wide range of bacterial species.[19] it's resistant to optochin, polymixin b, bacitracin, novobiocin confirmed in this research, previous researchers proved resistance to numerous antibiotics internationally[7,10] and locally as Al-Douri and Maaroof, mentioned *K. rosea* is β-lactamase producer[17] plus biofilm formation ability in association with different bacterial species[23-26], this ability qualify it to resist antibiotics effect and efficient defeating to immune system defenses also some of the virulence determinants activated when bacteria reach the quorum sensing[27,19] in other hand, one of *kocuria* spp. tolerate severe alkaline conditions.[5] Other important virulence factors detected in 2013 BS-1 strain of *K. rosea* producing substance consist of exopolysaccharide were recognized. It was the only strain that produced it -till now-then known as "Kocuran" which proved to have antioxidant and immunosuppression properties *in vitro*.[28] Standing on results and considering the previous fact that *K. rosea* to cause infections have been declared.

Data of *Kocuria* spp. Infections records were collected worldwide, particularly in Iraqi governorates within 2002–20 (the current study), summarized in Tables 3–5.

Peritoneal dialysis (PD) patients suffering from peritonitis caused by *kocuria* spp.[35] and within this medical condition, variable dialysis modal show differences in the required period to initiate infection influenced by bacterial colonization site on skin and adherence capability to surfaces like catheters.[34]

Apparently, infection of bloodstream and kidney are the highest frequent with 37% and 24% respectively, followed by Peritoneum 18%, demonstrating that most infection located in the bloodstream, particularly *K. rosea* infections this suggested to be rooted to low pathogenicity and absence of virulence factors required to penetrate cells and toxin production plus the malfunction of the immune system. While advanced disease varies, Catheter-related Bacteremia and Continuous Ambulatory Peritoneal Dialysis (CAPD)-related peritonitis are the highest frequent with 25% (while Automated Peritoneal Dialysis (APD)-related peritonitis 5%), followed by Exit-site infection 10%, Endocarditis 7.5% other diseases with less frequency. Comorbidity diseases were Kidney diseases 28%, Diabetes mellitus 14%, Cardiovascular diseases 5.5%, and variable other diseases with less frequency. As *K. rosea* is normal flora colonize skin and oropharynx, most infections are related to these sites in the light of collected data explaining

Table 4 A: International Case reports Recorded Bloodstream infections with *Kocuria spp.* and associated comorbidities

Reference(s)	*Age/sex*	*Type of infection and comorbidities*	*Treatment (antibiotics)*	*Species*	*Clinical prognosis*
Basaglia et al. 2002[29]	51/F	Catheter-related Bacteremia and ovarian cancer	Meropenem, ciprofloxacin and clindamycin	*K. kristinae*	Recovered
Becker et al. 2008[4]	8/M	Sepsis	Cefuroxime, vancomycin and amphotericin B	*K. rhizophilia*	Multiple febrile episodes, subsequent recovery
Lai et al. 2011[30]	89/F	Infective endocarditis and Ischemic bowel disease	Vancomycin, teicoplanin and oxacillin	*K. kristinae*	Improved
Lai et al. 2011[30]	37/F	Catheter-related Bacteremia and gastric cancer	Piperacillin-tazobactam and ciprofloxacin	*K. kristinae*	Improved
Lai et al. 2011[30]	2/M	Catheter-related Bacteremia with congenital short bowel syndrome and hypogammaglobulemia	Oxacillin and vancomycin	*K. kristinae*	Improved
Lai et al. 2011[30]	68/F	Catheter-related Bacteremia and gastric cancer	Oxacillin	*K. kristinae*	Improved
Dunn et al. 2011[20]	29/F	Catheter-related bacteremia and pulmonary septic emboli	Ceftriaxone, azithromycin, vancomycin, clindamycin and oxacillin	*K. kristinae*	Improved
Moissenet et al.2012[31]	3/F	Catheter-related Bacteremia and hirschsprung's disease	Vancomycin and gentamicin	*K. rhizophila*	Septic episodes resolved
Oncel et al.2012[32]	4 m/F	Black hairy tongue	Ceftriaxone and vancomycin	*K. kristinae*	Recovered
Citro et al.2013[33]	74/M	Endocarditis and sepsis	Sulbactam/ampicillin and gentamicin	*K. kristinae*	Severe sepsis, MOFe, expired

Table 4 B: International case reports recorded kidney infections with *Kocuria spp.* and associated comorbidities

Reference(s)	*Age/sex*	*Site of infection*	*Type of infection and comorbidities*	*Treatment (antibiotics)*	*Species*	*Clinical prognosis*
Marin et al. 2015[34]	5 cases*[1]	Kidney	Peritonitis, Arterial hypertension, Chronic kidney disease (PD patients)*	Vancomycin, Amikacin, Ciprofloxacine, Cephalotin, Ceftriaxona	*K. kristinae* 4 cases/ *K. varians* 1 case	recovered
Marin et al. 2015[34]	3 cases*[2]	Kidney	Exit-site infection, Arterial hypertension, Chronic kidney disease. (Peritoneal dialysis (PD) patients)*	•Topic[3] gentamicine •Trimetoprim suphametoxasol •Cephalexine	*K. kristinae*	recovered
Kandi et al. 2016[(7)]	65/F	Kidney	Urinary tract infection with a history of hemiparesis and cardiovascular disease	vancomycin, linezolid, imipenem, amikacin, trimethoprim-sulfamethoxazole, clindamycin, erythromycin, and tetracycline	*Kocuria spp*	_____

Table 4 (C): International case reports recorded variation of infections with *Kocuria spp.* and associated comorbidities

Reference(s)	*Age/sex*	*Site of infection*	*Type of infection and comorbidities*	*Treatment (antibiotics)*	*Species*	*Clinical prognosis*
Ma et al. 2005[35]	56/M	Gall bladder	Acute cholecystitis	Levofloxacin	*K. kristinae*	recovered
Lee et al. 2009[12]	57/M	Peritoneum	CAPD-related peritonitis	Ceftazidime and clindamycin	*K.marina*	recovered
Lee et al. 2009[12]	73/M	Peritoneum	CAPD-related peritonitis	Netilmicin	*K.marina*	recovered
Tsai et al.2011[24]	52/M	Brain	Brain abscess	Ceftazidime and ceftibuten	*K. varians*	recovered
Carlini et al.2011[36]	78/M	Peritoneum	CAPD-related peritonitis	Cefotaxime, tobramycin, tazobactam, ciprofloxacin, teicoplanin and amoxicillin/ clavulanic acid	*K. kristinae*	recovered
Cheung et al.2011[28]	69/M	Peritoneum	CAPD-related peritonitis	Cefazolin and cefepime	*K. kristinae*	recovered
Meletis et al. 2012[37]	70/M	Peritoneum	CAPD-related peritonitis	Vancomycin and aztreonam	*K. varians*	improved

Table 5 A: International case reports recorded bloodstream infections with *Kocuria rosea* and associated comorbidities

Reference(s)	*Age/ sex*	*Type of infection and associated comorbidities*	*Treatment (antibiotics)*	*Clinical prognosis*
Altuntas et al. 2004[1]	39/M	Catheter-related bacteremia	Imipenem/cilastatin, Amikacin and vancomycin	recovered
Corti, et al. 2012[25]	60/M	Bacteremia and AIDS	vancomycin and catheter removal	Recovered
Serefhanoglu and Oklu. 2017[23]	78/M	Primary bacteremia (central venous catheter-related) Hemodialysis for end stage kidney disease	Imipenem cilastatin	Improved
Serefhanoglu and Oklu. 2017[23]	68/M	Primary bacteremia with a history of cardiomyopathy and diabetes	Vancomycin	Improved

Catheter-related Bacteremia and CAPD-related peritonitis high frequency. Case reports in table 4 and 5 revealed the relation of comorbidities to recent infections sites in most recorded infections, immune disorders authorize patients for opportunistic infections, and the unsound organ is basically their target; as a result, revealed endocarditis in a patient, had compensated congestive heart failure then diagnosed with Splenomegaly, heart failure and signs of sepsis, also in cases of peritoneal dialysis (PD) patients

Most cases are recovered after treatment with antibiotics, and the highly frequently used antibiotic was: Vancomycin with 24%, Amikacine with 10% the other types itemized with less frequency.

The reason behind medical complications correlated to *K.rosea*, is the ignorance, even after a confirmed identification, it considers as contaminants, especially in hospitalized patients, as we can observe in the numbers of previewed papers, in addition to limited antibiotic sensitivity testing for the *Kocuria* spp in general, emphasizing low importance though it considers commensal bacteria. Furthermore, misidentification of *K. rosea* in the clinical laboratories as *micrococcus* and coagulase-negative *Staphylococci* (CoNS) based on its gram reaction, catalase-positive, and coagulase-negative properties.[8] Purty *et al.* mentioned identifying *Kocuria* using morphological, cultural characteristics and Kirby-Bauer disc diffusion method depending on differential

Table 5 (B): International case reports recorded variation of infections with *Kocuria rosea* and associated comorbidities in different sites of infection

Reference(s)	*Age/sex*	*Site of infection*	*Type of infection and associated comorbidities*	*Treatment (antibiotics)*	*Clinical prognosis*
Dotis et al. 2012[26]	8/F	Peritoneum	Peritonitis with a history of dysplastic kidneys (Peritoneal Dialysis)	Vancomycin and ceftazidime	Recovered
Purty et al. 2013[10]	57/M	Peritoneum	Peritonitis and diabetic nephropathy	Vancomycin, cefazolin and amikacin	Recovered
Montoya et al. 2016[21]	52/M	Brain	Brain abscess	Cefepime (third and fourth generation Cephalosporine)	Improved
Kyung Lee et al. 2013[38]	58/F	oropharyngeal	Descending necrotizing Mediastinitis with a history of gout and hypertension controlled with medications.	third-generation cephalosporin and clindamycin	Recovered
Moreira et al. 2015[39]	10/F	Heart	Endocarditis had compensated congestive heart failure, Splenomegaly, heart failure, and signs of sepsis	Clarithromycin, amoxicillin, and clavulanate	Recovered
Paul et al. 2016[9]	80/F	Brain and spinal cord	Acute bacterial meningitis	Ceftriaxone	Death
Marin et al. 2015[34]	70/F	Kidney	Exit-site infection, Diabetes mellitus, Arterial hypertension, Chronic kidney disease. (Peritoneal dialysis (PD) patients)	Ciprofloxacine	Recovered
Joshi et al. 2018[5]	32/M	soft tissue / arm	Necrotizing fasciitis, history of diabetes mellitus type 2, hypercholesterolemia and recurrent boils from methicillin-resistant Staphylococcus aureus (MRSA) initially presented with a right axillary boil	Linezolid and piperacillin–tazobactam, ampicillin–sulbactam and linezolid, amoxicillin–clavulanate	Recovered
Páez et al. 2019[27]	71/M	Lung	Pneumonia with diabetes mellitus and dysphagia consequent to a stroke	Piperacillin /tazobactam and clarithromycin	Recovered

antibiotic attributed to the differentiation from micrococcus coagulase-negative *Staphylococci* (CoNS) getting advantage of *Kocuria* spp. sensitivity to bacitracin, lysozyme, and resistance to nitrofurantoin, furazolidone, and lysostaphin.[10]

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