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EVALUATION OF MICROBIAL RISK FACTORS IN RELATION TO CLINICAL EFFECTIVENESS OF OFF-LABEL BEVACIZUMAB USE FOR SELECTIVE RETINAL DISEASE TREATMENT



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Abstract

The off-label application of Bevacizumab, which is a monoclonal antibody of vascular endothelial growth factor (VEGF), is extremely popular in the management of retinal diseases, such as diabetic retinopathy, age-related macular degeneration, and retinal vein occlusion. Even though there are clinical benefits of microbial contamination when using multi-dose vials, repackaging, and storing, the problem of contamination remains. The purpose of this study was to assess the microbiological safety of bevacizumab during repeated access of the vials, under the different storage conditions, and in the operating theatre (OT) setting.

The quota was the Helper Eye Hospital at Quetta, where an experimental/observational study was carried out. Twenty samples were sampled in five bevacizumab vials after multitasking at the various usage stages. Moreover, 20 repacked syringes were made with new and used vials and kept at room temperature and 4 °C during a maximum of 14 days. In the case of environmental surveillance, 120 swab samples of six OT sites were provided. All samples were grown in conventional microbiological media, and Kirby-Bauer disc diffusion test was applied to determine the antibiotic susceptibility test.

Bevacizumab samples showed no growth of microbes at any stage of vial use or storage condition, which proves the preserved sterility. Instead, there was evidence of contamination with *Escherichia coli* and *Klebsiella pneumoniae*, which are especially found on frequently touched OT surfaces in environmental samples. Isolates were resistant to a number of β -lactam antibiotics but sensitive to carbapenems, fluoroquinolones, and aminoglycosides.

These results indicate that bevacizumab is microbiologically stable under aseptic handling conditions, and the importance of taking stringent precautions to prevent infections in the OT setting to minimize the risk of post-injection infections.

Keywords: Age-related macular degeneration, Bevacizumab, Endophthalmitis, Microbial risks, Off-label, Retinal disease, VEGF

INTRODUCTION

Bevacizumab is a monoclonal antibody against the vascular endothelial growth factor (1). The monoclonal antibody, bevacizumab (Avastin), which targets the vascular endothelial growth factor (VEGF), is also used by ophthalmologists in the treatment of various retinal diseases, including diabetic retinopathy, wet age-related macular degeneration (AMD), and retinal vein occlusion (RVO) (2). Due to the risk of microbial contamination and sterility, the use of bevacizumab was frequently controversial, especially with



references to the formulations that can be repackaged or used off-label (3). The FDA considers it an off-label medication in the field of ophthalmology. Off-label implies the administration of a drug that does not appear on the label, so approving a disease or an indication not the disease in which it is approved in various dosages, frequency, or route of administration that is designated in the label (4). Nevertheless, there is no insignificant risk of contamination and endophthalmitis (5).

Vials of Bevacizumab contain neither preservatives nor antimicrobials (6). There are many other methods, such as pooling of patients that is administering the drug intravitreally to several patients with the same vial on the same day (7). Although the treatment is safer and more secure per se, endophthalmitis, severe impairment of vision, and other eye diseases may be developed because of using non-hygienic vials and poor aseptic practices (8). This has the potential to impact a massive number of patients and cause a severe impact on both the patient and the doctor. Delivery of bevacizumab intravitreally needs to be compounded by the compounding pharmacies into one-syringe doses to be used in the eye (9). Even though the US Food and Drug Administration allows the repackaging process, the obtained product fails to comply with the particular specifications of products that are approved to be used as an ophthalmic injectable, and the parenteral innovator solution does not conform to ophthalmic standards (10).

In third-world countries such as Pakistan, off-label prescription of drugs is a norm, but to a great extent, unregulated (11). Doctors often prescribe drugs with no explicit legal frameworks, evidence-based practice, or adverse event observance (12).

The application of bevacizumab in various eye disorders has significantly risen in recent years (13). It is pharmacologically and economically appropriate, but with risks and side effects of endophthalmitis (14). The incidence of endophthalmitis that is attributed to the contamination that is associated with treatment has been enumerated in many past researches (14, 15).

In addition to this, the safety and efficacy of bevacizumab in the eyes are probably well known, but the off-label use is disputable, as the associated pharmacokinetics and safety profile may not be similar to its FDA-approved cancer indications (16). Further exploration of microbiological contamination and the likely off-label effects of bevacizumab on eye patients is required to ascertain the safety of the patients, and also direct clinical practice (17). The research aimed to quantify the risk of microbiological contamination of the bevacizumab injection at the different stages of the vials' usage and the severity of the microbial spread in the bevacizumab injections after changing the storage temperature, and also to investigate the OT environment where it is being injected in the Helper Eye Hospital, Quetta.

MATERIALS AND METHODS

STUDY DESIGN

An experimental and observational study was conducted in "Helper's Eye Hospital" for evaluating the primary sources of microbial contamination using bevacizumab vials in ophthalmology. Emphasizing the risks associated with handling, storing, and the environment. Testing under different handling conditions was performed on the used vials. Analyzing the sources and routes of contamination at this stage, the sources of contamination related to vial storage were assessed. Samples were taken following a multi-pricking procedure from used vials and clinic surfaces on the routine Bevacizumab injection day, and additional samples were collected from the operating theater (OT) environment to identify the primary sources and routes of contamination. The samples were grouped and evaluated based on the temperature of storage of the vials. Nevertheless, the sensitivity to antibiotics was also determined in isolated bacteria of the OT environment. The Research Board Committee (RBC-921) of the University of Balochistan, Quetta, approved the research.

SAMPLE COLLECTION

Under aseptic conditions, ethyl alcohol and aseptic solutions were used to take the samples with utmost care. The used vials were labelled to ensure the record of samples after additional injections. Initially, 20 samples were collected in total, divided into 5 vials, with 4 samples sampled in each vial utilizing a multi-pricking procedure. The volumes used were 1ml, 2ml, 3ml, and 4ml, respectively (Table I). Samples were



sampled using a sterilized insulin syringe and placed on nutrient agar and brain heart infusion (BHI) media, and then incubated at 37 °C for 24 hours. The incubation was done twice to ensure additional confirmation. With Bevacizumab repack storage, 20 drug syringes (0.2 ml each) were prepared with 2 new vials, and 4 were used with 4ml vials of Avastin (at four various usage stages) (Table II). The insulin syringes were placed after preparation on 4 different injection days and stored under different storage conditions. The samples were also divided into two groups of storage conditions, i.e., room temperature and 4, in refrigeration, bearing in mind the various stages of vial use. Ten syringes were kept at room temperature (with and without light exposure), and the other 10 syringes were kept in a refrigerator at 4 °C, 1, 3, 7, and 14 days. All of these procedures were performed in sterile conditions in a laminar-flow cabinet (Table II).

The operating theatre (OT) was sampled in the environment, organized in a standardized way. Swab samples were taken on regular days of intravitreal injections, before the start of procedures, and before cleaning up the terminal to indicate a baseline level of environmental contamination. Sampling was performed after every four injection days in a period of one week. Where applicable, a uniform area of about 10 x 10 cm of the surface on all sites was swabbed with sterile cotton swabs that had been dipped in sterile saline. The chair, sterile trolley, oven, sterile tray, patient pouch, and laminar flow hood were identified because of their closeness to drug preparation and injection. This standard practice was taken to provide consistency, reproducibility, and reliability to possible contamination sources of microbes during intravitreal injections.

PROCEDURAL APPROACH OF MICROBIAL CULTURE

All samples were transported to the Center of Advanced Studies in Vaccinology and Biotechnology Quetta (CASVAB) Lab., where they underwent sterile examination. The microbiological testing to determine the accuracy and reliability of the test was carried out with positive and negative control all through the culture and antibiotic susceptibility process. Control Positive control strains were used to ensure the performance of the culture media and incubation conditions. In antibiotic susceptibility, the use of control strains was also used to check the potency of antibiotic discs and interpretation as per the Clinical and Laboratory Standards Institute (CLSI) guidelines. Negative controls were sterile culture media and sterile saline that did not contain a sample and were incubated under the same conditions to rule out contamination by the laboratory and the environment. The identification of diverse bacterial contamination of Avastin (Bevacizumab) aliquots was done using brain heart infusion (BHI) broth supplemented with specialized media. Various media were created based on the standard microbiological practice and autoclaved at 121 °C and 20 minutes: Eosin Methylene Blue (EMB) broth, MacConkey broth, Blood Agar (BA), Mannitol Salt Agar (MSA), and Mueller Hinton Agar (MHA). These cultures were incubated at 37°C and 24 and/or 72 hours to allow growth of microbes. In Mueller Hinton Agar (MHA), bacteria were grown, and antibiotic discs were put in it and allowed to incubate at 37 °C after 24 hours with the assistance of a scale (Figure I). The Kirby-Bauer disc diffusion method was used as the antimicrobial susceptibility test, and the diameter of the inhibition zones was measured in millimeters and interpreted based on Clinical and Laboratory Standards Institute (CLSI) guidelines. All inoculated culture media were incubated at 37°C and analyzed in terms of microbial growth at the times of 24, 48, and 72 hours.

RESULTS

SAMPLING AT DIFFERENT PHASES OF THE VIAL USED

Table I demonstrates the sterility assessment of Bevacizumab samples at different moments of vial use to estimate the possibility of microbial contamination during such a large number of withdrawals. After taking 1 ml, 2 ml, 3 ml, and 4 ml of each of the five vials, the samples were taken, and at every stage, the growth of bacteria was measured. All the samples displayed negative growth of the bacteria in the 1 ml, 2 ml, 3 ml, and 4 ml samples, which showed that no sampling contamination occurred during the repeated use. Based on these findings, bevacizumab does not lose its sterility with multiple withdrawals, provided aseptic processes and proper handling conditions are observed.

Table I. Evaluation of bacterial contamination of Bevacizumab vials at different usage phases

No. of vials	Usage phases	Bacterial growth (+/-) (after 24 hours)	Bacterial growth (+/-) (after 72 hours)
Vial 1	1 ml	-	-
	2 ml	-	-
	3 ml	-	-
	4 ml	-	-
Vial 2	1 ml	-	-
	2 ml	-	-
	3 ml	-	-
	4 ml	-	-
Vial 3	1 ml	-	-
	2 ml	-	-
	3 ml	-	-
	4 ml	-	-
Vial 4	1 ml	-	-
	2 ml	-	-
	3 ml	-	-
	4 ml	-	-
Vial 5	1 ml	-	-
	2 ml	-	-
	3 ml	-	-
	4 ml	-	-

*Bacterial growth; (+) = showing growth, (-) = No growth

VIAL STORED AT REFRIGERATED TEMPERATURE

The sterility experiment findings of Bevacizumab samples in six separate vials that were stored in a refrigerator (4 °C) and tested after 1, 3, 7, and 14 days to determine how long the microbiological stability lasts are presented in Table II. All vials were sampled at a particular time to determine whether there was any contamination, and 10 samples were sampled. The absence of microbial growth in all the samples after a period of 14 days indicated that bevacizumab is still considered sterile and microbiologically stable when kept in the appropriate refrigeration conditions, even after several openings of the vials.

Table II. Evaluation of bacterial contamination of Bevacizumab vials at two storage conditions

Vial type	Injection day	Usage phase	Storage condition	Light exposure	Temperature (°C)	Storage days	Bacterial growth (+/-)
New vial	-		Room	Yes	25 ± 2	1	-
			Refrigerator	-	4	1	-
Used vial	Day 1	1 ml	RT	Yes	25 ± 2	1	-
		2 ml	RT	No	25 ± 2	1	-
		3 ml	Ref	-	4	1	-
		4 ml	Ref	-	4	1	-
Used vial	Day 2	1 ml	Ref	-	4	3	-
		2 ml	RT	Yes	25 ± 2	3	-
		3 ml	RT	No	25 ± 2	3	-
		4 ml	Ref	-	4	3	-
Used vial	Day 3	1 ml	Ref	-	4	7	-
		2 ml	Ref	-	4	7	-
		3 ml	RT	Yes	25 ± 2	7	-
		4 ml	RT	No	25 ± 2	7	-
Used vial	Day 4	1 ml	RT	No	25 ± 2	14	-
		2 ml	Ref	-	4	14	-
		3 ml	Ref	-	4	14	-
		4 ml	RT	Yes	25 ± 2	14	-
New vial	-		RT	No	25 ± 2	14	-
			Ref	-	4	14	-

VIAL STORAGE FOR ROOM TEMPERATURE

Table II presents bevacizumab samples in six vials stored at room temperature and assessed on the 1st, 3rd, and 7th days to assess the microbiological stability of the samples during short-term storage and the sterility observation. This was done to 10 samples, and each vial was collected at given intervals to determine the presence of any possible contamination. Over the course of the fourteen days, no microbial growth was observed in all the samples, which indicates that bevacizumab proved to maintain its microbiological stability and sterility after over two weeks at room temperature.

SAMPLING FROM THE OT ENVIRONMENT

Table III illustrates the microbiological analysis of samples collected in different locations of the operating room (O.T) setup to determine potential sources of contamination. The total number of samples collected at all the locations was 20, which included the chair, sterile trolley, oven, sterile tray, patient pouch,

Table III. Evaluation of bacterial contamination of OT environment

Area of sampling	No. of growth positive	No. of growth positive	Bacteria identified	No. of total samples
Chair	13	7	<i>Klebsiella pneumoniae</i> and <i>E. coli</i>	20
Sterile trolley	10	10	<i>Klebsiella pneumoniae</i>	20
Oven	17	3	<i>Klebsiella pneumoniae</i> and <i>E. coli</i>	20
Sterile tray	12	8	<i>Klebsiella pneumoniae</i> and <i>E. coli</i>	20
Patient pouch	4	16	<i>E. coli</i>	20
Laminar flow hood	9	11	<i>Klebsiella pneumoniae</i> and <i>E. coli</i>	20

and laminar flow hood. The results showed that various sites had varying levels of bacterial development, with *Klebsiella pneumoniae* and *E. coli* being the predominant pathogen agents observed. The most contaminated samples were those in the oven and sterile tray, whereas the patient pouch contained a relatively low number of bacteria. In order to preserve sterility when preparing and delivering ocular drugs, the findings revealed a need to employ a high level of aseptic practices and cleanliness since certain areas of the O.T. setting are more vulnerable to microorganism intrusion.

ANTIBACTERIAL SENSITIVITY TEST FOR *ESCHERICHIA COLI*

The chance of b-lactamase enzymes production indicates that the *E. coli* isolates were resistant to the majority of b-lactam antibiotics, such as the Amoxicillin/ Clavulanic acid, Cefaclor, Cephadrine, Fosfomycin, and Ceftazidime (Fig. 1 a, b). It was however responsive to the fluoroquinolones, carbapenems and some amino glycosides but a little resistant to ceftaloridine, imipenem, tobramycin, chloramphenicol and norfloxacin. The ciprofloxacin and imipenem had highest areas of inhibition of 32 mm and 25 mm respectively.

ANTIBACTERIAL SENSITIVITY TEST FOR *KLEBSIELLA PNEUMONIAE*

The amoxicillin/clavulanic acid, cefaclor, cephradine, oxacillin, and tetracycline resistance was also found in the *Klebsiella pneumoniae*, which was isolated in the environment. It was vulnerable to Imipenem (20 mm), fosfomycin (20 mm), ciprofloxacin (17 mm), norfloxacin (15 mm), tobramycin (12 mm), and ceftazidime (13 mm), which means that the use of carbapenems, fluoroquinolones, and aminoglycosides can be effective. Overall, the antibiotics, which demonstrate the highest action against the identified bacteria, are imipenem and fosfomycin (Fig. 1 c, d).

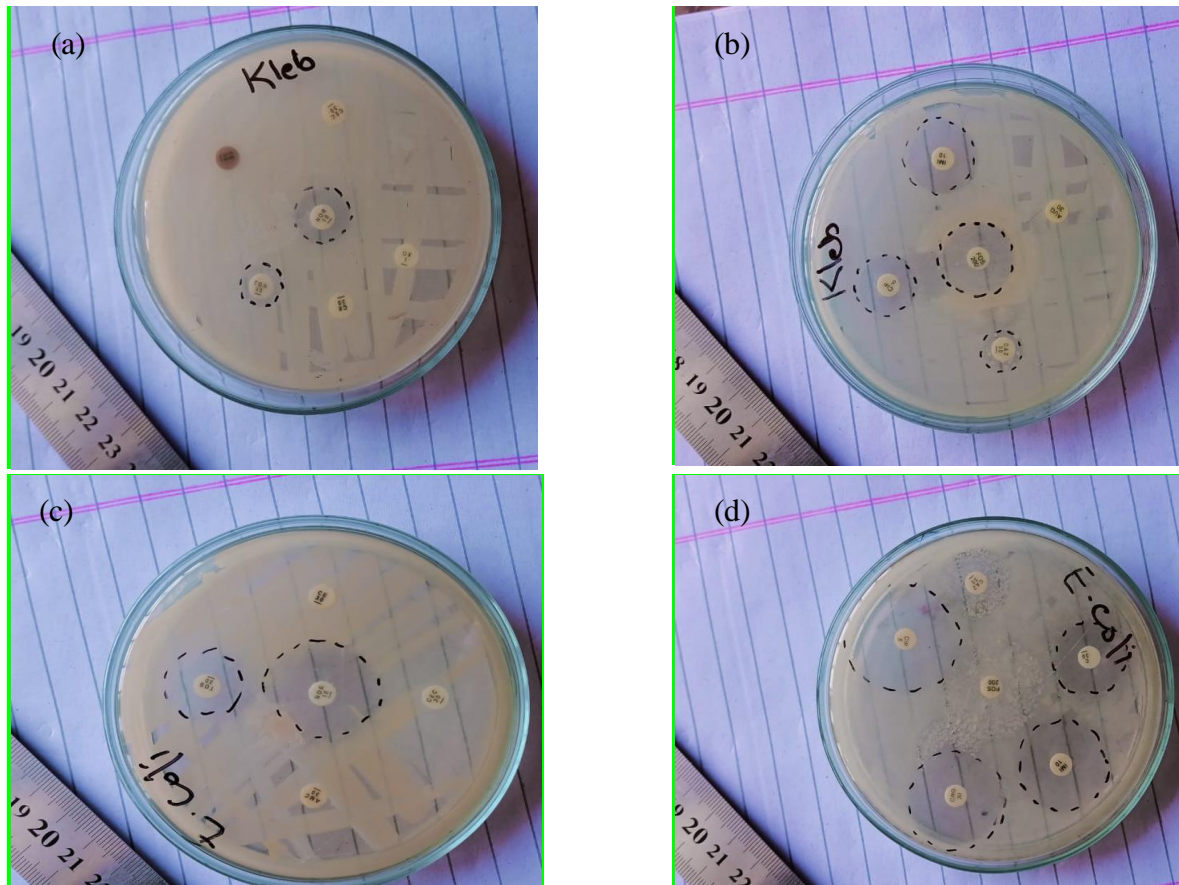


Fig. 1 (a, b). Antibacterial sensitivity test for *Klebsiella pneumoniae*; (c, d). Antibacterial sensitivity test for *Escherichia coli*

Table IV. Antibiotic susceptibility patterns and inhibition zone diameters (mm) of *Escherichia coli* and *Klebsiella pneumoniae* isolated from the OT environment

Antibiotics (Symbol-strength)	Resistance/Sensitive (R/S) and [Zone]	
	<i>Escherichia coli</i>	<i>Klebsiella pneumoniae</i>
Amoxicillin/clavulanic acid (AMC30)	R	R
Cefaloridine (CR30)	S [26mm]	
Cefaclor (CEC30)	R	R
Ceftazidime (CAZ30)	R	S [13mm]
Cephadrine (CE30)	R	R
Chloramphenicol(C30)	S [21mm]	
Ciprofloxacin (CIP5)	S [32mm]	S [17mm]
Fosfomycin (FOS200)	R	S [20mm]
Imipenem (IMI10)	S [25mm]	S [20mm]
Oxacillin (OX1)	-	R
Norfloxacin (Nor10)	S [22mm]	S [15mm]
Tobramycin (TOB30)	S [16mm]	S [12mm]
Tetracycline (TE30)	-	R

*Zone diameters are expressed in millimeters (mm). Interpretation was performed according to CLSI guidelines

ANTIBIOTIC SENSITIVITY

The Kirby-Bauer disc diffusion technique was utilized in determining the susceptibility of *Escherichia coli* and *Klebsiella pneumoniae* isolated at the OT environment to antibiotics. The patterns of resistance and sensitivity, as well as the corresponding inhibition zone diameter (mm), are summarized in Table IV.

DISCUSSION

In this study, the bevacizumab was investigated in terms of sterility. A lot of concern is also raised over the safety of Avastin injection in multi-pricking vials, storage, as well as the location of dispensing and injection of Avastin. According to the USP (chapter 797) the compounding of multiple doses of bevacizumab to be made into an intravitreal injection could be deemed as a medium-risk compounded sterile preparation and the quality assurance measures proposed to be used in preparation was proper personnel garb of the preparation of sterile preparation in a laminar-airflow workbench, regular disinfection, testing of the quality of the air to ensure an International Organization Standardization ISO Class 5 (3520 particles/m³) ambience in the air and annual media (18).

A study has been done on the stability of repacked bevacizumab at room temperature. The study demonstrated similar anti-VEGF activity between the reference and repacked bevacizumab stored ≤ 3 months at 4°C and ≤ 7 days at room temperature, even when exposed to indirect light sources. The other studies showed degradation of 1.6%, 8.8%, and 15.9% of repacked bevacizumab stored at 4°C after 1 week, 3 months, and 6 months, respectively (19, 20).

Multiple doses that are pulled out of a vial can be contaminated (21). More punctures will lead to higher chances of contamination, and bevacizumab must be injected into aseptic surroundings (22). To ascertain whether the contamination is occasioned by handling human error or the storage conditions kept at room and refrigerated temperatures for 1-14 days (23).

In this study, the outcomes revealed that no growth of bacteria was observed after 24 and 72 hours of incubation of the various samples, and all vials of Bevacizumab were sterile in all stages of usage. The next results are suggestive of the fact that the repeated insertion and recovery of the needles under proper aseptic conditions did not affect the sterility of the vials. Nevertheless, evidence of bacterial growth was not observed in Bevacizumab samples that were stored at room temperature ($25 \pm 2^\circ\text{C}$) and in a refrigerated (4°C) environment over a period of 14 days. Based on such findings as represented in figures I and II, bevacizumab does not lose its sterility or microbiological stability despite its use in multiple use phases and under various storage conditions when it is treated aseptically.

From the sampling area of the OT environment, there were some bacterial contaminations, which indicate it is not entirely sterile. Bacterial growth was found even in locations that should remain sterile, such as the sterile tray and laminar flow hood area, indicating a lack of cleaning or air quality control (24). *Klebsiella pneumoniae* and *E. coli* are frequent hospital-associated bacteria that can cause infections if aseptic procedures are not carefully followed (25). Their presence in these crucial regions is concerning, and bacterial resistance is a worldwide challenge for doctors (26). Based on this investigation, a majority of the usual antibiotics, such as Amoxicillin/clavulanic acid, Cefaclor, and Cephadrine, were resistant to both of the bacteria, and Imipenem, Ciprofloxacin, Norfloxacin, and Tobramycin were sensitive to both bacteria at different levels. These findings indicate that they still may be effective interventions in case of infections. The observed resistance to commonly used β -lactam antibiotics and preserved sensitivity to carbapenems, fluoroquinolones, and aminoglycosides is consistent with previously reported antimicrobial resistance patterns of nosocomial Gram-negative pathogens in comparable healthcare settings (27, 28).

This study has certain limitations. Although microbial contamination risk was evaluated, direct correlation with clinical outcomes, such as post-intravitreal injection endophthalmitis, was not assessed, as patient-level infection surveillance and clinical follow-up data were not included. Therefore, a direct association between microbiological findings and clinical infection risk cannot be established. Bacterial identification was primarily based on growth patterns on selective and differential culture media, and advanced biochemical or molecular confirmation methods, such as API identification or polymerase chain reaction (PCR), were not employed due to resource constraints. Although cultures were monitored at 24, 48, and 72 hours, incubation was not extended beyond this period. Longer incubation durations of up to seven days may allow detection of slow-growing organisms (29). Future studies incorporating molecular identification techniques, longer incubation periods, and clinical outcome data would further strengthen the validity and clinical relevance of these findings (30).

CONCLUSION

The contents of the multiple-dose bevacizumab (Avastin) vials are sterile, and multi-puncture multi-dose Avastin vial use is aseptically precautioned, and microbiologically safe storage is consistently reliable. The OT was not completely sterile. *E. coli* and *Klebsiella pneumoniae* were also resistant to the most commonly used antibiotics, i.e., Amoxicillin/clavulanic acid, Cefaclor, and Cephadrine, but sensitive to Imipenem, Ciprofloxacin, Norfloxacin, and Tobramycin. These results show that hygiene and careful administration of antibiotics are necessary.

Conflict of interest:

Authors declared no conflict of interest.

Authors' contribution:

SA Lab experiments, data Collection and data interpretation; QI & ISS Conceptualization, study design and supervision; ZA, HAA & AK Data curation, formal analysis and methodology; SP, PM & RT Data collection, patient enrollment, follow-up assessment; NR & MK Statistical analysis, data interpretation, tables and figures.

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