Dose and Schedule Choices to Suppress Emergence of Resistance

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Emergence of antibacterial resistance is now a national problem, both in the nosocomial setting as well as in the community. One pathway by which organisms become resistant is when a small, less susceptible bacterial population is present at the initiation of antimicrobial chemotherapy. In such circumstances, inadequate dosing regimens lead to the amplification of these resistant subpopulation, resulting in the majority of the total bacterial population being made up of these less-susceptible organisms.

In this presentation, we will examine the influence of the intensity of therapy on the emergence of resistance of *P. aeruginosa*. This was explored in a murine thigh model of infection. In addition, we developed an *in vitro* model of infection wherein the concentration-time profile of drug seen in man can be simulated. In both these evaluations, there was a clear relationship between the therapeutic intensity and the ability to amplify these resistant sub-populations. Also in both, prospective validations studies were undertaken to evaluate hypotheses generated from analysis of the data. In both, the hypotheses were validated.

The duration of therapy is also of fundamental importance in determining whether the subpopulations amplify. We examined a strain of *S. aureus* and modeled the relationship between drug intensity, the duration of therapy and the ability to prevent amplification of resistant mutant populations. Here, we could show the discordance between two regimens of differing intensity, but each producing the same (maximal) kill rate over 4-5 days when the endpoint was resistance suppression. The lesson learned from these evaluations is to go in with very intensive regimens and to stop therapy as early as possible.

Such lessons can also be applied to biodefense pathogens, such as *B. anthracis* and *Y. pestis*. Here, optimal regimens can be defined and validated in animal models and the impact of animal pharmacokinetics on the outcomes observed can be discerned.

Pharmacodynamics can provide valuable insights to suppress resistance by optimizing dose choice, schedule and duration of therapy.