MPC (Mutant Prevention Concentration)

Analysis of a key recent paper

J Antimicrob Chemother 2017; **72**: 3100–3107
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Journal of Antimicrobial Chemotherapy

Testing the mutant selection window hypothesis with *Staphylococcus aureus* exposed to linezolid in an *in vitro* dynamic model

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Objectives:

To test the mutant selection window (MSW) hypothesis applied to **linezolid**-exposed *Staphylococcus aureus* and to delineate the concentration–resistance relationship, a mixed inoculum of linezolid-susceptible *S. aureus* cells and linezolid-resistant mutants (RMs) was exposed to linezolid multiple dosing.

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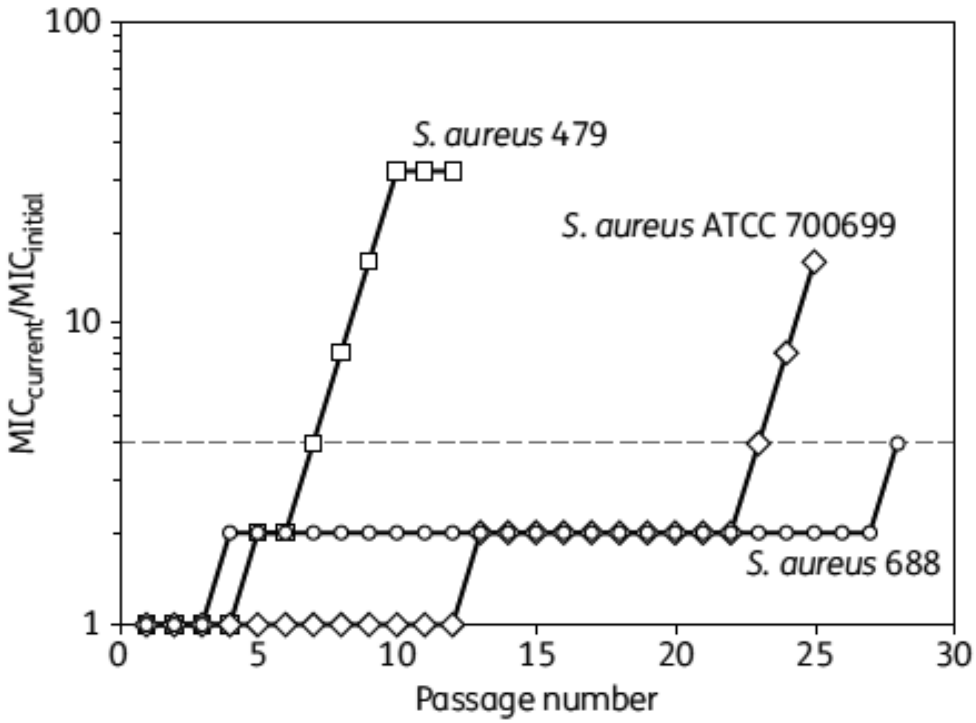

Figure 1. Loss in susceptibility of *S. aureus* strains passaged on linezolid-containing media. $MIC_{current}/MIC_{initial}$ ratio of 4 is indicated by the broken horizontal line.

1. **emergence of resistance by serial passages on LZD-plates (1-64 mg/L)**

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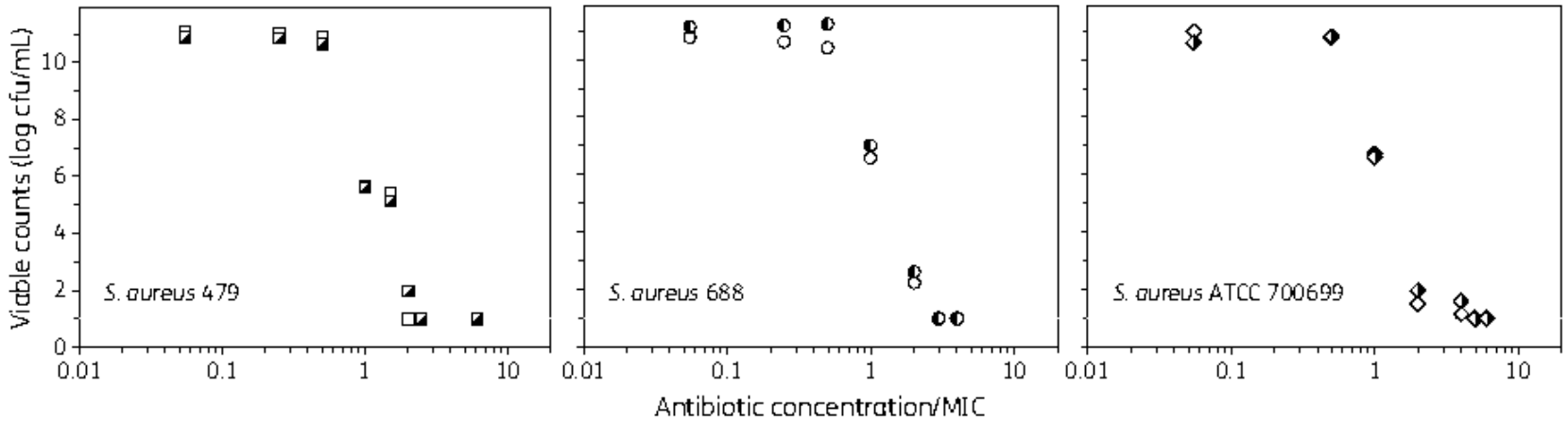

Figure 2. Linezolid MPC determination with *S. aureus* strains without (open symbols) and with (half-filled symbols) the respective RMs. Lower limit of detection is indicated by the broken horizontal line.

2. determination de la MPC (en multiples de la CMI)

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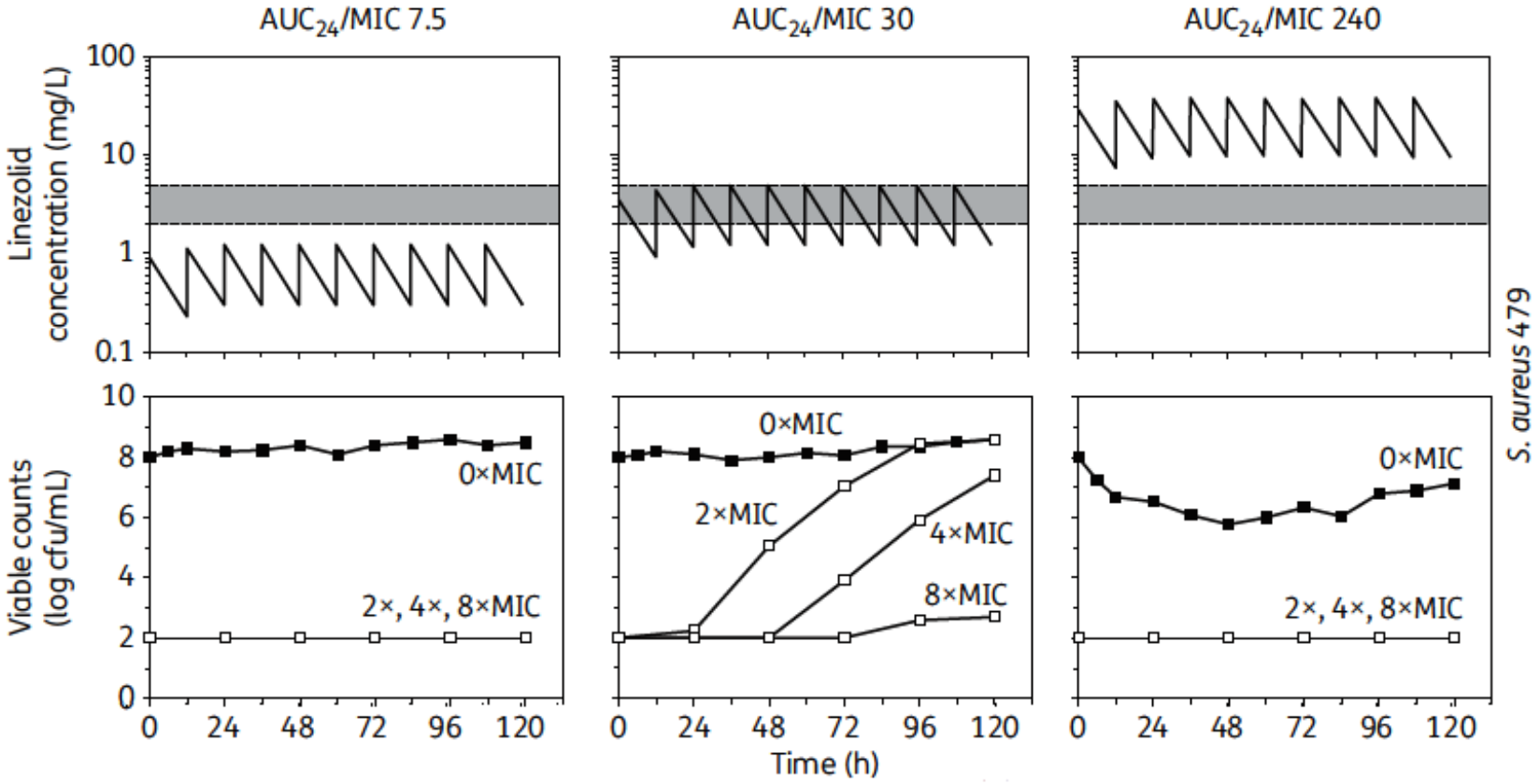

Figure 3. Simulated pharmacokinetics of linezolid and time courses of susceptible and resistant subpopulations of *S. aureus* at three characteristic AUC_{24}/MIC ratios. MSWs are marked by shaded areas.

3. **développement de la résistance si les taux sériques sont dans la MSW….**

Analysis of a key recent paper

$AUBC_M$ = area under the bacterial concentration–time curves of mutant bacteria
~ number of bacteria surviving to the antibiotic

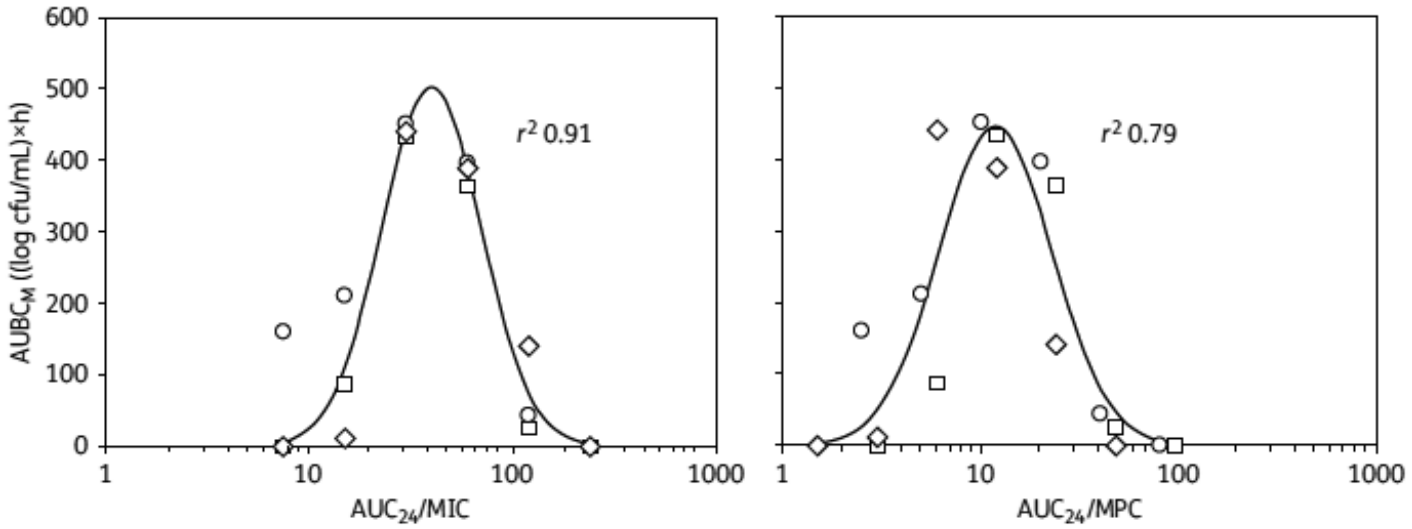

Figure 5. AUC_{24}/MIC and AUC_{24}/MPC relationships with $AUBC_M$ for mutants resistant to 2× MIC of linezolid; combined data on all three *S. aureus* strains fitted by Equation (2): $Y_0 = 1$, $x_0 = 1.600$, $a = 501.6$, $b = 0.2425$, $c = 1.991$ ($AUBC_M$ versus AUC_{24}/MIC); $Y_0 = 1$, $x_0 = 1.072$, $a = 446.0$, $b = 0.2860$, $c = 2.000$ ($AUBC_M$ versus AUC_{24}/MPC). Squares, *S. aureus* 479; circles, *S. aureus* 688; diamonds, *S. aureus* ATCC 700699.

3. relation AUC/MIC ou AUC/MPC vs. développement de la résistance

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$AUBC_M$ = area under the bacterial concentration–time curves of mutant bacteria
~ number of bacteria surviving to the antibiotic

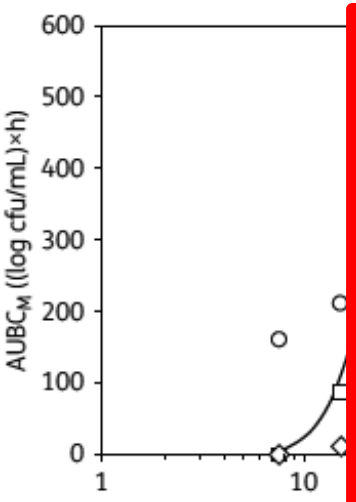

Figure 5. AUC_{24}/MIC and AUC_{24}/MPC relat
strains fitted by Equation (2): $Y_0 = 1$, $x_0 = 1$
$c = 2.000$ ($AUBC_M$ versus AUC_{24}/MPC). Squa

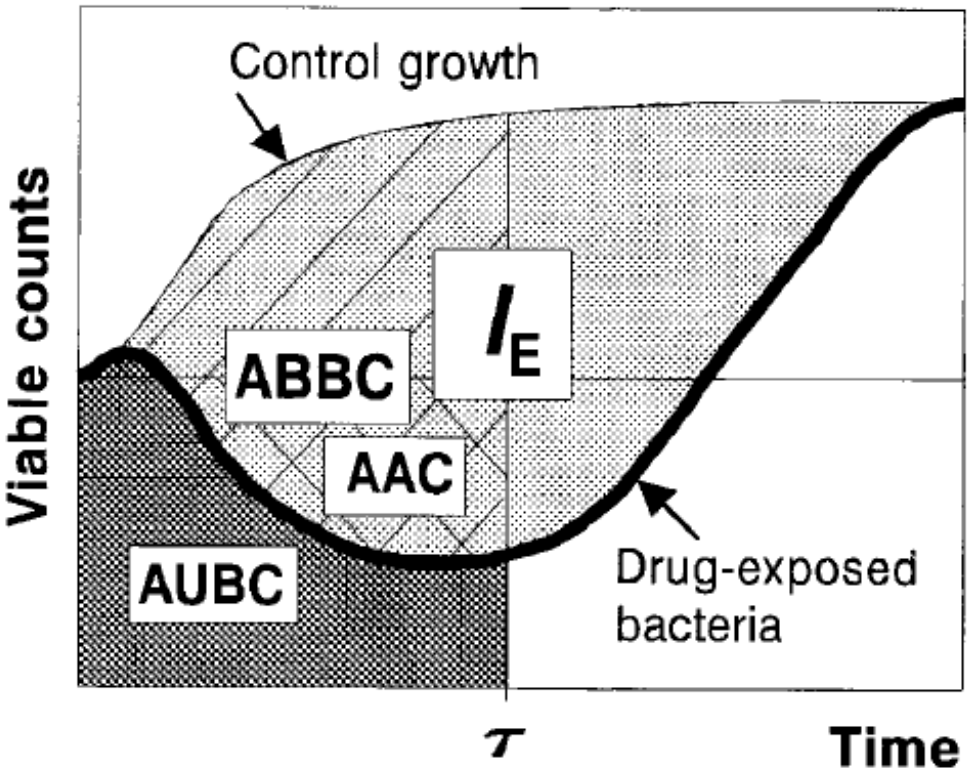

FIG. 1. Integral endpoints of the antimicrobial effect.

3. relation AUC/M
résistance

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Conclusions:

1. The bell-shaped pattern of AUC24/MIC and AUC24/MPC relationships with S. aureus resistance to linezolid is consistent with the MSW hypothesis.
2. ‘Antimutant’ AUC24/MIC ratios were predicted based on the AUC24/MIC relationship with AUBCM.