Acne Controversies: Perspective of a Pioneer

Acne expert James Leyden, MD weighs in on decreased antibiotic sensitivity, isotretinoin dosing, the problem with milk, and more.

When it comes to acne management, James Leyden, MD, Emeritus Professor CE of Dermatology at the University of Pennsylvania, is without question among the world’s foremost authorities. Involved in development of many of the drugs currently used for the management of acne, he provided an update on acne management at the Maui Dermatology for Dermatologists meeting in March. Practical Dermatology spoke with him about the talk and a range of related topics influencing patient care in acne today.

PROPIONIBACTERIUM ACNES SENSITIVITY TO ANTIBIOTICS

Although there is much discussion about antibiotic resistance, “decreased sensitivity” is a more precise term for describing the current status of P. acnes and the antibiotics commonly used to treat acne, Dr. Leyden stresses.

“When you say ‘antibiotic resistance,’ you are by definition implying that there is a change in the sensitivity of the organism, which results in antibiotic uselessness. When you say Neisseria gonorrhoeae is resistant, there’s a resistance to penicillin and related drugs that means that if you use those drugs, the person will not get better. They will get worse.

“In the case of acne, I think ‘antibiotic resistance’ is okay to say with erythromycin. It’s mostly okay with clindamycin. Things are changing with the tetracycline family,” he says.

But if decreased sensitivity is real, why do some clinicians insist they don’t see the evidence first hand? Acne is a multi-factorial disease, so patients rarely use antibiotics as monotherapy, Dr. Leyden points out; many also use a topical retinoid, for example. Even in the setting of decreased sensitivity, patients who use combination therapy and the doctors treating them will still see improvement, so skepticism about sensitivity builds.

“I think it’s better to say that there’s decreased sensitivity of the organism to antibiotics in general, with particular reference to erythromycin where as an antibiotic it is useless. In the case of clindamycin it’s evolving, but it’s becoming more and more compromised as an antibiotic. In the case of the tetracycline family, there is a change in sensitivity, not as dramatic as to erythromycin and clindamycin, but nonetheless, at a point it can mean less benefit in patients.”

An historic perspective helps elucidate the nature of decreased sensitivity and its development, Dr. Leyden says. In the 1970s, even with the introduction of topical tretinoin, benzoyl peroxide was the drug of choice for topical

AT-A-GLANCE

- Although there is much discussion about antibiotic resistance, “decreased sensitivity” is a more precise term for describing the current status of P. acnes and the antibiotics commonly used to treat acne, Dr. Leyden stresses.
- While there are in vitro studies that suggest some mechanistic basis for anti-inflammatory effect of clindamycin or erythromycin, there is no direct evidence to support the “very attractive hypothesis” that clindamycin has the ability to interfere with inflammation in human skin, Dr. Leyden says.
- There is no non-effective dose for isotretinoin. “I treat males with the highest dose of isotretinoin that they can take without any side effects. For some people, dry skin is an issue, so I go to the highest dose that they can tolerate without any problem,” Dr. Leyden says.
- Dr. Leyden discourages consumption of large quantities of milk by his acne patients. “I always ask new patients with bad acne, just casually, about milk ingestion and every once in a while you’ll find kids who ingest a lot of milk. I tell them to cut the milk out.”
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treatment of acne. It was frequently used in combination with antibiotics. “Benzoyl peroxide was suppressing whatever adverse effect from the minocycline, doxycycline, and tetracycline that was being used at the same time,” he says. Think of current guidelines, which call for use of topical benzoyl peroxide along with topical or oral antibiotics.

By the early 1980s, erythromycin and clindamycin largely supplanted use of benzoyl peroxide. “Within five years I found the first patients with decreased sensitivity,” Dr. Leyden says. “This is not an induction of resistance,” Dr. Leyden reiterates. “Resistance results from genetic mutations that antibiotics give those organisms an advantage. When a dermatologist uses antibiotics, he or she is not inducing anything. They’re only helping to put ecological pressure to select out strains that are less sensitive.”

In a recent survey of 100 patients in the metropolitan Philadelphia area, Dr. Leyden and colleagues found that about 70 percent of them carried strains of P. acnes that exceeded the MIC of 256mg/ml for clindamycin. “That seems to be pretty comparable around the world. There have been lots and lots of surveys, from just about any place you could name,” Dr. Leyden says. “One of the points to consider is that if you happen to have a patient who had a sensitive strain and you treat them just with topical clindamycin, within four months, the ecological pressure will select out all the insensitive strains and the antibiotic effect will be completely lost. That can be prevented by simultaneous use of benzoyl peroxide.” For this reason, the guidelines for the treatment of acne from the American Academy of Dermatology recommend using antibiotics for no more than three to four months.

P. acnes is also clearly significantly less sensitive to the tetracycline family than it had been, Dr. Leyden says. While tetracycline continues to offer better efficacy than clindamycin or erythromycin, issues of sensitivity are emerging. “One of the best ways of appreciating that, I think, is when you talk to dermatologists who are my vintage who used minocycline back in the 70s when I first introduced it to the specialty,” Dr. Leyden notes. “I ask from the podium, ‘How many of you are over 65, especially over 70?’ and there’s always some of us in the audience. I ask, ‘Do you think minocycline is as good as it was when you first used it?’ Without hesitation, they say, ‘No.’ “That’s a reflection of the organism. The drug used to smother acne. It doesn’t smother acne anymore, because the organism’s just not that sensitive,” Dr. Leyden says. Still, P. acnes is generally sensitive to the tetracycline class, as evidenced by a study, discussed below, that compared doxycycline to isotretinoin for severe acne. “Out on the horizon, I see the day when the specialty will not be using them, at least these classes of antibiotics, as part of the treatment of acne,” Dr. Leyden warns.

IS CLINDAMYCIN ANTI-INFLAMMATORY?

“A lot of dermatologists have been taught, and it’s firmly believed and really entrenched in the minds of the specialty, that topical clindamycin has non-antibiotic effects, so-called anti-inflammatory properties,” Dr. Leyden observes. The only problem is there is no evidence to support this belief.

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The perception could find its roots in research—some by Dr. Leyden himself—that suggested that topical erythromycin increased the tolerability of benzoyl peroxide. Topical clindamycin gained popularity in the 1970s because it was broadly effective (selectivity pressure was not yet apparent) and it offered benefits over benzoyl peroxide; it was non-bleaching and generally well-tolerated. When topical erythromycin was being developed, marketers wanted to differentiate the product from topical clindamycin. They conducted patch test studies that showed that patients developed irritation to benzoyl peroxide under occlusion but had far less irritation at sites where both benzoyl peroxide and erythromycin were applied under occlusion. Dr. Leyden questioned the results, so he conducted his own studies and published the findings, which were consistent with the initial study.

“You can interpret the finding in many ways. You could say, ‘Well, maybe the erythromycin is having some anti-inflammatory property.’ I was more in favor of it then being some interaction between erythromycin and benzoyl peroxide, which is a very, very reactive substance,” Dr. Leyden says. “Dermatologists said, ‘Aha! Erythromycin is making benzoyl peroxide tolerable as an anti-inflammatory property.’… Dermatologists, I believe, just assumed that if it was true for erythromycin, it was obviously going to be
true for clindamycin because it’s a cousin of erythromycin—similar molecule.”

One note of clarification: Dr. Leyden reminds that tetracyclines have been shown to confer anti-inflammatory effects. A non-antibiotic dose of doxycycline, approved to treat rosacea, has also been shown to provide some benefit in inflammatory acne.

**ISOTRETINOIN DOSING AND LONG-TERM REMISSION**

“There was a very good study that was published in the British Journal of Dermatology in very severe inflammatory acne.¹ The patients were clearly isotretinoin-type patients. They were treated either with isotretinoin or doxycycline 200mg, which is an interesting dose, because 200mg a day for a 100 lbs. cheerleader is very different than 200mg a day for the 300 lbs. left guard in terms of actual dose. Subjects receiving 200mg of doxycycline also used a topical combination of adapalene/benzoyl peroxide,” Dr. Leyden explains. “The way they discuss the results in the paper, it sounds like the two arms were equal, but if you browse through the data you can see clearly isotretinoin was more effective.”

The study is important because it confirms the potential benefit of oral tetracyclines, and Dr. Leyden has a preference of minocycline over doxycycline. “The point was something that those of us who were around treating difficult patients before isotretinoin remember, that you could control a lot of patients and get a lot of benefit—not to the same degree as isotretinoin—with minocycline plus topical retinoids and benzoyl peroxide.” For patients who refuse isotretinoin, Dr. Leyden says, such a regimen is an option: “I would use minocycline, because it’s a more effective antibiotic. Benzoyl peroxide. Retinoid. And this will help.”

Dr. Leyden maintains that isotretinoin is an important treatment option, especially for male patients. “In the case of a female patient with bad acne, I don’t find the need to get isotretinoin very much anymore, because I think the way to approach this is with spironolactone, which is our anti-androgen for the female. In other parts of the world cyproterone acetate is available. In America, we only have spironolactone, and that is very useful in a high percentage of girls, women. If it’s not sufficient, I recommend adding estrogen in the form of oral contraceptives, where estrogen is suppressing androgen production and spironolactone is blocking androgen receptors. Either spironolactone alone or the combination with estrogen is usually more than sufficient for most females,” Dr. Leyden observes.

Dr. Leyden urges dermatologists to thoughtfully assess their approach to isotretinoin prescribing. “I’m a big believer of early use of isotretinoin, Dr. Leyden says, “but at different dosing—kind of the way the specialty’s been doing it.”

Along with Alan Shalita, MD, John Strauss, MD and Peter Porchi, MD, Dr. Leyden was involved in the early work that brought isotretinoin to market. The story of isotretinoin for acne can be traced back to anti-cancer work at NIH, where researchers noted that the drug—the 13-cis isomer of retinoic acid—was beneficial for the management of ichthyosis and Darier’s disease. Attention then turned to acne. “When you had bad acne in those days, it got worse and worse and worse. I mean these people were almost systemically ill,” Dr. Leyden observes. “Nobody sees patients like that anymore, because nobody lets them get to that point… For those dose-ranging studies, on a scale of 10, they were 10; the worst patient anybody sees today is maybe a six.

“The dose-ranging studies in those patients—they were all males and they were all over 18, which is important as you’ll hear in a minute. The non-effective dose was not found. The non-effective dose in the worst acne that you’ve ever seen was not found.”

Subjects in the early study were recalled at one year, primarily for safety evaluation, as Dr. Leyden says no one anticipated that they’d remain clear. “One year after stopping, 60 percent of those who got the low dose, 0.1mg/kg, were still clear. There was a higher rate of maintained clearance at 0.5mg/kg and a higher rate than that at 1mg/kg. That’s where the 1mg/kg initial dose came from. So that was two miracles. One, these people who were just beyond belief got better and two, they stayed better.”

In light of these findings, Dr. Leyden raised a question. At the time, x-ray treatment was still used for acne, and it was thought to “turn off” sebaceous glands. “We knew then and everybody agreed that if we treated a 14- or 15-year-old with x-ray, that a percentage of those would have a bad relapse within a couple of years. If we treated people over 18, 20 then it was far, far less common to see a relapse,” Dr. Leyden says. He wondered about a similar phenomenon with isotretinoin. “We had no idea how this drug was working, other than quite well in terms of effectiveness. The reigning hypothesis at that time was that retinoids had profound effects on gene expression, that this was probably a receptor-mediated effect on genes. So, it was re-programming sebaceous glands. That’s what everybody thought. We hypothesized and presented the suggestion that there was a selective toxic effect and if there was a gene mediated receptor re-programming of sebaceous glands that this would be in addition to what we were describing. The concept of apoptosis hadn’t yet developed, and we got kind of boooed out of the room. That wasn’t
obviously the popular thinking. We now know there are no receptors for isotretinoin and we know it induces damage to sebocytes, which is what activates apoptosis.”

Against this background, Dr. Leyden continued to wonder if long-term clearance associated with isotretinoin therapy was a function of the patient’s age at treatment more so than the dose administered. “In recent years in isotretinoin literature, people are looking for the magic dose that you can use once and not have to do it again. The trend has been higher and higher doses.” Dr. Leyden looked at data for more than 30,000 patients treated with isotretinoin for acne. Ten percent of these went back on isotretinoin at one year. “When stratified by age, it was crystal clear that this was just like x-ray,” Dr. Leyden says. “If you look at those 16 and under, versus those over 18, it is night and day. The 12-year olds had a roughly 40 percent relapse rate, and for 15-year olds, it was roughly 30 percent; for those over 20, the relapse rate was eight percent.”

Certain factors such as strong hormonal mediators, or lithium treatment will also induce relapses, Dr. Leyden notes, but when these contributing factors are controlled for, he says, “By far the most important thing is, how old are you?

“We’re suppressing sebaceous glands, and if you’re at that age when acne isn’t coming back for other reasons, then you have a permanent remission. If you’re 12 or 13 and you get treated, and those factors in the skin have not yet evolved, then your acne is going to come back, and it’s likely to be as bad as it was before in a high percentage of cases.”

With these findings in mind, what does Dr. Leyden do clinically? “I treat males with the highest dose of isotretinoin that they can take without any side effects. For some people, dry skin is an issue, so I go to the highest dose that they can tolerate without any problem. I’m treating them until they are clear and then for another two months or so and then stop. If they’re young enough, in their early teens, mid-teens, I discuss with them the possibility that they may well have acne come back. If they do, then I retreat them.

“My algorithm now is I start everybody on a topical retinoid/benzoyl peroxide for three or four months. If they’re not totally suppressed, then I move the women onto spironolactone and I move the males onto whatever dose of isotretinoin they can tolerate without any side effects. It’s not the way the literature suggests, but there are people who’ve stumbled into this.”

WHAT ABOUT MILK?

When a team of anthropologists, biochemists, nutritionists, and community medicine physicians published a paper in Archives of Dermatology in 2002, a controversy over diet and acne erupted. The authors of that paper posited that low incidence rates of acne among Kitavan Islanders of Papua New Guinea and the Aché hunter-gatherers of Paraguay relative to Western societies must be related to different “environmental factors,” notably diet. The non-Western cultures had low rates of intake of dairy products, and while carbohydrate intake was high, most carbohydrates were low-glycemic load foods.2

Dr. Leyden was one of the reviewers who looked at the paper when it was first submitted, and although there was little data in the report, he found the discussion “damned interesting.” He suggested the paper be published along with an editorial.

“The authors had referenced some evolving concepts in the GYN and endocrinology area, for example, and I subsequently saw a patient like this: a high percentage of women with Polycystic Ovary Disease have Type II Diabetes and hyperinsulinemia. If you are in that situation, part of your treatment is a low carbohydrate diet. There are papers showing that by putting people on diets, all of a sudden they start having their periods on a regular basis. They start ovulating and they can now get pregnant,” he says. He hoped the publication would stimulate more research.

“Several groups jumped on it,” Dr. Leyden recalls. “A group at Harvard in particular and a couple of other places, jumped on it and they did some retrospective studies and what came out of the studies was a strong association with acne and those who ingested large amounts of milk…It turns out that, part of it at least, is if you look at the glycemic index of milk, you could predict what the insulin response would be. But apparently it’s about four times what it should be based on its glycemic index. So it’s stimulating insulin production.”

Now Dr. Leyden discourages consumption of large quantities of milk by his acne patients. “I always ask new patients with bad acne, just casually, about milk ingestion and every once in a while you’ll find kids who ingest a lot of milk. I tell them to cut the milk out.

“Another place where diet clearly is important is when you have a patient with Polycystic Ovary Disease and acne. I always bring it up. I have people that I refer to GYN endocrinologists and I say, ‘One of things they’re going to have you do is go on a diet that’s going help you get your period back. It’s also going to help your acne.’”
