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Clinical Evidence. Practical Advice

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Management of Adult Moderate-to-Severe Atopic Dermatitis: A Practical Guide for Primary Care

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Introduction

Atopic dermatitis (AD) is a chronic, relapsing, pruritic, inflammatory condition involving the skin which can have a significant impact on the quality of life (QoL).[1,2] Although many patients may be controlled with topical therapy, a subset of those affected will require systemic therapy to control their disease.[3] There are currently no approved systemic therapies in North America for the long-term management of moderate-to-severe atopic dermatitis and many treatments are currently being used off-label. This article will guide the family practitioner on how to manage adults with moderate-to-severe AD and when to refer for specialist management.

Abbreviations: AD – atopic dermatitis; ADHD – attention deficit hyperactivity disorder; BSA – body surface area; HPA – hypothalamic-pituitary-adrenal, HTN – hypertension; IL – interleukin; PGA – Physician's Global Assessment; QoL – quality of life; TCI – topical calcineurin inhibitors; TCS – topical corticosteroids; Th2 – T helper cell type 2; TPMT – thiopurine methyltransferase

Background

- Atopic dermatitis is a common chronic inflammatory disease in both children and adults.
- In developed countries, it is a common skin disorder, affecting up to 20% of children and 1% to 3% of adults.[4]
- Approximately 10% of adults are not controlled with topical therapy alone and require systemic therapy for disease control.[3]
- Many immunosuppressants are used off-label to control this disease. Cyclosporine is approved for use in AD only in Europe and Japan.[5,6]
- The pathogenesis of AD is thought to be due to a defect in the skin barrier primarily through abnormal filaggrin and alterations of the innate and acquired immune system, with interleukin (IL) 4 and 13 as key players.[7]
- Increased knowledge of the immunopathogenesis of AD has allowed for the development of new, targeted therapies.[8]

The Burden of AD

- Up to two thirds of patients with AD also suffer from other atopic comorbidities including asthma, rhinitis and food allergies.[9-11]
- A recent epidemiologic study from Germany showed that in addition to atopic comorbidities, patients with AD have a two-fold increased risk of developing ADHD.[11]
- In one Phase 2b study, 86% of patients reported daily pruritus and 55% reported that itch disturbed their sleep 5-7 nights per week.[12]
- AD has a significant impact on patients and their families: itch, sleep disturbance, anxiety and depression can lead to a reduced QoL and stress on the family.[13]
- Risk factors for depression in patients with AD include an increasing severity of AD, female gender and increasing age. In addition to depression, there is also an increased risk of suicidality in this population and therefore, patients should be screened appropriately.[13]
- In a large US study, (2013 National Health and Wellness Survey:N=75,000), patients with AD reported overall lost work productivity of 30% compared to 16% in those workers without AD; an even greater loss of work productivity was noted when moderate-to-severe patients were compared to those with mild AD, 37% versus 23%, respectively.[14]

ALSO IN THIS ISSUE: **The New Canadian Guideline for Acne Treatment** *(page 5)*

AD Management

- Non-prescription therapies are often used to help control the disease: moisturizers and emollients should be the cornerstone of any AD regimen.[15,16]
- Controlling itch is also key for management as frequent scratching may put the patient at risk for infection.
- Dilute bleach baths can be helpful for patients who suffer from frequent bacterial infections due to their anti-staphylococcal activity, when used in conjunction with intranasal mupirocin. To prepare a bleach bath see Tip #1.[15,17]
- Wet wrap therapy can also be an effective treatment to manage flares. This involves applying a wetted layer of gauze where TCS or TCI have been applied to the skin, and then cover with a second, outer dry layer of gauze. Wet wrap therapy provides more rapid improvement as it will increase medication penetration and provide a barrier to scratching.[18]

Tip #1: Dilute bleach baths at a concentration of 0.005% – 0.009% can help reduce colonization and recurrent infections in patients with AD.[15,17]

How to prepare a bleach bath

- ¼ cup of bleach in a half tub of water to ½ cup bleach in a full bath tub of water
- Repeat 2 times per week

Apply emollient after the bath to maintain the skin barrier and prevent dryness. Also add concomitant intranasal mupirocin.

Topical Treatment and Phototherapy

- The gold standard of topical therapy is treatment with TCS and/or TCI.[15,16]
- Both TCS and TCI can be used twice daily as needed for acute flares, or as maintenance therapy with a scheduled reduced frequency of application, such as 2-3 days per week.[15]
- Topical antihistamines and topical antimicrobials are not recommended for use in AD due to lack of efficacy and risk of contact dermatitis.[15]
- If available, phototherapy can be used in both the acute situation for management of flares, and as maintenance therapy for refractory or chronic disease; attention should be paid to any concomitant photosensitizing medications and underlying skin cancer risk.[19]

Tip #2: Topical or systemic antihistamines are NOT recommended for the routine care of patients with AD.

Candidates for systemic therapy have

- Moderate-to-severe atopic dermatitis
- Body surface area involvement ≥ 10%
- Areas with significant burden: involvement of face, hands or genitals
- Significant impact on QoL
- Ongoing pruritus
- Failed an adequate trial of TCS or TCI
- Failed phototherapy or cannot access it

Patient Selection for Systemic Therapy

- Patients with moderate-to-severe AD (PGA score ≥ 3) should be considered for systemic therapy when they have the following:
  - At least 10% body surface area (BSA) involvement
  - Ongoing significant impairment in QoL
  - Ongoing pruritus
  - Disease is not controlled with TCS or TCI or topical therapy is not appropriate
  - Treatment failure with phototherapy or phototherapy is not accessible
- Topical therapy is not appropriate if there is a history of adverse effects from TCS such as atrophy, telangiectasia and striae.[15]
- TCS are not appropriate if there is a need for application to large areas with a risk of absorption and hypothalamic-pituitary-adrenal (HPA) axis suppression.[15]
- TCI therapy can cause transient burning and stinging with application that may not be tolerated by some patients and, therefore, not considered an appropriate therapy.
- Special situations where systemic therapy may be considered appropriate include involvement of areas such as the face, hands or genitals, or when AD has a significant impact on a patient's daily functioning due to lack of sleep, fatigue, intractable pruritus or significant psychological distress.[19,20]

Physician Global Assessment (PGA)

0 – clear
1 – almost clear
2 – mild
3 – moderate
4 – severe
5 – very severe

Systemic Therapy

- Antihistamines are not recommended; antihistamines used for the sedating effects have little to no impact on itch and may lead to disturbed sleep, so these are not typically recommended for regular use.[15,19]
- Many immunosuppressants are used off label; the most commonly prescribed are cyclosporine, methotrexate, azathioprine and mycophenolate mofetil.[3]
- Evidence supporting use of these agents is lacking due to methodological limitations in most trials, small numbers and short duration of therapy.[3,21]
- The best evidence available supports the use of cyclosporine as first-line therapy for short-term use (Table 1).[3]
- Systemic therapy is often limited by intolerance to common side effects (nausea, vomiting, headache) or by potential end-organ toxicity and sequelae of immunosuppression.[21]
- Routine monitoring of these agents for adverse events is required.[19]
- Oral corticosteroids should be considered as a rescue intervention for severe exacerbations and are not a suitable treatment option for the ongoing management of patients with AD.[19]

Tip #3: Avoid the use of systemic corticosteroids in the management of AD unless required as a rescue or salvage therapy of acute severe exacerbations of disease.

Systemic Agents on the Horizon

- Due to an increased understanding of the pathogenesis of AD, several targeted therapies are being developed.[21] Monoclonal antibodies are among them, as they can provide reduced toxicity and improved efficacy compared to oral systemic agents that may have unintended effects and end organ toxicity.[8]
- A number of small molecule targets and monoclonal antibodies which target Th2 cytokines such as IL-4, IL-5, IL-13 and IL-31, or their receptors, are in development.[8]
- Dupilumab, a human monoclonal antibody against the receptor for IL-4 and IL-13 is the first agent to have demonstrated safety and efficacy in phase 3 trials.[21,22]
- Dupilumab is furthest along in development and poised to be the first commercially available biologic for AD.
- Tralokinumab and lebrikizumab, which target IL-13, mepolizumab which targets IL-5, and nemolizumab which targets the IL-31 receptor, are also in earlier stages of development.[7]

Treatment	Dosing	Duration of Treatment	Side Effects	Overall Recommendation
Cyclosporine	3-6 mg/kg/day; divided into BID dosing	**Maximum use:** 1-2 years **Minimum use:** N/A	Nausea, headache, paresthesia, renal impairment, HTN, sequelae of chronic immunosuppression	**First-line** short-term treatment option for moderate-to-severe AD due to highest quality of evidence to date for oral therapy.
Azathioprine	1-3 mg/kg/day; ideal dose is determined by TPMT activity	**Maximum:** There is no official recommendation **Minimum:** 12 weeks to see benefit	Common: nausea, vomiting, gastrointestinal symptoms (bloating, anorexia, cramping), headache, hypersensitivity reactions and elevated liver enzymes	**Second-line** treatment option for moderate-to-severe AD due to moderate-quality evidence for short- and long-term use (24 weeks).
Methotrexate	Single weekly dose: 7.5-25 mg/week Folic acid: 1 mg/day (except on methotrexate day)	**Maximum:** Based on toxicity **Minimum:** Clinical improvement as early as 4 weeks	Nausea, elevated liver enzymes, pancytopenia, pulmonary toxicity	**Third-line** treatment for adults with severe AD due to moderate quality evidence for short- and long-term use (24 weeks).
Oral Corticosteroids	0.75-1 mg/kg per day	**Maximum:** 3 weeks **Minimum:** 3 days	Diabetes, hypertension, gastric ulcers, osteoporosis, glaucoma, opportunistic infections and Cushing syndrome	**Not recommended for routine use.** May be used in short-term (up to 1 week) for acute flares in exceptional and severe cases of AD as salvage therapy only.

Table 1. Non-approved systemic therapies for AD [3,21]
BID – twice a day; HTN – hypertension; TPMT – thiopurine methyltransferase

Next Steps

- When your patient presents with ongoing difficulties managing AD, it is important to review their current treatment regimen and rule out other diagnoses, such as contact dermatitis.[23]
- Encourage regular and generous use of emollients.
- Discuss adherence to the application of topical medications; TCS and TCI should be applied twice daily when there is an acute flare, and when controlled, applied on a schedule of 2-3 times weekly for maintenance, to prolong the flare-free period.[15,16]
- During flares, consider wet wrap therapy to improve the efficacy of the applied topical agents, TCS and TCI, and reduce scratching.[18]
- If available and convenient, consider phototherapy for widespread acute or chronic disease.[19]
- For patients experiencing frequent skin infections, consider dilute bleach baths with intranasal mupirocin to reduce Staphylococcal colonization and infection.[17]
- Assess the patient for sleep loss, pruritus, and the impact on QoL and consider screening for depression, anxiety and suicidality.[13]
- If the disease cannot be controlled by these measures, the patient should be managed with systemic medication such as cyclosporine, azathioprine or methotrexate.[3,21]
- For physicians not familiar with prescribing immunosuppressive medications, a referral to a dermatologist should be made for the systemic management of AD.

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The New Canadian Guideline for Acne Treatment

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Introduction

Acne knows no borders. It is estimated that up to 85% of the world population between the ages of 12 and 24 is afflicted by acne at some point. [1,2] The disease often persists beyond young adulthood, despite treatment.[3-5] Acne can adversely affect quality of life[6–13] and may lead to emotional distress and physical scarring.[14,15] The clinical presentation of acne (Figure 1) varies from primarily comedonal to mixed comedonal and inflammatory acne.[16]

Background

In 2000, Canadian doctors proposed guidelines for the treatment of acne. Guidelines are considered to be effective in improving clinical decisions. They can be perceived, by specialists and generalists alike, as useful in evaluating a clinical situation and in weighing various options for treatment. Physicians will be particularly reassured if the suggested guidelines are supported by scientific evidence. Guidelines that are not validated scientifically, however, can pose a risk. Similarly, guidelines that are not regularly updated in light of new findings can become misleading.[17] This new Canadian clinical guideline for the treatment of acne was developed taking into account new data published up to March 2015, as well as expert opinion and clinical experience.

The recommendations in the Guideline are intended to assist Canadian health care professionals in the diagnosis of acne vulgaris; provide updates and information on the pathogenesis of acne; outline methods for evaluating acne severity; provide evidence-based guidance on treatments for acne vulgaris; and recommend treatments for acne according to severity.

Recommendations are made for three categories of acne severity:

1. **Comedonal acne**, which consists of small white papules (closed comedones) or grey–white papules (open comedones) resulting from complete or partial ductal occlusion, respectively, and sebum accretion (Figure 1A);
2. **Mild-to-moderate papulopustular acne**, which is characterized by mostly superficial inflammatory lesions (Figures 1B and 1C); and
3. **Severe acne**, consisting of deep pustules and/or nodules, which may be painful, may extend over large areas and can lead to tissue destruction (Figures 1D and 1E). A subtype of severe acne, conglobate acne, is rare and consists of extensive inflammatory papules, nodules and cysts and can lead to disfiguring scars. [16]

- A clinical algorithm for the most highly recommended treatments for comedonal, mild-to-moderate papulopustular and severe acne is presented in Figure 2.
- For a complete listing of recommendations and more detailed discussion of the evidence, please see the full guideline at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140665/-/DC1).

The Guideline Panel

Members of the guideline panel were selected by the steering committee of Drs. Charles Lynde and Jerry Tan. They were chosen according to their acknowledged expertise in acne, as indicated by peer-reviewed publications and reputation. Dermatologists from across Canada were included for geographic representation; Yuka Asai, Akerke Baibergenova, Maha Dutil, Shannon Humphrey, Peter Hull, Charles Lynde, Yves Poulin, Neil H. Shear, Jerry Tan, John Toole, and Catherine Zip. Two experts with dual credentials in epidemiology and dermatology (Y.A. and A.B.) served as methodologic experts and performed literature evaluation and grading. The guideline was developed in accordance with the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument[18] and the ADAPTE framework[19] for guideline adaptation.

Before submitting the guideline for publication, the committee sought input from the following stakeholders: a discussion group of university students representing patients (University of Windsor, Windsor, Ontario), the Canadian Dermatology Association, the Canadian Skin Patient Alliance, the Canadian Dermatology Nurses Association, the Canadian Pharmacists Association, family physicians, pediatricians and authors of the ES3 guidelines. Pilot testing was also undertaken in the clinic of one guideline panel member. Development of this guideline was funded by Valeant, Galderma, Cipher, Bayer and Mylan. Funding sponsors had no role in the development or approval of the guideline. The identity of sponsors was not disclosed to the guideline panel members until the time of submission of the draft for publication. None of the panel members received honoraria for their contributions to this work.

Recommendations

Comedonal Acne

- Topical therapies are recommended for first-line treatment of comedonal acne, namely retinoids, benzoyl peroxide and fixed-dose combinations of retinoids with benzoyl peroxide or clindamycin.
- Those with dry or sensitive skin may prefer creams or lotions, which tend to be less drying, whereas those with oily skin may prefer a less greasy formula, such as a gel. Convenience and treatment adherence may be enhanced with combination therapy or once-daily application instead of separate therapies or routines requiring multiple applications. Many acne medications may not be covered by provincial plans; in these cases, it may be particularly important to consider cost.
- For comedonal acne the committee recommends topical retinoids or benzoyl peroxide (medium-strength recommendation; confidence in effect estimate is moderate).
- Benzoyl peroxide in 2.5% and 5% gels was superior to vehicle for comedonal acne in eight grade A studies (level 1 evidence), with reduction in comedonal lesions of 21-52%, compared with increases of 11-42% for vehicle.[16]
- Benzoyl peroxide products have a fast onset of action[20] and are available over the counter, thus, they should be considered for initial treatment.
- Topical retinoids (tretinoin, adapalene and tazarotene) are also recommended for initial treatment. Despite one grade B study showing superiority, tazarotene is likely equivalent to adapalene (four grade B studies), but may result in more irritation.[16]
- For comedonal acne, the committee recommends the fixed-dose combinations adapalene–benzoyl peroxide and clindamycin–benzoyl peroxide (medium-strength recommendation; confidence in effect estimate is moderate).
- Fixed-dose combinations can be used as initial treatment. For treatment of comedones, the combination of adapalene 0.1% and benzoyl peroxide 2.5% was equivalent or superior to adapalene.
- If a fixed-dose combination is inadequately effective after a two-to-three-month trial, the addition of a topical retinoid

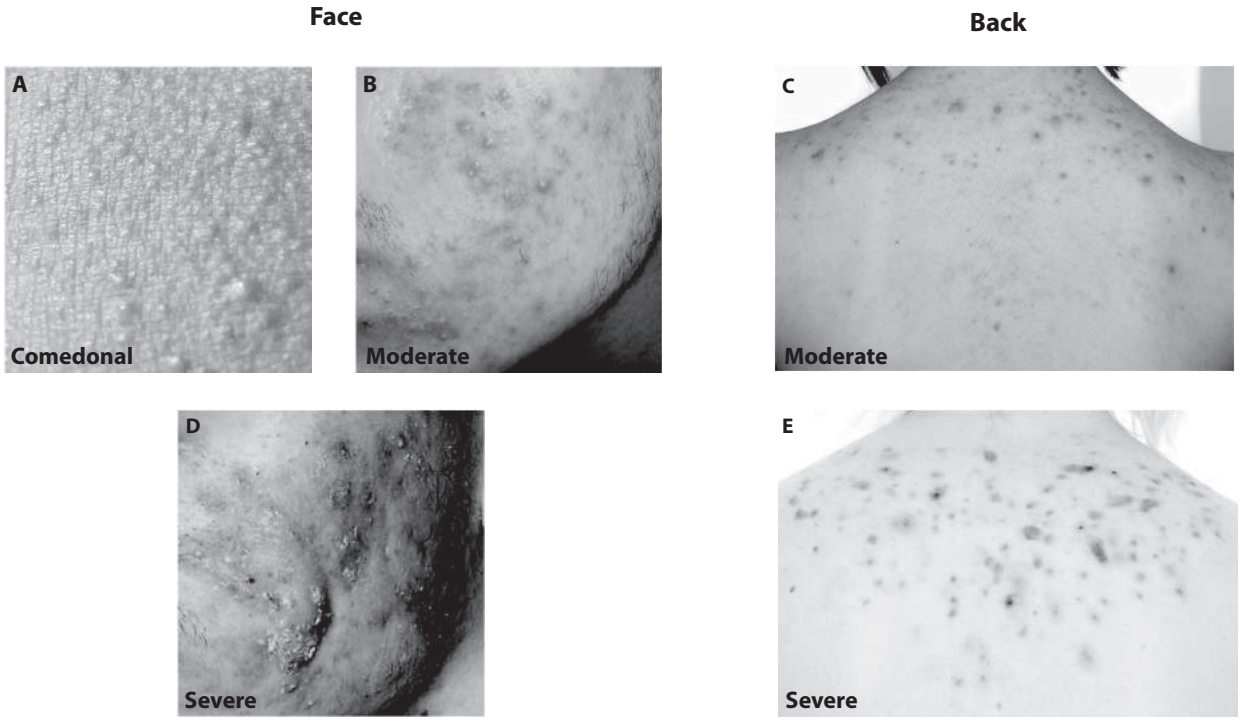

Figure 1. Representative photos of acne categories. (A) Comedonal facial acne. (B) Moderate inflammatory facial acne. (C) Moderate inflammatory acne of theback. (D) Severe facial acne. (E) Severe inflammatory acne of the back.

(especially tazarotene, adapalene or tretinoin) should be considered, if no retinoid is in use.
- If response to a topical retinoid or benzoyl peroxide alone or to a fixed-dose combination is inadequate, use of fixed-dose clindamycin–tretinoin or a combined oral contraceptive agent may be considered.

Localized Mild-to-Moderate Papulopustular Acne

- The presentation of mild-to-moderate papulopustular acne can vary with regard to inflammation and lesion distribution.
- Topical therapies are a reasonable intervention for patients with mild papulopustular acne. Given the strong evidence for use of topical retinoids, benzoyl peroxide and fixed-dose combinations to treat inflammatory lesions, all three options are strongly recommended for this type of acne.
- The treatment choice would be determined by factors such as type of vehicle, ease of use and cost. For more extensive papulopustular acne or areas not amenable to topical therapy (such as the back), systemic therapies, in addition to the topical therapies, are recommended.
- For benzoyl peroxide in concentrations ranging from 2.5-10%, in gel, cream and lotion formulations, 11 grade A studies and three grade B studies showed superiority over placebo, with reductions in inflammatory lesion counts of 19-62%, compared with increases of 12-46% for vehicle (level 1 evidence).[16] The onset of action of benzoyl peroxide may be superior to that of tretinoin.[20]
- Topical retinoids (adapalene, tazarotene and tretinoin) can also be used as first-line agents. Several fixed-dose combinations can be used as initial treatment for localized mild-to-moderate papulopustular acne.
- The combination of clindamycin 1% and benzoyl peroxide 5% gel was superior to vehicle and the individual components in four grade A studies, with lesion count reductions of 48-63%, while changes with vehicle ranged from an increase of 3% to a reduction of 30% (level 1 evidence).[16]
- The fixed-dose combination of adapalene 0.1% and benzoyl peroxide 2.5% gel was superior to vehicle and the individual components in reduction of inflammatory lesion counts in all three grade A studies, with reduction of 62-70%, compared with 34-46% for vehicle (level 1 evidence).[16]

Extensive Moderate Papulopustular Acne

- Although tetracycline and minocycline have been shown to be superior to placebo in reducing inflammatory acne lesions,[16] use of these agents on their own is discouraged because of concerns about selection of antibiotic-resistant bacteria.
- Other antibiotic classes, including penicillins, macrolides and fluoroquinolones, are also discouraged because they are indicated for use in community-acquired infections, such as pneumonia and urinary tract infections. Furthermore, given that minocycline is associated with an increased risk of drug-induced lupus and hepatitis,[21] tetracycline or doxycycline is preferred.
- The combinations of ethinyl estradiol 20 µg and levonorgestrel 100 µg (level 3 evidence), ethinyl estradiol 20 µg and drospirenone 3 mg (level 1 evidence) and ethinyl estradiol 35 µg and norgestimate 180, 215 or 250 µg (level 2 evidence) have all shown superiority over placebo.
- The committee noted that adjunctive use of topical agents with oral contraceptive agents has been inadequately studied.

Severe Acne

- Isotretinoin is the prescription of choice for severe acne but the practice should be limited to physicians who are trained and experienced in its use, monitoring and appropriate pregnancy-prevention measures.
- For patients unwilling or unable to use oral isotretinoin and those with intolerance, systemic antibiotics in combination with topical benzoyl peroxide, with or without a topical retinoid, may be considered. For women, hormonal therapy with a combined oral contraceptive may also be considered.

Discussion

This document will be updated at a minimum of every five years as required to maintain validity.[22] Updates may be provided sooner to include important new developments, such as evidence on benefits and harms of existing interventions, development of new treatments or changes in available treatments.

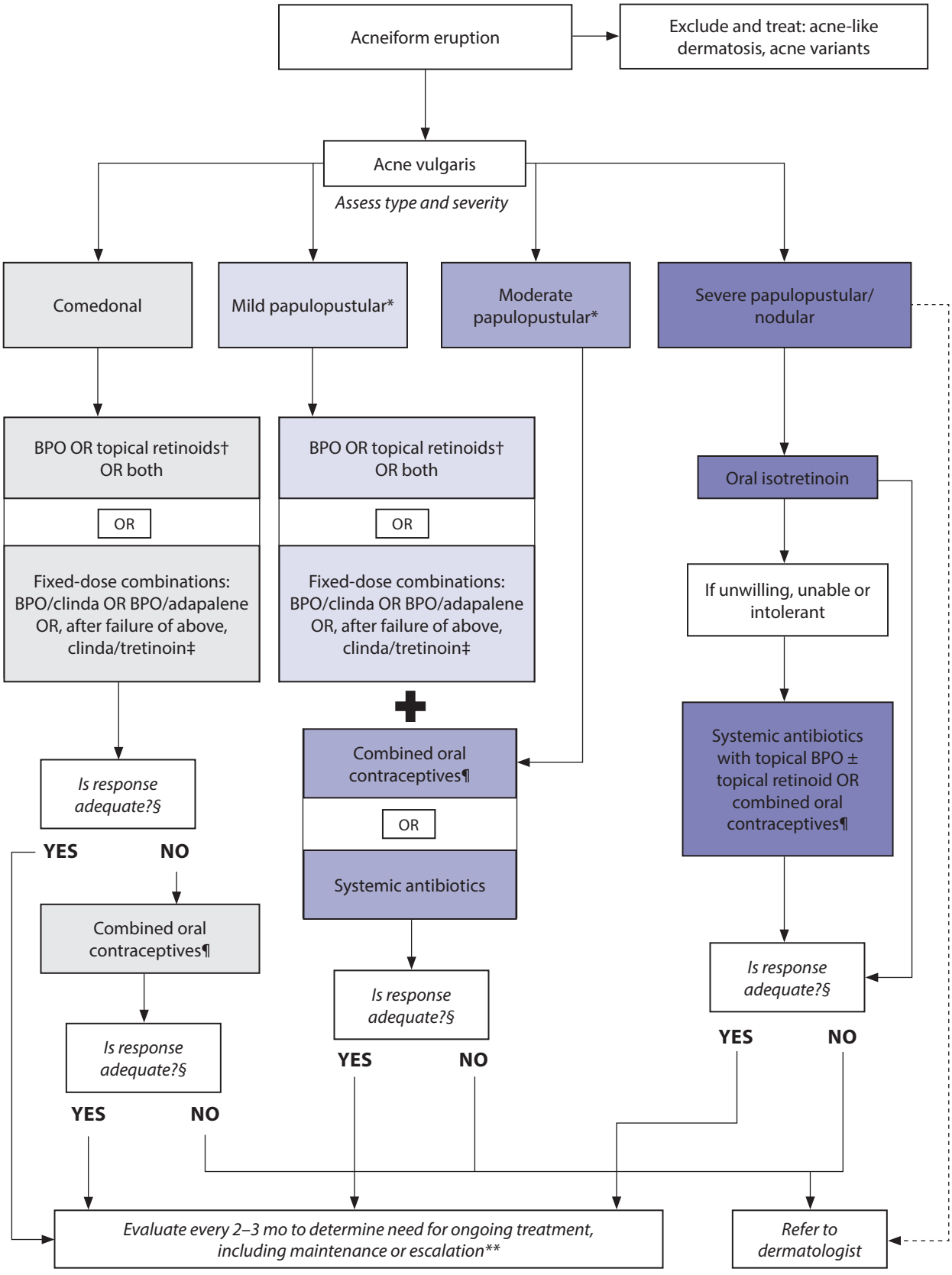

Figure 2. Clinical treatment algorithm for acne. A complete list of recommendations is available in the full guideline (Appendix 4, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140665/-/DC1).

BPO = benzoyl peroxide, clinda = clindamycin, dashed line = optional path. *Blue light and oral zinc may be considered for mild-to-moderate papulopustular acne (low strength of recommendation). †Best evidence is for adapalene and tazarotene. ‡Lower-quality evidence available for clindamycin–tretinoin gel. §Evaluate after 2–3 months. ¶For women only. **Evaluate monthly for isotretinoin.

Uncertainties in acne treatment encompass both general and specific factors. General factors include absence of information related to efficacy in truncal acne (the outcome measure for almost all studies being facial acne); lack of certainty about a minimal effect size that is relevant for patients; lack of a current, universally applied standard for global severity grading of acne; and lack of knowledge about the potential role of adjunctive support, including psychotherapy, for patients with impaired quality of life. Specific factors include uncertainty about durations of use of oral antibiotics to minimize development of antibiotic-resistant bacteria (at cutaneous and extracutaneous sites) and lack of higher levels of evidence for often-used treatments, including fixed-dose erythromycin–tretinoin, spironolactone and isotretinoin.

Conclusion

Dermatology continues to be challenged by acne and its sequelae. It is to be hoped that clear guidelines such as these along with new therapies and improved conversation between specialists and family doctors will hasten the march of progress and prevent the mental and physical scarring caused by this often debilitating condition. Guidelines such as these are not perfect nor are they error proof. The community must commit itself to testing these guidelines and to formulating new guidelines that will take into account continuing developments in clinical trials that now have more standardized outcome measures.

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CosmeticProcedureGuide.ca	DermatologyCare.ca	EczemaGuide.ca	FungalGuide.ca
GenitalWarts.ca	HandEczema.ca	HerpesGuide.ca	Lice.ca
MildCleanser.ca	MohsSurgery.ca	PsoriasisGuide.ca	PsoriaticArthritisGuide.ca
RosaceaGuide.ca	SkinCancerGuide.ca	SkinCoverup.com	Sweating.ca
UnwantedFacialHair.ca			

Medical professional sites:

Dermatologists.ca	PASItraining.com	SkinPharmacies.ca	SkinTherapyLetter.com

Social networking sites for patients and health care professionals:

PsoriasisPatients.com	Youtube.com/SkinExpertsTalk

We welcome your feedback. Please email us with your comments and topic suggestions to: info@skintherapyletter.com

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