

Role of Imipenem-resistant metallo-beta-lactamase positive pseudomonas aeruginosa carriers in nosocomial infections

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ABSTRACT

Background: Imipenem-resistant metallo-beta-lactamase Positive *Pseudomonas aeruginosa* (IR-MBLP-PA) infections occur as outbreaks and epidemics with a potential to spread within and between hospitals and intercontinentally. Limited data is available on IR-MBLP-PA carriers and their role as source and/or reservoir of nosocomial infection. **Objectives:** Detection and antibiogram typing of IR-MBLP-PA from healthy healthcare workers (HCW) from different areas of hospital and to assess role of carriers as source and/or reservoir of nosocomial infections. **Material and Methods:** Specimens from 200 HCWs [ICUs (120), General wards (40) and OPDs (40)] were collected from axilla, hands, stool and throat and processed by standard laboratory procedures. IR-MBLP-PA detection is done by IMIPENEM+EDTA combined disc test. Antibiogram typing is done. Association of carriers with clinical cases is done by IR-MBLP-PA with identical antibiogram type from carriers and cases. Distribution of carriers was assessed by Chi-square test. **Results:** Incidence of *P. aeruginosa* and IR-MBLP-PA carriers among HCWs was 25%, 3.21% in ICUs, 10% from general wards and 0% from OPDs. A total of five IR-MBLP-PA antibiogram types were observed from four carriers and none from general wards and OPDs. Distribution of *P. aeruginosa* and IR-MBLP-PA carriers in different areas of hospital was not statistically significant with *P* values of 0.058 and 0.76, respectively. **Conclusions:** Role of IR-MBLP-PA carriers as source and/or reservoirs of infections could not be assessed with certainty; however, the possibility cannot be ruled out. Periodic carrier studies in targeted high risk areas of hospital should be undertaken.

Key words: Imipenem-resistant metallo-beta-lactamase positive *P. aeruginosa* (IR-MBLP-PA), Carriers, Healthcare workers

INTRODUCTION

Acquired metallo-beta-lactamases (MBL: IMP and VIM), a class B carbapenemases have recently emerged globally since the first report from Japan in 1991. These are the most worrisome resistance mechanisms owing to their capacity to hydrolyze with the exception of aztreonam, all beta-lactam antibiotics, including carbapenems; the

last resort antimicrobials for serious multidrug-resistant gram-negative infection.^[1,2] MBLs also represent a clinical threat due to their unrivalled spectrum of activity and their resistance to therapeutic serine beta-lactamase inhibitors and nosocomial infections associated with increased morbidity and mortality.^[1,2]

The metabolic versatility of *Pseudomonas aeruginosa* contributes to its broad ecological adaptability, ubiquitous distribution, ability to acquire and disseminate resistance vertically and horizontally in the hospital environment and tendency to remain viable on both animate and inanimate objects around the patient, including antiseptic solutions.^[2,3]

Rapid emergence and spread of MBL positive *P. aeruginosa* in hospital has been reported by several studies. The propensity of acquired MBL determinants to spread

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within the hospital, between different hospitals, into the community, and intercontinentally highlights the possibility that introduction of resistance genes in the nosocomial setting can be followed by a rapid dissemination among the different species of gram-negative pathogens resulting in nosocomial infections.^[1-4]

Few studies have incriminated hospital environmental sources as reservoir of IR-MBLP-PA associated with increasing nosocomial infections. Early detection of MBL isolates is crucial to check the unnoticed spread with in institutions.^[1-2] Situation is further complicated by non-availability of standardized method proposed by CLSI for MBL detection.^[5] Several non-molecular screening tests are used for detection of MBL-producing *P. aeruginosa*.^[6]

IR-MBLP-PA nosocomial infections witnessed as outbreaks, epidemics spreading rapidly within the hospital, between hospitals and across the geographical barriers to different places and countries, made us to suspect the existence of healthy carriers among healthcare workers (HCWs) acting as reservoirs of infection. This prompted us to conduct a systematic carrier study of healthy HCWs in this rural tertiary care hospital.

MATERIALS AND METHODS

A hospital-based observational carrier study of healthy HCWs working in different areas of hospital was conducted for a period of 6 months in a rural tertiary care hospital for detection of Imipenem-resistant metallo-beta-lactamase positive *P. aeruginosa* (IR-MBLP-PA) carriers. A total of 200 random specimens (120 from HCWs in ICUs, 40 from HCWs in General wards and 40 HCWs from OPDs) were collected from equal number of male and female HCWs for targeted surveillance from different high risk areas of the hospital namely, MICU, ICCU, BURNS WARD, OPERATION THEATRE, POST OPERATIVE WARD and NICU. Four specimens per HCW were collected, namely web spaces of hands, axilla and throat by using sterile swab soaked in sterile normal saline and stool samples were collected in a universal container. Informed written consent was obtained from HCWs before sample collection. HCWs with less than 6 months experience in this hospital and those who were suffering from an infectious disease were excluded from the carrier study.

Swabs were inoculated into nutrient broth and incubated at 37°C for 24 h. Subcultures were then performed on nutrient agar with 0.02% cefrimide, and the plates were incubated for 48 h at 37°C. Identification was done by standard laboratory procedures.^[7] HCWs colonized at least at one of the body sites were considered as carriers of IR-MBLP-PA.

Susceptibility to Amikacin, Ciprofloxacin, Gentamicin, Tobramycin, Piperacillin, Piperacillin-Tazobactam, Cefotaxime, Ceftazidime, Cefoperazone, Cefoperazone-Sulbactam, and Imipenem was determined by Kirby-Bauer's disc diffusion method according to CLSI guidelines.^[5] Aztreonam, Polymyxin-B and Colistin were tested only against IR-MBLP-PA isolates.

P. aeruginosa isolates resistant to Imipenem were subjected to screening test for MBL production by Imipenem + EDTA combined disc test as described previously by Yong et al.^[8] Isolates with enhancement of zone size of more than or equal to 7 mm between Imipenem+EDTA disc compared to Imipenem disc alone were considered as IR-MBLP-PA. MBL negative ATCC (27853) standard strain of *P. aeruginosa* was used as negative control, which did not show any zone of enhancement around Imipenem + EDTA combined disc.

Typing of IR-MBLP-PA isolates was done by AntibioGram Typing. Association of IR-MBLP-PA isolate from carrier with different nosocomial infections in different areas of the hospital was done by circumstantial evidence (Temporospatial association) and IR-MBLP-PA isolate with identical antibiogram type from carriers and cases.

Distribution of *P. aeruginosa* and IR-MBLP-PA carriers in different areas of the hospital was assessed by Chi-square test.

RESULTS

Present study reported *P. aeruginosa* carrier rate of 25% (30/120) with 10.83% (13/120) and 14.17% (17/120) among male and female HCWs, respectively in ICUs. 10% (8/80) was the carrier rate of *P. aeruginosa* with equal number of male and female HCWs in General wards and OPDs. Highest incidence of *P. aeruginosa* carriers in ICUs were reported in staff nurses 35.71% (15/42), followed by doctors 26.19% (11/42) and attenders 11.11% (4/36) [Tables 1 and 2].

Site-specific carrier rate of *P. aeruginosa* was 18.33% (22/120), 9.2% (22/120), 9.2% (11/120) and 8.33% (10/120) at axilla, stools, throat and hands, respectively, in ICUs [Table 3].

Incidence of IR-MBLP-PA carrier rate in intensive care units was found to be 3.21% (4/120). IR-MBLP-PA carriers were not found in operation theatre, post-operative ward and NICU. Details of IR-MBLP-PA carriers. Distribution of *P. aeruginosa* and IR-MBLP-PA carriers in different areas of hospital was not statistically significant with *P* values 0.058 and 0.76, respectively.

- Staff nurse (45/F-MICU)–Strain 1 IR-MBLP-PA from axilla and stool
- Doctor (48/M-ICCU)–Strain 1 IR-MBLP-PA from hands
- Staff nurse (33/M–ICCU)–Strain 2 from axilla and stool, Strain 3 from hands
- Staff nurse (41/F–BURNS WARD)–Strain 4,5 from hands

Five distinct strains of IR-MBLP-PA were isolated from carriers. Strain 1 (resistant to all antibiotics tested) and strain 2 could be associated with IR-MBLP-PA infections

by antibiogram typing and temporospatial association (with time and place of carriers and cases). Other strains of IR-MBLP-PA could not be associated with clinical cases during the short study period. None of the IR-MBLP-PA carriers were found in OPDs or General wards [Table 2].

DISCUSSION

Pseudomonas aeruginosa is a non-fermentative aerobic, gram-negative rod that normally lives in moist environment and has a minimal nutritional requirement with the

Table 1: Distribution of *Pseudomonas aeruginosa* carriers among healthcare workers in different ICUs

Healthcare workers (n)	<i>P. Aeruginosa</i> carriers (n)	Males (n)	Females (n)
Doctors (42)	11	6	5
Staff nurse (42)	15	6	9
Attenders (36)	4	1	3
Total (120)	30	13	17

NOTE: n = number

Table 2: IR-MBLP-PA carriers in General wards and outpatient departments of the hospital

Area of the hospital	Total no. of HCW studied	Total no. of PA carriers	No. of IR-MBLP-PA carriers	Carrier site			
				Hands	Axilla	Stool	Throat
OPDs	40	5	0	2	4	3	2
General wards	40	3	0	3	1	1	2
Total	80	8	0	5	5	4	4

NOTE: HCW = Healthcare workers, IR-MBLP-PA = Imipenem-resistant Metallo-beta-lactamase positive *Pseudomonas aeruginosa*, OPD = Outpatient department, No. = Number

Table 3: IR-MBLP-PA carriers in intensive care units of the hospital

Area of the hospital	Total no. of HCW studied	Total no. of PA carriers	No. of IR-MBLP-PA carriers	Carrier site			
				Hands	Axilla	Stool	Throat
MICU	20	5	1	2	4 (1)	3(1)	2
ICCU	20	6	2	3 (2)	5(1)	1(1)	2
Burns ward	20	7	1	3 (1)	5	1	2
Operation theatre	20	3	Nil	Nil	1	2	1
Postoperative ward	20	6	Nil	1	4	2	2
NICU	20	3	Nil	1	3	2	2
Total	120	30 (P=0.058 NS)	4 (P= 0.76 NS)	10	22	11	11

NOTE: PA= *Pseudomonas aeruginosa*, IR-MBLP-PA = Imipenem resistant Metallo Betalactamsae positive *P. aeruginosa*, Number in parenthesis indicate IR-MBLP-PA, MICU= Medical intensive care unit, ICCU= Intensive cardiac care unit, NICU= Neonatal intensive care unit. () Number in parenthesis indicate number of IR-MBLP-PA carriers, NO. = Number, HCW = Healthcare workers

Table 4: Antibiogram types of 4 IR-MBLP-PA isolates

Strain of IR-MBLP-PA	Antibiogram	Number (n)	Number of nosocomial infections caused by particular strain
Strain 1	R- Resistant to all	1	6
Strain 2	R- G, Pip,Pip+Tz, Ce, Cs, Cs+Sul, To S- Cip, Cz, Ak	1	2
Strain 3	R- G, Pip, Pip+Tz, Ce, Cz, Ak Cs,Cs+Sul S- Cip, Ak, To	1	0
Strain 4	R- Pip, Pip+Tz, Cs, Cs+Sul, G, Ce, Cz, To, Cip S- Ak	1	0
Strain 5	R –Ak, Pip, Pip+Tz, Cs, Cs+Sul, Ce, Cz, Cip, G S-To	1	0

NOTE: Ak=Amikacin, Cip=Ciprofloxacin,G=Gentamycin,To=Tobramycin,Pip=Piperacillin,Pip+Tz =Piperacillin-Tazobactam, Ce=Cefotaxime,Cz= Ceftazidime,Cs= Cefaperazone, Cs+Sul =Cefaperazone-Sulbactam, R= Resistant, S= Susceptible, IR-MBLP-PA = Imipenem resistant Metallo-beta-lactamase positive *P. aeruginosa*

ability to use several organic compounds. This metabolic versatility contributes to a broad ecological adaptability and distribution. *P. aeruginosa* can colonize human body sites, with preference for moist areas, such as the perineum, axilla, ear, nasal mucosa and throat, as well as stools.^[3]

To the best of our knowledge, this is the first description of a large-scale, hospital-wide study of isolation of IR-MBLP-PA from healthy HCWs from different areas of the hospital.

Incidence of carrier rate in ICUs was 25% and 3.33% of *P. aeruginosa* and IR-MBLP-PA, respectively. Prevalence of colonization by *P. aeruginosa* and IR-MBLP-PA or either organism was higher than expected. Coexistence of IR-MBLP-PA isolates with non-MBL-producing *P. aeruginosa* in carriers was a worrisome finding as MBL-resistance allele on a transferable conjugative plasmid could be readily mobilized to these isolates, further increasing the burden of IR-MBLP-PA isolates among HCWs in the hospital.^[3]

Though carrier rate of *P. aeruginosa* was 10% from General wards and OPDs, none of the HCWs were carriers of IR-MBLP-PA. Apart from multiple samples collected from an HCW, multiple colonies were tested for the MBL production. Surveillance of the dissemination of this highly epidemic clone, however, appears to be an important goal.

Strain 1 IR-MBLP-PA isolate (Pan-Drug resistant) present in axilla and stool of a female staff nurse in MICU, strain 2 from axilla and stool of a male staff nurse and strain 1 from hands of male doctor were associated by temporospatial association and AntibioGram typing with four clinical cases of ventilator-associated pneumonia resulting in death and two cases of nosocomial tracheobronchitis with severe morbidity. Acquisition of an MBL determinant can significantly reduce the number and type of antimicrobials agents to which the microorganism is susceptible. IR-MBLP-PA isolates usually exhibit complex multi-drug-resistant phenotypes because of their nosocomial origin and because of the frequent links between MBL genes and other resistance genes on the mobile DNA elements that are involved in their dissemination. The unique problem with MBLs is their unrivalled broad-spectrum resistance profile. MBL-producing *P. aeruginosa* bacteria are slowly but steadily increasing within hospitals, causing outbreaks and/or hyperendemic situations in several centers, mostly in the Far East and south of Europe.^[3] Clinicians are practically left with no option for treating patients with Pan-Drug resistant IR-MBLP-PA infections. Selection of antibiotic for empirical therapy for IR-MBLP-PA should be based on antibiogram of locally prevalent IR-MBLP-PA strain. Antimicrobial resistance increases the likelihood of an inadequate initial antibiotic regimen and of

increased morbidity and mortality from inadequate initial treatment. As a result, the mere possibility of infections due to antimicrobial-resistant pathogens necessitates broad-spectrum initial empirical antimicrobial therapy, usually with combination of drugs including Imipenem. This increases the cost of treatment, the occurrence of adverse drug effects, and ironically, the local prevalence of antimicrobial resistance.^[9]

Prolonged incubation of specimens in a liquid media, testing of multiple colonies must be the reasons for detection of IR-MBLP-PA isolates from carriers. Due to high incidence of IR-MBLP-PA infections with different strains circulating in the hospital and a close association of HCW with such patients with ample of opportunities for transmission in ICUs, could have been the cause for IR-MBLP-PA carriers at this hospital. Very few studies conducted for carrier detection have reported no carriers. This is probably because of low affinity of the Beta-lactam targets, production of enzymes with very low rates of turnover against carbapenems (undetectable under the assay conditions adopted in the study) and presence of permeability barriers or efflux systems, as reported by Gianmaria Rossolini *et al.*^[10]

Two of the carriers from ICCU, one male doctor (strain 1), one male staff nurse colonized at hands (strain 3) and one female staff nurse from Burns ward were colonized at (strains 4 and 5) hands. Transient colonization of hands of HCWs by IR-MBLP *P. aeruginosa* may be underestimated during outbreak investigations and that reinforcement of hand disinfection and use of gloves should always be promptly initiated. Although strain 1 IR-MBLP-PA was reported from clinical cases during study, strains 3, 4 and 5 were not encountered as nosocomial pathogens during the short study period. However, this does not rule out the fact that they have not caused infections in the past or will not do so in future if stringent infections control measures are not practiced in the high risk areas of the hospital.

IR-MBLP-PA isolates from majority of nosocomial infections were not observed among carriers thus indicating other sources of IR-MBLP-PA isolates. Active surveillance is required to identify carries in different hospital environmental sources acting as source of infection. Several studies have reported colonized patients and environmental source of IR-MBLP-PA isolates. When carrier state was studied at hands, no carriers were found among the 10 HCWs by M.P. Crespo *et al.* in a tertiary care center in Cali.^[11] However, Crespo *et al.* identified 12 environmental sources of MBL-positive *P. aeruginosa*, 9 from sinks in adult ICU, 3 from sinks in NICU and a stethoscope from adult ICU. Overnight cleaning of sinks and their drains with hypochlorite, restricted use and

decommissioning of sinks resulted in eradication of MBL strain from these sites.^[11] Balazs Libish *et al.* report a patient with no related clinical history as a carrier of IR-MBLP-PA strain on admissions to hospital, suggesting the possibility of MBL-producing strains in the community^[12] They also describe another carrier patient transferred between ICUs of two different hospitals, providing epidemiological link between them.^[12] Tsakris *et al.* reported community-acquired IR-MBLP-PA isolates from feces of healthy adults in community resulting in the community-acquired IR-MBLP-PA urinary tract infections and bacteremias. This was reported to be due to prolonged carriage of MBL *P. aeruginosa* in digestive tract following an infection. Some as yet unknown environmental species also could be the sources of the mobile metallo-beta-lactamase determinants that recently appeared among gram-negative pathogens.^[13]

None of the carriers suffered from an infection due to IR-MBLP isolate during study period but could have been a source of infection to patients. Owing to the organizational difficulties, the HCW found to be IR-MBLP-PA carriers at our ICUs could not be reassigned to non-clinical activities.

Our study demonstrated that HCWs colonized at any site by IR-MBLP-PA strains may sometimes identify the pathogens' reservoir; However, in view of high incidence of IR-MBLP-PA infections at our hospital, small numbers of IR-MBLP-PA carriers alone cannot be considered as source and/reservoir alone. In view of strict barrier precautions, contact precautions and infections control measures being practiced at our tertiary care hospital, and aggregation of carriers in ICUs compared to general ward, increasing incidence of IR-MBLP-PA infections in ICUs; carrier state could be a mere colonization or contamination with IR-MBLP-PA isolates. Carriers alone cannot be considered as a source and/or reservoirs of IR-MBLP-PA.

Currently, in the absence of a standardized method proposed by CLSI^[5] for MBL detection in *P. aeruginosa*, several non-molecular methods like Imipenem (IMP)-EDTA combined disc test, Imipenem-EDTA double disc synergy test (DDST), EDTA disc potentiation test, MIC reduction test, MBL-E test etc. have been studied. Although, PCR is highly accurate and sensitive test for MBL detection and track their clonal spread, utility is limited by its high cost.

Surveillance for the presence and dissemination of this highly epidemic clone needs to be investigated further, if possible with molecular methods of typing. Molecular typing illustrated the ease with which MBL-producing strains accompanied patients when transferred to other acute care centers, nursing homes or the community.

However, these strains did not cause an outbreak outside acute care center, underlining yet again the importance of environmental reservoirs as a cause of nosocomial outbreaks due to MBL producing *P. aeruginosa*.^[11,14] Awareness of entry of MBL-producing isolates into a hospital environment is the first step that clinical microbiologists can take to address this problem. Outbreak was contained with strict isolation practices and the replacement of faucets at both the units.^[14]

Moreover, no further analyses have been performed to establish carriers' contribution to increasing nosocomial infections due to IR-MBLP isolates at our hospital. Timely identification of increased isolations of this pathogen, achieved by active surveillance, appears to be crucial to limit the spreading of IR-MBLP isolates in our hospital.

LIMITATIONS OF THE PRESENT STUDY

Carrier state and role of the carriers in nosocomial infections due to IR-MBLP-PA could not be assessed with certainty. Whether isolation of IR-MBLP-PA from HCWs represents transient colonization or carrier state was not assessed beyond doubt. Role of carrier state as a cause of (acting as source and/or reservoir of infection) nosocomial infections due to IR-MBLP-PA isolate in ICUs could not be assessed with certainty. IR-MBLP-PA carrier state among HCWs could have been the effect of frequent contact of HCWs with patients suffering from IR-MBLP-PA nosocomial infections. Possibility of acquisition of IR-MBLP-PA from patients could not be ruled out in the present study.

CONCLUSIONS OF THE STUDY

Role of IR-MBLP-PA carriers among HCWs as a source and/or reservoirs of IR-MBLP-PA nosocomial infections is doubtful, but possibility cannot be ruled out

- Role of IR-MBLP-PA carrier during outbreaks cannot be ruled out thus necessitating targeted surveillance of HCWs for IR-MBLP-PA carrier state in high risk areas of the hospital and practicing strict infection control measures especially hand hygiene.
- Further research is needed to explore other sources and/or reservoirs of IR-MBLP-PA by molecular methods namely, environmental sources and colonized patients

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