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## 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<sup>[1]</sup>. *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<sup>[2]</sup>. *S. marcescens* outbreaks in intensive care units (ICUs) are associated with considerable mortality rates, ranging from 14% to 60%<sup>[3,4]</sup>. Previous *S. marcescens* outbreaks in Italy has been mostly reported in neonatal ICUs (NICUs)<sup>[5-9]</sup>. 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'Étoile, 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<sup>[10]</sup>. 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<sup>[11]</sup>. Many hospital outbreaks have been reported after that<sup>[12]</sup>. 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 polymyxins<sup>[13]</sup>. It also carries a chromosomal AmpC beta-lactamase which when overexpressed can render all beta-lactams except carbapenems ineffective<sup>[14]</sup>. 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<sup>[12]</sup>.

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

Nosocomial outbreaks of VIM-producing *S. marcescens* has been reported infrequently in literature, most of them are from NICUs<sup>[18,19]</sup>. 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 pneumoniae* 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<sup>[19]</sup>. The high mortality is probably due to the inappropriate use of antibiotics for the treatment of severe infections in ICU patients<sup>[20]</sup>. 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<sup>[21]</sup>. 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 <sup>[29]</sup>                    | <i>Pseudomonas aeruginosa</i>  | University Hospital                     | ICU patients        | 83        | All patients from ICU   |
| 2000 | Thessaloniki, Greece; 1996-1998 <sup>[30]</sup>                                 | <i>Pseudomonas aeruginosa</i>  | University Hospital                     | ICU patients        | 211       | More than one sample for patient;   |
| 2001 | Southern Taiwan; January 1999 - December 2000 <sup>[31]</sup>                   | <i>Klebsiella pneumoniae</i>   | University Medical Center               | ICU and Other Wards | 5         | Multidrug-resistant <i>Klebsiella pneumoniae</i>                                  |
| 2004 | Heraklion, Greece; Summer 2001 <sup>[32]</sup>                                  | <i>Escherichia coli</i>        | University Hospital                     | ICU patients        | 4         | All patients from ICU   |
| 2004 | Cali, Colombia; February 1999 - July 2003 <sup>[33]</sup>                       | <i>Pseudomonas aeruginosa</i>  | Tertiary Care Medical Center            | ICU patients        | 66        | All patients from ICU   |
| 2005 | Larissa and Thessaloniki, Greece; December 2004 - March 2005 <sup>[34]</sup>    | <i>Klebsiella pneumoniae</i>   | University Hospital                     | ICU and Other Wards | 27        | Outbreaks in distinct regions due to a single <i>Klebsiella pneumoniae</i> clone  |
| 2005 | Calgary, Canada; May 2002 - April 2004 <sup>[35]</sup>                          | <i>Pseudomonas aeruginosa</i>  | 1 pediatric and 3 large adult hospitals | ICU and Other Wards | 228       | Population-based epidemiological study of infections                              |
| 2005 | USA; May 2013 <sup>[36]</sup>   | <i>Pseudomonas aeruginosa</i>  | Public Teaching Hospital                | ICU and Other Wards | 17        | First outbreak of carbapenemase in USA  |
| 2005 | Porto Alegre, southern Brazil; January - October 2004 <sup>[37]</sup>           | <i>Pseudomonas aeruginosa</i>  | Tertiary-care Teaching Hospital         | ICU and Other Wards | 135       | Outbreak of carbapenem-resistant  |
| 2006 | Athens, Greece; March 2002-October 2002 <sup>[38]</sup>                         | <i>Acinetobacter baumannii</i> | Tertiary Care Hospital                  | ICU and Other Wards | 15        | Outbreak of multiple clones of imipenem-resistant                                 |
| 2006 | Paris, France; 2003-2004 <sup>[39]</sup>  | <i>Klebsiella pneumoniae</i>   | 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 <sup>[40]</sup>                            | <i>Pseudomonas aeruginosa</i>  | University Hospital                     | ICU and Other Wards | 91        | Nosocomial setting of high-level endemicity                                       |
| 2006 | Hungary; October 2003-November 2005 <sup>[41]</sup>                             | <i>Pseudomonas aeruginosa</i>  | seven hospitals in Hungary              | ICU and Other Wards | 19        | Molecular epidemiology of VIM-4 <i>Pseudomonas sp</i>                             |
| 2007 | Madrid, Spain; March 2005 - September 2006 <sup>[42]</sup>                      | <i>Enterobacteriaceae</i>      | University Hospital                     | ICU and Other Wards | 25        | (52% of patients were in ICU)   |
| 2007 | Warsaw, Poland ; September 2003 - May2004/July 2005-January2006 <sup>[43]</sup> | <i>Pseudomonas aeruginosa</i>  | Tertiary Care Hospital                  | ICU and Other Wards | 41        | Outbreak of <i>Pseudomonas aeruginosa</i> infections                              |
| 2007 | Athens, Greece; 14 September -3 October 2005 <sup>[44]</sup>                    | <i>Pseudomonas aeruginosa</i>  | University Hospital                     | ICU and Other Wards | 5         | Ventilator-Associated Pneumonia (VAP)   |
| 2008 | Serres, Greece; April 2005 - March 2007 <sup>[45]</sup>                         | <i>Acinetobacter baumannii</i> | General Hospital                        | ICU patients        | 31        | All patients from ICU   |
| 2008 | Piraeus, Greece; 2005-2006 <sup>[46]</sup>                                      | <i>Acinetobacter baumannii</i> | General Hospital                        | ICU and Other Wards | 6         | 4 ICU patients  |
| 2008 | Genoa, Italy; September 2004 - March 2005 <sup>[47]</sup>                       | <i>Klebsiella pneumoniae</i>   | Tertiary Care Hospital                  | ICU and Other Wards | 9         | Bloodstream infections  |
| 2008 | Athens, Greece; February 2004 - March 2006 <sup>[48]</sup>                      | <i>Klebsiella pneumoniae</i>   | three hospitals in Athens               | ICU and Other Wards | 67        | 77% ICU patients  |
| 2008 | Thessaloniki, Greece; November 2006 - April 2007 <sup>[49]</sup>                | <i>Klebsiella pneumoniae</i>   | Tertiary Care Hospital                  | Wards               | 9         | Patients hospitalized in different medical and surgical wards                     |

|      |   |                                |   |                              |     |   |
|------|---|--------------------------------|---|------------------------------|-----|---|
| 2008 | Nantes, France; April 1996 - July 2004 <sup>[50]</sup>              | <i>Pseudomonas aeruginosa</i>  | University Hospital                       | ICU and Other Wards          | 59  | Mostly urinary tract infections and pneumonia   |
| 2008 | UK; November 2003- November 2007 <sup>[51]</sup>                    | <i>Pseudomonas aeruginosa</i>  | 12 UK Hospital                            | ICU patients                 | 32  | 15 cases from same hospital   |
| 2009 | Greece; February 2008 - December 2008 <sup>[52]</sup>               | <i>Klebsiella pneumoniae</i>   | 21 Greek hospitals                        | ICU patients                 | 52  | All patients from ICU   |
| 2009 | Thessaloniki, Greece; November 2004 - December 2005 <sup>[53]</sup> | <i>Pseudomonas aeruginosa</i>  | University Hospital                       | ICU patients                 | 29  | All patients from ICU   |
| 2010 | Zonguldak, Turkey; 2003-2006 <sup>[54]</sup>                        | <i>Acinetobacter baumannii</i> | 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-June 2009 <sup>[55]</sup>      | <i>Enterobacter cloacae</i>    | Children's Hospital                       | Children ICU and Other Wards | 3   | Fecal colonization  |
| 2010 | France; 2003-2004 <sup>[56]</sup>                                   | <i>Klebsiella pneumoniae</i>   | care centre for abdominal surgery         | ICU and Other Wards          | 8   | Rectal swab, urine culture, blood culture, tracheal aspirates   |
| 2010 | Athens, Greece; February - December 2009 <sup>[57]</sup>            | <i>Klebsiella pneumoniae</i>   | University Hospital                       | ICU and Other Wards          | 42  | Hospital-acquired infections  |
| 2010 | Wuerzburg, Germany; November - December 2007 <sup>[58]</sup>        | <i>Pseudomonas aeruginosa</i>  | retrograde urography associated infection | ICU and Other Wards          | 11  | Strains from urine or urological infection  |
| 2010 | Kobe, Japan; September 2007-July 2008 <sup>[59]</sup>               | <i>Pseudomonas aeruginosa</i>  | Medical Center General Hospital           | ICU patients                 | 35  | All patients from ICU   |
| 2011 | Athens, Greece; March 2004 - November 2005 <sup>[60]</sup>          | <i>Enterobacteriaceae</i>      | University Hospital                       | ICU patients                 | 23  | All patients from ICU   |
| 2011 | Kasserine Tunisia; 2009 - June 2010 <sup>[61]</sup>                 | <i>Escherichia coli</i>        | University Hospital                       | ICU patients                 | 2   | Rectal swab   |
| 2011 | Essen, Germany; July 2010 - January 2011 <sup>[62]</sup>            | <i>Klebsiella pneumoniae</i>   | University Hospital                       | ICU and Other Wards          | 7   | Perianal or rectal swabs  |
| 2011 | Tunis, Tunisia; January - November 2008 <sup>[63]</sup>             | <i>Pseudomonas aeruginosa</i>  | 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 <sup>[64]</sup>                       | <i>Pseudomonas aeruginosa</i>  | Tertiary Care Hospital                    | ICU and Other Wards          | 6   | 4 ICU patients; strains from blood and sputum   |
| 2011 | Central Japan; January 2006 - June 2009 <sup>[65]</sup>             | <i>Pseudomonas aeruginosa</i>  | 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 <sup>[66]</sup> | <i>Pseudomonas aeruginosa</i>  | 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 <sup>[67]</sup>           | <i>Acinetobacter baumannii</i> | University Hospital                        | ICU patients                                | 77   | All patients from ICU   |
| 2012 | Madrid, Spain; January 2009 - December 2009 <sup>[68]</sup>          | <i>Klebsiella pneumoniae</i>   | University Hospital                        | ICU patients                                | 28   | Fatality rate was 13/28 (46%)   |
| 2012 | UK; 2005 - 2011 <sup>[69]</sup>                                      | <i>Pseudomonas aeruginosa</i>  | 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 <sup>[70]</sup>   | <i>Pseudomonas aeruginosa</i>  | 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 <sup>[71]</sup>                       | <i>Citrobacter freundii</i>    | University Hospital                        | ICU patients                                | 8    | Rectal swab   |
| 2013 | Abidjan, Ivory Coast; February 2009 - November 2011 <sup>[72]</sup>  | <i>Pseudomonas aeruginosa</i>  | University Hospital                        | ICU patients                                | 12   | All patients from ICU   |
| 2013 | Thessalia, Larissa, Greece; 2010-2012 <sup>[73]</sup>                | <i>Pseudomonas aeruginosa</i>  | University Hospital                        | ICU and Other Wards                         | 49   | All patients from ICU   |
| 2013 | Taiwan; 2003-2007 <sup>[74]</sup>                                    | <i>Pseudomonas aeruginosa</i>  | Regional Hospital                          | ICU and Other Wards                         | 50   | 8 ICU patients  |
| 2013 | Buenos Aires, Argentina; July-September 2011 <sup>[19]</sup>         | <i>Serratia marcescens</i>     | 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 <sup>[75]</sup>                   | <i>Enterobacter cloacae</i>    | 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 <sup>[76]</sup>                                    | <i>Klebsiella pneumoniae</i>   | Tertiary Care and University Hospitals     | ICU patients                                | 21   | All patients from ICU   |
| 2014 | Rome, Italy; 2011-2012 <sup>[77]</sup>                               | <i>Pseudomonas aeruginosa</i>  | 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 <sup>[78]</sup>              | <i>Pseudomonas aeruginosa</i>  | University Hospital                        | ICU patients                                | 20   | All patients from ICU   |
| 2014 | China; December 2006 - July 2008 <sup>[79]</sup>                     | <i>Pseudomonas aeruginosa</i>  | Tertiary Care Hospitals                    | ICU patients                                | 1    | All patients from ICU   |
| 2015 | Madrid, Spain - January 2009 - February 2014 <sup>[80]</sup>         | <i>Klebsiella pneumoniae</i>   | University Hospital                        | ICU and Other Wards                         | 37   | OXA-48 ST11 clone   |
| 2015 | Athens, Greece; September-November 2011 <sup>[81]</sup>              | <i>Providencia stuartii</i>    | Tertiary Care Hospital                     | ICU patients                                | 10/5 | Strains from blood/urine; fatality rate was 7/15 (46.6%)  |
| 2015 | Rotterdam, Netherlands; January - April 2012 <sup>[82]</sup>         | <i>Pseudomonas aeruginosa</i>  | University Hospital                        | ICU and Other Wards                         | 30   | 9 ICU patients; patients undergone ERCP using a specific duodenoscope (TJF-Q180V)   |

|      |  |                               |  |                     |          |  |
|------|--|-------------------------------|--|---------------------|----------|--|
| 2015 | UK, 2003 – 2012 <sup>[83]</sup>                                  | <i>Pseudomonas aeruginosa</i> | 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 <sup>[84]</sup>     | <i>Klebsiella pneumoniae</i>  | University Hospital                                | ICU and Other Wards | 45       | 1668 carbapenemase-producing isolates  |
| 2016 | Athens, Greece; December 2012 – March 2013 <sup>[85]</sup>       | <i>Providencia stuartii</i>   | Tertiary Care Hospital                             | ICU patients        | 6        | Fatality rate was 3/6 (50%)  |
| 2016 | China; August 2011– July 2012 <sup>[86]</sup>                    | <i>Pseudomonas aeruginosa</i> | 27 Tertiary Care Hospitals                         | ICU and Other Wards | 49/44/42 | Strains from pus/blood/urine   |
| 2017 | Norway; 2007–2014 <sup>[87]</sup>                                | <i>Enterobacteriaceae</i>     | University Hospital                                | ICU and Other Wards | 14       | <i>Klebsiella pneumoniae</i> (n = 10) and <i>E. coli</i> (n = 4)   |
| 2017 | Jalisco, Mexico; September 2014 – July 2015 <sup>[88]</sup>      | <i>Enterobacteriaceae</i>     | Hospital Civil                                     | ICU and Other Wards | 3        | <i>Klebsiella pneumoniae</i> (n=2), <i>C. freundii</i> (n = 1)   |
| 2017 | Madrid, Spain – February 2014 <sup>[89]</sup>                    | <i>Klebsiella oxytoca</i>     | 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 <sup>[90]</sup>                                    | <i>Pseudomonas aeruginosa</i> | 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 <sup>[91]</sup> | <i>Klebsiella pneumoniae</i>  | University Hospital                                | ICU and Other Wards | 25       | Strain producing both KPC-2 and VIM-1 carbapenemases   |
| 2018 | Cairo, Egypt, March 2015 – August 2015 <sup>[18]</sup>           | <i>Serratia marcescens</i>    | 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.

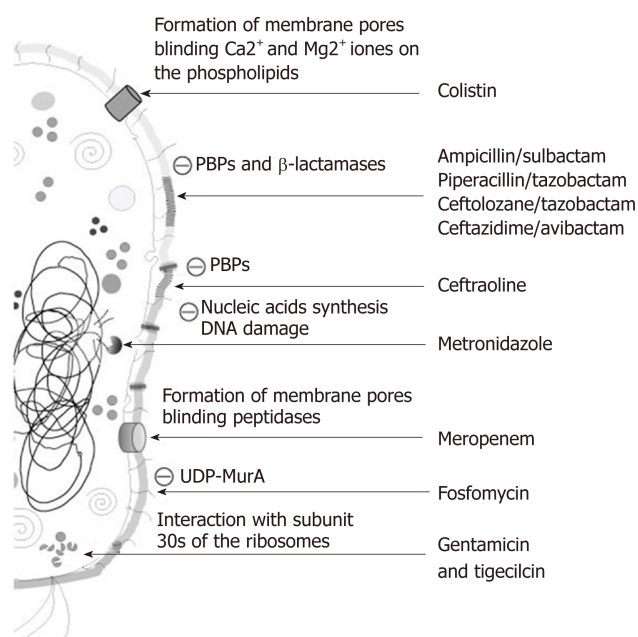
**Table 4 Previous hospital outbreaks of *Serratia marcescens* in Italy**

| Year | City                   | Setting                     | Number of cases(Infection and/or colonization) | Comments  |
|------|------------------------|-----------------------------|--|---|
| 1984 | Naples <sup>[22]</sup> | NICU and Nursery            | 88   | Outbreak linked to contaminated mucus aspiration apparatus and other contaminated instruments. Case fatality rate: 19%                                      |
| 1988 | Genoa <sup>[23]</sup>  | Adult ICU and surgical ward | 11   | Ventilators for assisted breathing became contaminated from index patient   |
| 1994 | Varese <sup>[24]</sup> | 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 <sup>[25]</sup>  | NICU      | 14  | 56 cases of colonization by <i>S. marcescens</i> 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 <sup>[26]</sup>  | 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 <sup>[27]</sup>  | NICU      | 15  | Simultaneous outbreak of <i>Serratia marcescens</i> and <i>Klebsiella pneumoniae</i> (11 cases). One preterm baby died in which both organisms were involved  |
| 2007 | Pavia <sup>[9]</sup>    | NICU      | 21  | Occurred in two separate outbreaks in 10 mo interval  |
| 2009 | Verona <sup>[28]</sup>  | NICU      | 16  | 6 patients developed clinical diseases which included bacteremia, UTI, conjunctivitis and umbilical wound infection   |
| 2011 | Pescara <sup>[7]</sup>  | NICU      | 6   | 5 cases were linked to an index case hospitalised for <i>S. marcescens</i> sepsis. Mortality was 40%  |
| 2013 | Modena <sup>[6]</sup>   | NICU      | 127 | Reported two long term outbreaks occurred over a period of 10 years. 43 developed infection and 3 died  |
| 2015 | Florence <sup>[5]</sup> | NICU      | 14  | In the surveillance post outbreak, 18 out of 65 patients tested positive for <i>S. marcescens</i>   |

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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