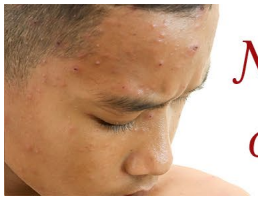


New Strategies and Best Practices in the Management of Pediatric Facial and Truncal Acne

Editor's Note: This is a transcript of a presentation on October 24, 2022. It has been edited and condensed for clarity.

Acne Overview

Hello, everyone. It's a pleasure to be here to talk about New Strategies and Best Practices in the Management of Pediatric Facial and Truncal Acne. My name is Hillary Baldwin and I'm medical director of the Acne Treatment and Research Center in Brooklyn, New York, and I'm also a clinical associate professor of dermatology at Rutgers Robert Wood Johnson Medical Center. This deck was prepared in concert with my good friend and acne expert, Julie Harper, who is the owner of the Dermatology and Skin Care Center of Birmingham in Birmingham, Alabama. It's our pleasure for me to be able to present this deck to you.

Let's start with talking a little bit about the background of acne. You know, we have to start somewhere, so let's start in the beginning. It's the most common skin condition in the United States, affecting up to 50 million individuals. It affects 40% of patients 7 to 18 and about 85% of people 18 to 24. It ends up being in the teenage years that everyone has acne. The only real question is, how bad is it? Is it a pimple here or there? Or is it a lot of acne which requires therapy? This results in 14% of primary care office visits and 27% of visits to dermatologists.

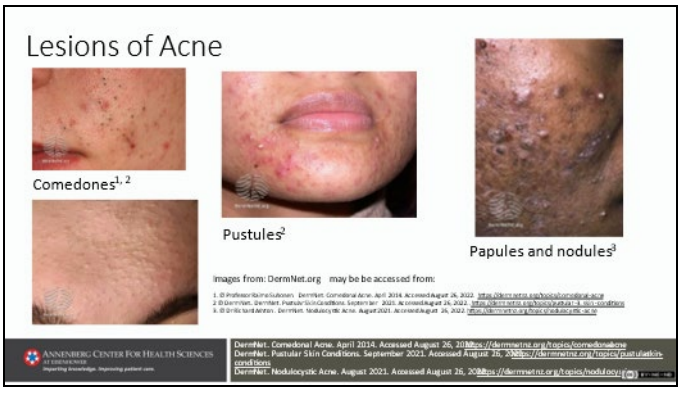
We're not going to spend a whole lot of time talking about pathophysiology, but it's important to make sure we're all on the same page so that we recognize why we pick the treatment options that we pick, because it's really based on the 4 pillars of acne pathophysiology which include increased sebum production which, of course, occurs during puberty when the sebaceous glands wake up for the first time thanks to the introduction of androgens. We also see follicular hyperkeratinization and clogging of the pores, if you will, follicular colonization with *cutibacterium acnes,* and finally, the inflammatory pathway.

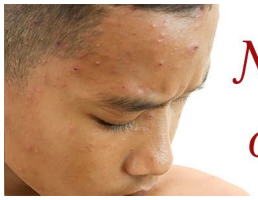
It wasn't a long time ago that we used to think that acne was an infectious disease and that *c. acnes* was the pathogen that was causing the disease. Now, we consider acne to be an inflammatory condition from start to finish. In fact, finish being even past the time when they may have some sequela like PIH or PIE.

When we look at the lesions specifically that we see on the face and the trunk of our acne patients, of course we see comedones. We also see inflammatory papules and pustules. When they get larger, usually more than a centimeter, is when we start calling them nodules. They can leave behind macular hyperpigmentation and macular erythema as well as scarring of various sorts. I like to group them into innies and outies. Most of the scars that we see on the face are innies, but you can also see keloids, for example, and atrophic scarring on the trunk which gives you an elevated lesion. It can leave behind an awful lot of sequelae that serve as a reminder to the patient, for life, that they had acne during their teenage years.

It can be present on the face, the chest, the back and even the upper arms. And about 50% of patients have truncal lesions, have lesions off of the face. It's very important that we make the patient take off their shirt so that we can examine the trunk because studies have shown that although it's very common, people often don't mention it to us. Yet, 78% of people want their trunk to be treated. It's sort of like we need some kind of a Ouija board or a crystal ball to be able to understand what it is that they want. Far easier to take a look at their trunk while they're in the office.

The lesions of acne, as we mentioned—here we see some pictures of them—include comedones on the left, pustules and papules in the middle, and papules and larger nodules.





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When we 're talking about acne sequela, we're talking about hyperpigmentation, which often bothers the patient more than the acne lesions that they had to begin with that created the hyper pigmentation, erythema and, as we said, scarring. And here you can see perfect examples of outies on the cheeks, and innies on the back.

As we're well-aware, acne affects the quality of life of the patients who are suffering from the condition. It also, we recently discovered, changes the quality of life of the family, as well who's suffering—along with the patient. We see reduced self-esteem. Dermatologic disease, and acne in particular, has been associated with increased odds of anxiety and depression, and even suicidal ideation and suicide attempt. Patients with acne have been shown to have an increased risk of major depressive disorder, all the way up to 5 years, following the diagnosis of acne. This is not a trivial concern.

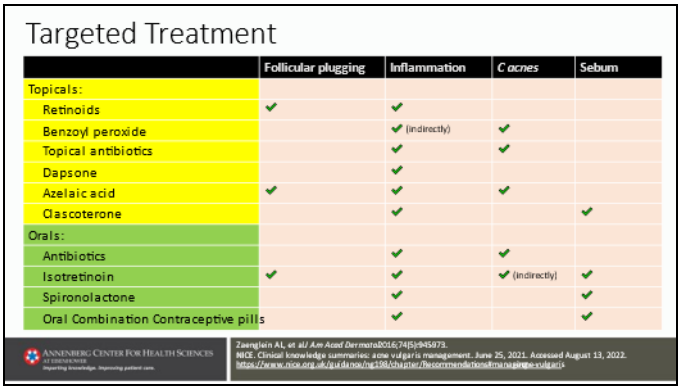
Truncal acne also has an impact on the quality of life. I've had patients who avoid doing activities that require them to take off their shirt, like going to the beach. I've had kids who were on the swim team, who quit because they couldn't take off their shirt. Patients who alter their clothing choices to cover everything up and, of course, many of our patients with truncal acne are going to require assistance to put their medications on and, "Mom, help me put my medication on my back," is something that a teenage boy has never said, ever! We see a loss of independence and a loss of privacy that also affects the quality of life.

This study looked at the quality of life for patients with facial and truncal acne vs facial alone. And it was an online, international survey where patients self-graded their acne severity and completed the DLQI. 694 patients had both, 615 had facial only. And what they found was that the participants who had facial and truncal acne were twice as likely to report very large to extremely large impact on their quality of life. Do not belittle the trunk. Just because it's covered up doesn't mean that the patients don't care and doesn't mean that the patients aren't suffering with it.

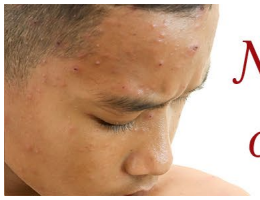
Treatment Considerations

Let's move on to treatment, and we're going to keep our eye again on those 4 pathogenic factors when we're talking about it. And here they are, follicular plugging, inflammation, *C. acnes* and sebum. And we see that we have many medications to choose from. In yellow, we're looking at the topicals and in green, we're talking about the orals. And we can see what each one of them does in terms of treating acne.

When we're choosing our acne treatment, we're going to choose 1 from column A, 1 from column B. The more of these 4 columns we hit with our medication, the more likely the patients are to get better. In fact, your average successfully treated acne patient is on 2.53 different medications. The importance here, because we need to keep it simple as possible, is to use combination products, right, to attack more than 1 of these things at the same time with a single application. We can use 1 topical that, for example, has benzoyl peroxide and a topical retinoid in it, and then we're going to get follicular plugging, inflammation and we're going to kill *C. acnes*, right? Or throw in a spironolactone as well which is going to decrease sebum production. We're thinking about the acne pathophysiology all the time when we're making our therapeutic choices.



The first thing we have to do though, of course, is to assess the patient, and that's going to help us to determine our



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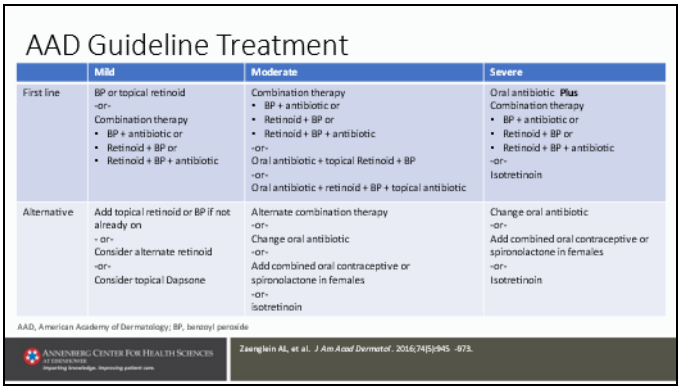
treatment considerations. I base my decision on how old the patient is, what kind of lesions do they have, do they have mostly comedones, do they have a lot of nodules, is it on the trunk as well as the face or both and what is its severity, what's its extent? Is it all over the place, from the top of their shoulders all the way down to the waist? Is there scarring? Is there hyperpigmentation? And perhaps most importantly, does the patient seem to be suffering psychically as well?

Our treatment options in general can loosely be divided into topicals and orals. Of course, we also have procedural changes but those are beyond the scope of today's presentation. For topicals, we're talking about retinoids, the mainstay of acne treatment, antibacterials, sebum inhibitors, and anti-inflammatory agents. And for orals, we have again our antibiotics, our hormonal treatment, and finally, isotretinoin.

It's important that we remember that acne treatment really falls into 2 categories. When the patient walks in at 13 or 14, we know that they're going to have this condition probably until they're 19 or 20. We want to make them better today with acute therapy, but then we're going to have to figure out how to keep them better for 5, 6, 7 years and often acute therapy and maintenance therapy looks completely different. The goal of acute therapy is to control the condition as soon as possible. We can use topicals, but it very often also includes an oral antibiotic for hopefully a limited duration. For maintenance therapy, obviously we want to maintain improvement, but it needs to have excellent tolerability. With acute treatment, people are sort of no pain, no gain, about it. But once you're talking about maintenance therapy, the tolerability has to be great. Their treatment plan needs to be simple. Hopefully, it's also cosmetically elegant, so they don't mind putting it on every day. It must be a nonantibiotic regimen. We cannot have our patients being on antibiotics, obviously, for years and years to reduce the risk of antibiotic resistance and to be good stewards of antibiotics. Typically, our maintenance therapy is going to look like a topical retinoid with or without benzoyl peroxide.

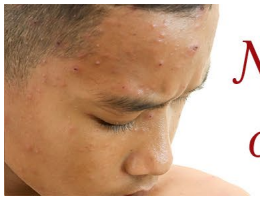
This is the AAD Treatment Guidelines which are now actually quite old. They date back to 2016, which means they were written in 2015, so there are medications that are missing. They're undergoing a new permutation right now and actually the Acne Treatment Guidelines—the Pediatric Acne Treatment Guidelines—goes back to 2013. In general, what you see here for mild, moderate and severe disease, is a whole lot of plus signs, once again indicating that combination therapy is the name of the game. For mild, a benzoyl peroxide and an antibiotic and a retinoid. For moderate, same thing but you might think about introducing oral antibiotics as well. And for severe, you're still looking at that topical therapy with an antibiotic or the addition of isotretinoin. I think the art of treating acne is knowing how to combine things, and when to combine them, and when you can combine them in the patient sitting in front of you.



Topical Treatment

Let's start with topical retinoids. What's the mechanism of action? It's manifold in acne. It's comedolytic, so it gets rid of the comedones that they already have, but it's also anticomedogenic, so it stops new ones from happening. Retinoids are the only medications that we have that are preventing the formation of the microcomedo, which is the first lesion that turns into all the lesions after that. It also normalizes epithelial hyperkeratinization and is anti-inflammatory. It's the first line, it's for long-term maintenance and, as far as most of us acne people are concerned, for retinoids, it's birth to death.

The effect usually takes a little while. It can sometimes be seen as early as 1 to 3 weeks, but you're expecting it out at 4 to 6 to 8 weeks. And the optimal effect is going to take up to about 12 weeks to occur. This is a problem, because they can be drying and irritating, so the patient is going to have a little bit of irritation early on in the treatment phase and they're not going to be better yet. We call this the crisis of confidence. They look in the mirror, they're no better, and now, on top of everything else, they might be a little red and a little scaly and stinging and burning. Thank you very much, doctor, for helping me so much, right? The educational process is very important here to make sure that they realize



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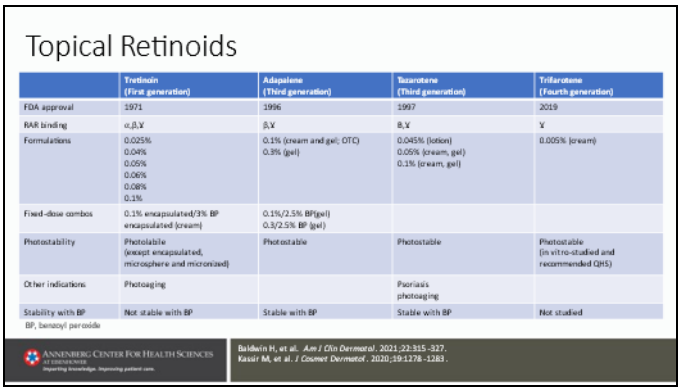
that topical irritation may happen in the first week or 2, but it's going to go away. And topical retinoids also may help to reduce scarring when used over the long haul.

This is a complicated chart which looks at the topical retinoids that we have available to choose from, tretinoin being the oldest, dating back to 1971, the year the first email was sent, by the way; adapalene and tazarotene which came out in '96 and '97; and trifarotene, which is the newest kid on the block, in 2019. They bond to different receptors within the keratinocytes, and we're not going to get into too much detail here, but we see the trifarotene, the fourth generation, is very specific for the gamma receptor which might be the reason why, if you look down 1 level lower than that, you'll see that trifarotene has been manufactured in .005% cream, probably because it has such high selectivity for the gamma receptor, which is the most common receptor in the skin.



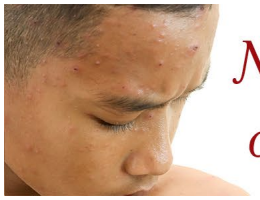
We have many formulations of the other products to choose from. We have gels and lotions and creams. In general, creams are more soothing and better tolerated than are lotions than are gels. But, with good formulation, that's not always a true statement. We also have fixed-dose combinations that include topical retinoids. We have a .1% encapsulated benzoyl peroxide/tretinoin combination and we also, with adapalene, have a combination of .1% adapalene and 2.5% benzoyl peroxide or .3% adapalene and 2.5% benzoyl peroxide.

Photostability is something that differs between the various medications. Tretinoin is photolabile. If you put it on and you walk out into the sun, it's going to get inactivated and is not going to be effective. But you can do things to help tretinoin. You can microencapsulate it, you can put it into microspheres, you can micronize it and that protects it from being gobbled up by the sun. The other active retinoids are all photostable.

Other indications for retinoids include photoaging for tretinoin, psoriasis and photoaging for tazarotene, and the last thing that we need to concern ourselves with, since we're often going to want to use benzoyl peroxide, is that both adapalene and tazarotene are known to be stable with benzoyl peroxide. Tretinoin, unless it's microsphered, micronized or microencapsulated, is not stable along with benzoyl peroxide. If you want to use them together, you cannot use a generic tretinoin along with benzoyl peroxide. The ability of trifarotene to play well in the sandbox with benzoyl peroxide has not yet been studied.

How are we going to improve this problem with retinoid tolerability? Well, the first thing we can do is to make sure that we're only using a pea-sized amount. I like to separate my pea between my index finger and my other index finger, so put it on the index finger, split it up, put a little puddle here, a little puddle here, a little puddle there and then go back and rub the puddles in really well. We are not spot applying 2 zits. We've said before that retinoids work by being anticomedogenic, so they are going to help to prevent the formation of new pimples. You don't just want to put it on the zit; you want to put it all over the face.

You can start every other day if your patient is particularly concerned about irritation. You can moisturize regularly, maybe even under the retinoid, put the moisturizer on first, let it dry, and then put on the retinoid. We don't have a lot of data for that in terms of whether or not it reduces efficacy, so you want to pick a moisturizer which is not too heavy. This is the time to use a relatively light lotion. You might consider changing formulations if there's an alternate vehicle, if there's a cream instead of a gel, but the most important thing, as far as I'm concerned, frankly, is to go with a branded product that has really good quality vehicles that can reduce irritation and improve efficacy. We have the microsponge delivery system that reduced irritation with tretinoin, we have micronization which reduced irritation with topical tretinoin, we have polymeric emulsion technology that we saw with tretinoin and tazarotene, and we also have the microencapsulation technology, which we'll talk about a little bit more, which also improved the tolerability of .1% tretinoin.



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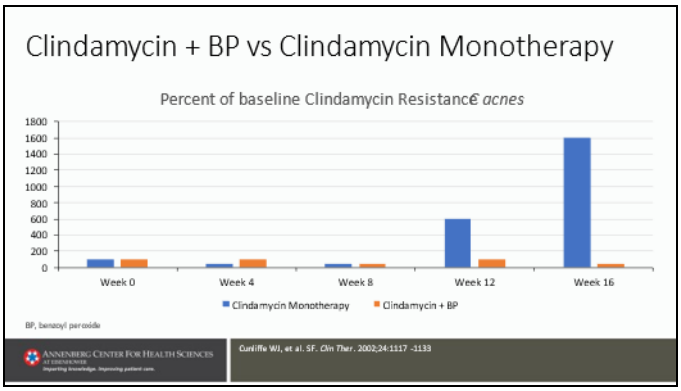
The bottom line is to make sure that your patients are persistent. Retinoids need to be part of all regimens. And I don't care how they're using it; they just need to be using it. I ask my patients to make sure that they're being consistently inconsistent. If they can only use it every 3 days, that's great. Use it every 3 days. Don't use it 4 days in a row, get irritated, and then stop it for 2 weeks. Right?

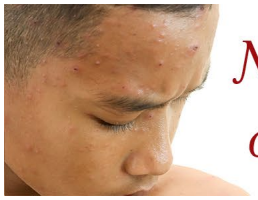
Let's move on benzoyl peroxide. Benzoyl peroxide is available as washes, but also as something that you leave on your skin. And it's also available in fixed combinations with retinoids and with clindamycin. The adverse effects of benzoyl peroxide is contact sensitization which is actually quite uncommon. It's gotten a bad reputation in this regard. When your patient comes in and says they're allergic to benzoyl peroxide, they usually have been irritated by benzoyl peroxide in the past, using a product with a poor vehicle, for example. It is a concentration-dependent irritant. In general, without something being done to it, the higher the concentration, the more irritating it is. But many of our benzoyl peroxide leave-ons have added moisturizers, have microencapsulated and done all sorts of things to reduce the irritation.

Benzoyl peroxide really has a dual purpose when we use it for acne. Of course, it treats acne. It kills faster and more effectively than topical antibiotics and alone, it significantly improves primarily inflammatory, but also to some extent comedonal acne. It also reduces the risk, though, of antimicrobial resistance when it's used in combination with either topical or oral antibiotics. It, itself, is not associated with antimicrobial resistance. And it can actually prevent the development of resistance to topical and oral antibiotics with which it is co-used and can even reverse resistance that has already occurred.

This is a study that looked at the development of *C. acnes* resistance over time, with clindamycin as monotherapy in blue, and clindamycin plus benzoyl peroxide in orange. What you see here is, over time, the organisms become resistant when they're just using clindamycin alone, in blue, especially starting at week 12. Whereas, when in combination with benzoyl peroxide, no such clindamycin resistance to *C. acnes* occurs.



The other thing we have to recognize is that benzoyl peroxide adherence is not terribly good. We have 1 study on the left that looked at adherence to over-the-counter benzoyl peroxide purchasing. In this study, 84 patients were told to go ahead and buy benzoyl peroxide at the pharmacy. Two weeks later, they came back and it turns out that only 30% of patients recalled even being told that this ingredient existed, right, that they were supposed to get this. 36% didn't purchase anything at all, and 64% made purchases but only 32% of them contained benzoyl peroxide. Sending your patient to the pharmacy to get benzoyl peroxide to go along with their clindamycin prescription that you've given them, thinking in your head that, okay, you're being a good steward of antibiotics, you're using benzoyl peroxide along with clindamycin and that's a good thing, think again, because the patients don't actually do that! Better, in my opinion, that you combine the clindamycin and benzoyl peroxide in 1 container to avoid that. Additionally, benzoyl peroxide, probably because of its bleaching effect, doesn't get used very compliantly. It was a computer chip study. It's a MEMS cap so that the top of the tube, when the patient actually opens it, the cap recognizes that the tube has been opened. Presumably, when they open the tube, they're actually using it.



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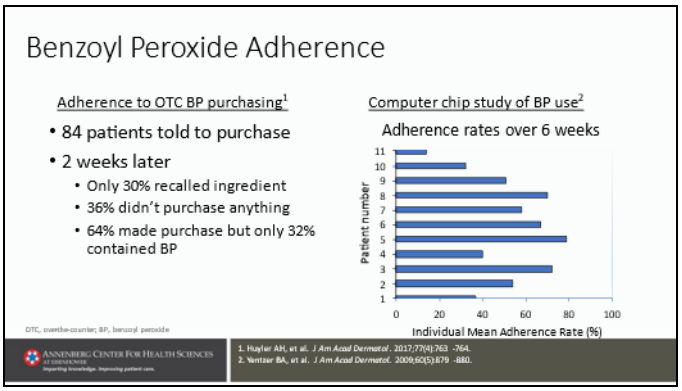
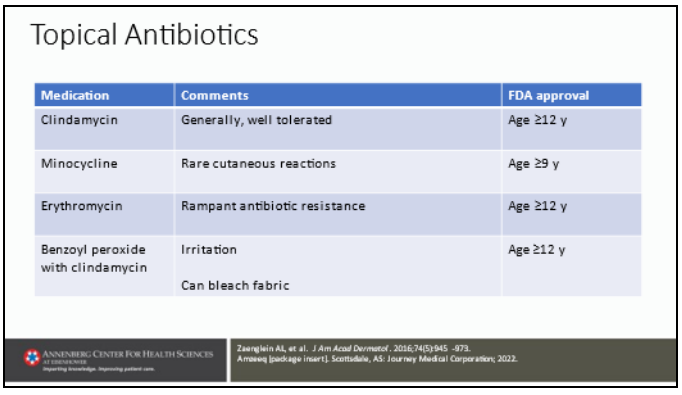
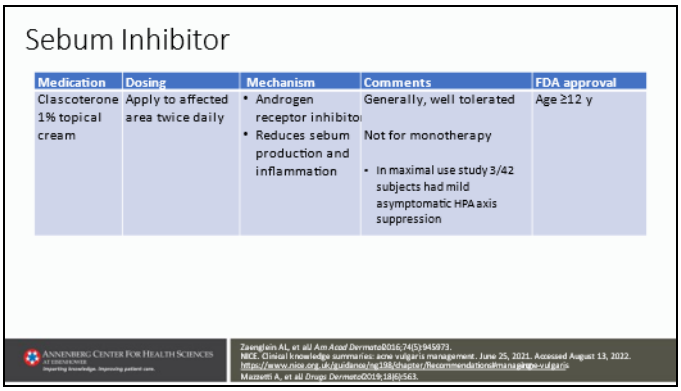


This was a study of 11 patients who were asked to use their benzoyl peroxide. When they came back, of course, everybody said, "Oh yeah, I used it every day." Well, not. As you can see here, only patient 6, it looks like, was actually adherent to therapy and everyone else was not. They don't buy it and they don't use it. Just keep that in the back of your mind when you're combining it with clindamycin.

Let's take a look at the topical antibiotics that we have for use. We have clindamycin which is generally well-tolerated. We have minocycline which has very rare cutaneous side effects. We have erythromycin which has shown to have rampant antibiotic resistance, and we acne people do not use it at all for our treatment of acne. And then we have benzoyl peroxide along with the clindamycin, as we mentioned before, which can bleach fabric but has very little in the way of irritation. You see the FDA approval down to the age of 12, with the exception of minocycline, which is new and was FDA-approved down to the age of 9.

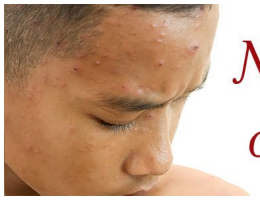


We also have topical sebum inhibitor called clascoterone 1% cream. This came out only last year. It's applied twice a day to the entire affected area, the same thing, that little pea-sized amount. It's an androgen receptor inhibitor. It binds to the androgen receptor and makes it so that DHT cannot bind to the receptor and cannot end up creating an increase in sebum and an increase in the production of proinflammatory cytokines. This reduces sebum and is also anti-inflammatory in nature. It's generally very well tolerated. We don't usually use it as monotherapy; we generally use it along with a topical retinoid, for example, or my favorite combination is a retinoid plus benzoyl peroxide.



In a maximal use study using 6 times the normal amount, a very low number of patients had an asymptomatic, mild HPA axis suppression. Now, you're thinking to yourself, why on earth would that happen if clascoterone is an androgen receptor inhibitor? Well, in the skin, it's converted into cortexolone and cortexolone is in the pathway of cortisol. Cortexolone itself is a very, very weak glucocorticoid. It's also a nonandrogen. Within the epidermis, clascoterone is converted into cortexolone. It's no longer an androgen, so it allows it to be safe for use in men, and this is our only sebum inhibitor that we have, other than isotretinoin, which can be used in a man, however it is converted into a very, very mild glucocorticoid. The study showed so little that the FDA actually approved the product without forcing HPA axis suppression to be evaluated during the phase 3 trial, but they did however suggest that it be FDA approved only down to the age of 12.

As a pure anti-inflammatory agent, with no other activities in acne, we have topical dapsone, as 5% twice a day or 7.5% once a day. It's generally well tolerated. It's FDA approved down to the age of 9, and the G6PD deficiency that's written



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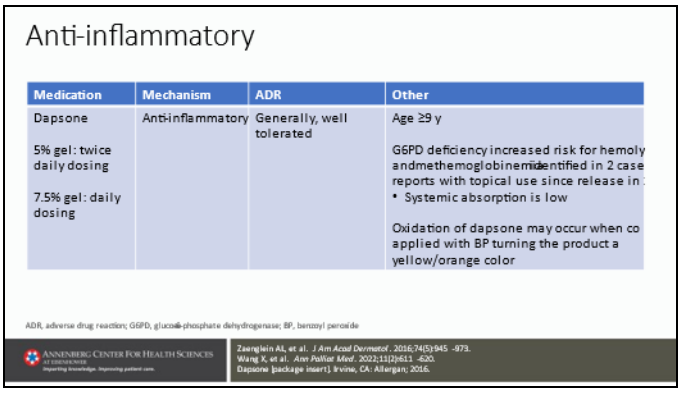
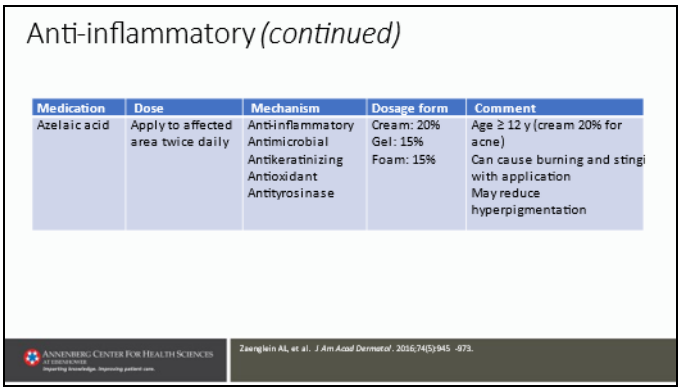
about here, yeah, it happened, but it's happened in 2 case reports since the medication was released back in 2005. It's something that I'm certainly not concerned with. The oxidation of dapsone may occur if it's co-applied with benzoyl peroxide, so the patients will complain about this, so you need to know, but it has no medical ramifications whatsoever. If you take a big glob of dapsone and a big glob of benzoyl peroxide and put them both on at the same time, the benzoyl peroxide will oxidize the dapsone, turning it a yellow color, and then the skin will look yellow. It's not the skin itself that has turned yellow; it's the medication sitting on the skin and all you have to do is rinse it off. But it's something that usually is worth mentioning to your patient, especially if they're using it along with benzoyl peroxide.

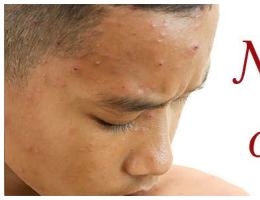


We also have azelaic acid which is a BID drug. It has many mechanisms of action, as you can see here, although it doesn't do any of them particularly well. And it comes in a cream, a gel and a foam. It has been reported, especially with the gel, to cause burning and stinging with initial application, up to 25% of patients complaining of a little bit of burning and stinging. But it also may reduce hyperpigmentation by virtue of being an antityrosinase medication. In your patients who have both acne and hyperpigmentation, this may be a good choice.



We also have topical combination therapy, and we mentioned before that that's the most important thing for us to do, to be combining as many of those 4 pathogenic factors as possible to increase efficacy of our topical care. We also, of course, want to minimize antibiotic resistance with the use of benzoyl peroxide any time you're using a topical or an oral antibiotic. And the fixed combination agent is usually best in terms of compliance, but multiple agents also are effective. To combine it in such a way that you are either hitting 2 pathogenic factors especially hard, like benzoyl peroxide and clindamycin, or hitting the bacteria with benzoyl peroxide and the follicular hyperkeratinization with a retinoid. With our fixed combinations, you see an improved compliance thanks to fewer applications and, frankly, we tell our patients to co-apply medications all the time, put 1 on, then put the other on top of it, but we have no data that that doesn't cause some kind of a decrease in efficacy or an increase in tolerability issues. When you tell patients to co-apply medications, you're really not sure of what the outcome may be.

Here we're looking at the fixed combinations that are available for our use. We have combination of adapalene and benzoyl peroxide, referred to as Epiduo or Epiduo Forte, which is the higher concentration of adapalene at .3%. We have benzoyl peroxide with clindamycin, which goes by many names, and the one you choose determines whether it can be



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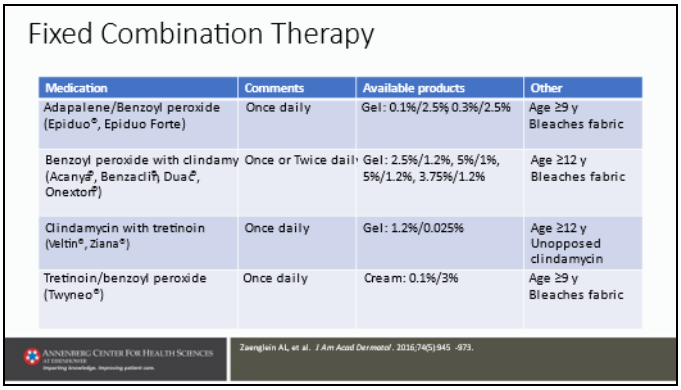
used once or twice a day. I personally use all of these named products, just once a day. There are varying combinations, as you see here. Clindamycin with tretinoin is a product that I generally do not use because you already know that I think that clindamycin should be combined with benzoyl peroxide, but that does exist. And we have a combination, that's brand new, of tretinoin and benzoyl peroxide, called Twyneo, which is a once-a-day cream. Epiduo and Twyneo are FDA approved

down to the age of 9, whereas the other products, including Epiduo Forte, are approved down to the age of 12.

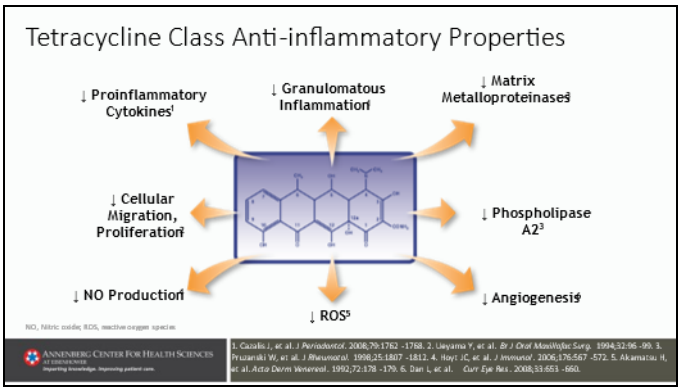


Systemic Treatment

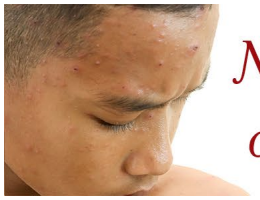
Let's move on to oral medications, starting with oral antibiotics. Monotherapy with systemic antibiotics is never recommended. We always want to be using benzoyl peroxide, remember that. We want to limit their use to the shortest amount of time possible. It's always been said that we should discontinue oral antibiotics by 3 months, but it's important that you know that that number, 3 months, has just been plucked from the sky. It's just a number that somebody said once. It has no medical meaning whatsoever. Antibiotic resistance, as you know, starts from the very first pill. Yes, we want to stop it as early as possible, but 3 months, I suppose because it's in all the literature, would be the outside limit that we would want to aim for.

The tetracycline class of antibiotics is what we use most commonly because not only do they do a good job of killing *C. acnes*, but they're extraordinarily good anti-inflammatory drugs, and they're generally quite safe.

This is the reason why we're using the tetracyclines in our acne treatment. Look at all of the anti-inflammatory properties that the tetracycline class shares. Not only killing *C. acnes*, but reducing a lot of the inflammation, therefore making the oral antibiotics something that we use particularly for our patients with lots of inflammation. The red lesions, as opposed to comedonal acne.



Here we're looking at the various drugs that we have available within the tetracycline class, doxycycline, minocycline and sarecycline. FDA approved to the age of 8 and to 9, but that FDA approval for doxy and minocycline is a grandfathered approval, so those 2 drugs were already out before they were evaluated for acne and they were grandfathered in, whereas sarecycline was tested down to the age of 9. They're utilized once or twice a day, minocycline and doxycycline, that is. Minocycline comes in 2 formulations, extended-release formulation and immediate-release formulation. The extended-release formulation only needs to be taken once a day. It can be taken with or without food. For sarecycline, it too can be taken with or without food. The impact of food and dairy for doxycycline is that it does reduce the bioavailability of doxycycline slightly, but it has not seemed to be a problem in the treatment of our patients. Most of us do not recommend to our patients that they try to stick to taking their doxycycline on an empty stomach simply because it's too difficult because it needs to be 2 hours on either side of a meal and that really makes compliance a difficult issue.



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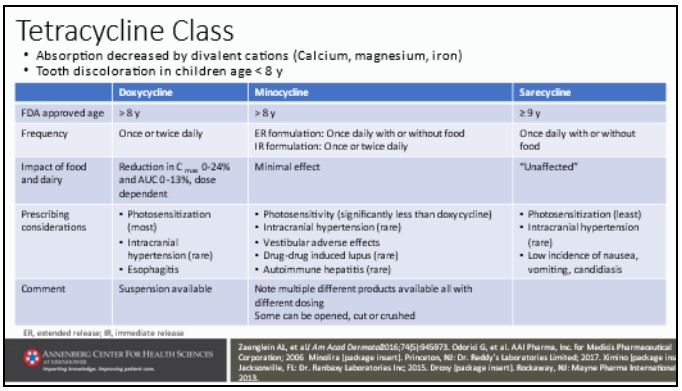


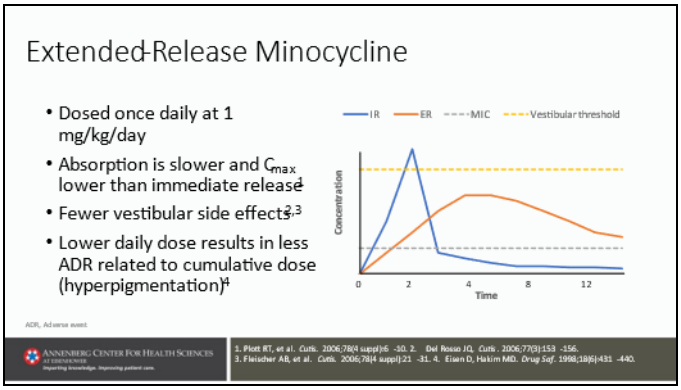
When we're thinking of prescribing considerations for doxycycline, we know that it causes photosensitization, especially at higher doses. It rarely has been associated with intracranial hypertension and that esophagitis, if you dry swallow and lie right down, can be a problem. We get around this by asking the patient to make sure they take their doxy with a big 8-ounce glass of water and do not recline for the next 30 minutes. That way, the pill can fall directly from the mouth to the stomach. It's when it gets stuck in the middle, in the esophagus, that, especially overnight, it can create irritation to the wall of the esophagus. Eventually, the patient starts complaining of heartburn and finally, actually, chest pain. I've had a patient who ended up in the emergency room for rule out of MI, believe it or not.

Minocycline does not have photosensitivity. Rarely see intracranial hypertension. Vestibular side effects with the immediate-release formulation are actually quite common, somewhere around 10%. But the extended-release formulation does not have vestibular side effects and I tend to use, exclusively, the extended-release formulations. Very rarely we see drug-induced lupus-like eruption and autoimmune hepatitis. That's extremely uncommon, but it is something that you need to keep in the back of your mind.

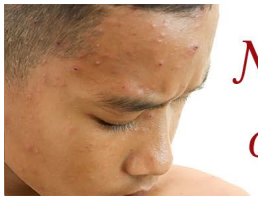
For sarecycline, there has been no reported cases of photosensitization. One, I think, reported case of intracranial hypertension only with a very low incidence of nausea, vomiting and candidiasis. It's very well tolerated.

For pediatric use, it's important to recognize that doxycycline is available in a suspension and there are some forms of minocycline that can be opened, cut or crushed, but sarecycline needs to be taken as a pill.

This is a slide talking to you about extended-release minocycline and the importance of it in reducing vestibular side effects. Let me ground you first. We're looking at plasma concentration of drug on the Y axis over time and the yellow bar indicates the toxicity threshold, the threshold for developing vestibular side effects. And the gray line is the MIC of the drug. Extended-release minocycline is dosed at 1 mg/kg/d and, as you can see in the blue, that is the immediate-release formulation. For that, it goes into the stomach, immediately gets absorbed, the plasma level goes shooting up, zero to 60 in 10 seconds, and then plummets right back down again below the MIC. Whereas the extended-release formulation goes up much slower, does not exceed the threshold for vestibular side effects and sticks around above the MIC for a very long period of time. Absorption is slower, C_{max} is lower, there's fewer vestibular side effects and also fewer of those long-term side effects for minocycline, like hyperpigmentation, because you're taking so much lower a dose on a daily basis.



We have some alternative systemic antibiotics that we can use. We generally reserve those for people who are unable, for one reason or another, to tolerate the tetracycline class. People, for example, who are under the age of 8 or pregnant or allergic. None of these other agents are specifically FDA-approved for the treatment of acne and they include azithromycin, primarily. Erythromycin, I don't even consider a choice for our patients with acne. There are other systemic antibiotics that we discourage, either due to limited data or their adverse event profile or the fact that they're very important antibiotics. Trimethoprim-sulfamethoxazole works great in acne, but we need it for more important infections, so we only turn to trimethoprim-sulfamethoxazole when things get particularly dicey. I utilize it, for example, in someone who tells me they're getting married in a month



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and they came in with a ton of inflammatory lesions. You can use trimethoprim alone, removing the sulfamethoxazole and removing that very low risk of Stevens Johnson Syndrome that exists with the combination product.

We have been suggesting for quite some time now that we reduce the use of antibiotics in our treatment of acne. We have several studies that looked at this. In 1 primary care setting, 1 in 4 patients with antibiotics were given antibiotics during that initial consultation. In a dermatology setting, we saw that the duration of the use of systemic antibiotics before they actually switched over to isotretinoin was 331 days, even longer, 380 days if they have been transferred from another physician. And then they ended up using isotretinoin anyway. The concept here is to move over to isotretinoin earlier if the patient is isotretinoin-worthy, right?

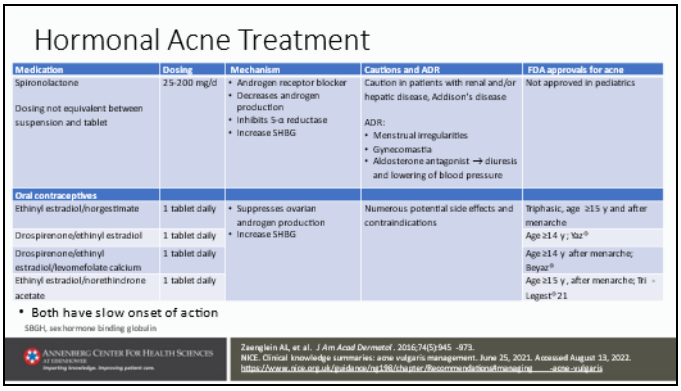
Another study looked at a cohort of dermatologists and found that antibiotic prescriptions had dropped between 2008 and 2016 by 36%. Good news, right? And antibiotic prescriptions for acne had also decreased by 28%. However, in 2016, another study showed that 57.5% of prescriptions for an extended course were for acne. We're making a little bit of progress, but probably not enough. How are we going to transition away from antibiotics? We're going to use retinoids, we're going to use benzoyl peroxide, we're going to use hormonal therapy that we're going to talk about in a second, and we're going to turn over to isotretinoin earlier.

Let's talk a little bit about antibiotic resistance. We know very well what factors contribute to resistance. For example, not using enough drug which could be because of poor adherence, the patient simply doesn't take their antibiotics or that we have under-dosed and now, because we've used such a low dose, that the drug isn't reaching its intended target which, of course, is within the very fatty content of the follicle.

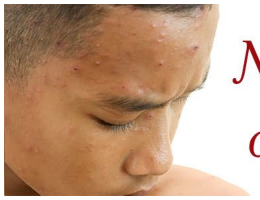
Antibiotic monotherapy, without the use of benzoyl peroxide or a topical retinoid. Sequential antibiotic exposure. I can't tell you the number of my colleagues who tell their patients, use the antibiotics when you need them and then stop and then use them again and then stop. The patients are using them, many women are using them therefore for the week before they get their period because that's when they have a premenstrual flare and then they stop for three weeks. It's insane. It promotes the development of resistant organisms. Or treating for a long period of time. But, as I said before, all of these numbers are sort of plucked from the sky. We just don't want to use it for a long period of time.

We're looking at the rates of resistance to *C. acnes*. In recent studies, we see the topical macrolides somewhere around 50%. Topical clindamycin, if you don't use it along with benzoyl peroxide, you're not solving a problem, you're creating a problem. And the oral tetracyclines, still holding on there, especially minocycline. For some reason, minocycline appears to be quite resistant to resistance, but, you know, any time you have good news about resistance, we know we're only a plane ride away from those numbers changing, right?

Now let's move on to hormonal therapy. For hormonal therapy, we have spironolactone and we have oral contraceptives. Let's talk about spironolactone first. I'd like to note, for pediatric use, that the dosing is not equivalent between the suspension and the tablets, so if you have somebody who's unable to take the tablets, make sure that you're looking at a dose conversion. We generally dose somewhere between 25 and 200 mg, although that 200 mg is really reserved for patients with hirsutism or alopecia. You usually don't need anything more than 100 for your acne patient. This is an androgen receptor blocker. It also decreases androgen production, inhibits 5-alpha reductase and also increases sex hormone-binding globulin. It does all sorts of wonderful things for patients with acne.



We see that it's not FDA-approved for acne. It's not FDA-approved in pediatrics. Knowing that, go forward with mild trepidation. I utilize it, I can't get through my practice without utilizing spironolactone for my patients. We do see, as side effects, menstrual irregularities. That happens in about 10% of patients. Gynecomastia occurs in men, but we can have breast tenderness in our women at about 10% to



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15% also. This is a diuretic, so it will cause diuresis. You want to warn your patients about it, but it has not been shown to lower blood pressure in healthy women taking this for the treatment of acne.

Now let's move on to oral contraceptives. We have 4 that are FDA-approved in the United States for the treatment of acne as well as birth control. It's important to note that, as far as the FDA is concerned, oral contraceptives are approved for the treatment of acne in patients who desire contraception. Technically, if you're someone who likes to follow FDA rules, this drug should not be utilized just to treat acne in a patient who does not need birth control.

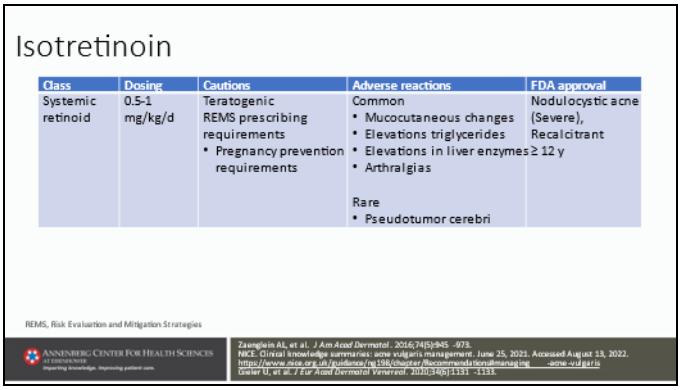
It works by suppressing ovarian androgen production and by increasing sex hormone binding globulin. And we know that [with] it, and spironolactone, that's an important activity because it's gobbling up the circulating androgens.

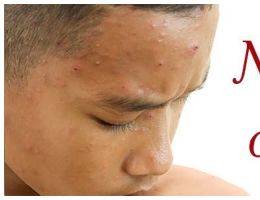
It has numerous potential side effects that we'll look at in a second, and contraindications. You want to make sure you're taking a very good history from your patient. There's a couple of caveats for the approval for this medication. In general, it's approved for ages 14 to 15 and above in people who have been menstruating for the preceding year.

When I mentioned before, the importance of taking a history, that's because there are a lot of contraindications for the use of oral contraceptives, as I know you're very well aware. We just want to make sure that we're asking the right questions of our patients, the most important, as far as I'm concerned, is smoking. Here it says heavy smoking. If you're a smoker, you're not getting an oral contraceptive prescription from me.

Another specific issue with spironolactone that comes up a lot is do you need to follow potassium levels in these patients. Well, in a retrospective review of 974 healthy women, ages 18 to 45, taking spironolactone for acne vs 1,165 age-matched controls, they found nothing, 3 abnormal measurements in all of those patients, adding up to an incidence of .72%, whereas baseline hyperkalemia in this population is .76%. The conclusion of this study is that routine monitoring for healthy young women is unnecessary. It might be necessary for older women, for people with abnormal renal function, or for concomitant medications affecting the renin angiotensin aldosterone system. SMake sure that you ask the patients if they're on any blood pressure medications and, if so, what kind. I also send my patients out with 2 words of advice. The first is that this medication interacts with a lot of others, so if a doctor is about to give you an oral medication, please make sure that you say, by the way, I'm also on spironolactone. The second is that although we don't think that potassium is an issue, I prefer not to rock the boat too far. I ask them, I point out that this is not the time for them to go on an all-banana, all-the-time diet, and coconut water contains an enormous amount of potassium. I'd like them to limit their intake of that. And some people say processed meats, as well, or low sodium meats that replace the sodium with potassium.

Finally, we're going to talk very briefly about isotretinoin. We can spend the whole hour talking about this amazing drug. It's, of course, a systemic retinoid. It's dosed at .5 to 1 mg/kg/d. You're well aware, I'm sure, of the cautions. It's teratogenic, requiring a risk management program to monitor the patients. The system that we use is called I-Pledge. In the beginning, it's a little daunting, but once you get used to it, it's incredibly simple, a couple of mouse clicks and you're done. Common adverse reactions for isotretinoin are primarily mucocutaneous changes which we see in almost 100% of people: really dry eyes, dry nose, dry eyes, manageable stuff. We can see elevated triglycerides in about 11%, elevated liver enzymes in about 25% and arthralgias in about 18%. But those are the only adverse reactions for isotretinoin that exceed 1%. All of the rest of the stuff that the patients are going to be seeing on the internet and are going to worry them a great deal are all 1% or less or, frankly, kind of hype, right? This is, when used correctly, really quite a very safe drug.





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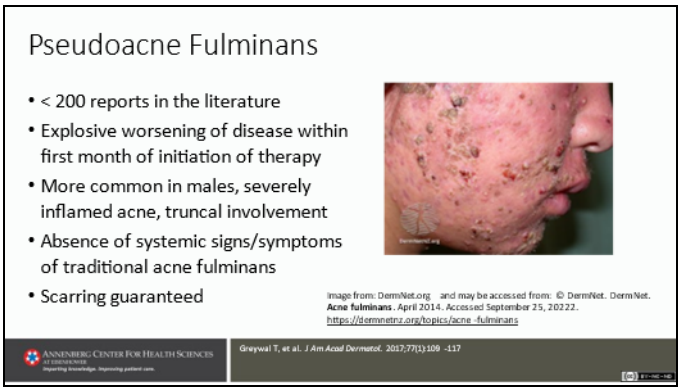
A true, but very rare, side effect of isotretinoin is pseudotumor cerebri, but of course that's also a rare side effect of your oral tetracyclines that the patient has probably already used successfully without having pseudotumor cerebri. It's FDA-approved, technically, for treatment of nodulocystic acne unresponsive to conventional therapy, including antibiotics, unquote. What that means is that a patient walks in with a face full of pimples, technically they're not candidates until they have tried other modalities to make them better. We use it for severe recalcitrant acne and it's FDA-approved down to the age of 12.

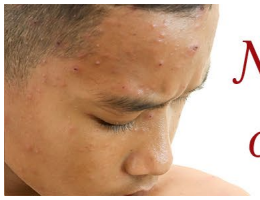
Let's talk specifically about the risk of depression with isotretinoin because, when your patient looks the drug up on the internet, that's what they're going to see. I think it's important that we remember, before we look at the study on the screen, that depression is incredibly common between the ages of 18 and 25. We have a lot of background noise. Depression is also incredibly common in patients with acne and that too gives us a lot of background noise. So you're dealing with a patient population that's already highly likely to be depressed. But still, in a meta-analysis of 31 studies in patients receiving isotretinoin, the relative risk of depression was shown to be significantly declined vs comparators, post-treatment, compared to baseline. The mean depression score had actually decreased. So not only does it not seem that isotretinoin causes depression, it seems as though it makes the patients actually somewhat better.

Another thing that I want to make very, very sure that everybody's aware of is an event called pseudoacne fulminans. There are about 200 reports of this in the literature and it's an explosive worsening of acne within the first month of initiation of isotretinoin. It's more common in males, in those with very severely inflamed acne and those with bad truncal involvement. There's no systemic signs and symptoms of the traditional disease called acne fulminans which is why this is referred to as pseudoacne fulminans. The skin looks very similar, but the rest of the body is unphased. Scarring is virtually a guarantee in these patients.



You want to avoid this at all costs, and you avoid it by, when you see somebody who's high risk—so a male with very inflammatory acne including the trunk—you want to start them on very low doses. Personally, I use 10 mg a day, 10 mg every other day. Some people like to start off with prednisone at the beginning. I usually don't do that. I want to see what's going to happen to them over time, but I do make sure that they have a filled bottle of prednisone in their homes with them so that when they call me up and say, you know, I think I'm getting worse, I can start the prednisone immediately to avoid what you just saw.

Once it's happening, and I see this all the time, patients come to me, when it starts to happen, the acne gets worse and the physician increases the dose of isotretinoin. Completely the wrong thing to do. Stop or cut the isotretinoin dose by at least 50% and add prednisone 1 mg/kg immediately. May seem like a high dose, but 1 mg/kg immediately. And then, over time, you can sort of ying-yang it, right? You're trying to reduce the prednisone, trying to reduce, also introduce the isotretinoin though because paradoxically, although isotretinoin causes pseudoacne fulminans, it's also the solution to the problem and it will get rid of the pseudoacne fulminans as well as the acne that the patient had to begin with.



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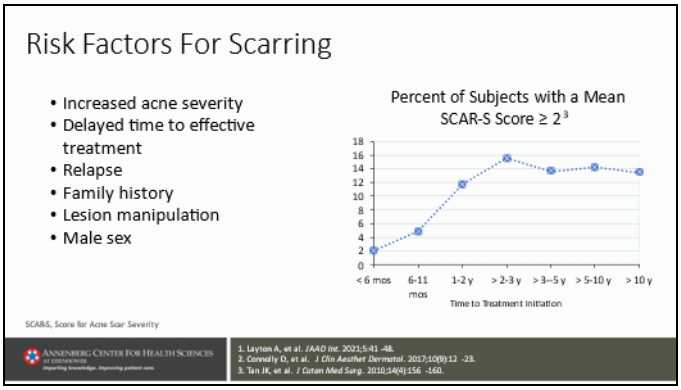
Over time, we're going to be reassessing our patients, and eventually we're going to stop our acute therapy and switch over to maintenance therapy. How frequently are you going to reassess? Well, during the acute therapy phase when I'm trying to get them better, I like to look at them about every 6 weeks. Once we're on maintenance therapy, I'm looking at them every couple of months. Our primary goals here are to maintain clear or almost clear skin and to avoid antibiotics. Generally, I'm doing this with a maintenance retinoid, with or without benzoyl peroxide.

Acne Sequalae and Management

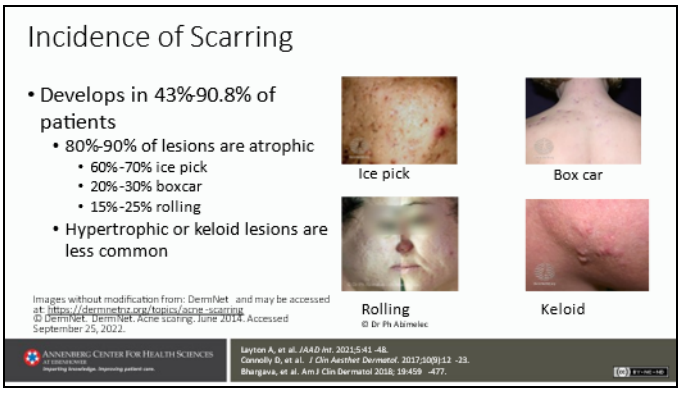
Now let's talk about acne sequelae and the management thereof. With our sequelae, we have pigmentary alterations. We have too much dark spots and too much red spots. The incidence of hyperpigmentation, as you can see, is very high, especially in our patients with darker Fitzpatrick skin phototypes, particularly the type IVs and Vs are likely to develop this hyperpigmentation, whereas erythema is usually seen in lighter Fitzpatrick skin.

The risk for scarring in our patients increases with acne severity, but it can happen in any kind of acne. You've all seen patients with very minimal acne, but with a lot of scars. The tendency to scar is something that the patient has. They have a scarring diathesis and those who have it are going to scar, regardless of how bad their acne is.



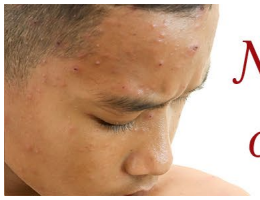
We have a study that shows that the longer you wait to treat the patient effectively, the more likely they are to form scars. Patients who relapse are more likely to scar. Patients with a family history, patients who manipulate their lesions, squeeze and poke and pluck, and men. This study that looked at how many scars the patients had, depending on how long it took them to get on treatment and you can see that scars increase over time until about 3 years and, at 3 years, it seems to be very steady. But the bottom line is get your patients onto quality treatment as soon as humanly possible to avoid scarring.

As we've said before, very common. You see ice pick scars in the upper left-hand corner, looks as if they were stabbed. They're very thin and very deep. Box cars, which look like a square, and keloidal scars are also possible down at the bottom. About 80% to 90% of lesions are atrophic or innies and they are the ice picks and the box cars, and also rolling scars which are very gradual, as opposed to the box cars which are cut off and square. And then the hypertrophic or keloidal lesions are much less common.



What are we going to do with the patients who have post-inflammatory hyperpigmentation? You can see a list here of products that we can utilize and procedures that we can do for our patients. Topical retinoids are my favorite addition, as well as azelaic acid, for this problem, as they both treat acne and treat and prevent post-inflammatory hyperpigmentation. Once it's already occurred, hydroquinone works well, as does superficial chemical peels along with hydroquinone and topical retinoids. There are lasers that are specific for this and we always want to make sure that our patients with post-inflammatory hyperpigmentation are utilizing adequate sunscreen so that the spots don't get worse.

Once we see scarring, things become much more difficult. Scarring is something you want to avoid because the treatment is difficult, ineffective and expensive and time-consuming. Topical retinoids can be of help over the long haul, we're talking 6 to 12 months, as are chemical peels, along with topical retinoids. There's a technique where TCA is used with a tiny little needle and poked into scars to



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release the adhesions that are holding them down and subcision does the same thing. We can excise a particularly deep scar, replacing a large box car scar, for example, with something which is linear and less noticeable, as long as it's within the skin tension lines. We can use lasers, we can use microneedling and we can fill in those more shallow scars, like the sloping scars.

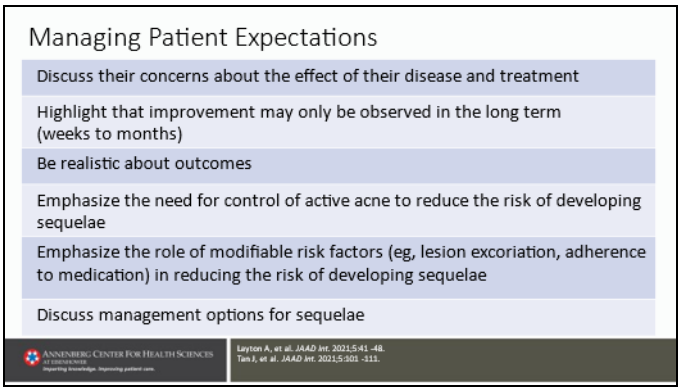
Ensuring Success

Let's talk about what we're going to do to make sure that we're as successful as we can possibly be and that includes, on our end, right, which is all the things we just talked about, picking the right medications, but it's also improving compliance with therapy. And one of the best ways to improve compliance with therapy is to make sure that the patients are well educated.

This study showed that the vast majority was dissatisfied with the information that they received from their healthcare provider. Another study showed that overall knowledge of acne is extremely poor. You know where people are getting their information these days? Very short TikToks, for example. And 85% presume that if they just have the willpower to control their diet, they could either reduce or prevent their acne. They think that increased water consumption is going to make their acne better. I'm sure that came from the bottled water industry. And they also think that if they just ate more fruits and vegetables, they would be able to get better.

A lot of this stuff is coming from the internet, again, and although we are unsure of dietary changes that might make acne better, we know that there are a couple of poorly done and inconclusive studies that showed that reducing intake of non-fat or low-fat milk products and consuming a diet which is low-glycemic index and avoiding the use of whey protein, may be helpful. You can always recommend to your patients that they consume a diet which is low-glycemic index, it's after all a healthy diet, but the whey protein avoidance, as far as I'm concerned, is the most important thing. I have many patients whose acne got dramatically worse or failed to respond thanks to the use of whey protein during weightlifting training, for example.

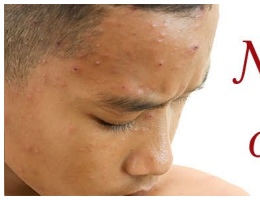
When we're managing our patients' expectations, which is absolutely crucial, we want to talk to them about their concerns about the effect of their disease and their treatment. Let them be heard. Let them interact with us as much as possible. Make, let them make choices. You know, if you're on the fence between one drug and another, why not let them make the decision? Teenagers have control over nothing, and [if] you've given them control over their acne treatment, they're more invested and more likely to use their drug.



We want to make sure that we highlight that improvement may only be seen long haul; that this is, this is going to take a long time for you to get better. This is not a sprint; this is a marathon. Be realistic about the outcomes, especially short-term. Emphasize the need of control of active acne to reduce developing the sequelae. That statement comes from patients who come in with a lot of acne, but also a lot of hyperpigmented macules from their acne, and many of them don't care about treating their acne. They care about treating their spots, right? And you have to kind of convince them that both of them need to be treated, otherwise the pimples are going to create new spots. You want to make sure to emphasize the need for overall control of acne.

You want to emphasize the role of anything that might be modifiable, like scratching and poking. Adherence to their medications in reducing the development of sequelae and the improvement of their acne. And also we can discuss management options for sequelae. Frankly, I don't discuss that on the first visit or even the second or maybe even the third. Once we have things under control is when I want to start talking about what we're going to do to fix problems which may be permanent or semi-permanent.

I was honored to be part of a panel of expert reviews from around the world which was called the PACE panel, for personalized acne consensus of experts, right? And we talked



about the goals of treatment and our goals of treatment were to get our patients to clear or almost clear with a minimal number of adverse events, to prevent sequelae, and also to improve our patients' quality of life as much as we can, and to reduce the disease burden. We recommended overall early intervention to prevent sequelae, early aggressive therapy with combination regimens that target those 4 pillars of pathogenesis of acne, right, picking 1 from column A, 1 from column B, using as many medications as you can get away with to hit the patient hard from all directions. And use of topical retinoids in everyone to make them better, as well as to prevent scarring or to treat scarring over the long haul.

How are we going to optimize adherence? That's difficult. We can do our part, right, but how do we convince the patient to do their part? Well, I think first of all, listening to your patient and obtaining buy-in for the treatment plan. There are people, for example, who are morning people or evening people. Asking an evening person who rolls out of bed at the last moment in the morning to put 3 things on in the morning and wash their face is ridiculous, right? You need to listen to your patient and make sure that you are suggesting a treatment plan that's actually going to fit into their lives. You want to keep it simple, stupid, right? Once daily dosing, if possible. Fixed combinations, if possible. As few administration rules as possible. Picking an oral medication, for example, that has no rules that go along with it, like you have to take it in the morning, you can't take it with food, right? So, as few rules as humanly possible.

Preferably, utilizing a medication which has a rapid onset of action so that the patients see right away, oh using this medication is going to make me better, I can see that now. Product with good tolerability so that that moment of the crisis of confidence doesn't happen, they don't have a problem with bad tolerability issues before they actually get better. And finally, set expectations. Your average teenager thinks he or she is going to be better in 2 weeks on acne medications and that's simply not going to happen. You sort of have to erase the entire internet and tell them the truth.

When should you refer to a dermatologist is a question that often comes up. If you're not sure of the diagnosis, that's not going to happen to you very often, of course, because you're dealing with younger children, but with older patients, we have to, the difference between rosacea and acne can be quite difficult. I think, in patients with very severe acne, it's best to just get them off your hands. Anybody who's scarring, either physically or emotionally, and people who are failing conventional therapy.

Summary

Our summary is going over all of those things that we just talked about that are of maximum importance. The first is knowing that acne affects the majority of pediatric patients. You already know that, but sometimes it's nice for the patients to recognize that they're not alone. Acne peaks, by the way, generally at about age 16. So that might be a useful factoid for you to have. It can have significant impact on the quality of life of your patient. While we're making sure that we're treating their acne correctly and well and we're improving their quality of life, we need to remember that we should not be doing so with antibiotics over the long haul. We need to be good stewards of antibiotics to prevent the development of resistant strains, and we do this by not using them as monotherapy, and by using them for as short a period of time as possible, and never alone without benzoyl peroxide and preferably a retinoid as well. We know that overall adherence rates are poor, so even if we're doing our job, the patients may not be doing their job. And one of the ways to avoid this loss of adherence is with education, to make sure that the patient understands his or her disease and understands why you picked the medications that you did. You did this on purpose, and you did this very carefully, tailoring it to their specific needs. And each one of the drugs that you have given them is part of their improvement.

Often, patients will come back after I've given them 3 medications and they'll say, "Well I stopped that one because it wasn't working." How on earth do they know that? And that shows that I did a poor job in my education efforts. We want to help to anticipate and to manage adverse reactions. Make sure that we recognize that expert treatment and quality treatment is going to improve the mental health of our patients and the relationship with their siblings and their parents. And we want to make sure that we prepare for sequelae, but hopefully avoid them. And recognize that delayed treatment or inadequate treatment is what's going to lead to the risk of scarring.