S061

1-hour Symposium

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D. Livermore[1]

[1]*University of East Anglia, Norwich, United Kingdom*

The basic tenets of pharmacodynamics are surely valid. But, good models can be extrapolated too far. Real, often elderly, patients are more variable than Monte-Carlo simulations often acknowledge and MIC determinations are less precise, being determined on log2 scale with an accepted variability of +/- one doubling dilution. What is more, the susceptibility testing done in routine diagnostic laboratories is less precise than in the pharmacodynamicist's excellent research laboratory. There is also the point that pharmacodynamicists keep changing target values for the critical parameter. All agree that the critical parameter for a beta-lactam is T >MIC but, according to the pathogen, setting, drug and author the 'required' T > MIC varies from 30-50% of the dosage interval, and the target from achieving bacteriostasis to achieving a log10 reduction in bacterial count. All this would matter little if pharmacodynamics were only a theoretical concept but, in reality, they are weighted heavily in breakpoint selection and, in antibiotic development, they are used to guide dosage selection. In the case of breakpoints, the weight placed on pharmacodynamics leads to some isolates with clear resistance mechanisms, notable ESBLs and OXA-48 beta-lactamases, being categorised as 'susceptible' when the evidence that isolates with these mechanisms are clinically responsive to the drug is scanty or weak. In the case of dosage selection there has been a long catalogue, though the last 15 years, of antibiotics being developed for pharmacodynamically-perfected regimens, then having their dosages increased based on clinical experience... In short, pharmacodynamics are like long-range weather forecasts: useful for general planning but no substitute for taking an umbrella if the sky looks dark and gloomy.