

Successful use of daptomycin and cefazolin in a case of persistent bacteremia caused by community acquired-methicillin resistant *Staphylococcus aureus* in a pregnant woman. Case report

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We present the case of a pregnant woman with community-acquired methicillin-resistant Staphylococcus aureus bacteremia who required combined treatment with daptomycin and cefazolin for control after failure of an initial treatment with vancomycin. She had a favorable evolution, and the study of family contacts revealed a phenotypic and genetically similar isolate in a nasal sample from his mother. The carriage study on three household cats was negative. This case reveals that bacteremia caused by methicillin-resistant Staphylococcus aureus can affect pregnant women, and that the use of combined therapies may be necessary for its control. Sometimes, family contacts can carry this agent, and an eradication treatment is suggested..

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Key words: Bacterial Typing Techniques; Bacteremia; Community-Acquired Infections; Pregnancy; Staphylococcus aureus.

Uso exitoso de daptomicina y cefazolina en un caso de bacteriemia por *Staphylococcus aureus* resistente a meticilina adquirido en la comunidad, en una mujer embarazada. Reporte de caso

Presentamos el caso de una mujer embarazada con bacteriemia por Staphylococcus aureus resistente a meticilina adquirido en la comunidad que requirió un tratamiento combinado con daptomicina y cefazolina para su control luego del fracaso de un tratamiento inicial con vancomicina. Tuvo una favorable evolución y el estudio de los contactos familiares reveló un aislado fenotípica y genéticamente similar en una muestra nasal de su madre. El estudio de portación en 3 gatos mascotas fue negativo. Este caso revela que las bacteriemias por este agente pueden afectar mujeres embarazadas y que puede ser necesario el uso de terapias combinadas para su control. En ocasiones, los contactos familiares pueden ser portadores de este agente y se sugiere un tratamiento de erradicación.

Palabras clave: Bacteriemia; Embarazo; Infecciones Comunitarias Adquiridas; Staphylococcus aureus; Técnicas de Tipificación Bacteriana.

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Community-acquired methicillin-resistant *Staphylococcus aureus* isolates (CA-MRSA) are generally characterized by their resistance to cloxacillin, carrier of the Panton-Valentine Leukocidin factor (PVL, a cytotoxin), and their ability to cause invasive infections mainly as skin and soft tissues infections (SSTI, 70-80% of cases). They also belong to different genotypes or pulse types (ST1/USA 400 or ST8/USA300) when compared to those classically associated with healthcare-associated infections^{1,2}. Resistance to methicillin is explained by the carriage of the *mecA* gene in a chromosomal region called the staphylococcal chromosomal cassette (SCCmec), which, like MRSA isolates associated with health care infections, codes for an alternative penicillin binding protein (PBP2a), without affinity for this compound. The size of SCCmec in CA-MRSA isolates is smaller compared to other homologous cassettes in non-CA MRSA and does not integrate resistance to other antimicrobial drugs or heavy metals. When resistance to other families of antimicrobials in CA-MRSA isolates is present, is explained by the carriage of plasmids that code for resistance to other compounds^{1,2}.

In Chile, MRSA-CA infections have progressively increased since their appearance in 2007 and represent an emerging problem³⁻⁵ and, as in the rest of the world, they are mostly associated with SSTI. Very few cases have been associated with bacteremia or pulmonary infections^{3,5}. It is thought that the CA-MRSA reservoir is the human being and that its acquisition occurs through direct contact in family, sports or military settings, with cases presenting as sporadic events or in outbreaks¹. The evidence accumulated in the last 2 decades indicates that the reservoir is sometimes shared with companion animals and that they participate in its transmission and possibly in reintroduction to human beings^{6,7}.

The purpose of this communication is to report the case of a pregnant woman with bacteremia by CA-MRSA and discuss its management and the study of relatives and animal environment.

Case report

During 2021, we attended a 37-year-old woman during her first pregnancy with a past history

of hypothyroidism. She presented with a picture of hyperemesis gravidarum requiring hospitalization on three occasions.

At the first hospitalization, at 13 weeks of gestation, the condition was managed conservatively, with iv hydration and antiemetic drugs. She evolved satisfactorily being discharged on the 5th day of hospitalization. She presented a symptomatic relapse requiring a second hospitalization at 15+5 weeks of gestation, evolving again in good conditions, and discharged with symptomatic treatment with prokinetics (metoclopramide) and proton pump inhibitors. In this second hospitalization, she presented phlebitis associated to a peripheral venous catheter (PVC) with a positive local culture for MRSA without other associated resistance. The condition regressed spontaneously when the line was removed and did not require treatment. Due to the persistence of gastrointestinal symptoms, she was hospitalized for third time at 17+4 weeks of gestation without the possibility of enteral feeding, so total parenteral feeding was started through a central venous catheter (CVC).

At 16 days, she presented high fever (39°C), tachycardia (110 bpm), without hemodynamic or fetal compromise. This event was accompanied by leukocytosis (13,000/ μ L), neutrophilia (11,960/ μ L), elevated C-reactive protein 14.81 mg/dL (reference < 0.5 mg/dL), urine analysis without inflammatory findings with a negative urine culture and a negative PCR test for SARS-CoV-2. Empirical management was started with ceftriaxone (1 g every 12 hours). At 10.7 hours positive peripheral blood cultures were reported for gram-positive bacteria which were later reported as MRSA (MIC < 4 μ g/mL) identified by MALDI-TOF and with the broth microdilution method (VITEK 2 COMPACT, [®]BioMérieux), with no associated resistance to other compounds (Table 1). A complementary study with the FilmArray[®] Blood Culture Identification 2 Panel (BCID2) detected the presence of the *mecA* gene in the isolate.

Patient was managed with CVC removal and change to vancomycin (MIC \leq 0.5 μ g/mL; 1.5 g loading dose and then 1 g every 12 h). The same isolate was identified in the CVC tip (uncountable colonies).

Given the persistence of positive blood cultures at 4 days for the same agent together with suboptimal pre-dose plasma levels of vancomycin

(4.5 µg/mL; desirable 15-20 µg/mL), a continuous infusion of vancomycin (3.5g in 24 h) was prescribed allowing adequate plasmatic levels (20.6 µg/mL). She evolved with persistence of positive blood cultures despite 8 days of vancomycin, so treatment was changed to daptomycin (initially not available; 500 mg every day IV; 6 mg/kg/day) associated to cefazolin (2 g every 8 h iv). Negative blood cultures were attained on the second day after change. The patient completed 14 days of combined treatment after negative cultures and was discharged. Infective endocarditis was ruled out by two transthoracic echocardiograms and absence of minor criteria. She delivered a healthy newborn at 39 weeks.

Family contacts included her husband and her mother as well as three household cats that sleep at the same room of the patient. It was decided to carry out a study of human contacts by means of a nasal sample and also of feline pets with nasal, oral and vaginal samples. We identified a MRSA in the mother of the patient but not in the cats (Table 1). The mother was treated with cotrimoxazole forte.

Studies of the strains isolated on the patient and her mother showed a similar antibiotype, presence of the *mecA* and the Panton Valentine Leukocidin *pvl* gene by PCR (Table 1). Also, a clonality study was carried out by pulsed field electrophoresis (PFGE) using the restriction enzyme *SmaI*, which allowed the identification of the same genetic subtype in both cases (CL-Sau-Com-Sma-003), thus establishing that the strains from the patient and her mother were genetically related (Table 1, Figure 1).

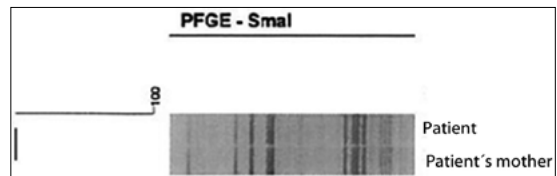


Figure 1. Pulse type obtained by *SmaI* PFGE on the isolates identified in patient and her mother.

Discussion

The MRSA bacteremia event in our patient had a nosocomial presentation, and linked to a CVC, but it was not associated with the multiresistance pattern of *S. aureus* infections observed in healthcare facilities. This microorganism was identified in her second hospitalization in a PVC-phlebitis and then in a bacteremia in her third hospitalization. CA-MRSA bacteremia is an infrequent presentation for this group of microorganisms^{1,8}. In obstetric series, CA-MRSA infections predominantly affect skin and soft tissues, including mastitis, especially with abscess formation, operative wound infection, pneumonia, and vaginitis^{9,10}. CA-MRSA infections can also be transmitted from mother to child by contact or breast milk with neonatal sepsis. In addition, they can present as outbreaks in obstetric wards for several months^{11,12}.

The treatment of MRSA bacteremia has traditionally been vancomycin. Daptomycin has not been more effective but it has been associated with a lower rate of nephrotoxicity compared to vancomycin¹³. The addition of a beta-lactam

Table 1. Microbiological characterization of bacterial isolates

Source	Antibiotype	PVL gene*	SCC**	Genotype/Pulse type by <i>SmaI</i> PFGE
Patient	Only resistance to beta-lactams Susceptible to macrolides, quinolones, cotrimoxazole, clindamycin, linezolid, glycopeptides and daptomycin	Positive	Not characterized	CL-Sau-Com-Sma-003***
Mother of patient	Same pattern	Positive	Not characterized	CL-Sau-Com-Sma-003

*PVL: Panton-Valentine Leukocidin factor; **SCC: Staphylococcal chromosomal cassette; ***: PFGE pattern is denominated after comparison with a Chilean (CL) database of *S. aureus* community typed isolates (Sau-Com) performed at the National Reference Laboratory.

as a synergistic molecule for MRSA isolates has not shown an advantage with respect to mortality, microbiological eradication or relapsing rate when compared to vancomycin monotherapy¹⁴. Despite being counterintuitive, the addition of a beta-lactam to vancomycin or daptomycin for MRSA infections, has been associated with *in vitro* synergy, better outcomes in animal studies and a lower rate of prolonged MRSA bacteremia in clinical trials^{14,15}. In our case, the persistence of bacteremia despite vancomycin therapy at adequate levels and low MIC values, made necessary to change the treatment to daptomycin plus ceftazolin. A rapid eradication of the agent with no nephrotoxicity or relapse was demonstrated. Vancomycin failure is in line with its slower bacterial killing rate (compared to beta-lactams) and tolerance to this compound among *S. aureus* isolates. Linezolid, a bacteriostatic compound, is another alternative when endocarditis has been ruled out. Cotrimoxazole was also not used for fetal safety reasons and ceftarolin, a cephalosporin with MRSA activity, was not locally available¹⁶. The combined use of daptomycin with ceftarolin significantly improved survival compared to vancomycin in a small randomized study of patients with MRSA bacteremia¹⁷. Daptomycin is a molecule with no safety restrictions in pregnancy¹⁸.

We could not confirm a CA-MRSA reservoir among pets, although several reports indicate their participation as carriers of this agent or infections in animals^{6,7}. This could explain the re-introduction of already treated human beings and the persistence of skin infections. CA-MRSA carriage has been described with variable frequencies in companion animals (up to 50%) and also in pigs (17%), especially under industrial farming systems and under antibiotic pressure¹⁹⁻²¹. There are no established criteria for when to screen family contacts or pets associated with a clinical case. In military scenarios, the risk of skin infection is 10 times higher when carrying CA-MRSA versus methicillin-susceptible *S. aureus* isolates. Treatment of family members who are carriers has been applied in the few published cases in our country^{3,4}. Due to reports of mupirocin resistance¹ and the fact that colonization occurs at multiple sites in both humans and pets, it is preferable to attempt eradication with systemic compounds in addition to general hygiene measures.

Studies in Chile have predominantly iden-

tified strains belonging to the ST8/USA 300 genotype/pulse-type with variable detection of the *pvl* gene (29.4% of strains studied in the reference laboratory in Chile)³⁻⁵. Besides, the CL-Sau-Com-Sma-003 subtype identified in our patient, belongs to the ST8 pulse type and is the most frequent PGFE type in Chile (25.4%)⁵. The antibiotic resistance pattern, the similar PFGE profile with known national reference patterns, the similitude with international described patterns, and the harboring of the *pvl* gene, strongly suggests that the strains isolated in our patients belong to CA-SAMR clones even if the SCC was not characterized.

This case indicates that CA-MRSA infections can affect pregnant women with bacteremia and that can be difficult to manage, requiring unconventional treatments. In addition, they may have an associated human reservoir and the antibiotic remains an important element of initial suspicion.

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