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Association between the methicillin resistance profile in *taphylococcus aureus* and the spectral signature by FTIR

Abstract

The objective of this work was to determine whether the Fourier Transform Infrared (FTIR) spectroscopy technique is optimal for the detection of methicillin-resistant *Staphylococcus aureus* (MRSA) strains. For this study, 29 strains of *S. aureus* isolated from skin and soft tissues were collected from patients at the "Santos Aníbal Dominicci" hospital, Carúpano, Sucre state. To determine methicillin resistance, several methods were used, such as antimicrobial susceptibility testing, minimum inhibitory concentration (MIC), and PCR for the *mecA* gene, tests known for their effectiveness, and strain analysis by FTIR was incorporated. Of 29 strains, 17 (59%) were MRSA, correlating this with the presence of the *mecA* gene, only two discrepancies were observed, which were a methicillin-resistant strain with absence of the *mecA* gene and a methicillin-sensitive *Staphylococcus aureus* (MSSA) strain with presence of the *mecA* gene. In turn, of these 29 strains, 21% were resistant to erythromycin and clindamycin, respectively. All strains remained sensitive to glycopeptides. The IR (infrared) spectra of methicillin-sensitive and -resistant strains were examined, specifically in the 1480–1450 cm^{-1} and 1380–1280 cm^{-1} regions, which constitute a window of lipids and proteins where the CH_2/CH_3 functional group is present, with higher values being evident for MRSA strains. This is consistent with the increased content of lipids and/or membrane proteins driven by the expression of the SCC*mec* cassette genes.

Keywords: Methicillin, oxacillin, resistance, Carúpano, antibiotic resistance, *Staphylococcus aureus*

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Introduction

Infections caused by resistant microorganisms are a challenge for the doctor, since the spectrum of antibiotic therapies is becoming smaller and smaller.[1] The laboratory's time to issue a result, not only of identification but also of susceptibility profile, is imperative for the survival of the patient and the avoidance of complications in skin and soft tissue infections.[2] These wait times have been measured and shown to cause 43% of delayed treatment and 61% of prolonged hospital stay, increasing hospitalization costs.[3] Nowadays, it is common for skin and soft tissue infections to be caused by bacteria with resistance to antibiotics. This is a public health problem, which threatens the achievement of the Sustainable Development Goals, especially in low- and middle-income countries.[4] In the search to reduce the impact of turnaround time, the efficiency of species identification of *Staphylococcus aureus* strains, the detection of conventional methicillin resistance mechanisms and their detection by FTIR were compared.

Material and methods

Strains studied and identification

Strains were taken from the IIBCAUDO Bacterial Resistance Laboratory strain collection, in Cumaná, Sucre state, Venezuela. 29 strains of *Staphylococcus aureus* were studied, coming from the "Santos Aníbal Dominicci" Hospital, Carúpano, Sucre state during a period of five months (January to June 2014), from an outbreak of skin and soft tissue infections coming from various services.

The strains stored at -20°C in vials with BHI (Brain heart infusion) broth plus 20% glycerol, were reactivated by plating it on BHI agar plates, incubating at 35°C, in an aerobic environment, for 18 hours. The viability and purity of the strains were subsequently verified, and the biochemical identification was confirmed using the API STAPH gallery (BioMérieux, France), following the manufacturer's instructions,[5] including colony morphology, and Gram staining smears light microscopy.

Antimicrobial susceptibility testing

We used Kirby–Bauer disk (BD BBL; Rosco; Mast) diffusion method on Mueller–Hinton agar (BD BBL; Rosco; Mast) plates for manual AST.[6] AST was done with these antibiotics: cefoxitin (FOX) (30µg), ampicillin (AMP) (10µg), amoxicilin-clavulanic acid (AMC) (20/10µg), eritromycin (E) (15µg), clindamycin (CD) (2µg), vancomycin (VA) (30µg) and teicoplanin (TEC) (30µg). All results were interpreted according to criteria of M100-S29.[7] The methicillin resistance phenotype was detected with the cefoxitin disk. The strains were classified as resistant with inhibition zones ≤21mm, which indicates the presence of the *mecA* gene and therefore resistance to all ß-lactams, and sensitive when the inhibition zone was ≥22mm.[7] Strain resistance to >2 drugs were considered to be multi-drug resistance.[8]

Minimum inhibitory concentrations (MIC) of oxacillin

The agar dilution method, was performed to measure the MIC of oxacillin. The concentrations used to determine the MIC for oxacillin were 0.5; 1; 2; 4; 8; 16; 32; 64; 128 and 256µg/mL. The bacterial inoculum at 0.5McFarland was diluted 1:10 to adjust the inoculum to 10^7 CFU/ml (1.0 x 10^4 CFU). The strains were classified as oxacillin resistant when MIC was ≥4µg/mL, and sensitive when the MIC was ≤2µg/mL.[7]

Quality control

For the quality control of the antimicrobial susceptibility tests, the certified strains *S. aureus* ATCC 29213 and *S. aureus* ATCC 25923 were used, and for the quality control of the PCR the strains *S. aureus* 77906 (MRSA-hetero- resistant), 77907 (MRSA-Hospital) and 77908 (MRSA-Community) and *S. aureus* ATCC 25923.

PCR (Polymerase chain reaction) protocol for the *mecA* gene

DNA extraction was carried out from pure cultures on BHI agar, incubated at 37°C for 18hours, in an aerobic atmosphere. Colonies were placed in 100µl of digestion buffer (10mM tris-HCl [pH 8.0], 0.45% triton minutes, frozen at -20°C and then thawed and centrifuged. The supernatant containing the DNA was immediately used for PCR.[9] The gene encoding methicillin resistance (*mecA*) was amplified using a pair of oligonucleotides (MECA P4: TCCAGATTACAACTTCACCAGG and MECA P7: CCACTTCATATCTTGTAACG), to amplify a 162base pair (bp) product, following the previous amplification protocol published.[10]

Characterization of methicillin resistance by Fourier transform infrared spectrometry

Oxacillin-susceptible and resistant strains were passed by FTIR. All the samples were dried in a muffle at 110°C, then they were mixed with potassium bromide (KBr), each one, subsequently crushed and pressed in order to obtain a translucent tablet through which the light beam passed. Then, they were analyzed in PERKIN ELMER brand FTIR, model 1000PC, previously calibrated with a resolution of 2cm^{-1} in a range of 450 to 4500cm^{-1}. Based on the spectra of each sample, the total and corrected areas in absorbance mode were determined. Once these areas were obtained, the spectra were analyzed, with the spectrum of strains sensitive to methicillin with strains resistant to different levels to locate the functional groups.[11]

The spectral characteristics of microbial IR compared to IR spectra of building blocks inherent to intact cells are described below.[12] The –CH3, >CH2 and CH functional groups of fatty acid aliphatic chains are on the spectral region of 3000–2800cm^{-1}. The protein and peptide components such as amides I and II are on the spectral region of 1800–1500cm^{-1}. The phospholipids, polysaccharides, free amino acids, proteins, phosphate and nucleic acids are on the spectral region of 1500–1200cm^{-1}. The cell-wall carbohydrates are on the spectral region of 1200– 900 cm^{-1}. Some microbial components not identified are on the spectral region of 900–700cm^{-1}.

Statistical analysis

The unpaired t-test and Cohen's d-test were performed using IBM SPSS statistic v26 2019 software for Windows. The results obtained in the present investigation were expressed in tables, percentages and figures.

Results

In April 2019, 29 strains of *S. aureus* from skin and soft tissue secretions, isolated in the Bacteriology Laboratory of the "Santos Aníbal Dominicci" Hospital in Carúpano, Sucre state, in Venezuela, were studied during a period of six months (January to June 2014), of which 17 strains (59%) were MRSA, various services (Table 1).

Table 1 Origin of the *S. aureus* strains obtained during the months of January to June 2014 in the Bacteriology Laboratory of the "Santos Aníbal Dominicci" Hospital in Carúpano, Sucre state, in Venezuela

Service	Number	(%)
Emergency	10	35
Surgery	8	28
Pediatrics	7	24
Maternity	2	7
External consultation	1	3
Traumatology	1	3

Regarding the antibiotype, it can be seen (Table 2) that 17 *S. aureus* strains (59%) were resistant to methicillin. This was successful to determine the possible clonal dissemination in the different hospital services. As you can see, MRSA strains predominate in this hospital.

Table 2 Antibiotypes of *S. aureus* strains isolated in the Bacteriology Laboratory of the "Santos Aníbal Dominicci" hospital in Carúpano, Sucre state, in Venezuela

# Strains	FOX	E	CD	VA	TEC
10	R	S	S	S	S
9	S	S	S	S	S
7	R	R	S	S	S
1	S	R	S	S	S
1	S	I	I	S	S
1	S	S	I	S	S

Fox, Cefoxitin; E, Eritromycin; CD, Clindamycin; VA, Vancomicin; TEC, Teicoplanin; R, resistant; I, intermediate; S, susceptible.

In this work it was demonstrated that there is a direct relationship between the methicillin-resistant phenotype observed in *S. aureus*, with qualitative detection and quantitative detection through the MIC to oxacillin (Table 3). It was observed that LRB6B5, LRB6B6, LRB6B7, LRB6H1 and LRB9D4 were heteroresistant strains.

In this study, a relationship between the phenotype, genotype and MIC was evidenced by PCR (Table 3), except for the LRB6B6 strain, which was observed as methicillin-resistant in the antimicrobial susceptibility testing and in the PCR there was no amplification for the *mecA* gene. A phenotypic test for beta-lactamase production was performed on this strain and it was positive. Furthermore, the LRB9A10 strain was susceptible (MIC 1µg/mL) in the antimicrobial susceptibility testing but presented amplification for the *mecA* gene.

Table 3 Phenotype, genotype and MIC in *S. aureus* strains isolated in the Bacteriology Laboratory of the "Santos Aníbal Dominicci" Hospital in Carúpano, Sucre state, in Venezuela, during the months of January to June 2014

Strains	OXACILLIN	MIC (µg/mL)	*mecA* gene
LRB6B5	Resistant	16	Positive
LRB6B6	**Resistant**	**8**	**Negative**
LRB6B7	Resistant	32	Positive
LRB6C1	Resistant	16	Positive
LRB6C3	Susceptible	≤ 0,5	Negative
LRB6C7	Susceptible	1	Negative
LRB6C8	Resistant	16	Positive
LRB6H1	Resistant	128	Positive
LRB6H4	Susceptible	1	Negative
LRB6H9	Susceptible	≤ 0,5	Negative
LRB6I2	Susceptible	1	Negative
LRB7I2	Susceptible	1	Negative

Table 3 Continued.....

LRB7I4	Susceptible	I	Negative
LRB7I5	Resistant	16	Positive
LRB7I6	Resistant	32	Positive
LRB7I7	Resistant	32	Positive
LRB7I8	Resistant	32	Positive
LRB7J1	Resistant	64	Positive
LRB7J4	Resistant	16	Positive
LRB7J8	Resistant	32	Positive
LRB8A3	Resistant	128	Positive
LRB8J10	Susceptible	I	Negative
LRB9A9	Susceptible	I	Negative
LRB9A10	**Susceptible**	**I**	**Positive**
LRB9B1	Resistant	64	Positive
LRB9D1	Resistant	128	Positive
LRB9D2	Susceptible	≤ 0,5	Negative
LRB9D4	Resistant	32	Positive
LRB9D7	Susceptible	I	Negative

In this study, oxacillin-susceptible strains such as LRB6C3 (MIC: <0.5µg/ml), and LRB1A3, and LRB9A10 (MIC: 1µg/ml), and resistant strains such as LRB6H1, LRB8A3, LRB9D1 (MIC: 128µg/ml). All superimposed spectra indicate that the same species is present (Figures 1&2).

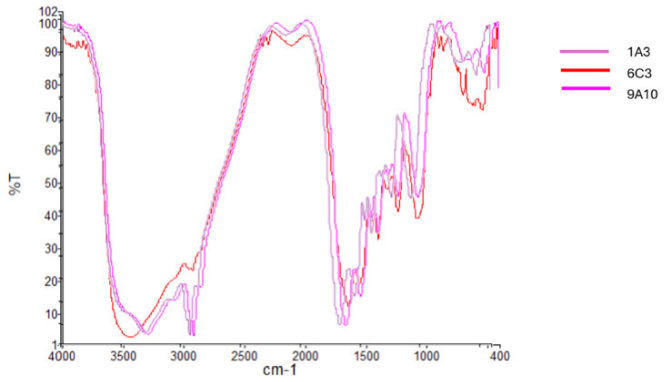

Figure 1 Spectra of *S. aureus* methicillin susceptible strains (LRB1A3, LRB6C3, and LRB9A10).

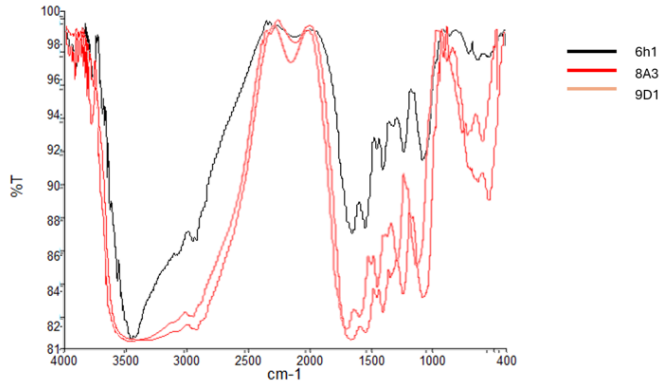

Figure 2 Spectra of *S. aureus* methicillin resistant strains (LRB6H1, LRB8A3, and LRB9D1).

Analyzing the graphs of the sensitive strains, it was observed (data not shown) that *S. aureus* LRB1A3 strain, compared to the other two, has all its characteristic functional groups: the primary alcohol CH2-OH, OH tension, amide A (N-H stretching), asymmetric stretching CH3 asymmetric, amide I (carbonyl group, C=O), amide II (N-H band), $(CH3)_3N+$ of the symmetric band, amide III (C-H stretching), and an amine (N-H bending), all determined at a characteristic wave number (cm^{-1}). The *S. aureus* LRB6C3 strain lacks the functional group CH2-OH in addition to the amide A group (N-H stretching).

Likewise, MRSA strains with different MICs for oxacillin (16, 32, 64 and 128µg/ml) were studied. The IR spectrum that was compared to the others was that of the strain with the highest MIC (LRB8A3). The MRSA LRB8A3 strain, compared to LRB9D1, and LRB6H1 (data not shown), has all its characteristic functional groups: the primary alcohol CH_2-OH, OH tension, amide A (N-H stretching), asymmetric stretching CH3 asymmetric, amide I (carbonyl group, C=O), amide II (N-H band), $(CH_3)_3N+$ of the symmetric band, amide III (C-H stretching) and an amine (N-H bending), all determined to a characteristic wave number (cm^{-1}). MRSA strains LRB6H1, and LRB9D1 are missing the amide A functional group and reduced CH_3 asymmetric stretching is observed compared to MRSA strain LRB8A3.

According to the literature, the region between 1480–1450 cm^{-1} is a window of lipids and proteins where the CH_2/CH_3 functional group is present and for that reason, that region was taken to analyze the methicillin-sensitive and resistant strains; the percentage of T was made linear, converting it into absorbance values and the ± SD was obtained. For MSSA strains the value was 0.138 ± 0.009, while for MRSA strains, the value was 0.157 ± 0.012. The unpaired t-test on the integrated area 1480–1450 cm^{-1} was $p = 0.032$, and Cohen's $d = 1.4$, large effect size.

Even with only few isolates, the CH_2 bending vibration at ≈1453 cm^{-1} is significantly higher in MRSA than in MSSA (Figure 3). This is consistent with increased lipid and/or membrane protein content driven by the SCC*mec* cassette. The difference is encouraging, but validation with ≥30 isolates per group is still required before any clinical claim.

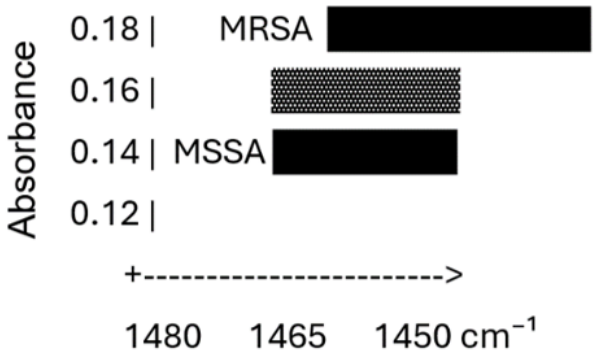

Figure 3 Absorbance of methicillin-sensitive and -resistant strains in the region 1480–1450 cm^{-1}.

The 1380–1300cm^{-1} region is dominated by symmetric CH_3 deformation of aliphatic chains (lipids) and amide III contributions from proteins, while 1300–1280cm^{-1} contains vibrations from PO_2^- symmetric stretch of nucleic acids and phospholipids. The interest in looking at this area comes because those vibrations are sensitive to changes in membrane lipid composition and cell-wall turnover, both of which are altered in MRSA because of the large SCC*mec* cassette and increased peptidoglycan cross-linking.

For MSSA strains the value was 0.152 ± 0.007 (1355 cm^{-1}) and 0.114 ± 0.006 (1295 cm^{-1}), while for MRSA strains, the value was 0.169 ± 0.010 (1355 cm^{-1}) and 0.129 ± 0.009 (1295 cm^{-1}). The unpaired t-test on the integrated area 1480–1450 cm^{-1} was p = 0.018, and Cohen's d = 1.6, large effect (Figure 4).

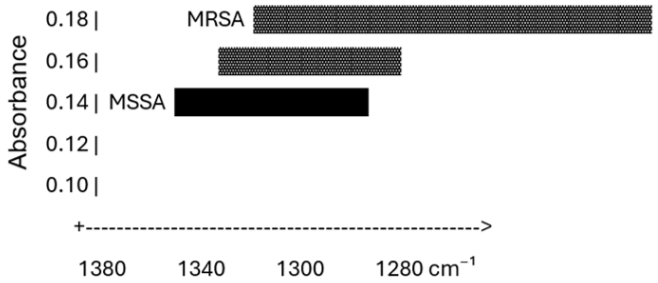

Figure 4 Absorbance of methicillin-sensitive and -resistant strains in the region 1380–1280 cm^{-1}

That means, that 1380–1280cm^{-1} region is statistically significant, medium-to-large separation between MRSA and MSSA even in this small set. The higher absorbance in MRSA is consistent with additional lipid and nucleic-acid content driven by SCC*mec* genes. As you can see, the CH_3 bending (~1375cm^{-1}), amide III (~1320cm^{-1}) and PO_2^- symmetric stretch (~1295cm^{-1}) vibrations are all stronger in MRSA (Figure 4).

An overlay of the absorbances of a sensitive strain with a resistant one was made to show the high concentration expected by the increase in lipid, protein and nucleic-acid content driven by the methicillin resistance, that is due in the area to deformation vibrations of C-H bonds in methylene (CH_2) groups of lipids and proteins (1480–1460 cm^{-1}) (Figure 5), and attributable to symmetric stretching vibrations of carboxyl groups of amino acid side chains or free fatty acids (1352–1315cm^{-1}) (Figure 6).

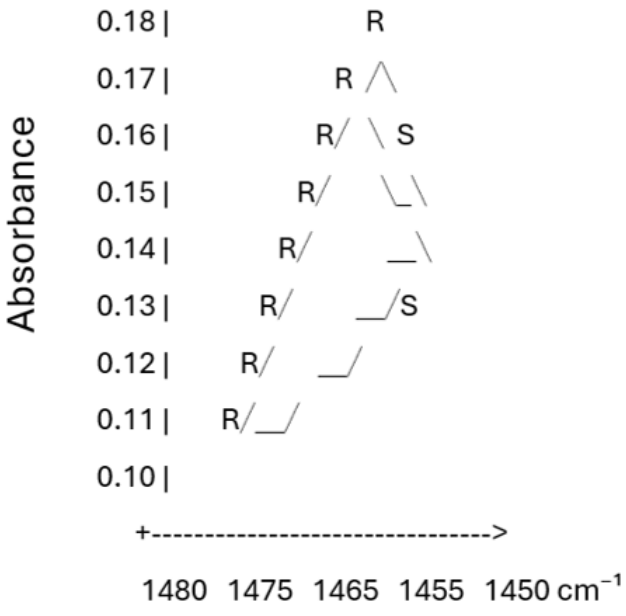

Figure 5 A simple ASCII-style overlay for one MSSA (Strain LRB1A3) and one MRSA (Strain LRB6C8) isolate in the 1480–1450 cm^{-1} window, plotted from the absorbance after baseline correction. The resistant strain line is marked with "R" symbols, the sensitive strain with "S".

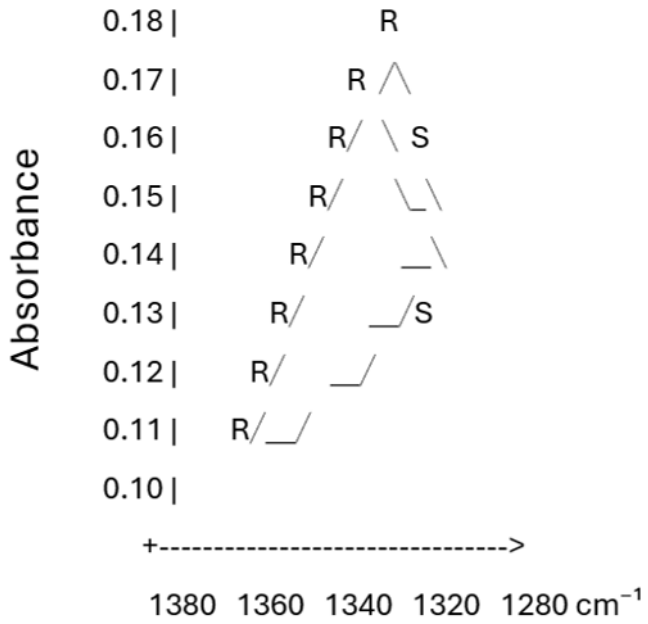

Figure 6 A simple ASCII-style overlay for one MSSA (Strain LRB1A3) and one MRSA (Strain LRB6C8) isolate in the 1380–1280 cm^{-1} window, plotted from the absorbance after baseline correction. The resistant strain line is marked with "R" symbols, the sensitive strain with "S".

Discussion

Given the impact of clinical and therapeutic complications associated with the presence of MRSA strains, this study sought a rapid and cost-effective option for laboratory detection of MRSA strains. In the United States of America, the main pathogen of skin-and-soft-tissue infections (SSTIs) is *Staphylococcus aureus*. Treating these infections is complicated when the bacteria are resistant to methicillin. This increases costs and hospital stays. methicillin-resistant *S. aureus* (MRSA), must be treated with vancomycin, with the imminent risk of developing a *Clostridioides difficile* infection.[13] Around 64% of people having MRSA infections are more likely to die than people with MSSA strains.[14] One of the therapeutic options associated with reducing the impact of the virulence of MRSA strains is to combine macrolides and make the immune system more effective.[15]

In a Shanghai hospital, 46.9% of the isolated MRSA strains came from internal medicine, and 21.9% from ICU,[16] which differs from this study, since 35% of the strains came from emergency and 28% from surgery. 38% of MRSA strains isolated from 30 hospitals in Orange County, California, came from the ICU and 32% from the emergency room.[17] As can be seen, there is a strong presence of this pathogen in hospitals.

Detecting methicillin resistance is important because some strains exhibit heterogeneous phenotypic expression, while others are homogeneous. The former can go undetected and lead to therapeutic failures. One of the most accurate methods is PCR of the *mecA* gene; however, it is expensive, laborious, and time-consuming. Other genes, such as the Panton-Valentine Leukocidin toxin (PVL), are used to monitor the epidemiology of methicillin resistance. In many cases, laboratory results cannot be awaited before antibiotic therapy can be initiated, so it is important to implement highly effective treatments to reduce the likelihood of death in these patients.[18]

There are strains carrying the *mecA* gene that have very low MIC values (<2µg/ml). If detection is performed only by antimicrobial susceptibility testing, staff may report the strain as susceptible, when in fact it is not. These strains are called OS-MRSA (oxacillin-susceptible MRSA).[19] In this study conducted in Carúpano, a strain with these characteristics was found (LRB9A10).

In a study carried out in Spain, the same case was observed in two strains of *S. aureus*, where they presented MICs of 0.5 to 1µg/ml, respectively, when they were actually *mecA* positive,[20] a case that agrees and can be evidenced with the results obtained in the present study. The combination of genotypic and phenotypic testing is necessary to avoid false-positive or false-negative results in the identification of MRSA. All OS-MRSA isolates had an oxacillin MIC <2µg/ml, indicating that the presence of the *mecA* gene does not confer high-level resistance to oxacillin.[21]

OS-MRSA carrying *mecA* can lead to the emergence of highly resistant MRSA under treatment with β-lactam antibiotics, underscoring the need for precautions when treating OS-MRSA infections. Because of this risk, treatment of OS-MRSA should avoid β-lactam antibiotics.[22] The reason for this phenotype remains to be elucidated. A recent study suggested that amino acid mutations in FemXAB proteins (involved in cell wall synthesis) might contribute to the MSSA phenotype, but the association of the mutations with the phenotype has not been previously tested.[21]

These types of strains pose a danger, as it has already been shown that, under selective pressure, they are capable of achieving high levels of resistance, as occurred in Africa, where strains with a heteroresistant phenotype, treated with mupirocin, expressed PBP2A.[23]

Strains with false negatives for methicillin resistance may be the result of overproduction of penicillinase or overexpression or alterations of constitutive PBPs, since it has been shown that penicillins stable to penicillins can be altered when these enzymes are present.[24] In addition to this, according to a previous study,[25] these are strains that are associated with MICs between 8 and 16 µg/ml, a case that agrees with the results expressed in said table. The strain LRB6B6 had a MIC of 8 µg/ml and was *mecA* negative in this study. Beta-lactams remain the first choice for the treatment of staphylococcal infections,[26] which is why it is essential to make a good diagnosis, and we must not forget that MRSA is the leading cause of morbidity and mortality worldwide.[27]

If we are looking for a revolutionary tool to obtain great results in the laboratory, we have to use FTIR, which is an emerging technique for analyzing spectra in microbial domains.[28] The principle of the technique is simple, the molecules of microorganisms absorb infrared light at specific vibrational frequencies, which recognizes chemical bonds of the compounds (C-H, O-H, and N-H bonds), giving a characteristic fingerprint for each molecule.[29] Thus, not only rapid but also precise identification of the microorganism can be achieved.[30]

This technique is very good for providing timely diagnoses, and is even being used to detect antibiotic resistance mechanisms, since it detects microbial structures, metabolic activities and environmental changes.[31-33]

In a study to reveal the interaction between blue light (470nm) and MRSA with FTIR, functional groups corresponding to proteins were found at vibrations 1683, 1656, 1596, 1542cm^{-1}, as well as lipids at vibrations 1743, 1409cm^{-1}, nucleic acids 1060, 1087cm^{-1}.[34] In this study, such vibrations were also found in the MRSA strains analyzed here (data not shown).

In the past, FTIR technique was used to detect capsular serotypes,[35] *Staphylococcus aureus* small-colony variants strains,[36] to track outbreaks caused by *S. aureus*,[37] and to identify MRSA strains.[38] Detecting MRSA strains with FTIR is not difficult, as it is a technique that works very well to determine the surface molecules of bacteria.[39]

In this study, we were unable to perform HCA (Hierarchical Cluster Analysis) or PCA (Principal Component Analysis) analysis due to the small number of strains we tested for FTIR. Both analyses, give a spectrum to identify the degrees of antibiotic resistance. However, analyzing the absorbance data from the MSSA and MRSA samples, read using FTIR, revealed statistically significant differences between those strains. In the MRSA strains, there is clear evidence of vibrational changes in the cell wall composition.

Using FTIR, structural changes were demonstrated in MRSA strains in the patterns of proteins, lipids, and carbohydrates (peptidoglycans) compared to MSSA strains. These changes were primarily evident in the membranes and their fluidity, with an increase in saturated fatty acids and a reduction in unsaturated fatty acids. This led to a thickening of the membrane wall, which generates resistance to wall-acting antibiotics.[38]

The use of this technique, which was new to us, did yield satisfactory results, which motivates us to continue using it and expand the number of samples of clinically and environmentally isolated bacteria for rapid diagnosis and to conduct studies not only of identification but also of the dissemination of resistance mechanisms in different environments.

Conclusion

The FTIR technique was not difficult to differentiate between susceptible and resistant strains, whereas with traditional methods, two strains were classified as methicillin-susceptible when they actually carried the *mecA* gene (LRB9A10) and methicillin-resistant when they lacked the *mecA* gene (LRB6B6); this misidentification was not observed with FTIR. The IR spectra of methicillin-sensitive and -resistant strains were examined, specifically in the 1480–1450cm^{-1} and 1380–1280cm^{-1} regions, which constitute a window of lipids and proteins where the CH_2/CH_3 functional group is present, with higher values being evident for MRSA strains. This is consistent with the increased content of lipids and/or membrane proteins driven by the expression of the SCC*mec* cassette genes. The FTIR technique allowed us to differentiate between methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* strains. We believe the FTIR should have software designed to determine the functional groups of each resistance mechanism so that it can be widely adapted in healthcare centers; for now, it remains an excellent research tool.

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Conflicts of interest

The authors of the work declare that they have no conflict of interest.

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