Comment on: Functional relationship between bacterial cell density and the efficacy of antibiotics

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Sir,

We read with great interest the article by Udekwu et al.,1 on the relationship between bacterial cell density and antibiotic efficacy. These authors have nicely shown by using in vitro time–kill, MIC estimation and antibiotic bioassay experiments modest or substantial inoculum effects on the efficacy of six antibiotics against Staphylococcus aureus. Using a sophisticated mathematical model, the authors conclude that the course of antibiotic treatment can be affected by cell density and suggest that PK/PD indices would be more predictive of the efficacy of antibiotics if, instead of using conventional estimates of the MIC, density-dependent functions of MICs were employed as the denominators of these indices.1

We studied the possible therapeutic relevance of the inoculum effect shown by β-lactams against Escherichia coli strains by using in vitro and in vivo models,2,3 and Udekwu et al.,1 comment on a couple of other papers of our group. However, we would like to add some other information that reinforces the main conclusion of their paper and that was obtained using a standard inoculum. Therefore, we concluded that ‘the time that the levels in serum exceed the MIC is a significant parameter determining the efficacies of β-lactam antibiotics, but the correlation is much better when the MICs obtained with the large inoculum instead of those obtained with the standard (low) inoculum are considered’.3 What was the rationale of these experiments? Pharmacodynamics is undoubtedly a very useful tool for selecting drugs, doses and intervals for treating infectious diseases and several indices for predicting efficacy are well established. If the time that the levels of a β-lactam exceed the MIC is the most significant pharmacodynamic index for predicting efficacy, it should be expected that with antibiotics for which MIC values (determined with standard inoculum) are very low, e.g. cefotaxime for some Gram-negative organisms, a low dose of such an antibiotic (50 mg rather than 1–2 g every 6–8 h as usually administered) should be sufficient.4

Experiments to test this prediction in patients would clearly be unethical, but such experiments have been carried out on small animals. What occurs if we administer a low dose of, for example, cefotaxime, piperacillin or aztreonam that achieves serum concentrations moderately above the MIC (determined with standard inoculum) during 30% to 50% of the dose interval? Simply, the animals die.

Transparency declarations

None to declare.

References