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ORIGINAL RESEARCH

Molecular Characteristics and Antimicrobial Resistance of Linezolid-Resistant *Staphylococcus aureus* in Osteoarticular Infections: A 11-Year Study From a Hospital in Xi'an

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Purpose: This study examines the distribution of pathogens and the characteristics of linezolid-resistant *Staphylococcus aureus* (LRSA) in osteoarticular infections (OAIs) over an 11-year period.

Methods: Identification and initial antimicrobial susceptibility testing were conducted using the VITEK2 compact system. Broth microdilution method (BMD) to confirm linezolid-resistant isolates. The results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guideline. Polymerase chain reaction (PCR) screening identified linezolid-resistance-related genes and molecular typing loci.

Results: From 2012 to 2022, 2049 clinical isolates were collected, with *S. aureus* identified as the leading pathogen, constituting 38.90% (797/2049) of cases. Among the 797 *S. aureus* isolates, eight strains were initially identified as LRSA through VITEK2; however, only one isolate was confirmed as LRSA by BMD. For the eight strains, molecular typing revealed four spa types (t030, t037, t002, t437) and three MLST types, with ST239-t030 as the dominant clone. No transferable resistance genes (*cfr, optrA, poxtA*) were detected, but a G2576T mutation, associated with reduced linezolid sensitivity, was identified in two isolates (included the isolate confirmed as LRSA by BMD) subjected to extended linezolid therapy.

Conclusion: Our findings highlight the importance of accurate susceptibility testing and proactive monitoring of LRSA in the treatment of chronic OAIs to mitigate potential therapeutic challenges.

Keywords: *Staphylococcus aureus*, osteoarticular infections, antimicrobial resistance, linezolid

Introduction

Osteoarticular infections (OAIs) are serious conditions affecting bones and joints, frequently caused by various pathogens, with *Staphylococcus aureus* (*S. aureus*) as the primary etiologic agent.[1] The overuse and inappropriate application of antibiotics have accelerated antimicrobial resistance, especially in *S. aureus*, where methicillin-resistant *Staphylococcus aureus* (MRSA) now exhibits resistance to numerous antibiotics.[2] Despite this, most MRSA strains remain susceptible to glycopeptides and oxazolidinones, with vancomycin and linezolid serving as cornerstone therapies for MRSA-related OAIs.[3]

Linezolid, the first oxazolidinone antibiotic approved for clinical use, functions by binding to the 50S ribosomal subunit, thereby inhibiting protein synthesis.[4] While linezolid resistance is relatively rare, reports suggest its emergence,[5] especially following prolonged treatments—a common requirement in chronic OAIs.

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Linezolid-resistant *Staphylococcus aureus* (LRSA) has become an emerging concern in the management of various infections worldwide. Although the global prevalence of linezolid resistance remains relatively low, its increasing incidence in clinical settings is alarming. Reports from Europe and North America indicate sporadic cases, often linked to prolonged linezolid therapy and the presence of multidrug-resistant bacterial populations.[6,7] In Asia, particularly in China, studies have shown a higher frequency of LRSA isolates, suggesting a rising trend that requires closer attention.[8,9] Locally, in Xi'an, the burden of LRSA in osteoarticular infections has been increasingly recognized, with Xijing Hospital observing a growing number of resistant strains over the past decade. This local trend reflects the broader regional pattern and underscores the importance of ongoing surveillance and robust antimicrobial stewardship programs to curb the spread of resistance and guide effective treatment strategies.

This study aims to (1) assess the distribution of pathogens in OAI cases over the past decade, (2) evaluate the antimicrobial resistance profiles of isolated *S. aureus*, (3) provide recommendations to clinical Microbiology laboratories on how to accurately review linezolid resistant reports in routine work, and (4) elucidate the molecular mechanisms underlying linezolid resistance in MRSA-related OAIs. Findings from this study emphasize the critical need for accurate susceptibility testing and vigilant monitoring to effectively manage and control chronic OAIs.

Materials and Methods

Bacterial Strains

This study included 2049 non-duplicated clinical isolates collected from patients with osteoarticular infections (OAIs) at Xijing Hospital, Air Force Medical University, from January 2012 to December 2022. Information about these isolates was extracted from the laboratory information system. Duplicate isolates from the same patient were excluded to ensure data accuracy. All clinical isolates were stored in CRYOBANK Conservative Tube (MAST, UK) at −70°C. All isolates were identified using the VITEK2 Compact system (bioMérieux), with Columbia Agar Base, Mueller-Hinton Agar (MHA), and Mueller-Hinton Broth (MHB) (Thermo Fisher Oxoid, England) serving as culture media. *S. aureus* strains ATCC 25923 and ATCC 29213 were used as quality-control references.

Antimicrobial Susceptibility Testing and Identification of MRSA

Initial antimicrobial susceptibility testing was conducted using the VITEK2 compact system following the manufacturer's protocols. Minimum inhibitory concentrations (MIC) for the eight LRSA clinical isolates were confirmed using both the broth microdilution (BMD) method and the E-test (bioMérieux) following the recommendations given in the CLSI guidelines M100-ED33.[10] Resistance rates were analyzed using WHONET 5.6 software. Methods for detection of MRSA according to the CLSI guidelines.[10] *S. aureus* isolates with an oxacillin MIC ≥4.0 μg/mL are classified as MRSA. For the eight LRSA clinical isolates by VITEK, we further confirmed the presence of the *mecA* gene using PCR,[11] providing a definitive identification of MRSA.

LRSA Genomic DNA Extraction

Eight LRSA isolates with VITEK2 initial screening were cultured overnight on Columbia Blood Agar Plates at 35°C. Single colonies were suspended in 200 μL of TE buffer with 4 μL lysostaphin mixture, and genomic DNA was subsequently extracted using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's instructions. Extracted DNA was stored at −40°C for subsequent analysis.

Molecular Detection of Resistance Genes and Mutations

PCR screening identified resistance genes *cfr, cfr(B), optrA* and *poxtA*.[12] Meanwhile mutations in domain V of the 23S rRNA gene, L3, L4, L22 ribosomal proteins were investigated using PCR.[13] The acquired DNA sequences of 23S rRNA and L3, L4, L22 were compared with the *S. aureus* reference sequence (GenBank accession No. NR_076325.1). Mutations were analyzed through SnapGene 4.1.9 software. Primers for each target in this study were detailed in Table 1.

Table 1 Primer Sequences Used for the Amplification and Sequencing of mecA, 23S rRNA, optrA, Cfr, Cfr(B), L3, L4, and L22 Ribosomal Proteins as Well as Amplicon Product Size of the Amplified Regions

	Primer Sequence	Length of Sequence (bp)	Tm (°C)
Cfr[13]	5′-TGAAGTATAAAGCAGGTTGGGAGTCA-3′ 5′-ACCATATAATTGACCACAAGCAGC-3′	746	55°C
Cfr(B)[13]	5′-TGAGCATATACGAGTAACCTCAAGA-3′ 5′-CGCAAGCAGCGTCTATATCA-3′	293	58°C
optrA[13]	5′-AGGTGGTCAGCGAACTAA-3′ 5′-ATCAACTGTTCCCATTCA-3′	1395	55°C
Domain V of 23SrRNA[13]	5′-GCGGTCGCCTCCTAAAAG-3′ 5′-ATCCCGGTCCTCTCGTACTA-3′	390	60°C
L3_rplC[13]	5′-AACCTGATTTAGTTCCGTCTA-3′ 5′-GTTGACGCTTTAATGGGCTTA-3′	822	55°C
L4_rplD[13]	5′-TCGCTTACCTCCTTAATG-3′ 5′-GGTGGAAACACTGTAACTG-3′	1200	55°C
L22_rplV_[13]	5′-CAACACGAAGTCCGATTGGA-3′ 5′-GCAGACGACAAGAAAACAAG-3′	350	55°C
PoxtA[12]	5′-GGAAGTTGCTCAGTACGGCT-3′ 5′-TCAATGCAGAGCAGGAAGCA-3	975	55°C
mecA[11]	5′-TGCTATCCACCCTCAAACAGG-3′ 5′-AACGTTGTAACCACCCCAAGA-3′	310	55°C

Note: LZD MIC results based on the broth microdilution method.

Protein A (Spa) and Multilocus Sequence Typing (MLST)

Spa and MLST typing were performed for all eight LRSA isolates with VITEK2 initial screening. PCR assays were conducted to amplify the spa and MLST loci, according to previously published primers and protocols.[14–16] The resultant amplicons were then subjected to Sanger sequencing (Sangon, China). All spa sequences were analysed using the Ridom web server (http://spa.ridom.de/spaserver), and sequences of seven housekeeping genes (*arcC, aroE, glpF, gmk, pta, tpi, yqi*) were compared to the MLST database (http://www.pubmlst.org) for type assignment.[15,16]

Results

Distribution of Clinical Isolates (2012-2022)

From 2012 to 2022, a total of 2049 non-duplicate bacterial isolates were identified in patients with diagnosed osteoarticular infections (OAIs). Among these, the ten most common isolates included: *Staphylococcus aureus* 38.90% (797/2049), *Pseudomonas aeruginosa* 10.00% (205/2049), *Klebsiella pneumoniae* 7.42% (152/2049), *Escherichia coli* 6.78% (139/2049), *Enterobacter cloacae* 4.98% (102/2049), *Acinetobacter baumannii* 4.73% (97/2049), *Proteus mirabilis* 3.95% (81/2049), *Brucella melitensis* 3.61% (74/2049), *Serratia marcescens* 3.32% (68/2049), and *Staphylococcus epidermidis* 2.98% (61/2049) (Figure 1). This distribution highlights *S. aureus* as the predominant pathogen in OAIs.

Specimen Source of *S. aureus* in OAIs

Out of the 797 *S. aureus* isolates, 55.33% (n = 441) were derived from bone and joint tissues collected during orthopedic surgeries, 29.36% (n = 234) from postoperative wound secretions after bone and joint surgery, 10.79% (n = 86) from joint fluid, 2.76% (n = 22) from blood with patients diagnosed as hematogenous osteomyelitis, and 1.76% (n = 14) from marrow. These data underline tissue samples as the major source of *S. aureus* in OAIs.

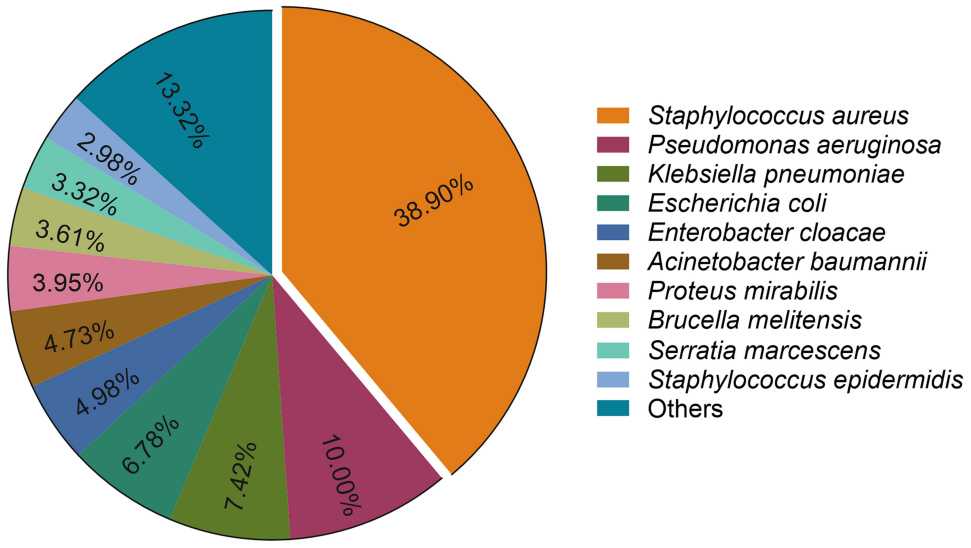

Figure 1 Distribution of Clinical Isolates.

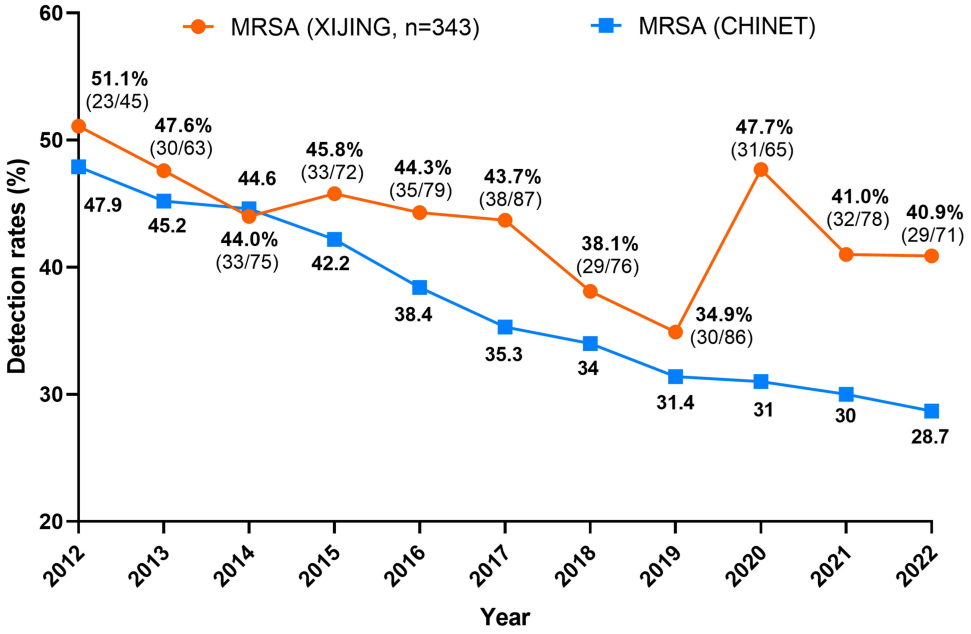

Figure 2 Prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA)from 2012 to 2022 compared with the China Antimicrobial Surveillance Network (CHINET) data.

MRSA Detection Rates and Antimicrobial Susceptibility

Among the *S. aureus* isolates, MRSA accounted for 343 isolates, with an average detection rate of 43.04%. A notable decline in MRSA prevalence was observed, from 51.11% in 2012 to 34.88% in 2019, mirroring trends reported by the China Antimicrobial Surveillance Network (CHINET) (http://www.chinets.com). However, MRSA rates surged to 47.69% in 2020, coinciding with COVID-19 epidemic control measures, before decreasing again to 40.85% in 2022 (Figure 2). This fluctuation likely reflects pandemic-related disruptions, such as fewer inpatients and prolonged hospital stays. Compared with methicillin-sensitive *Staphylococcus aureus* (MSSA), MRSA strains demonstrated higher resistance rates to clindamycin (63.85% vs.19.82%), ciprofloxacin (46.06% vs.8.37%), levofloxacin (44.90% vs.7.71%), gentamicin (42.86% vs.10.57%), and rifampin(35.28% vs.3.08%). Notably, no isolates showed resistance to vancomycin, or tigecycline (Figure 3). Six strains of the eight isolates were identified as MRSA carrying the *mecA* gene (Table 2).

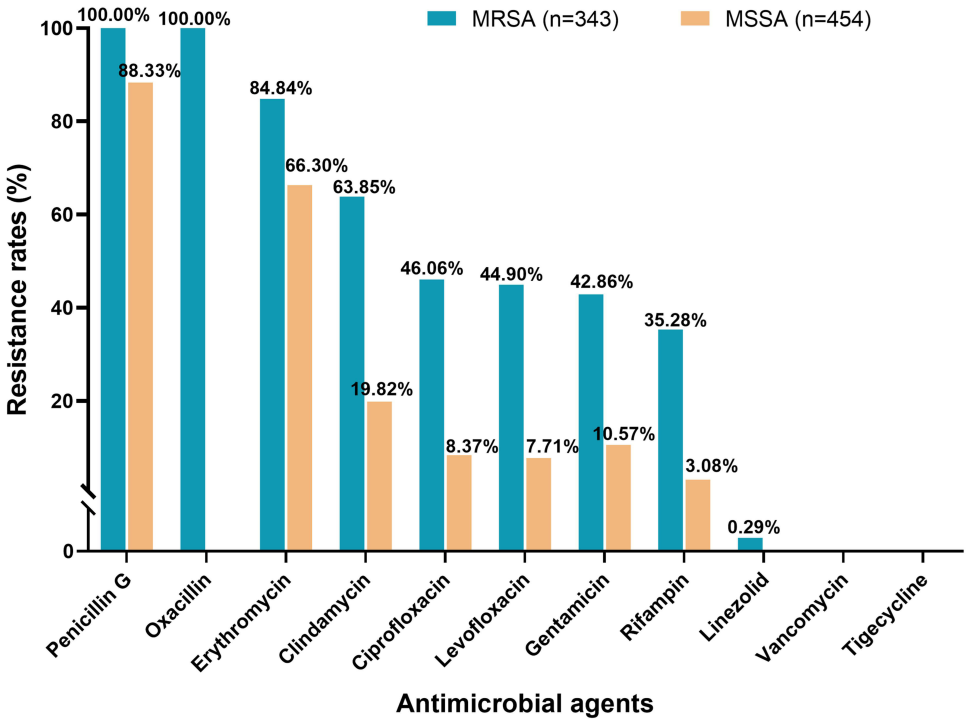

Figure 3 Resistance profile of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) for 11 commonly used antimicrobials.
Note: LZD MIC results based on the broth microdilution method.

LRSA Isolates and Clinical Characteristics

Of the 797 *S. aureus* isolates, eight exhibited elevated linezolid MIC ≥8μg/mL according to VITEK2 AST-GP67 results. However, only one isolate has been confirmed as linezolid-resistant (MIC 8μg/mL). The MIC results of the eight strains were consistent across BMD and E-test susceptibility methods and were significantly different from the VITEK2 results. Clinical data, including diagnosis, specimen source, and treatment duration, were reviewed for these eight isolates, with findings detailed in Table 2 and Table 3.

Molecular Detection of Linezolid Resistance Genes

Linezolid resistance-associated genes, including transferable element genes (*cfr, cfr(B), optrA, poxtA*) and ribosomal mutations (23S rRNA and L3, L4, L22), were analyzed in the eight isolates. None of the genes were detected except for G2576T mutations among two isolates with MICs of 4 μg/mL and 8 μg/mL by BMD, respectively. Detailed molecular findings were presented in Table 2.

Spa and MLST Typing of LRSA Isolates

Spa typing of the eight isolates identified four spa types: t030 (62.5%, 5/8), t037 (12.5%, 1/8), t002 (12.5%, 1/8), and t437 (12.5%, 1/8). Multilocus sequence typing (MLST) identified three types, with ST239 (75.0%, 6/8) being the most prevalent, followed by ST59 and ST5 (Table 2).

Discussion

Among the 2049 clinical isolates analyzed in this investigate, *S. aureus* was the predominant pathogen, accounting for 38.90% of osteoarticular infections (OAIs). In this study, 78.92% of the 797 *S. aureus* cases involved osteomyelitis, confirming this as the primary clinical manifestation of *S. aureus* OAIs. A downward trend in MRSA isolation was observed, though it remained slightly above the national rate, likely due to regional and infection-site variations.[17–19] MRSA's resistance is primarily due to the *mecA* gene, which encodes the modified penicillin-binding protein 2a (PBP2a), reducing its affinity for β-lactam antibiotics (except ceftaroline).[20] Our data showed that MRSA strains had high

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Table 2 Clinical Characteristics and Molecular Analysis of Eight S. Aureus Isolates with Elevated Linezolid MICs (≥8μg/mL)

Isolate No.	Specimen	Age	Sex	Clinical Diagnosis	*mecA* gene	Linezolid MIC			Spa	MLST	Detection of Resistance Genes and Mutations			Linezolid	M/Y
						VITEK2 GP76	E-test	BMD			23S rRNA	L3, L4, L22	*cfr, cfr*(B), *optrA*, poxtA	Treatment	
1	Tissue	15	M	Tibia osteomyelitis	*mecA*	≥8.0 (R)	4.0 (S)	4.0 (S)	t030	ST239	G2576T	-	-	>4 weeks	01/2014
2	Secretion	49	M	Tibia osteomyelitis	-	≥8.0 (R)	2.0 (S)	2.0 (S)	t437	ST59	-	-	-	-	12/2015
3	Secretion	19	M	Femur fracture	-	≥8.0 (R)	2.0 (S)	2.0 (S)	t002	ST5	-	-	-	-	01/2016
4	Tissue	41	M	Femoral osteomyelitis	*mecA*	≥8.0 (R)	2.0 (S)	2.0 (S)	t030	ST239	-	-	-	-	02/2016
5	Secretion	48	M	Tibia osteomyelitis	*mecA*	≥8.0 (R)	8.0 (R)	8.0 (R)	t030	ST239	G2576T	-	-	>4 weeks	08/2019
6	Tissue	38	M	Tibia osteomyelitis	*mecA*	≥8.0 (R)	2.0 (S)	2.0 (S)	t037	ST239	-	-	-	-	09/2019
7	Tissue	17	M	Tibia osteomyelitis	*mecA*	≥8.0 (R)	4.0(S)	4.0(S)	t030	ST239	-	-	-	12 days	03/2020
8	Joint fluid	24	M	After joint replacement	*mecA*	≥8.0 (R)	4.0(S)	4.0(S)	t030	ST239	-	-	-	7 days	05/2021

Abbreviations: E-test, antibiotic concentration gradient method; BMD, broth microdilution test; M/Y, Month/Year.

Table 3 The Antimicrobial Susceptibility Testing Results of Eight S. Aureus Isolates by Using VITEK 2 AST-GP67 Card

Isolate No.	PEN	OXA	ERY	CLI	CIP	LVX	GNE	RIF	LZD	VAN	TGC
1	≥0.5 (R)	≥4.0 (R)	≥8.0 (R)	≥8.0 (R)	≥8.0 (R)	≥8.0 (R)	≥16.0 (R)	≥32.0 (R)	≥8.0 (R)	1.0 (S)	0.25 (S)
2	≥0.5 (R)	1.0 (S)	≥8.0 (R)	≥8.0 (R)	1.0 (S)	0.25 (S)	≤0.5 (S)	≤0.5 (S)	≥8.0 (R)	≤0.5 (S)	≤0.12 (S)
3	≥0.5 (R)	1.0 (S)	≥8.0 (R)	≥8.0 (R)	≤0.5 (S)	≤0.12 (S)	≤0.5 (S)	≤0.5 (S)	≥8.0 (R)	≤0.5 (S)	≤0.12 (S)
4	≥0.5 (R)	≥4.0 (R)	≥8.0 (R)	≥8.0 (R)	≥8.0 (R)	≥8.0 (R)	≤0.5 (S)	≤0.5 (S)	≥8.0 (R)	1.0 (S)	0.25 (S)
5	≥0.5 (R)	≥4.0 (R)	≥8.0 (R)	≥8.0 (R)	≥8.0 (R)	≥8.0 (R)	≥16.0 (R)	≥32.0 (R)	≥8.0 (R)	1.0 (S)	0.25 (S)
6	≥0.5 (R)	≥4.0 (R)	≥8.0 (R)	≥8.0 (R)	≥8.0 (R)	≥8.0 (R)	≥16.0 (R)	≥32.0 (R)	≥8.0 (R)	1.0 (S)	0.25 (S)
7	≥0.5 (R)	≥4.0 (R)	≥8.0 (R)	≥8.0 (R)	≥8.0 (R)	≥8.0 (R)	≥16.0 (R)	≥32.0 (R)	≥8.0 (R)	1.0 (S)	≤0.12 (S)
8	≥0.5 (R)	≥4.0 (R)	≥8.0 (R)	≥8.0 (R)	≥8.0 (R)	≥8.0 (R)	≤0.5 (S)	≤0.5 (S)	≥8.0 (R)	≤0.5 (S)	≤0.12 (S)

Abbreviations: PEN, Penicillin G; OXA, Oxacillin; ERY, Erythromycin; CLI, Clindamycin; CIP, Ciprofloxacin; LVX, Levofloxacin; GNE, Gentamicin; RIF, Rifampin; LZD, Linezolid, VAN, Vancomycin; TGC, Tigecycline.

resistance rates to macrolides (>80%), clindamycin (>60%) and quinolones (>40%). As MRSA-related osteomyelitis often requires prolonged antibiotic therapy, selecting agents with high bone penetration, minimal adverse effects, and reliable efficacy is critical.[21,22] According to the 2021 Guideline on Diagnosis and Management of Acute Hematogenous Osteomyelitis in Pediatrics,[23] linezolid is the preferred oral treatment for clindamycin-resistant MRSA osteomyelitis, and its use has been increasingly adopted in clinical practice.

Linezolid is a synthetic bacteriostatic drug, and demonstrates comprehensive antibacterial activity against a variety of gram-positive bacteria.[24] With the widespread use of linezolid, the prevalence of linezolid-resistant *Staphylococcus spp*. has gradually increased in recent years.[6,7,25] According to the report of 2023 CHINET the linezolid resistance rates of methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS) was 1.8%, however linezolid resistant MRSA case was not detected.[26] In *Staphylococcus*, linezolid resistance is primarily due to (1) mutations in the linezolid-binding sites, such as in the 23S rRNA gene (particularly in the domain V and L3, L4, and L22 ribosomal proteins) and (2) the acquisition of resistance genes (eg, *cfr, optrA, poxtA*).[5]

Our data revealed that among the 797 *S. aureus* isolates, the VITEK2 AST-GP67 detected eight strains with linezolid MIC ≥8 μg/mL. However, BMD and E-test method confirmed only one strain at 8 μg/mL, indicating that the VITEK2 compact system may overestimate linezolid resistance. Previous studies,[13] such as Yoo et al, have reported similar discrepancies. Both the CLSI standard[10] and the EUCAST guideline[27] clearly emphasize that: (BMD) method is the recommended method for antimicrobial susceptibility testing (AST). The VITEK 2 AST methodology undergoes quick determination of MICs through the examination of the growing dynamics of bacteria in test cards treated with antibiotics.[28] It was explicitly stated in VITEK®2 AST-GP67 manual that the ability of the AST card to detect resistance with linezolid is unknown because resistant strains were not available at the time of comparative testing (VITEK®2 AST-GP67 manual. bioMérieux. REF22226). Therefore, every linezolid resistance detected through VITEK2 should be confirmed and verified with the recommended method in routine clinical work.

Although LRSA in OAIs remains rare, our study detected decreased linezolid susceptibility in two strains (MICs of 4.0 and 8.0 μg/mL) with a G2576T mutation in the 23S rRNA gene. The G2576T mutation as the most common mutation reduced the affinity of linezolid for the peptidyl transferase center (PTC) binding site, thereby reducing linezolid-sensitivity.[28–31] The 23S rRNA G2576T gene mutation of *S. aureus* cannot completely determine its resistance phenotype because *S. aureus* has 5 to 6 rRNA operon copies, and its resistance level increases with the increase in the number of 23S rRNA allele mutations and copies.[31] So in this study, the two isolates (MICs of 4.0 and 8.0 μg/mL) with G2576T mutation were possible have different allele mutations copy sizes. And the molecular typing results showed that both G2576T mutation strains belonged to ST239-t030, which was the most common molecular type of MRSA isolated in Mainland China currently,[11] underscoring the need for vigilant monitoring and containment to prevent further spread.

A review of clinical data for the eight patients with LRSA (by VITEK 2) infection isolates revealed that, both patients harboring G2576T-mutant isolates had chronic osteomyelitis and had undergone prolonged linezolid at 600 mg every 12 hours for over four weeks, and the other two patients with LZD MIC of 4.0μg/mL isolates have also received linezolid treatments not more than two weeks. The remaining four patients have not undergone any linezolid. The reduced susceptibility to linezolid in these cases suggests a potential risk of resistance emergence with extended treatment durations. These findings highlight the importance of periodic MIC monitoring for linezolid in patients undergoing prolonged therapy. Should susceptibility decrease to (MIC 4.0ug/mL) or resistance (MIC ≥ 8.0ug/mL) develop, early adjustments to the treatment regimen are essential to ensure therapeutic efficacy.

This study provides valuable insights into the molecular characteristics and antimicrobial resistance of LRSA in osteoarticular infections; however, certain limitations must be acknowledged. First, the relatively low number of confirmed LRSA isolates (only one by BMD) limits the generalizability of our findings and the ability to draw robust epidemiological conclusions. Second, the absence of transferable resistance genes (*cfr, optrA* and *poxtA*) suggests the potential involvement of other, yet unidentified, mechanisms of linezolid resistance, which were not explored in this study. Third, the study relied on retrospective data from a single tertiary hospital, which may not fully reflect the broader regional or national epidemiology of LRSA in osteoarticular infections.

Currently, the researches on the resistance mechanisms of linezolid in *S. aureus* were limited, due to the rarity of the LRSA. So, the trend of linezolid resistance in *S. aureus* warrants continuous monitoring, both clinical and laboratory-derived should unexplained resistance mechanisms, requiring further investigation and verification.

Conclusion

S. aureus remains the primary pathogen in OAIs, with osteomyelitis as a predominant clinical outcome. Extended linezolid therapy poses a potential risk of resistance development, particularly in chronic cases. Although linezolid resistance in OAIs is still rare, confirmatory testing for suspected resistance, especially those detected by VITEK2, is essential for reliable diagnosis. Continued surveillance and responsible linezolid use are necessary to prevent resistance emergence and preserve effective treatment options for MRSA-related osteomyelitis.

Ethics Approval and Consent to Participate

This research adhered to the Declaration of Helsinki[32] and received approval from the Ethics Committee of Xijing Hospital, Air Force Medical University (reference number KY202113306-1). The isolates we used in this study came from the normal clinical testing and were stored in the strains bank of Clinical Laboratory, Xijing Hospital, Xi'an, China. The patients provided informed consent. This study would not do harm to rights, benefits, and health of the subjects, and the privacy and personal identity information of the subjects will not be included in this study.

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Disclosure

The authors report no conflicts of interest in this work.

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