Practical management of acne for clinicians: An international consensus from the Global Alliance to Improve Outcomes in Acne

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Scientific advances are continually improving the knowledge of acne and contributing to the refinement of treatment options; it is important for clinicians to regularly update their practice patterns to reflect current standards. The Global Alliance to Improve Outcomes in Acne is an international group of dermatologists with an interest in acne research and education that has been meeting regularly since 2001. As a group, we have continuously evaluated the literature on acne. This supplement focuses on

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providing relevant clinical guidance to health care practitioners managing patients with acne, with an emphasis on areas where the evidence base may be sparse or need interpretation for daily practice. (J Am Acad Dermatol 2018;78:S1-23.)

Key words: acne vulgaris; adult acne; scar; post-inflammatory hyperpigmentation.

INTRODUCTION

Acne is a chronic inflammatory skin disease that is estimated to affect approximately 85% of the population at some point in their lives.[1] Generally straightforward to recognize clinically, acne has a variable presentation with a constellation of lesion types including open and closed comedones, papules, pustules, nodules, and cysts.[1,2] The face is involved in most cases, and the trunk is affected in up to 61% of patients.[3-6] Acne lesions can progress to scars, postinflammatory hyperpigmention (PIH), or both, which can be bothersome to patients.[3,7,8] The pathogenesis is multifactorial, involving the hormonal influence of androgens along with excess sebum production, disturbed keratinization, inflammation, and stimulation of the innate immune system by several pathways including hypercolonization by *Propionibacterium acnes*.[9-11]

Although acne is a very common disease, little time is spent on it in medical curricula, even within dermatology modules.[12] In fact, dermatology education as a whole is lacking in medicine in some countries; 33 US medical schools have no undergraduate dermatology programs, and more than half of American medical schools teach <10 hours of dermatology.[12,13] In Europe, which is home to 25,000 dermato-venereologists, teaching hours vary between 18 to 60 hours during medical undergraduate training; however, all medical schools teach dermato-venereology. Scientific advances are continually improving the knowledge of acne and contributing to the refinement of treatment options; it is important for clinicians to regularly update their practice patterns to reflect current standards. The Global Alliance to Improve Outcomes in Acne is an international group of dermatologists with an interest in acne research and education that has been meeting regularly since 2001. As a group, we have continuously evaluated the literature on acne. We created consensus recommendations about acne management based on our experience and available research, which were published in 2 previous supplements to the *Journal of the American Academy of Dermatology*.[9,10] Outside of the Global Alliance, we have also each been involved in creating evidence-based national and international guidelines for acne management, including those published by the European Dermatology Forum (EDF); the Colegio Ibero-Latinoamericano de Dermatología; the Indian Society Dermatology, Venereology, and Leprosy; and the American Academy of Dermatology (AAD).[3,14,15] In our experience, evidence-based guidelines and clinical consensus recommendations can be quite different. Evidence-based guidelines rate the quality of evidence supporting available

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Abbreviations used:

AAD:	American Academy of Dermatology
A/BPO:	adapalene/benzoyl peroxide
EDF:	European Dermatology Forum
FASET:	Facial Acne Severity Evaluation Tool
FDA:	Food and Drug Administration
IGA:	Investigator Global Assessment
OC:	oral contraceptive
OG:	olumacostat glasaretil
PIH:	postinflammatory hyperpigmention

treatment options, but do not strongly advise the clinician about creating a practical treatment approach. Clinical consensus recommendations use expert opinion and experience and focus more on the philosophy of treatment, the individual patient, as well as clinical experience of what options work well in particular situations.

In this supplement, we aimed to identify the core principles of an effective acne management strategy using the Delphi method to reach consensus. The goal was to help guide clinicians to understand efficient acne therapeutic strategies that could be readily implemented in the office. We particularly focused on areas where the existing evidence base is less robust and expert opinion could have a role in refining practice patterns.

DELPHI METHODOLOGY

A live meeting of the Steering Committee of the Global Alliance group was held to identify areas of acne management that could be useful to clinicians but that were not well defined in existing evidence-based guidelines. Topics discussed included acne grading, recent data with topical therapies, combination regimens for acne, and special topics of interest (acne in women, postinflammatory hyperpigmentation, and scarring). It was agreed that the Delphi methodology could be used to help create a strategic approach to acne.

A Delphi panel and questionnaire method was used to provide a systematic framework for arriving at consensus. This methodology incorporates expertise into a collective judgment via a panel of experts who respond to a set of questionnaires.[16] The panel comprised 36 internationally recognized dermatologists from 27 countries (Argentina, Australia, Belgium, Brazil, Canada, Chile, China, Colombia, France, Germany, India, Italy, Japan, Mexico, Malaysia, Morocco, Philippines, Russia, Saudi Arabia, Singapore, South Korea, Spain, Sweden, Thailand, United States, United Kingdom, Venezuela). All were members of the Global Alliance international and regional groups.

An online questionnaire was developed by a selected subgroup of the Global Alliance Steering Committee and then distributed to panel members. Participants were asked to rate agreement with each statement on a 5-point Likert scale (strongly agree, agree, disagree, strongly disagree, unable to answer). Those who selected disagree, strongly disagree, or unable to answer were prompted to provide a written explanation of what they disagreed with. Responses from the first survey were classified as round 1, analyzed, and a summary of all areas of consensus and individual statements of disagreement was prepared. The results, along with modified survey questions (round 2), were sent to respondents. Again, results were collected and analyzed to arrive at the final results, which are presented here. The final statements and document were edited and reviewed by the panel. Consensus was defined as agreement among ≥75% of the dermatologists who participated in the panel. The statements and voting results are presented as Supplemental Table I (availale at http://www.jaad.org).

CONSENSUS RECOMMENDATIONS

Assessing acne severity: impact of new topical medications

There is no standardized acne grading or classification system; however, acne is often categorized by an overall gestalt as mild, moderate, and severe in guidelines and recommendations as well as by clinicians treating patients.[2,3,14] These categories are useful to help guide selection of therapy but are chosen on the basis of the subjective opinion of the physician. As a more objective measure of severity, lesion counts or estimates may be used to help define acne severity.[3,17] For example, acne research trials typically associate a range of lesion counts to objectively classify acne severity, along with an Investigator Global Assessment (IGA).[3,17,18] But one problem in defining objective assessments is that lesion counts alone do not accurately convey subjective aspects of acne, such as variations in lesion size and visibility (Fig 1).[18] Furthermore, clinical studies in the past did not differentiate between small nodules >0.5-1 cm and those >1 cm, which is of clinical importance regarding selection of treatments and response rate. Therefore, comparison of evidenced-based clinical studies in moderate-to-severe acne is often not possible.[3]

Another problem in categorizing acne severity has emerged with the development of new, highly efficacious topical acne medications: how to denote acne severity in patients who might be good candidates for strong topical medications versus those who are best suited by early institution of

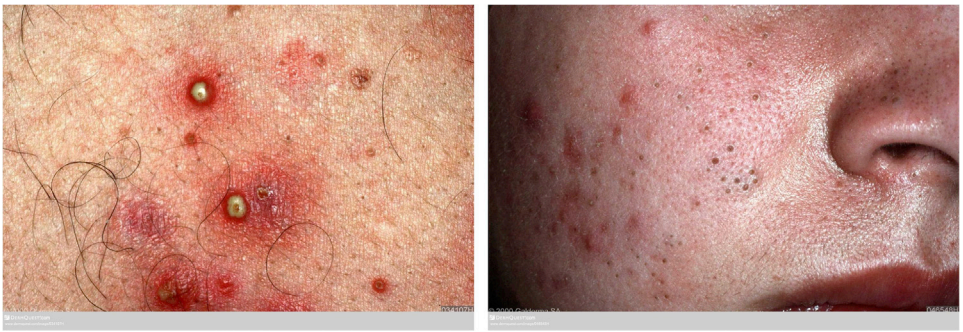

Fig 1. Illustration of differences in lesions of acne vulgaris that could affect overall assessment of acne severity but not lesion counts. Photos courtesy of DermQuest.com. Copyright © 2006 Galderma S.A. All rights reserved.

Table I. Investigator Global Assessment scale recommended by the US Food and Drug Administration[17]

Grade	Clinical description
0	Clear skin with no inflammatory or noninflammatory lesions
1	Almost clear; rare noninflammatory lesions with more than one small inflammatory lesion
2	Mild severity; greater than grade 1; some noninflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; greater than grade 2; up to many noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4	Severe; greater than grade 3; up to many noninflammatory and inflammatory lesions, but no more than a few nodular lesions

Scale not intended to cover candidates for oral isotretinoin therapy.

oral isotretinoin.[19,20] Many practicing dermatologists perceive the term severe to refer primarily to nodular/conglobate acne, which is appropriately treated with oral isotretinoin.[2] Now, however, there might be a need for a more refined system of classifying moderately severe, severe, and very severe that aligns with additional potential first-line treatment options. The 2016 European S3 Acne Guideline has used the following 4-point classification system that might help to approach these issues in a practical fashion[3]: 1) comedonal acne, 2) mild-moderate papulopustular acne; 3) severe papulopustular acne, moderate nodular acne; and 4) severe nodular acne, conglobate acne. Similarly, the IGA scale recommended by the US Food and Drug Administration (FDA) considers quality of lesions and quantity (Table I).[17] This scale also includes a grade of severe acne that is separate from nodular/conglobate acne. We propose that the designation very severe be reserved for cystic and conglobate acne, which are illustrated in Fig 2.

Single-agent topical therapy for severe inflammatory acne. Recently, there have been several studies of topical combination therapy that included patients that would be categorized as severe inflammatory acne (grade 3 on the European Union scale or grade 4 on the US FDA scale). In 2016, Stein Gold et al reported that the fixed combination adapalene 0.3%/benzoyl peroxide 2.5% (A/BPO 0.3%) was the "first topical fixed–combination agent therapy developed for severe inflammatory acne."[20] A/BPO 0.3% was evaluated in a 50%-50% population of subjects with moderate and severe acne (defined as moderate [IGA score of 3] or severe [IGA score of 4] with 20-100 inflammatory lesions, 30-150 noninflammatory lesions, and ≤2 nodules on the face).[20] A/BPO 0.3% was efficacious across the population and well tolerated (Fig 3); further, in the severe population A/BPO 0.3% showed significantly greater efficacy in achieving success (clear or almost clear or a 3-grade improvement) and reductions in lesion counts versus vehicle (P = .029 for success and P < .001 for lesion counts).[20] Stein Gold et al concluded that A/BPO 0.3% could have an important systemic antibiotic-sparing role for patients with moderate and severe inflammatory acne, particularly because it targets the microcomedone.[20] These investigators also suggested A/BPO 0.3% could be used alone or in combination with other therapies before moving to oral isotretinoin or while gaining access to oral isotretinoin therapy.[20]

Phase 2 studies with novel agents have also been published recently for moderate-to-severe acne. A

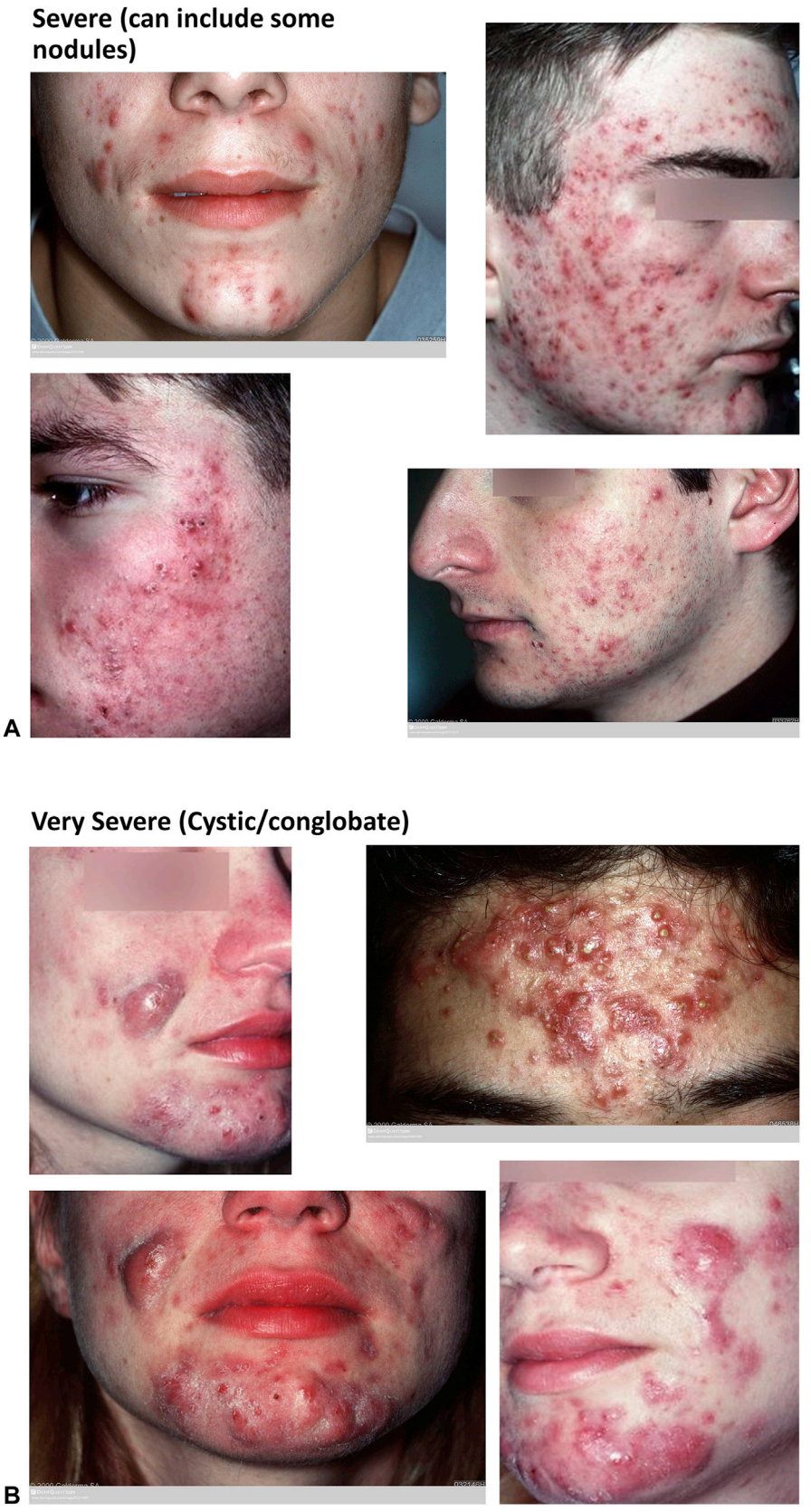

Fig 2. Illustrative photos of severe inflammatory acne vulgaris, largely without nodules (**A**). **B**, Very severe acne with cysts. Photos courtesy of DermQuest.com. Copyright © 2006 Galderma S.A. All rights reserved.

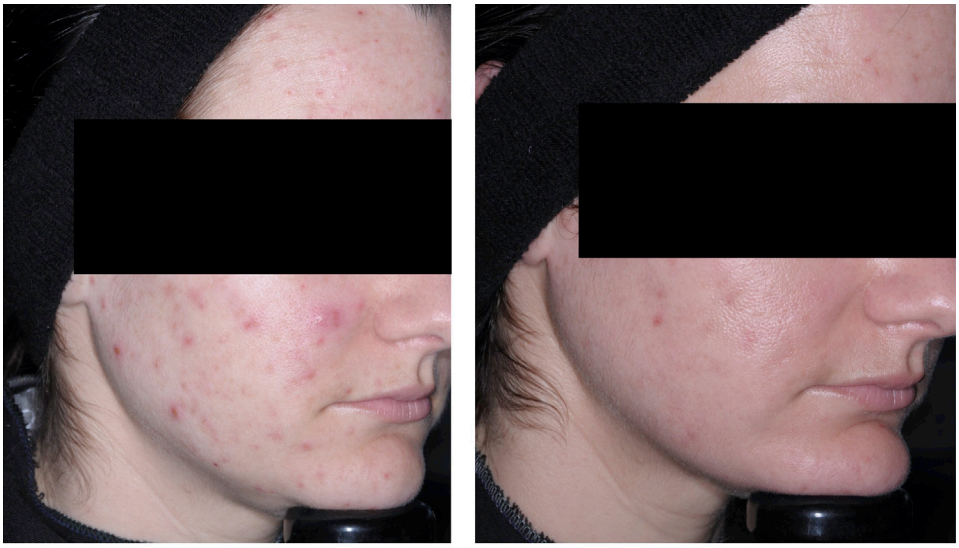

Fig 3. Patient with severe acne vulgaris treated with adapalene/benzoyl peroxide at baseline and week 12.

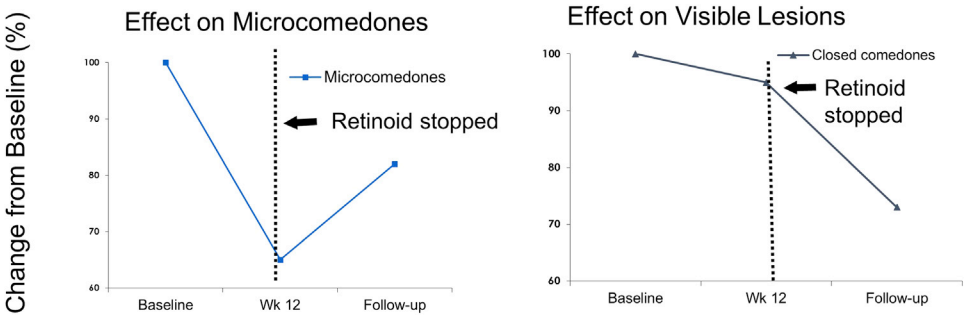

Fig 4. Action of retinoids on microcomedones (acne vulgaris precursor lesions) and visible lesions. Note the lag time after cessation of retinoid therapy before visible lesions begin to reappear. Reprinted with permission from Thielitz et al.[30]

new topical agent, olumacostat glasaretil (OG) 7.5% (an inhibitor of acetyl coenzyme-A carboxylase with putative action as a topical sebum inhibitor), has shown promise for treating moderate-to-severe acne.[21] A phase 2 study of 108 patients treated with OG twice daily for 12 weeks showed that OG was significantly superior to vehicle in reducing inflammatory lesions (−63.9% vs −45.9%, $P = .0006$) and noninflammatory lesions (−48.1% vs −28.8%, $P = .0025$); in addition, more patients had improvement of at least 2 grades in IGA (24.5% vs 7.3%, $P = .007$). OG was well tolerated, with mild-to-moderate application-site adverse events.[21] A topical foam formulation of minocycline 4% was evaluated in subjects with a mean of 33.5 inflammatory lesions at baseline. In a phase 2 study, minocycline foam was superior to vehicle in reducing both inflammatory and noninflammatory lesions (−71.7% vs −50.6%, $P = .0001$; −72.7% vs −56.5%, $P = .0197$, respectively), as well as in improving IGA score.[22] Two phase 3 studies were completed with the minocycline foam, with one reporting statistically significantly superior results to vehicle but the other failing to demonstrate a significant difference in IGA (1 of 2 co-primary endpoints). An additional phase 3 study is planned.[23] However, it should be noted that monotherapy with a topical antibiotic is advised against in current guidelines and recommendations because of the potential for antimicrobial resistance.[2,3,14] For additional details, see Zouboulis et al.[24]

Gold et al reported a post-hoc subgroup analysis of a phase 3 study of clindamycin 1.2%/BPO 3.75% in moderate-to-severe acne (n = 498) that specifically compared results in participants with severe acne (n = 86) with those in participants with moderate acne (n = 412).[25,26] An improvement in global severity of at least 2 grades was achieved in 55.1% of patients with severe acne compared with 31.3% of those with moderate acne. The proportion of

Table II. Strategies to minimize the likelihood of tolerability problems associated with induction of topical retinoid therapy

- Take a detailed patient history
  - Have there been tolerability problems in the past?
- Educate patient
  - Mild irritation can be part of the treatment process, but usually subsides within 1-2 weeks and can be managed with appropriate steps
  - A small dose of retinoid (demonstrate fingertip or pea-sized dose) should be applied in a thin layer to the entire affected area
  - Patient should use a gentle cleansing regimen and avoid overcleansing
- Select most tolerable retinoid formulation for climate and season
  - Creams and lotions might be best for dry or sensitive skin and gels or foam for more oily skin (although newer aqueous gels might also be suitable for sensitive skin)
- Titrate retinoid dose at initiation
  - Apply retinoid every other day for first 2-4 weeks (based on clinical trial evidence that this is when irritation is most likely to occur)
  - Apply gentle, noncomedogenic moisturizer
  - Use a short contact method for first 2-4 weeks (apply retinoid to full face for 30-60 minutes then wash off)

Adapted with permission from Leyden et al.[32]

participants rated clear or almost clear at study endpoint was 30.6% in the severe group and 35.7% in the moderate group. The authors commented that "topical therapy may indeed be more valuable than often assumed in patients with severe acne vulgaris." Gold et al also note that in their study persons with severe acne were more likely to be female and younger compared with the moderate group, which might have affected the results.[25]

Combination regimens for severe acne. Combination regimens with newer agents might also provide alternatives to oral isotretinoin or serve as an intermediate treatment step before isotretinoin. In a comparative study, Tan et al reported that A/BPO 0.1% plus doxycycline 200 mg/day was a noninferior alternative to oral isotretinoin.[19] The combination regimen compared with isotretinoin had a significantly earlier onset of action in reducing acne lesions at week 2. Overall, isotretinoin was superior to A/BPO 0.1% plus doxycycline in reducing nodules (95.6% vs 88.7%), inflammatory lesions (95.2% vs 79.6%), and total lesions (92.9% vs 78.2%; all $P < .001$) at week 20. However, treatment-related, medically relevant adverse events were less frequent in the combination treatment arm versus isotretinoin arm (33 events in 18% of subjects vs 73 events in 33.8%, respectively). The investigators concluded "D-A/BPO showed a favourable composite efficacy/safety profile compared to ISO [isotretinoin]." Further, they indicated A/BPO 0.1% plus doxycycline is an acceptable alternative to isotretinoin for treatment of acne in patients who are unable or unwilling to have isotretinoin prescribed.[19] In a noncomparative study, Gold et al had shown that the combination of A/BPO 0.1% plus doxycycline 100 mg was significantly more effective than vehicle plus doxycycline 100 mg in potential candidates for oral isotretinoin.[27] In a similar European study, Dreno et al studied A/BPO 0.1% plus lymecycline 300 mg in patients with moderate-to-severe acne, and reported statistically significantly superior improvements in acne with the combined regimen versus lymecycline alone.[28] Zaenglein et al reported results from a phase 4, open-label study of a population with a large proportion (77%) of patients with acne severe enough to warrant isotretinoin as judged by independent review of digital photographs.[29] In this study, a triple combination regimen of oral minocycline, BPO 6%, and clindamycin phosphate 1.2%/tretinoin 0.025% gel significantly improved acne, reducing lesion counts and improving IGA scores.[29] By the end of study at week twelve, 84% of those patients who were potential candidates for isotretinoin at baseline had experienced enough improvement that isotretinoin was no longer a necessary treatment approach.[29]

Delphi results: strategic approach to acne therapy

Consensus recommendation 1: retinoids have an essential role in treatment of acne.[3,14] For most patients with inflammatory acne, comedonal acne, or both, a topical retinoid plus BPO is first-line therapy.[2] Together, these agents target multiple aspects of acne pathophysiology, working to normalize keratinization, reduce inflammation, and kill *P. acnes*.[9,10] Further, retinoids

have a unique class action reducing formation of acne precursor lesions (microcomedones) and limiting development of new lesions (Fig 4).[10,30] Using cyanoacrylate strips, Thielitz et al demonstrated that microcomedones rebound almost immediately after treatment is discontinued, whereas reductions in visible lesions continue for several weeks because of normal skin turnover.[30] This finding is why the AAD guidelines state topical retinoids "allow for maintenance of clearance."[14] Thielitz et al also showed the efficacy of azelaic acid in maintenance therapy was equivalent to that of adapalene as mentioned in the S3 EDF guideline.[3,31]

Generally, retinoids are similar in efficacy, and the efficacy improves with higher concentrations.[32] Dose-dependent effects were first shown with tretinoin in animal models and ultra-structural studies.[30,33] After 2 weeks of treatment, tretinoin 0.1% reduced microcomedones by 80% and tretinoin 0.025% achieved a 35% reduction.[30,34] Studies have shown that adapalene has a dose-dependent effect on down-regulating expression of molecules important in the innate immune response, including toll-like receptor 2, B-defensin 4, and interleukin-8, and increases expression of CD1d.[35,36] This helps to explain the greater clinical effect in patients with more severe acne reported with A/BPO 0.3% by Stein Gold et al.[20] Similarly, the pivotal trials of adapalene gel 0.3% found efficacy superior to adapalene 0.1% across all measures, and both dosages were similarly tolerated.[37,38] In the phase 3 study of adapalene gel 0.3%, the greatest improvements were achieved in patients who had higher lesion counts at baseline.[37] Thus, there are now more treatment options for patients with severe inflammatory acne.[20] For these patients, higher concentration retinoid therapy may be used as an option before adding systemic therapy. A once-daily topical agent can readily be added to the patient's existing skin care habits and may be preferred by some patients who do not wish to use an oral therapy. A simple regimen is also beneficial for patient adherence.[39,40]

Although there is a solid rationale and strong recommendations for use of topical retinoids in both the EDF and AAD guidelines,[3,14] a study of prescribing practices during 2012-2014 reported that dermatologists prescribed retinoids for just 58.8% of almost 75,000 acne patients and nondermatologists prescribed them for only 32.4% of cases.[41] Clinician perceptions of the irritation potential of topical retinoids can limit their use in practice.[2,42] However, when present, most topical retinoid side effects resolve within 2-3 weeks and can be managed by use of moisturizers.[2] Table II presents strategies that can be employed to minimize the likelihood of irritation.[2,32,43,44]

Consensus recommendation 2: the role of antibiotics in acne therapy has changed. Neither topical nor systemic antibiotics should be used as monotherapy for acne treatment.[2,45,46] Antibiotic resistance is a worldwide problem and should be an essential consideration when selecting therapy for acne.[45-47] Resistant microbial organisms are increasing throughout the world's populations, and worldwide health authorities have called upon the medical community to limit antibiotic use in situations where other management approaches may be used.[48-50] Use of antibiotics in acne affects a large number of people, considering that resistance can occur in both treated individuals and their close household contacts.[51] In addition, antibiotics are often prescribed for a much longer duration in acne than for typical infections (eg, months rather than days).[52] Thus, antibiotic use in acne exerts considerable selective pressure on microbes, including pathogenic and nonpathogenic organisms. However, some studies could not confirm the resistance problem following topical antibiotic treatment.[53] There are currently multiple nonantibiotic therapies for acne with proven efficacy, and it is reasonable for clinicians to develop antibiotic-sparing approaches for this disease.[45] Subantimicrobial-dose doxycycline is used in the treatment of acne due to anti-inflammatory properties but this treatment has not been studied in detail regarding the possible implications for antibiotic resistance.[54]

BPO is the preferred topical antimicrobial agent due to the current climate of antimicrobial stewardship.[2,3,14,45,47] BPO is a potent bactericidal agent, with strong oxidative activity. In a review article discussing management of acne in the era of antimicrobial resistance, Tzellos et al state "overall, BPO combined with topical or oral antibiotics or topical retinoids is the most efficacious evidence-based treatment option to prevent the development of antibiotic resistance in patients with acne and to confer significant clinical improvement on patients who have already developed antibiotic-resistant acne."[55,56] However, there is an urgent need for an antimicrobial agent with better tolerability than BPO in monotherapy and fixed combination therapies.

Systemic antibiotics are useful for moderate-to-moderately severe acne, but efforts should be made to limit the duration of therapy to 3-4 months.[2,45-47] In our clinical experience, the top 3 factors to consider when determining duration of antibiotic therapy include the severity of acne, the potential for bacterial resistance, and the response to treatment. Factors that make it difficult to limit the duration of systemic antibiotic therapy include acne recurrence and patient preference.

Reducing antibiotic use in acne: Real-world strategies

Topical therapy[2,10,14]

- First-line acne therapy = topical retinoids and BPO
- Topical antibiotics should not be used as monotherapy
  - Rapid development of resistance
- BPO ± a topical retinoid should be added if topical antibiotic is prescribed
  - Speeds response and achieves superior clearing
- All strains of *P acnes* are sensitive to BPO
- Topical retinoids (with or without BPO) or azelaic acid are treatment of choice for maintenance

Systemic therapy

- Assessing risk-benefit analysis for systemic antibiotics should balance individual need versus public interest in preserving antibiotic effectiveness
  - Antibiotics should be avoided when effective alternatives are available
- Oral antibiotics are indicated when inflammatory acne is not responding well to topical treatments and acne involving trunk or multiple bodily areas
  - Response to therapy should be evaluated at 6-8 weeks
  - Target duration of therapy less than 3-4 months
  - A topical retinoid and BPO or azelaic acid can be used at discontinuation of antibiotic
- Avoid systemic antibiotic monotherapy
- Subantimicrobial dose antibiotics, which have anti-inflammatory actions, can be useful to minimize potential for resistance

Consensus recommendation 3: oral isotretinoin should be first-line therapy for very severe (cystic and conglobate) acne.[2] Isotretinoin is a highly efficacious acne treatment, proven to clear acne lesions, including nodules and cysts, and achieve a prolonged remission period.[57,58] It usually has been recommended at a dose of 0.5-1.0 mg/kg administered over a period of ~4-6 months to reach a cumulative dose of 120-150 mg/kg—a target that has been recommended to reduce relapse and improve remission rates.[59,60] However, more modern thinking is reflected in core principle 4.[61] Systemic corticosteroids may be used at initiation of therapy to help speed lesion clearing. Many experts and researchers in the field think that isotretinoin use should not be restricted to cases with demonstrated failure to conventional therapy.[62]

Consensus recommendation 4: oral isotretinoin therapy should proceed until full clearance of acne. Additional studies are needed to define a total cumulative dose that maintains remission. After the introduction of oral isotretinoin, a threshold dose of 120-150 mg/kg over a period of 4-6 months has been recommended to reduce relapse and improve remission rates. Tan et al performed a systematic literature search to evaluate evidence supporting cumulative dosing for isotretinoin.[61] Tan reported that the cumulative dose is based on data from studies that were not designed to evaluate the role of cumulative dose in relapse rates.[61,63] Further, a retrospective chart review of 1453 patients treated with oral isotretinoin showed that 22.4% required a second course of isotretinoin (follow-up ≥12 months, range 12 months-5 years) and that daily and cumulative doses did not influence relapse as long as treatment was continued for ≥2 months after complete resolution of acne.[63] The authors suggest proceeding with treatment until full clearance, independent of the cumulative dose.[63] We agree this is a reasonable and effective strategy for patients with severe acne. For those with moderate acne, full clearance can be achieved with lower cumulative doses. A rule of thumb may be to treat until full clearance plus an additional month.

In addition to the need for treatment to remission (dosage will vary by individual), there is also a goal of maintaining remission. For maintaining remission, specific dosing has not been established by high-quality clinical trials. Factors that have been implicated as higher risk for relapse include severe seborrhea, young age, family history of acne, prepubertal acne, and truncal acne.[63-66]

Similarly, although it has been suggested that higher cumulative doses of oral isotretinoin may be needed for severe truncal acne, in our clinical experience severe truncal acne can usually be treated with the same dose as that for severe facial acne. There are no clear statistical data supporting a different dose.

Consensus recommendation 5: acne flare with oral isotretinoin can be minimized by initiating therapy at a low dose. Acne flare occurs in a small proportion of patients (up to 15%) at the initiation of oral isotretinoin therapy.[67] The group reached consensus that starting with a low dose (0.5 mg/kg in the United States and ≤0.2 mg/kg in some countries as reported by Borghi et al)[67] reduces the likelihood of flare, although several panelists felt that sometimes the propensity for inflammatory flare is independent of dose.

Consensus recommendation 6: most patients with acne should receive maintenance therapy with a topical retinoid with or without BPO. Topical antibiotics should not be used as acne maintenance therapy. Topical retinoid monotherapy may be sufficient in some cases, with BPO or an oral antibiotic added as needed.[68-72]

Thielitz et al were able to demonstrate that maintenance therapy with a topical retinoid achieved sustained reductions in microcomedones, which in turn translated to fewer active acne lesions.[71] Clinical trials with adapalene, A/BPO, and tazarotene have shown significant superiority over their respective vehicles when used as maintenance therapy after successful acute phase therapy.[69,70,72-74] Thielitz et al showed that good results could be achieved with retinoid therapy applied every other day, which might be appealing for patients.[71] Azelaic acid may be a maintenance option for women with acne.[31]

Consensus recommendation 7: azelaic acid cream 20% or gel 15% is a useful acne treatment in pregnant women and patients with acne and PIH. The group reached consensus that azelaic acid should be recommended as a second-line therapy[3,14]; however, dissenting panelists commented that it has a relatively high potential to cause irritation and aggravate already inflamed skin. Further, it was noted that azelaic acid is not available in all regions of the world and is a risk category B drug in pregnancy. Although there was a consensus that azelaic acid is useful in patients with acne and PIH, data supporting its use in this setting are sparse.[75] Kircik et al reported that azelaic acid gel 15% twice daily improved both mild-moderate acne and PIH in 20 adults with Fitzpatrick skin type V and VI. At study conclusion (week 16), PIH was cleared in 31% of subjects and slight or mild improvement was noted in 69% of subjects.[75]

Consensus recommendation 8: at present, devices, including laser, intense pulsed light, and photodynamic therapy should not be considered first-line treatment for inflammatory acne. Although laser and light devices have some benefit in the setting of acne, well-designed studies evaluating their effectiveness versus standard medical therapies are lacking.[76] In addition, standardized regimens have not been agreed upon; multiple treatments are generally necessary (and costly), and the results are temporary.[14] A recent Cochrane database systematic review of light therapies in acne found "high-quality evidence on the use of light therapies for people with acne is lacking."[76] In the AAD guidelines, Zaenglein et al report that photodynamic therapy with a photosensitizer has the best supporting evidence and shows great promise, but that more studies are needed to optimize the treatment regimen, including the optimal sensitizer, incubation time, and light source.[14]

Consensus recommendation 9: a minority of women ≥25 years of age have acne lesions localized only to the lower face. Topical retinoids with or without BPO are important components in therapy of adult acne. There is a clinical impression that women with acne have a subtype of acne that is difficult to treat and primarily driven by hormonal abnormalities. However, a large-scale international study showed that 89% of women have a facial distribution of acne lesions that is similar to adolescent acne (Fig 5).[77] Further, analysis of clinical registration data for adapalene and A/BPO have both shown good efficacy in the adult female population.[78,79] Adding skin care regimens, such as moisturizers and pH-balanced cleansers, has been shown to improve both efficacy and tolerability for women.[80] Long-term maintenance is particularly important in the adult female population because frequent recurrences are common. In addition, dry and sensitive skin is more common in this group, supporting use of strategies to minimize irritation from topical treatments (application every other day initiation; short-contact therapies; use of moisturizers and gentle, nonsoap cleansers).[81,82]

Oral therapies, including limited-duration antibiotics, isotretinoin, and hormonal treatments, can be useful for adult female acne.[81,82] A discussion on the use of oral contraceptives and hormonal therapy is provided later in this supplement.

Consensus recommendation 10: early and effective treatment is important to minimize potential risk for acne scarring. Acne lesions can evolve into more permanent scars, which can be either atrophic or hypertrophic. It is challenging to identify which patients will scar, but early administration of effective therapy can reduce one modifiable risk factor for scarring: prolonged uncontrolled acne.[8,83-85] There are a number of risk factors that have been linked to the development of atrophic acne scars, including severe acne (although scars can occur even with mild acne), family history, extent and duration of inflammation, and (perhaps most important) the time to effective treatment of acne.[8,83,84] Additional risk factors might include manipulation of lesions, onset of acne at a young age, frequent relapses, localization to the trunk, and ethnicity.[8] Histologic data suggest that an early strong inflammatory response in the skin appears to be associated with less scarring then milder forms of acne that demonstrate delayed inflammatory response.[86] A tool to assess risk of acne scarring was recently developed after a review of the literature and clinical trials and a modified Delphi

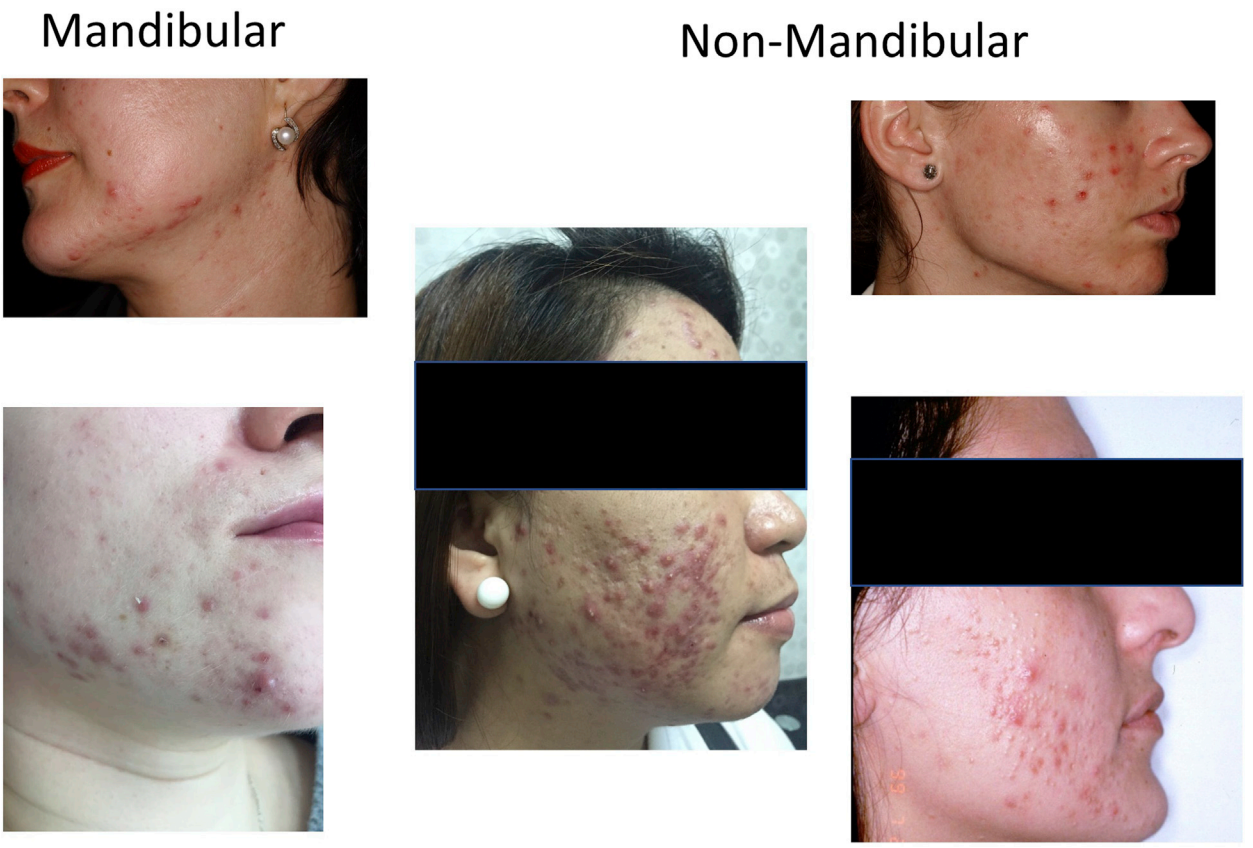

Fig 5. Examples of adult female acne vulgaris. Photos courtesy of Dr Araviiskaia of the Department of Dermatology and Venereal Diseases First Pavlov Medical University of St. Petersburg, St. Petersburg, Russia; Dr Castinahan; Dr Kemeny of the Department of Dermatology and Allergology, University of Szeged; and Dr Troielli.

process involving an expert panel (Fig 6).[87] The tool is a short, simple, self-administered questionnaire that can readily be used both to educate patients and to help assess risk for acne scarring and raise awareness. The outcome is dichotomous, ranking patient risk as either low or high. The creators found the tool correctly categorized nearly two thirds of the population and had a sensitivity of 82% and specificity of 43%.[87]

In a split-face, randomized controlled trial, Dreno et al showed that A/BPO 0.1% reduced the risk for atrophic scar formation in subjects with moderate inflammatory acne.[88] Over a period of 6 months, scar counts remained stable with A/BPO treatment but increased by 25% with vehicle treatment (P = .036).[88] To the best of our knowledge, this is the first study to confirm the clinical impression that effective treatment of acne minimizes risk of scarring.

In our clinical experience, a higher concentration of topical retinoid with BPO may be useful for patients at high risk of scarring. However, higher concentrations might be less well tolerated, so selection of retinoid concentration should be individualized. Recent publications have shown that scars continuously form during the course of acne and some resolve[8,89]; in addition to having greater efficacy in treating existing lesions, a higher concentration of retinoid might have a greater impact on skin healing and, thereby, reduce formation of scars. Further studies are needed to elucidate the dose-dependent differences in topical retinoid formulations.

Summary: acne management algorithm

Fig 7 shows an algorithm that summarizes a treatment approach on the basis of the consensus recommendations described above.

PRACTICAL APPROACH TO TREATMENT IN VARIOUS SETTINGS

A literature review was performed to address what is known about acne and PIH, acne and scarring, and acne in women. In addition, because there are some aspects of these topics that are not

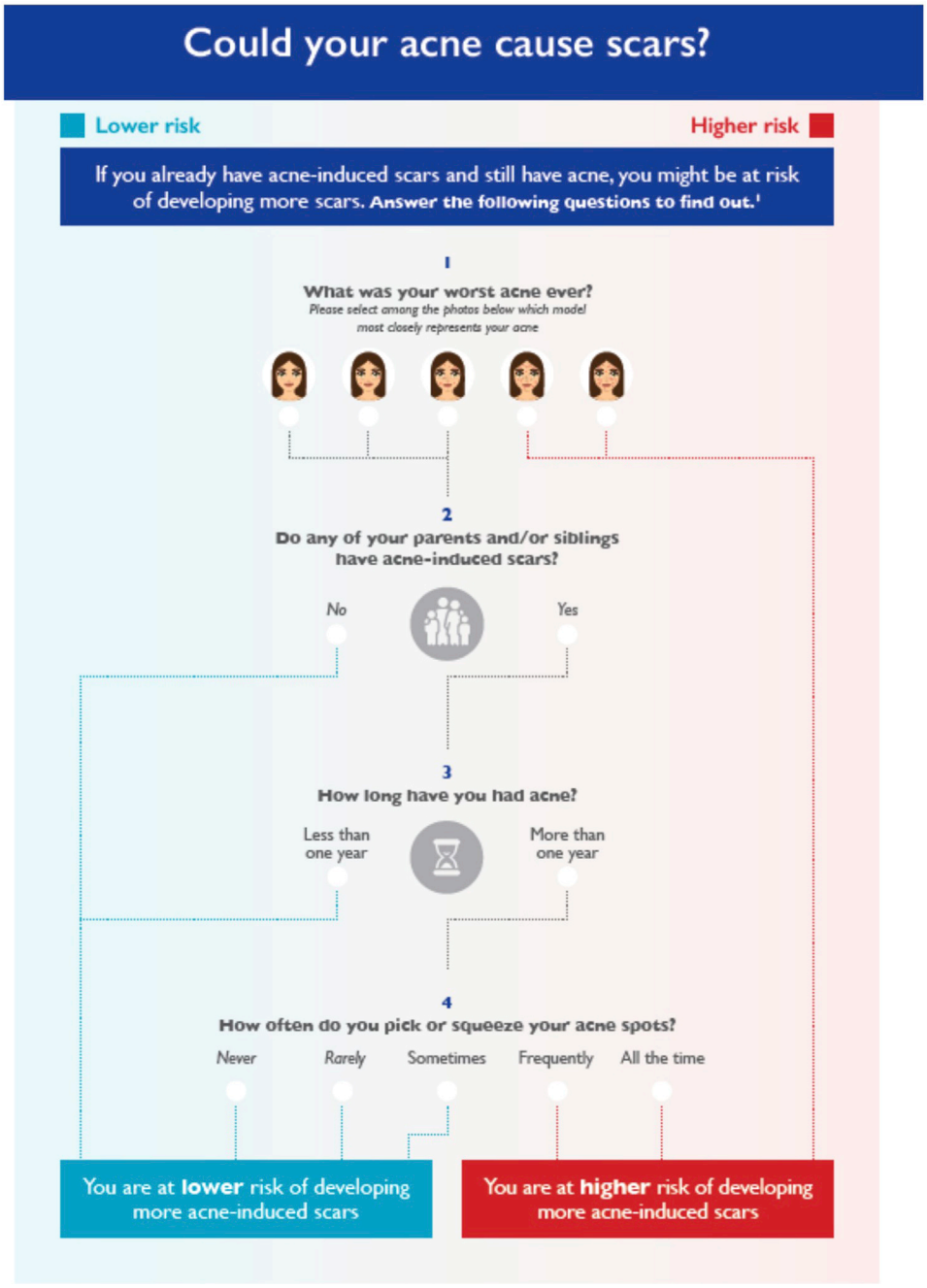

Fig 6. Atrophic acne scar risk assessment tool.[87]

well explored in the literature, a secondary online questionnaire was provided to the Delphi panel members. This questionnaire did not follow the Delphi process but rather asked a series of open-ended questions to allow the panel members to share their clinical pearls and practice tips. These are incorporated below.

Acne and PIH

Human skin has a wide variety of hues, including pinks, yellows, and browns that arise from the individual contributions of melanin, bluish-white connective tissue, and hemoglobin. Generally, darker skin reacts to injury or insult with localized melanin deposition, resulting in uneven skin tones, but even pale skin can have long-lasting dark or red spots after resolution of an acne lesion (Fig 8). PIH is a common occurrence in patients with acne, particularly in those with darker skin and those who excoriate their lesions.[7] Patients and clinicians both report that PIH often has a prolonged duration and can be more

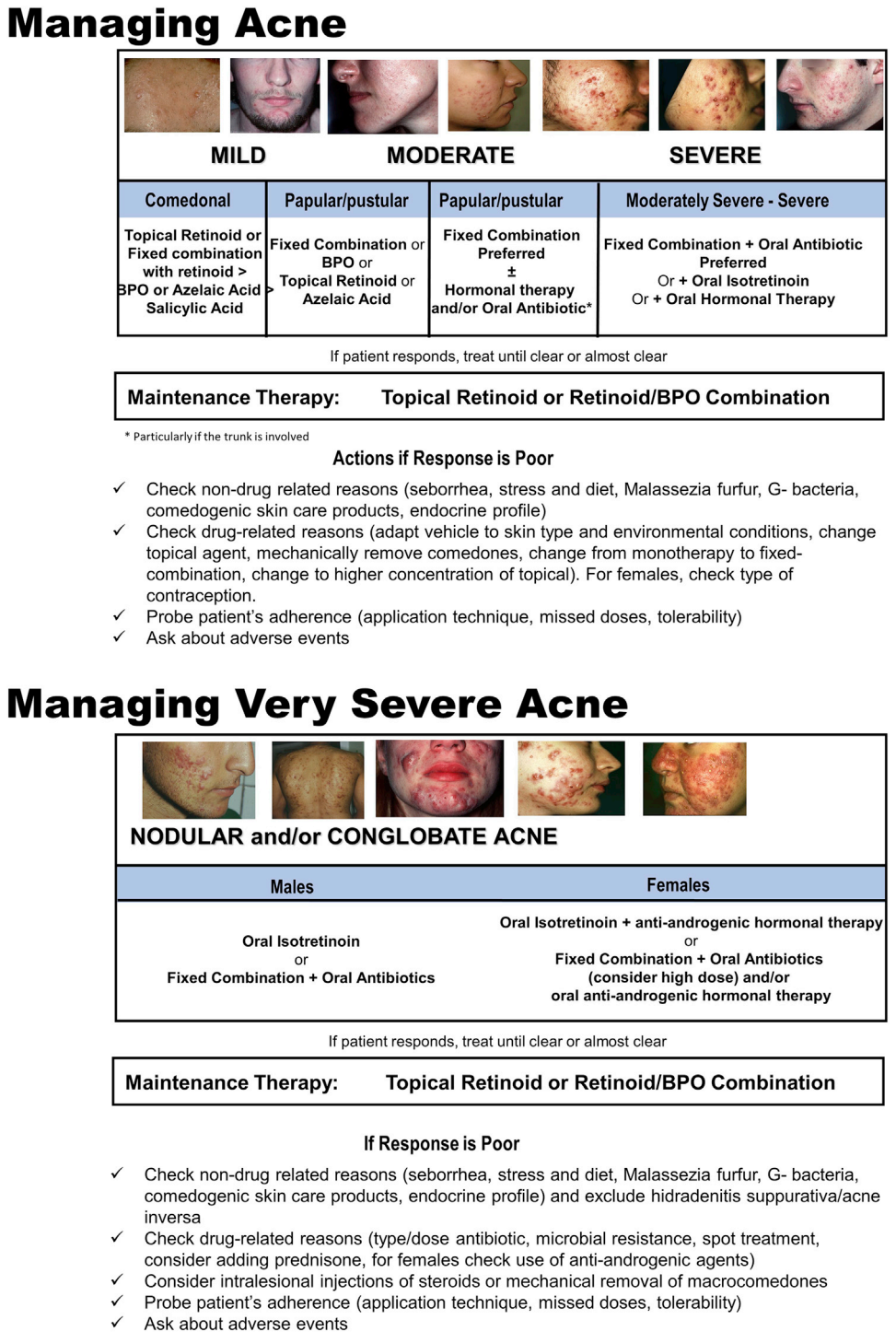

Fig 7. Practical approach to acne management.

bothersome than active acne lesions for the patient.[7,90] In a study of Middle Eastern acne patients, more than half (56.4%) were primarily concerned with uneven skin tone, and 49.4% had acne lesions as their top concern.[91]

There are few published epidemiologic data, but what does exist suggests that half or more acne patients with dark skin tones also have PIH.[92] In an Asian population (324 persons from 7 countries), Abad-Casintahan et al found PIH in 60% of acne patients evaluated sequentially.[7] PIH typically has a long duration, and in the same study 65.2% of patients reported having PIH for ≥1 year.[7]

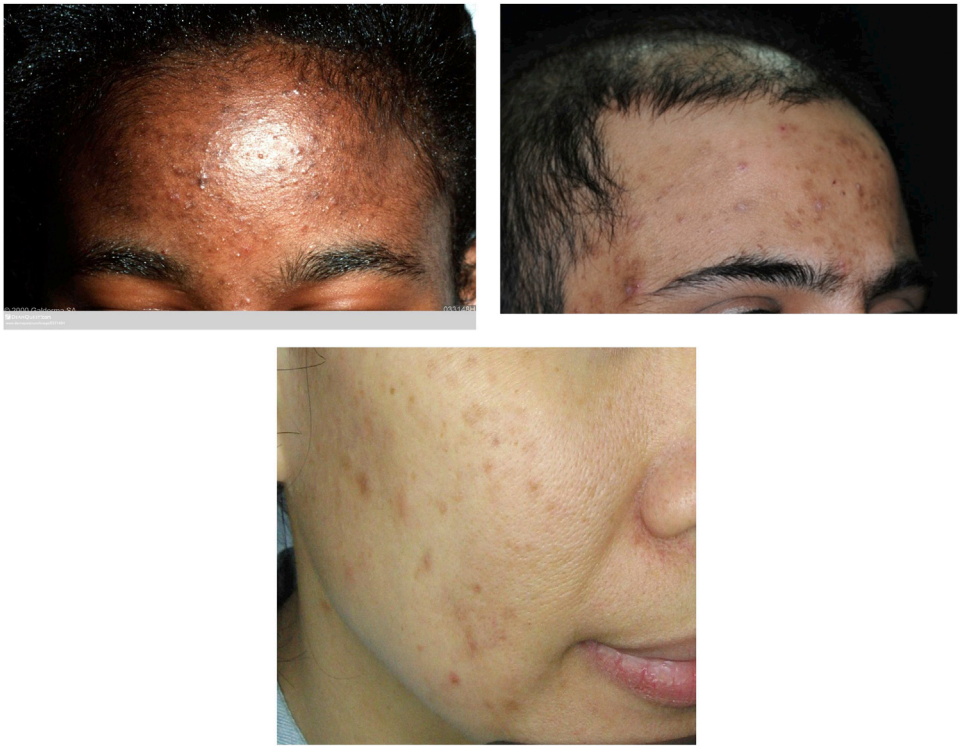

Fig 8. Spectrum of postinflammatory hyperpigmentation. *BPO*, Benzoyl peroxide. Photos courtesy of DermQuest.com, Dr C. L. Goh, and Dr R. Kubba. Copyright © 2006 Galderma S.A. All rights reserved.

PIH affects individuals of all genders and ages.[93] Clinically, PIH might present as localized or diffuse colored macules at the sites of former acne lesions.[93] Dyspigmentation often becomes more apparent after acne lesions and associated erythema have resolved.[93] PIH ranges in color from light brown to grey or black; dark purple lesions may be an early form of PIH.[93]

PIH is a hypermelanotic reaction to skin inflammation.[94] Conversion of tyrosine in melanocytes creates melanin, which can be packaged into melanosomes and transferred to keratinocytes.[93,95] When acne is present, melanocytes are stimulated by inflammatory mediators, cytokines, and arachidonic acid metabolites to increase melanin synthesis and deposition of pigment to nearby keratinocytes. Excess melanin production or an abnormal distribution of melanin pigment deposited in skin produces visible PIH.[96] Mechanical insults to skin such as excoriation can exacerbate PIH.

Treating acne patients prone to PIH. A variety of methods may be used to determine which patients to treat, including assessment of overall clinical severity (eg, visibility from a distance and with and without makeup), patient preferences, stated impact on quality of life, and known excoriation. Prevention (including sun protection) and treatment of underlying acne-associated inflammation early and effectively is a primary approach to PIH management.[97] Table III reviews pathways that are targets of medical intervention in pigmentation disorders.[98,99] Chemical peels, lasers, and other light therapies may also be used for PIH; however, these methods can also cause pigmentation problems so should be used with care.[99] In addition, it is important to weigh the cost-benefit of a procedural approach because the reduction in time to resolution might be relatively small.

Topical retinoids effectively manage acne and can also improve pigmentation by inhibiting melanosome transfer to keratinocytes and increasing epidermal turnover and lessening pigmentation.[9,93,97,100,101] Combination acne therapy can improve the speed and degree of lesion resolution.[10,97]

Variations of the classic Kligman's formula of a retinoid + hydroquinone + corticosteroid are also used for skin lightening or brightening.[100] These products may be used during acne therapy but are more commonly prescribed after resolution of acne lesions.[100] Cosmeceuticals with skin-lightening ingredients may be a cost-effective approach, and azelaic acid may also be helpful.[102] Results can be

Table III. Actions of agents used to treat postinflammatory hyperpigmentation

Agent	Mechanism
Retinoids	Increase keratinocyte turnover and remove pigmentation, inhibit tyrosinase, and reduce pigment transfer
Hydroquinone	Inhibition of melanogenesis via reduction in active tyrosinase
Kojic acid	Inactivates tyrosinase by chelating copper atoms
Azelaic acid	Selectively influences hyperactive and abnormal melanocytes, prevents tyrosine-tyrosinase binding
Flavonoids (aloesin from aloe vera plants, stilbene derivatives such as resveratrol, licorice extracts)	Inhibit tyrosinase activity at distal portions of the melanogenic pathway
Antioxidants/Redox agents (beta carotene and vitamin C and E)	Prevent oxidative damage to skin, scavenge reactive oxygen species, inhibit second messengers that stimulate melanogenesis, interact with copper at active site of tyrosinase
Niacinamide	Interrupts melanosome transfer from melanocyte to keratinocyte
Alpha hydroxy acids, salicylic acid, linoleic acid	Accelerate skin turnover, dispersing melanin; linoleic acid also reduces tyrosinase activity
Arbutin	Structural homolog for tyrosinase (competitive inhibitor), inhibits melanosome maturation

Reprinted with permission from Gollnick et al.[99]

improved by combining modalities; for example, in a study of 45 patients, salicylic acid peel plus a topical retinoid improved PIH more than either treatment alone, with good tolerability and a low recurrence rate.[103]

Education for patients is a key aspect of management. It is important for the patient to be aware that many PIH lesions resolve spontaneously, but slowly. They should also know that adhering with acne therapy and preventing new acne lesions will minimize the potential for PIH. Avoidance of sun exposure plus sun protection should be recommended, along with avoidance of excoriation of any skin lesions. Improving insulin resistance through diet and lifestyle can have a positive impact on both acne and the propensity for PIH. Table IV presents additional recommendations for patient counseling, which might be more or less relevant, depending on the individual being treated.[99]

Medical colleagues should be aware that early acne therapy has a vital role in minimizing PIH, and that PIH is a very bothersome problem for some patients and should not be trivialized. Maintenance therapy can be useful in limiting development of PIH. In some cases, ephelides, lentigines, and melasma-like pigmentation can be mistaken for PIH. Clues that the skin lesion is not caused by PIH include a localization to the temple area, zygomas, and accompanying dermal elastolysis.

Clinical pearls for acne and PIH

- Oftentimes, identifying the patient who requires PIH management involves discussing how bothersome the problem is for the individual person, but the presence of visible PIH merits a discussion with the patient
  - A score of ≥4 on the Visual Analog Scale of 1-10 may be an indicator of need for treatment
- Most patients want to know how long it will take before dark spots resolve
  - For these patients, it is important to emphasize the need for effective treatment of acne, regular use of photoprotection, and avoidance of lesion excoriation
- Cosmeceuticals including antioxidants or exfoliants, chemical peels, intense pulsed light, lasers, and iontophoresis with transexamic gel may be useful although there is a lack of evidence-based studies on these approaches, particularly among dark skin types
- Treating hormonal pathologies can help mitigate underlying factors
- Early treatment with retinoids can diminish the risk of PIH by inhibiting tyrosinase and blocking pigment transfer from melanocytes to keratinocytes

Table IV. Patient counseling for postinflammatory hyperpigmention

Physician action	Counseling/Recommendation
Evaluate use of cosmetic products to lighten skin tone	• Cocoa butter should be avoided due to potential to exacerbate acne • Recommend alternatives such as prescription topical retinoids, azelaic acid, or hydroquinone
Review hair care product use	• Avoid oil-based, heavy pomades • Select silicone-based products
Discuss use of exfoliants, witch hazel, and potentially irritating treatments	• Avoid
Educate about role of sun in pigmentation	• Use sunscreen
Review goals of acne therapy and potential duration of PIH	• Goals are to minimize and prevent new acne lesions and sequelae such as PIH and scarring • While PIH can resolve spontaneously, it is often long-lasting

Reprinted with permission from Gollnick et al.[99]
PIH, Postinflammatory hyperpigmentation.

Acne and scarring

In a recent study of 1942 subjects with acne, 43% had acne scarring.[8] Further, 69% of all patients with scars had mild-to-moderate acne at the time of evaluation.[8] These data agree with older published studies by Layton et al and Tan et al, and highlight the importance of this acne sequela.[83,85] Acne-associated scarring often includes an emotional toll, with depression, anxiety, poor self-esteem, and social impairment all reported.[104,105] The day-to-day impact of emotional problems from scarring can include lowered academic performance and underemployment.[106] This underscores the need for dermatologists and other clinicians to evaluate and address scarring as well as counsel patients about treatment.[106]

Acne scars have very diverse presentations, with widely varying shapes and sizes. A popular method for classifying atrophic scarring uses scar shapes. This method is appealing, but very subjective and poorly reproducible even among acne researchers.[107] Kang et al reported that classifying atrophic scars based on size (<2 mm, 2-4 mm, and >4 mm) is reproducible both for sequential ratings by the same individual and for agreement between raters.[108] A size-based classification was the basis for a validated tool to assess severity of scars (Facial Acne Severity Evaluation Tool or FASET).[109] This tool incorporates 3 domains: scar counts, overall global assessment of severity, and estimation of involved skin area.[109] It can be used for patients with acne scarring with or without active acne lesions and might have utility assessing the performance of interventions for atrophic acne scars.[109]

Managing acne in scar-prone and scarred patients. Scar treatment is determined by scar type and severity as well as the size of the involved area.[106,110] Management considerations encompass cost, patient expectations and physician goals, and the psychologic effect of the scars.[106] Fife recently suggested practical questions for an acne scar history (Table V).[106] During physical examination, it is useful to shine light on the skin to highlight atrophic areas, use a mirror to help the patient identify areas of concern, assess physical characteristics of the scar (color, depth, width, size), and stretch skin to see if the scar disappears.[106]

A variety of scar treatments are available (Table VI),[106] and often a combination of modalities is superior to a single approach.[110,111] Unfortunately, a rapid, permanent solution that fully eliminates atrophic scars is rarely available.[106] Procedures can be grouped by function into resurfacing, lifting, excisional, and other. Resurfacing approaches depend on injuring the epidermis and superficial dermis and, thereby, stimulating neocollagenesis and epidermal repair. Lifting techniques attempt to match the scar base with the surrounding skin surface, and excisions remove deep, sclerotic, or hypopigmented scars. Many techniques have risks, such as infection, hyperpigmentation, prolonged erythema, or poor healing; these may be exacerbated in darker skin patients.[106]

Clinical pearls for atrophic acne scars

- Mild-to-moderate acne can lead to atrophic scars in a surprising proportion of patients, and it is important to implement effective treatment as quickly as possible
- Inflammation is present in all acne lesions
- Combining treatment modalities can achieve best results
- Pigmentary changes (red or brown) are not scarring
- Treating acne is easier than treating scarring
- It is useful to have a baseline idea of which patients might be more prone to scars

Keloids and hypertrophic scars. Keloids and hypertrophic scars form when abnormal wound healing leads to excess tissue, usually in dark-skinned individuals.[112] There is sustained and intense localized inflammation at the site, with recruitment of inflammatory cells and fibroblasts, formation of new blood vessels, and deposition of collagen, which collectively create the scar. Keloids and hypertrophic scars occur in both sexes and across age groups (although rarely in very young or old individuals).[112] They most often first appear during adolescence or pregnancy and tend to affect the lateral face, jawline and neck, and upper torso.[106] Treatment for hypertrophic scars may include intralesional injection of 5-fluorouracil or triamcinolone acetonide, cryotherapy, silicone gel sheeting, pulsed dye laser, fractional laser, surgical excision plus radiation, or triamcinolone acetonide injections.[106] Currently, the best practice known includes cryotherapy followed by tissue injection of triamcinolone in edematous tissue.

Clinical pearls for hypertrophic or keloidal scars

- Adding pulsed dye laser to intralesional steroid injections helps reduce erythema associated with hypertrophic scars and reduces steroid-induced telangiectasias on the face
- Use a silicone sheet after intralesional steroids
- Intralesional bleomycin might be useful
- For disseminated lesions, off-label use of oral pentoxifylline and topical pirfenidone plus steroid injection may be considered
- Avoid trauma and surgical intervention
- There is rarely a quick fix; successful treatment might take multiple treatments and modalities

Acne in women

Efficacy of topical therapy. There is a growing population of women consulting physicians for treatment of acne. There is a clinical perception that acne in women requires systemic treatment, but recent analyses of clinical trials have shown that topical therapy can be efficacious in this group.[31,78,80,113,114] In addition, a recent large-scale study of acne in adults has shown that most patients have an acne presentation that is similar to adolescent acne, with mixed inflammatory and noninflammatory lesions on multiple facial areas (not limited to the mandibular area).[77]

There are data supporting use of retinoids in adult acne, including A/BPO in both 0.1% and 0.3% concentrations,[78] tretinoin 0.04%,[113] and retinaldehyde 0.1%/glycolic acid 6% cream.[115] Among antimicrobial agents, both dapsone and clindamycin/BPO have shown efficacy for acne in women in subgroup analyses and studies.[114,116] These products are not recommended as monotherapy; a topical retinoid should be added to expand pathophysiologic features targeted and achieve best results.[78] Finally, azelaic acid 15% gel has also shown good results in a small study (n = 55) of women with acne.[31] In our judgment, topical therapy with a retinoid and antimicrobial can be a good option for adult female patients and should be given trial. This patient population might also appreciate the beneficial effects of topical retinoids on photoaging.[78]

Table V. Acne scar history

Current acne assessment
- Are you using an acne treatment now?

Patient-specific questions
- What aspect of your skin is most bothersome? (dark spots, acne, wrinkles, other)
- Please identify scars or areas of your face that bother you the most
- How do the scars affect your lifestyle?
- Do you have time constraints due to work or travel?

Questions that could affect the therapeutic regimen
- Have you done anything in the past to treat your scars?
  - If yes, how many sessions, what was the associated down time, how well did the treatment work, and were there any problems healing?
- What do you want to achieve with treatment?
- Did you need isotretinoin to treat your acne? If yes, when was your last dose?
- Does your skin have a tendency to darken after acne lesions, surgery, or other injury?
- Do you have any painful, thick, or itchy scars?

Adapted with permission from Fife.[106]

Hormonal therapy: the secret weapon. Hormonal therapy, including oral contraceptives (OCs), can play an important role in management of acne in women. It is typically used in combination with topical acne therapy, in part because onset of action is relatively slow and results might not be apparent for at least 3 months. OCs for acne include both estrogen and progestin. These agents are as effective as oral antibiotics in reducing acne lesions at 6 months of treatment, and the AAD guidelines assign OCs a grade A recommendation for use.[14,117,118] Female patients with acne who desire contraception or do not intend to become pregnant may be candidates for hormonal therapy. Table VII

Table VI. Interventions for treating facial atrophic acne scars

Resurfacing procedures
- Chemical peels
  - Full face
  - CROSS technique
- Dermabrasion
- Laser resurfacing
  - Ablative
  - Nonablative
  - Fractional (ablative vs nonablative)

Lifting procedures
- Subcision
- Fillers
  - Directly under scars
  - Volumizing
  - Autologous fat transfer
- Punch elevation

Excisional techniques
- Punch excision
- Elliptical excision
- Punch grafting

Other
- Microneedling
- Facelift
- Combination techniques

Reprinted with permission from Fife.[106]
CROSS, Chemical reconstruction of skin scars.

shows contraindications and situations where OCs may be used with caution or special monitoring.[14,119]

OCs vary in formulation, although all combine an estrogen (usually ethinyl estradiol) and a progestin. There are 4 generations of OCs (Table VIII) and efficacy for treating acne seems to be comparable among those studied.[120] Table IX shows the OCs approved by the US FDA for treatment of acne, and Table X shows the AAD recommendations for hormonal agents.[14] Cyproterone acetate and spironolactone are additional agents that might be available, depending on country availability.

It is important for dermatologists to formulate an approach to prescribing OCs for acne. Many women have knowledge, experience, or perceptions about OCs that the dermatologist should know. When counseling, ask the patient about her knowledge of and expectations. For patients new to OC therapy, discuss that acne requires long-term treatment.

Contraceptives other than OCs. The birth control patch (ethinyl estradiol plus norelgestromin) uses a hormonal combination that is similar to OCs and has a beneficial effect on the skin. Compliance is better because of once-weekly administration. The pharmacokinetic profile is different from OCs, and the patch delivers higher steady state concentrations but lower peak concentrations. It is not known whether the increased estrogen exposure increases risk of adverse events. However, the patch is linked to higher failure rates (unintended pregnancies) in patients >198 lb (98 kg) and caution is advised with use in this setting. The patch can be applied to a variety of body sites (abdomen, upper outer arm, upper torso, buttock) on the first day of the patient's menstrual period and once per week for the next 2 weeks (3 total) followed by one patch-free week.[120]

Injectable contraception (medroxyprogesterone acetate) delivers only progestin; this drug might not improve acne but rather exacerbate it. Some implanted birth control methods (intrauterine devices) also do not include estrogen. Some include progestin and might trigger hormone-induced acne flares, which usually diminish after a few months. The intravaginal ring (etonogestrel/ethinyl estradiol) is similar to a combined oral contraceptive and should have similar effects on acne.

Although hormonal therapy can be effective against acne in women, side effects related to the proportion of estrogen and progestin can lead to discontinuation of the therapy (Table XI).[120] For example, women who have nausea, vomiting, bloating, or decreased libido might benefit from a contraceptive with a lower estrogen dose, while those experiencing acne or hirsutism might have too much progestin and would benefit from reducing the progestin content.[120] It is important for clinicians to be aware that many progestins also have an androgenic effect; hormonal therapies involving these agents should be avoided in acne when androgenic clinical effects appear.

Serious adverse effects can occur with systemic hormonal therapy, although they are generally quite safe. OCs are linked to higher incidence of breast cancer; cervical cancer; and cardiovascular problems, including myocardial infarction, stroke, venous thromboembolism (including deep venous thrombosis), and pulmonary embolism. Overall, risks are small and usually can be anticipated by assessment of the woman's health status (presence of cardiovascular risk factors) and estrogen dose. Greater risk is associated with smoking; obesity; family history of coronary artery disease; age ≥35 years; and comorbidities, such as hypertension, diabetes, and hyperlipidemia. These risk factors should be assessed during history taking.[120] Acne flare can occur after discontinuation of OCs or hormonal therapy.

Table VII. World Health Organization recommendations for selecting patients for oral contraceptives therapy

Not recommended	Use with caution or requires special monitoring
Pregnancy	Breastfeeding (6 weeks-6 months postpartum)
Current breast cancer	Postpartum (<21 days)
Breastfeeding <6 weeks postpartum	Age ≥35 years and light smoker (<15 cigarettes per week)
Age ≥35 years and heavy smoker (≥15 cigarettes/day)	History of hypertension (including pregnancy) or if monitoring is not feasible
Hypertension: systolic ≥160 mm Hg or diastolic ≥100 mg Hg	Hypertension: systolic 140-159 mm Hg or diastolic 90-99 mm Hg or controlled and monitored
Diabetes with end organ damage	Headaches: migraine without focal neurologic symptoms <35 years
Diabetes >20 years duration	Known hyperlipidemia should be assessed (eg, type and severity)
History of or current deep vein thrombosis or pulmonary embolism	History of breast cancer ≥5 years of no disease
Major surgery with prolonged immobilization	Biliary tract disease
Ischemic heart disease (history or current); valvular heart disease with complications	Mild compensated cirrhosis
History of cerebrovascular accident	History of cholestasis related to oral contraceptive use
Headaches (eg, migraine with focal neurologic symptoms at any age, or without aura if ≥35 years)	Concurrent use of drugs that affect liver enzymes
Active viral hepatitis	
Severe decompensated cirrhosis	
Liver tumor (benign or malignant)	

Reprinted from Zaenglein et al[14] with permission from Elsevier.

Table VIII. Generations of oral contraceptives

Generation	Progestin	Estrogenic	Progestational	Androgenic
First	Norethindrone	++	++	++
	Ethynodiol diacetate	++	+++	+
	Norgestrel	−−	+++	+++
	Norethindrone acetate	++	++	++
Second	Levonorgestrel	−−	++++	++++
Third	Norgestimate	−−	++	++
	Desogestrel	+/−−	++++	++
Fourth	Drospirenone	−−	+/−−	−−

Reprinted with permission from Rice et al, [120] *US Pharmacist*.
+ indicates low activity, −− indicates no activity.

Clinical pearls for acne in women

- When taking history, ask about prior experience with any hormonal or birth control therapies; women often have preformed opinions that should be taken into account when designing a regimen
- Work with the patient to evaluate existing skin care and makeup regimen, substituting products as needed to minimize potential negative impact on acne and maximize positive impact
- When possible, use simple regimens that dovetail with the patient's existing daily routines
- Be willing to consider a management approach for women that is similar to what is used for adolescents, but also be alert that hormonal approaches can add significant benefit

Table IX. Overview chart of oral contraceptives approved for treatment of acne in women

Generic drug name	Brand
Norgestimate-ethinyl estradiol	Ortho Tri-Cyclen
Norethindrone acetate-ethinyl estradiol	Estrostep Fe
Drospirenone-ethinyl estradiol	Yaz

Many more contraceptives exist, and there is variability among countries.

CONCLUSIONS

Acne is a widespread disease and dermatologists should take the lead in not only implementing best practices but also in educating other health care professionals about treatment strategies. New and improved treatments are continuously being developed, and the role of various agents is changing. In

Table X. American Academy of Dermatology recommendations for hormonal agents

Estrogen-containing combined oral contraceptives are effective and recommended in treatment of inflammatory acne in female patients.
Spironolactone is useful in treatment of acne in select females patients.
Oral corticosteroid therapy can be of temporary benefit in patients with severe inflammatory acne while starting standard acne treatment.
In patients who have well-documented adrenal hyperandrogenism, low-dose oral corticosteroids are recommended.

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Table XI. Estrogen and progestin dose-related adverse effects

Estrogen	Progestin
Excess	Excess
✓ Nausea, vomiting	✓ Acne
✓ Bloating, edema	✓ Increased appetite, weight gain
✓ Hypertension	✓ Fatigue
✓ Migraine headache	✓ Hypertension
✓ Breast tenderness	✓ Depression
✓ Decreased libido	✓ Hirsutism
✓ Weight gain	✓ Vaginal yeast infections
✓ Heavy menstrual flow	
✓ Leukorrhea	
Deficiency	Deficiency
✓ Early cycle spotting/ breakthrough bleeding	✓ Late breakthrough bleeding
✓ Amenorrhea	✓ Amenorrhea
✓ Vaginal dryness	✓ Heavy menstrual flow

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the era of antimicrobial resistance, there should be diminished use of antibiotics. Because of their preventive action in acne by targeting microcomedones, retinoids should form the cornerstone of therapy. The variety of formulations and concentrations of available agents provides great flexibility for clinicians to individualize therapeutic regimens for patients, while achieving good results.

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Supplemental Table I. Results of Delphi voting and statements that reached consensus with round 1 and round 2

Statement	Strongly agree, %	Agree, %	Consensus	Disagree, %	Strongly disagree, %	Unable to answer, %
Round 1						
Topical antibiotics should no longer be used as monotherapy for acne treatment.	73.5	17.7	91.2%	5.9	2.9	0
BPO is the preferred topical antimicrobial agent due to the current climate of antimicrobial stewardship.	70.6	23.5	94.1%	2.9	2.9	0
Antibiotic resistance should be an essential consideration when selecting therapy for acne.	65.6	25.0	90.6%	9.4	0	0
Systemic antibiotics should be prescribed for a limited duration (up to 4 months) in moderate-to-severe acne.	51.5	39.4	90.9%	6.1	3.0	0
Systemic antibiotics should not be used as monotherapy.	70.6	17.7	88.3%	5.9	5.9	0
Topical retinoid plus benzoyl peroxide is first-line therapy for most patients with inflammatory or comedonal acne.	58.8	32.4	91.2%	5.9	0	2.9
Retinoids have a unique class action in reducing formation of acne precursor lesions and limiting development of new lesions.	72.7	27.3	100%	0	0	0
Topical retinoid side effects resolve within 2-3 weeks in most patients and can be managed by use of a gentle cleanser and moisturizers.	55.9	41.2	97.1%	2.9	0	0
Azelaic acid 20% cream or 15% gel is a second-line therapy for acne vulgaris.	24.2	45.5	No	18.2	6.1	6.1
Azelaic acid is a useful acne treatment in pregnant women.	32.4	50.0	82.4%	8.8	2.9	5.9
Azelaic acid is useful for acne patients who have PIH.	36.4	51.5	87.9%	9.1	3.0	0
Cumulative dose is an important consideration in determining duration of oral isotretinoin therapy.	26.5	23.5	No	41.2	5.9	2.9
Acne flares with oral isotretinoin can be minimized by initiating therapy with a low dose ($\leq$0.5 mg/kg).	50.0	37.5	87.5%	9.4	0	3.1
Higher cumulative doses of oral isotretinoin are needed for severe truncal acne.	33.3	33.3	No	27.3	0	6.1
Oral isotretinoin should be first-line therapy for severe nodulocystic acne.	75.0	21.9	96.9%	3.1	0	0
Most patients with acne should receive maintenance therapy with a topical retinoid $\pm$ BPO.	36.4	54.6	91.0%	9.1	0	0
Topical antibiotics should not be used as acne maintenance therapy.	84.9	9.1	95.0%	3.0	3.0	0
At present, laser, IPL, or PDT should not be considered as first-line treatment for inflammatory acne.	69.7	24.2	93.9%	6.1	0	0
A minority of women with acne have lesions localized only to the lower face.	15.2	69.7	84.9%	15.2	0	0
Topical retinoids $\pm$ BPO are important components in therapy of adult acne.	48.5	48.5	97.0%	3.0	0	0
Early and effective treatment is important to minimize potential risk for acne scarring.	81.8	18.2	100%	0	0	0
Round 2						
Azelaic acid 20% cream or 15% gel could be considered a second-line therapy for acne vulgaris.	15.2	69.7	84.9%	9.1	6.1	0
Cumulative dose should no longer be considered the primary consideration in determining duration of oral isotretinoin therapy in patients with severe acne.	28.1	31.3	No	28.1	9.4	3.1
Oral isotretinoin treatment should proceed until full clearance of acne. Additional studies are needed to define a total cumulative dose that maintains remission.	56.3	28.1	84.4%	12.5	0	3.1
Higher cumulative doses of oral isotretinoin are needed for severe truncal acne.	35.5	25.8	No	25.8	3.2	9.7
A higher concentration of topical retinoid (such as adapalene 0.3%) with BPO should be considered for patients with higher risk of scarring.	32.3	41.9	No	6.4	0	19.4

BPO, Benzoyl peroxide; *IPL*, intense pulsed laser; *PDT*, photodynamic therapy; PIH, postinflammatory hyperpigmentation.