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CASE REPORT

First Italian outbreak of VIM-producing *Serratia marcescens* in an adult polyvalent intensive care unit, August-October 2018: A case report and literature review

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Informed consent statement: Although no personal details are revealed in the present report, informed consent was obtained for publication of this case report

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Abstract

BACKGROUND

Carbapenem-resistant *Enterobacteriaceae* has become a significant public health concern as hospital outbreaks are now being frequently reported and these organisms are becoming difficult to treat with the available antibiotics.

CASE SUMMARY

An outbreak of VIM-producing *Serratia marcescens* occurred over a period of 11 wk (August, 1 to October, 18) in patients admitted to the adult polyvalent intensive care unit of the University of Campania "Luigi Vanvitelli" located in Naples. Four episodes occurred in three patients (two patients infected, and one patient colonized). All the strains revealed the production of VIM.

CONCLUSION

After three decades of carbapenem antibiotics use, the emergence of carbapenem-resistance in *Enterobacteriaceae* has become a significant concern and a stricter control to preserve its clinical application is mandatory. This is, to our knowledge, the first outbreak of VIM-producing *Serratia marcescens* in Europe. Surveillance policies must be implemented to avoid future outbreaks.

along with the related clinical details and images. All clinical data contained in this case report can be made available, in an absolutely anonymized form, upon request to marco.fiore@unicampania.it.

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Core Tip: An outbreak of VIM-producing *Serratia marcescens* occurred in patients admitted to the adult polyvalent intensive care unit of the University of Campania "Luigi Vanvitelli" located in Naples. All the strains revealed the production of VIM. After three decades of carbapenem antibiotics use, the emergence of carbapenem-resistant *Enterobacteriaceae* has become a significant concern and is mandatory a stricter control to preserve its clinical application. This is, to our knowledge, the first outbreak of VIM-producing *Serratia marcescens* occurred in a European hospital.

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INTRODUCTION

Carbapenem-resistant *Enterobacteriaceae* (CRE) has become a significant public health concern as hospital outbreaks are now being frequently reported and these organisms are becoming difficult to treat with the available antibiotics. Early recognition through molecular characterization, epidemiologic studies, and surveillance is essential to prevent hospital outbreaks of these organisms[1]. *Serratia marcescens* (*S. marcescens*), an aerobic Gram-negative pathogen belonging to the family of *Enterobacteriaceae*, is known to cause hospital-acquired infections, commonly in an outbreak setting. Carbapenem resistance in *S. marcescens* may be chromosomal (SME), or plasmid (KPC, Oxa-48, IMP, NDM and VIM) mediated. Carbapenem resistance in is an ominous event as this pathogen is intrinsically resistant to polymyxins[2]. *S. marcescens* outbreaks in intensive care units (ICUs) are associated with considerable mortality rates, ranging from 14% to 60%[3,4]. Previous *S. marcescens* outbreaks in Italy has been mostly reported in neonatal ICUs (NICUs)[5-9]. The present study aimed to describe the first Italian nosocomial outbreak of VIM-producing *S. marcescens* occurred in our adult polyvalent ICU located in Campania region, Southern Italy.

CASE PRESENTATION

Chief complaints and history of illness

The index case of the outbreak of three patients infected and/or colonized by VIM-producing *S. marcescens* was a 49-year-old man with a history of schizophrenia admitted with a diagnosis of descending necrotizing mediastinitis whose CRE screening at admission was negative.

The second patient was a 69-year-old woman with a history of recurrent episodes of urinary tract infection (UTI) admitted from the community with UTI and septic shock (SS).

The third patient was a 67-year-old woman with various underlying diseases (Paranoid personality disorder, diabetes mellitus, ulcerative colitis, hypothyroidism and hypertrophic cardiomyopathy) who was admitted to our ICU for a hypovolemic haemorrhagic shock.

Examinations

For every patient admitted to our six-bed adult polyvalent ICU, a rectal swab (RS) was obtained (CRE screening) using a Copan Amies sterile transport swab (Copan Diagnostics, Murrieta, CA). The RS was streaked onto Mac Conkey Agar (Biomerieux, Marcy l'Etoule, France) with a 10 μg meropenem disk. Mac Conkey agar plates were incubated aerobically at 37°C overnight. Antibiotic susceptibility was determined

using the disk diffusion method. Suspicious colonies growing into the meropenem disk-halo were picked up and identified using MALDI-TOF MS (Matrix- Assisted Laser Desorption/Ionization Time of Flight mass spectroscopy).

Carbapenem resistance were identified in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines using updated EUCAST breakpoint tables (EUCAST clinical breakpoint valid from 15/05/2018) (Table 1).

Molecular analysis to identify carbapenemase genes was performed using the Xpert Carba-R Cartridge (GeneXpert®, Cepheid, Sunnyvale, CA).

The Xpert Carba-R Assay, conducted on the GeneXpert® device, is an automated qualitative real-time polymerase chain reaction based test that detects specific gene associated with carbapenem resistance(blaKPC , blaNDM, blaVIM, blaOXA-48 and blaIMP-1).

FINAL DIAGNOSIS

After 65 d of the first patient hospitalization, a blood culture grew VIM-producing *S. marcescens*. Three days after the diagnosis of bacteraemia his RS was positive for the same organism. The same patient developed a new episode of bacteraemia during further ICU stay.

The second patient, eleven days after admission in ICU, developed lower respiratory tract infection (LRTI) with bronchial culture positive for VIM-producing *S. marcescens*. Her RS also tested positive for *S. marcescens* on the same day.

VIM-producing *S. marcescens* was isolated in the third patient from tracheal aspirate after seven days and from urine after eleven days of hospitalization. In both cases, the isolated was considered as a contaminant. During the ICU admission she developed an acute respiratory distress syndrome due to *Enterococcus faecium*.

TREATMENT

The first episode of VIM-producing *S. marcescens* bacteraemia was treated with ceftazidime-avibactam (CZA) plus gentamicin for 14-d. The second episode was initially treated with amikacin (AMK) and Fosfomycin. Fosfomycin was later substituted with meropenem due to hypernatremia. The total duration of the antibiotic treatment in this episode was 47 d.

The second patient was treated by the ward of origin with piperacillin-tazobactam (TZP) in association with AMK; initially (September, 12) we treated the SS with ceftolozane-tazobactam (C/T) and metronidazole; ceftaroline, not active against VIM-producing *S. marcescens*, was added later (September, 24), as her condition deteriorated, for a suspected methicillin-resistant *Staphylococcus aureus* infection[10]. The duration of total antibiotic therapy was 14 d.

The third patient was initially empirically treated with tigecycline and TZP; subsequently, due to the worsening of clinical conditions, antibiotic therapy was modified with the introduction of CZA, AMK, Colistin and ampicillin-sulbactam. VIM-producing *S. marcescens*, considered as a contaminant, in the third patient was not treated.

OUTCOME AND FOLLOW-UP

Both episodes of bacteraemia of the first patient resulted in a favourable outcome: The patient was transferred to a rehabilitation unit at the end of the ICU stay.

The second and the third patient died. Unfortunately for the third patient the microbiological result, with the isolation of the *Enterococcus faecium*, arrived posthumously.

The main clinical and epidemiological characteristics of the patients are reported in Table 2.

DISCUSSION

S. marcescens is an essential cause of hospital-acquired infections. Although most infections have been linked to hospital outbreaks, occasional infections can occur outside the outbreak settings also. The first hospital outbreak was reported in San Francisco in 1950 where 11 patients developed UTI by *S. marcescens*, one of them

Table 1 Antibiotic susceptibilities, in accordance with the European Committee on Antimicrobial Susceptibility Testing of VIM-producing *Serratia marcescens* isolates with the date and first site of identification

	MIC (μg/mL)			
AMK	≤ 4	8	≤ 4	≤ 4
AMC	> 32/2	> 32/2	> 32/2	> 32/2
AMP	> 8	> 8	> 8	> 8
FEP	> 8	> 8	> 8	> 8
CTX	> 4	> 4	> 4	> 4
CAZ	> 8	> 8	> 8	> 8
CIP	1	> 1	0.5	0.5
CST	> 4	> 4	≤ 1	≤ 1
ETP	> 1	> 1	> 1	> 1
FOF	≤ 32	64	≤ 32	≤ 32
GEN	> 4	> 4	4	4
IPM	> 8	> 8	> 8	> 8
LVX	2	> 2	1	≤ 0.5
MEM	> 8	> 8	> 8	8
PIP	> 16	> 16	> 16	> 16
TZP	> 16/4	> 16/4	> 16/4	> 16/4
TGC	> 2	> 2	> 2	> 2
TOB	> 4	> 4	> 4	> 4
SXT	> 4/76	> 4/76	> 4/76	> 4/76
Date	Aug, 1	Aug, 17	Sep, 20	Sep, 24
Site	Blood	Blood	RS	RT

AMC: Amoxicillin-clavulanic acid; AMK: Amikacin; AMP: Ampicillin; CAZ: Ceftazidime; CIP: Ciprofloxacin; CST: Colistin; CTX: Cefotaxime; ETP: Ertapenem; FEP: Cefepime; FOF: Fosfomycin; GEN: Gentamicin; IPM: Imipenem; LVX: Levofloxacin; MEM: Meropenem; PIP: Piperacillin; RS: Rectal swab; RT: Respiratory tract; SXT: Trimethoprim-sulfamethoxazole; TGC: Tigecycline; TOB: Tobramycin; TZP: Piperacillin-tazobactam.

complicated by endocarditis[11]. Many hospital outbreaks have been reported after that[12]. It has been associated with various infections including UTI, bloodstream infection, pneumonia, skin and soft tissue infections, meningitis and ocular infections.

Antibiotic resistance has been a worrisome issue to physicians treating infections caused by *S. marcescens*. This organism is intrinsically resistant to a large number of antibiotics including ampicillin, amoxicillin, amoxicillin-clavulanate, ampicillin-sulbactam, narrow-spectrum cephalosporins, cefuroxime, nitrofurantoin, macrolides and polymixins[13]. It also carries a chromosomal AmpC beta-lactamase which when overexpressed can render all beta-lactams except carbapenems ineffective[14]. They also can produce plasmid-mediated extended spectrum beta-lactamase (ESBL) and carbapenemases. Carbapenemases in *S. marcescens* can be chromosomal (SME) or plasmid-mediated (KPC, OXA-48, IMP, VIM, and NDM). Quinolone resistance can arise due to alterations in gyrA, outer membrane proteins, and expression of efflux pumps[12].

Carbapenem resistance can be devastating in case of Serratia infections considering its intrinsic resistance to polymixins. Many outbreaks of KPC2 producing *Serratia marcescens* has been reported[15,16]. Plasmid-mediated Metallo-β-lactamases (IMP, VIM, and NDM-1) which inactivate carbapenems can be produced by some Serratia strains[17].

Nosocomial outbreaks of VIM-producing *S. marcescens* has been reported infrequently in literature, most of them are from NICUs[18,19]. Nosocomial outbreaks of VIM-producing pathogens have been reported in multiple major Gram-negative bacteria, making VIM-producing bacteria a severe public health concern. The first VIM-producing Gram-negative pathogen and the most frequently reported in the literature is *Pseudomonas aeruginosa*, followed by *Klebsiella pneumonia* and *Acinetobacter baumannii* (Table 3). In our study, VIM-producing *S. marcescens* was isolated in a University Hospital ICU. This is in line with previous reports in the literature because most cases of VIM-producing Gram-negative pathogens have been isolated in ICUs of tertiary care teaching hospitals (Table 3). Unlike what has been reported in the last ten years in our Country, where the *S. marcescens* outbreaks have mostly taken place in

Table 2 Clinical and epidemiological data of patients

Patient	Admission from	Age(yr)	Sex	Underlying disease(s)	Previous AT	Admission diagnosis	Date of admission	Stool screening	1° site of identification
1	Community	49	M	SC	No	DNM	May, 28	Yes	Blood
1	ICU	49	M	SC	Yes	DNM	May, 28	Yes	Blood
2	Community	69	F	rUTI	Yes	SS	Sep, 9	Yes	RS
3	Internal ward	67	F	PPD, DM, UC, SHT, HCM	Yes	HS	Sep, 17	Yes	RT
Patient	**Infection (1° site)**	**Date of 1° isolation**	**2° site of identification**	**Infection (2° site)**	**Date of the 2° isolation site**	**Initial AT**	**Final AT**	**AT duration(d)**	**Outcome**
1	Yes	Aug, 1	RS	No	Aug, 4	CZA + GEN	CZA + GEN	14	Favourable
1	Yes	Aug, 17	-	-	-	AMK + FOF	AMK + MEM	47	Favourable
2	No	Sep, 20	RT	Yes	Sep, 20	C/T + MTZ	C/T + MTZ + CPT	14	Death
3	No	Sep, 24	Urine	No	Sep, 28	AFG + TGC + TZP	CST + SAM + CZA + AMK + AFG	16	Death

AFG: Anidulafungin; AMK: Amikacin; AT: Antibiotic treatment; CPT: Ceftaroline; CST: Colistin; C/T: Ceftolozane-tazobactam; CZA: Ceftazidime-avibactam; DM: Diabetes mellitus; DNM: Descending necrotizing mediastinitis; FOF: Fosfomycin; GEN: Gentamicin; HCM: Hypertrophic cardiomyopathy; HS: Hypovolemic hemorrhagic shock; ICU: Intensive care unit; MEM: Meropenem; MTZ: Metronidazole; PPD: Paranoid personality disorder; RS: Rectal swab; RT: Respiratory tract; SAM: Ampicillin-sulbactam; SC: Schizophrenia; SHT: Hypothyroidism; SS: Septic shock; TGC: Tigecycline; TZP: Piperacillin-tazobactam; UC: Ulcerative Colitis; rUTI: Recurrent urinary tract infection.

NICUs (Table 4) this first Italian outbreak of VIM-producing *Serratia marcescens* occurred in an adult ICU. Fatality rate in our outbreak was 50% (2 of 4 episodes), similar to the first nosocomial outbreak of VIM-producing *S. marcescens* happened in Argentina, which however occurred in NICU setting[19]. The high mortality is probably due to the inappropriate use of antibiotics for the treatment of severe infections in ICU patients[20]. In Figure 1 are represented the mechanisms of action of antibiotics used in our patients with VIM-producing *S. marcescens* infection. Given that no effective treatment is known, isolated reports describe successful therapy combining CZA and Aztreonam. The rationale of this antibiotic association is that Aztreonam remains intact in the presence of carbapenemases but hydrolyzed by ESBLs and CZA neutralizes the ESBLs and AmpC beta-lactamases[21]. In our study CZA was never co-administered with aztreonam, though there was clinical success in one of two patients who were given CZA in combination with other antibiotics (Table 2).

CONCLUSION

We report the first European outbreak of VIM-producing *Serratia marcescens* in adult polyvalent ICUs. Two patients developed an infection (bacteremia and LRTI) while one had colonization. No effective therapy is available for the treatment of VIM-producing *S. marcescens*. Methods to detect expression of carbapenem resistance should be widely available in all health care units to prevent the spread of multi-drug organisms and to limit horizontal transfer of the genes associated with drug resistance. Such active surveillance methods will help in averting future outbreaks.

Table 3 Previous reported hospital outbreaks around the world of VIM-producing Gram-negative pathogens

Year	City, Country, time span	Pathogen	Type of Hospital	Setting	VIM cases	Comments
2000	Verona, Italy; February 1997 - February 1998[29]	*Pseudomonas aeruginosa*	University Hospital	ICU patients	83	All patients from ICU
2000	Thessaloniki, Greece; 1996-1998[30]	*Pseudomonas aeruginosa*	University Hospital	ICU patients	211	More than one sample for patient;
2001	Southern Taiwan; January 1999 - December 2000[31]	*Klebsiella pneumoniae*	University Medical Center	ICU and Other Wards	5	Multidrug-resistant *Klebsiella pneumoniae*
2004	Heraklion, Greece; Summer 2001[32]	*Escherichia coli*	University Hospital	ICU patients	4	All patients from ICU
2004	Cali, Colombia; February 1999 - July 2003[33]	*Pseudomonas aeruginosa*	Tertiary Care Medical Center	ICU patients	66	All patients from ICU
2005	Larissa and Thessaloniki, Greece; December 2004 - March 2005[34]	*Klebsiella pneumoniae*	University Hospital	ICU and Other Wards	27	Outbreaks in distinct regions due to a single *Klebsiella pneumoniae* clone
2005	Calgary, Canada; May 2002 - April 2004[35]	*Pseudomonas aeruginosa*	1 pediatric and 3 large adult hospitals	ICU and Other Wards	228	Population-based epidemiological study of infections
2005	USA; May 2013[36]	*Pseudomonas aeruginosa*	Public Teaching Hospital	ICU and Other Wards	17	First outbreak of carbapenemase in USA
2005	Porto Alegre, southern Brazil; January - October 2004[37]	*Pseudomonas aeruginosa*	Tertiary-care Teaching Hospital	ICU and Other Wards	135	Outbreak of carbapenem-resistant
2006	Athens, Greece; March 2002-October 2002[38]	*Acinetobacter baumannii*	Tertiary Care Hospital	ICU and Other Wards	15	Outbreak of multiple clones of imipenem-resistant
2006	Paris, France; 2003-2004[39]	*Klebsiella pneumoniae*	Teaching Hospital	ICU and Other Wards	8	Recovered from clinical specimens or rectal swabs - Surgical ward or ICU patients
2006	Trieste, Italy; 1996-1997/ 2000-2002[40]	*Pseudomonas aeruginosa*	University Hospital	ICU and Other Wards	91	Nosocomial setting of high-level endemicity
2006	Hungary; October 2003-November 2005[41]	*Pseudomonas aeruginosa*	seven hospitals in Hungary	ICU and Other Wards	19	Molecular epidemiology of VIM-4 *Pseudomonas sp.*
2007	Madrid, Spain; March 2005 - September 2006[42]	*Enterobacteriaceae*	University Hospital	ICU and Other Wards	25	(52% of patients were in ICU)
2007	Warsaw, Poland ; September 2003 - May2004/July 2005-January2006[43]	*Pseudomonas aeruginosa*	Tertiary Care Hospital	ICU and Other Wards	41	Outbreak of *Pseudomonas aeruginosa* infections
2007	Athens, Greece; 14 September -3 October 2005[44]	*Pseudomonas aeruginosa*	University Hospital	ICU and Other Wards	5	Ventilator-Associated Pneumonia (VAP)
2008	Serres, Greece; April 2005 - March 2007[45]	*Acinetobacter baumanni*	General Hospital	ICU patients	31	All patients from ICU
2008	Piraeus, Greece; 2005-2006[46]	*Acinetobacter baumannii*	General Hospital	ICU and Other Wards	6	4 ICU patients
2008	Genoa, Italy; September 2004 - March 2005[47]	*Klebsiella pneumoniae*	Tertiary Care Hospital	ICU and Other Wards	9	Bloodstream infections
2008	Athens, Greece; February 2004 - March 2006[48]	*Klebsiella pneumoniae*	three hospitals in Athens	ICU and Other Wards	67	77% ICU patients
2008	Thessaloniki, Greece; November 2006 - April 2007[49]	*Klebsiella pneumoniae*	Tertiary Care Hospital	Wards	9	Patients hospitalized in different medical and surgical wards

2008	Nantes, France; April 1996 - July 2004[50]	*Pseudomonas aeruginosa*	University Hospital	ICU and Other Wards	59	Mostly urinary tract infections and pneumonia
2008	UK; November 2003-November 2007[51]	*Pseudomonas aeruginosa*	12 UK Hospital	ICU patients	32	15 cases from same hospital
2009	Greece; February 2008 - December 2008[52]	*Klebsiella pneumoniae*	21 Greek hospitals	ICU patients	52	All patients from ICU
2009	Thessaloniki, Greece; November 2004 - December 2005[53]	*Pseudomonas aeruginosa*	University Hospital	ICU patients	29	All patients from ICU
2010	Zonguldak, Turkey; 2003–2006[54]	*Acinetobacter baumannii*	University Hospital	ICU and Other Wards	116	Tracheal aspirates (32%), wound swabs (22%), blood (14%), bronchoalveolar specimens (11%) and urine, sterile fluids, catheter tips, abscess and sputum (each < 5%).
2010	Texas, USA; February-June 2008/March-June2009[55]	*Enterobacter cloacae*	Children's Hospital	Children ICU and Other Wards	3	Fecal colonization
2010	France; 2003-2004[56]	*Klebsiella pneumoniae*	care centre for abdominal surgery	ICU and Other Wards	8	Rectal swab, urine culture, blood culture, tracheal aspirates
2010	Athens, Greece; February - December 2009[57]	*Klebsiella pneumoniae*	University Hospital	ICU and Other Wards	42	Hospital-acquired infections
2010	Wuerzburg, Germany; November - December 2007[58]	*Pseudomonas aeruginosa*	retrograde urography associated infection	ICU and Other Wards	11	Strains from urine or urological infection
2010	Kobe, Japan; September 2007-July 2008[59]	*Pseudomonas aeruginosa*	Medical Center General Hospital	ICU patients	35	All patients from ICU
2011	Athens, Greece; March 2004 - November 2005[60]	*Enterobacteriaceae*	University Hospital	ICU patients	23	All patients from ICU
2011	Kasserine Tunisia; 2009 - June 2010[61]	*Escherichia coli*	University Hospital	ICU patients	2	Rectal swab
2011	Essen, Germany; July 2010 - January 2011[62]	*Klebsiella pneumoniae*	University Hospital	ICU and Other Wards	7	Perianal or rectal swabs
2011	Tunis, Tunisia; January - November 2008[63]	*Pseudomonas aeruginosa*	University Hospital	ICU and Other Wards	16	All patients of the kidney transplantation unit; 20 strains from urine, 3 from cutaneous pus, and 1 from blood
2011	Murcia, Spain; 11-25 May 2009[64]	*Pseudomonas aeruginosa*	Tertiary Care Hospital	ICU and Other Wards	6	4 ICU patients; strains from blood and sputum
2011	Central Japan; January 2006 - June 2009[65]	*Pseudomonas aeruginosa*	University Hospital	ICU and Other Wards	51	Mainly detected by urine culture in the first half, whereas isolation from respiratory tract samples became dominant in the latter half of the outbreak

2011	Rooterdam, Netherlands; January 2008 - November 2009[66]	*Pseudomonas aeruginosa*	University Hospital	ICU and Other Wards	35	161 carbapenemase-producing: 74 (70%) were isolated from respiratory tract specimens, 6 (6%) from urine, 5 (5%) from blood, 8 (8%) from soft tissue or bone, 7 (7%) from intra-abdominal specimens and 6 (6%) from various other specimens.
2012	Chosun, Korea; January 2004 - December 200[67]	*Acinetobacter baumannii*	University Hospital	ICU patients	77	All patients from ICU
2012	Madrid, Spain; January 2009 - December 2009[68]	*Klebsiella pneumoniae*	University Hospital	ICU patients	28	Fatality rate was 13/28 (46%)
2012	UK; 2005 – 2011[69]	*Pseudomonas aeruginosa*	Tertiary Care and University Hospitals	ICU and Other Wards	89	Fatality rate was 34/89 (38.2%)
2012	Cape Town, South Africa; January 2010 - April 2011[70]	*Pseudomonas aeruginosa*	Tertiary Care and University Hospitals	ICU patients	15	10 strains from blood, 2 from stool, 1 from bile, 1 from urine and 1 from a catheter tip
2013	Bologna, Italy; 1-15 June 2012[71]	*Citrobacter freundii*	University Hospital	ICU patients	8	Rectal swab
2013	Abidjan, Ivory Coast; February 2009 - November 2011[72]	*Pseudomonas aeruginosa*	University Hospital	ICU patients	12	All patients from ICU
2013	Thessalia, Larissa, Greece; 2010-2012[73]	*Pseudomonas aeruginosa*	University Hospital	ICU and Other Wards	49	All patients from ICU
2013	Taiwan; 2003-2007[74]	*Pseudomonas aeruginosa*	Regional Hospital	ICU and Other Wards	50	8 ICU patients
2013	Buenos Aires, Argentina; July–September 2011[19]	*Serratia marcescens*	Tertiary Care Neonatal University Hospital	Neonatal ward patients	3	Rectal swab; fatality rate was 1/2 (50%) and one lost at follow-up
2014	Split, Croatia; June - August 2012[75]	*Enterobacter cloacae*	University Hospital	ICU patients	6	Strains from lower respiratory tract, blood, abdominal cavity and rectum; fatality rate was 4/6 (66.6%)
2014	Greece; 2003-2007[76]	*Klebsiella pneumoniae*	Tertiary Care and University Hospitals	ICU patients	21	All patients from ICU
2014	Rome, Italy; 2011-2012[77]	*Pseudomonas aeruginosa*	Tertiary Care Paediatric Hospital	Children with onco-haematological diseases;	27	12 cases of bacteraemia, 6 other infections and 9 colonized; mortality rate was 67%
2014	Leiden, Netherlands; 2004- January 2012[78]	*Pseudomonas aeruginosa*	University Hospital	ICU patients	20	All patients from ICU
2014	China; December 2006 - July 2008[79]	*Pseudomonas aeruginosa*	Tertiary Care Hospitals	ICU patients	1	All patients from ICU
2015	Madrid, Spain - January 2009 - February 2014[80]	*Klebsiella pneumoniae*	University Hospital	ICU and Other Wards	37	OXA-48 ST11 clone
2015	Athens, Greece; September–November 2011[81]	*Providencia stuartii*	Tertiary Care Hospital	ICU patients	10/5	Strains from blood/urine; fatality rate was 7/15 (46.6%)
2015	Rotterdam, Netherlands; January - April 2012[82]	*Pseudomonas aeruginosa*	University Hospital	ICU and Other Wards	30	9 ICU patients; patients undergone ERCP using a specific duodenoscope (TJF-Q180V)

2015	UK, 2003 – 2012[83]	*Pseudomonas aeruginosa*	89 Tertiary Care Hospitals	ICU and Other Wards	267	Strains from urine (24%), respiratory (18%), wounds (17%) and blood (13%)
2016	Patras, Greece, January 2005 December 2014[84]	*Klebsiella pneumoniae*	University Hospital	ICU and Other Wards	45	1668 carbapenemase-producing isolates
2016	Athens, Greece; December 2012 - March 2013[85]	*Providencia stuartii*	Tertiary Care Hospital	ICU patients	6	Fatality rate was 3/6 (50%)
2016	China; August 2011-July 2012[86]	*Pseudomonas aeruginosa*	27 Tertiary Care Hospitals	ICU and Other Wards	49/44/42	Strains from pus/blood/urine
2017	Norway; 2007-2014[87]	*Enterobacteriacee*	University Hospital	ICU and Other Wards	14	*Klebsiella pneumoniae* (*n* = 10) and *E. coli* (*n* = 4)
2017	Jalisco, Mexico; September 2014 - July 2015[88]	*Enterobacteriacee*	Hospital Civil	ICU and Other Wards	3	*Klebsiella pneumoniae* (*n*=2), *C. freundii* (*n* = 1)
2017	Madrid, Spain - February 2014[89]	*Klebsiella oxytoca*	Children hospital	NICU	8	8 VIM-Kox/4 also had VIM-Serratia/3 patients VIM - Enterobacteriaceae. NICU, In neonates with any symptom of infection, urine, blood, broncho-alveolar lavages and other samples based on the most likely focus of infection
2017	UK; 2005-2011[90]	*Pseudomonas aeruginosa*	Two University Hospitals in London and South Coast	ICU and Other Wards	85	31 ICU patients; fatality rate was 34/85 (40%)
2018	Thessaloniki, Greece; January 2013- January 2015[91]	*Klebsiella pneumoniae*	University Hospital	ICU and Other Wards	25	Strain producing both KPC-2 and VIM-1 carbapenemases
2018	Cairo, Egypt, March 2015 August 2015[18]	*Serratia marcescens*	University Teaching Hospital	NICU	15	Isolates obtained from blood stream infections

ICU: Intensive care unit; NICU: Neonatal ICU. UK: United Kingdom; USA: United States of America.

Table 4 Previous hospital outbreaks of *Serratia marcescens* in Italy

Year	City	Setting	Number of cases(Infection and/or colonization)	Comments
1984	Naples[22]	NICU and Nursery	88	Outbreak linked to contaminated mucus aspiration apparatus and other contaminated instruments. Case fatality rate: 19%
1988	Genoa[23]	Adult ICU and surgical ward	11	Ventilators for assisted breathing became contaminated from index patient.
1994	Varese[24]	Adult ICU	43	Strains from the ICU outbreak were multidrug resistance. 23 isolates from 18 other patients from other wards showed wide range of antibiotic susceptibility

2001	Naples[25]	NICU	14	56 cases of colonization by S marcescens over a 15-month period. Fourteen of the 56 colonized infants developed clinical infections, 50% of which were major (sepsis, meningitis, or pneumonia)
2003	Naples[26]	Adult ICU	13	Strain was multidrug resistant, inducible AmpC betalactamase producing. There were three cases of sepsis, nine pneumonia and one surgical wound infection. Mortality was 84.6%
2005	Modena[27]	NICU	15	Simultaneous outbreak of *Serratia marcescens* and Klebsiella pneumonia (11 cases). One preterm baby died in which both organisms were involved
2007	Pavia[9]	NICU	21	Occurred in two separate outbreaks in 10 mo interval
2009	Verona[28]	NICU	16	6 patients developed clinical diseases which included bacteremia, UTI, conjunctivitis and umbilical wound infection
2011	Pescara[7]	NICU	6	5 cases were linked toan index case hospitalised for *S. marcescens* sepsis. Mortality was 40%
2013	Modena[6]	NICU	127	Reported two long term outbreaks occurred over a period of 10 years. 43 developed infection and 3 died
2015	Floerence[5]	NICU	14	In the surveillance post outbreak, 18 out of 65 patients tested positive for *S. marcescens*

ICU: Intensive care unit; NICU: Neonatal ICU.

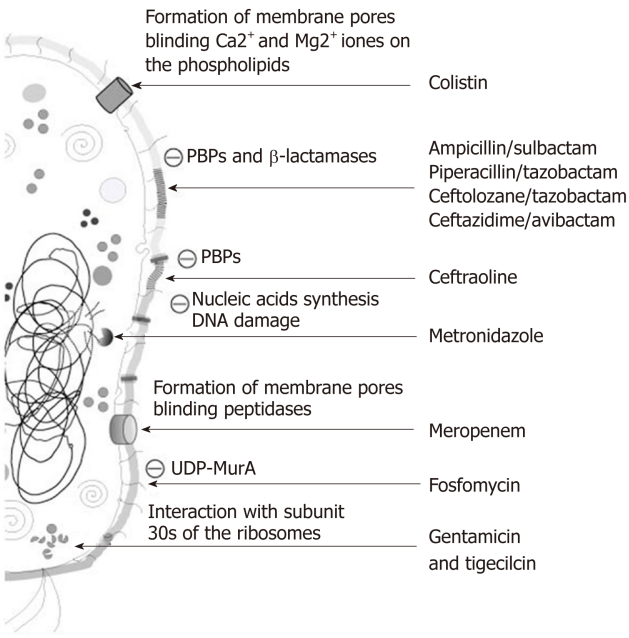

Figure 1 Mechanism of antibiotics used in our patients with VIM-producing *Serratia marcescens*. DNA: Deoxyribonucleic acid; PBPs: Penicillin-binding proteins; UDP-MurA: Uridine diphosphate-N-acetylglucosamine enolpyruvyl transferase.

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