

# The New Face of Preadolescent and Adolescent Acne: Beyond the Guidelines

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doi: 10.12788/jfp.0430

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## DISCLOSURES

Dr. Eichenfield discloses that he serves as an investigator or consultant for Allergan, Almirall, Cassiopea, Dermata, Galderma, L'Oreal, Ortho Dermatologics, and RBC Consultants. Dr. Hebert discloses that research funds are paid to UTHealth McGovern Medical School – Houston by Cassiopea, Galderma, Allergan, Pfizer, and Novan, and honoraria are received from Verrica, Pierre Fabre, and Relife. She serves on the Data Safety Monitoring Board for Sanofi-Regeneron, Ortho Dermatologics, and GlaxoSmithKline. Dr. Desai serves as a consultant for or on the speakers bureau for Galderma, Almirall, Cassiopea, Foamix, Scientis, Ortho Dermatologics, Dermira, and Pfizer; and as a principal investigator of research grants for AbbVie, Watson, Symbio, and Novan. Dr. Levy discloses that he serves as an investigator and/or advisor for Cassiopea, Regeneron, Janssen, Abeona, Castle Creek, and Krystal; and as an author and section editor for UpToDate. Dr. Mancini discloses that he serves on the advisory board and has received an honorarium from Cassiopea. Dr. Rice serves on the advisory board for Cassiopea, Pfizer, and Medscape; as a consultant for Brickell Bio, Cassiopea, Dermira, and Pfizer; as a principal investigator of research grant for Anacor, Celgene, Galderma, Regeneron/Sanofi-

Genzyme, Merck, and AbbVie; and on the speakers bureau for Dermira, International Hyperhidrosis Society, Pfizer, and PRIME. Dr. Sugarman discloses that he serves on the advisory board or as a consultant for Cassiopea, Bausch, Galderma, and Solgel. Dr. Zaenglein discloses that she serves on the advisory board or as a consultant for Cassiopea, Pierre Fabre, and Pfizer; as a researcher for Incyte and AbbVie; and as an editor for *Pediatric Dermatology*.

## ACKNOWLEDGMENTS

Editorial support was provided by Anne Carter, MA (Cantab), of Medicalwriters.com and Elisabetta Lauretti, PhD, of AlphaBioCom, LLC. Medical writing support from Medicalwriters.com was supported by Cassiopea; medical writing support from AlphaBioCom was supported by Sun. The authors thank Fred Ghali, MD, for his participation in The Preadolescent Acne Roundtable discussions and contributions to earlier drafts of this article.

## SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium and supported by funding from Cassiopea SpA and Sun Pharmaceutical Industries, Inc. The Preadolescent Acne Roundtable discussions were funded by Cassiopea SpA.

## **ABSTRACT**

Acne is a highly prevalent condition, affecting the majority of people at some point in their lifetimes, most often during adolescence. Acne has also become increasingly common among preadolescents (aged  $\geq 7$  to  $\leq 12$  years old).

Acne is often treated in primary care settings by non-dermatologists. The most recent acne guidelines were

published in 2016; since then, there have been important developments in the acne treatment landscape. Familiarity with these options is important for physicians who manage patients with acne.

The Preadolescent Acne Roundtable group of dermatologists was convened in July 2019 to support discussion around modernizing the approach to treatment and evalua-

tion of preadolescent acne. During a face-to-face meeting, 5 key areas requiring careful communication emerged: acne pathophysiology, specifically the role of hormones; psychological aspects of acne; management of acne in younger patients; acne in skin of color; and evaluation of clinical success.

This roundtable report describes these 5 focus areas, with the aim of empowering primary care physicians to refine the care they provide for patients with acne. This report can help bridge the information gap until new acne treatment guidelines are published.

## INTRODUCTION

Acne is estimated to affect >90% of adolescents (aged 12 to 20 years) in some populations.<sup>1,2</sup> Globally, as of 2017, nearly 120 million people were affected by acne.<sup>3</sup> While typically associated with mid- to late adolescence, acne can also affect preadolescents,<sup>4</sup> and its prevalence in this population may be increasing.<sup>5</sup>

The last American Academy of Dermatology (AAD) guidelines on acne treatment were published in 2016,<sup>6</sup> and the American Academy of Pediatrics–endorsed evidence-based clinical guidelines for the management of pediatric acne were published in 2012.<sup>7</sup> As consensus reports have noted, practice guidelines may become outdated before new ones are published.<sup>8</sup> Therefore, it is important for practicing physicians to stay up to date on recent advances in the acne field.

The Preadolescent Acne Roundtable group of dermatologists was convened in 2019 to support discussion around modernizing the approach to the treatment and evaluation of preadolescent acne. During the meeting, 5 key areas were discussed: acne pathophysiology, specifically the role of hormones; psychological aspects; acne management in younger patients; acne in skin of color; and evaluation of clinical success.

The group also discussed that not all patients with acne are managed by a dermatologist; a survey reported that 26% of preadolescent patients with acne were managed by a general or family practitioner.<sup>9</sup> This report, therefore, was developed to provide the latest updates and information to primary care professionals before new guidelines are published. For each topic, “clinical pearls” from the authors are included.

This report follows the terminology used in the American Academy of Pediatrics/American Acne and Rosacea Society Evidence-Based Recommendations for the Diagnosis and Treatment of Pediatric Acne; preadolescent acne refers to patients aged  $\geq 7$  to  $\leq 12$  years old, or before menarche in female patients.<sup>7</sup>

## PATHOPHYSIOLOGY OF ACNE

### Androgens in acne pathogenesis

Acne pathophysiology involves 4 main components: increased production of sebum, follicular hyperkeratinization, colonization with *Cutibacterium* (formerly *Propionibacterium*) *acnes* (*C. acnes*), and inflammation.<sup>10-12</sup> Androgens, such as testosterone and dihydrotestosterone, enhance sebaceous gland activity and stimulate sebum production.<sup>10,11,13</sup> The **FIGURE** shows an overview of the role of androgens in acne pathophysiology.<sup>11,13,14</sup>

Systemic treatments targeting hormones have become a mainstay of treatment for moderate to severe acne in adolescent girls and older women, usually in combination with other therapies.<sup>6</sup> Combined oral contraceptives (COCs) and spironolactone are commonly used hormonal treatments.<sup>6</sup> However, spironolactone is not approved by the US Food and Drug Administration (FDA) for this indication, and limited safety data exist in adolescents.<sup>6,15</sup> Furthermore, some adolescents and their parents are not comfortable with COC use.<sup>16</sup> The use of topical hormonal therapy such as clascoterone cream 1% can target androgen-stimulated sebaceous gland activity and decrease acne in both male and female patients, with a favorable safety profile.<sup>17</sup>

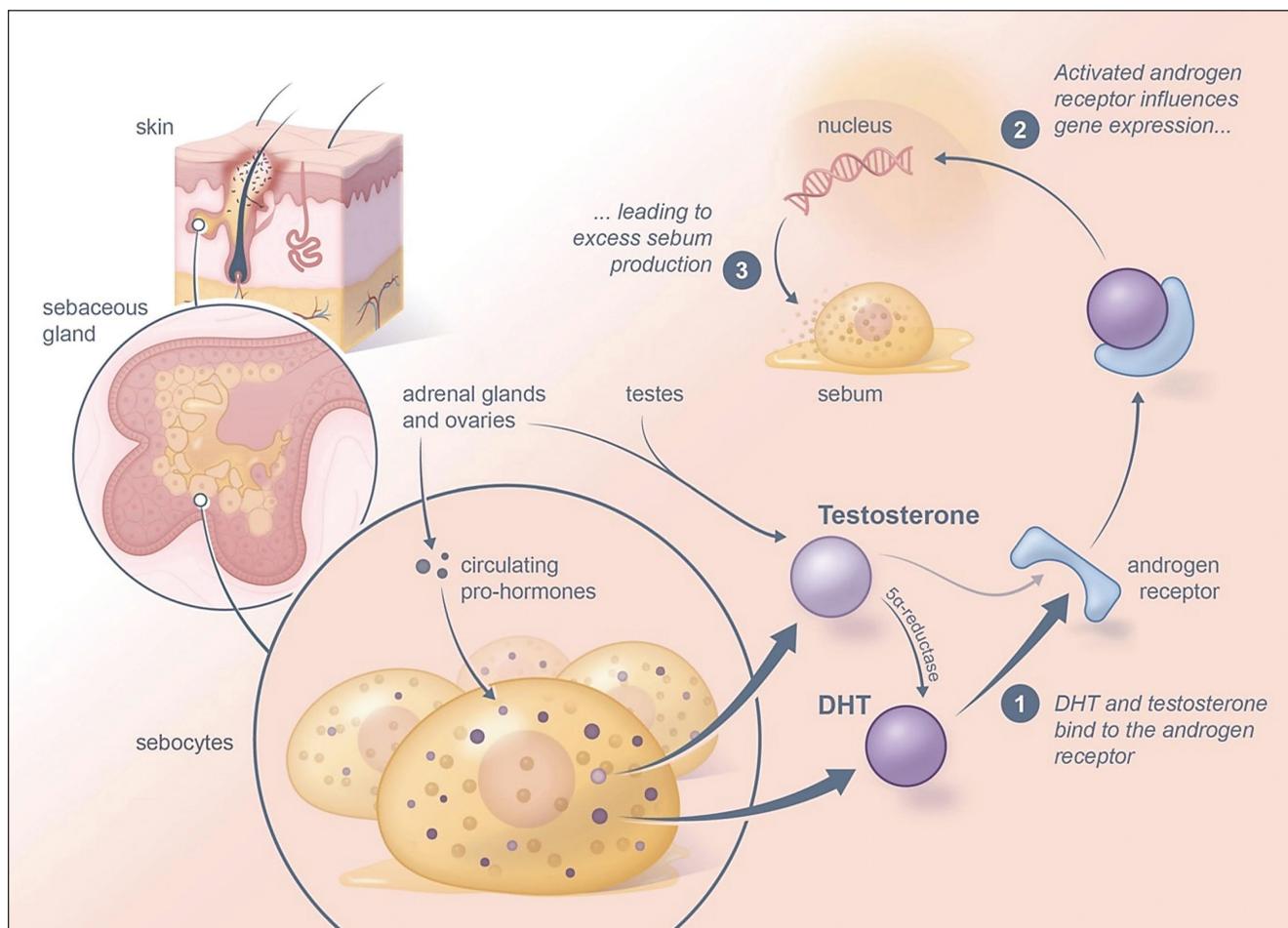
**Clinical pearl:** Teach patients and families some of the basics of acne pathophysiology so that they can better understand the rationale behind management decisions.

### Preadolescent acne microbiome

The skin microbiome changes with age and is known to influence skin conditions,<sup>18</sup> but limited information is available on the microbiome of preadolescents with acne. A pilot study found a greater diversity of cutaneous bacteria in preadolescents with acne than without acne.<sup>19</sup> In pretreatment observations, the relative abundance of bacterial species differed between the groups: those with acne had more *Staphylococcus* and *Cutibacterium* species than controls. All participants had a relatively high amount of *Streptococcus*.<sup>19</sup> Following treatment with benzoyl peroxide (BP) or tretinoin, diversity of the skin microbiome was reduced to levels similar to those of control subjects.<sup>19</sup>

A larger study with 51 girls aged 7 to 12 years old found that changes in microbiome diversity were associated with increasing age and acne lesion number. *Streptococcus mitis* was more abundant in younger individuals and those with fewer lesions, and *C. acnes* was more abundant in older individuals and those with higher numbers of acne lesions. *C. acnes* was more prevalent in sebaceous vs less sebaceous sites (forehead/nose vs cheeks/chin), consistent with these being areas of early sebaceous gland activity.<sup>20</sup> The num-

FIGURE. **The role of androgens in acne pathophysiology**



Circulating pro-hormones produced by the adrenal glands and ovaries can be converted within sebaceous glands in the skin into testosterone and dihydrotestosterone (DHT).<sup>13</sup> Circulating testosterone is produced by adrenal glands, testes, and ovaries. Sebocytes express 5α-reductase, which converts testosterone into the more potent dihydrotestosterone.<sup>13,14</sup> Dihydrotestosterone and testosterone bind to the androgen receptor within sebocytes, causing it to translocate to the nucleus and act as a transcription factor.<sup>14</sup> This can lead to the excess sebum production seen in acne, which can result in inflammation and influence keratinocyte proliferation and differentiation, leading to follicular hyperkeratinization.<sup>11</sup>

ber of acne lesions decreased after BP treatment (average 7 weeks), but changes in the microbiome were not observed.<sup>20</sup>

**PSYCHOLOGICAL ASPECTS OF ACNE**

Acne can have a significant adverse impact on quality of life (QOL),<sup>7,8</sup> and even mild acne may be troubling for patients.<sup>7</sup> A cross-sectional study of 1531 respondents aged 11 to 19 years reported the adverse effects of acne on QOL and psychological health.<sup>21</sup> Nearly half of respondents with mild acne reported embarrassment and reduced self-esteem, while nearly one-third reported feelings of unworthiness and teasing due to their acne.<sup>21</sup> Results of questionnaires sent to a national acne dermatologic support group found a likely correlation between respondents with higher levels of

skin-related social anxiety and reports of lower self-esteem and less intention to participate in sports and exercise.<sup>22</sup>

While some QOL impairments may be short-term or easily managed, patients may experience more serious problems. A questionnaire-based study of 3775 adolescents in Norway found that 24.1% of respondents with substantial acne vs 9.5% with no to little acne reported suicidal ideation in the previous week.<sup>23</sup> Other recent studies have further confirmed the serious impact of acne on QOL.<sup>24-26</sup>

The psychological aspects of acne focusing on pre-adolescent patients have not been reported; with increasing numbers of younger patients presenting with acne, the authors encourage research into this important area.

Numerous measures to assess the impact of dermatologic

logic conditions on QOL exist.<sup>8</sup> In the authors' experience, completing a detailed, formal QOL assessment in clinical practice can be challenging due to time constraints. However, simple questions about how the patient is feeling can yield information about their emotional well-being and indicate whether further investigation or intervention is required. The high risk for anxiety and depression among patients with acne warrants aggressive treatment and consideration of routine psychiatric screening.<sup>27</sup>

Previous consensus recommendations have noted the importance of physician counseling for patients with acne, setting expectations for when treatment effects can be seen and understanding the causes of acne.<sup>8</sup> It is important that treating physicians show empathy for their patients' emotional distress due to acne.<sup>8</sup>

**Clinical pearl:** *Ask the patient how acne is impacting daily life. This can elicit valuable information about the patient's emotional well-being.*

## SOCIAL MEDIA

Over the last decade, the environment for adolescents has changed considerably with the widespread use of smartphones and the impact of social media. Social media can be a valuable source of easily accessible information and support from others with similar conditions.<sup>28</sup> Discussions on acne treatment can be found on numerous social media platforms.<sup>29</sup> Healthcare professionals should be aware of the benefits and risks of social media use by acne patients.

A systematic review of social media use in healthcare categorized the reasons patients use social media for health-related purposes as emotional support, esteem support, information support, network support, emotional expression, and social comparison.<sup>28</sup> These may represent unmet needs for patients, although the results were not specific to dermatology or acne. The review reported that patients typically use social media as a complement to their interactions with healthcare professional services.<sup>28</sup> Better informed and more confident patients may be able to communicate on a more equal footing with healthcare professionals.<sup>28</sup>

Risks of social media include possible dissemination of imbalanced information or incorrect and even dangerous healthcare myths.<sup>30</sup> For example, only a small portion of English tweets regarding mask-related acne posted in September 2020 were from healthcare providers and organizations (1.7%) or dermatologists (0.1%), while the majority (68.8%) were from patients. Of tweets from commercial business sources, 83.7% promoted acne treatments or encouraged online shopping.<sup>31</sup> The top 50 TikTok videos categorized as "Accutane Check" focused on improvement

in acne severity before and after isotretinoin treatment, with minimal discussion of side effects,<sup>32</sup> and a cross-sectional study evaluating acne-related medical information on TikTok raised serious concerns regarding the low quality of such information.<sup>33</sup>

Use of social media has also been associated with diminished subjective well-being. A data analysis from nationally representative surveys reported that adolescents who spent more time on screen activities were more likely to have high depressive symptoms or a suicide-related outcome vs those who spent more time on nonscreen activities.<sup>34</sup> Furthermore, adolescents who used social media sites every day were 13% more likely to have high levels of depressive symptoms than those who used social media less often.<sup>34</sup>

Healthcare professionals should be aware that patients may access inaccurate information online and should directly address this to avoid misunderstanding. However, optimal utilization of social media for its beneficial aspects could be encouraged to empower patients and make them stakeholders in their treatment.

**Clinical pearl:** *Suggest reliable online resources to help prevent the spread of misinformation. Remember that patient use of social media should complement, not replace, interactions with healthcare professionals.*

## ACNE IN YOUNGER PATIENTS

### Epidemiology of acne in younger patients

While typically associated with puberty, acne is not rare in preadolescent children.<sup>4</sup> A prospective observational study from Italy reported acne prevalence of 34.3% in children aged 9 to 14 years and 6% in 9-year-old children.<sup>4</sup> Results from 2 retrospective multicenter studies in Korea found that patients aged <13 years accounted for 11% of the total non-adult acne patients, and that the number of children <10 years old with acne had increased by 73% over the past 10 years.<sup>5</sup> A survey in the United States showed similar results: 4.8% of acne visits among patients 18 years of age and younger were for preadolescent patients (aged 7 to 11 years).<sup>9</sup>

### EARLIER ACNE ONSET

Studies have noted a trend toward younger age at first acne presentation, possibly due to earlier onset of puberty.<sup>7,35</sup> In the authors' experience, additional factors pertaining to both patients and healthcare professionals may lead to earlier acne presentation. For example, increased media coverage and direct-to-consumer advertising have improved awareness of treatment options among patients and their families. Family history may play a role; parents may advo-

cate for treatment earlier if they experienced successful treatment themselves. Finally, as discussed previously, social media has increased pressure for clear skin, meaning patients may be more likely to seek acne treatment.

Regarding physicians, improved messaging and education has led to increased referrals to dermatologists from primary care physicians and pediatricians. The recognition of the importance of early treatment to reduce sequelae such as scarring has also increased among physicians.

### Treatments for preadolescent patients with acne

The treatment of uncomplicated acne in preadolescent patients is typically comparable with that in older patients, although some agents are used off label.<sup>7</sup> As guiding principles, the treatment of preadolescent acne should be the least aggressive regimen that is effective, while avoiding development of antibiotic resistance and targeting the greatest number of pathogenic factors.<sup>7</sup> Over-the-counter products containing ingredients such as salicylic acid or BP may be effective for preadolescent patients with mild acne, as in older patients.<sup>7</sup>

While a growing number of FDA-approved acne medications such as topical retinoids and a fixed combination of adapalene and BP are available for preadolescent acne patients  $\geq 9$  or  $\geq 10$  years old,<sup>6,36-40</sup> the safety and effectiveness of the majority of acne treatments have not been established in pediatric patients  $< 12$  years of age (TABLE).<sup>6</sup>

COCs are useful treatment options for older adolescents when indicated; however, there is some concern regarding bone mass accrual in younger adolescent patients.<sup>6,7</sup> The FDA has approved 4 COCs for the treatment of acne in female patients who desire contraception: norgestimate/ethinyl estradiol, norethindrone acetate/ethinyl estradiol/ferrous fumarate, drospirenone/ethinyl estradiol, and drospirenone/ethinyl estradiol/levomefolate.<sup>6,7</sup> However, none are approved for patients  $< 14$  years old,<sup>6</sup> and the pediatric acne recommendations suggest withholding oral contraceptives for acne unassociated with endocrinologic pathology until 1 year after onset of menstruation.<sup>7</sup> The safety and efficacy of spironolactone in preadolescent patients with acne have not been well studied.

An analysis of prescribed acne treatment for preadolescents and adolescents found that the top 3 most commonly prescribed medications for preadolescent acne were all topical: adapalene, BP, and tretinoin.<sup>9</sup> There was some disparity in treatments prescribed by different specialists, with primary care physicians preferring antibiotics (topical and oral) and dermatologists preferring topical retinoids. The findings of this study highlighted a potential knowledge gap among primary care providers based on their prescribing

behaviors.<sup>9</sup> It should be noted that off-label prescribing for acne in preadolescent patients is common,<sup>9</sup> possibly due to the limited number of approved therapies.<sup>7</sup>

### Considerations for managing younger patients with acne

In the authors' experience, adherence can be challenging with all patients, including adolescent and younger patients. For preadolescent patients, parents are often involved in treatment and are crucial for maintaining adherence. For all patients, streamlined regimens with combination products or fewer medications should be considered to maximize treatment adherence.

Earlier onset of comedonal acne is associated with more severe disease later on.<sup>41,42</sup> Recognition of early significant acne should encourage close monitoring to ensure prompt treatment for more severe disease, if indicated, with more aggressive therapy considered when needed.

**Clinical pearl:** *Appropriately treat patients—regardless of their age—according to the severity of their acne.*

### ACNE IN SKIN OF COLOR

Despite similar etiology, the clinical presentation of and therapeutic approach to acne can differ in patients with Fitzpatrick skin types IV to VI.<sup>43</sup> Adolescents with darker skin types have increased risk of post-acne keloid formation and are more likely to develop postinflammatory pigmentary changes, such as postinflammatory hyperpigmentation (PIH), compared with lighter-skinned adolescents.<sup>44,45</sup> In a study of photographs from 2895 women and girls (aged 10 to 70 years), clinical acne and hyperpigmentation were more prevalent in African American (37% and 65%) and Hispanic subjects (23% and 48%) relative to continental Indian (23% and 10%), Caucasian (24% and 25%), and Asian (30% and 18%) subjects.<sup>46</sup> In a survey of 208 adult women 25 to 45 years of age with facial acne (49% non-white/Caucasian [Black/African American, Hispanic/Latina, Asian, and other], 51% white/Caucasian), PIH incidence was greater in non-white/Caucasian women compared with Caucasian women.<sup>47</sup>

PIH can be very concerning for patients, who may be worried about long-term appearance. Often interpreted as scarring, PIH is reversible, although long lasting. Treatment counseling for patients with skin of color should therefore include discussion of PIH, with reassurance that these are surface changes—which are usually temporary and fade over time—in contrast to true scars. For physicians, PIH can be difficult to assess. A study reported significant variability among dermatologists reviewing potential PIH cases, with

TABLE. Management of pediatric acne: Selected recommendations from the 2016 AAD guidelines<sup>6</sup>

Product	Indication/pediatric use
<b>Topical treatments</b>	
BP	Safety and effectiveness have not been established in pediatric patients <12 years of age
Salicylic acid	Salicylic acid 6% cream, lotion, and gel and 15% plaster are not recommended in children <2 years of age. Increased risk of toxicity with prolonged use in pediatric patients <12 years of age
Azelaic acid	Safety and efficacy have not been established in pediatric patients <12 years of age
<b>Antibiotics</b>	
Erythromycin	Safety and efficacy of single-entity topical gel or solution have not been established in children
Erythromycin/BP	Safety and effectiveness have not been established in pediatric patients <12 years of age
Clindamycin	Safety and effectiveness have not been established in pediatric patients <12 years of age
Clindamycin/BP	Safety and effectiveness have not been established in pediatric patients <12 years of age
Clindamycin/tretinoin	Safety and effectiveness have not been established in pediatric patients <12 years of age; clindamycin phosphate 1.2%/tretinoin 0.025% gel is approved for patients ≥12 years
Minocycline foam <sup>54</sup>	Approved for use in patients ≥9 years
<b>Retinoids</b>	
Adapalene	Safety and effectiveness have not been established in pediatric patients <12 years of age
Adapalene 0.1%/BP 2.5%	Approved for use in patients ≥9 years
5% dapsone	Safety and effectiveness have not been established in pediatric patients <12 years of age
Tretinoin	Safety and effectiveness have not been established in pediatric patients <10 years of age; 0.05% micronized tretinoin gel is approved for patients >10 years of age
<b>Systemic treatments</b>	
<b>Antibiotics</b>	
Tetracycline	Should not be used in children <8 years of age
Minocycline	Should not be used in children <8 years of age
Doxycycline	Safety or efficacy not established for pediatric use
<b>Hormonal agents</b>	
Estradiol/drospirenone	Safety and efficacy established if started after menarche
Spironolactone	Safety or efficacy not established for pediatric use; used off-label for acne treatment
Isotretinoin	Safety and effectiveness have not been established in pediatric patients <12 years of age

Source: Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2016;74(5):945-973 e933. Used with permission.

highest variability when acne was also present.<sup>48</sup> Clear and simple criteria to assess PIH are an unmet need in the management of acne in skin of color.

Given their proven efficacy in clearing acne and improving PIH, topical retinoids are the first-line therapy in patients with dark skin.<sup>43</sup> Antimicrobial agents are also particularly important to minimize inflammation in these patients.<sup>43</sup> Azelaic acid, topical tretinoin 0.05% lotion, and topical dapsone 7.5% improve both acne and PIH and are considered safe in adolescents with darker skin types. Topi-

cal adapalene and tazarotene as well as clindamycin/BP can also ameliorate hyperpigmentation and acne lesions in adolescents with dark Fitzpatrick skin types.<sup>44</sup> Bleaching creams, such as hydroquinone, should be carefully evaluated when planning a skin-color-tailored treatment strategy for acne and used appropriately as advised by a dermatologist due to their potential for skin irritation.<sup>49</sup> The underlying inflammation (ie, acne) should be addressed first; initiating treatment early may prevent further darkening.<sup>50</sup> However, there is a balance to strike, as irritation from acne treat-

ments could cause or exacerbate PIH.<sup>49,51</sup> The importance of sun protection should be emphasized.<sup>45,49,50</sup>

There are no reports focusing on preadolescent acne in skin of color; this is an area of research that requires further attention.

**Clinical pearl:** Address PIH with patients. Thoroughly discuss the differences between active acne, PIH, and scarring, as well as the expected duration of these findings.

## EVALUATING CLINICAL SUCCESS

Although numerous acne grading scales are used in clinical research and practice, the AAD guidelines identified tools to better characterize acne as a research/knowledge gap.<sup>6,11</sup> The FDA's Investigator's/Physician's Global Assessment (IGA/PGA) for acne has been proposed as a simple, intuitive measure of disease severity that could be used in everyday clinical practice, with reports of high initial physician compliance.<sup>11,52</sup>

While it is important to assess if treatments reduce acne symptoms, the authors emphasize that individual patients determine clinical success. One patient may be satisfied with an IGA score of 2 (mild), while another will only be happy with a score of 0 (clear). Therefore, it is important to practice shared decision-making and identify what is most important to each patient.

**Clinical pearl:** Recognize that treatment success is ultimately determined by each patient's expectations.

## EVOLVING THERAPIES

The treatment landscape for preadolescent acne has evolved since the previous guidelines,<sup>6</sup> with a number of treatments investigated and/or FDA approved. For existing modes of action, 2 tetracycline antibiotics were recently approved by the FDA to treat moderate to severe acne in patients aged  $\geq 9$  years old: sarecycline (oral) and minocycline (topical foam).<sup>53,54</sup> Novel formulations of retinoid medications also approved for the topical treatment of acne vulgaris in patients aged  $\geq 9$  years include tretinoin lotion 0.05%<sup>36</sup>; tazarotene lotion 0.045%<sup>39</sup>; and trifarotene cream 0.005%.<sup>40</sup>

Additionally, 1% clascoterone topical cream is an androgen receptor inhibitor recently approved by the FDA for the treatment of acne vulgaris in patients 12 years of age and older.<sup>55</sup> Results from in vitro studies suggest that clascoterone competes with dihydrotestosterone for binding to the androgen receptor.<sup>56,57</sup> This results in inhibition of downstream signaling and therefore reduced sebum production, reduced secretion of inflammatory cytokines, and inhibition of inflammatory pathways.<sup>56,57</sup> Systemic hor-

monal therapy, while effective for managing acne, is limited to treatment of girls and women aged  $\geq 14$  years.<sup>6,10,11</sup> However, clascoterone has limited systemic activity,<sup>56</sup> meaning it is suitable for male and female patients.

Results of 2 phase 3 studies demonstrated that clascoterone cream 1% was significantly more effective than vehicle at achieving IGA success ( $P < .001$ ) in patients aged  $\geq 9$  years with facial acne vulgaris.<sup>17</sup> Nineteen patients in the trials were  $\geq 9$  to  $< 12$  years of age.<sup>58</sup> Results indicated a favorable safety profile and improvement in efficacy measures in pediatric patients with moderate to severe acne, although patient numbers for the 9- to 11-year age group were small, and further study is needed in this subpopulation.<sup>58</sup>

**Clinical pearl:** Maximize the care provided to patients by staying abreast of recent advances in the treatment of acne and being alert to evolving therapies on the horizon.

## CONCLUSION

This roundtable report covers expert opinions on the current state of acne treatment in preadolescent and adolescent patients. Before new guidelines are published, it is important that experts communicate the latest updates to all physicians who treat patients with acne to ensure optimized patient care. ●

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