

# Practical Considerations for Antibiotic Use in Dermatology

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Antibiotic resistance is a growing concern that threatens the effective treatment of infectious diseases. A 2014 report published by the World Health Organization on the global surveillance of antimicrobial resistance demonstrates the severity of this issue and calls for concerted action among all government sectors and society to mitigate antimicrobial resistance.<sup>1</sup> Dermatologists prescribe antibiotics more often than any other specialty, based on the prescribing rate per clinician,<sup>2</sup> with at least two-thirds of these prescriptions written for the treatment of acne vulgaris. Not surprisingly, the prevalence of strains of *C. acnes* resistant to antibiotics, especially to erythromycin, has increased and can be found in more than 50% of patients, resulting in treatment failure.<sup>3,4</sup> However, of potentially greater concern from a public health standpoint is the emergence of resistant strains of commensal bacteria. As an example, among the erythromycin-resistant staphylococci that have resulted from the use of topical erythromycin, many strains are also cross-resistant to clindamycin. It is the development of this type of resistance that warrants concern over a future threat of emergence of multidrug-resistant pathogen isolates.<sup>5,6</sup>

While it is difficult to prevent the creation of mutants, there are ways to restrict their amplification.<sup>7</sup> One important strategy involves adjusting the dosing of antibiotics. Doses can be adjusted to ensure that all susceptible cells are killed or that the drug level remains at a concentration capable of restricting mutant growth. This raises the question of how much drug is enough. It has long been conventional wisdom that, when treating with antibiotics, the best approach is to “hit hard” (Paul Ehrlich, 1913) or “use enough” (Alexander Fleming, 1943), by using the highest recommended dose to treat the infection. This means dosing above the minimum inhibitory concentration (MIC) until the infection is cleared.<sup>8</sup> In many cases, dose-limiting toxicities are the main factor in determining a therapeutic dose, but theoretically, a dose exists that would inhibit the growth of all single-step resistant mutants—it just may not be achievable in practice due to the associated adverse events, especially with systemic therapy.

Topical antibiotics may offer an approach to treatment aimed at slowing the emergence of resistance, provided an appropriate antibiotic is used. This is because topical antibiotics may allow dosing outside of the

mutant selection window (MSW).<sup>8,9</sup> The concept of the MSW is illustrated in the model example of *Streptococcus pneumoniae* treated with moxifloxacin (Figure 1). Here it was demonstrated that drug doses outside the MSW did not selectively enrich for resistant bacterial mutants.<sup>10,11</sup> The lower boundary of the MSW is the MIC, or the drug concentration at which growth of 10<sup>5</sup> wild-type cells is blocked. The upper boundary represents the drug concentration that blocks the growth of all single-step bacterial mutants. This is called the mutant prevention concentration (MPC). The MSW, therefore, is the concentration range extending from the MIC up to the MPC, within which resistant mutants are likely to emerge. If drug concentrations fall into the MSW for a prolonged period, resistant mutant bacterial strains are likely to develop. This concept is illustrated in an experiment with where *S. aureus* infected rabbits were treated with various doses of levofloxacin and the MIC of the bacterial population was evaluated over time (Figure 2).<sup>12</sup>

The selection of an appropriate dose depends upon, among other things, the relationship between the MSW and the therapeutic window of the antibiotic.<sup>8</sup> The therapeutic window can be defined as the dosing window between the lowest effective dose and the highest tolerable dose. A high-dose strategy best prevents resistance when a maximum tolerable dose can suppress emergence of resistant strains. Conversely, when the maximum tolerable dose of a drug is ineffective at suppressing resistant strains, a low-dose strategy may be more effective at preventing resistance than a high-dose approach in some cases. In most cases, prescribed doses are inside the MSW and apply antibiotic selection pressure. Resistance in an individual patient is held in check by the immune system, which clears pathogens after they are exposed to antimicrobials. However, over hundreds of millions of antibiotic prescriptions, even small numbers become important if the resistant mutants spread.<sup>10</sup>

The potential advantage of topical antibiotics, in terms of selection for resistance, is that they can allow for delivering concentrations above the MPC in the skin but with low systemic exposure.<sup>8,9</sup> Since topicals typically have much lower toxicity, they can be dosed much higher. The key is to dose outside the MSW: drug concentrations below the MIC largely eliminate selective pressure for bacteria, while drug concen-

FIGURE 1. *Streptococcus pneumoniae* treated with moxifloxacin

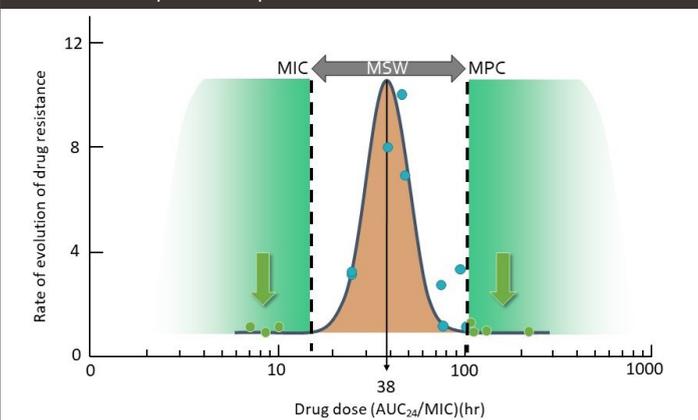
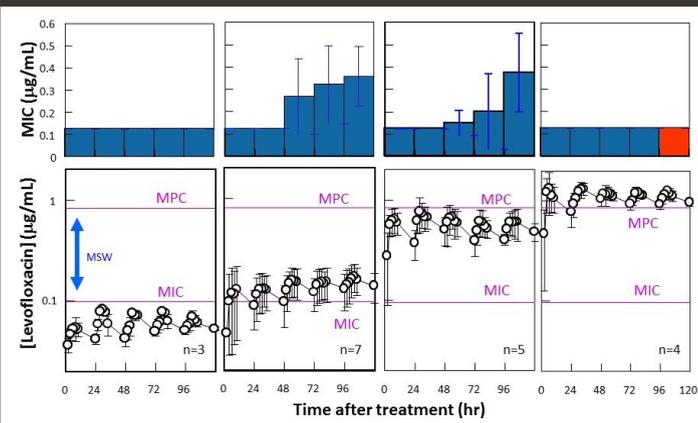


FIGURE 2. Selection of levofloxacin-resistant *S. aureus* in rabbits after oral levofloxacin



trations above the MPC inhibit the entire population, including resistant mutants (shaded green areas of Figure 1). Therefore, dosing outside the MSW has the potential to impede resistance.

## References

- World Health Organization. Antimicrobial resistance: global report on surveillance 2014. Geneva, Switzerland: World Health Organization; 2014.
- Del Rosso JQ, et al. *J Clin Aesthet Dermatol*. 2016;9(4):18-24.
- Ross JI, et al. *Br J Dermatol*. 2003;148(3):467-478.
- Eady EA, et al. *Br J Dermatol*. 1989;121(1):51-57.
- Mills O Jr, et al. *Acta Derm Venereol*. 2002;82(4):260-265.
- Coates P, et al. *Br J Dermatol*. 2002;146(5):840-848.
- Drlica K, et al. Chapter 11. In: Fong IW, Drlica K, eds. *Antimicrobial Resistance and Implications for the 21st Century*. New York: Springer; 2008.
- Day T, Read AF. *PLoS Comput Biol*. 2016;12(1):e1004689.
- Kouyos RD, et al. *Proc Bio Sci*. 2014;281(1794):20140566.
- Drlica K. *J Antimicrob Chemother*. 2003;52(1):11-17.
- Zinner SH, et al. *J Antimicrob Chemother*. 2003;52(4):616-622.
- Drlica K, Zhao X. *Clin Infect Dis*. 2007;44(5):681-688.

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