

Therapeutic Controversies

The Changing Face of Antibiotic Prescribing: The Mutant Selection Window

Benjamin J Epstein, John G Gums, and Karl Drlica

OBJECTIVE: To describe the mutant selection window, discuss supporting evidence and limitations, and suggest potential applications for clinical practice.

DATA SOURCES: A MEDLINE search (1990–December 2003) of the English-language literature was conducted using the key words antibiotic, antimicrobial, resistance, mutant, selection window, prevention, MPC, and MSW in various combinations. Original investigations and reviews evaluating the mutant selection window, including abstracts and proceedings, were considered for inclusion. Published articles were also cross-referenced, and experts were contacted to locate additional pertinent data.

STUDY SELECTION AND DATA EXTRACTION: All data sources identified were evaluated and all information deemed relevant was included.

DATA SYNTHESIS: Until recently, physicians have had few ways to preserve antimicrobials from resistance other than by prescribing the agents less often. The mutant selection window hypothesis may modify this paradigm by shifting the focus to dosing strategies that reduce the growth of resistant mutants. Conventional dosing strategies have been formulated on the likelihood of curing an individual patient. Unfortunately, doses that cure patients appear to enrich resistant subpopulations of bacteria, thus promoting resistance. Antimicrobial–pathogen combinations can be identified that minimize mutant selection and cure patients while possibly restricting the progression of resistance.

CONCLUSIONS: The mutant selection window hypothesis provides a framework for considering the contribution of dosing to resistance, and it offers ideas for restricting the enrichment of resistant mutants and antimicrobial resistance.

KEY WORDS: antimicrobial resistance, mutant prevention concentration, mutant selection window.

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Resistance to antimicrobials is emerging at an alarming rate that has reduced treatment options for nearly every pathogen infecting humans.^{1,2} Many bacteria now display a variety of mechanisms that help protect them during antimicrobial exposure. These include production of extended-spectrum β -lactamases and cephalosporinases, alterations in penicillin-binding proteins, multidrug efflux pumps, transferable resistance to vancomycin, and mutations in genes encoding DNA gyrase and DNA topoisomerase IV. Contributing to the resistance “epidemic” are

increases in antibiotic use and human population density.³ We may soon find ourselves in a post-antimicrobial era in which bacterial infections are a more serious health problem than they were in the pre-antibiotic era due to an increased frequency of immunosuppression from factors such as AIDS, transplant pharmacotherapy, and an aging population.

Until recently, new, more effective antimicrobials have been developed and approved rapidly enough to keep us slightly ahead of bacterial resistance. Unfortunately, this differential is difficult to maintain due to expense and difficulties in discovering new drug targets. Meanwhile, surveillance studies show that resistance is growing. For example, the nationwide TRUST (Tracking Resistance in the United

Author information provided at the end of the text.

States Today) surveillance project has revealed an increase in drug resistance among common respiratory pathogens for 7 of 9 agents tested during the 1998–1999 and 1999–2000 respiratory infection seasons.⁴ Among gram-positive organisms, *Streptococcus pneumoniae* and *Staphylococcus aureus* have received most of the attention. From the 1940s to the 1960s, *S. pneumoniae* was universally susceptible to penicillin, exhibiting minimum inhibitory concentrations (MICs) <0.10 µg/mL for >99% of isolates. During the succeeding 20 years, penicillin resistance began to flourish, which led to the widespread use of macrolides in the 1980s and 1990s.^{5,6} In some localities in the US, 25% of clinical isolates are now resistant to macrolides.⁴ Resistance in *S. aureus* developed along similar lines, that is, penicillin initially provided an excellent treatment, but its effectiveness deteriorated when the pathogen began to synthesize β-lactamase.^{7,8} The penicillinase-resistant penicillins, typified by methicillin, supplanted penicillin; however, by the 1960s, alterations in penicillin-binding proteins rendered this class ineffective.⁸ Methicillin-resistant *S. aureus* subsequently spread through many hospitals.⁹ In the early 1990s, many isolates became resistant to ciprofloxacin and, in May 1996, the first clinical isolate of *S. aureus* having intermediate resistance to glycopeptides was reported.¹⁰ Six years later, the first case of vancomycin-resistant *S. aureus* was documented.^{11,12}

Gram-negative resistance is also troublesome, with *Pseudomonas aeruginosa* and *Acinetobacter* spp. eliciting special concern.^{13–16} The National Nosocomial Infections Surveillance System reported that, during 1999, >20% of *P. aeruginosa* isolates had become resistant to fluoroquinolones and imipenem, representing an increase of >50% compared with data from 1994 to 1998.¹³ *Acinetobacter* spp. were once considered commensal organisms; however, in the 1970s, *Acinetobacter calcoaceticus* was identified as a potential cause of nosocomial infection.^{17,18} Today, *Acinetobacter baumannii* is recognized as a resilient, opportunistic, multidrug-resistant pathogen accounting for 8% of bloodstream infections and 10% of pneumonias in many intensive care units.^{19,20} Most isolates of *A. baumannii* are resistant to β-lactams (except ceftazidime and cefepime), tetracyclines, macrolides, rifampin, and chloramphenicol.^{21,22} Many clinical isolates are also resistant to gentamicin and fluoroquinolones, and nearly 11% of clinical isolates are imipenem–non-susceptible *Acinetobacter* spp., depending on geographic location.²¹

A variety of medical organizations have advocated more judicious use of antimicrobials for both clinical and agricultural applications.^{23–27} However, these recommendations have not deterred widespread, inappropriate use in hospitals and communities. Some compounds are still jokingly called “vitamins” due to their indiscriminate institutional use. Patients are not always informed of the consequences of inappropriate antibiotic use, and they frequently fail to consume them as prescribed.²⁸ Even when progress against resistance appears to have been made, we may simply be squeezing the resistance “balloon,” that is, exchanging one resistance problem for another.²⁹ For example, in one hospi-

tal, implementing a formulary restriction on cephalosporin use decreased the incidence of cephalosporin-resistant *Klebsiella* infection and colonization at the expense of an increase in imipenem-resistant pseudomonal infection.³⁰

While the task of preserving available antimicrobial agents sometimes seems hopeless, a new concept, the mutant selection window hypothesis, has evolved that may offer a way to slow the development of resistance arising from therapy. The heart of the hypothesis is that a drug concentration range (selection window) exists in which mutants are enriched. Current dosing practices tend to place antimicrobial concentrations inside that window. By identifying and then avoiding concentrations inside the window, it may be possible to significantly slow the amplification of resistant mutants. We describe the mutant selection window, discuss supporting evidence, suggest potential applications, and list current limitations.

The Mutant Selection Window Hypothesis

Baquero^{31,32} first suggested that a dangerous drug concentration zone exists; exposure to antimicrobial concentrations inside this zone confers a survival advantage to organisms having reduced susceptibility. Subsequent studies with mycobacteria, treated in vitro with fluoroquinolones, defined the boundaries for the dangerous zone, which was renamed the mutant selection window.^{32–35} In these experiments, the recovery of mycobacterial mutants was measured after large, susceptible populations were applied to agar plates containing various concentrations of fluoroquinolones.³⁶ As drug concentration increased, the number of colonies recovered dropped sharply, leveled to a plateau, and then dropped sharply a second time.

A similar response was observed with *S. aureus* (Figure 1).³⁶ The first decline in colony recovery corresponds to the MIC with wild-type bacteria, the plateau or inflection is due to the presence of resistant mutant subpopulations, and the second drop in recovery arises when the MIC of the least susceptible mutant is reached. The latter value has been termed the mutant prevention concentration (MPC) because, above that concentration, a cell must acquire 2 concurrent resistance mutations for growth, an event that is expected to occur rarely. The lower boundary of the selection window is approximated by the MIC and the upper boundary by the MPC. The window corresponds to the range of drug concentrations that exert selective pressure on microbial growth; in this range, cells that harbor resistance genes grow preferentially (Figure 1 inset).

The existence of a selection window was recently supported by a dynamic experiment conducted by Firsov et al.³⁷ They designed an in vitro model in which *S. aureus* was exposed to fluctuating fluoroquinolone concentrations above the MPC, inside the mutant selection window, or below the MIC. *S. aureus* was then recovered, and MIC was measured as an indicator of mutant enrichment. Only drug concentrations inside the mutant selection window were associated with an increase in MIC. A similar conclusion was reached with moxifloxacin treatment of *S. pneumoni-*

*ae.*³⁸ A third study, performed with *Escherichia coli*, extended the selection window hypothesis to gram-negative organisms.³⁹ In that work, the MPC was calculated for a variety of antimicrobials, and pharmacokinetic parameters were then used to estimate the length of time that drug concentrations would fall in the selection window. Those investigators also examined the impact of temperature and oxygen tension on the selection window to simulate varying conditions encountered in vivo.

The window hypothesis is potentially important, because dosing guided by traditional pharmacodynamic standards tends to place antimicrobial concentrations inside the mutant selection window where they selectively enrich resistant mutant subpopulations. Once amplified, the mutant cells disseminate to a fresh host, bacterial population expansion occurs, and a new round of antimicrobial pressure further enriches the mutant population. In this scenario, the physician rarely observes the development of resistance, but over the course of many antimicrobial treatment courses, the mutant fraction of the bacterial population eventually predominates. Only at that point do surveillance studies begin to report isolates as resistant. The practice of “dosing to cure” leads to resistance by placing drug concentrations inside the mutant selection window for long periods of time.

Measurement of Mutant Selection Window

While the selection window is characterized by the types of plot shown in Figure 1, determination of the upper and lower boundaries is sufficient for most applications.

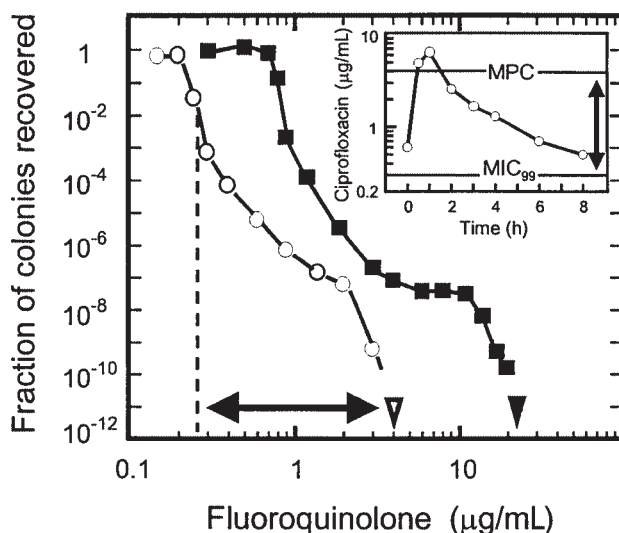


Figure 1. Mutant selection window. *Staphylococcus aureus* was applied to agar containing the indicated concentrations of ciprofloxacin (open circles) or norfloxacin (solid squares). The number of colonies recovered after incubation is expressed as a fraction of input cells. The MIC_{99} , indicated by the dashed line, represents the bottom of the selection window. The upper boundary of the window is estimated by the concentration that blocks growth of $\geq 10^{10}$ cells (vertical arrowhead). The mutant selection window is represented by the double-headed arrow. The selection window is also shown in the inset, in which serum drug concentration is shown at various times after treatment of human volunteers with ciprofloxacin. MIC_{99} = minimum inhibitory concentration for 99% of the cells; MPC = mutant prevention concentration. Figure adapted with permission from University of Chicago Press.³⁶

The upper limit of the window, MPC, is the concentration that inhibits the growth of the least-susceptible mutant subpopulation, a value estimated as the concentration that prevents colony formation when more than 10^{10} cells are tested. To assure that the colonies recovered represent mutants, colonies are retested for growth on agar containing the same concentration of drug used initially for selection. In some cases, large inocula affect the concentration that prevents colony formation. In such cases, tests examining 10^{10} cells are obtained by applying smaller numbers of cells to large numbers of agar plates.

The procedure described above is generally too laborious for surveys involving large numbers of isolates. An abbreviated protocol has been used in which drug concentrations vary by twofold, and 10^9 to 10^{10} colony-forming units are applied to each agar plate.⁴⁰ This assay is not very precise because growth is frequently seen either as a lawn or as no growth. However, when the MPC is measured for a large number of isolates, on the order of 100, the relative values observed for related compounds is similar to that observed when isolated colonies are recovered with lower inocula using large numbers of agar plates.

The lower limit of the selection window can be estimated as MIC or, more accurately, as MIC_{99} . For the latter determination, a series of agar plates is prepared containing drug concentrations that differ by linear increments rather than by the standard twofold difference. Dilutions of cells are applied to the plates and, after incubation, the number of colony-forming units is measured. MIC_{99} is then determined by interpolation of a plot of the fraction of colony-forming units recovered versus drug concentration. The subscript parentheses are used to distinguish the measurement from MIC_{99} , a term used in surveillance studies to signify a concentration that exceeds the standard MIC for 99% of the isolates tested.

Antimicrobial Resistance and Shortcomings of Current Practice

Clinicians have been taught that appropriate prescribing of antibiotics involves identifying a bacterial etiology, selecting a suitable agent, and choosing the right dose, frequency, and duration of therapy.^{41,42} But what is the appropriate dose? MIC is frequently employed as a threshold since antimicrobial concentrations above MIC are expected to inhibit expansion of the pathogen population. By how much and by how long drug concentrations at the site of infection (approximated by serum drug concentrations) must exceed the MIC to elicit a favorable outcome can be estimated from empiric pharmacodynamic considerations. Depending on the particular agent, the pharmacodynamic goal of antimicrobial therapy may be to administer the agent such that (1) the serum concentration exceeds the MIC of a pathogen for the majority of the dosing interval, (2) maximal serum concentration exceeds the MIC by a factor of 10–12, or (3) the AUC exceeds the MIC by a factor of 100–125 for gram-negative bacteria and 30–50 for gram-positive bacteria.^{43–45}

The definition of MIC, the lowest concentration of an antimicrobial necessary to inhibit bacterial growth in vitro when 10^4 to 10^5 cells are tested, does not allow the measurement to reveal the presence of small, resistant subpopulations.^{46,47} Since 10^9 to 10^{10} organisms can sometimes be found at a site of infection and since bacterial mutants can be recovered at a frequency of 10^{-6} to 10^{-9} , hundreds, or even thousands, of mutants may be present without being detected by standard susceptibility testing.⁴⁸⁻⁵⁰ Moreover, organisms harboring resistance genes that are not fully protective are ignored because treatment generally leads to cure when individual patients are considered. The presence of these “low-susceptibility” organisms can increase the likelihood that mutants displaying even lower susceptibility are enriched by subsequent antimicrobial treatment. Over time and after millions of exposures worldwide, these mutants gradually lower the susceptibility of the bacterial population as a whole.⁵¹ Thus, MIC is a poor threshold to use for preventing the outgrowth of mutant subpopulations present prior to therapy.

Susceptibility breakpoints serve as a quick test for resistance that has already developed. When the MIC is above the breakpoint, the dominant members of the bacterial population are judged to be resistant, and the antimicrobial is unlikely to have much effect (in some cases, local drug concentrations may be much higher than serum concentrations; this feature, along with host defenses, could contribute to the resolution of infections by pathogens considered by in vitro standards to be resistant⁵²). Thus, breakpoints are useful for revealing resistance at the dissemination phase, but not at the mutant enrichment phase of resistance development.

MPC and Restricting the Enrichment of Mutants

MPC, as the upper boundary of the mutant selection window, represents a conceptual threshold for antimicrobial concentrations above which the enrichment of resistant mutants is expected to be severely restricted. Antibacterial-pathogen combinations fall into 2 categories with respect to MPC. One includes combinations for which monotherapy generates serum concentrations above the MPC during standard dosing. Examples include some fluoroquinolones with many gram-negative and some gram-positive bacteria.^{36-40,53-55} These drug-pathogen combinations are characterized by enhanced antimicrobial activity against resistant mutants, attainment of high serum/tissue drug concentrations, and relatively long drug half-life. The second category comprises drug-pathogen combinations in which serum drug concentrations do not exceed the MPC. Examples include rifampin against *S. aureus* and *E. coli*, treatment of *Mycobacterium tuberculosis* with most agents, and many cases of plasmid-mediated resistance. Situations exist in which some agents in the same class attain serum concentrations above MPC while others do not (Table 1).⁵⁶

The distinction between categories with respect to MPC is important because each mandates a different treatment strategy for restricting the amplification of mutants. In principle, antimicrobial-pathogen combinations belonging

to the first category may be used as monotherapy since concentrations exceed the MPC throughout the dosing interval. In this scenario, antimicrobial therapy would rarely enrich resistant mutant subpopulations because 2 concurrent, spontaneous resistance mutations must occur for cell growth. On the other hand, infections that must be managed with agents from the second category require combination drug therapy to minimize mutant selection (dual drug therapy with agents that have different genetic targets also requires a double mutation for cell growth).

Use of MPC as a dosing guide is distinct from currently accepted practice since compounds are selected by virtue of their anti-mutant activity and likelihood of cure rather than solely on favorable patient outcome (cure) rate. The latter may be similar for many members of the same drug class despite differences in activity against mutants. Consideration of the selection window hypothesis suggests that combination therapy should be implemented much more often than is currently the practice.

Potential Applications of the Mutant Selection Window to Clinical Practice

The selection window hypothesis provides general guidance for dosing practices (limitations are listed in the following section). For example, mutant selection within the window is not uniform; that is, lower drug concentrations enrich mutant subpopulations to a greater extent than higher concentrations.⁵⁷ This relationship, which has been identified for β -lactams with *S. pneumoniae* and fluoroquinolones with mycobacteria, suggests that low antimicrobial doses contribute substantially to the development of resistance.⁵⁸ Accordingly, prescribing low doses of antimicrobials is no longer advisable; with respect to resistance, clinicians should favor the highest recommended dose.

The mutant selection window can also be used to help distinguish the resistance potential among similar compounds by examining MPC, dosing regimens, and pharmacokinetics for a given drug-pathogen combination (Table 1). These parameters can be compared to determine which agent maintains serum concentrations above the

Table 1. Relationship of Pharmacokinetics and MPC^{56,a}

Fluoroquinolone	MPC ₉₀ (mg/L)	Dose (mg)	C _{max} (μ g/L)	t _{1/2} (h)
Gemifloxacin	1	320	1.6	7-8
Moxifloxacin	2	400	4.5	12-14
Gatifloxacin	4	400	4.2	8-10
Levofloxacin	8	500	5.7	5-7

C_{max} = maximum serum concentration; MPC = mutant prevention concentration; t_{1/2} = half-life.

^aMPC was measured with 146 clinical isolates of *S. pneumoniae* for the indicated fluoroquinolones. Also shown are pharmacokinetic parameters. Some compounds have a value of MPC that is below the C_{max} while others, such as levofloxacin, have a value of MPC that is above the C_{max}.

MPC for the longest time. For example, moxifloxacin achieves a serum concentration of 4.5 $\mu\text{g/mL}$ when administered at the recommended dose of 400 mg/day.⁵⁹ This is well above its MPC of 2 $\mu\text{g/mL}$ with clinical isolates of *S. pneumoniae*. Based on an average elimination half-life of 12 hours, serum concentrations should remain above the MPC for most of the dosing interval (18 h).^{40,56} In contrast, the maximum serum concentration achieved with levofloxacin after a dose of 500 mg is 5.7 $\mu\text{g/mL}$ and the MPC is 8.0 $\mu\text{g/mL}$.⁶⁰ Thus, serum concentrations are not expected to surpass the MPC during treatment. Additional refinement for such comparisons involves using available drug concentrations at the site of infection rather than total serum concentration.

When antimicrobial concentrations cannot be maintained above the MPC with the maximum recommended dose, combination therapy is indicated for restricting enrichment of resistant mutants.⁵⁸ If ≥ 2 antimicrobials are present at the site of infection and at concentrations above their MICs, the mutant selection window will be “closed” (Figure 2).³³ For example, the MPC is out of reach for first-line agents used to treat *M. tuberculosis*, but when combination therapy with multiple agents that have different molecular targets is used, the ability of bacteria to develop resistance is reduced.

In principle, 2 criteria should be met to curtail resistance with combination therapy: ≥ 2 active agents with different sites of action should be administered to minimize cross-resistance, and both agents should be maintained at concentrations above their respective MICs. Maximal suppression of mutant growth is expected when ≥ 2 agents are prescribed whose pharmacokinetic profiles are superimposed because concentrations will rise above and fall below the MIC simultaneously (Figure 3). If at any time during the dosing

interval the concentration of one drug falls below the MIC, the drug remaining above its MIC will allow resistant mutant growth. Such is the likely explanation for the rapid development of resistance in a trial involving the anti-tubercular agents rifapentine and isoniazid.⁶¹ (Nonadherence to therapy regimens is generally considered to be the major factor in resistance to anti-tubercular agents.⁶²) Considering that antimicrobials are prescribed in doses that are intended to surpass the MIC of the organism being treated, maintaining suitable pharmacokinetic overlap may require little more than initiating and terminating individual agents concurrently. Refinement of this idea involves consideration of factors such as the post-antibiotic effect, which prolongs the action of antibiotics.

The MPC has been measured in vitro for a handful of antimicrobial–pathogen combinations, and it appears that maintaining drug concentrations above the MPC is unrealistic in several cases. Some of the best examples are anti-tubercular agents.³⁵ Other examples are seen with *S. pneumoniae* for some fluoroquinolones (Table 1). If combination therapy cannot be used for those situations, clinicians may wish to consider other treatment options. One may be to prescribe a higher dose more frequently. For example, gatifloxacin serum concentrations may surpass the MPC with *S. pneumoniae* only briefly (1–2 h), if at all.^{56,63} If a larger dose is given more often, time above the MPC is expected to increase. For higher, more frequent dosing to be suitable, it must be shown not to result in unacceptable adverse effects. If compelling reasons justify avoiding high-dose or multi-agent strategies, patients should be monitored closely for signs of bacterial resistance (ie, therapeutic failure), especially if they are in a setting where they can serve as a reservoir for the dissemination of resistant strains. Compelling reasons for avoiding high doses may include renal or hepatic dysfunction that could lead to drug accumula-

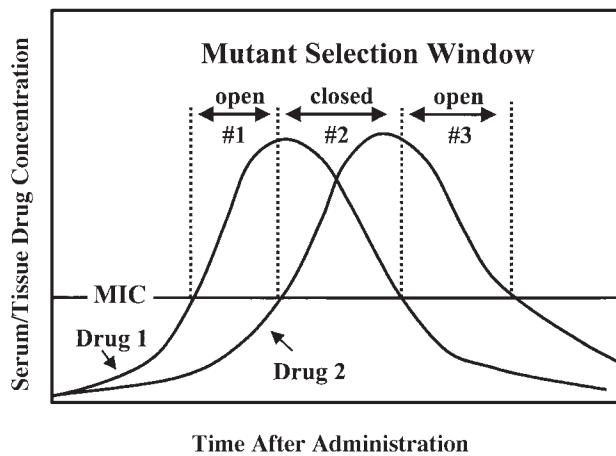


Figure 2. Closing the mutant selection window. Effect of pharmacokinetics on selection of resistant mutants during dual-drug therapy: mutant selection windows open due to insufficient overlap of pharmacokinetic profiles. Two antibiotics are shown, with concentrations rising above and dropping below the MIC at different times, creating situations in which only one drug is above its MIC (situations #1 and #3). Mutants are enriched in these conditions. Only in situation #2 are both agents above their respective MICs.³³ MIC = minimum inhibitory concentration.

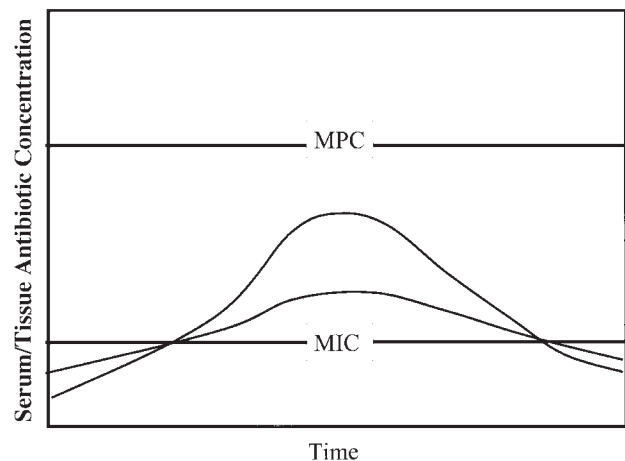


Figure 3. Mutant selection window largely closed. Two drugs with separate bacterial targets can close the mutant selection window if pharmacokinetic parameters are optimized. The concentrations of both drugs rise to above the MIC at approximately the same time and remain above the MIC for similar amounts of time. MIC = minimum inhibitory concentration; MPC = mutant prevention concentration.

tion or dose-related toxicity (eg, QTc prolongation with fluoroquinolones).

The most important application of the selection window hypothesis may ultimately involve the design of new drugs. Activity against mutant subpopulations can be monitored early in the development process, and drugs can be sought that have a very narrow window. The latter would be especially advantageous because it would reduce the effect of patient-to-patient pharmacokinetic fluctuation on resistance. In principle, such fluctuation could cause an agent whose concentrations normally fall outside the selection window with one patient to fall inside the window with another. Drugs with very narrow selection windows would rarely amplify mutants. With fluoroquinolones, window size can be manipulated by altering drug structure.³⁶

Limitations

The selection window hypothesis is a new idea that has not been tested in many different situations; consequently, its applications are currently limited by lack of data. For example, values of MPC measured on agar plates have not been calibrated with concentrations required to prevent mutant amplification in either animal systems or clinical situations. Thus, we do not know how effective keeping concentrations above the MPC will be at slowing the development of resistance.

Another limitation concerns resistance that enters a bacterial population at high frequency. When this occurs and pathogen populations are large, drug concentrations may need to be high enough to block growth of mutants with 3 or perhaps even 4 concurrent mutations rather than the 2 required for the rare spontaneous resistance mutations discussed in previous sections. High-frequency resistance can be associated with horizontal transfer of resistance determinants, such as plasmid-borne resistance. If the level of protection is high, attaining concentrations above the MPC may not be possible. Even if protection is initially low, its frequency of occurrence may be so high that acquisition of an additional resistance mutation is likely to occur. In both cases, combination therapy is required, although resistant mutants may represent a low percentage of the population. Smith et al.⁶⁴ pointed out that application of laboratory data derived for spontaneous mutations to clinical situations in which resistance is largely plasmid borne can lead to incorrect conclusions.

A third limitation is that the selection window hypothesis fails to consider lethal action, a central feature of pharmacodynamic approaches. Antimicrobial agents have been traditionally categorized as either time- or concentration-dependent killers, and therapy regimens are designed accordingly. Reducing the bacterial population size through lethal activity reduces the probability that new mutations will be fixed in the population. However, drug concentrations inside the selection window do not generally kill resistant mutants. Consequently, such treatment will cause mutant enrichment with infections that contain mutant sub-

populations prior to initiation of therapy. Removal of these mutants probably depends on host defenses rather than antimicrobial treatment.

Determining whether the MPC threshold can be relaxed due to mutant killing may require case-by-case consideration using empiric pharmacodynamic methods in which drug dose is gradually raised until a point is found in which resistant mutant subpopulations fail to increase in size.⁶⁵ Such an approach, if conducted with a sufficiently large starting bacterial population, should reach the same threshold as the selection window method if lethal activity is an insignificant factor.

Summary

The goal of antimicrobial therapy currently focuses on curing disease while minimizing toxic consequences. To achieve this goal, treatment regimens have been designed to block susceptible cell growth or kill vulnerable cells. Pharmacokinetic and pharmacodynamic considerations based on empiric measurements of clinical outcome have been adopted as estimates of how far above or for how long serum concentrations should remain above the MIC. If these drug concentrations are not also above the MPC, which *in vitro* data suggest they usually are not, resistant mutants will be enriched. Use of this strategy to treat large numbers of patients eventually leads to bacterial populations in which resistant mutants are the dominant members. It is only at this point that surveillance methods detect resistance. Thus, the true magnitude of the resistance problem may be grossly underestimated. The mutant selection window hypothesis provides a framework for considering the contribution of antimicrobial dosing to resistance. It also offers ideas for restricting the enrichment of resistant mutants that can be added to established efforts for diminishing the spread of resistant strains.

ADDENDUM: The mutant selection window hypothesis has recently been tested with a rabbit model of pneumococcal pneumonia.^{66,67} The emergence of resistance fits better with the mutant selection window than with traditional pharmacodynamic analysis, and the recovery of mutants was restricted when moxifloxacin concentration reached and exceeded the MPC determined with agar plates.

Benjamin J Epstein PharmD, at time of writing, Internal Medicine Resident, North Florida/South Georgia Veterans Affairs Health-System, Gainesville, FL; now, Postdoctoral Fellow, Departments of Pharmacy Practice and Community Health and Family Medicine, Colleges of Pharmacy and Medicine, University of Florida, Gainesville

John G Gums PharmD, Professor of Pharmacy and Medicine, Departments of Pharmacy Practice and Community Health and Family Medicine, College of Pharmacy and Medicine, University of Florida, Gainesville

Karl Drlica PhD, Member, Public Health Research Institute, Newark, NJ

Reprints: Benjamin J Epstein PharmD, Department of Pharmacy Practice and Investigational Drug Service, North Florida/South Georgia Veterans Affairs Health-System, 1601 S.W. Archer Rd. (119), Gainesville, FL 32608-1197, fax 352/379-7496, benjamin.epstein@med.va.gov

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2003. Como palabras clave se usaron antibiótico, antimicrobiano, resistencia, mutante, ventana de selección, prevención, MPC, y MSW en varias combinaciones. Se incluyeron los trabajos originales y las revisiones que evalúan la ventana de selección de mutantes, incluyendo resúmenes y actas de congresos. También se buscaron referencias en los artículos publicados y se contactó con expertos para localizar datos adicionales de interés.

SELECCIÓN DE FUENTES DE INFORMACIÓN Y MÉTODOS DE OBTENCIÓN DE INFORMACIÓN: Se evaluaron todas las fuentes de datos identificadas y se incluyó toda la información considerada relevante.

SÍNTESIS: Hasta hace poco tiempo, los médicos disponían de pocos medios para limitar la aparición de resistencias, a parte de prescribir menos antimicrobianos. La hipótesis de la ventana de selección de mutantes puede modificar este paradigma, desplazando el objetivo hacia estrategias de dosificación que reduzcan la aparición de mutantes resistentes. Se han formulado estrategias convencionales de dosificación en base a la probabilidad de curar a un determinado paciente. Desgraciadamente, las dosis que curan son capaces de aumentar la subpoblación de bacterias resistentes y, por lo tanto, promover la aparición de resistencias. Se pueden identificar las combinaciones de antimicrobiano y patógeno que minimicen la selección de mutantes y que permitan la curación de pacientes, posiblemente limitando la aparición de resistencias.

CONCLUSIONES: La hipótesis de la ventana de selección de mutantes ofrece la oportunidad de considerar la contribución de la dosis en la resistencia y aporta ideas para limitar el aumento de mutantes resistentes y de resistencia a antimicrobianos.

Maria Font

RÉSUMÉ

OBJECTIF: Décrire la fenêtre d'émergence de mutants, revoir les limites et les preuves qui supporte le sujet, et suggérer des utilisations potentielles en pratique clinique.

SOURCE DE DONNÉES: Une recherche de la littérature médicale de langue anglaise a été réalisée de janvier 1990 à décembre 2003, à l'aide d'un MEDLINE, en utilisant les mots clés antibiotique, antimicrobien, résistance, mutant, fenêtre d'émergence, prévention, concentration préventive de mutation (CPM), et fenêtre d'émergence de mutants. Des recherches originales et revues évaluant la fenêtre d'émergence de mutants, incluant les résumés et comptes rendus, ont été considérées pour inclusion. Les références d'articles publiés ont aussi été revues et des experts ont été contactés afin de localiser d'autres données pertinentes.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Toutes les sources de données identifiées ont été évaluées et toutes les informations jugées pertinentes ont été incluses.

SYNTHÈSE DES DONNÉES: Jusqu'à récemment, les médecins avaient à leur disposition peu de moyens pour préserver les agents antimicrobiens de résistance à moins de les prescrire moins souvent. L'hypothèse de la fenêtre d'émergence de mutants pourrait modifier ce paradigme en transférant le point de mire sur des stratégies de dosage qui réduiraient la croissance des mutants résistants. Les stratégies de dosage conventionnelles ont été formulées afin de guérir un patient. Malheureusement, les doses qui guérissent les patients semblent enrichir les sous-populations de bactéries résistantes et de ce fait promouvoir la résistance. Des combinaisons d'agents antimicrobiens qui minimisent l'émergence de mutants et guérissent les patients tout en limitant la progression de résistance peuvent être identifiées.

Chantal Guévremont

EXTRACTO

OBJETIVO: Describir la ventana de selección de mutantes y discutir las evidencias científicas que lo apoyan y sus límites, y sugerir sus potenciales aplicaciones en la práctica clínica.

FUENTES DE INFORMACIÓN: Se realizó una búsqueda en MEDLINE de los artículos en inglés publicados desde enero de 1990 hasta diciembre de