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BEST PRACTICES

Antibiotic Resistance: What the Dermatologist Needs to Know

What is the potential magnitude of concern regarding antibiotic resistance? Is it clinically relevant to dermatologists in their day-to-day practice?

It is important to discuss antibiotic resistance from two different angles.

First, there is the concern that if a specific bacterium develops resistance to a commonly used antibiotic, that antibiotic will no longer be effective in treating conditions caused by that bacterium, whether it be an infection or an inflammatory disorder such as acne.

However, what is also a great concern from a public health standpoint is the emergence of resistant strains in commensal or "off-target" bacteria that are coincidentally exposed to an antibiotic during treatment. This is what my colleague Dr. Jim Leyden has termed "ecologic mischief." Bacteria that are present as innocent bystanders are still exposed to the antibiotic, leading to the potential for their own selection pressure and emergence of resistant bacterial strains.

What can dermatologists do to slow the development of antibiotic resistance?

Some of the strategies include reducing environmental contamination and limiting the unnecessary use of antimicrobial agents that engender bacterial resistance. However, one important strategy involves adjusting the dosing.[1] It may be possible, especially with topical therapy, to adjust the dosing in such a way as to ensure that all susceptible bacterial cells are killed up front or that the drug level remains at a concentration capable of preventing or restricting bacterial mutant growth. This raises the following questions: How much drug is enough? Does the drug achieve relevant systemic levels when applied topically? And, Is the drug safe?

Conventional wisdom suggests that the best approach to treating with antibiotics is to "hit hard" or "use enough" by prescribing the highest recommended dose to treat the infection.

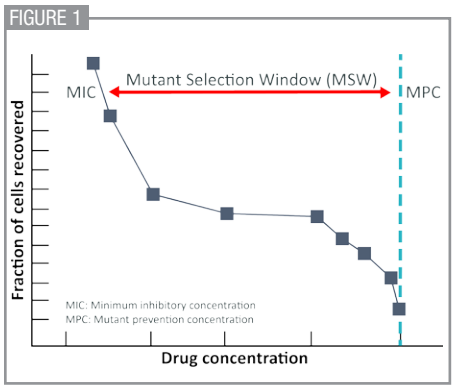
This means that the dosing needs to achieve drug levels above the minimum inhibitory concentration (MIC) until the infection is cleared.[2] In many cases, dose-limiting toxicities are the main factor in determining a therapeutic dose. Theoretically, a dose does exist that would inhibit the growth of all single-step resistant mutant bacteria—it just may not be achievable in practice due to the associated adverse events. In addition, if treatment involves an oral agent, the microbiologic effects beyond the skin must be factored in, such as alteration of the gastrointestinal tract microbiome.

Topical antibiotics may be particularly suited to a treatment approach aimed at impeding the emergence of resistance, provided the correct type of antibiotic is used. This is because some topically applied antibiotics have the potential to achieve levels beyond the mutant selection window (MSW) without producing adverse effects.[2,3]

What is the mutant selection window?

The concept of the MSW is that a drug concentration range exists whereby resistant bacterial mutants are selected most frequently. The MSW is best described as the range of antibiotic concentration that lies in between the MIC and the level at which all bacteria are inhibited and no mutants are then produced, called the mutant prevention concentration (MPC). Ultimately, the MPC is the MIC of the least susceptible single-step mutant, meaning that all bacteria are then eradicated and no mutants are produced (**Figure 1**).

FIGURE 1



The goal is to achieve at the disease target site an applied dose that is safe and that adequately exceeds both the MIC and the MPC in order to eradicate the bacteria, including any potential emerging mutant strains. There must also be negligible systemic exposure, so that no ecologic mischief occurs systemically at other sites remote from the site of application within the body, such as the gastrointestinal tract or the genitourinary tract (including the vaginal canal), the oral tract, the nasopharynx, etc. For treatment of a skin disease, it may be easier to achieve a dose that meets these requirements with a topical agent, and harder to do so with a systemic agent.

Levels below the MIC are known to avoid antibiotic selection pressure and require modes of action other than antibiotic activity to produce efficacy.[4]

As an example of what happens with drug doses above the MPC, consider the over-the-counter topical antifungals.[1]

Since these are widely used in the treatment of fungal vaginosis, azole resistance among vaginal yeast isolates would be expected to be very high. However, the opposite is true. The reason for that is probably related to the MPC for *C. albicans* and *C. glabrata*, which is about 10 to 20 mg/L. Since the topical antifungals are usually 1% formulations, or 10 mg/mL, the local drug concentration would be more than 500 times the MPC, which would account for the lack of resistance to these products.

The selection of an appropriate dose depends upon, among other things, the relationship between the MSW and the therapeutic window of an antibiotic.[2] The therapeutic window is the dosing window between the lowest effective dose and the highest tolerable dose. In many cases, prescribed doses are inside the MSW and apply selection pressure when they are administered.

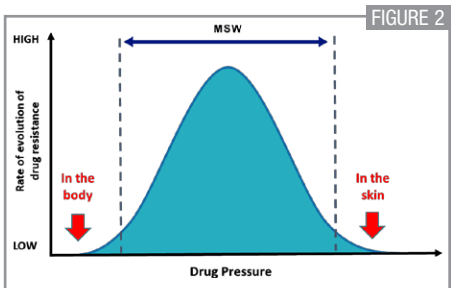
For the most part, resistance in an individual patient is held in check by the principle of high fitness cost and by the action of the host immune system, which clears pathogens after they are exposed to antibiotics. Over the hundreds of millions of antibiotic prescriptions that are dispensed, however, even small numbers of resistant mutant pathogens become important, as over time they continually increase in number and distribution.[5]

How does the mutant selection window apply to topical antibiotics?

Topical formulations may be advantageous when considering selection for resistance because they can allow for delivering concentrations above the MPC on the skin but with very low systemic exposure. Since well-formulated topical agents typically provide favorable skin tolerability and usually preclude systemic toxicity, they can be dosed much higher than with oral administration.

Obviously, this is going to depend on which antibiotic is being considered. If there was a topical antibiotic that could deliver concentrations higher than the MPC at the site of infection, but at the same time induce less systemic exposure than the MIC, the selection of resistant bacterial mutants might be avoided (**Figure 2**).

FIGURE 2



Abbreviation: MSW, mutant selection window.

As topical agents may be best suited to deliver doses outside of the MSW, they have the potential to be an effective approach to impeding resistance if we can find the right antibiotic, formulation, concentration, and recommended dosing.

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