Oral Antibiotics are FDA-approved for primary management of acne vulgaris. FALSE
The discovery of the use of antibiotics for acne vulgaris was serendipitous. Antibiotics were first tried in the treatment of acne on the assumption that pustules indicated a bacterial infection. It is now known that while P. acnes plays a role in the pathogenesis, acne vulgaris is not an infectious disease. The tetracyclines and erythromycin act against P. acnes and reduce colonization, however, we now know that much of the benefit attributed to these antibiotics for acne depend on anti-inflammatory effects, as well.

Oral antibiotics are well-established treatment options for the management of moderate to severe acne vulgaris; they have a somewhat narrow indication for use. The package inserts for tetracycline, doxycycline, and minocycline state, “In severe acne, [doxycycline, tetracycline, minocycline] may be useful adjunctive therapy.” Erythromycin has no acne indication. Only one oral antibiotic formulation has a specific indication for the management of acne-Solodyn (minocycline extended release, Medicis). Solodyn is an extended release formulation of minocycline indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne. The once-daily formulation is given in a low dose of 1mg/kg/day. Consistent delivery of active drug via the extended-release capsules is associated with a decrease in acute vestibular adverse events.¹

Take-Home Tips. The primary mechanism of action for antibiotics commonly used in acne may be anti-inflammatory rather than anti-infective. Tetracycline HCl is not a frequent photosensitizer, and the tetracycline antibiotics are not shown to interfere with oral contraceptive pills. Data document lower rates of birth abnormalities when fetuses are exposed to topical tretinoin than in unexposed pregnancies. ●
Anti-inflammatory properties of tetracyclines have been under investigation for at least three decades. Studies had demonstrated that various tetracycline analogues, modified so that the dimethylamino group from the carbon-4 position (the side-chain required for antimicrobial activity) is removed, inhibit matrix metalloproteinases (collagenases and gelatinases) and lead to decreased expression of cytokines, including TNF, IL-1, and IL-6. Further research showed that these anti-inflammatory effects are mediated at the carbon-11 and carbon-12 positions and, therefore, that anti-inflammatory effects are evident regardless of any modification at the C4 position.

Studies have shown that minocycline has roughly 12-times the anti-inflammatory effect of tetracycline hydrochloride, and doxycycline has 33 times the effect of tetracycline hydrochloride. More than 25 years ago, Webster, McGinley, and Leyden showed that sub-MIC doses of tetracycline and erythromycin inhibited in vitro lipase production by \textit{P. acnes}. Subsequent in vitro investigations showed that tetracycline, minocycline, and erythromycin at sub-MIC levels produced decreased neutrophil chemotactic activity in \textit{P. acnes} culture supernatants.

A handful of studies demonstrate the benefits of standard doses of tetracyclines in moderate to severe acne; likely none of these studies would be sufficient support for a New Drug Application (NDA) today. These studies lack large cohorts, are rarely blinded, and frequently do not have placebo controls. In fact, dosing for oral antibiotics in acne vulgaris is largely empiric, as no studies have been conducted to define therapeutic windows.

\textbf{Tetracycline hydrochloride is a frequent and potent photosensitizer. FALSE}

Class labeling for tetracycline antibiotics indicates that they may produce photosensitivity, and many prescribers caution patients about this possible side effect of tetracycline therapy. However, no studies establish photosensitivity as a side effect specific to tetracycline hydrochloride. The class labeling for the tetracycline antibiotics can be traced to research by Weinstein and Frost, which documented photosensitization associated with demeclocycline.

In a 1984 study investigating the photosensitivity of seven tetracyclines, Hasan, et al. showed via an in vitro assay that doxycycline is the most photosensitizing tetracycline, followed by chlortetracycline and demeclocycline. Their analysis of the available literature reporting clinical experience showed that demeclocycline produced photosensitivity in 90 to 100 percent of subjects, while doxycycline induced photosensitivity in about 20 percent of subjects, and methacycline in about seven percent. Minocycline was not significantly associated with photosensitizing reactions in clinical reports or in their assay.

Despite this evidence to the contrary, the notion that tetracycline hydrochloride is a frequent and potent photosensitizer persists, and any patient who happens to develop a sunburn while using tetracycline may attribute it to the drug. Advise patients at the start of therapy that tetracycline (or minocycline) is not shown to produce sun sensitivity, therefore, standard sun protection measures—which the patient should already follow—are sufficient. This includes, of course, daily use of a UVA/UVB SPF 30 sunscreen each morning (let the patient choose a brand and vehicle base that is cosmetically acceptable to him or her), wearing of hats and other protective clothing when outdoors, and the avoidance of prolonged direct sun exposure.

\textbf{Tretinoin is a frequent and potent photosensitizer. FALSE}

Like tetracycline, topical tretinoin has been associated with potential photosensitivity. The label suggests patients may have enhanced sensitivity to the sun while undergoing therapy and advises avoidance of “other photosensitizing drugs.” In vitro studies show that tretinoin has the potential to induce photohaemolysis, but clinical evidence of induced photosensitivity is inconclusive.

Current opinion suggests that tretinoin is not a true photosensitizer. Rather, as suggested as early as 1975, apparent photosensitivity reactions may...
actually be manifestations of the well-known irritation associated with topical tretinoin therapy. In light of this enhanced skin irritancy, some clinicians refer to a sort of “environmental sensitivity” in treated patients, including sensitivity to sunlight, cold, and wind. Interestingly, data suggest that topical tretinoin may actually confer photoprotective effects by inhibiting c-Jun induction and subsequently inhibiting UV induction of AP-1-regulated matrix-degrading metalloproteinases in human skin. To minimize irritation, patients should be advised to use a ceramide-containing cleanser and moisturizer (CeraVe Cleanser and Moisturizer), UVA/UVB SPF 30 sunscreen, and standard UV avoidance strategies.

**Topical tretinoin is a documented teratogen in humans. FALSE**

Topical tretinoin is rated as category C by the FDA, meaning that it has been shown to be teratogenic in animals. As such, the drug is contraindicated in women who are known to be pregnant. However, in the event that a pregnant woman is inadvertently exposed to topical tretinoin, data suggest there is no cause for concern.

Daily cosmetic or therapeutic application of all-trans-retinoic acid results in absorption of a dose below 0.015mg/kg—more than 30-fold lower than the lowest teratogenic dose of isotretinoin in the human. Furthermore, topical all-trans-retinoic acid does not appreciably alter endogenous plasma retinoid levels, leading Nau to conclude that, “The influence of nutrition, diurnal variation and in particular oral vitamin A supplements are more important determinants of plasma retinoic acid compounds than topical all-trans-retinoic acid.”

Two publications in the Lancet have shown a lower rate of fetal abnormalities among women exposed to tretinoin during the first trimester of pregnancy compared to non-exposed women. Data collected in one prospective showed that the relative risk estimate for having a baby with a major congenital anomaly for exposed versus non-exposed women was 0.7 (95% CI 0.2-2.3). A recent case report documenting no adverse effects associated with exposure to topical tretinoin during the first trimester included a review of the literature revealing, “no serious adverse outcomes or congenital anomalies.” The authors note that very few cases had exposure in the first trimester.

**Antibiotics interfere with the efficacy of oral contraceptives. FALSE**

If antibiotics were shown to interfere with oral contraceptives (OCs), this interaction would clearly present a significant concern for many female patients and the physicians who treat them. Given the frequency with which dermatologists use systemic antibiotics to treat acne and rosacea, specialists are especially sensitive to this somewhat controversial issue. Importantly, clinicians should recognize that data indicate that systemic antibiotics—with the exception of rifampin—do not interfere with oral contraceptives.

Based on clinical surveys, Dickinson, et al. found that the apparent OC failure rates among patients concomitantly taking oral antibiotics other than rifampin were within the usual range expected for patterns of typical use. Furthermore, pooled analysis of data from relatively small populations show that oral antibiotics, “with the exception of rifampin, have not significantly affected the pharmacokinetics of ethinyl estradiol, levonorgestrel, and norethindrone or reduced the serum concentrations of gonadotropins.”

A meta-analysis of the literature concluded that, “Pharmacokinetic evidence demonstrates that plasma levels of oral contraceptive steroids are unchanged with the concomitant administration of antibiotics, including ampicillin, ciprofloxacin, clarithromycin, doxycycline, metronidazole, ofloxacin, roxithromycin, tetracycline, and tetracycline.” Additionally, the researchers noted that clinical reports of OC failure associated with antibiotics are, “retrospective, have multiple potential biases, and are not supported by pharmacokinetic data.”
American College of Obstetricians and Gynecologists (ACOG) management guidelines now reflect that oral antibiotics, with the exception of rifampin, do not routinely interfere with oral contraceptives. Package inserts contain a specific warning about interference of rifampin with OCs. Among other potential interactions, the PI does still contain the non-specific wording: “possibly certain antibiotics.”

Doxycycline and minocycline are not effective for treating CA-MRSA. FALSE.
Community acquired methicillin-resistant Staphylococcus aureus infections are now common across the country, though assertions that such infections are on the rise remain to be proven. In my own practice, annually since 2004, the proportion of all bacterial cultures testing positive for CA-MRSA has consistently been seven to eight percent (19-27 percent of cultures positive for S. aureus). Nonetheless, dermatologists must be prepared to identify and treat CA-MRSA infections when present. Incision and drainage is standard of care (with adjunctive oral antibiotics when indicated) for abcesses. Often trimethoprim/sulfamethoxazole is identified as the first-line antibiotic of choice, however tetracyclines are effective.

Both doxycycline and minocycline are effective, safe, and inexpensive for the treatment of CA-MRSA. Recommended dosing is 100mg bid for 10 days.

Dr. Bikowski has served on the advisory board, served as a consultant, received honoraria, and/or served on the speaker’s bureau for Allergan, Barrier, CollaGenex, Coria, Galderma, Intendis, M edics, OrthoNeutrogena, PharmaDerm, Quinova, Ranbaxy, Sanofi-Aventis, SkinMedica, Stiefel, UCB, and Warner Chilcott.