The Utility of the Minimum Biofilm Eradication Concentration (MBEC) for Predicting Periprosthetic Joint Infection Treatment Outcome

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<u>Takeaway:</u> Independent of methicillin resistance status, *S. aureus* biofilms in PJI are not eradicated at clinically achievable oxacillin concentrations.

Introduction

- Periprosthetic joint infections (PJI) are commonly caused by bacteria that persist within **biofilms**.
- Clinically, **antibiotic selection** is guided by the **minimum inhibitory concentration (MIC),** which measures susceptibility of planktonic bacteria.
- Biofilm-associated bacteria can demonstrate substantially greater antimicrobial tolerance compared to planktonic bacteria.
- Biofilm-associated antimicrobial tolerance is quantified by the **minimum biofilm eradication concentration (MBEC)**, but standardized clinical MBEC testing is not currently available.
- It is unclear whether MBEC provides clinically relevant information beyond MIC and the predictive value of MBEC for PJI treatment remains unknown.

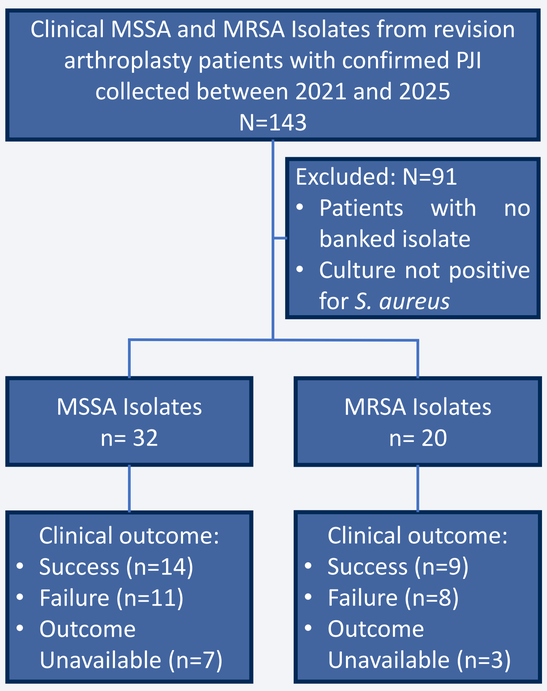
Objective

- We **aimed** to evaluate whether MBEC, MIC, or their ratios can predict PJI treatment failure, and to quantify the MBEC of oxacillin for methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) *Staphylococcus aureus* biofilms.
- We **hypothesized** that MSSA isolates would demonstrate lower oxacillin MBEC values than MRSA isolates, and MBEC would predict treatment outcomes better than MIC alone.

Methods

Figure 1. Patient selection and definition of treatment outcome.

A.



B.

Clinical Outcome	Definition
Tier 1	Infection control without continued antibiotics
Tier 2	Infection control with the patient on suppressive antibiotics
Tier 3	Need for reoperation and/or revision:
3B	Septic revision at >1 year from initiation of PJI treatment
3D	Septic revision at ≤1 year from initiation of PJI treatment
3E	Amputation, resection arthroplasty, or arthrodesis
Tier 4	Death:
4A	Death ≤1 year from initiation of PJI treatment
4B	Death >1 year from initiation of PJI treatment

Fillingham et al. J Bone Joint Surg Am. 2019.

Figure 1. Patient selection and definition of treatment outcome. (A) Patient screening, exclusion, and stratification by MSSA or MRSA infection. (B) One-year treatment outcomes classified using the 2018 MSIS Tier Classification System. Successful outcome tiers are shaded gold and failed outcome tiers are shaded blue.

Figure 2. Experimental workflow for determination of the MBEC of oxacillin.

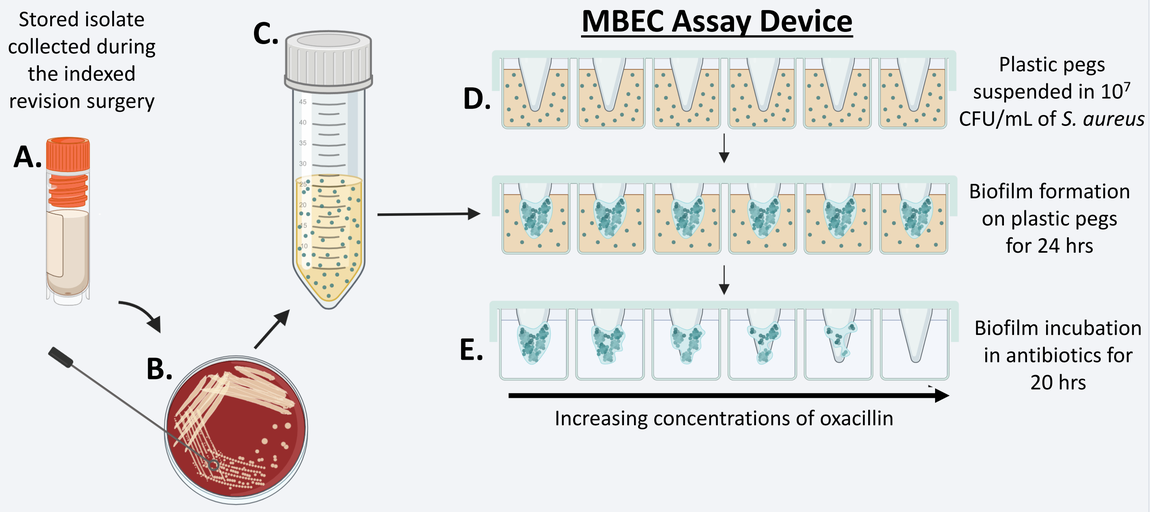


Figure 2. Experimental workflow for determination of the MBEC of oxacillin. *S. aureus* biofilms were formed for 24 hrs, then exposed to oxacillin (4-27,500 µg/mL) for 20 hrs, and viable bacteria were assessed via standard plate counting. MBEC was defined as the lowest concentration with no viable bacteria detected and was averaged across three independent experiments performed in technical duplicates.

Results

- Biofilm tolerance exceeded planktonic susceptibility by **2,600–55,000×**; **combined MBEC+MIC** best predicted **MSSA treatment failure (AUC 0.77)**.
- Oxacillin MBEC surpassed **clinically achievable levels** in most isolates; **single-marker prediction was weak**.
- Biofilms resisted eradication **regardless of resistance phenotype**; predictive value emerged only when **MBEC and MIC were modeled together**.

Figure 3. Oxacillin MBEC, MIC, and MBEC/MIC ratios in MSSA and MRSA isolates.

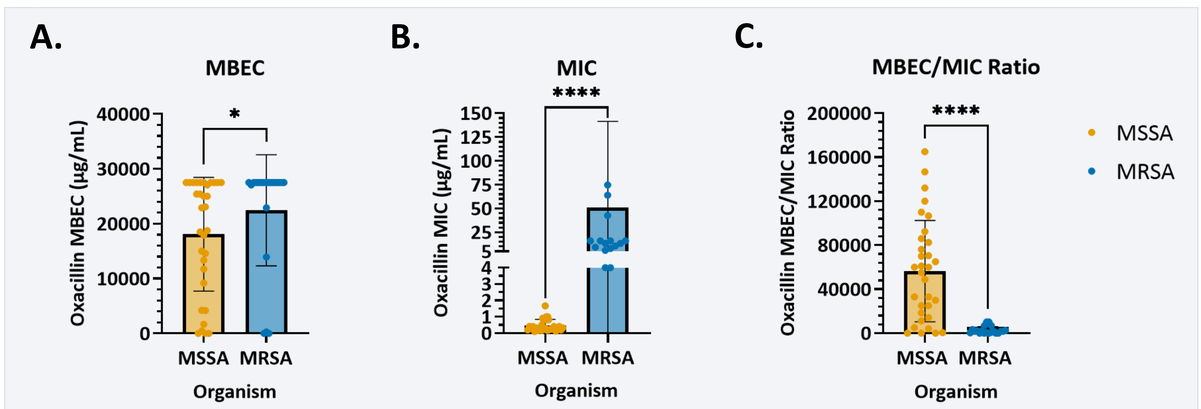
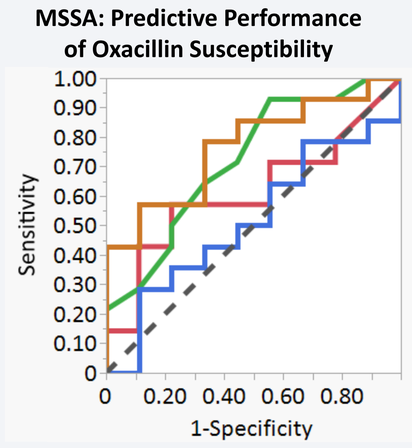


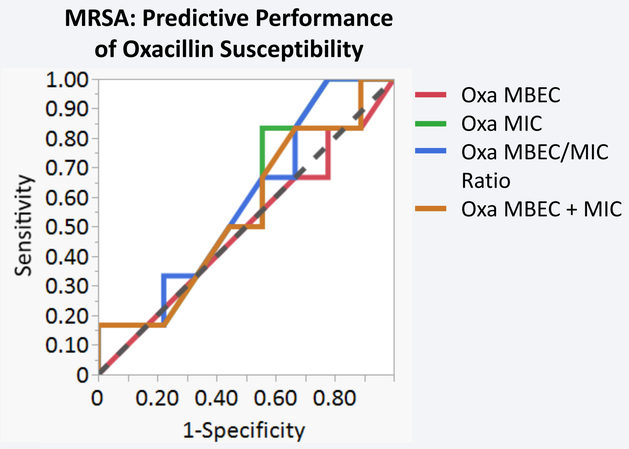
Figure 3. Oxacillin MBEC, MIC, and MBEC/MIC ratios in MSSA and MRSA isolates. Comparative analyses of oxacillin (A) MBEC, (B) MIC, and (C) MBEC/MIC ratio were compared between MSSA (n=32) and MRSA (n=20) isolates. MBEC exceeded the maximum tested concentration (27,500 µg/mL) in 31.25% of MSSA and 70% of MRSA isolates; these were assigned the ceiling value, so group means are conservative. Points represent individual isolate means from three independent experiments performed in technical duplicates; bars indicate the mean and SD. Statistical significance [(A) P=0.03*; (B,C) P<0.0001****] determined by the Mann-Whitney test.

Figure 4. Predictive performance of oxacillin susceptibility for PJI treatment outcome.

A.



B.



C.

Predictor	Organism	AUC	95% CI	Sens %	Spec %
MBEC	MSSA	0.61	0.36-0.81	78	57
	MRSA	0.49	0.24-0.74	83	22
MIC	MSSA	0.72	0.46-0.89	44	93
	MRSA	0.58	0.28-0.83	83	44
MBEC/MIC Ratio	MSSA	0.52	0.28-0.75	89	29
	MRSA	0.58	0.28-0.83	100	22
MBEC + MIC	MSSA	0.77	0.52-0.91	89	57
	MRSA	0.59	0.25-0.81	83	33

95% CI, 95% confidence interval; AUC, Area under the curve; MBEC, minimum biofilm eradication concentration; MIC, minimum inhibitory concentration; Sens, Sensitivity; Spec, Specificity.

Figure 4. Predictive performance of oxacillin MBEC, MIC, and MBEC/MIC Ratio for treatment outcome of MSS and MRSA PJI. ROC model comparison examining the predictive value of oxacillin susceptibility models for predicting treatment failure for (A) MSSA-associated (n=23) and (B) MRSA-associated PJI. (C) The AUC, 95% confidence interval, sensitivity, and specificity at the optimal cutoff for each model are summarized.

Conclusions

- **MBEC values >27,500 ug/mL** were observed for **31.25% of MSSA** and **70% of MRSA** isolates, exceeding clinically achievable concentrations.
- Mean **MBEC/MIC ratios** of **55,000 for MSSA** and **2,600 for MRSA** isolates were observed, indicating a substantial increase in **biofilm-associated tolerance** compared to planktonic susceptibility, regardless of phenotypic resistance.
- Modeling **MBEC and MIC together** had the highest success **predicting treatment failure**.
- Treatment failures are likely **multifactorial**. Considering **MBEC alongside MIC** may be useful during **treatment planning for MSSA PJI**; further validation in larger cohorts is needed before clinical adoption.

References & Acknowledgments

1. Fillingham, et al. The Journal of Bone and Joint Surgery American Volume. 2019;101:e69.

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