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IN VITRO EVALUATION OF ANTIBIOTIC SYNERGY AGAINST BIOFILM-FORMING PSEUDOMONAS AERUGINOSA ISOLATED FROM POST-CESAREAN SURGICAL SITE INFECTIONS AND ITS MOLECULAR RESISTANCE PROFILE

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ABSTRACT

Background: *Biofilm-associated Pseudomonas aeruginosa infections complicate post-cesarean surgical site infections (SSIs) and contribute to treatment failure.*

Objective: *To evaluate antimicrobial susceptibility, disc-diffusion–based synergy of selected antibiotic pairs against biofilm-forming P. aeruginosa, and molecular detection of a carbapenemase gene (blaVIM) and a biofilm-associated gene (pelA).*

Methodology: *This prospective in-vitro study was conducted after the approval of IRB of Azra Naheed Dental College, Superior University, from Aug 25 to Feb 26, on 100 cultured pus swabs from post-cesarean SSIs. Isolates were identified using standard microbiological methods. Biofilm formation was assessed using crystal violet ring assay. Antimicrobial susceptibility testing was done by Kirby–Bauer disc diffusion on Mueller–Hinton agar following CLSI guidance. Synergy testing involved paired discs, 20mm apart, interpreted qualitatively and by an interaction-zone size (≥18 mm) indicating synergy. PCR was used for blaVIM and pelA detection in a subset of biofilm-forming isolates.*

Results: *Seventy-seven (77%) samples were culture-positive, and P. aeruginosa were 32/77 (41.5%), and biofilm was seen in 24/32 (75%). Resistance among P. aeruginosa was high to meropenem (83%) and imipenem (75%), and ciprofloxacin (75%). Among biofilm-forming isolates (n=24), synergy was most frequent with meropenem+gentamicin (22/24, 91.7%) and meropenem+ciprofloxacin (20/24, 83.3%), while cefixime-based combinations reported limited synergy (≤12.5%). blaVIM was detected in 5/8 tested isolates and pelA in 5/8.*

Conclusions: *Biofilm-forming P. aeruginosa was common in post-cesarean SSIs and reported significant resistance to tested antipseudomonal agents. Meropenem combined with gentamicin or ciprofloxacin reported strong in-vitro synergistic activity, indicating further validation using quantitative synergy, biofilm-eradication assays and in-vivo studies.*

Keywords: *Antibiotic synergy, Biofilm, Carbapenem resistance, Cesarean section, Pseudomonas aeruginosa, Surgical site infection*

INTRODUCTION

Surgical site infections (SSIs) is a frequent and deadly healthcare complication after operative procedures leading to longer hospitalization, higher cost, and maternal morbidity.[1] Recent studies estimate that post-cesarean SSI incidence varies widely across regions and health systems, indicating differences in cases, cross infection control and peri-operative procedures.[2, 3] A recent review on cesarean SSIs reported significant heterogeneity in pooled incidence and highlighted modifiable factors like obesity, prolonged labor or rupture of membranes, and inadequate prophylaxis as contributors.[4]

In low and middle income countries, overcrowding, limited resources, inadequate sterilization and delayed identification amplify adverse outcomes.[1] *Staphylococcus aureus* is a major SSI pathogen, but the microbiology of postoperative wound infections has shifted toward Gram-negative organisms in many settings.[5] *Pseudomonas aeruginosa* is a nosocomial pathogen as it resides on moist hospital surfaces, equipment, and adapts rapidly leading to difficult-to-treat wound, bloodstream, respiratory, and device associated infections.[6]

Previous studies have reported that *P. aeruginosa* is difficult to manage due to its intrinsic resistance by membrane impermeability and efflux systems, coupled with acquired mechanisms like β-lactamases, target-site changes, and porin loss, especially in postoperative wounds.[6, 7] Moreover, another reason of chronic and recurring infection associated with *P. aeruginosa* is biofilm formation that reduce antibiotic penetration, create nutrient/oxygen gradients, and favor slow-growing "persister" phenotypes. Recent studies have also reported that bacteria inside biofilms can survive antibiotic levels that are much higher than the MIC observed in routine testing.[2, 6, 8]

Carbapenems are important antibiotics for *P. aeruginosa*, however, their efficacy is decreasing due to resistance spreading globally and one major cause is metallo-β-lactamases, including VIM (Verona integron-mediated metallo-β-lactamase).[9] Public health alerts and genomic surveillance have reported outbreaks of VIM-producing carbapenem-resistant *P. aeruginosa*. Moreover, hospitals with limited resources report multidrug-resistant *P. aeruginosa* in surgical site infections, highlighting the need for local antibiotic stewardship and better cross-infection prevention.[10]

Single-drug treatment often fail against resistant, biofilm-forming *P. aeruginosa, therefore, attention has been directed to* combination therapy and synergy.[11] Synergistic pairs enhance attack by targeting complementary pathways like cell-wall disruption improving aminoglycoside entry, and penetration into biofilms. Recent in vitro studies on clinical *P. aeruginosa* isolates reported that certain antibiotic combinations reduce biofilm growth and eradicate biofilms effectively.[11, 12] However, synergy depends on strain type and the combination of drug.

Simple screening tests that can be done in routine labs may help identify the best combinations for more detailed testing.[13] In Pakistan, cesarean rates are rising and antimicrobial resistance is prevalent, and the data linking SSI pathogens, biofilm, resistance genes, and synergy screening is limited.[14]

The study aimed to assess biofilm formation in *P. aeruginosa* isolates from post-cesarean SSIs, determine their resistance to selected antipseudomonal antibiotics, evaluate the synergy of four antibiotic combinations using a disc-diffusion approach, and identify **blaVIM** and **pelA** genes as markers of carbapenem resistance and biofilm formation.

METHODOLOGY:

This laboratory-based, cross-sectional in vitro study was conducted after the approval of Institutional Review Board of Azra Naheed Medical College, Superior University Lahore, from August 2025 to February 2026 (Ref:___________________), dated _____________, on bacterial isolates recovered from post-cesarean surgical wound swab samples. A total of **100** wound swabs were processed.

One hundred (n=100) pus swab samples were collected from patients with post-cesarean SSIs admitted to gynecology ward in Azra Naheed Hospital. The minimum sample size of 93 was calculated using the **WHO sample size calculator for a single proportion** using the formula **$n=Z^2 \times p(1-p)/d^2$**, with an **expected proportion (p)=0.59** (59.29% bacterial growth among post-cesarean wound swabs), **Z=1.96** for **95% confidence** and an **absolute precision (d)=0.10**.[15] To account for incomplete records or unusable samples, the final sample size was rounded to **100 wound swabs**.

Inclusion criteria were clinical SSI samples yielding *P. aeruginosa*. Exclusion criteria were environmental contaminants, duplicate isolates from the same patient, and non–*P. aeruginosa* isolates. The Swabs were obtained aseptically from infected surgical sites and transported immediately to minimize overgrowth by commensal flora.

Swabs were inoculated onto MacConkey agar, blood agar, and cetrimide agar and incubated aerobically at 37°C for 18–24 h. Probable *P. aeruginosa* colonies were identified by colony morphology and pigment production, followed by Gram staining and oxidase testing.

Biofilm formation was assessed qualitatively using the crystal violet ring assay. 100 µL of a 0.5 OD600 standardized overnight culture was inoculated into nutrient broth and incubated statically at 37°C for 24 h. After incubation, tubes were stained with crystal violet for 20 min, rinsed gently with sterile water, air-dried, and examined for a stained ring on tube walls. Ring intensity was used to classify isolates as weak, moderate, or strong biofilm formers.

Kirby–Bauer disc diffusion testing was done on Mueller–Hinton agar using a 0.5 McFarland inoculum (≈1.5×10^8 CFU/mL). Plates were incubated at 37°C for 18–24 h and zones were measured in millimeters and interpreted following CLSI guidance (M100).[16] Antibiotics analyzed included ciprofloxacin (5 µg), imipenem (10 µg), and meropenem (10 µg).

The synergy testing was done on imipenem-resistant isolates using paired antibiotic discs placed 20 mm apart on inoculated Mueller-Hinton agar. The combinations tested were cefixime+doxycycline, cefixime+meropenem, meropenem+gentamicin, and meropenem+ciprofloxacin. Plates were incubated at 37°C for 18 to 24 h. Synergy was recorded when enhanced inhibition (keyhole/bridge) occurred between discs, and for quantitative reporting, an interaction-zone diameter ≥18 mm was used as a synergy threshold.

Genomic DNA was extracted from selected biofilm forming isolates using a commercial gram-negative bacterial gDNA kit (Thermo Scientific). PCR assays targeted blaVIM (carbapenemase, expected amplicon 125 bp per primer design) and pelA (biofilm-associated gene and expected amplicon ~105–110 bp). PCR cycling included initial denaturation at 96°C for 4 min, 30 cycles of 94°C for 30s, 57°C for 30s, and 72°C for 1 min, and final extension at 72°C for 10 min. Amplicons were visualized on 1% agarose gel electrophoresis in TAE buffer.

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 25 (IBM Corp). Categorical variables were presented as frequencies and percentages. Chi-square tests compared proportions, with statistical significance set as $p<0.05$.

RESULTS:

Overall, 77 out of 100 (77%) post-cesarean SSI specimens yielded bacterial growth. Culture positivity increased across age strata, from 64% in 21 to 25 years, to 88% in 36 to 40 years (Table 1 and Figure 1).

Table 1. Prevalence of culture-positive growth by age group (n=100).

Groups	Age (years)	Samples size	Growth	(%)
Group I	21-25years	25	16	64%
Group II	26-30 years	25	18	72%
Group III	31-35 years	25	21	84%
Group IV	36-40 years	25	22	88%

Total	100	77	77%

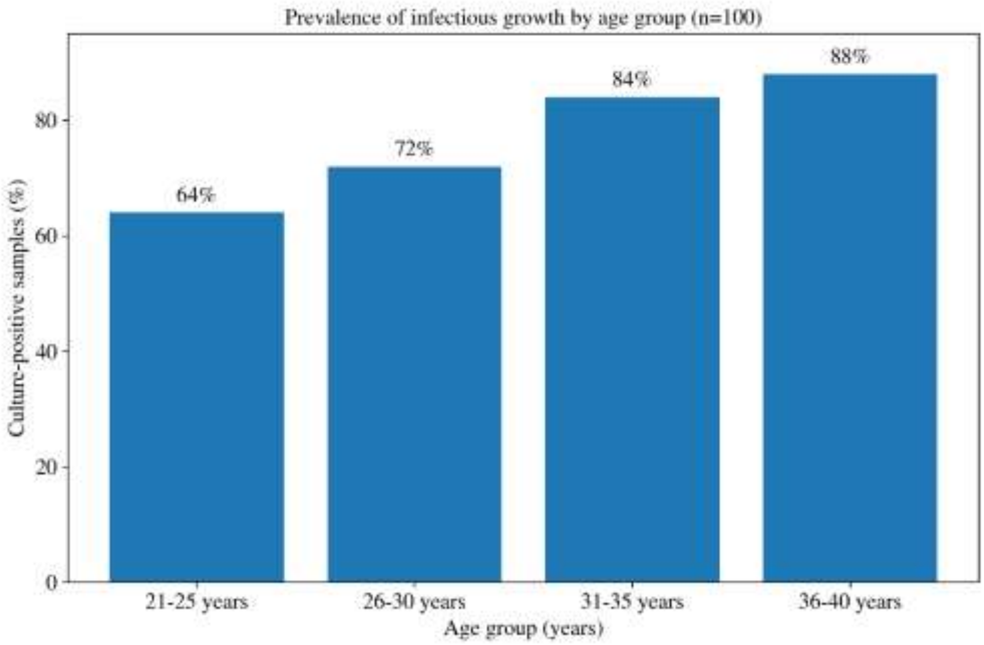

Figure 1: Prevalence of culture-positive samples by age group

Among culture-positive samples (n=77), *P. aeruginosa* was the most frequent isolate (n=32, 41.5%), followed by *Klebsiella spp*. (n=14, 18.1%), *Staphylococcus aureus* (n=12, 15.5%), *Escherichia coli* (n=11, 14.2%), and *Streptococcus spp*. (n=8, 10.3%) (Table 2 and Figure 2).

Table 2. Distribution of organisms across age groups (culture-positive samples, n=77)

Microorganisms	**Group I (21–25) n(%)**	**Group II (26–30) n(%)**	**Group III (31–35) n(%)**	**Group IV (36–40) n(%)**	**Total n(%)**
S. aureus	2 (2.6)	2 (2.6)	4 (5.2)	4 (5.2)	12 (15.5)
P. aeruginosa	8 (10.4)	8 (10.4)	10 (13.0)	6 (7.8)	32 (41.5)
Klebsiella sp	3 (3.9)	3 (3.9)	2 (2.6)	6 (7.8)	14 (18.1)
E. coli	1 (1.3)	3 (3.9)	3 (3.9)	4 (5.2)	11 (14.2)
Streptococcus sp	2 (2.6)	2 (2.6)	2 (2.6)	2 (2.6)	8 (10.3)
Total	16 (20.8)	18 (23.4)	21 (27.3)	22 (28.6)	77 (100)

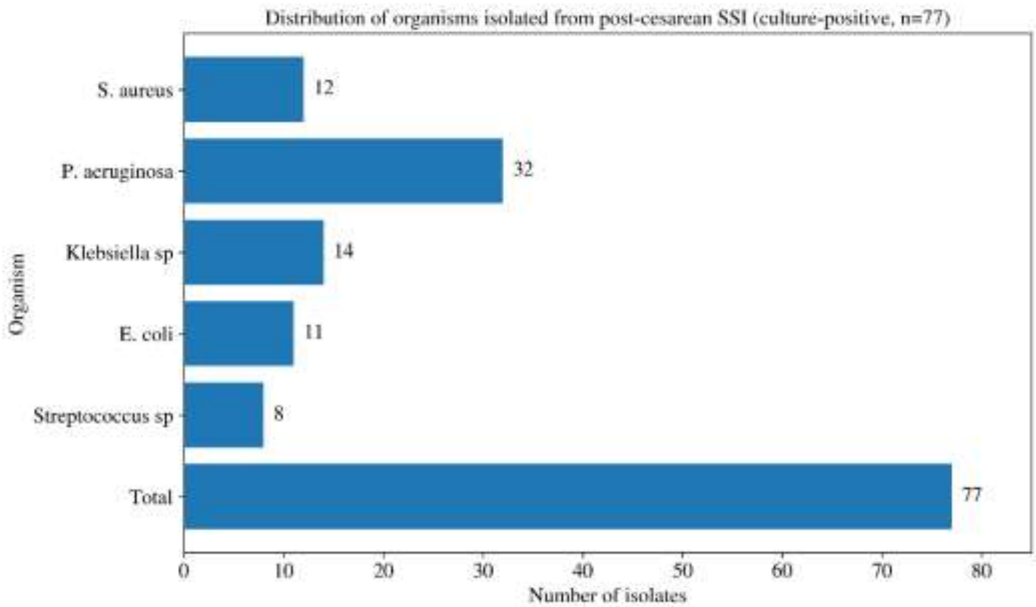

Figure 2: Organism distribution among culture-positive post-cesarean SSI specimens.

P. aeruginosa isolates (n=24/32, 75%) formed a visible biofilm ring, using crystal violet ring assay. Among the biofilm-forming subset used for synergy testing (n=24), 11 were classified as strong, 10 as moderate, and 3 as weak biofilm formers.

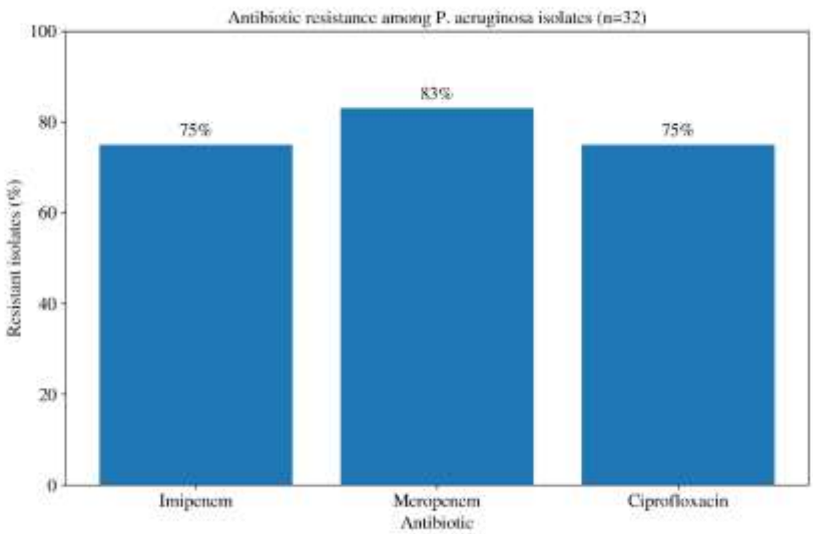

Figure 3: Resistance rates among *P. aeruginosa* isolates to key antipseudomonal agents.

Disc diffusion testing showed high resistance rates among *P. aeruginosa* isolates i.e., meropenem 83%, imipenem 75%, and ciprofloxacin 75% (Figure 3).

Synergy was assessed for four antibiotic pairs against the **24 biofilm-forming** isolates (PA-1 to PA-24) and reported that meropenem+gentamicin indicated largest interaction zones and the highest synergy (≥18 mm in 22/24, 91.7%) (χ^2=27.94, p<0.001), followed by meropenem+ciprofloxacin (20/24, 83.3%). Cefixime-based combinations rarely reached synergy threshold (≤12.5%) (Table 3 and Figure 4). Meropenem+gentamicin showed significantly higher synergy compared with cefixime-based combinations i.e., (cefixime+meropenem, McNemar's χ^2=17.05,

$p=3.64\times10^{-5}$), (cefixime+doxycycline, McNemar's χ^2 = 18.05, $p = 2.15\times10^{-5}$).

Table 3. Interaction-zone diameters (mm) for antibiotic combinations against biofilm-forming *P. aeruginosa* (n=24)

Strain ID	Biofilm strength	Cefixime+ Doxycycline (mm)	Cefixime+ Meropenem (mm)	Meropenem+ Gentamicin (mm)	Meropenem+ Ciprofloxacin (mm)
PA-1	Strong	8	10	21	20
PA-2	Strong	7	9	20	19
PA-3	Moderate	9	14	26	23
PA-4	Strong	6	11	22	21
PA-5	Moderate	8	16	25	23
PA-6	Strong	7	10	20	19
PA-7	Moderate	10	15	26	22
PA-8	Strong	6	9	17	20
PA-9	Moderate	9	17	24	23
PA-10	Moderate	8	15	25	23
PA-11	Strong	5	11	20	18
PA-12	Moderate	11	16	24	21
PA-13	Weak	18	21	28	26
PA-14	Moderate	11	16	24	22
PA-15	Strong	8	10	17	17
PA-16	Weak	16	20	27	27
PA-17	Moderate	12	15	23	24
PA-18	Strong	7	12	21	16
PA-19	Strong	6	9	20	17
PA-20	Strong	7	10	19	16
PA-21	Moderate	10	16	23	20
PA-22	Strong	6	11	18	18
PA-23	Weak	18	20	27	25
PA-24	Moderate	12	16	24	20

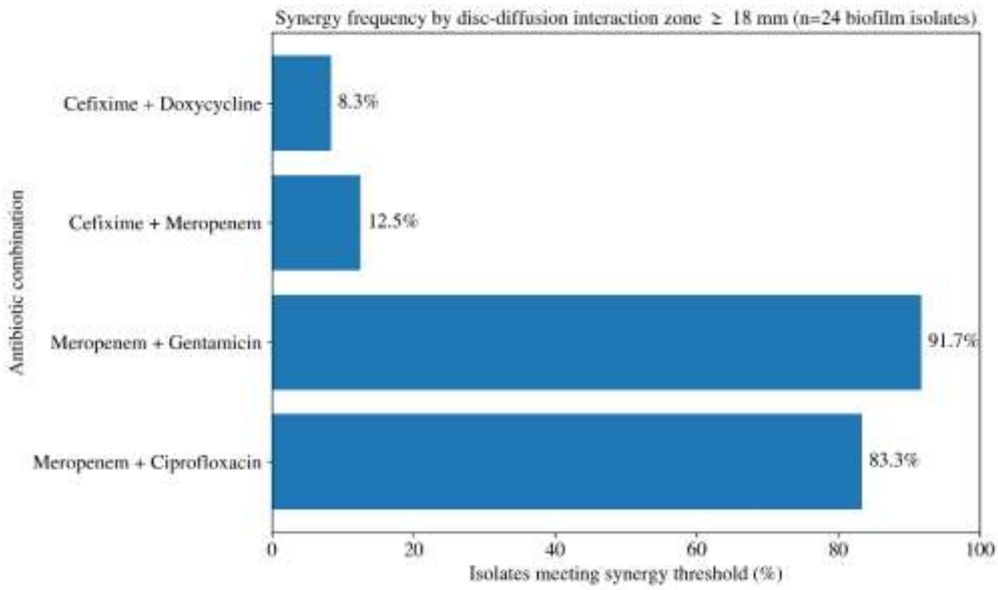

Figure 4. Frequency of isolates meeting the synergy threshold (interaction zone ≥18 mm) by antibiotic pair.

PCR assays on eight selected biofilm-forming isolates detected blaVIM in 5/8 (62.5%) isolates and pelA in 5/8 (62.5%) using gel electrophoresis (Table 4).

Table 4. PCR detection of blaVIM and pelA in selected isolates (n=8).

Isolate	blaVIM (PCR band ~400 bp)	pelA (PCR band ~110 bp)
PA-1	Positive	Positive
PA-2	Negative	Positive
PA-3	Positive	Negative
PA-4	Negative	Positive
PA-5	Positive	Positive
PA-6	Positive	Positive
PA-7	Positive	Negative
PA-8	Negative	Negative

DISCUSSION

The findings study reported that post-cesarean SSI samples in this setting were mostly culture-positive (77%), and the *P. aeruginosa* was the predominant isolate (41.5% culture positive). Recent studies still report a high burden of post-cesarean SSIs worldwide with high variability between the regions indicating that Infection-prevention and antimicrobial stewardship are strong influencing factors.[2, 17] *S. aureus* is a major SSI pathogen in many studies, however, many hospitals now report more gram-negative isolates.[12] The high proportion of *P. aeruginosa* in this study is consistent with its ability to persist and survive in healthcare settings as it can survive in moist reservoirs and contaminated and medical devices.[18]

Biofilm formation was common in *P. aeruginosa* isolates (75%) in this study, which supports the role of biofilm in postoperative wound infection, delayed healing, and relapse. Previous studies have reported that biofilm-embedded *P. aeruginosa* shows reduced antibiotic response due to limited drug penetration, altered environment, and slow-growing subpopulations producing tolerance.[6, 11] This produces antibiotic tolerance even when classical resistance genes are not present.[19, 20]

We used a qualitative tube-ring method rather than a quantitative microtiter assay, even though, the high proportion of visible biofilm indicate that antibiofilm strategies are relevant for post-cesarean wound management in the current setting.

In the present study, antimicrobial susceptibility testing reported high resistance to meropenem (83%), imipenem (75%), and ciprofloxacin (75%) which is concerning because carbapenems and fluoroquinolones are frequently relied as key antipseudomonal options. Recent studies reported several mechanisms that drive carbapenem non-susceptibility, including loss of OprD porin, increased efflux pump activity, and β-lactamase production, which along with biofilm growth further reduces the effects of antibiotic.[9, 20, 21] In the current study, high resistance together with biofilm formation likely increases the risk of treatment failure if therapy is based only on planktonic susceptibility testing.

Synergy screening reported that meropenem and gentamicin combination had the highest synergy rate i.e., 91.7% meeting the ≥18 mm interaction-zone criteria, followed by meropenem and ciprofloxacin combination (83.3%), likely due to the reason that β-lactams can increase aminoglycoside uptake by disrupting cell-wall integrity, which may explain the strong signal observed for the carbapenem-aminoglycoside pair. The literature also reported that certain β-lactam/aminoglycoside or β-lactam/fluoroquinolone combinations can improve activity against *P. aeruginosa*, but results vary by strain and experimental model.[22, 23] An in-vitro study including 266 isolates reported strong antibiofilm synergy for cefepime+gentamicin and cefepime+ciprofloxacin compared with monotherapy.[24] Memar et al., in study reported that synergy depends on the antibiotic pair and that results can vary between planktonic and biofilm conditions, in carbapenem-resistant biofilm-forming burn isolates, highlighting the need to test combinations with clinically relevant biofilm endpoints.[25]

Cefixime-based combinations reported low synergy in this study, which was expected as *P. aeruginosa* has limited intrinsic susceptibility to many oral cephalosporins and can express β-lactamases and permeability barriers, limiting cephalosporin activity.[26] Doxycycline has been studied as a virulence-modulating or quorum-sensing agent in some models, but tetracyclines are not standard antipseudomonal drugs, and are unlikely to provide strong bactericidal activity in severe SSIs, which aligns with the minimal synergy reported in this study.[27]

CR detected blaVIM in 5 of 8 tested isolates, which supports a genetic basis for carbapenem resistance in subsets of the isolates. VIM metallo-β-lactamases are clinically important because they hydrolyze carbapenems and are often carried on mobile genetic elements, supporting rapid spread. Public health surveillance have reported outbreaks of VIM-producing carbapenem-resistant *P. aeruginosa*, indicating the need for early detection and infection-control.[28] The current study also detected pelA in 5 of 8 isolates aligning with the role of Pel polysaccharide in biofilm matrix structure and protection. The combination of blaVIM and pelA suggests a difficult phenotype, resistance combined with biofilm capacity, which can promote persistence and recurrence in postoperative wounds.

The study has limitations like qualitative assessment of biofilm. Future studies should quantify biofilm and evaluate antibiotic activity using biofilm inhibitory and eradication endpoints. The disc-diffusion test is useful but it does not standardized FIC indices. Molecular testing was performed on a subset of isolates, and expanded typing for additional carbapenemases, porin/efflux markers, and high-risk clones can better help understand local transmission.

Conclusion:

P. aeruginosa was the most common isolated pathogen and reported biofilm formation in post-cesarean SSIs. High resistance to carbapenems and ciprofloxacin was observed. Disc diffusion synergy testing indicated that meropenem coupled with gentamicin, and to a lesser extent meropenem coupled with ciprofloxacin, may enhance in-vitro activity against the biofilm forming isolates. These findings require further confirmation using quantitative synergy methods like checkerboard and time–kill, and by testing biofilm eradication endpoints.

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