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PRACTICAL MANAGEMENT OF ACNE FOR CLINICIANS An International Consensus from the Global Alliance to Improve Outcomes in Acne

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[Title page]

PRACTICAL MANAGEMENT OF ACNE FOR CLINICIANS

An International Consensus from the Global Alliance to Improve Outcomes in Acne

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INTRODUCTION

Acne is a chronic inflammatory skin disease that is estimated to affect the 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 the majority of cases, and the trunk may also be affected in up to 61% of patients.³⁻⁶ Acne lesions can progress to scars and/or post-inflammatory hyperpigmentation (PIH) both of which can be very 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: as an example, 33 United States 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 during medical undergraduate training; however, all medical schools teach Dermato-Venereology. Scientific advances are continually improving 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 two 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 (CILAD), the Indian Society Dermatology, Venereology and Leprosy, the Australasian Dermatological Society 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 treatment options, but do not strongly advise the clinician about creating a practical treatment approach. Clinical consensus recommendations utilize expert opinion/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 in 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 in acne, and special topics of interest (acne in women, post-inflammatory 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 judgement 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, USA, United Kingdom, Venezuela). All were members of the Global Alliance international and regional groups.

An online questionnaire was developed by a selected sub-group of the Global Alliance Steering Committee and 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 at least 75% of the dermatologists who participated in the panel. The statements and voting results are presented as a supplemental table.

CONSENSUS RECOMMENDATIONS

Assessing Acne Severity: Impact of New Topical Medications

There is no standardized acne grading/classifying system; however, acne is often categorized by an overall gestalt as mild, moderate, and severe in guidelines/ recommendations as well as by clinicians treating patients.^{2, 3, 14} These categories are useful to help guide selection of therapy, but rely on 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 to 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 may be good candidates for strong topical medications versus those who are best suited by early institution of oral isotretinoin.^{19, 20} Many practicing dermatologists perceive the term “severe” to refer primarily to nodular and/or conglobate acne, which is appropriately treated with oral isotretinoin.² Now, however, there may 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 a four-point classification that may 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
- 4 Severe nodular acne, conglobate acne

Similarly, the IGA scale recommended by the US FDA considers quality of lesions as well as quantity (Table 1).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/conglobate acne, and have illustrated the differences in Figure 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 EU 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 non-inflammatory lesions, and up to 2 nodules on the face).²⁰ A/BPO 0.3% was efficacious across the population and well tolerated; further, in the severe population A/BPO 0.3% showed significantly greater efficacy in achieving success (clear/almost clear or a 3-grade improvement) and reductions in lesion counts vs vehicle ($P=.029$ for success and $P<.001$ for lesion counts).²⁰ A representative subject is shown in Figure 3.²⁰ Stein Gold and colleagues concluded that A/BPO 0.3% could have an important systemic antibiotic-sparing role for patients with moderate and severe inflammatory acne, particularly since 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 II studies with novel agents have also been published recently in moderate to severe acne. A 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 in moderate to severe acne.²¹ A phase II 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 non-inflammatory 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 mean inflammatory lesions of 33.5 at baseline. In a phase II study, minocycline foam was superior to vehicle in reducing both inflammatory and non-inflammatory 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 III studies were completed with the minocycline foam, with one reporting statistically significant superior results to vehicle but the other one failing to demonstrate significant difference in IGA (one of two co-primary endpoints). An additional phase III study is planned.²³ However, it should be noted that monotherapy with a topical antibiotic is advised against in current guidelines and recommendations due to the potential for antimicrobial resistance.^{2, 3, 14} For additional details, see Zouboulis, et al, *Anti-Acne Drugs in Phase 1 and 2 Trials*.²⁴

Gold et al reported a post-hoc subgroup analysis of a phase III study of clindamycin 1.2% /BPO 3.75% in moderate to severe acne ($n=498$) that specifically compared results in subjects with severe ($n=86$) acne versus moderate ($n=412$).^{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 subjects rated clear or almost clear at study endpoint was 30.6% in the severe group compared with 35.7% in the moderate group. The authors comment 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 subjects with severe acne were more likely to be female and younger compared with the moderate group which may have impacted results.²⁵

Combination Regimens for Severe Acne. Combination regimens with newer agents may also provide alternatives to oral isotretinoin or at least a step before. In a comparative study, Tan et al reported that A/BPO 0.1% plus doxycycline 200 mg per day was a non-inferior alternative to oral isotretinoin.¹⁹ The combination regimen had a significantly earlier onset of action in reducing acne lesions at week 2 compared with isotretinoin. 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 non-comparative study, Stein Gold 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 IV, 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 12, 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 the majority of patients with inflammatory and/or comedonal acne, 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 in 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 due to normal skin turnover.³⁰ This is the reason 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 equivalent to 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% while 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 CD1d expression.^{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 superior efficacy vs adapalene 0.1% across all measures, and both dosages were similarly tolerated.^{37, 38} In the phase III 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 those 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 EDF and AAD guidelines,^{3, 14} a study of prescribing practices from 2012 to 2014 reported that dermatologists prescribed retinoids for just 58.8% of almost 75,000 acne patients while non-dermatologists 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, the majority of topical retinoid side effects resolve within 2-3 weeks and can be managed by use of moisturizers.² Table 2 presents strategies that can be employed to minimize the likelihood of irritation.^{2, 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, since 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 traditional infections (eg, months rather than days).⁵² Thus, antibiotic use in acne exerts considerable selective pressure on microbes, including pathogenic and non-pathogenic organisms. However, some studies could not confirm the resistance problem following topical antibiotic treatment.⁵³ There are currently multiple non-antibiotic therapies for acne with proven efficacy and it is reasonable for clinicians to develop antibiotic-sparing approaches for this disease.⁴⁵ Sub-antimicrobial 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 very 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 as compared to BPO in mono- 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 3 to 4 months.^{2, 45-47} In our clinical experience, the top three 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.

[box]

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

[end box]

Consensus Recommendation 3

Oral isotretinoin should be first-line therapy for very severe (cystic/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 traditionally has been recommended in a dose of 0.5-1.0 mg/kg administered over a period of approximately 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 feel 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 1,453 patients treated with oral isotretinoin showed that 22.4% required a second course of isotretinoin (follow-up ≥ 12 months, range 12 months to 5 years), and that neither daily nor cumulative doses influenced relapse as long as treatment was continued for at least 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 may be achieved with lower cumulative doses. A rule of thumb may be to treat until full clearance plus one 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 in 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 and there are no clear statistical data supporting a different dose.

Consensus Recommendation 5

Acne flare with oral isotretinoin can be minimized by initiating therapy with 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 US 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 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 may be appealing for patients.⁷¹ Azelaic acid may be a maintenance option for adult females 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 category B in pregnancy. While 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 had cleared in 31% of subjects and was slight or mild in 69% of subjects.⁷⁵

Consensus Recommendation 8

At present, devices including laser, intense pulsed light (IPL), and photodynamic therapy (PDT) should not be considered first line treatment for inflammatory acne.

While laser and light devices may have some benefit in the setting of acne, well-designed studies evaluating their effectiveness versus traditional 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 PDT 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 or older 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 adult females with acne have a sub-type of acne that is difficult to treat and primarily driven by hormonal abnormalities. However, a large-scale international study showed that 89% of adult women have 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 adult women.⁸⁰ Long-term maintenance may be particularly important in the adult female population, since frequent recurrences are common. In addition, dry and/or sensitive skin may be more common in this group, supporting use of strategies to minimize irritation from topical treatments (every other day initiation, short contact therapies, use of moisturizers and gentle, non-soap cleansers).^{81, 82}

Oral therapies, including limited-duration antibiotics, isotretinoin, and hormonal treatments, can be useful in 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 development of atrophic

acne scars, including severe acne (but 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 may 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 than milder forms of acne that demonstrate delayed inflammatory response.⁸⁶ A tool to assess risk of acne scarring was recently developed after review of literature and clinical trials along with a modified Delphi process involving an expert panel (Fig 6).⁸⁷ It 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 2/3 of the population, and had a sensitivity of 82% plus 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=0.036).⁸⁸ To the best of our knowledge, this is the first study to confirm the traditional 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 may 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 may 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

Figure 7 shows an algorithm that summarizes a treatment approach based upon 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 adult women. In addition, since there are some aspects of these topics that are not 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). Post-inflammatory hyperpigmentation (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 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 while 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 (n=324 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 one year or longer.⁷

PIH affects individuals of both genders and all ages.⁹³ Clinically, PIH may 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.

Managing 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/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 3 reviews pathways that are targets of medical intervention in pigmentation disorders.⁹⁸ Chemical peels, laser and other light therapies may also be used for PIH; however, these methods may 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 since the reduction in time to resolution may 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.^{9,93,97,99,100} 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.⁹⁹ These products may be used during acne therapy but are more commonly prescribed after resolution of acne lesions.⁹⁹ Cosmeceuticals with skin lightening ingredients may be a cost-effective approach and azelaic acid may also be helpful.¹⁰¹

Results may be improved by combining modalities; for example, salicylic acid peel plus a topical retinoid improved PIH more than either treatment alone in a study of 45 patients, with good tolerability and a low recurrence rate.¹⁰²

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 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 may have a positive impact on both acne and the propensity for PIH. Table 4 presents additional recommendations for patient counseling, which may be more or less relevant depending on the individual being treated.

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 may be useful in limiting development of PIH. In some cases, ephelides, lentigines, and melasma-like pigmentation may be mistaken for PIH. Clues to this are a predilection for temples and zygomas and accompanying dermal elastosis.

[box]

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 or higher on a VAS 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, IPL, lasers, and iontophoresis with tranexamic 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 may diminish the risk of PIH by inhibiting tyrosinase and blocking pigment transfer from melanocytes to keratinocytes

[End box]

Acne and Scarring

In a recent study of 1,942 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.^{103, 104} The day-to-day impact of emotional problems from scarring may include lowered academic performance and under-employment.¹⁰⁵

This underscores the need for dermatologists and other clinicians to evaluate and address scarring as well as counsel patients about treatment.¹⁰⁵

Acne scars have very diverse presentations, with widely varying shapes and sizes. A popular method to classify atrophic scarring uses scar shapes. This is appealing, but very subjective and poorly reproducible even among acne researchers.¹⁰⁶ 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.¹⁰⁷ A size-based classification was the basis for a validated tool to assess severity of scars (Facial Acne Severity Evaluation Tool or FASET).¹⁰⁸ This tool, shown in Figure 9, incorporates three domains: scar counts, overall global assessment of severity, and estimation of involved skin area.¹⁰⁸ It can be used for patients with acne scarring with or without active acne lesions and may have utility in assessing the performance of interventions for atrophic acne scars.¹⁰⁸

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.¹⁰⁵ Management considerations encompass cost, patient expectations and physician goals, and the psychological impact of the scars.¹⁰⁵ Fife recently suggested practical questions for an acne scar history (Table 5). 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.¹⁰⁵

A variety of scar treatments are available (Table 6) and often a combination of modalities is superior to a single approach.^{109, 110} Unfortunately, a rapid, permanent solution that fully eliminates atrophic scars is rarely available.¹⁰⁵ Procedures can be grouped by function into resurfacing, lifting, excisional, and other. Resurfacing approaches depend on injuring the epidermis and superficial dermis and thereby stimulate neocollagenesis and epidermal repair. Lifting techniques attempt to match the scar base with the surrounding skin surface while 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.¹⁰⁵

[box]

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 may 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 may be more prone to scars (family history, and other factors presented in tool above)

[End box]

Keloids and Hypertrophic Scars

Keloids and hypertrophic scars form when abnormal wound healing leads to excess tissue, usually in dark-skinned individuals.¹¹¹ 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 genders and across age groups (although rarely in very young or old individuals).¹¹¹ Frequently they first appear during adolescence or pregnancy, and tend to affect the lateral face, jawline/neck, and upper torso.¹⁰⁵ Treatment for hypertrophic scars may include intralesional injection of 5-fluorouracil or triamcinolone acetonide, cryotherapy, silicone gel sheeting, pulsed dye laser, fractional laser, or surgical excision plus radiation or triamcinolone acetonide injections.¹⁰⁵ Currently, best practice known includes cryotherapy followed by tissue injection of triamcinolone in edematous tissue.

[Box]

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 may 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 may take multiple treatments and modalities

[End box]

Acne in Adult Females

Efficacy of Topical Therapy

There is a growing population of adult females consulting physicians for treatment of acne.

There is a clinical perception that adult female acne requires systemic treatment, but recent analyses of clinical trials have shown that topical therapy can be efficacious in this group.^{78, 80,}

¹¹²⁻¹¹⁵ In addition, a recent large-scale study of adult acne has shown that the majority of patients have an acne presentation that is similar to adolescent acne, with mixed inflammatory and non-inflammatory 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,¹¹⁴ tretinoin 0.04%,¹¹² and retinaldehyde 0.1%/glycolic acid 6% cream.¹¹⁶ Among antimicrobial agents, both dapson and clindamycin/BPO have shown efficacy in adult female acne in subgroup analyses and studies.^{113, 117} These products are not recommended as monotherapy; a topical retinoid should be added to expand pathophysiologic features targeted and achieve best results.¹¹⁴ Finally, azelaic acid 15% gel has also shown good results in a small study (n=55) of adult women with acne.¹¹⁵ 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 may also appreciate the beneficial effects of topical retinoids on photoaging.¹¹⁴

Hormonal Therapy: The Secret Weapon

Hormonal therapy, including oral contraceptives, 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 may not be apparent for at least 3 months. Oral contraceptives (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, 118, 119}

Female patients with acne who desire contraception or do not intend to become pregnant may be candidates for hormonal therapy. Table 7 shows contraindications and situations where OCs may be used with caution or special monitoring.^{14, 120}

OCs vary in formulation, although all combine an estrogen (usually ethinyl estradiol [EE]) and a progestin. There are four generations of OCs (Table 8) and efficacy in acne seems to be comparable among those studied.¹²¹ Table 9 shows the OCs approved by the US FDA for treatment of acne and Table 10 shows the American Academy of Dermatology recommendations for hormonal agents. Cyproterone acetate and spironolactone are additional agents that may be available, depending on country availability.

It is important for dermatologists to formulate an approach to prescribing OCs for acne. Many women have knowledge or experience or perceptions about OCs that the dermatologist should

know. When counseling, ask the patient about her knowledge of and expectations. For patient 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 skin. Compliance is better due to 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, or buttock) on the first day of the patient's menstrual period and once per week for the next two weeks (3 total) followed by one patch-free week.¹²¹

Injectable contraception (medroxyprogesterone acetate) delivers only progestin; it may not improve acne but may rather exacerbate it. Some implanted birth control methods (intrauterine devices) also do not include estrogen. Some include progestin and may 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 adult female acne, side effects can cause discontinuation which are related to the proportion of estrogen and progestin (Table 11). As

examples, adult women who have nausea/vomiting, bloating, of decreased libido may benefit from a contraceptive with a lower estrogen dose while those experiencing acne or hirsutism may have too much progestin and would benefit from reducing the progestin content.¹²¹ 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. COCs 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 or older, and comorbidities such as hypertension, diabetes, and hyperlipidemia. These risk factors should be assessed during history taking.¹²¹ Acne flare may occur after discontinuation of OCs or hormonal therapy.

[Box]

Clinical Pearls for Adult Female Acne

- When taking history, ask about prior experience with any hormonal or birth control therapies. Women often have pre-formed opinions that should be taken into account when designing 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 adult women that is similar to what is used for adolescents, but also be alert that hormonal approaches can add significant benefit

[End box]

CONCLUSIONS

Acne is a widespread disease and dermatologists should take the lead in not only implementing best practices but also in educating other healthcare professionals about treatment strategies. New and improved treatments are continuously being developed, and the role of various agents is changing. In 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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Figure 1. Acne vulgaris. Illustration of differences in lesions that could impact overall assessment of acne severity but not lesion counts. Photos courtesy of DermQuest.com.

Figure 2. Acne vulgaris. Illustrative photos of severe inflammatory acne, largely without nodules (A) and very severe acne with cysts (B). Photos courtesy of DermQuest.com.

Figure 3. Acne vulgaris. Subject with severe acne treated with ADA-BPO at baseline, week 1, and week 12. From Stein Gold with permission.²⁰

Figure 4. Acne vulgaris. Action of retinoids on microcomedones (acne precursor lesions) and visible lesions. Note the lag time after cessation of retinoid therapy before visible lesions begin to reappear. From Thielitz et al.

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

Figure 6. Atrophic acne scar risk assessment tool.⁸⁷

Figure 7. Practical approach to acne management.

Figure 8. Spectrum of PIH. Photos courtesy of DermQuest.com, Dr CL Goh, and Dr R Kubba.

Figure 9. Facial acne severity evaluation tool (FASET).

1322 **Table 1.** IGA scale recommended by the US FDA, which is not intended to cover candidates for
 1323 oral isotretinoin therapy.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

Table 2. Strategies to minimize the likelihood of tolerability problems associated with induction of topical retinoid therapy. Adapted from Leyden et al.³²

- 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 over-cleansing
- Select most tolerable retinoid formulation for climate and season
 - Creams and lotions may be best for dry or sensitive skin, gels or foam for more oily skin (although newer aqueous gels may 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, non-comedogenic moisturizer
 - Use a short contact method for first 2 - 4 weeks (apply retinoid to full face for 30 - 60 minutes then wash off)

1349 **Table 3.** Actions of agents used to treat PIH. From Gollnick et al.¹²²

Agent	Mechanism
Retinoids	Increase keratinocyte turnover and remove pigmentation, tyrosinase inhibition, reduced 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 and inhibit second messengers that stimulate melanogenesis, interact with copper at active site of tyrosinase
Niacinamide	Interrupts melanosome transfer from melanocyte to keratinocyte
Alpha Hydroxyacids, 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

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Table 4. Patient Counseling for PIH. From Gollnick et al.¹²²

Physician Action	Counseling/Recommendation
Evaluate use of cosmetic products to lighten skin tone	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Avoid oil-based, heavy pomades • Select silicone-based products
Discuss use of exfoliants, witch hazel, and potentially irritating treatments	<ul style="list-style-type: none"> • Avoid
Educate about role of sun in pigmentation	<ul style="list-style-type: none"> • Use sunscreen
Review goals of acne therapy and potential duration of PIH	<ul style="list-style-type: none"> • Goals are to minimize and/or prevent new acne lesions and sequelae such as PIH and scarring • While PIH can resolve spontaneously, it is often long-lasting

Table 5. Acne scar history. Adapted from Fife.¹⁰⁵

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?

Table 6. Interventions for treating facial atrophic acne scars. Reprinted with permission from Fife.¹⁰⁵

Resurfacing Procedures

- Chemical peels
 - Full face
 - CROSS technique
- Dermabrasion
- Laser resurfacing
 - Ablative
 - Non-ablative
 - Fractional (ablative vs. non-ablative)

Lifting procedures

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

Excisional techniques

- Punch excision
- Elliptical excision
- Punch grafting

Other

- 1397 • Microneedling
- 1398 • Facelift
- 1399 • Combination techniques
- 1400
- 1401

Table 7. Selecting patients for OC therapy: WHO recommendations. From Zaenglein et al and Arrington et al.^{14, 120}

Not recommended	Use with caution or requires special monitoring
<ul style="list-style-type: none"> ✓ Pregnancy ✓ Current breast cancer ✓ Breastfeeding <6 weeks postpartum ✓ Age ≥ 35 years and heavy smoker (≥ 15 cigarettes per day) ✓ Hypertension: systolic ≥ 160 mm Hg and/or diastolic ≥ 100 mm Hg ✓ Diabetes with end organ damage ✓ Diabetes >20 years duration ✓ History of or current deep vein thrombosis or pulmonary embolism ✓ Major surgery with prolonged immobilization ✓ Ischemic heart disease (history or current); valvular heart disease with complications ✓ History of cerebrovascular accident ✓ Headaches (eg, migraine with focal 	<ul style="list-style-type: none"> ✓ Breastfeeding (6 weeks – 6 months postpartum) ✓ Postpartum (<21 days) ✓ Age ≥ 35 years and light smoker (<15 cigarettes) ✓ History of hypertension (including pregnancy) or if monitoring is not feasible ✓ Hypertension: systolic 140-159 mm Hg and/or diastolic 90-99 mm Hg or controlled and monitored ✓ Headaches: migraine without focal neurologic symptoms <35 years ✓ Known hyperlipidemia should be assessed (eg, type and severity) ✓ History of breast cancer ≥ 5 years of no disease ✓ Biliary tract disease

neurologic symptoms at any age, or without aura if ≥ 35 years)	✓ Mild compensated cirrhosis
✓ Active viral hepatitis	✓ History of cholestasis related to OC use
✓ Severe decompensated cirrhosis	✓ Concurrent use of drugs that affect liver enzymes
✓ Liver tumor (benign or malignant)	

1405

1406 **Table 8.** Generations of OCs. From Rice et al.¹²¹

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

1407 +/-- indicates low to no activity, == indicates no activity.

1408

1409

1410 **Table 9.** Overview chart of oral contraceptives approved for treatment of acne in adult women

1411 (many more contraceptives exist, and there is variability among countries)

	Brand
Norgestimate-ethinyl estradiol	Ortho Tri-Cyclen
Norethindrone acetate-ethinyl estradiol	Estrostep Fe
Drospirinone-ethinyl estradiol	Yaz

1412

1413

1414 **Table 10.** AAD Recommendations for hormonal agents. From Zaenglein et al.

1415 Estrogen-containing combined OCs are effective and recommended in treatment of inflammatory

1416 acne in females

1417 Spironolactone is useful in treatment of acne in select females

1418 Oral corticosteroid therapy can be of temporary benefit in patients with severe inflammatory

1419 acne while starting standard acne treatment

1420 In patients who have well documented adrenal hyperandrogenism, low-dose oral corticosteroids

1421 are recommended

1422

1423 **Table 11.** Estrogen and progestin dose-related adverse effects. From Rice et al.¹²¹

Estrogen	Progestin
<p>Excess</p> <ul style="list-style-type: none"> ✓ Nausea/vomiting ✓ Bloating/edema ✓ Hypertension ✓ Migraine headache ✓ Breast tenderness ✓ Decreased libido ✓ Weight gain ✓ Heavy menstrual flow ✓ Leukorrhea <p>Deficiency</p> <ul style="list-style-type: none"> ✓ Early cycle spotting/breakthrough bleeding ✓ Amenorrhea ✓ Vaginal dryness 	<p>Excess</p> <ul style="list-style-type: none"> ✓ Acne ✓ Increased appetite/weight gain ✓ Fatigue ✓ Hypertension ✓ Depression ✓ Hirsutism ✓ Vaginal yeast infections <p>Deficiency</p> <ul style="list-style-type: none"> ✓ Late breakthrough bleeding ✓ Amenorrhea ✓ Heavy menstrual flow

1424

1425

1426 **Supplemental Table.** Results of Delphi voting and statements that reached consensus with
 1427 round 1 and round 2.

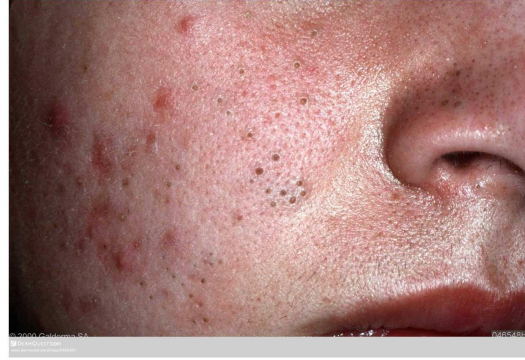
Statement (Round 1)	Strongly agree	Agree	Consensus	Disagree	Strongly disagree	Unable to answer
Topical antibiotics should no longer be used as monotherapy for acne treatment	73.5%	17.7%	91.2%	5.9%	2.9%	0
Benzoyl peroxide (BPO) is the preferred topical antimicrobial agent due to the current climate of 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 the majority of patients with inflammatory and/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 the majority of patients and can be managed by use of a gentle cleanser and	55.9%	41.2%	97.1%	2.9%	0	0

moisturizers						
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 in acne patients who have post-inflammatory hyperpigmentation (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 (0.5mg/kg or less)	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 of 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	48.5%	48.5%	97.0%	3.0%	0	0

are important components in therapy of adult acne						
Early and effective treatment is important to minimize potential risk for acne scarring	81.8%	18.2%	100%	0	0	0
Statement (Round 2)	Strongly agree	Agree	Consensus	Disagree	Strongly disagree	Unable to answer
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%

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ACCEPTED

Severe (can include some nodules)



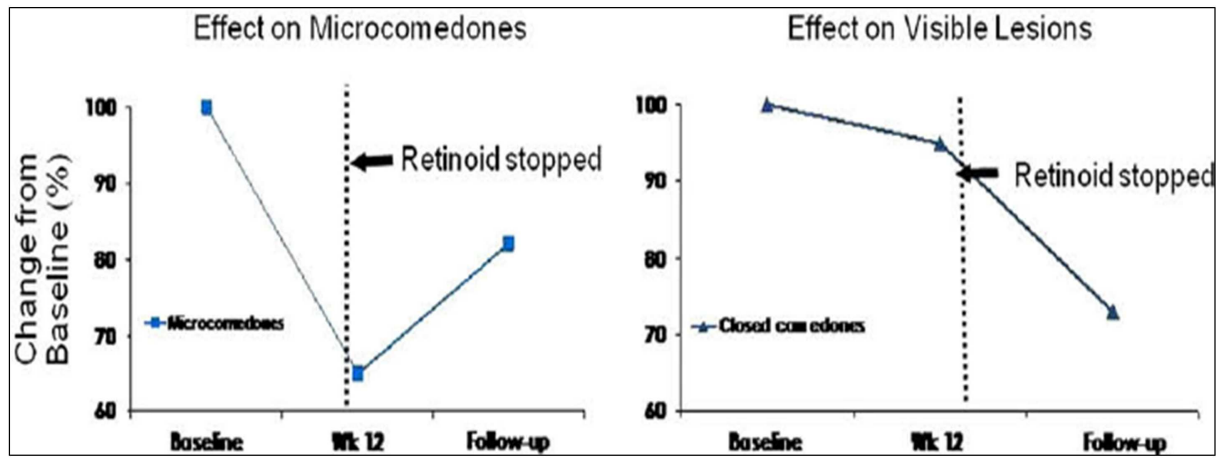
ACCEPTED

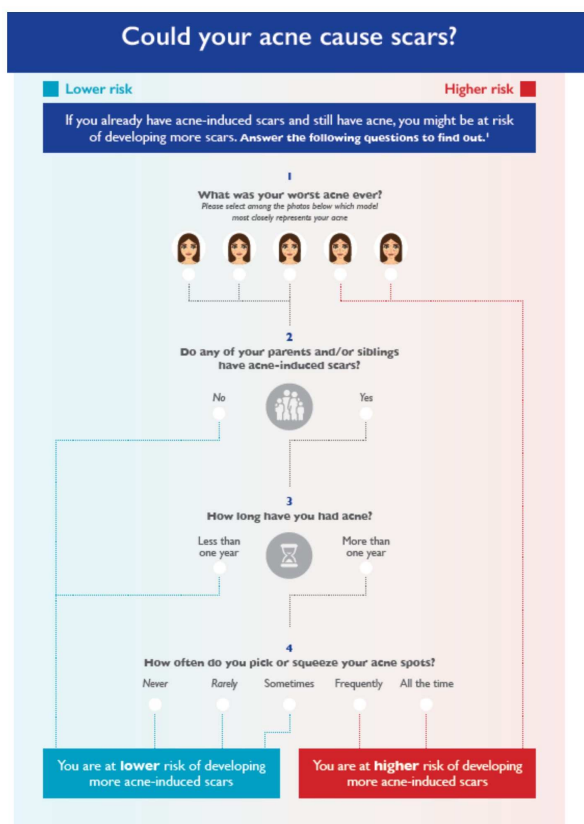
Very Severe (Cystic/conglobate)

ACCEPTED










ACCEPTED





Managing Acne

						
MILD		MODERATE		SEVERE		
Comedonal	Papular/pustular	Papular/pustular	Moderately Severe - Severe			
Topical Retinoid or Fixed combination with retinoid > BPO or Azelaic Acid Salicylic Acid	Fixed Combination or BPO or Topical Retinoid or Azelaic Acid	Fixed Combination Preferred ± Hormonal therapy and/or Oral Antibiotic*	Fixed Combination + Oral Antibiotic Preferred Or + Oral Isotretinoin Or + Oral Hormonal Therapy			

If patient responds, treat until clear or almost clear

Maintenance Therapy: Topical Retinoid or Retinoid/BPO Combination

* Particularly if the trunk is involved

Actions if Response is Poor

- ✓ Check non-drug related reasons (seborrhea, stress and diet, Malassezia furfur, G- bacteria, comedogenic skin care products, endocrine profile)
- ✓ Check drug-related reasons (adapt vehicle to skin type and environmental conditions, change topical agent, mechanically remove comedones, change from monotherapy to fixed-combination, change to higher concentration of topical). For females, check type of contraception.
- ✓ Probe patient's adherence (application technique, missed doses, tolerability)
- ✓ Ask about adverse events

Managing Very Severe Acne



NODULAR and/or CONGLOBATE ACNE

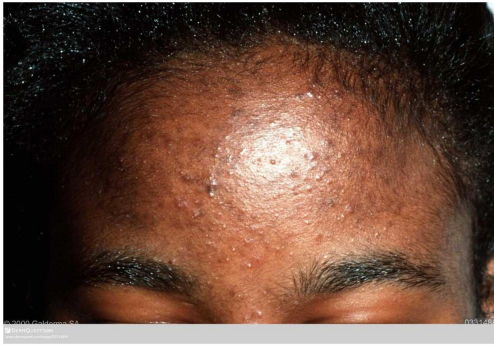
Males	Females
Oral Isotretinoin or Fixed Combination + Oral Antibiotics	Oral Isotretinoin + anti-androgenic hormonal therapy or Fixed Combination + Oral Antibiotics (consider high dose) and/or oral anti-androgenic hormonal therapy

If patient responds, treat until clear or almost clear

Maintenance Therapy: Topical Retinoid or Retinoid/BPO Combination

If Response is Poor

- ✓ Check non-drug related reasons (seborrhea, stress and diet, Malassezia furfur, G- bacteria, comedogenic skin care products, endocrine profile) and exclude hidradenitis suppurativa/acne inversa
- ✓ Check drug-related reasons (type/dose antibiotic, microbial resistance, spot treatment, consider adding prednisone, for females check use of anti-androgenic agents)
- ✓ Consider intralesional injections or mechanical removal of macrocomedones
- ✓ Probe patient's adherence (application technique, missed doses, tolerability)
- ✓ Ask about adverse events



ACCEPTED

FACIAL ACNE SCAR ASSESSMENT TOOL (FASAT)

Section 1

Scar Global Assessment = _____

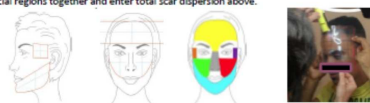
Please assess the overall severity of atrophic acne scars using the following scale.

Category	Score	Global Assessment Description
Clear	0	None, no visible atrophic scars from acne
Almost clear	1	Few small scattered atrophic scars visible at 20-50 cm
Mild	2	Easily recognizable, (at 20-50 cm) less than half the face is involved, some small atrophic scars
Moderate	3	Many small atrophic scars, and in addition no more than 3 large scars (>4mm), up to 75% of the face is involved
Severe	4	Multiple small and large atrophic scars (>4mm), more than 75% of the face is involved

Section 2

Estimate of Scar Dispersion = _____ % of face overall

Using facial grid and anatomical areas defined in the graphic, estimate scar dispersion. Place grid in front of face, and count boxes occupied by scar in each facial region. If a scar overlaps two boxes, count the box with majority of scar. Estimate percentage by dividing total number of boxes for region/number of affected boxes (eg, 4 boxes containing scars in grid with 20 squares = 20%). Add percentages from all facial regions together and enter total scar dispersion above.



Section 3

Scar Counts by Facial Region

Recommended: use 2-mm and 4-mm biopsy punch to evaluate size of scars.

2 - 4 mm scars					
Forehead	R Temple	L Temple	R Cheek	L Cheek	Mandible
> 4 mm scars					
Forehead	R Temple	L Temple	R Cheek	L Cheek	Mandible