Antibiotic dosing: do we dose to cure the individual or do we treat the greater societal needs?

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'Antimicrobial resistance is an undeniable fact and will continue to be a problem for as long as we use (and misuse) antimicrobial agents.'

Historically, the introduction of sulfonamide drugs and penicillin in the 1930s and 40s was initially thought to signal the beginning of the end of many infectious disease related to morbidity and mortality. Since that time, we have witnessed more than 70 years of development and use of antimicrobial compounds and, along the way, we have uncovered novel and unique sites of antimicrobial action. Still, bacteria continue to outsmart us. Despite these shortcomings, these agents have clearly altered the course of medical history for both individuals and society and continue to redefine the antibiotic era. Unfortunately, initially witnessing the emergence of antimicrobial resistance of clinical isolates of penicillinase-producing *Staphylococcus aureus* strains in the early 1940s was not a sufficient warning and, despite this, we have failed to recognize that bacteria take, on average, only 3 years to adapt to the new challenges we develop and become resistant [1].

Paradoxically, we have only developed two new classes of antibacterials in the last 30 years – all other approved drugs have been chemical modifications of existing classes. Our ability to outsmart bacteria has been feeble. In 1960, Gould stated "we are as yet at an elementary stage in correlating the clinical administration of antibiotics with *in vitro* sensitivity determinations" [2]. Other therapeutic disciplines have adopted a quite different approach to ridding the body of unwanted invaders, for example, cancer and HIV chemotherapy have both employed the most potent agents from a class as well as use of combinations of these drugs with the clear intent to remove every last possible unwanted cell. Antibacterial therapy has not followed this approach, using the philosophy of 'there will be a new drug developed soon'. The use of antibacterials, unlike antivirals or antifungals, has clear societal consequences. Fungi do not appear to develop or disseminate resistance mechanisms in a manner similar to bacteria and while some viruses rapidly developed resistance, we were very happy to use combinations of the most potent agents to combat HIV. Antibacterials, on the other hand, have continued to be used in a 'dripping water torture' fashion, merely tormenting the bacteria to become ever more resistant, to the extent that they pass around these new found genetic elements to their progeny and others. Society has a diminishing and limited number of options left as we face a very sparse antibacterial development pipeline and, for some pathogens such as *Enterococci*, only a couple of agents have predictable activity.

As previously summarized and based on current knowledge, one can surmise five inherent principals involved with antimicrobial agents and antimicrobial resistance [3]:

- Antimicrobial resistance is an undeniable fact and will continue to be a problem for as long as we use (and misuse) antimicrobial agents
- Bacteria are remarkably adaptive and will continue to acquire and transfer new mechanisms of resistance to antimicrobial agents
- Prior strategies of dealing with antibiotic resistance have failed to slow its progression and therefore, novel approaches for understanding, predicting and dealing with resistance are required
- Changes to susceptibility breakpoints by regulatory bodies does not alter the fact that some bacteria are no longer as susceptible to antimicrobial agents as they once were and this observation is, or will be, clinically important
- Finally, the changing methods by which we utilize antibiotics, in particular, fewer doses per day, shorter courses of therapy resulting in decreased sales for pharmaceutical companies by which to recoup the outlay/investment into new drug development, presents us with a classic 'Catch 22' – we want better and effective drugs but we are not prepared to pay for them

At a time of escalating antimicrobial resistance, when fewer drugs are being developed by the pharmaceutical industry, should clinical outcome in noninferiority trials be the only measure for drug approval or should other parameters be

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insisted upon? Clinicians tend to favor clinical outcome; the microbiologists, bacterial eradication; and the pharmacologists, various pharmacokinetic/pharmacodynamic parameters. Is it now time to recognize that the clinical, microbiological and pharmacological interactions occur in patients treated with drugs for infectious diseases?

'In an ideal world, drugs would be dosed above the MPC for as long as necessary to inhibit all bacteria within the typical bacterial population.'

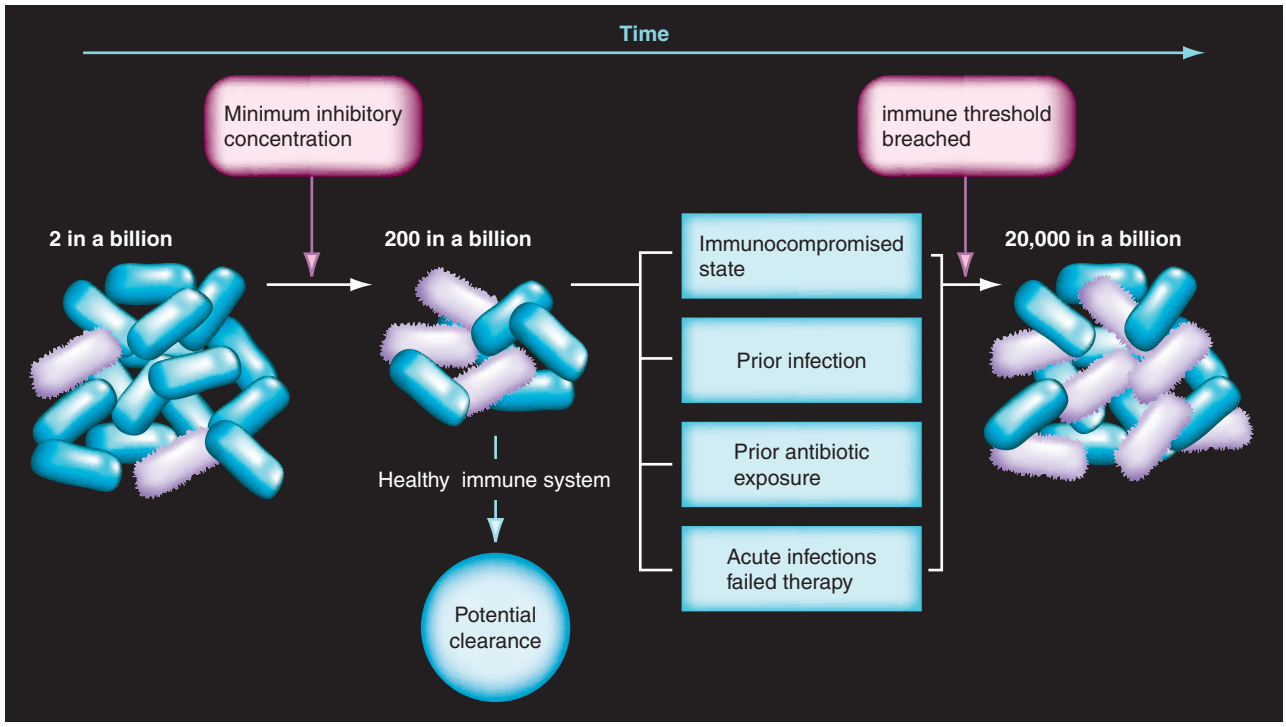
In order that we begin to better understand the way in which simple population dynamics and antimicrobial activity interplay, a new concept needs to be applied. Currently we use methods to establish a pathogen's susceptibility to an antimicrobial using inocula that are simply not representative of many infectious bioloads. Almost 60 years ago, Frisch showed that a patient with pneumonia typically has over $10^{10–12}$ organisms in the lung and yet we use only 10^5 colony-forming units (cfu)/ml as a likely predictor of resistance or susceptibility [4]. Additionally, we have dosed antibiotics at the lowest effective level so as to cause fewer adverse events and to reduce costs. Conversely, HIV and oncology therapists adopt a totally different approach in order to prevent resistance developing and subsequent infections or metastases. Total annihilation is their goal. Why not aim for the same objective with 'simple' bacterial infections? Indeed, Dagan and colleagues showed that bacterial eradication was reported for a favorable clinical outcome in patients with respiratory tract infections [5].

A novel way to try and establish how to better develop and dose antibiotics can be based on the mutant prevention concentration (MPC) concept introduced by Dong and colleagues. The MPC was coined following the recognition of a two-stage decline in bacterial load, when high-density bacterial inocula were exposed to varying antimicrobial drug concentrations [6]. When over 10^9 bacterial cells were exposed to fluoroquinolones, a sharp decline in colony recovery occurred at the MIC drug concentration. This was followed by a plateau, from which cells containing first-step resistant mutations could be recovered. The second decline in colony recovery occurred at a drug concentration that was sufficiently high to prevent the growth of these previously mentioned first step resistant mutants. This drug concentration is the MPC. A second component of the MPC concept is the mutant selection window (MSW). This range defines the drug concentration between the MIC and MPC drug concentrations. When drug concentrations are below the MIC, neither susceptible nor first-step resistant cells are inhibited with no selective amplification of resistant subpopulations. For drug concentrations above the MPC, both susceptible and first step resistant cells are inhibited and no selective amplification of resistant subpopulations occurs. However, when drug concentrations fall between these concentrations, that is, within the MSW, selection of resistant subpopulations occurs more rapidly. In an ideal world, drugs would be dosed above the MPC for as long as necessary to inhibit all bacteria within the typical bacterial population (**Figure 1**).

Much of the expansion of this conceptual work for this novel approach has come from studies with fluoroquinolones and two particularly problematic species, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*. Marked differences were observed for various fluoroquinolone–pathogen combinations such that the plateau in mutant recovery and MSW will be different. For example, for organisms that remain highly susceptible to fluoroquinolones, such as *S. pneumoniae*, the plateau in colony recovery will be relatively short, and the MPC may fall within a susceptible break point for the drug. Conversely, *P. aeruginosa* represents an organism where the differences between MIC and MPC measurements are large and mutant selection occurs over broad drug-concentration ranges. However, despite these differences, the utility of the MPC concept for reducing the selection of fluoroquinolone-resistant mutants remains significant.

MPC measurements have been used to identify key differences in the selective capacity of various fluoroquinolones generally deemed clinically equivalent [7]. When MPC values are applied to specific drug pharmacokinetics profiles, the ratios can rank the potential of each agent to select for resistance. In order of descending *in vitro* MPC/pharmacokinetic activity, a hierarchy of selectivity for resistance in *S. pneumoniae* based on the ability to inhibit first-step resistant mutants was determined with gemifloxacin > moxifloxacin > gatifloxacin = trovafloxacin > grepafloxacin > levofloxacin.

Figure 1. Selective amplification of resistant mutants.



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Moxifloxacin and gemifloxacin were the only compounds tested whose serum/tissue concentrations are expected to remain in excess of the MPC for over 12 h of the dosing interval. This suggests that they may be appropriate for once-daily dosing when preventing mutant subpopulation selection and amplification is considered [8]. Levofloxacin selected mutants at the highest rate of any quinolone tested and serum concentrations of levofloxacin remained above the MPC for approximately only 3 h of the dosing (500 mg once daily) interval (the shortest of any quinolone tested). The clinical evidence to support these *in vitro* findings comes from over 25 cases of levofloxacin therapy failure, with several patients being infected with strains of pneumococci that developed resistance while on therapy [9–12]. A schematic representation of how this may occur is shown in Figure 2. Thus, a higher or more frequent dose of levofloxacin may be required to prevent the selection of fluoroquinolone resistant *S. pneumoniae*, and subsequent clinical failures with drug-resistance organisms. Even more worrying is the extent of cross resistance conferred by these mutations to other class members. Thus, suboptimal use of one drug can damage other related compounds, unless those agents possess some intrinsic or unique activities such as dual targeting.

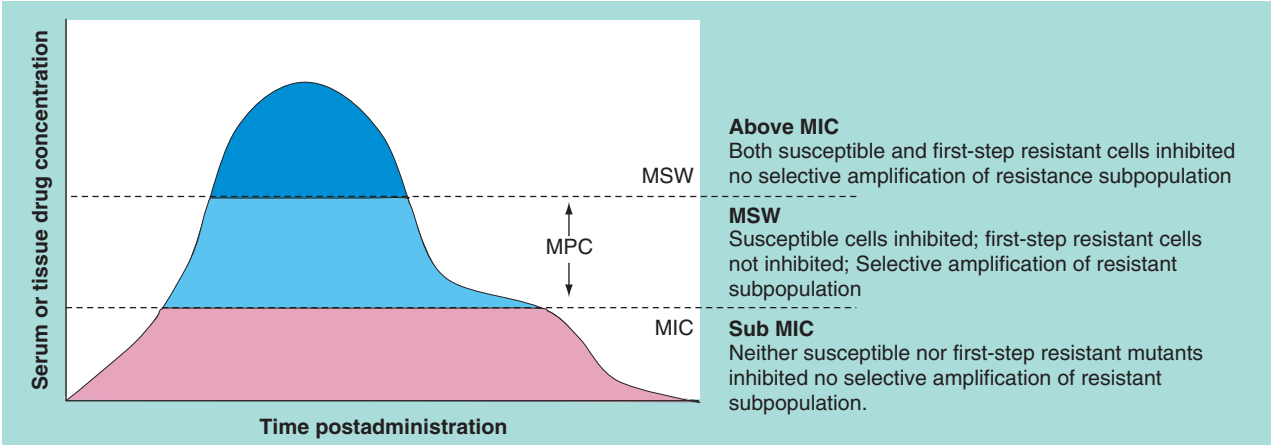
'...once the prevalence of resistance begins to increase, it can advance from below 5 to above 20% within a few years.'

Another unexpected benefit to the application of MPC criteria was the observation that killing of *S. pneumoniae* by fluoroquinolones at the MPC drug concentration resulted in increased killing and bacterial eradication, suggesting MPC dosing or better may also improve the speed of clinical symptom resolution [13,14].

There is little doubt that fluoroquinolone resistance in *S. pneumoniae* has increased during the past decade [10,15–17]. A number of studies have shown that once the prevalence of resistance begins to increase, it can advance from below 5 to above 20% within a few years [18,19]. Recent data from Canada has shown the impact of the less active macrolide azithromycin on overall macrolide resistance [20].

Past lessons, such as the escalation of penicillin resistance within *S. pneumoniae* has shown us that low-dose, long-duration therapy caused an increase in the carriage of resistant isolates such that curing infections required higher

Figure 2. Mutant selection window.



MIC: Minimum inhibitory concentration; MSW: Mutant selection window.
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doses of penicillin or new derivatives having greater potency or different binding targets [21]. Prolonged and gradual step-wise selection with β-lactams coupled with transposon dissemination and plasmid-borne factors resulted in the selective enrichment of resistant isolates which has made penicillin less effective against over 40% of the *S. pneumoniae* isolates in some areas of the USA and Canada [22,23]. Therefore, MPC testing for fluoroquinolones and *S. pneumoniae* represents a realistic approach for dealing with resistance before it becomes highly disseminated among clinical isolates and is of particular clinical importance. The extensive use of empiric therapy makes this approach even more important.

Prior to the landmark studies by Forrest and colleagues and Craig and colleagues, there was little convincing evidence linking pharmacokinetic/pharmacodynamic and microbiological observations and break points with clinical success/failure and resistance development/prevention [24,25]. There are few instances from which clinical evidence has supported pharmacodynamic differences. One good example is the case of trovafloxacin compared with gemifloxacin, two highly potent agents against *S. pneumoniae* but area under the curve (AUC)/minimum inhibitory concentration (MIC) data suggest that gemifloxacin is 30 to 40% more potent if the AUC is divided by the MIC of the given pathogen, such as *S. pneumoniae* [26]. Two clinical trials in lower respiratory tract infections actually demonstrate statistical superiority in favour of the more pharmacodynamically potent agent in both acute exacerbations of chronic bronchitis and community-acquired pneumonia [27,28]. MPC values further support these observations in terms of clinical superiority and also the lower potential for resistance selection with gemifloxacin [29].

Thus, drug development was geared to the lowest, least frequent dosages to be clinically effective with potentially fewer adverse events that could be conveniently administered so as to improve compliance, be less expensive due to lower manufacturing costs and thus be more cost effective. In today's environment, we now recognize that some of the same dosages that were shown to be clinically effective may, in fact, be the very dosages that escalate resistance, and thus not be cost-effective due to more office visits, hospitalizations and time off work – all of which are added to the need for further antibiotics. All of these events come at an extra cost, not savings as originally thought. In the USA, antimicrobial resistance is thought to cost the economy over US$4 billion annually.

The application of MPC testing to non-quinolone antimicrobials is an area that requires further investigation. While most experiments describing the MPC have been conducted with fluoroquinolones, additional studies on other antimicrobial agents have been preformed [30]. Zhao and colleagues published MPC data for chloramphenicol, penicillin G, rifampicin and tobramycin against *Escherichia coli* [31]. Recently, the effect of antimicrobial concentrations on the colony-forming ability of resistant mutant subpopulations of *Mycobacterium smegmatis* and

S. aureus for chloramphenicol, erythromycin, moxifloxacin, penicillin and tetracycline was described [32]. Ongoing investigations on MPC measurements with macrolides and *S. aureus* and *S. pneumoniae* suggest MPC studies are relevant to this class of agents [33,34].

Ultimately and unfortunately, science has nothing to do with cost and we must determine if we will be guided by cost or by science. We are prepared to accept higher prices for HIV and cancer therapies because they are life threatening. However if we fail to nurture the currently available antibiotics we will return to the pre-antibiotic era of the 1940s when pneumonia had a mortality rate of over 40%, even among healthy adults, and chronic diseases such as bronchitis led to a premature death as a result of untreatable, recurrent infections. If we truly value antibiotics and the benefits they presently afford then we need to employ new criteria such as the MPC (or other novel strategies that may be developed) for developing drugs, and be prepared to work with the pharmaceutical industry for the investments needed to bring new drugs to the doctors office.

It is probably true that when fear meets science, fear wins.

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