

First reported nosocomial outbreak of *Serratia marcescens* harboring bla_{IMP-4} and bla_{VIM-2} in a neonatal intensive care unit in Cairo, Egypt

Doaa Mohammad Ghaith¹
 Mai Mahmoud Zafer²
 Dalia Kadry Ismail¹
 Mohamed Hamed
 Al-Agamy^{3,4}
 Marie Fe F Bohol⁵
 Ahmed Al-Qahtani⁵
 Mohammed N Al-Ahdal⁵
 Sherif M Elmagdy⁶
 Islam Yousif Mostafa⁷

¹Department of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt; ²Department of Microbiology and Immunology, Faculty of Pharmacy, Ahram Canadian University, Giza, Egypt; ³Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia; ⁴Department of Microbiology and Immunology, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt; ⁵Department of Infection and Immunity, Research Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; ⁶Department of Botany and Microbiology, Faculty of Science, Cairo University, Cairo, Egypt; ⁷Department of Microbiology, Faculty of Dentistry and Oral Medicine, Future University, Cairo, Egypt

Correspondence: Mai Mahmoud Zafer
 Department of Microbiology and Immunology, Faculty of Pharmacy, Ahram Canadian University, 4th Industrial Zone, Banks Complex, Giza, 12556, Egypt
 Tel +20 111 111 2472
 Email mai_zaffer@hotmail.com

Introduction: *Serratia marcescens* is a significant hospital-acquired pathogen, and many outbreaks of *S. marcescens* infection have been reported in neonates. We report a sudden breakout of *S. marcescens* harboring the bla_{IMP-4} and bla_{VIM-2} metallo- β -lactamase (MBL) genes that occurred from March to August 2015 in the neonatal intensive care unit of Cairo University Hospital, Cairo, Egypt.

Methods: During the study period, 40 nonduplicate clinical isolates of *S. marcescens* were collected from blood culture samples. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry was used to identify each isolate. Then, minimum inhibitory concentrations of different antibiotics were assessed by the Vitek 2 compact system. Screening of the MBL genes bla_{IMP} , bla_{VIM} , bla_{SIM-1} , bla_{SPM-1} , and bla_{GIM-1} as well as the carbapenemase genes KPC, NDM, OXA-48, SME-1, and SME-2 were evaluated. Pulsed field gel electrophoresis was performed to detect the genetic relationship of the isolates.

Results: Analysis showed that 37.5% of the *S. marcescens* clinical isolates were resistant to meropenem (minimum inhibitory concentrations ≥ 2 μ g/mL), and bla_{IMP-4} and bla_{VIM-2} were the most prevalent MBL genes (42.5% and 37.5%, respectively). None of the other investigated genes were observed. Pulsed field gel electrophoresis typing revealed two discrete clones; 33/40 (82.5%) were pulsotype A and 7/40 (17.5%) were pulsotype B.

Conclusion: Here, we report for the first time the detection of MBL-producing *S. marcescens* isolates, particularly IMP-4 and VIM-2 recovered from inpatients with bacteremias from the intensive care unit at Cairo University Hospital.

Keywords: PFGE, outbreak, MALDI-TOFF, SME-1, SME-2, carbapenemases, MBL genes

Background

Serratia marcescens was thought to be a harmless saprophyte up to the last half of the 20th century. During World War I and until 1968, it was used by military forces to trace the transmission of other pathogens due to its characteristic pigment.¹ Now, *S. marcescens* is recognized as a significant clinical pathogen that causes hospital-acquired infections, especially in high-risk settings. Several outbreaks have been reported in neonates, in whom the gastrointestinal tract is the main reservoir for transmission.²

In *S. marcescens*, antibiotic resistance is conferred by several chromosomal and plasmid-mediated determinants, which facilitate the spread of resistance among species.³ The production of distinct carbapenemases, of a kind that KPC, OXA-48, and SME-type, as well as metallo- β -lactamases (MBLs) (NDM, IMP, VIM, SPM, SIM, and GIM) is a characteristic feature of carbapenem resistance in *Enterobacteriaceae*.³⁻⁵

Although IMP-like MBL was the earliest transferable carbapenemases reported in gram-negative bacteria, which was followed by VIM types, few reports have attributed carbapenem resistance in *Serratia* to carbapenemase production.^{6–8}

To our knowledge, there are no existing descriptions of outbreaks caused by MBL-producing *S. marcescens* in Egypt. Here, we outline the first nosocomial outbreak of *S. marcescens* harboring the MBL-encoding genes *bla*_{IMP-4} and *bla*_{VIM-2} retrieved from neonate in-patients with bacteremias at Cairo University Hospital.

Methods

Description of the outbreak

This is a descriptive study of an outbreak of sepsis in a neonatal intensive care unit (NICU) of Cairo University Teaching Hospital, Cairo, Egypt, from March 2015 to August 2015; where 40 nonduplicate *S. marcescens* clinical isolates were recovered from neonates with bacteremia.

Outbreak investigation

Precautionary measures were instituted such as determination of trends of isolation of *S. marcescens* over time and reviewing the infection control policies and hand antisepsis practices.

Environmental studies

All potential reservoirs (suction devices, sinks, counter tops, bed rails, isolation room, air, disinfectants, total parenteral nutrition, health care workers, etc) were sampled and cultured.

Bacterial isolates collection and identification

Forty nonduplicate *S. marcescens* clinical isolates were recovered from neonates with bacteremias from the NICU at Cairo University Hospital, Cairo, Egypt, from March 2015 to August 2015. All clinical isolates were isolated from blood culture samples.

Each isolate was identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry on a Microflex LT instrument (Bruker Daltonics GmbH, Leipzig, Germany) with FlexControl software (version 3.0; Bruker Daltonics) for the automatic acquisition of mass spectra in linear positive mode within the range of 2–20 kDa, according to the manufacturer's instructions. For isolate identification, the row spectra were compared with those in the Biotyper 56 database, and a log (score) ≥ 2 was used for species identification. Spectra were recorded in a positive linear mode at

a laser frequency of 20 Hz, ion source 1 voltage 20 kV, ion source 2 voltage 8.5 kV, and a mass range of 2,000–20,000 kDa, as described previously.⁹

Antimicrobial susceptibility testing

Minimal inhibitory concentrations of cefazolin, ceftazidime, ceftazidime, ceftriaxone, cefepime, meropenem, amikacin, gentamicin, tobramycin, ciprofloxacin, levofloxacin, nitrofurantoin, and trimethoprim/sulfamethoxazole were detected by using the Vitek2 Compact System (bioMérieux, Marcy l'Étoile, France).

For the 15 isolates showing resistance to meropenem, the minimum inhibitory concentration of aztreonam was checked by the E-test strips (bioMérieux). Modified Hodge test was used to test the presence of carbapenemases, and Clinical and Laboratory Standards Institute criteria was applied to explain the results.¹⁰ Each isolate was examined for MBL production by the imipenem/EDTA synergy E-test (bioMérieux), and the interpretations of results were done as stated in manufacturer's recommendations.

All isolates were stored as stocks with 20% glycerol at -80°C until subsequent molecular analysis.

Molecular characterization

All isolates were characterized molecularly to identify *bla*_{IMP}, *bla*_{VIM}, *bla*_{SIM-1}, *bla*_{SPM-1}, and *bla*_{GIM-1} as well as *KPC*, *NDM*, and *OXA-48* using multiplex PCR as described previously.^{11–14} *SME-1* and *SME-2* were examined by PCR as previously described.¹⁵ The QIAquick PCR Purification Kit (Qiagen, Crawley, UK) was used to purify *bla*_{IMP-4} and *bla*_{VIM-2} amplicons and sequenced in both directions using an ABI Prism 3700 DNA Sequencer (Applied Biosystems, Foster City, CA, USA). The sequences of the genes were identified by comparison with sequences in the GenBank nucleotide database using BLAST (<http://blast.ncbi.nlm.nih.gov/Blast.cgi>).¹⁶

Pulsed field gel electrophoresis (PFGE)

Clinical strains were pulsed electrophoresed on a degraded field agarose gel. The Tenover criteria were applied for the identification and interpretation of the result of each band.¹⁷ DNA relatedness was based on DICE coefficient with 4% optimization and 2% tolerance using BioNumerics Software (Applied Maths, Sint-Martens-Latem, Belgium). Each isolate was aerobically cultured on tryptic soy agar plates (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) at 37°C overnight. A plug slice of 3×5 mm wide was placed to a 1.5 mL microcentrifuge tube containing 200 μL of $1 \times$ CutSmart buffer (New England Biolabs, Ipswich,

MA, USA) and incubated at 4°C for 30 minutes. Plugs were placed in a new 200 µL 1× CutSmart buffer containing 50 U of *SpeI* (New England Biolabs) and incubated overnight at 37°C. Plug slices were placed on the well of 1% agarose gel and overlay the wells with 1% low melting point agarose dissolved in 0.5× TBE (Sigma Life Science, St. Louis, MO, USA). Subsequently, the gel was run with CHEF-DRIII apparatus in 3 L of 0.5× TBE buffer following solidification. PFGE was performed under the following working order: Initial switch time 2.2 seconds, final switch time 54.2 seconds; running time 22 hours; gradient 6 volt/cm; angle 120; temperature 14°C. The gel was stained for 30 minutes in 300 mL of sterile distilled water containing 1 µg/mL of ethidium bromide (Sigma Life Science).

Preventive measures

General infection control measures were taken to stop the outbreak and to prevent cross-transmission. Neonates were strictly isolated until repeated cultures were negative. Staff were reinstructed in hand antisepsis. Procedures for environmental cleaning and disinfection were reviewed with the nurses.

Results

Forty nonduplicate *S. marcescens* strains (numbered 1–40) were recovered from blood culture samples collected from septic neonates admitted to the NICU of Cairo University Hospital. All potential reservoirs (suction devices, sinks, counter tops, bed rails, isolation room, air, disinfectants, total parenteral nutrition, health care workers, etc) were sampled and cultured. All cultures were negative for *S. marcescens*.

Antibiotic susceptibility testing of the isolates showed that 15 of 40 (37.5%) were resistant to meropenem (Table 1).

All 15 of these isolates were positive by the imipenem/EDTA synergy E-test and negative by the modified Hodge test. All meropenem-resistant isolates were sensitive to aztreonam.

Molecular analysis of the MBL genes *bla*_{IMP}, *bla*_{VIM}, *bla*_{SIM-1}, *bla*_{SPM-1}, and *bla*_{GIM-1} and the other carbapenemase genes *KPC*, *NDM*, *OXA-48*, *SME1*, and *SME2* showed that

*bla*_{IMP-4} and *bla*_{VIM-2} were the most prevalent genes (42.5% and 37.5%, respectively). No other tested genes were detected.

PFGE of all 40 *S. marcescens* isolates using a >80% similarity cutoff showed two distinctive pulsotypes (Figure 1), confirming the horizontal spread. Of the 40 strains, 33 (82.5%) were pulsotype A strains, whereas the remaining 7 (17.5%) were pulsotype B. A summary of the phenotypic, genotypic, and typing results is shown in Table 2.

Discussion

S. marcescens was previously thought to be a nonpathogenic environmental organism but was subsequently identified as a significant pathogen involved in hospital-acquired infections.¹ Here, we described the determinants of antimicrobial resistance in *S. marcescens* clinical isolates obtained from blood stream infections in an NICU. *S. marcescens* outbreaks have been described and are difficult to eliminate, and thus are a considerable challenge in hospital settings, particularly in NICUs. According to the PFGE analysis, which is a reliable tool for the investigation of outbreaks, the *S. marcescens* population responsible for the bloodstream infections in the NICU of Cairo University Hospital has a strong clonal structure, with a restricted clone number. The 40 isolates were categorized into two types: the more prevalent was type A (33/40) and the less prevalent was type B (7/40). Most type B isolates were carbapenem resistant (71.4%), while only 30.3% of the type A isolates were carbapenem resistant. This suggests that the two types of isolates may have a repeated ancestor and that the *bla*_{IMP-4} and *bla*_{VIM-2} genes were acquired by horizontal transfer. The presence of two different clones has been observed in other studies.^{2,18}

In our study, the mortality rate of neonates was 17.5% (7/40). High rates of mortality and morbidity as well as higher care costs were usually accompanied by infection with MBL-producing organisms.¹⁹ The findings of this study demonstrated that 37.5% of the isolates were MBL producers. *Bla*_{IMP-4} was the most commonly detected gene (42.5%) in this study, followed by *bla*_{VIM-2}, which was detected in 37.5% of the isolates. The other tested MBL-encoding genes, *bla*_{GIM}, *bla*_{SIM}, and *bla*_{SPM}, were not detected. In Egypt, the MBL

Table 1 Antibiotic susceptibility patterns of *Serratia marcescens* clinical isolates

	KZ	FOX	CAZ	CTX	FEP	MEM	AK	GM	TOB	CIP	LEV	NI	SXT
Sensitive	0%	0%	62.5%	62.5%	62.5%	62.5%	67.5%	92.5%	12.5%	80%	42.5%	0%	95%
Intermediate	0%	0%	0%	0%	0%	0%	2.5%	0%	67.5%	15%	0%	0%	0%
Resistance	100%	100%	37.5%	37.5%	37.5%	37.5%	30%	7.5%	20%	5%	15%	100%	5%

Abbreviations: AK, amikacin; CAZ, ceftazidime; CIP, ciprofloxacin; CTX, ceftriaxone; FEP, cefepime; FOX, ceftoxitin; GM, gentamicin; KZ, ceftazolin; LEV, levofloxacin; MEM, meropenem; NI, nitrofurantoin; SXT, trimethoprim/sulfamethoxazole; TOB, tobramycin.

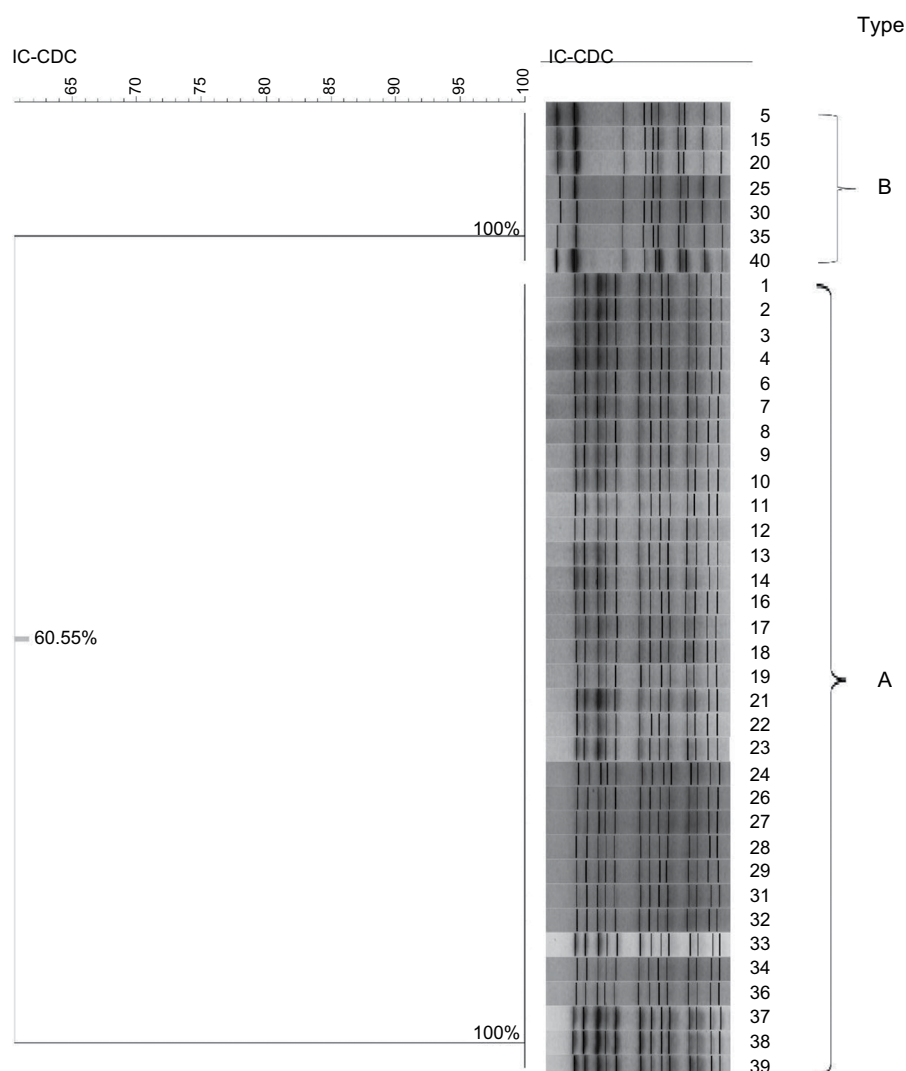


Figure 1 Dendrogram of the pulsed field gel electrophoresis patterns showing the genetic relatedness of the 40 *Serratia marcescens* isolates.

Abbreviation: IC-CDC, Centers for Disease Control and Prevention pulsotype.

VIM-2 has been detected in non-*Serratia* species, including *Pseudomonas aeruginosa*, and it was the major MBL detected in imipenem-nonsusceptible *P. aeruginosa*.²⁰ The first reported IMP-producing strain was a *bla*_{IMP-1}-containing *S. marcescens* strain isolated in Japan in 1991.²¹ Then, *bla*_{IMP-4} was reported in *Acinetobacter baumannii* in Hong Kong in the 1990s.²²

In a health care setting, carbapenems are mainly used as the last-line treatment for MDR gram-negative bacterial infections. Acquired resistance to carbapenems due to carbapenemase production has been increasingly reported over the last 15 years in *P. aeruginosa* and *Acinetobacter* spp. as well as *Enterobacteriaceae*. In the present study, 37.5% of isolates were meropenem resistant; all these strains are MBL producers, and none of the isolates produced carbapenemases by modified Hodge test. The same result was also observed

in case of the genotypic detection of carbapenemases by multiplex PCR as none of the investigated genes were detected. Neither *bla*_{OXA-48} nor *bla*_{NDM} genes, which are considered the predominant carbapenemases observed in our country, were detected.²³ These results are unlike the results described by other authors, which reported the existence of carbapenemase-producing *Serratia*.²⁴ Reporting carbapenemase production by *Serratia* species is very important as carbapenemase-encoding genes confer broad-spectrum antimicrobial resistance. This knowledge is crucial for choosing the most appropriate antibiotics to achieve better patient outcomes, especially because *Serratia* species are intrinsically resistant to polymyxins; therefore, they remain the last treatment option.

As stated by Schwab et al in 2014, “the published outbreaks are only the tip of the iceberg.”²⁵ Extensive

Table 2 Antibiotic susceptibilities (minimum inhibitory concentrations, mg/L), molecular characterization of carbapenemases genes, and clonal relatedness of 40 *Serratia marcescens* clinical isolates

Isolate #	KZ	FOX	CAZ	CTX	FEP	MEM	AK	GM	TOB	CIP	LEV	NI	SXT	Carried genes	Clone
1	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	4	≤0.25	≤0.12	256	≤20	–	A
2	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	256	≤20	–	A
3	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	0.5	≤0.12	256	≤20	–	A
4	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	4	≤0.25	≤0.12	256	≤20	–	A
5	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	256	≤20	<i>bla</i> _{IMP1}	B
6	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
7	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
8	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
9	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
10	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
11	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
12	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
13	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
14	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
15	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	<i>bla</i> _{IMP1}	B
16	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
17	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
18	≥64	≥64	≥64	≥64	≥64	≥16	≥64	8	≥16	≥4	≥8	≥512	160	<i>bla</i> _{IMP1} , <i>bla</i> _{VIM2}	A
19	≥64	≥64	≥64	≥64	≥64	≥16	≥64	≥16	≥16	≥4	≥8	256	≥320	<i>bla</i> _{IMP1} , <i>bla</i> _{VIM2}	A
20	≥64	≥64	16	≥64	≥64	≥16	≥64	≤1	4	≤0.25	≤0.12	128	≤20	<i>bla</i> _{IMP1} , <i>bla</i> _{VIM2}	B
21	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
22	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
23	≥64	≥64	≥64	≥64	≥64	≥16	≥64	≤1	≥16	0.5	≥8	256	≤20	<i>bla</i> _{IMP1} , <i>bla</i> _{VIM2}	A
24	≥64	≥64	32	≥64	≥64	≥16	4	2	≥16	0.5	≥8	128	≤20	<i>bla</i> _{IMP1} , <i>bla</i> _{VIM2}	A
25	≥64	≥64	≥64	≥64	≤1	≥16	4	≤1	≥16	0.5	≥8	128	≤20	<i>bla</i> _{IMP1} , <i>bla</i> _{VIM2}	B
26	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
27	≥64	≥64	16	≥64	≥64	≥16	≥64	≤1	2	0.5	1	128	≤20	<i>bla</i> _{IMP1} , <i>bla</i> _{VIM2}	A
28	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
29	≥64	≥64	≥64	≥64	≥64	≥16	≥64	≤1	4	0.5	1	256	≤20	<i>bla</i> _{IMP1} , <i>bla</i> _{VIM2}	A
30	≥64	≥64	16	≥64	≥64	≥16	≥64	≤1	2	≤0.25	0.25	256	≤20	<i>bla</i> _{IMP1} , <i>bla</i> _{VIM2}	B
31	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
32	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
33	≥64	≥64	≥64	≥64	≥64	≥16	≥64	≥16	≥16	2	2	256	≤20	<i>bla</i> _{IMP1} , <i>bla</i> _{VIM2}	A
34	≥64	8	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
35	≥64	≥64	≥64	≥64	≥64	≥16	≥64	4	≥16	2	2	256	≤20	<i>bla</i> _{IMP1} , <i>bla</i> _{VIM2}	B
36	≥64	≥64	16	≥64	≥64	≥16	≥64	≤1	4	≤0.25	≤0.12	128	≤20	<i>bla</i> _{IMP1} , <i>bla</i> _{VIM2}	A
37	≥64	≥64	8	≥64	≥64	8	≥64	≤1	8	≤0.25	≤0.12	128	≤20	<i>bla</i> _{IMP1} , <i>bla</i> _{VIM2}	A
38	≥64	16	≤1	≤1	≤1	≤0.25	≤2	≤1	8	≤0.25	≤0.12	128	≤20	–	A
39	≥64	≥64	≥64	≥64	≥64	≥16	≥64	≤1	≥16	0.5	≥8	256	≤20	<i>bla</i> _{IMP1} , <i>bla</i> _{VIM2}	A
40	≥64	≥64	16	≥64	≥64	≥16	≥64	≤1	2	≤0.25	0.25	256	≤20	<i>bla</i> _{IMP1} , <i>bla</i> _{VIM2}	B

Abbreviations: AK, amikacin; CAZ, ceftazidime; CIP, ciprofloxacin; CTX, ceftriaxone; FEP, cefepime; GM, gentamicin; KZ, ceftazolin; FOX, ceftoxitin; LEV, levofloxacin; MEM, meropenem; NI, nitrofurantoin; SXT, trimethoprim/sulfamethoxazole; TOB, tobramycin.

surveillance measures and molecular analyses are important for infection control and to understand the spread of these clinically important microorganisms.

Conclusion

In this study, IMP-4 and VIM-2 were detected in *S. marcescens* clinical isolates obtained from samples of blood cultures isolated from neonates admitted to the NICU. This is the first

description of MBL-producing *S. marcescens* nosocomial outbreak in neonatal intensive care unit in Egypt. Of the 40 *S. marcescens* isolates, 37% were carbapenem resistant; they belonged to one of two clones. Fast detection methods should be carried out in every health care unit to prevent the horizontal transfer of drug-resistant genes and the spread of these multidrug-resistant isolates. Surveillance policies must be implemented to avoid future outbreaks.

Ethical approval

Ethical committee of the Clinical and Chemical Pathology Department, Faculty of Medicine, Cairo University, has approved the study as the whole isolates described in this work were originally recovered for the purpose of diagnosis for patient care and were not obtained for the aim of the study. Therefore, participants consent was not necessary as this study included previously collected data and no participants were involved.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Acknowledgment

The authors extend their appreciation to the College of Pharmacy Research Center, Deanship of Scientific Research, King Saud University, for funding this study.

Author contributions

DMG conceived the idea. DMG and MMZ carried out the literature search and drafted the manuscript. MHAA, IYM, and AAQ performed the molecular analysis. DMG, MMZ, DKI, and SME contributed to the acquisition, analysis, and interpretation of data. All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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