Linezolid and clindamycin improve the outcome of severe, necrotizing pneumonia due to community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA)

Laura Soavi¹, Liana Signorini², Roberto Stellini², Annamaria Acquarolo³, Bertilla Fiorese², Silvia Magri², Annalisa Pantosti³, Fredy Suter¹, Giampiero Carosi²

¹U.S.C. Malattie Infettive, Ospedali Riuniti di Bergamo, Bergamo, Italy; ²Istituto di Malattie Infettive e Tropicali, Spedali Civili di Brescia, Brescia, Italy; ³Dipartimento di Anestesia e Rianimazione, Spedali Civili di Brescia, Brescia, Italy; ⁴Dipartimento di Malattie Infettive, Parassitarie ed Immuno-mediate, Istituto Superiore di Sanità, Rome, Italy

INTRODUCTION

Methicillin-resistant Staphylococcus aureus (MRSA) is a major cause of nosocomial infection. The emergence of MRSA as a cause of life-threatening, invasive infections in the community in patients who never had healthcare contacts is a recent, important public health problem [1]. Such infections include, among others, septic shock and necrotizing pneumonia, which is rapidly progressive, haemorrhagic and often fatal (mortality rate: 60-75%) [2, 3]. The high virulence potential of CA-MRSA is associated with the production of the Panton-Valentine leukocidin (PVL), a toxin that creates lytic pores in cells membranes of neutrophils and induces release of neutrophil pro-inflammatory chemotactic factors which, in turn, cause widespread tissue necrosis [4]. A recent in vitro study evaluating the effect of vancomycin, nafcillin, clindamycin and linezolid on clinical isolates of Methicillin-susceptible S. aureus (MSSA) and MRSA has shown that antibiotics have different effects on the expression of staphylococcal toxins. Linezolid and clindamycin markedly suppress PVL production in MRSA, whereas nafcillin and vancomycin stimulate continued PVL expression [5].

We here report a case of CA-MRSA necrotizing pneumonia and septic shock, in which patient’s outcome was strongly influenced by the choice of antibiotic therapy, providing clinical support to the findings of in vitro studies.

CASE REPORT

A previously healthy, caucasian, 49-year-old woman became ill with fever and productive cough on January 1st, 2008. The next days her symptoms worsened and, on January 6th, she was taken to our Emergency Department (ED) in respiratory distress. On examination, she had a temperature of 38.5°C, an oxygen saturation of 90% on room air, a blood pressure of 160/90 mmHg, a heartbeat rate of 86 beats per minute and...
a respiratory rate of 35 breaths per minute. Arterial blood gases revealed a pH of 7.429, a PaO\textsubscript{2} of 57 mmHg and a PaCO\textsubscript{2} of 37 mmHg. Blood exams showed a creatinine of 1.4 mg/dl and a pro-inflammatory state (leukocyte count 13110 cells/\mu l, CRP 270 mg/l, procalcitonin 128.2 ng/ml). A CT scan revealed bilateral multiple alveolar infiltrates in all lung fields with a small cavitory lesion and enlargement of mediastinal lymph nodes (Figure 1). She was started on ampicillin-sulbactam and amphotericin B-liposomal. The patient worsened, failed to respond to oxygen supplementation and was admitted to the intensive care unit (ICU), where she was intubated and put on mechanical ventilation. Within hours, she became hypotensive, requiring inotropic support, and developed pancytopenia (leukocyte count 3400 cells/\mu l, platelet count 95000/\mu l) with multi-organ failure (MOF) requiring continuous veno-venous hemofiltration (CVVH). Because of septic shock, hydrocortisone was added to the antimicrobial treatment. Bronchoscopy was performed, which showed abundant white secretions covering an edematous bronchial mucosa with focal necrosis and mild bleeding. On day 2, broncho-alveolar lavage (BAL) cultures were reported as growing S. aureus (>5 \times 10^{6} CFU/ml), later referred as MRSA, and Aspergillus fumigatus. Antibiotic therapy was immediately modified and linezolid and levofloxacin were started, while continuing liposomal amphotericin B. After 3 days of therapy, while the clinical conditions of the patient seemed to improve, platelet count dropped to 29000/\mu l. Linezolid, levofloxacin and amphotericin B-liposomal were replaced by vancomycin, rifampin and caspofungin. Four days thereafter, her lung oxygenation and haemodynamic parameters worsened, and chest X-ray revealed widespread bilateral alveolar infiltrates with multiple cavities in the upper right lobe. Doses of inotropes were increased and antibiotic therapy was changed: linezolid and clindamycin replaced vancomycin and rifampin, caspofungin was continued. The patient’s condition progressively improved: she rapidly became afebrile, arterial blood gases, as well as leukocyte and platelet count, CRP and procalcitonin, returned to normal values. On January 20\textsuperscript{th}, CVVH and mechanical ventilation were discontinued and, after 5 more days, antibiotic therapy was stopped.

The patient was discharged on day 72: she is currently healthy with complete recovery of respiratory function.

**DISCUSSION**

In the patient we described, the finding of lung necrosis was consistent with the production of PVL, later confirmed by PCR. We observed a clear relationship between different antibiotic regimens and clinical conditions of the patient, in that ampicillin-sulbactam and vancomycin were associated with worsening of respiratory function and pulmonary infiltrates, whereas resolution of pneumonia was achieved only after starting two toxin-suppressing agents, clindamycin and linezolid.

The main reasons that explain why beta-lactams and glycopeptides may fail in infections associated with toxin-producing organisms are that these cell-wall-active agents, in contrast to protein-synthesis inhibitors, do not suppress toxin production and that lysis of the bacteria increases the release of intracellular toxins [5]. These data suggest that, for treatment of MRSA strains producing potent extracellular toxins, linezolid and clindamycin demonstrate a clear advantage over vancomycin. Linezolid, moreover, has an excellent lung tissue penetration, which is approximately 6 times higher than that of vancomycin [6, 7].

Starting early appropriate antibiotic treatment is considered essential to ensure a favourable outcome, and highlights the importance of suspecting CA-MRSA in previously healthy patients presenting to ED with severe respiratory illness, especially when associated with pul-

![Figura 1 - CT scan of the thorax shows bilateral pulmonary infiltrates with one small cavitory lesion in the inferior, left lobe and enlargement of mediastinal lymph nodes.](image-url)
monary necrosis, septic shock, high fever, haemoptysis and leucopenia [8]. Unlike the American counterpart, the latest European guidelines on CAP management do not take in consideration potential occurrence of CA-MRSA [9, 10]. We believe that there is the case to review them now. Surveillance of community acquired S. aureus and optimal treatment strategies are also required.

Key words: CA-MRSA, pneumonia, Panton-Valentine leukocidin (PVL), linezolid, clindamycin

Acknowledgements
The authors thank Dr. Alberto Matteelli for his critical comments and his precious suggestions.

Potential conflicts of interest: none declared.

SUMMARY
The last decade has been characterized by the emergence of CA-MRSA strains associated with the production of Panton-Valentine leukocidin. We report a case of necrotizing pneumonia and septic shock caused by CA-MRSA, in which early recognition of the syndrome and appropriate treatment with two toxin-suppressing antibiotics improved the patient’s outcome.

REFERENCES