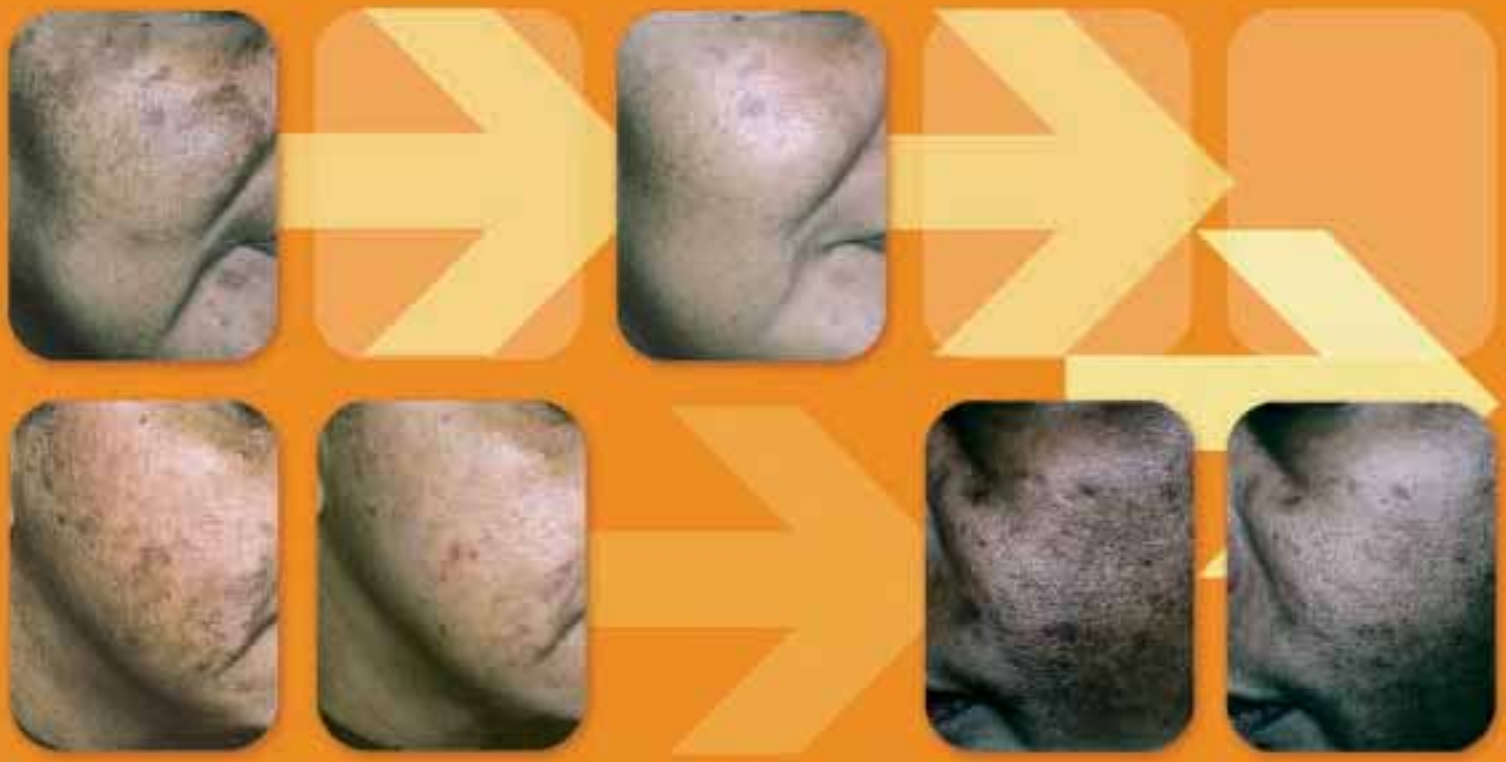
Supplement to the September 2005

skin & AGING

Evaluating the Risks and Benefits of Treatment Modalities for Hyperpigmentation

Experts Discuss Practical Approaches to Treating this Condition



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Introduction

Disorders of hyperpigmentation are global issues of major cosmetic concern. They impact every racial ethnic group and in some instances, dermatologists underestimate the psychological impact of these diseases (both hyper- and hypopigmentation).

A group of experts met in San Diego in May to discuss the various issues surrounding the available treatment modalities for hyperpigmentation disorders including melasma, post-inflammatory hyperpigmentation and photoaging.

This supplement will cover the following areas, as related to the use of hydroquinone therapy for the treatment of hyperpigmentation:

- General background information on hyperpigmentation and its available treatments
- A closer look at topical lightening agents
- Some aspects of safety related to hydroquinone
- How to stratify patients
- How to choose an agent
- Patient concerns.

I hope that you will find the information contained in these articles to be useful in your dermatology practices.

Pearl E. Grimes, M.D.
Moderator

MODERATOR

Pearl E. Grimes, M.D., is Clinical Professor at the University of California, Los Angeles. She serves on the Board of Directors of the American Society for Dermatologic Surgery, the Board of Directors and Executive Committee of the Women's Dermatologic Society and she is Chair of the Diversity Task Force for the American Academy of Dermatology. Dr. Grimes is also Director of the Vitiligo and Pigmentation Institute of Southern California, which is nationally and internationally recognized for its work on pigmentary disorders.

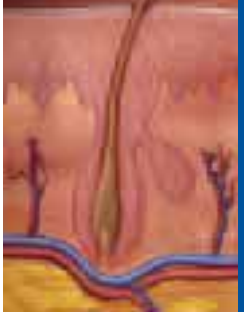
PANELISTS

Deborah H. Atkin, M.D., is Co-Director of Dermatology and Laser of Del Mar in Del Mar, CA. She is a Fellow of the American Society for Laser Medicine and Surgery and is a member of the American Society for Dermatologic Surgery and the American Academy of Dermatology. Dr. Atkin is an active volunteer for the American Cancer Society and the American Liver Foundation and serves as a consultant to laser and pharmaceutical companies.

Fran E. Cook-Bolden, M.D., is Director of the Skin Specialty Group and the Ethnic Skin Specialty Group. She is currently an Assistant Clinical Professor of Dermatology at Columbia University in New York and is a member of the American Academy of Dermatology, the American Society for Laser Medicine and Surgery, the American Society for Dermatologic Surgery and the Women's Dermatologic Society. Dr. Cook-Bolden also serves as a consultant to the health and beauty industry and is a researcher and consultant to the pharmaceutical industry.

Mark G. Rubin, M.D., is a cosmetic dermatologist who practices at the Lasky Skin Center in Beverly Hills, CA. He specializes in skin rejuvenation and has published numerous articles and chapters related to this topic. In addition to his clinical practice, Dr. Rubin serves as a consultant and clinical researcher for multiple pharmaceutical companies.

Howard K. Steinman, M.D., is an Assistant Clinical Professor of Dermatology at the University of California, San Diego. He is Director of South Bay Spa MD, a dermatology/cosmetic surgery center and medical spa in Chula Vista, CA. He has also served as President of the American Society for Mohs Surgery (ASMS), on the Executive Committee of the American Academy of Dermatology Advisory Board, and on the Board of Directors of the ASMS, the California Dermatological Society and California Academy of Cosmetic Surgery. Dr. Steinman has served as consultant to several cosmetic and pharmaceutical companies.



About Hyperpigmentation and Hydroquinone

The background details of this condition and its treatments.

Dr. Pearl E. Grimes: Conditions such as melasma and post-inflammatory hyperpigmentation (PIH) are more common in darker racial ethnic groups, whereas the dyschromia of photoaging, lentigines and freckles are more common in lighter-complexioned individuals.

Melasma is a symmetrical disorder of hyperpigmentation characterized by brown-gray areas of discoloration commonly affecting the cheeks, forehead, upper lips and chin. (The arms, chest and back are also affected in some patients.) Factors implicated in the pathogenesis of melasma include a genetic predisposition, oral contraceptives, hormone replacement therapy, pregnancy and thyroid dysfunction. Treating melasma is difficult; therefore, not surprisingly, treatment failures and recurrences are common.

In contrast, PIH results from a preceding inflammatory disorder such as acne, atopic dermatitis, allergic contact dermatitis and lichen planus. Hyperpigmented macules and/or patches affecting the site of inflammation characterize PIH. If we can control the primary disease, then we can achieve a cure.

Photodamage is characterized by prematurely aged skin from the deleterious effects of acute and chronic ultraviolet light exposure. Clinical features of photodamage include coarse and fine wrinkling, mottled pigmentary changes, lentigines, sallowness and telangiectasias.

Treating disorders of hyperpigmentation can prove challenging. Medical therapies include broad-spectrum sunscreens, hydroquinone, tretinoin, tazarotene, retinol, kojic acid, licorice, azelaic acid, alpha hydroxy acids and salicylic acid. However, the mainstay for treating these conditions is most often hydroquinone **(see Figure 1)**, which inhibits the conversion of dopa to melanin by inhibiting the tyrosinase enzyme. Dermatologists can use varying concentrations depending on the severity of the condition being treated. ■

FIGURE 1: Hydroquinone 4% Marketed Products

Products	Microsponge Technology	Tretinoin	Retinol	Cortico-steroid	Glycolic Acid	Hyaluronic Acid	Vitamins C and E	Sunscreens
EpiQuin Micro	▼		▼				▼	
Claripel								▼
Eldoquin Forte								▼
Eldopaque Forte								▼
Glyquin XM					▼	▼	▼	▼
Lustra					▼		▼	
Lustra-AF					▼		▼	▼
Solaquin Forte								▼
Tri-Luma		▼		▼				

Putting Hydroquinone to the Test

Dr. Pearl E. Grimes: I first tested 2% hydroquinone and 0.15% retinol and then moved on to work with the 4% formulation, marketed as EpiQuin Micro, which contains 0.15% retinol entrapped in the Microsponge formulation. It also contains the antioxidants vitamin C and vitamin E. For a list of some hydroquinone 4% marketed products, **see Figure 1**.

We conducted an open-label study of EpiQuin Micro in 28 patients (16 with melasma and 12 with post-inflammatory hyperpigmentation). Twenty-five patients completed the study and they had a statistically significant decrease in pigmentation intensity and lesional area that steadily improved from baseline to 12 weeks. There was also a significant decrease in disease severity at 4, 8 and 12 weeks. The drug was well-tolerated and no statistically significant issues regarding dryness or peeling arose. We did see a decrease in oiliness at week 4.

Another randomized, investigator-blinded, two-arm, split-face study compared EpiQuin Micro, Alustra (hydroquinone 4%) and Tri-Luma Cream (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%). In arm one (13 patients), EpiQuin Micro was applied to one side of the face and Alustra was applied to the other side b.i.d. — both for 12 weeks. In arm two (21 patients), EpiQuin Micro was applied b.i.d. to one side for 12 weeks and Tri-Luma was applied to the opposite side q.d. for 8 weeks, with a placebo taking its place for an additional 4 weeks. (Tri-Luma labeling limited use to 8 weeks at the time of the study.)

The melasma area and severity index (MASI) score for arm one is shown in **Figure 2**. A statistically significant decrease in disease severity was also evident with EpiQuin Micro compared to Alustra. The global evaluation trend (although not significant) suggested that at 8 and 12 weeks, EpiQuin Micro showed a greater improvement than Alustra.

The MASI score for arm two is shown in **Figure 3**. With regard to overall severity of disease, no statistically significant difference was seen. There was worsening at 12 weeks with Tri-Luma because the drug was discontinued at 8 weeks. There were no differences in overall global improvement either, suggesting that these drugs were comparable in efficacy. ■

FIGURE 2: MASI Score — EpiQuin Micro vs. Alustra

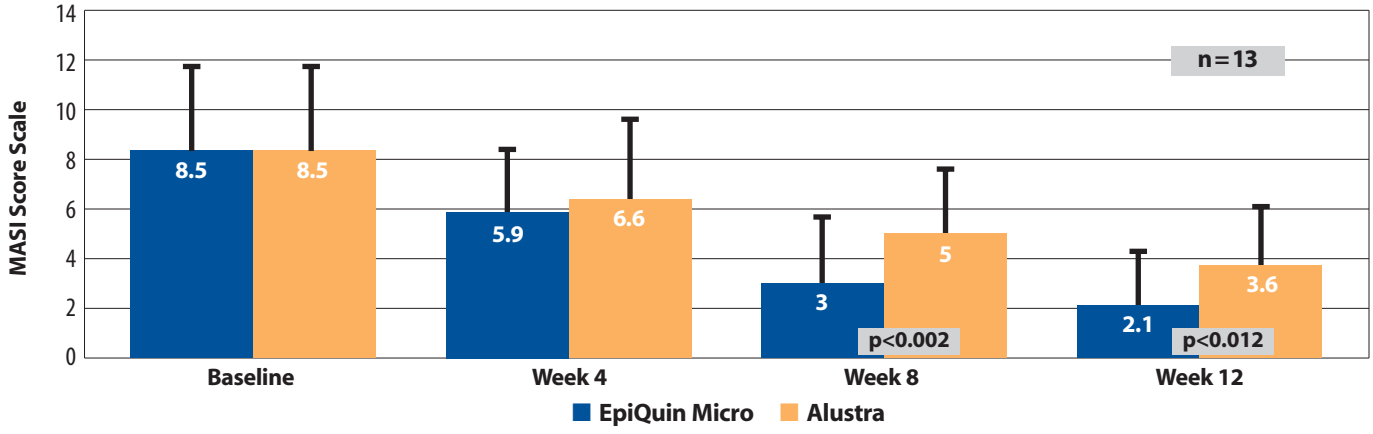
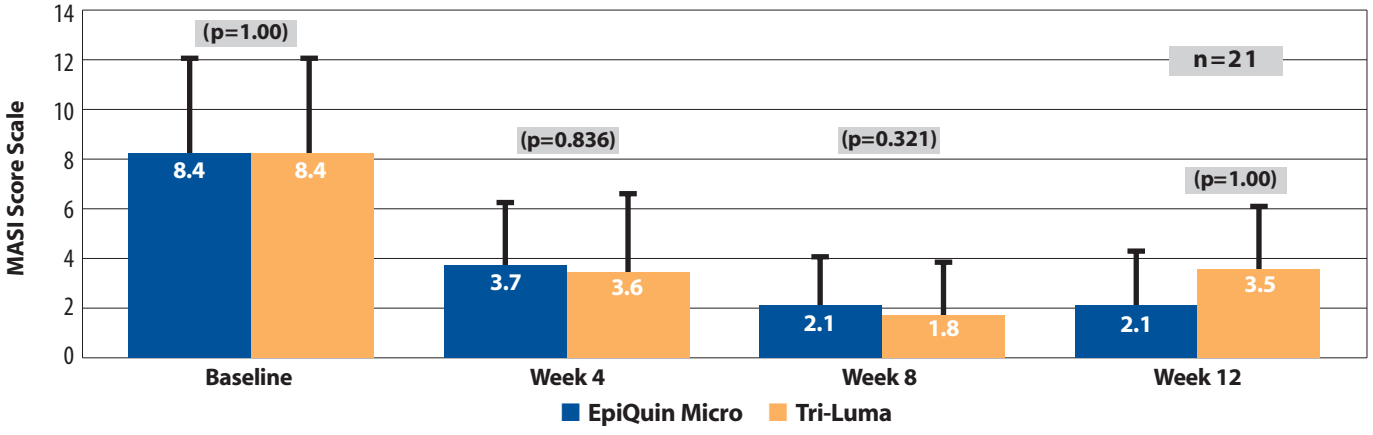
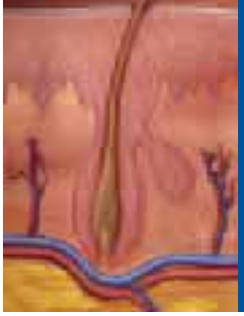


FIGURE 3: MASI Score — EpiQuin Micro vs. Tri-Luma





Topical Lightening Products

How and when leading dermatologists use these agents.

Topical lightening agents used to treat hyperpigmentation include hydroquinone, retinoids and other lightening agents such as kojic acid, azelaic acid and alpha hydroxy acid. Antioxidants and steroids are also helpful in combating this condition. (See "A Look at Current Therapies for Hyperpigmentation" on page 10).

Hydroquinone-containing bleaching creams are used worldwide for pigment imperfections. Such products have been shown to hinder the conversion of dopa to melanin by inhibiting tyrosinase.

— Dr. Grimes

Dr. Pearl E. Grimes: Hydroquinone-containing bleaching creams are used worldwide for pigment imperfections. Such products have been shown to hinder the conversion of dopa to melanin by inhibiting tyrosinase. Other mechanisms include inhibition of DNA and RNA synthesis, degradation of melanosomes and destruction of melanocytes.

RETINOL

Dr. Grimes: Retinol is a pure, active form of vitamin A. It is converted to retinaldehyde, which is also an active product that is ultimately converted to retinoic acid. Studies suggest that we need to deliver about 10 times as much retinol to give us the same level of retinoic acid in the skin. Retinol has been shown to increase dermal thickness. It increases the compactness of the stratum corneum and thickens the epidermal granular layer. It improves hyperpigmentation as well as skin hydration.

I think we have better, more stable, retinol formulations than ever. We have a substantial database on retinoic acid that establishes its overall efficacy and safety when it's used as a monotherapy agent for hyperpigmentation or in combination products (retinol is converted to retinaldehyde, which is converted to retinoic acid, which is the after-product). With these products, even though you need a higher concentration of retinol, you still have a comparable effect of increasing epidermal thickness, increasing the compactness of the stratum corneum, thinning the epidermal granular layer, improving hyperpigmentation, skin hydration and skin texture. How many of you believe in retinol?

Dr. Howard K. Steinman: I have come full circle on retinol. I think I'm a victim of what we were initially taught — that retinol is just not as effective as tretinoin and manufacturers put retinol in their over-the-counter products because they couldn't use tretinoin. Therefore, retinol was sort of a hokier substitute for the truly effective agent, tretinoin. And since attending several meetings in the last year and reading studies, I'm now a believer that retinol is nearly as effective as tretinoin without the side effects. I

now feel that retinol is an effective adjunct in both facial rejuvenation and in treating hyperpigmentation.

Dr. Grimes: The other key point is that when you apply topical retinol, it's not nearly as irritating as tretinoin; there's a marked difference.

According to studies, the added benefit of Microsponge technology is that the system allows gradual release of ingredients into the skin, reducing potential side effects such as skin irritation.

Dr. Fran E. Cook-Bolden: I haven't switched over yet. I'm still looking at the data that are being presented and would love to hear what other people think in terms of retinols versus retinoids.

Dr. Steinman: In initially comparing fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05% (Tri-Luma) to hydroquinone 4% (EpiQuin Micro), I quite honestly felt that fluocinolone acetonide-hydroquinone-tretinoin must be better because it is a Kligman formulation that had tretinoin in it, but I don't believe that's the case anymore, based on the studies that I've seen comparing retinol to tretinoin.

Dr. Deborah H. Atkin: There are two compelling reasons to use retinol for photoaging. These relate to the decrease in irritation and less capillary development.

1. Retinol eventually becomes converted to retinoic acid in the skin via retinaldehyde. As retinoic acid builds up to a point where you're going to get irritation, the skin stops this conversion. When the buildup of retinoic acid subsides, then this conversion moves forward again.
2. Because there is often less irritation with retinol, you may end up with less blood vessel development, and I think for photoaging, that is important.

I don't think the erythema and capillary development you can see with tretinoin is necessarily all reversible. We may then be doing a disservice to patients who are coming in for cosmetic treatments, such as intense pulsed light or pulsed dye laser to decrease redness, if we keep them on a retinoid that may increase their redness. This is especially a concern to me if they have a component of rosacea.

Dr. Mark G. Rubin: I don't use retinol as a single-line therapy in my office, and I don't sell it, mainly because when there were several products on the market, there were no good comparative studies showing that they were stable and clinically capable of doing anything specific. I think it's sometimes difficult to be able to take a product and say that this product can do what the studies show. And that's been the issue for me with retinol.

Dr. Grimes: I've used retinol for a number of years now and have achieved nice results in my patients who are Fitzpatrick skin types V and VI who want to perhaps be on an anti-aging regimen and don't tolerate tretinoin. I also use retinol as a monotherapy for many lighter-skinned patients who don't tolerate tretinoin (Avita, Renova, Retin-A) or tazarotene (Tazorac). To minimize irritation, I also utilize regimens in which I alternate tretinoin and/or tazarotene with retinol.

I don't think the erythema and capillary development you can see with tretinoin is necessarily all reversible. We may then be doing a disservice to patients who are coming in for cosmetic treatments if we keep them on a retinoid that may increase their redness.

— Dr. Atkin

Dr. Atkin: Another benefit of retinol is that because it is often less irritating than tretinoin, patients are more likely to be able to tolerate the additional products we are asking them to use to treat photoaging. For instance, someone irritated by tretinoin may not tolerate the topical growth factors, topical vitamin C, sunscreen and/or lightening agents that we recommend to them. This can be a real problem.

Dr. Cook-Bolden: In your clinical experience, do your photo-aged patients develop telangiectasias associated with retinoid use?

Dr. Atkin: Yes, and the retinoids also have an irritation potential that may make them unable to tolerate the additional topicals that we want them to use. Even the group of patients who can tolerate tretinoin will periodically get to a point where their skin dries out and exfoliates. Then

their other topicals feel more irritating. In some patients, though, who have thick, sebaceous skin and comedones, I will still suggest tretinoin. These patients are often less irritated by topicals in general and are less prone to telangiectasias.

Dr. Grimes: I think that we tend to underestimate the potential of tretinoin to induce telangiectasias.

Dr. Steinman: When I first examine a patient for aging, if they're fair-skinned and have facial telangiectasias, I don't use tretinoin. I am concerned that it may induce or worsen telangiectasias. For patients who have telangiectasias, I use glycolic acid, vitamin C and/or growth factors.

I think [steroids] definitely have anti-inflammatory effects. The limiting factors in using these preparations in topical bleaching agents are atrophy, telangiectasia, acne and acne rosacea.
— Dr. Grimes

STEROIDS

Dr. Grimes: We talked about retinol. Let's talk about the use of steroids in bleaching formulations. How do steroids work in bleaching agents? I think they definitely have anti-inflammatory effects. The limiting factors in using these preparations in topical bleaching agents are atrophy, telangiectasia, acne and acne rosacea. When we compound formulations that contain a fluorinated steroid or a non-fluorinated steroid, I think we're increasing the likelihood that we may experience some of these side effects.

Dr. Cook-Bolden: Amy McMichael, M.D., and colleagues conducted an 8-week, clinical, histologic and biochemical study of 20 patients with psoriasis.[1] The results were published in 1996 in the *British Journal of Dermatology*. They had biopsies in 16 patients and I think 17 patients finished the study. They looked at the differences in response to the use of a steroid alone versus the steroid betamethasone diproprionate plus tretinoin 0.1%. At the end of 8 weeks, the patients who were treated with the steroid alone had a 19% reduction in epidermal thickness, whereas the steroid plus retinoic acid group experienced a 1% increase in epidermal thickness, suggesting that the retinoid balances out the atrophogenic affects of the steroid.

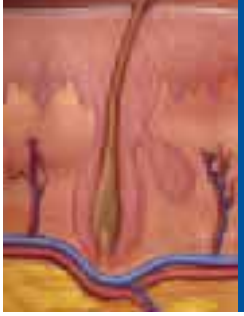
Dr. Grimes: Dr. McMichael's group also looked at the percent reduction in procollagen I, and for the steroid alone ,it decreased by 55%, whereas the steroid plus retinoic acid group showed a reduction of 45%. So it didn't save procollagen I much. The difference between those two was not statistically significant. These findings suggest that, despite the addition of retinoic acid, betamethasone decreases collagen synthesis.

Dr. Atkin: In this study, the researchers noted no clinical change in terms of atrophy, but that was probably because they were evaluated at 8 weeks. The procollagen was decreased by 45%, so this likely would lead to atrophy at a later date. I think, actually, this study was a compelling indication that retinoids do not completely reduce the risk of atrophy from steroids used as a combination therapy. If we have a steroid-free choice, it is prudent to choose it.

Dr. Rubin: The idea of keeping a patient on a topical steroid for a year does not make me comfortable. I have been unimpressed with telangiectasia as being an issue, but it concerns me, and in my own mind, if I have a choice between a product that makes me comfortable or one that makes me uncomfortable with similar efficacy, obviously I'd take the one that makes me feel better. I won't keep a patient who needs long-term therapy on fluocinolone acetonide, hydroquinone and tretinoin, but I certainly have patients that I'll put on fluocinolone acetonide, hydroquinone and tretinoin in the beginning and then back them down to a non-steroid-containing lightening agent as part of their long-term routine. ■

Reference

1. McMichael AJ, Griffiths CE, Talwar HS, et al. Concurrent application of tretinoin (retinoic acid) partially protects against corticosteroid-induced epidermal atrophy. *Br J Dermatol* 1996;135(1):60–64.



Choosing an Agent

Insight into when and why physicians choose certain treatment strategies.

Dr. Pearl E. Grimes: When we choose a topical lightening agent, do we consider the diagnosis? There is a difference in treating melasma and treating post-inflammatory hyperpigmentation (PIH). We will never cure melasma with the current armamentarium of drugs. I often think of active phase versus maintenance phase, and I think we have to factor that in to the drug that we choose.

Hydroquinone is still our gold standard. We use it in combination with the retinoids, such as tretinoin and retinol. What are the other lightening agents that we use? There are multiple kojic acid formulations on the market. I use the newer formulation of azelaic acid (Finacea gel 15%) more than the older azelaic acid formulation because I think it's better absorbed and has enhanced efficacy. We have many formulations that contain alpha hydroxy acids (e.g., Glyquin [hydroquinone 4%] and Glyquin-XM [40 mg hydroquinone, 80 mg octocrylene, 40 mg oxybenzone and 30 mg avobenzone]). Many of these products also contain other antioxidants. The only FDA-approved combination hydroquinone formula is fluocinolone acetonide 0.01%, hydroquinone 4% and tretinoin 0.05% (Tri-Luma).

Briganti has given us a new classification for lightening agents. These agents act at various points of melanin synthesis (before, during and after).

During melanin synthesis, agents that inhibit tyrosinase include hydroquinone, 4-hydroxy-anisole, arbutin, aloesin, azelaic acid, kojic acid, methyl gentisate, ellagic acid, resveratrol and oxyresveratrol.

Agents acting during melanin synthesis via inhibition of reactive oxygen species include ascorbic acid and vitamin E.

An agent that impacts tyrosinase degradation after melanin synthesis is alpha linoleic acid. The serine protease inhibitors (e.g., soy bean milk extract and niacinamide) inhibit the transfer of melanosomes to keratinocytes. Lactic acid, glyocolic acid, retinoic acid and retinol accelerates skin turnover.

Figure 1 on page 10 shows the classification of these lightening agents.

We will never cure melasma with the current armamentarium of drugs. I often think of active phase versus maintenance phase, and we should consider this when choosing a drug.

— Dr. Grimes

If you have a good formulation, many patients can see improvement with hydroquinone at 4 weeks. **Figure 2** on the next page shows a summary of therapies. I think you can actually see improvement with retinol even as a monotherapy for pigmentation, but you're going to see much better improvement if you combine it with hydroquinone or another bleaching agent.

I think many dermatologists still use tretinoin as a monotherapy for hyperpigmentation. But patients

FIGURE 1: Classification of Depigmentation Agents According to Activity

(adapted from Briganti S, Camera E, Picardo M. Chemical and instrumental approaches to treat hyperpigmentation. *Pigment Cell Res* 2003; 16(2):101–110)

Stage of melanin synthesis	Deposition	Compounds	
Before melanin synthesis	**Tyrosinase transcription**	▪ C2-ceramide	▪ Tretinoin
	Tyrosinase glycosylation	▪ PaSSO3Ca	
During melanin synthesis	**Tyrosinase inhibition**	▪ Hydroquinone ▪ 4-hydroxy-anisole ▪ 4-S-CAP and derivatives ▪ Arbutin ▪ Aloesin ▪ Azelaic Acid	▪ Kojic acid ▪ Methyl gentisate ▪ Ellagic acid ▪ Resveratrol ▪ Oxyresveratrol
	Peroxidase inhibition	▪ Methimazole	▪ Phenols/catechols
	Product reduction and reactive oxygen species (ROS) scavengers	▪ Ascorbic Acid ▪ Ascorbic acid and palmitate ▪ VC-PMG ▪ Thioctic acid	▪ a-TOC ▪ D-L-a TF ▪ Hydrocumarins
After melanin synthesis	**Tyrosinase degradation**	Linoleic acid	a-linoleic acid
	Inhibition of melanosomes transfer	Serine protease inhibitors Lecithins and neoglycoproteins Soybean milk extracts	Niacinamide RW-50353
	Skin turnover acceleration	Lactic acid Glycolic acid Liquirtin	Retinoic acid Linoleic acid

FIGURE 2: A Look at Current Therapies for Hyperpigmentation

Therapy	Description		Side Effect
Hydroquinone (HQ) 4%	▪ Gold Standard ▪ Phenolic agent ▪ Efficacy correlated with concentration and vehicle	▪ Often combined with other bleaching agents ▪ Effective in about 12 wks	Irritation, allergic skin reaction, nail discoloration, hyper/hypopigmentation
Retinol **(pure active form of Vitamin A)**	▪ Combined with HQ ▪ Enhances HQ penetration, depigmentation, exfoliation	▪ More complete skin penetration than tretinoin = more effective delivery of retinoic acid (Duell AE, J Invest Derm 1997)	Some dose-dependent irritation, less than seen with tretinoin
Tretinoin **(synthetic form of Vitamin A)**	▪ Monotherapy or combined with HQ	▪ Enhances HQ penetration, depigmentation, exfoliation	Irritation, swelling, scaling, pruritus, hyperpigmentation, increased sun sensitivity
Other Bleaching Agents **(Azelaic acid, Kojic acid, alpha hydroxy acids)**	▪ Naturally occurring plant substances ▪ Used to promote exfoliation in OTC products	▪ Shown to reduce hyperpigmentation alone or combined with HQ	Irritation, scaling, pruritus, contact allergy
Antioxidants **(synthetic form of Vitamin A)**	▪ Vitamin C and E ▪ Combined with HQ	▪ Combined with HQ to prevent sun damage	None reported

don't want to wait 24 weeks to notice improvement in their condition. These other agents (e.g., azelaic acid, kojic acid and alpha hydroxy), by themselves, don't work as well as hydroquinone monotherapy agents.

Dr. Mark G. Rubin: We've all had patients who get irritancy from a fading cream, whatever the fading product happens to be, so why switch to azelaic acid? It doesn't work nearly as well. In my experience with monotherapy using azelaic acid for hyperpigmentation, patients often fade little, if at all.

Dr. Fran E. Cook-Bolden: We have quite a bit of experience using azelaic acid in the treatment of hyperpigmentation and do find the main limiting factor to be irritation — even more so than with hydroquinone. When treating these patients, we add a low-potency topical steroid to the azelaic acid, which increases tolerability and the "lightening" potential. Many of these patients had previously used hydroquinones with limited response and insisted on a completely different therapy that did not include hydroquinones. In some patients, we added the azelaic acid combination to their hydroquinone therapy with improved efficacy.

In clinical practice, I find that there is overall less irritation and peeling with the EpiQuin Micro (hydroquinone 4%), probably because of the Microsponge technology, than with many other hydroquinone formulations. We almost uniformly start all hydroquinone therapy with a three-times-each-week-at-night regimen and increase the frequency of application as tolerated.

Dr. Grimes: If you put a patient on hydroquinone and you keep them on the same concentration, they get a plateau effect. If you increase the concentration, they might see a difference, but the take-home message is that we should probably rotate bleaches. It's tachyphylaxis — the same phenomena that we see with steroids. If you discontinue the drug or adjust the concentration or formulation, chances are you're going to get a response again.

Dr. Cook-Bolden: That is not an uncommon scenario in our patients. Often, when presenting with a history of long-term hydroquinone use and lack of improvement, we discontinue the therapy and start with a clean slate. We call this "hydroquinone break." If a patient has been experiencing irritation from his current therapy, we often prescribe soothing treatments and strict sun protection during this period before resuming some form of hydroquinone therapy.

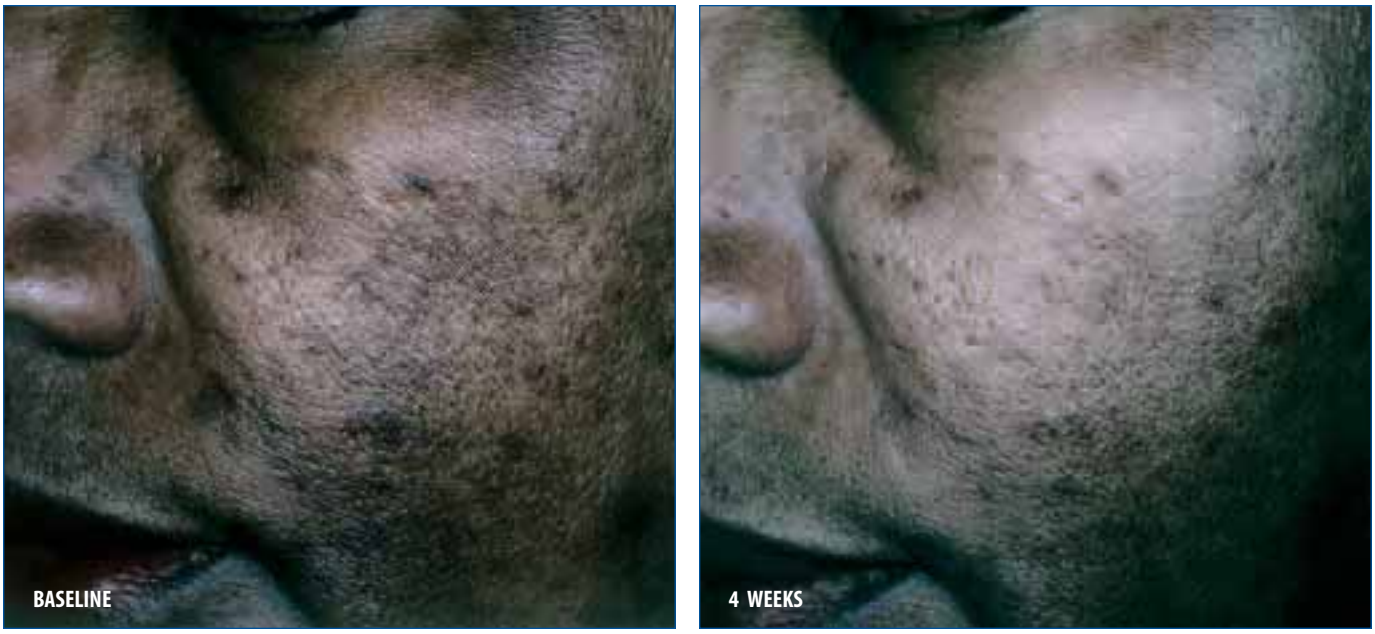
Dr. Grimes: I'm certainly not uncomfortable using a fluorinated steroid for melasma, but I have a cohort of patients who are virtually impossible to treat, and I have to pull out my heavy hitters. I extemporaneously compound hydroquinone in higher concentrations with a steroid for enhanced efficacy. The protocol I use for my challenging patients also includes the use of the hydroquinone 4%, fluocinolone 0.01%, tretinoin 0.05% formulation for melasma. I use it for a limited time (≤ 3 months), and then switch that patient to either a non-fluorinated preparation or a preparation that has no steroid at all. What are you using as a maintenance lightening agent?

…I have a cohort of patients who are virtually impossible to treat, and I have to pull out my heavy hitters. I extemporaneously compound hydroquinone in higher concentrations with a steriod for enhanced efficacy.

— Dr. Grimes

Dr. Howard K. Steinman: I tend to keep patients on the product they were using that got them to 70% unless they backslide. And then I'll switch to an alternative fading product. I think some people get to a certain point with just topicals, and they're not going to get any better. But a lot of those people, particularly women who wear makeup, are not nearly as upset by it because almost any makeup will cover light melasma.

Dr. Deborah H. Atkin: I use a lot of hydroquinone 4%, retinol 0.15%, and if people are clearing well, then I tend to decrease them to once a day and consider adding other topicals that may also help lighten the skin. I expect to increase it back to twice a day if they have exacerbations, especially in the summer. Even my patients who are religious about sunscreen do not always understand how important sun avoidance is. Sunscreen is just not enough. So in summer, when exposed to more light, I usually increase their hydroquinone use. For the rest of the year,



Improvement in hyperpigmentation symptoms in an African-American patient treated with hydroquinone 4%, retinol 0.15%.
Photos courtesy of Pearl E. Grimes, M.D.

again, I add other lighteners and keep them on topicals such as retinol and growth factors such as TNS Recovery Complex (Transforming Growth Factor, Vascular Endothelial Growth Factor, Keratinocyte Growth Factor, Interleukins). Interestingly, TNS tends to help lighten hyperpigmentation too, even on its own.

I keep everyone on hydroquinone long term. I don't take them off at all. My experience has been that everybody I've ever taken off of hydroquinone ends up going back on again.
— Dr. Rubin

Dr. Cook-Bolden: In the studies conducted using TNS Recovery Complex, researchers have found that it shows benefit in clearing hyperpigmentation. Maintenance therapy will often consist of a retinol or retinoid, TNS and a sunscreen. We will add intermittent hydroquinone therapy as needed.

Dr. Atkin: I agree that some patients can be rotated to other therapy and then you can add the hydroquinone back in the summer or when exposed to more light. I think patients do get tolerance or tachyphylaxis after a while. If you can jump-start them again with hydroquinone during exacerbations, they often get better results. I also consider peeling and intense pulsed light (IPL) treatments for exacerbations.

Dr. Rubin: My initial treatments are fairly limited with what I use for the majority of patients until they're fairly stable, then I start looking at their lifestyle, the time of the year, and what else they're interested in for their skin in the long term? I like the idea of using hydroquinone 4%, retinol 0.15% long term for patients who are interested in photorejuvenation. I really start to play a lot with different medications for maintenance. But I keep everyone on a hydroquinone long term. I don't take them off at all. My experience has been that everybody I've ever taken off of hydroquinone ends up going back on again.

Dr. Grimes: I think the people whom you can't get off a hydroquinone are primarily your melasma patients. Photodamaged patients may have to go on it intermittently, but I don't think that requires long-term therapy, nor is it required for our PIH patients. With melasma patients, if I can't get a patient off of hydroquinone, then I try to go up and down on concentrations and try to work them down to as little as I can every other day, every third day, knowing that I can go back if I

have to. For any given patient, I know that if I can intermittently discontinue hydroquinone, then they're going to have a better response than keeping them on it continuously.

Dr. Rubin: We can cure PIH patients. They have their pigment because of an insult that occurs, and as long as they stop the insult, and you clean up their pigment, that's it. I think most of the photodamaged patients who do well on hydroquinones re-pigment when you take them off (unless they're on retinoids or some heavy exfoliating kind of therapy). What you're doing to them physiologically with hydroquinone is decreasing the amount of pigment that they're making in that area. But the lesion itself, if there's a lentigo that's there in the beginning and is still there after they've been on hydroquinone, it's a lighter lentigo and when you stop the hydroquinone, they gradually darken again.

Dr. Grimes: You're going to have a longer window of clearing the dyschromia of photoaging if you go from, say, the hydroquinone to just a retinoid, which is going to continue to increase epidermal turnover, and that's going to give you a longer time frame before you have to put them back on that combination regimen versus what you're going to have to do in your melasma patients.

Dr. Steinman: One place that I'm more comfortable using hydroquinone 4%, retinol 0.15% than fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05% is with older women who have lentigines on the tops of their hands. Their skin is thinner than thin to begin with, so I do not recommend fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%. I prefer to not use a cortisone-containing product.

Dr. Rubin: What do you use as your criteria for diagnosing melasma?

Dr. Grimes: The pigmentary features of melasma are rather characteristic if a patient has typical pigmentation of the upper lip. Chances are photodamage isn't going to give you pigmentation of the upper lip. If I see it on the nose and cheeks extending up to the zygomatic rim, that's typical of melasma. Clinical photos of melasma show a classic distribution versus photodamage, which is much more marbled and diffuse.

Dr. Atkin: There's also a striking symmetry with melasma. Sometimes you may initially think it is photodamage, but then realize that the patient's hyperpigmentation is so symmetric that there is probably at least a component of melasma.

Dr. Cook-Bolden: Symmetry is a key component, in addition to the patient's history of disease.

RESURFACING

Dr. Grimes: How do we incorporate resurfacing procedures (which include chemical peels, microdermabrasion, ablative laser resurfacing and non-ablative laser resurfacing) for lightening skin? I use chemical peels and microdermabrasion. I think we use substantially less ablative laser resurfacing now, given all of the complications associated with it. Any preference on peels versus microdermabrasion versus IPL for hyperpigmentation?

Dr. Steinman: I have sufficient faith in both hydroquinone 4%, retinol 0.15% and fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%, that if they're not working after a few months, then I suggest a Vitalize Peel or Cosmelan mask or IPL. And only in those patients who are unwilling to go to that level would I want to try other topicals.

Dr. Grimes: We often see IPL complication in darker-skinned patients treated with this modality for melasma. Many dark-skinned patients just don't want peels because peels, depending on the depth of injury, could increase the likelihood that they're going to experience some PIH. Hence, I have a much smaller window of efficacy/safety in Fitzpatrick skin types V and VI versus what I would have in my patients who have a skin type I, II, or III. And that's one of the things that I'm constantly struggling with.

Dr. Steinman: Clearly with the IPL, you have to set it sufficiently low for skin types V or VI and it's going to require multiple treatments. With the consequences of peeling in mind, if you have other tools available, you should at least offer them to patients. I let them know my proposed treatment plan at the onset. I'm adamant about the requisite use of a sunscreen and a fading cream. I usually prescribe these first and if the patient isn't getting better as quickly

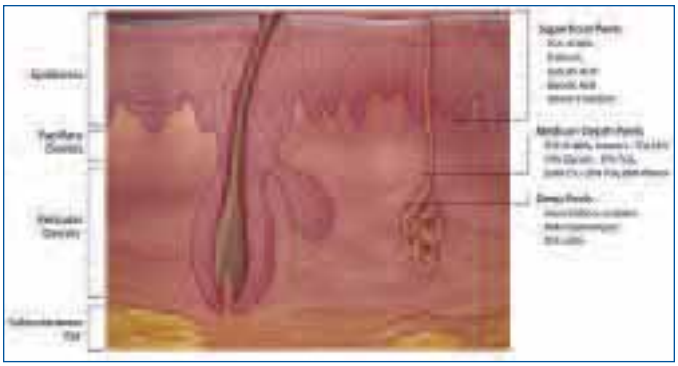


FIGURE 3: Diagram of the skin showing wounding depth of superficial-, medium- and deep-depth peels. ***Courtesy of Pearl E. Grimes, M.D.***

as they'd like, then I go to the next step, which is some sort of physical treatment.

Dr. Rubin: Peels **(Figure 3)** and microdermabrasion are the last step. I don't ever do anything as a procedure for pigment until I have control of their skin first, with some kind of a topical therapy. And then I think for the majority of people, if they're responding to topical therapy, I'll use superficial peeling or microdermabrasion, although I prefer peeling to microdermabrasion as a drug delivery device, just as a way of making the medication penetrate better and to speed up their epidermal turnover so they're going to shed pigment faster. However, if they're not responding to topical therapy, then I would be more inclined to move to IPL rather than peeling. I think that you can do better with IPL for being a destructive modality for pigment than you can with chemical peeling when you're doing medium-depth peels.

I don't ever do anything as a procedure for pigment until I have control of [the patient's] skin first, with some kind of a topical therapy.

— Dr. Rubin

The minimal wounding that goes along with chemical peels or microdermabrasion is a whole different world from the more reactive wound induced by IPL or medium-depth trichloroacetic acid (TCA). Either modified Jessner's or salicylic acid (fairly non-inflammatory peels) and the topical tretinoin peels are the better of the therapies in my mind, because they create good exfoliation, but with minimal inflammation. And I think microdermabrasion, unfortunately, is inflammatory in a fair number of people. So I would prefer chemical peeling agents.

Dr. Cook-Bolden: I do microdermabrasion on my more sensitive patients who tend not to tolerate the chemicals of a peel. I explain to patients that these types of procedures can help the medications penetrate better, ultimately helping to break up the little pigment packages. We have observed that alternating microdermabrasion with chemical peels (in those who can tolerate the peels) delivers even greater efficacy.

Dr. Grimes: I probably do an equal amount of peels versus microdermabrasion when I need superficial wounding that's safer than IPL in darker skin. I agree that microdermabrasion is more forgiving. We've actually done some side-by-side comparisons of microdermabrasion and a peel and we found that we had longer-lasting effects with the peel.

One other point to be made for microdermabrasion: If you have a darker-skinned patient on a retinoid and you peel them, that patient is going to frost, hence the potential to develop PIH is greater. If I have a patient on hydroquinone 4%, retinol 0.15% or fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%, then I have them stop it for at least 7 to 10 days if I'm going to peel them, or as I said, they may develop significant frosting during the procedure. In contrast, in my experience, these products can be used up to 1 to 2 days before microdermabrasion.

Dr. Atkin: I perform IPL in up to Fitzpatrick skin type IV **(Figure 4)** and occasionally V. I am careful when I do it, and I always do a test spot. If a patient is clearing from topical treatment or topicals and peels but has a few recalcitrant areas, I will treat these with IPL and at times, laser. I think it works well for a lot of people.

Dr. Cook-Bolden: For melasma, do you just treat the area, or you treat the whole face? I have cautiously done both and feel that a more uniform appearance is obtained when carefully treating the entire face, especially if the area of involvement is significant.

Dr. Atkin: It depends on what other problems they have. If they also have telangiectasias, then I like to treat the

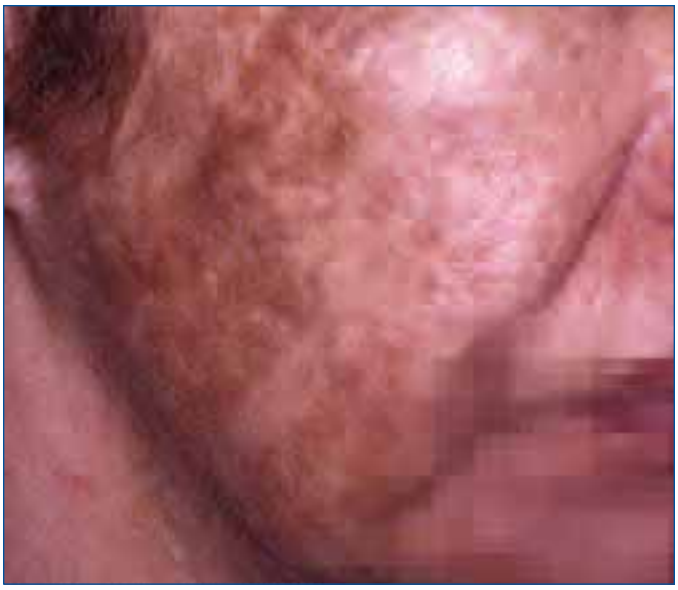


FIGURE 4: Post-intense pulsed light for melasma in Fitzpatrick skin type IV.
Photo courtesy of Pearl E. Grimes, M.D.

whole face, because one of the benefits of IPL is that you can use a wavelength that treats both red and brown lesions. I sometimes use an Alexandrite laser for melasma, but I always do a test spot and rarely treat higher than a skin type IV. After I do IPL or laser on skin types IV and V, I will use topical steroids to prevent PIH. This is generally only necessary for a few days and not long enough to have negative side effects.

Dr. Steinman: I believe that you usually have to keep the depth of your treatment partial epidermal or epidermal if you're treating melasma. So with respect to the chemical peels, I'm comfortable (if the patient is off of retinoids) using a glycolic acid or a modified Jessner's.

Dr. Cook-Bolden: It's really tough with pigmentation and lasers. In patients who have darker skin and hyperpigmentation, laser therapy remains a challenge. I tell patients that we're not there yet. Lasers are not smart enough to distinguish between the pigmentation that you want to keep and the pigmentation that you don't want to keep in darker skin.

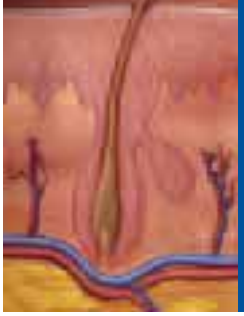
Dr. Grimes: I think most of you would probably agree that we use hydroquinone 4%, retinol 0.15% and fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05% in our active phase of treatment. And we continue hydroquinone 4%, retinol 0.15% during the maintenance phase of treatment, where we also consider other drugs. Certainly we have to be more aggressive in treating melasma versus PIH. We've addressed anatomic sites. Are there any other issues or special pearls that we should talk about? Is anyone using these products in the peri-orbital area?

Dr. Cook-Bolden: That's my classic protocol. Periorbital hyperpigmentation is common in patients who have Fitzpatrick skin types IV, V and VI (even skin type III) and these patients have already used all there is over the counter and in the mass market. We prescribe a regimen consisting of a morning application of sunblock along with one of our favorite moisturizing eye creams and a hydroquinone preparation at night along with the eye cream. The hydroquinone, however, is only applied 3 times each week at night. Rarely will we increase the hydroquinone use to nightly in this region, but we have never recommended more frequent application.

Combination hydroquinone therapy goes hand in hand when treating dermatoses that result in hyperpigmentation of the affected area such as pseudofolliculitis barbae (PFB). These patients not only benefit from the lightening effect of the hydroquinone, but also from the retinol. For PFB patients, the best treatment is laser hair removal, but you are limited as to the amount of energy that can be safely delivered in darker-skinned patients who are more prone to this condition. Further limiting the amount of energy that can be delivered is the significant pigmentation in the area of involvement, which often presents as a dark mask over the beard area. PFB is a chronic condition, and the area can be lichenificed and scarred. We have observed a "nonablative resurfacing" effect even with the hair removal laser when treating these patients. Coupled with the benefit of the retinol, topical therapy with a combination hydroquinone and retinols and retinoids provide an ideal complement to laser hair removal therapy.

Combination hydroquinone therapy goes hand in hand when treating dermatoses.
— Dr.Cook-Bolden

Dr. Grimes: I use hydroquinone 4%, retinol 0.15% and fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05% and some extemporaneous compounding along with acne products in my pseudofolliculitis barbae patients. ■



Patient Concerns

Experts address issues related to condition improvement, duration of treatment, irritation, steroid side effects and cosmetic feel.

Dr. Deborah H. Atkin: Many of my patients didn't like Alustra (hydroquinone 4%) because it would oxidize and turn brown. Tri-Luma (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) created problems with erythema in some of my patients. And again, I am not an advocate of long-term steroid use, even one as weak as hydrocortisone. So I am not prone to the use of a topical with fluocinolone, which is stronger, particularly in patients who are concerned about stimulating collagen and other anti-aging issues. I am concerned about the long-term effects of even hydrocortisone on collagen synthesis.

Treating melasma involves a global understanding on the patient's part of lifestyle and skincare changes that they have to make.
— Dr. Steinman

Dr. Pearl E. Grimes: It's impractical to think that you can use a steroid long term without having some effects. Some of the higher-strength formulation bleaches will use 2.5% hydrocortisone as the vehicle to hold the hydroquinone, and some of those patients come back with acne. I have also seen patients who get a steroid-induced rosacea with 2.5% hydrocortisone.

Dr. Howard K. Steinman: I noticed that a lot of us use the term "bleaching cream." I always say "fading cream" because I've had people say that they don't want to use a bleaching cream because they don't want their faces to turn white.

EDUCATION & COMPLIANCE ISSUES

Dr. Steinman: The big challenge for me with fading creams — especially for melasma — is that you can't just give patients a fading cream and have them get better. If they're not protecting their faces from the sun, avoiding irritants, avoiding heat, and they don't understand that improvement will be fairly gradual over 8 or 12 weeks or longer, then they're going to be disappointed. When I have a patient who is not responding, I query her intently regarding what she's doing at home. Is she using a facial scrub or toner? Is she properly wearing her broad-spectrum sunscreen, applying her fading cream, etc.?

Treating melasma involves a global understanding on the patient's part of lifestyle and skincare changes that they have to make. I tell them that one afternoon

of unprotected sun exposure is going to ruin weeks of treatment. So another challenge is that you have to do a lot of explaining. And when you have a treatment failure, you have to delve into what they're doing that may be contributing to it to make sure that the treatment failure is unrelated to the product they are using to treat the pigmentation.

Dr. Grimes: I agree that you have to query these people on irritants, because I think we're probably going to see more and more data on the role of irritants as triggers for melasma.

Dr. Steinman: A little fact of this to get more and more play is that it's not just ultraviolet light. I think infrared heat from a sunny, hot climate or work environment is an exacerbating factor.

Dr. Mark G. Rubin: I've seen that a lot in Asian patients whose melasma we'd had under control. But they change jobs and work in the kitchen of a restaurant and then we have problems. That was the first time I ever realized there was a role for heat-inducing hyperpigmentation, and I've seen that over the years a lot.

You're always changing what you're doing because patient lifestyles change and their vacations change and things happen and they plateau. I think our goal initially is education, then to be like a motivational coach. When patients do go away and they lose ground, it is important that everybody doesn't just panic and that the patient doesn't try to find a new doctor, hoping that he or she will have the "cure" for melasma.

Dr. Fran E. Cook-Bolden: We have participated in many of the clinical studies for the treatment of hyperpigmentation and we have treated many patients in our practice. In clinical studies, overall compliance tends to be higher than in the real world because you have even more motivated patients. Even when we treat patients for hyperpigmentation in our daily clinical practice, we almost treat them like they're in a study. We give them a detailed explanation of the challenges and the process, timeframe, etc. We get colorimetry (mexameter) readings, take pictures and have patients come back sometimes in the beginning every 4 weeks. Sometimes I have them come back in 2 weeks to make sure they're not overusing the topical medication in desperation to achieve quicker results. If they overuse the treatment or use it incorrectly,

The Benefits of Makeup

Dr. Howard K. Steinman: One thing you can do for melasma patients who are frustrated after seeing other doctors or who expect immediate improvement is to offer a mineral makeup with good coverage. If you can establish a relationship with either a makeup artist or teach your estheticians to apply it, then your melasma patients will experience immediate appearance improvement while you treat their condition. This really makes patients happy. We provide this service for free to our new melasma patients. They see our makeup artist, who applies mineral makeup and they walk out the door "without melasma," because that's what they really want. I find that patients are more tolerant of medical, laser or peel treatment because they aren't seeing their melasma.

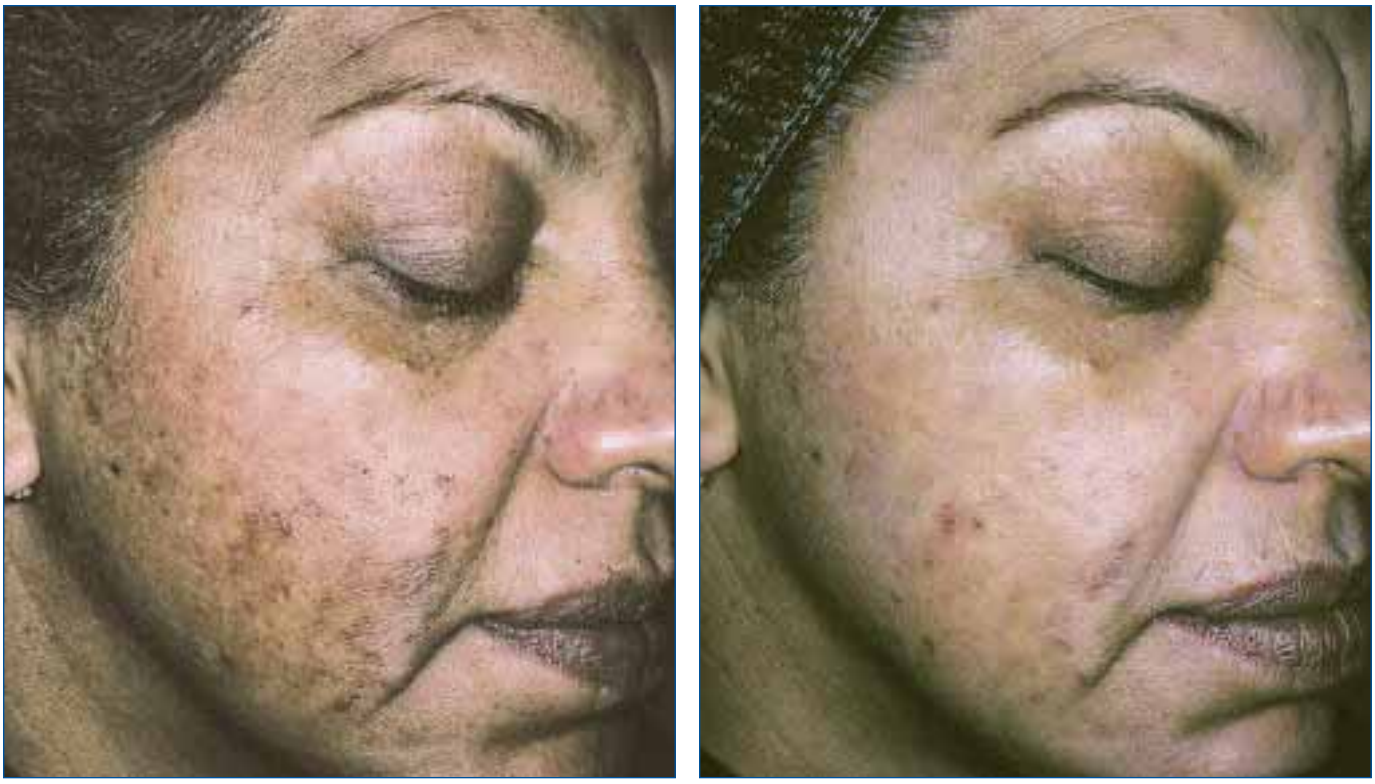
You don't have to carry a makeup line (especially if you don't have an in-office esthetician or makeup artist)— you just have to find a line that has good coverage and refer the patient to that line. Makeup is one thing that is almost never discussed in melasma forums and melasma articles, but what melasma patients want is for other people not to see their melasma. And one reason they're impatient with the usual 8-, 12- or 24-week course of topical therapy is that they can still see their melasma.

Dr. Deborah H. Atkin: We carry GloMinerals. I think that teaching patients how to camouflage their hyperpigmentation during the process of treatment with topicals, peels, pulse light and laser does help them be patient with the process. It is also good for them to know how to do this when they have exacerbations because this is a chronic condition.

Dr. Steinman: Other good makeup lines include Youngblood Mineral Makeup and Jane Iredale.

I'm not suggesting that you have to have a makeup artist in your office or even have makeup in your office, but I find that it helps to have it available for my patients, and not just melasma patients, but those receiving laser and peel treatments, which occasionally cause discoloration. If we cause hyperpigmentation or a burn, patients are quite displeased. Having someone who can provide makeup services in your office permits these patients to leave the office looking normal, or near normal.

Dr. Fran E. Cook-Bolden: Makeup coverage for hyperpigmentation has been another challenge faced by darker-skinned patients. The pigment ranges have dramatically increased to include darker hues, allowing us to give our patients with pigmented skin real coverage options (e.g., DermaBlend, Covermark, Color Fx, etc.) ■



Improvement in hyperpigmentation symptoms in a Hispanic patient treated with hydroquinone 4%, retinol 0.15%. Photo at left shows baseline, while photo at right depicts results after 4 weeks. ***Photos courtesy of Pearl E. Grimes, M.D.***

irritation can be the result, which can worsen the hyperpigmentation.

Dr. Grimes: I monitor patients closely, too. Depending on the patient and the diagnosis and what I choose to initiate therapy with, I'll see patients in 2 weeks rather than 4, and I cannot overemphasize the importance of having your staff photograph patients to monitor change.

Copies of every patient chart and prescription (including the number of refills) is a good way to protect yourself from [problem] patients.

— Dr. Rubin

Dr. Steinman: One issue that I think is interesting is the questions from female patients about in what order they should apply their various creams, makeups, sunscreens and medications. For male patients, there is no question — they just put on their hydroquinone and their sunscreen. But many male physicians are perplexed when female patients pose these types of questions. It would be nice to have an instruction sheet of what order things should go on.

Dr. Grimes: We have an instruction sheet and I'll run patients through it during the consultation. If I'm not clear what a patient is using at home, I will have that patient bring in her daily regimen so I can try to simplify the regimen. My routine is: cleanser first, bleach second, moisturizer third and sunscreen fourth. Ideally, the patient should wait at least 5 to 10 minutes between applications of the bleach, moisturizer and sunscreen.

Dr. Atkin: My understanding is that topical growth factors should be the first thing applied to the skin, as they may be less effective if applied over other topicals.

Dr. Cook-Bolden: Sometimes we tell patients to use a hydroquinone product on the dark spots at night and to just put a tiny bit all over in the morning (especially if a

large area is affected), and that increases their likelihood of a twice daily application. There is often no time for spot application of a large area in the morning rush.

Dr. Grimes: How does patient compliance impact you?

Dr. Steinman: I think you need to set up expectations of how often you'll need to see patients and to educate them about how slow the process is going to be compared to the treatment of other skin rashes. (People sort of expect pigmentation to go away like athlete's foot does, and it does not.) I think patients are more compliant if you take the time to educate them at the get-go.

Dr. Grimes: I have treated some patients in the past who tend to abuse bleaching agents. Sometimes they have their prescriptions filled without your approval and then they'll come back to you in a year and blame your prescription for complications.

Dr. Rubin: Copies of every patient chart and prescription (including the number of refills) is a good way to protect yourself from such patients. Electronic medical records are another good way to protect yourself by documenting how many refills you gave to a patient.

Dr. Grimes: I think we have more savvy patients than ever. Many patients want immediate gratification; they want to be able to use a product and have efficacy or see some evidence of efficacy within the first 4 weeks.

Dr. Steinman: That's the advantage of products such as hydroquinone 4%, retinol 0.15%. They often see improvement relatively quickly.

Dr. Grimes: For most of the agents available today (including EpiQuin Micro and Tri-Luma), patients invariably see some improvement after about 4 weeks. Sometimes you see it as early as 2 weeks.

Dr. Rubin: For some patients, tolerance of a bleacher is an issue, and you think about what you can use that's gentle but that doesn't take forever to work. Over the years, I've used other products besides topical steroids. For patients who are going to be on something long term and I want to get them tolerant of something, we've used bovine tracheal cartilage extract as an anti-inflammatory, as a cleaner or something like that in combination with a bleach.

It has been my experience that a vast majority of melasma patients, even those who have type II and III skin, have a tendency for PIH. I've had several fairly complected patients (Fitzpatrick skin type II) over the years who get PIH.

Dr. Grimes: I think any patient who gets melasma can also get PIH. I think melasma is underdiagnosed in Fitzpatrick skin types II and III and I think people may call it photodamage when it's actually melasma.

SUNSCREEN

Dr. Grimes: I have a protocol that I use for lentigines on the hands and the arms. I use hydroquinone 4%, retinol 0.15% in the morning and tazarotene 0.1% (Tazorac) in the evening. After several weeks, I perform a TCA peel or use IPL. This protocol has been quite effective.

Given the conditions that we've talked about, we probably all are beginning to rely more on the physical blockers (e.g., microfine titanium zinc) versus other chemical sunscreens. And I've even had physicians mention that maybe some of the ingredients in the chemical sunscreens might actually cause irritation, further contributing to their hyperpigmentation. Dr. Rowell conducted many of the original studies comparing azelaic acid to hydroquinone, and she published a book on hyperpigmentation and sunscreens. She's done testing to show irritation with sunscreens. I haven't abandoned chemical sunscreens in my melasma patients. However, most often, I try to use the physical blockers.

I also prefer to have my lightening agents and sunscreen be separate products, as there is no reason to apply something with an SPF at night.
— Dr.Atkin

If a bleaching agent has a sunscreen in it, are any of us comfortable in just relying on that sunscreen in the bleaching agent as adequate protection? Or do we all layer on a broader spectrum sunscreen?

Dr. Cook-Bolden: I layer. I instruct patients to re-apply their sunscreen or sunblock after 2 hours have passed if there is continued sun or ultraviolet light exposure or re-exposure.

Dr. Atkin: I also prefer to have my lightening agents and sunscreen be separate products as there is no reason to apply something with a sun protection factor (SPF) at night.

Dr. Steinman: These patients have to be fastidious and fanatical in their avoidance of excess ultraviolet light. They must apply and possibly reapply a broad-spectrum sunscreen daily, and the sunscreens in most cosmetics and topical hydroquinones are not potent enough.

Dr. Grimes: I always layer on a broader-spectrum (see the sidebar above right for a list) sunscreen or an additional sunscreen. And I do push the physical sunscreens. We need better physical blockers that address the skin tone of the darker individuals who complain of ashen skin color with the use of physical blocks. These patients also often complain about the greasiness of many sunscreens.

I instruct patients to reapply their sunscreen or sunblock after 2 hours have passed if there is continued sun or ultraviolet light exposure or re-exposure.

— Dr. Cook-Bolden

Dr. Cook-Bolden: Many of the sunscreens use micronized formulations, gels, ultra lightweight lotions and sprays that result in a less chalky appearance.

Dr. Atkin: I think one of the real benefits to physical sunscreens is that they work as soon as you put them on. There is a large percentage of the population who just put their sunscreen on and immediately go outside. They don't realize that with chemical sunscreens, they may not be protected for 30 minutes or so and by that time, they have had excessive sun exposure.

Broad-Spectrum Sunscreens

Chemical

- Anthranilates
- Benzophenones
- Benzotriazoles (Tinosorb)
- Camphor derivatives (Mexoryl)
- Cinnamates
- Dibenzoylmethanes (Parsol; 1789)
- Para-minobenzoic acid (PABA)
- Salicylates

Physical

- Ferrous oxide
- Titanium dioxide
- Zinc oxide

Dr. Steinman: You have to tell patients that the SPF number only refers to the burning rays of the sun — that it doesn't protect them from fluorescent bulbs and the light coming through windshields and window glass.

Dr. Cook-Bolden: Most patients are savvy now about the need to use a sunscreen. But, what they don't know is what ingredients to look for and that these products need to be reapplied. We instruct patients on the correct way to use sunscreen, then have our staff reinforce it.

Dr. Grimes: I now realize that patients would much rather buy sunscreen from us rather than going to the drugstore.

Dr. Cook-Bolden: How do you help patients with the reapplication issue? We talk to them about what they need to do with regard to their makeup and their sunscreens. Some people are just not going to take off their makeup and reapply it just to reapply sunscreen. So we tell them to get a good application first thing in the morning, and then a reapplication at some point in the day. Something is better than nothing if they are unable to accomplish the ideal "application every 2 hours" with continued sun exposure or re-exposure. There are also many options that make reapplication less of a chore such as make-up lines that include loose

or dusting powders that contain sunscreen as well as sunscreen sprays.

Dr. Grimes: For my melasma patients, in addition to encouraging them to apply a great sunscreen in the morning, if they happen to go outdoors, I emphasize wearing a hat. (But they've got to get that large-brim hat and large sunglasses. Large sunglasses protect the zygomatic rim, which I find is inherently one of the most difficult areas to bleach out.)

SAFETY

Dr. Grimes: In regard to toxicities related to hydroquinone, the main concern for most people is ochronosis. Findley first identified ochronosis in South Africa in 1975. He described asymptomatic hyperpigmentation, erythema, papules, papulonodules and colloid milium in African patients who used high concentrations of hydroquinone — probably 8% and above. Conversely, our experience in seeing ochronosis in the United States has not mirrored the African experience. Most of the cases of ochronosis reported in the United States are a result of the 2% concentration of hydroquinone. Another reason for less reporting in the United States may be that our patients use sunscreen. If you look at the data in the literature, it's difficult to treat ochronosis. I have gotten some improvement in ochronosis with topical steroids and chemical peels.

We don't know for sure what causes ochronosis, but among some of the theories that have been suggested are that you actually inhibit homogentisic acid and that leads to the deposition of homogentisic acid as we see in endogenous ochronosis. Findley suggested that you overwhelm the melanocytes, because you have to have melanocytes in an area to get ochronosis. Dr. Bologna reported a case of a patient with ochronosis and changes in the ochronotic pigment were only evident in the pigmented areas. The patient also had vitiligo and there was nothing in the depigmented areas of skin.

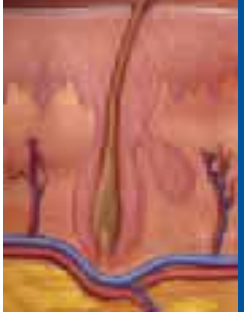
What about other hydroquinone toxicity issues? Hydroquinone is a naturally occurring chemical and is also a benzene derivative. It's in grains, fruits such as blueberries and pears, vegetables, wine, beer, coffee and tea. It is also present in photography chemicals. The key data on side effects are in animal studies, where you see an increase in genotoxic effects and mutagenic effects, but we don't have similar data on hydroquinone toxicity in humans. In a compilation of studies, the main side effect noted in humans is ochronosis. Hydroquinone has been our gold standard and we have no data in humans now to suggest that the hazards of treating with it outweigh the benefits of therapy.

Dr. Steinman: We have experience from Africa and the United States where people have been using hydroquinone extemporaneously compounded at high concentrations for decades. It would seem to me that if there was an association with the topical application of hydroquinone and serious human disease, it would have been found by now.

Dr. Cook-Bolden: Although dermatologists have a history of "off-label" usage with many treatments to include hydroquinones, there have been few cases reported of exogenous ochronosis. I also feel that the condition is under-reported in the United States, as I have seen three to four cases, if not more. A segment of our practice does focus on pigmented skin issues, hence it is likely that we have seen more than the average.

Hydroquinone has been our gold standard [for hyperpigmentation] and we have no data in humans now to suggest that the hazards of treating with it outweigh the benefits of therapy.
— Dr. Grimes

Dr. Grimes: I participated in an FDA panel that reviewed hydroquinone around 7 years ago and some of the very issues that we're talking about now came up. The FDA even recommended that pharmaceutical companies conduct more animal studies. I think we can be relatively comfortable knowing that the benefits of hydroquinone outweigh the side effects. I have not changed my prescribing patterns, but we should be aware of hydroquinone toxicity issues so that if anything comes up, we have some familiarity with the database. ■



Roundtable Summary

Physicians make final points about skin types, diagnoses, severity of disease and more.

Dr. Pearl E. Grimes: What is the disease severity? Does the patient have mild, moderate or severe involvement? What is her skin type? How do we manage patients' expectations? We must also consider patient compliance. If we don't think a patient is going to come back in at 4, 6 or 8 weeks, then I wouldn't use a formulation that contains a fluorinated steroid. It's important that we establish protocols and some algorithms for how we approach patients.

We get requests to treat other areas for hyperpigmentation (e.g., dark spots on the elbows, knees, trunk, leg) and I find that I have to be more aggressive in treating non-facial areas versus the bleach that I would choose for facial lesions.

Dr. Mark G. Rubin: Getting back to anatomic site, you have to make sure the site is pigmentation solely. If the spots are on the patient's elbows and knees, then they often have mild psoriasis that's pigmenting (maybe not in Fitzpatrick skin types V and VI), but in my practice, if patients have pigmentation of the elbows and knees, I often use a fluorinated cortisone along with a fading product, or they may have acanthosis nigricans if it's around their neck or in their underarms — not a truly melanin-induced process. So for non-facial and dorsal hand areas, determine whether the pigmentation is secondary or primary.

Dr. Fran E. Cook-Bolden: With hyperpigmentation involving the elbows and knees, even in Fitzpatrick skin types V and VI, there's sometimes a component of keratodema and this diagnosis should not be ignored. Also, as mentioned previously, acanthosis nigricans is common and can occur in a number of places, including the extremities (i.e., the fingers) and lips, in addition to the classic areas. Involvement in the traditional areas as well as the patient's history can serve as a clue. Many of these areas can be cautiously treated with hydroquinone combinations such as hydroquinone 4%, retinol 0.15% (EpiQuin Micro) or fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05% (Tri-Luma). Combining the hydroquinone with an emollient is helpful. This is another instance in which we limit application to 3 times each week initially.

Dr. Grimes: Treatment of hyperpigmentation, including melasma and post-inflammatory hyperpigmentation (PIH), remains therapeutically challenging. I believe the key therapeutic advance has been the use of combination hydroquinone-based bleaching agents. While other therapies have emerged, the current database suggests that hydroquinone remains the number-one safe and efficacious agent. No other topical agents to date have proven superior to the improvement achieved with hydroquinone formulations. The choice of a topical lightening agent should be based on diagnosis (melasma vs. PIH vs. photodamage), severity of disease, site of treatment, ethnicity/skin type and patient compliance.

Current formulations such as hydroquinone 4%, retinol 0.15% have proven superior to hydroquinone 4%, retinol 0.3% (Alustra) and comparable to fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%. Side effects with hydroquinone 4%, retinol 0.15% are minimal, and this agent has proven beneficial for the treatment of melasma and PIH. These combination formulations offer safety, efficacy and minimal complications for the treatment of hyperpigmentation. ■

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