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Practicing the Fundamentals: How an Anti-infective Regimen is Logically Determined



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In the past, empiricism - the practice of medicine that disregards scientific theory and relies solely on practical experience - was often used to determine how much of and how often a drug was given to treat bacterial infections. Today, such artistry has of necessity given way to more predictable approaches steeped in understanding the target organisms, and the kinetics and dynamics of the drug in question. It is important to understand and put in practice the fundamentals of antimicrobial therapy when determining a successful regimen to treat infectious diseases.

The primary principal that must be attained is the potential to effectively treat 90% of the target organisms. This is begun by careful in-vitro studies where the spectrum of activity is defined for a drug. Is it a drug with broad Gram positive spectrum, or Gram negative activity or both? Does it have anaerobic activity or aerobic activity or both? When these general descriptors are understood the question turns to the specific activity within each of these categories for individual bacteria by genus and species.

One then does a survey of organisms by genus and species from a solid representative number of such specific organisms, preferably from disperse geographic areas and of organisms that were determined to have been truly pathogenic or disease causing from recent infections whenever possible. Having performed this survey, the minimum concentration of drug needed to inhibit at least 90% of the organisms of this genus and species is identified. This is referred to as the MIC90.

Now that we have determined the kinds of disease causing bacteria that are susceptible to the drug in question and have identified the MIC90 for each, we need to understand if that concentration of drug can be achieved in the plasma of the animal to which the drug is given in a safe, predictable way. But this fact alone will not be sufficient to understand an optimized regimen or course of therapy.

After Phase I trials have identified the absorption, distribution, metabolism and excretion of the investigational drug, we need to understand which kinetic feature is most associated with optimized outcome. Does the time during the dosing day that the concentration of drug is above the specific MIC of the organism involved in the infection best predict outcome or does the area under the time curve predict this best? Perhaps it is worth reflecting on the term bactericidal, or the ability of a drug to kill a bacterium. If penicillin is bactericidal and a quinolones is bactericidal, then they might be considered the same with respect to bacterial killing, correct? This is actually not the case.

Arsenic and cyanide are both mammalian poisons however one must eat arsenic for a period of time to die while exposure to cyanide would kill us instantly. Such is true for bacterial poisons. Exposure to beta-lactams, such as penicillins, is more like our arsenic analogy while the quinolones are more like cyanide. So for a quinolones it is not how long the bacterium is exposed but rather, has it been exposed to sufficient amounts. For the penicillin it must be adequate amounts for long enough to optimize outcome. And yet this is not all we must understand!

Let's consider beta-lactams which include, for example, penicillins, cephalosporins and carbapenems. They all work by targeting various penicillin binding proteins that prevent restructuring of the bacterial wall, an essential process for the growth and reproduction of bacteria. Carbapenems are more efficient than penicillins which in turn are more efficient in killing than cephalosporins such that the time needed for the concentration of each of these classes to be above the MIC of the pathogen is variable and shortest for carbapenems.

The next step is identifying the organisms that you think you can effectively treat and that you feel are important in the sites of infections where your drug will be used and to where your drug is capable of attaining sufficient concentrations. Among these target organisms, the highest MIC90 from among the key site pathogens must be identified. Thus if all important organisms for a claim, such as nosocomial

pneumonia, have MIC90s of 1 ug/ml or less except *P.aeruginosa* which has an MIC90 of 4ug/ml, if *P.aeruginosa* is crucial, then a regimen that can attain the plasma concentrations above this MIC 90 for the appropriate time frame during a dosing day, becomes the regimen to be tested (providing such a plasma profile is felt to be likely safe).

This can be accomplished by one of three methods: higher doses, more frequent doses or prolonged infusion times. To demonstrate how this can play out, the same dose of a beta lactam given with the same frequency can be made to capture an organism with a higher MIC90 by increasing the infusion time from 1 hour to 3 or 4 hours rather than by necessitating a higher dose or more frequent dosing. The cost of goods, safety profile, convenience issues and stability once constituted all must be considered in determining which of these methods or which combination of methods is to be used.

If beta-lactams determined how we treat bacteria in one universe, quinolones would define therapy in a parallel and certainly different universe. Unlike beta-lactams which are time dependent in their killing, quinolones are concentration-dependent. It matters far less how long exposure is compared to how much the exposure is. For a quinolone, once a certain threshold of exposure occurs, the death of that bacterium is irrevocable. So with quinolones we must give the entire daily dose once a day. By doing this we drive two parameters: AUC/MIC and Cmax/MIC. The former formula determines the likelihood that the quinolones and dose chosen will effectively treat a specific pathogen. The second formula predicts the potential of selecting a resistant mutant. Nonetheless, for quinolones and aminoglycosides the key is to hit hard, fast and all at once, the “shock and awe” of antimicrobial warfare. For beta-lactams the key is to maintain pressure with constant exposure, the guerilla war that never lets the bacterium get a chance to regroup.

Paul Ehrlich, the microbiologist’s rock star, told us to treat patients such that they are the better for therapy. So we aim to preserve our patient’s health and to kill the microbial pathogens that threaten them. And indeed dead is dead, but how we get there makes the difference, so understanding the first principals of antimicrobial therapy is crucial. After all it was the American philosopher, Yogi Berra who said, “You gotta know where you’re going or when you get there, you won’t know where you are.”

Michael L. Corrado, MD, FIDSA is the Chief Scientific Officer at INC Research. After nearly two decades within large pharma in executive regulatory and clinical leadership roles, Dr. Corrado co-founded Advanced Biologics and established himself as an infectious disease expert. He has been integral to the development of numerous infectious disease compounds, from pre-clinical work through marketing application submission. In addition to working on an extensive list of infectious disease compounds, he is involved with local and regional authorities to combat bioterrorism and supports their efforts for bio-preparedness. Dr. Corrado is frequently published as an anti-infective authority and has served as a member of the IDSA-FDA Anti-infective Guidelines Committee.