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Antibiotic Concentrations, What is taking so Long?

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It is widely understood in the medical community that outcomes in the treatment of infectious diseases are improved by decreasing the amount of time to the administration of appropriate antibiotic therapy. This premise hold true regardless of the pathogen or site of infection [1,2]. It is important to note that this idea has progressed beyond the idea of just administration of the correct antibiotic to the patient, it now implies that the correct antibiotic is used at a dose that will achieve optimal pharmacodynamics indices. This is where clinicians fail. In spite of the pursuit of personalized medicine, individualized dosing for antimicrobials is virtually non-existent in clinical practice. The concept of individualized dosing on antibiotics to achieve and document attainment of target pharmacodynamics indices us an idea that has been advocated for sometime. However, the clinical implementation of this practice has not emerged, owing largely to our inability to determine antimicrobial concentrations in our patients in a timely and cost-effective manner.

The outcome resulting from the treatment of an infectious process is influenced by three factors: host, pathogen, and antimicrobial (Figure 1). It is the interplay among these elements that drive the probability of success in one direction or the other. For each example, if one considers the pathogen there are complex interactions that occur between the pathogen and the host's immune system that affect the body's ability to fight off an infection or limit it's spread throughout the body. We typically attempt to simplistically characterize this interaction by examining the patient white count, vaccination history, or presence of a state that is thought to compromise immunity. However, our true understanding of factors such as expression of virulence factors or host deficiencies in specific cellular or humoral immune function are rarely known. Regarding the interaction between the pathogen and the antimicrobial, we typically attempt to characterize this interaction with susceptibility profiles. However, in many cases the true susceptibility of the pathogen to selected agents is poorly described owing to our failure to account for inoculum, growth phase, and impact of the body on a pathogen's susceptibility to antibiotic. Similarly, if one considers the interaction between the drug and the host, this relationship can be described using pharmacokinetics. This information then relates back to the pathogen through pharmacodynamics. Although scores of data exist in various patient populations for most agents, with the exception of the aminoglycosides and vancomycin, we are not able to obtain timely pharmacokinetic information on individual patients.

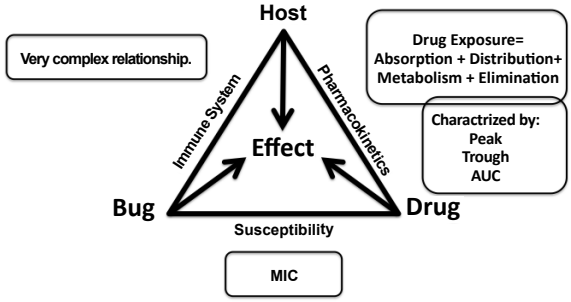

Figure 1: Host, pathogen, drug relationship.

So for a specific patient being treated for a given infection we may know an infecting pathogen and the patient's immune status. If the pathogen has been identified then we can determine the minimum inhibitory concentration (MIC). Thus the patient's pharmacokinetics and pharmacodynamics are rarely ever considered. At a time when we must be judicious stewards of our existing antimicrobials, one is led to ponder why we continue to attempt to manage patients without a full understanding of the factors that will contribute to the patient's outcome.

One obvious barrier to the optimal treatment of patients is the lack of drug assay techniques that allow for the rapid, onsite determination of antibiotic concentrations. Currently, most hospital laboratories are only able to provide timely information on patient serum concentrations for gentamicin, tobramycin, and vancomycin. For decades, the availability of timely drug levels have allowed clinicians to individualize dosing regimens to optimize outcomes and/or minimize the risk for toxicity. However, for other classes of antibacterials, antifungals, and antivirals the ability to order drug concentrations and have results available before the administration of the next dose is not an option. This means that the ability to assess the absorption of an antifungal will take weeks until the sample is sent out and results are reported. It means that the clinicians can do little more than guess about the dose needed to achieve adequate exposure in an ICU patient infected with a multi-drug resistant pathogen or the infant receiving extracorporeal membrane oxygenation or the morbidly obese patient. This ability to rapidly assess drug levels to ensure adequate exposure would seem a fundamental aspect to patient care; however, these technologies remain unavailable.

Recently, an informal poll of infectious diseases trained pharmacists was taken (Information of file). Ninety-four percent of the 89 respondents agreed that timely knowledge of antibiotic concentrations would be useful in their practice. Rationale for desiring this knowledge included ability to achieve pharmacodynamics targets, document drug absorption, monitor for drug-drug interactions, and monitor for drug-associated toxicities. Greater than 91% of the clinicians stated that in order for this information to be useful that data needed to be available to them within 24 hours. Any further delay, it was implied would serve little value in the management of a patient with an acute infectious process. It was further evident that the patient populations for whom such information would be useful were robust and virtually all patients on antibiotics but especially ICU patients, burn patients, pediatric patients, and patients with renal or hepatic impairment. Additionally,

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drugs that exhibit non-linear pharmacokinetic or erratic absorption were attractive candidates for therapeutic drug monitoring. The classes of agents for which rapid drug concentration knowledge was deemed to be most useful were the β-lactams, azole antifungals, quinolones, and daptomycin.

The reality is that most patients who are treated in the hospital for infections will receive between 3-7 days of therapy as inpatients. During this time of acute illness, they have fluctuation volumes of distribution and drug clearance. Failure to account for these types of patient variability can compromise our ability to effectively treat patients and can result in increased lengths of hospitalization, longer duration of antibiotic therapy, and increase healthcare costs. If antibiotic concentration determination is to be used to affect these outcomes it is evident that speed is of the essence. If it takes a week to get antibiotic concentrations back patients are typically dead or discharged.

In order for medicine to progress and allow for the improved management of patients with infectious processes it is evident that our tools and approach need to change. We need better information about what is going on with individual patients, not what the literature says about various patient populations that are largely dissimilar.

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