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Research Article

Detection of Methicillin-resistant *Staphylococcus aureus* (MRSA) resistant to vancomycin and linezolid in bulk tank milk by E-test method

Bahar Onaran Acar[1], Erhan Keyvan[2]

[1]Department of Food Hygiene and Technology, Faculty of Veterinary Medicine, Ankara University,Ankara, Türkiye
[2]Department of Food Hygiene and Technology, Faculty of Veterinary Medicine, Burdur Mehmet Akif Ersoy University, Burdur, Türkiye

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Correspondence:
B. ONARAN ACAR
(bonaran@ankara.edu.tr)

ORCID
B. ONARAN ACAR : 0000-0002-3515-7548
E. KEYVAN : 0000-0002-2981-437X

ABSTRACT

Staphylococcus aureus is considered a serious threat to public health, besides is one of the most common causes of subclinical mastitis in dairy cows. Therefore, especially methicillin-resistant *Staphylococcus aureus* (MRSA) is among the most critical reasons for antibiotic treatment. Monitoring the antibiotic resistance of MRSA from livestock animals and foods is of great significance. This study aimed to detect vancomycin, teicoplanin, and linezolid resistance of bulk tank milk-borne 34 MRSA isolates by the E-test method to determine MIC values. In the study, it was determined that 8.8% of MRSA isolates were also resistant to vancomycin, and 11.7% to linezolid, while none of the isolates were determined to be resistant to teicoplanin. Data from the study reveal the status of the efficacy of the commonly used antibiotics vancomycin and linezolid against MRSA infections. Especially before MRSA treatment, MIC values of antibiotics should be determined, and appropriate antibiotics should be used in effective doses.

INTRODUCTION

Staphylococcus aureus is a ubiquitous, opportunistic, and commensal pathogen that may result in both community-acquired or nosocomial infections (Kadariya et al., 2014). On the other hand, *S. aureus* is one of the most common causes of subclinical mastitis in dairy cows and, therefore one of the most common causes of antibiotic treatment (Bouzidi et al., 2023). Nonetheless, methicillin-resistant *Staphylococcus aureus* (MRSA) is considered a critical threat, with 10,600 deaths and 323,700 cases per year, according to Antibiotic Resistance Threats 2019 report in the US (Centers for Disease Control and Prevention, 2019). Therefore, the treatment of staphylococcal infections is of great importance in terms of public health.

MRSA is often analyzed from food and livestock samples (Aires-de-Sousa et al., 2017; Sergelidis and Angelidis, 2017). Besides their resistance to almost all beta-lactam antibiotics, resistance to vancomycin and linezolid, which are considered last resort antibiotics and therefore critical, has become a significant concern for human and animal health for reducing treatment choices of severe infections caused by MRSA (Onaran et al., 2019; Mamfe et al., 2021).

Over the years, the common use of vancomycin in healthcare institutions has led to the emergence of glycopeptide-resistant strains of *S. aureus*. Vancomycin-resistant *S. aureus* (VRSA) cases are increasing daily; this situation is considered an important threat to public health. Following the first report from Japan in 1997, VRSA has been reported in various countries (Adegoke et al., 2014). However, most of these reports are related to hospitalized human patients with pre-existing MRSA infections (Lienen et al., 2022).

Linezolid-resistant *S. aureus* (LRSA) strains in humans, livestock, and food have been reported in studies; however, the prevalence of resistance was generally lower compared to other antibiotics (Timmermans et al., 2021). In one health context, the handling of livestock or food has been indicated as a risk factor for livestock-associated MRSA infections in animals (George et al., 2017). Therefore, it should be taken into account that the ingestion of LRSA from livestock animals can lead to antibiotic-resistant infections in people related to the food or livestock industry. In conclusion, monitoring antibiotic resistance in MRSA from livestock and food is highly significant (Lienen et al., 2022).

The E-test method is a suitable option because it is an easy-to-apply and quick-result analysis used to determine whether an isolate is antibiotic-resistant by detecting the Minimal Inhibition Concentration (MIC) value of the determined antibiotic. The results are also easy to interpret. For the reasons mentioned above, it has been suggested to use the E-test method as a routine test to determine the MIC values of antibiotics (Tandel et al., 2012; Phillips et al., 2016). For this reason, this study aimed to detect vancomycin, teicoplanin, and linezolid resistance of milk-borne MRSA isolates with subclinical mastitis by the E-test method.

MATERIAL AND METHODS

Bacterial isolates

The current study used 34 MRSA isolates that were previously isolated in a study conducted by Keyvan et al. (2020).

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Briefly, bulk tank milk samples were subjected to plating on a medium known as rabbit plasma fibrinogen agar (BP-RPF, Oxoid, Italy) and subsequently incubated at a temperature of 37°C for a duration of 24-48 hours. The isolates verified by PCR analysis with primer pairs of species-specific *nuc*, *coa,* and *mecA* genes were used.

Minimal Inhibition Concentration values

The resistance profiles of these isolates against vancomycin, teicoplanin, and linezolid antibiotics were investigated using the E-test method to determine MIC values. Using the swab technique, bacterial suspensions of a 0.5 McFarland standard inoculum in BHI (Brain Heart Infusion) broth (Merck 110493, Darmstadt, Germany) were spread on Mueller Hinton Agar (Oxoid CM0337, Dublin, Ireland) plates. Vancomycin and teicoplanin MIC values of the isolates were determined using Himedia EM111-60ST (Maharashtra, India), and linezolid MIC values were determined using Himedia EM029-60ST (Maharashtra, India) E-test strips. E-test strips were placed onto the agar plates and incubated at 35°C for 24-48 h. After incubation, isolates were categorized as susceptible, intermediate, or resistant to related antibiotics considering the breakpoints stated by the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2023).

According to EUCAST breakpoint tables for interpretation of MICs and zone diameters version 13.0, 2023, for *S. aureus*, breakpoints for teicoplanin and vancomycin is 2 µg/ml and the linezolid breakpoint is 4 µg/ml. In other words, isolates with vancomycin and teicoplanin MIC values above 2 µg/ml were evaluated as vancomycin and teicoplanin-resistant isolates, and linezolid MIC values above 4 µg/ml were evaluated as linezolid-resistant *S. aureus* isolates (European Committee on Antimicrobial Susceptibility Testing, 2023).

On the other hand, according to CLSI (2023), breakpoint table M100, 33 rd. edition, isolates with vancomycin MIC values of 4-8 µg/ml were considered intermediate, and those with 16 µg/ml and above were considered resistant; teicoplanin MIC values of 32 µg/ml and above were considered resistant, and those with 16 µg/ml were considered intermediate; linezolid MIC values of 8 µg/ml and above were considered resistant (Clinical and Laboratory Standards Institute, 2020).

RESULTS

The vancomycin, teicoplanin, and linezolid MIC values of the isolates are given in Table 1.

According to EUCAST MIC values, three of the MRSA isolates were determined as vancomycin-resistant and four as linezolid-resistant, but none of the isolates were determined as teicoplanin resistant. In addition, one of the isolates was found resistant to both vancomycin and linezolid. By the MIC values reported by CLSI, one of the isolates was intermediate resistant to vancomycin, and two isolates were resistant to linezolid, while none of the isolates were analyzed to be resistant to teicoplanin. The numbers of isolates defined as vancomycin, teicoplanin, and linezolid resistant, intermediate, and susceptible according to EUCAST and CLSI are given in Table 2.

DISCUSSION

Antibiotic resistance has increased among various pathogens and the risk of transmission of resistant microorganisms to humans, as well as the ineffectiveness of current antibiotic therapy, has become a critical public health concern (Campos et al., 2022). In the livestock industry, subclinical mastitis causes problems related to the use of antibiotics and hence economic losses not only in Turkey but also worldwide (Vanderhaeghen et al., 2010). Although herd management programs can help reduce the number of clinical cases, *S. aureus*-related mastitis is one of the leading causes of bovine mastitis. Moreover, MRSA, which causes nosocomial infections and high mortality in humans, has been frequently isolated from subclinical mastitis cases in recent years (Bouzidi et al., 2023; Algammal et al., 2020).

Food can also be contaminated with MRSA at various stages of food processing from food-producing animals or by infected food industry workers (Al-Amery et al., 2019) such as the incidence of subclinical mastitis in dairy farming, mistreatment of animals, and poor sanitation conditions. Treatment failure is due to the ineffective use of antibiotics, the emergence of multidrug-resistant pathogens, and chronic infections with fibrosis (Seegers and Fourichon, 2003; Keyvan, 2023).

The study determined that 8.8% of MRSA isolates isolated from milk with subclinical mastitis were also resistant to vancomycin and 11.7% to linezolid, according to EUCAST. Data from the study reveal the status of the efficacy of the commonly used antibiotics vancomycin and linezolid against MRSA infections.

Vancomycin is widely used for the treatment of serious MRSA infections. To date, intermediate or resistant to vancomycin (MIC>2 µg/ml) animal-origin MRSA isolates are rarely encountered (Al-Amery et al., 2019). However, MRSA isolates with vancomycin MICs at the upper end of the sensitive range (MIC=1.5 to 2.0 µg/ml), which constitute the majority (82.3%) of our isolates, are also more common, especially in patients who received prior treatment with vancomycin. Vancomycin MICs of 1.5 and 2.0 µg/ml are associated with the ineffectiveness of vancomycin treatment (Maor et al., 2009; Soriano et al., 2008). It should be noted that contamination of the environment with VRSA in human health facilities leads to further colonization of food-producing animals (Charlton et al., 2014). The study conducted by Ozturk et al. (2019) demonstrated that *S. aureus* strains isolated from goat milk in a similar region of Turkey showed sensitivity to vancomycin.

The isolates with vancomycin MIC values of ≤2 µg/ml used in the study were reported susceptible according to EUCAST and CLSI breakpoints. However, for some MIC values, there is a discrepancy between the relevant guidelines regarding the identification of resistant and susceptible isolates. EUCAST breakpoints state that MICs>2 µg/ml should be reported as resistant (European Committee on Antimicrobial Susceptibility Testing, 2023), while CLSI considers MICs of 4–8 µg/ml to be moderate and those ≥16 µg/ml as resistant (Clinical and Laboratory Standards Institute, 2020). The resistance status of isolates varies depending on which guidelines are taken

Table 1. Vancomycin, teicoplanin, and linezolid MIC values of the MRSA isolates (µg/ml)

Sample Code	VAN	TEI	LIN
8b	2	0,5	3
10b	1,5	1	0,75
11a	2	1	1
15a	1,5	0,5	2
16	1,5	0,5	3
17b	1,5	<0,5	4
19a	1,5	0,75	2
20a	2	<0,5	2
25b	4	0,5	8
26a	3	0,5	2
26b	1,5	0,5	3
29a	1,5	0,5	6
29b	2	0,5	4
31a	1,5	<0,5	<0,5
31b	2	0,5	1,5
32b	1,5	0,75	8
38a	1,5	0,75	0,75
39a	1,5	0,5	3
41a	1,5	0,75	2
46b	2	0,5	2
48a	1,5	0,75	3
57	1,5	0,75	4
62	2	0,75	3
65	1	1	2
89b	1	0,5	2
99	1,5	<0,5	2
100	3	<0,5	3
101b	1,5	<0,5	6
102a	2	0,75	4
104b	2	0,5	3
107a	2	0,75	2
109a	2	0,75	2
115b	2	0,5	3
120b	1	0,5	2

VAN: vancomycin, TEI: teicoplanin, LIN: linezolid

Table 2. Number of isolates defined as resistant, intermediate, and susceptible to vancomycin, teicoplanin, and linezolid, according to EUCAST (2023) and CLSI (2023).

Number of isolates	VAN			TEI			LIN		
	R	I	S	R	I	S	R	I	S
EUCAST	3	-	31	-	-	34	4	-	30
CLSI	-	1	33	-	-	34	2	-	32

VAN: vancomycin, TEI: teicoplanin, LIN: linezolid; R: Resistant; I: Intermediate; S: Susceptible

as a basis. To cite an example from our study, only one isolate (2.9%) in the study was intermediate for CLSI, while 3 (8.8%) were resistant to vancomycin for EUCAST guidelines. As a striking detail from the results, the intermediate-resistant isolate was also completely resistant to linezolid according to both EUCAST and CLSI. In addition, 5.8% (2/34) of the isolates, according to CLSI, and 11.7% (4/34) of the isolates according to EUCAST were resistant to linezolid. Therefore, when determining vancomycin resistance, the MIC value of the isolate or the guideline for which the resistance was determined should be specified.

The use of vancomycin in the treatment of MRSA infections is becoming more and more suspicious, especially as reports of decreased susceptibility of isolates become more common (Al-Amery et al., 2019; Charlton et al., 2014). On the other hand, various studies had highlighted the association of vancomycin with nephrotoxicity, which is more common in higher doses (≥4 g/d) in treatment for *S. aureus* (Stokes, 2017). In light of the data obtained from our study, it can be said that the use of linezolid in MRSA infections has become useless.

Determination of MIC values is frequently used in making treatment decisions, especially to determine the decreased vancomycin susceptibility in MRSA isolates and to increase treatment efficiency. Alternative treatments to vancomycin are limited in MRSA infections. Linezolid is frequently used in the treatment of MRSA. However, the increasing number of LRSA isolates in studies from both isolates from hospital-acquired infections and isolates from food-producing animals makes the efficacy of this treatment problematic (Leao et al., 2022; Lienen et al., 2022). The results of our study also support this data.

It has been shown that daptomycin is effective in treating MRSA bacteremia, except when caused by left-sided endocarditis, and can maintain bactericidal activity despite slightly elevated MICs (Cui et al., 2006; Humphries et al., 2013). However, the use of daptomycin is limited because it is expensive and not routinely used. It has also been reported that some MRSA isolates develop daptomycin and vancomycin resistance in parallel (Humphries et al., 2013). A recent study reported that fosfomycin showed potent antimicrobial activity against MRSA isolates with resistance or reduced activity to other anti-MRSA antibiotics, including vancomycin, linezolid, and daptomycin (Saravolatz and Pawlak, 2023).

It has been widely reported that teicoplanin, which has a lipoglycopeptide structure similar to vancomycin in terms of its mechanism of action and efficacy, has fewer side effects than vancomycin (Svetitsky et al., 2009). However, studies on the dose of teicoplanin that should be used to effectively treat MRSA infections are limited. Studies conducted within this scope emphasized that the use of higher teicoplanin maintenance dose is very important especially in severe infections due to MRSA (Lee et al., 2022).

CONCLUSION

In our study, all MRSA isolates were sensitive to teicoplanin, and similar studies on clinical and food-borne isolates also found complete sensitivity to teicoplanin (Sukri et al., 2023; Yucel et al., 2011). Concomitant susceptibility to linezolid, teicoplanin, and/or vancomycin in clinical and food-borne isolates in the aforementioned studies is remarkable and shows different results from our study. For these reasons, the determination of antibiotic MICs to determine antimicrobial susceptibility is of critical importance internationally.

DECLARATİONS

Ethics Approval: Ethics committee approval is not required since humans/animals were not used in our study.

Conflict of Interest: Authors do not have any conflict of interest to disclose nor do they endorse the use of any product/technology/service over the other.

Consent for Publication: Not applicable

Competing Interest: The authors declare that they have no competing interests

Author contribution

Idea, concept and design: BO, EK

Data collection and analysis: BO, EK

Drafting of the manuscript: BO, EK

Critical review: BO, EK

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