Antibiotic resistance—What's dosing got to do with it?

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Objective: **This review seeks to identify original research articles that link antibiotic dosing and the development of antibiotic resistance for different antibiotic classes. Using this data, we seek to apply pharmacodynamic principles to assist clinical practice for suppressing the emergence of resistance. Concepts such as mutant selection window and mutant prevention concentration will be discussed.**

Data Sources: **PubMed, EMBASE, and the Cochrane Controlled Trial Register.**

Study Selection: **All articles that related antibiotic doses and exposure to the formation of antibiotic resistance were reviewed.**

Data Synthesis: **The escalation of antibiotic resistance continues worldwide, most prominently in patients in intensive care units. Data are emerging from *in vitro* and *in vivo* studies that suggest that inappropriately low antibiotic dosing may be contributing to the increasing rate of antibiotic resistance. Fluoroquinolones have widely been researched and publications on other antibiotic classes are emerging. Developing dosing regimens that adhere to pharmacodynamic principles and maximize antibiotic exposure is essential to reduce the increasing rate of antibiotic resistance.**

Conclusions: **Antibiotic dosing must aim to address not only the bacteria isolated, but also the most resistant subpopulation in the colony, to prevent the advent of further resistant infections because of the inadvertent selection pressure of current dosing regimens. This may be achieved by maximizing antibiotic exposure by administering the highest recommended dose to the patient. (Crit Care Med 2008; 36:2433–2440)**

KEY WORDS: antibiotic; resistance; dosing; exposure; pharmacodynamics

Despite over 70 yrs of clinical antibiotic use, bacteria continue to out-perform clinicians by developing increasing levels of resistance to both old and new antibiotics. Just as bacteria continue to adapt, clinicians must continue to adapt their practice. In the field of antibiotic resistance, this is essential given the lack of antibiotics in development that possess novel mechanisms of action (1). Protecting the efficacy of our existing antibiotic armamentarium is essential.

Antibiotic dosing and administration to optimize clinical treatment of infections has been widely studied (2–5). *In vitro* and *in vivo* data are now emerging that suggest inappropriate antibiotic dosing may be contributing to the increasing rate of antibiotic resistance, in particular for fluoroquinolones (6), although data on other antibiotic classes are emerging (7). Antibiotic resistance may also develop from poor infection control (leading to acquisition of resistant organisms), selection of resistant organisms in the gut and plasmid transfer (8). It is noteworthy that interpretation of resistance depends on how it is defined: differences exist between American (Clinical and Laboratory Standards Institute) and European (European Committee on Antimicrobial Susceptibility Testing) breakpoints (9). Regardless of this issue, the global trend toward decreased antibiotic susceptibility demands that vigorous research is undertaken to develop dosing regimens that minimize the advent of resistance as opposed to just treating the infective process.

The aim of this review is to identify original research articles that examine the effect of antibiotic dosing and exposures on the development of antibiotic resistance for different antibiotic classes. Pharmacodynamic parameters describing these relationships will be sought for fluoroquinolone, aminoglycoside, β-lactam, carbapenem, and glycopeptide antibiotics. Furthermore, we seek to apply pharmacodynamic principles to assist clinical practice for suppressing the emergence of resistance.

Search Strategy and Selection Criteria

Data for this review were identified by searches of Pubmed (1966–July 2007), EMBASE (1966–November 2007) and the Cochrane Controlled Trial Register, and references from relevant articles. Search terms were "antibiotic" or "antibacterial," "resistance" or "susceptibility," and "dosing" or "exposure." English language articles were reviewed. Numerous articles were identified through searches of the extensive files of the authors. All articles that related antibiotic doses and exposure to the formation of antibiotic resistance were reviewed.

Resistance Development can Depend on the Level of Antibiotic Exposure

In 1976, Stamey and Bragonje (10) produced the first publication of an *in vitro* model that correlated antibiotic

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underdosing with resistance formation. They examined 100 strains of *Enterobacteriaceae* and showed that resistance to nalidixic acid increased with lower concentrations and concluded that underdosage was probably the cause of resistance. Similar results have been found for subtherapeutic levels of other fluoroquinolones (11, 12). Because of these initial reports, an improved understanding of antibiotic pharmacodynamics has provided potential explanations as to how this occurs.

Mutant Prevention Concentration

The Mutant Prevention Concentration (MPC) is defined as the drug concentration required to prevent emergence of all single step mutations in a population of at least 10^{10} bacterial cells (13). It is determined using wild-type bacteria not resistant populations. This concept may be important for determining optimal dosing regimens that can attain specific target concentrations and minimize the formation of resistant mutants (14). In the original study, Dong et al. (14) determined the effect of different concentrations of various fluoroquinolones on the selection of resistant mutants. Figure 1 is an adaptation of the results observed and shows that with increasing antibiotic concentrations, colony numbers exhibited a sharp drop (first-step resistant mutants), followed by a plateau and then a second sharp drop in colony numbers. Mutants were not recovered at concentrations above those required for the second sharp drop, thereby defining the MPC.

Certainly most of the information regarding the MPC exists for fluoroquinolones, although data for other classes are increasing (7, 15). Determination of MPCs for individual antibiotics may be an important step in developing dosing guidelines that will prevent the emergence of mutant colonies. This area requires further investigation.

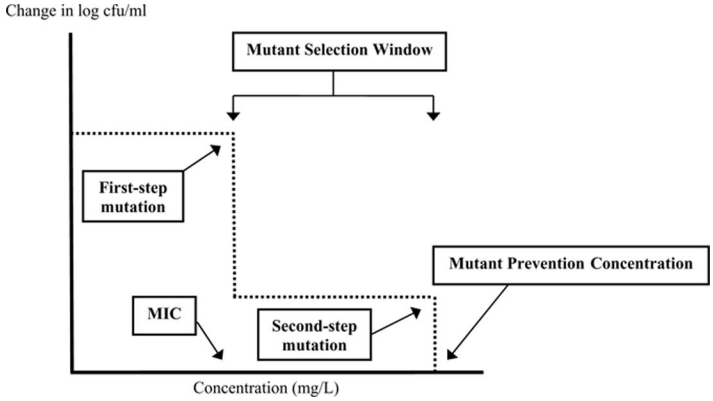

Figure 1. Mutant selection window and mutant prevention concentration. This graph represents reducing bacterial colonies with increased antibiotic exposure for a concentration-dependent antibiotic (e.g., fluoroquinolone). As exposure is increase, a greater reduction in colony forming units is observed. For bacterial colonies to survive the first "drop-off" at the bacteria's minimum inhibitory concentration (*MIC*), a first step mutation is required. For bacterial colonies to survive the second drop-off, a second step mutation is required. Selective antibiotic growth may occur when antibiotic concentrations are in the mutant selection window. The mutant prevention concentration requires at least a second-step mutation for bacterial survival. Adapted from Dong Y, Zhao X, Domagala J, et al (14). *cfu*, colony-forming units; C_{max}, maximum serum antibiotic concentration.

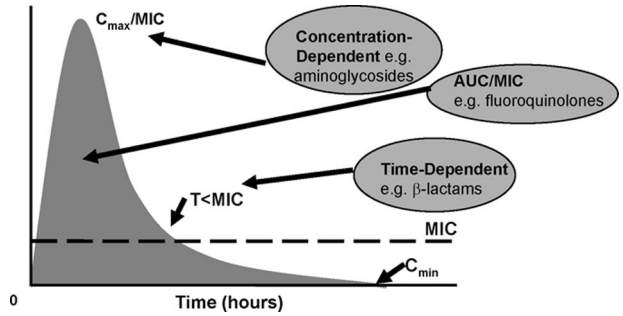

Figure 2. Pharmacokinetic and pharmacodynamic parameters of antibiotics on a concentration vs. time curve. *AUC*, area under the curve; *MIC*, minimum inhibitory concentration.

Mutant Selection Window

The term mutant selection window was first proposed by Zhao and Drlica (13), although Baquero had previously referred to the same concept as "the selective window" (16, 17). The mutant selection window describes the range of antibiotic concentrations between the minimum inhibitory concentration (MIC) and MPC in which resistant mutants may be selected (Fig. 1). Below the MIC, there is no selective pressure and thus mutants are not allowed to grow (i.e., be selected). Above the MPC, no mutants will be selected because it is thought that a double mutation for growth is necessary. The mutant selection window has been defined for many of the fluoroquinolones and some β-lactams against various organisms (7, 18–23), although its clinical relevance is still not clear.

Resistance Depends on the Antibiotic Administered

For some bacterial species, it has become apparent that some antibiotics are associated with higher rates of resistance despite similar antibiotic exposure to comparator antibiotics. Research into the relative activities of fluoroquinolones suggests that some are better than others at minimizing the development of mutants for certain organisms (24, 25). Ba et al. (24) found moxifloxacin to be superior to ciprofloxacin for delaying the selection of resistant mutants in an *in vitro* pharmacodynamic *Stenotrophomonas maltophilia* model. Furthermore, moxifloxacin has been shown to suppress efflux-containing mutants better than levofloxacin to *Streptococcus pneumoniae* (20).

Antibiotic Pharmacodynamics

Pharmacodynamics relate pharmacokinetic parameters to pharmacologic effect (26). For antibiotics, pharmacodynamics relates the concentration of the antibiotic to its anti-infective ability (27). Fundamental pharmacodynamic parameters (28, 29) illustrated in Figure 2 include the following:

- the time for which a drug's serum concentration remains above the MIC for a dosing period ($T >$ MIC),

- the ratio of the maximum serum antibiotic concentration (C_{max}) to MIC (C_{max}:MIC),
- the area of the concentration time curve during a 24-hr time period (area under the curve $[AUC]_{0-24}$) divided by the MIC (AUC_{0-24}/MIC).

Pharmacodynamically, the rate and extent of an antibiotic's activity is dependent on the interaction between drug concentrations at the site of infection, bacterial load, phase of bacterial growth, and the MIC of the pathogen (30). It follows that a change in any of these factors will affect the pharmacodynamic profile of the antibiotic against a particular pathogen and may affect not only the outcome of therapy but also predispose to formation of antibiotic resistance.

Pharmacodynamic characteristics that correlate with clinical efficacy, bacterial eradication and resistance for multiple classes of antibiotics are shown in Table 1. Individual antibiotic classes are discussed below.

Fluoroquinolones

Fluoroquinolones display largely concentration-dependent kill characteristics but also some time-dependent effects. The pharmacodynamic properties associated with fluoroquinolones have been widely studied. Previous research has suggested that depending on the pathogen, achieving a high C_{max}:MIC ratio (e.g., C_{max}: MIC up to 10 for ciprofloxacin and lomefloxacin) assists bacterial killing (21, 31–33) and is also associated with minimizing the development of resistant mutants (32, 34, 35).

AUC_{0-24}/MIC has also been shown to be important with an AUC_{0-24}/MIC >125 for successful clinical outcome for infections caused by Gram-negative organisms (36). Some authors have also shown that a high AUC_{0-24}/MIC can reduce the development of resistance (37–39). This was further quantified by Gumbo et al. (40) who found that an AUC_{0-24}/MIC of 53 is required with moxifloxacin for complete suppression of a drug-resistant mutant population of *Mycobacterium tuberculosis*. Using Monte Carlo simulations, the probability of target attainments for the recommended daily dose (400 mg/day) was 59%. When higher doses were used, the probability of target attainments improved considerably, 600 mg/day was 86% and 800 mg/day was 93%. Although the toxicity of moxifloxacin 800 mg has not been determined in a large patient cohort, high doses of ciprofloxacin up to 1200 mg/day, have previously been shown to be safe in critically ill patients (41, 42). Other studies have also shown that a high AUC_{0-24}/MPC also predicts the prevention of resistant mutants (7).

These studies all provide evidence that the recommended dose of fluoroquinolones may be inappropriately low and that reevaluation of existing dosing regimens are appropriate to ensure that clinical efficacy is optimized and formation of fluoroquinolone resistance is minimized. Given the association of high AUC_{0-24}/MIC with clinical efficacy and reduced development of antibiotic resistance, dosing that attains high C_{max}:MIC is suggested, because this will increase the AUC_{0-24}/MIC. Thus, to use ciprofloxacin as an example, doses of 400 mg 8-hourly or 600 mg 12-hourly in patients with normal organ function is appropriate. Further research that defines the precise AUC_{0-24}/MIC and toxicities for different antibiotics and dosing regimens is required.

Aminoglycosides

Aminoglycosides exhibit concentration-dependent kill characteristics, where

Table 1. Pharmacodynamic parameters that have been shown to correlate with clinical efficacy, bacterial eradication and reduced resistance for different antibiotic classes

Antibiotic Class	Pharmacodynamic Parameter Correlating with Efficacy	Pharmacodynamic Parameter Associated with Bacterial Eradication	Pharmacodynamic Parameter Correlating with Reduced Development of Resistance
Fluoroquinolones	AUC_{0-24}/MIC (36, 83–85) (e.g., ciprofloxacin AUC_{0-24}/MIC >125 hrs for Gram negative organisms)	C_{max}:MIC (31) (e.g., levofloxacin C_{max}: MIC >10)	C_{max}:MIC (32, 35) (e.g., ciprofloxacin C_{max}: MIC >4) AUC_{0-24}/MIC (37, 40) (e.g., garenoxacin AUC_{0-24}/MIC >190; moxifloxacin AUC_{0-24}/MIC >53) AUC_{0-24}/MPC (7)(e.g., ciprofloxacin AUC_{0-24}/MPC >22)
Aminoglycosides	C_{max}:MIC (45)	C_{max}:MIC (44, 86) (e.g., tobramycin C_{max}/MIC >10)	C_{max}:MIC prevent adaptive resistance[a] and possibly mutation frequency (46, 48, 51)
β-lactams	$T >$ MIC (6, 87–89)	$T >$ MIC (54)	$T >$ MSW (6) (the time within MSW increases resistance) AUC_{0-24}/MIC (58) (e.g., various β-lactams AUC_{0-24}/MIC >100)
Carbapenems	$T >$ MIC (90)	$T >$ MIC (91)	C_{min}/MIC (61) (e.g., meropenem C_{min}/MIC >6.2)
Glycopeptides	AUC_{0-24}/MIC (26, 92)	$T >$ MIC (65–67) and C_{max}: MIC (68)	AUC_{0-24}/MIC (23, 69) (e.g., vancomycin AUC_{0-24}/MIC >382)
Combination Therapy	nd[a]	nd[a]	MPC/MIC [e.g., levofloxacin/colistin (74)] AUC_{0-24}/MIC [e.g., moxifloxacin/doxycycline (70)]

Note that these published values may be derived from *in vitro* studies and may not be directly transferable to clinical settings.

[a]Adaptive resistance is the reduced drug uptake by the bacteria that survive a suboptimal dose of an aminoglycoside.

AUC, area under the curve; MIC, minimum inhibitory concentration; C_{max}, maximum serum antibiotic concentration; MSW, mutant selection window; MPC, mutant prevention concentration; nd, not defined.

C_{max}:MIC ratio >10 is recommended for optimal efficacy (28, 43–45). Suboptimal dosing of aminoglycosides may lead to adaptive resistance by virtue of a period of reduced drug uptake by the bacteria. Improved C_{max}:MIC seems to reduce this (46, 47) that may be due to use of the postantibiotic effect. Once-daily dosing adheres to C_{max}:MIC principles and the drug-free period associated with this minimizes the effect of adaptive resistance (46–48). Other forms of aminoglycoside resistance, including enzyme-mediated inactivation, have been elucidated (49, 50), although are not known to be associated with particular dosing regimens. Other data from Henderson-Begg et al. (51) have reported that bacterial mutability can occur with subtherapeutic aminoglycoside exposure.

The available data indicate that therapeutic aminoglycoside dosing should seek to maximize C_{max}:MIC and inherent postantibiotic effect that has been shown to correspond to reduced toxicity (2, 3). Thus, once daily dosing for most indications (i.e., gentamicin and tobramycin 7 mg/kg; and amikacin 30 mg/kg) is recommended in the absence of renal dysfunction or other contraindications.

β-Lactams

β-Lactam antibiotics have been associated with resistance since their early clinical use (52, 53). They are understood to be time-dependent antibiotics where bacterial killing is reported to be related to the time for which concentrations exceed the MIC of the infecting organism ($T >$ MIC) (26). Maximal killing occurs when the antibiotic concentration is maintained at 4–5× MIC (54, 55). As a minimum standard, *in vitro* and *ex vivo* data suggest that the time above MIC should be maintained for about 50% of the dosing interval for penicillins, 60%–70% for cephalosporins, and 40% for carbapenems (56). Fantin et al. (57) used an experimental *Pseudomonas aeruginosa* aortic endocarditis in rabbits using cefpirome and ceftazidime to propose that bacterial resistance to β-lactams may develop should the antibiotic concentration fall below the MIC for more than half the dosing interval.

Although some studies have been undertaken (15, 58) more are required to accurately define how β-lactam exposures may prevent resistance. Until such data become available, dosing that targets concentrations greater than 4× MIC for extended intervals would appear most appropriate (54). This has recently been reviewed (59) and is probably best achieved by using more frequent dosing or even extended- or continuous-infusion.

Carbapenems

Although carbapenems belong to the β-lactam family, they have been shown to require a reduced percentage of $T >$ MIC for bacteriostatic and bactericidal activity compared with other β-lactams (56). However, when carbapenems are used to treat serious *P. aeruginosa* infections, there is a substantial risk of development of resistance during therapy. For example, a large comparative study by Fink et al. in which imipenem 1-g 8-hourly was used found that 50% of *P. aeruginosa* strains (22 of 44 isolates) developed resistance (60). How might this emergence of resistance be prevented? Tam et al. (61) used an *in vitro* hollow-fiber infection model to show that a C_{min}:MIC (or trough concentration) >6.2 could suppress the development of resistant *P. aeruginosa* subpopulations. These data follow results of similar studies in β-lactams and suggest that it is probably optimal to maintain carbapenem concentrations at 4–6× MIC. To achieve these target concentrations, high doses are suggested. Extended infusions may also be beneficial for these antibiotics (59, 62). A study by Drusano et al. (63) deemed high-dose meropenem 2-g 8-hourly administered as a prolonged 3-hr infusion (coadministered with tobramycin 5 mg/kg 24-hourly and vancomycin 1-g 12-hourly) to be effective at minimizing resistance of *Pseudomonas* in a cohort of 120 patients with ventilator-associated pneumonia where 52 of 61 pathogens were eradicated by day 7. Although only 2 of 36 patients (and 2 of 61 pathogens) were resistant to meropenem at day 7, the effect of lower meropenem doses on rates of resistance was not examined. Chastre et al. (64) used extended infusion doripenem and compared this regimen with conventional infusion imipenem. Only 18% (5 of 28) patients treated with the extended infusion carbapenem developed resistance of *P. aeruginosa* during therapy, compared with 50% (11/22) who received the conventional infusion.

Glycopeptides

The pharmacodynamic properties of glycopeptides are not fully understood. Some data suggest that the bactericidal activity of vancomycin is time-dependent (65–67) and other data have shown that C_{max}:MIC to be important (68). However, clinical efficacy has been correlated with AUC_{0-24}:MIC (26). Although sparse data exist, it would seem that formation of resistance to glycopeptides is directly related to total exposure. Tsuji and Rybak (69) presented data that low doses of vancomycin (<500 mg 12-hourly; AUC_{0-24}/MIC <250) were associated with decreased susceptibility. Higher doses (equivalent of 750 mg or 1000 mg 12-hourly; AUC_{0-24}/MIC = 510 or 382) showed no changes in susceptibility. Similar results have been obtained by Firsov et al. (23). Certainly, these data suggest that higher dosing of glycopeptides (up to 40 mg/kg) may be important for reducing the development of resistance. Dosage adjustments based on concentrations obtained as part of therapeutic drug monitoring services can assist the clinician achieve target concentrations (15–25 mg/L).

Other Antibiotics

Data exist suggesting that low-dose linezolid (200 mg 12-hourly) is more likely to result in the development of resistance to *Enterococcus faecium* and *E. faecali* than higher doses (600 mg 12-hourly) (70). Sites of infection that are difficult to penetrate may also be associated with the development of resistance as reported by Wilson et al. (71) in isolates from a patient with a thoracotomy wound with contingent empyema. When devising linezolid courses, clinicians also need to be aware of data that suggest that longer courses (>2 wks) of linezolid treatment may increase the possibility of the development of antibiotic resistance (72). Data supporting courses >2 wks leading to development of antibiotic resistance also exist for daptomycin (73).

Combination Antibiotic Therapy

Combination antibiotic therapy has been advocated for some bacterial infections (e.g., enterococcal endocarditis or serious pseudomonal infections) on the basis of *in vitro* synergy between the antibiotics used. From a theoretical point of view, combination therapy may assist in avoiding the development of resistance because the AUC_{0-24}/MIC of the antibiotics seem to be additive or even synergistic (61, 74–76). These studies show that

combination therapy is an appropriate way to reach target exposure and may reduce the chance of resistance by avoiding excess total time in mutant selection window. Randomized clinical studies have not shown that combination therapy reduces emergence of antibiotic resistance (77). Appropriate dosing of individual antibiotics may negate the need for combination therapy infections caused by organisms with a high potential for resistance formation (e.g., *Pseudomonas* infections). If combination therapy does provide an advantage, it is likely to be early in the course of infection when the inoculum of infecting organisms is highest.

Effect of Bacterial Factors—Species, Subpopulation, Fitness, Load

Dosing requirements have been reported to change depending on bacterial species, subpopulations, "biological fitness," and the bacterial load. An additional factor that may require further research is the impact of antibiotic treatment on the development of resistance in normal commensal flora.

Data and clinical experience suggest that the rate of resistance formation of a pathogen depends on the bacterial species. *P. aeruginosa* has been shown to develop resistance to moxifloxacin more readily than *S. pneumoniae* (78). Although moxifloxacin is not indicated for use in *P. aeruginosa* infections, these data demonstrate that different bacterial species may be more capable of developing antibiotic resistance to certain antibiotics.

The opportunities for development of resistance also seem to increase with the presence of resistant bacterial subpopulations in a culture. Croisier et al. (20) used an *in vivo* model to demonstrate that therapeutic moxifloxacin and levofloxacin were both efficient with wild-type experimental *S. pneumoniae*, with only moxifloxacin being effective against *S. pneumoniae* with a resistant subpopulation.

Bacterial fitness is a measure of the ability of a pathogen to infect a host, persist and proliferate, and be transmitted to a new host (79). As such, if a patient acquires a pathogen from a hospital environment, then this pathogen is more likely to have had previous antibiotic exposure and be more capable of developing resistance.

Bacterial load may also be an important factor for dosing recommendations. Jumbe et al. (80) developed a mathematical model for *P. aeruginosa* to show that dose requirements increase by a factor of 2–6 for each increase in bacterial population by a factor of 10 (e.g., 10^7–10^8). Although Craig et al. (81) have recently expressed doubts over the clinical relevance of the inoculum effect it does provide additional rationale for the importance of clinicians achieving adequate source control when managing patients with infection.

Predicting the effect of bacterial species, subpopulations, and bacterial load during empirical therapy is impossible, and as such, use of maximum tolerated antibiotic doses may be required to ensure optimal treatment of the infection and prevention of the development of resistant mutants.

Cross Resistance

Data on resistance across antibiotic classes are developing and suggest exposure to an antibiotic can induce resistance to antibiotics with different modes of action (known as cross-resistance). An *in vitro* model by Fung-Tomc et al. (82) found exposure of methicillin-resistant *Staphylococcus aureus* to subinhibitory levels of ciprofloxacin promoted the development of low-level resistance to tetracycline, imipenem, fusidic acid, and gentamicin. Similar ciprofloxacin exposure to a *P. aeruginosa* variant promoted decreased susceptibilities to imipenem, amikacin, and cefepime. Similar results were found by Henderson-Begg et al. (51) using *S. pneumoniae*. This phenomenon may not occur with all antibiotic agents or classes. The Fung-Tomc et al. (82) model also tested an aminoglycoside and found no cross-resistance to other antibiotics whereas Henderson-Begg et al. (51) found contrary results for streptomycin.

What About Patient Factors?

A considerable body of evidence exists describing the altered pharmacokinetic characteristics of antibiotics in organ dysfunction and various disease states (e.g., sepsis) (27). Recommendations for either decreased dosing in patients with organ dysfunction, or increased dosing in patients with supranormal renal function are available. However, there is scarce documentation of the dose-exposure relationships and the effect of such regimens on antibiotic resistance. Further research must address optimal dosing in specific patient populations and disease states to ensure appropriate plasma, and more importantly, tissue levels are achieved.

The available data suggest that a paradigm change in antibiotic dosing may be required to ensure that maximal doses given in such a way to achieve high drug exposures (without causing toxicity) to suppress the formation of antibiotic resistance. We propose the term "highest tolerated dose" to describe this dosing strategy. Other pharmacokinetic and pharmacodynamic studies to determine the precise doses for different antibiotics in different patient populations are also required.

CONCLUSIONS

Emerging data suggest that achieving specific pharmacodynamic targets for antibiotic exposure can help reduce the development of resistance. Research has defined pharmacodynamic parameters for different antibiotic classes particularly fluoroquinolones, and different bacterial species that are reported to correlate with clinical efficacy and reduce the formation of antibiotic resistance. Although substantial data on fluoroquinolone exposure to prevent resistance formation exist, there is a dearth of information on other antibiotic classes.

The combination of the escalation of worldwide antibiotic resistance and reduced development of new antibiotics behooves us to optimize our use of available antibiotics. The evidence that has been identified in this structured review supports the notion that antibiotic dosing must target the most resistant subpopulation in the bacterial population in an effort to prevent the emergence of resistant organisms because of selective pressure. This may require a research and practice paradigm change so antibiotic selection and dosing strategies are designed to consider limiting antimicrobial resistance by administering the highest tolerated dose of antibiotic.

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