Appendix 4 (as supplied by the authors): Canadian Clinical Practice Guideline on the Management of Acne (full guideline)

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Appendix to: Asai Y, Baibergenova A, Dutil M, et al. Management of acne: Canadian clinical practice guideline. *CMAJ* 2015. DOI:10.1503/cmaj.140665.

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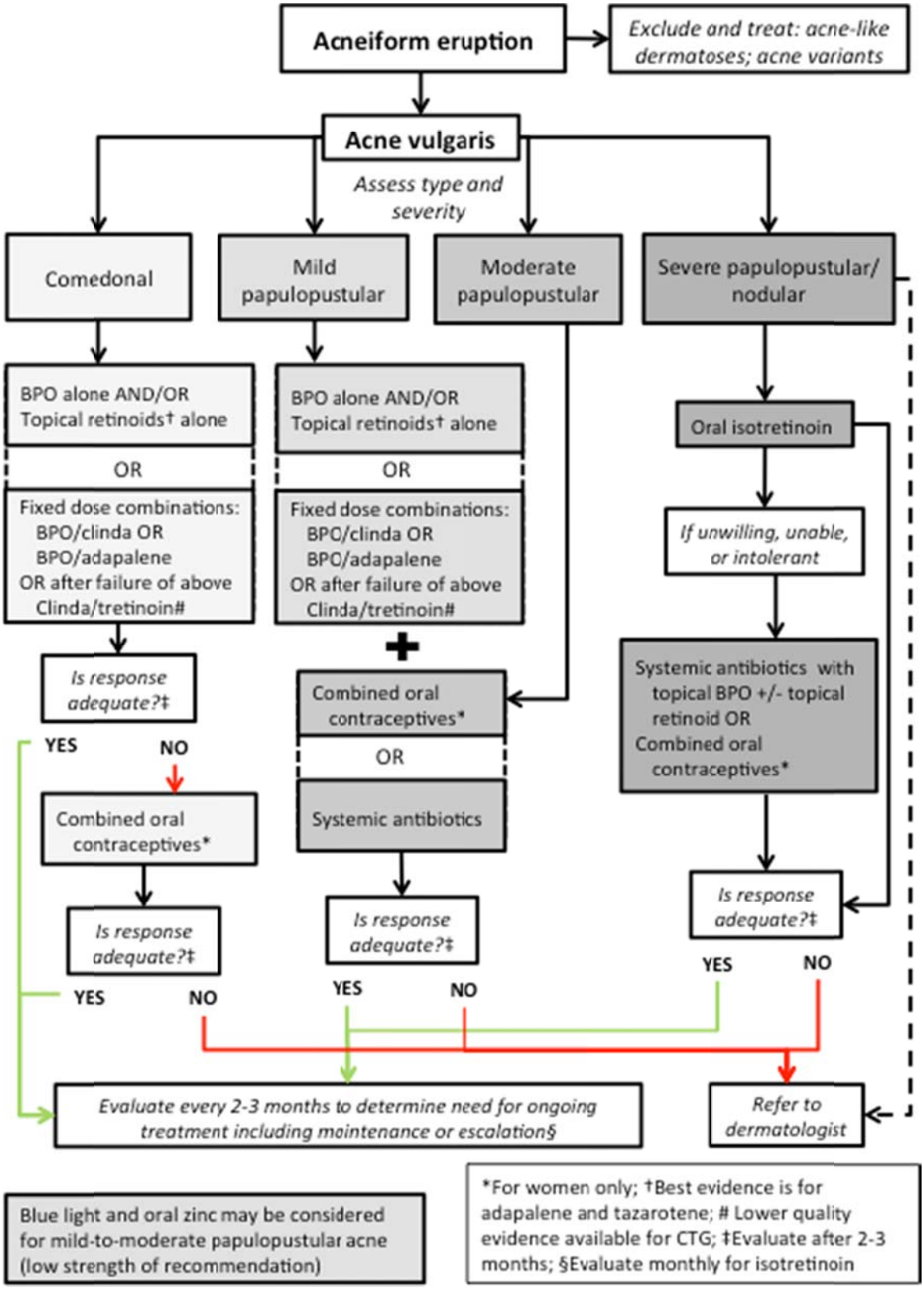

Figure 1 Clinical treatment algorithm for acne For a complete list of recommendations consult Section III and Tables 1, 2, and 3.

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Canadian Acne Clinical Practice Guidelines

I. Introduction

I.1 Is a Clinical Practice Guideline Needed?

The objective of this document is to provide evidence-based acne clinical practice guidelines (CPG) adapted for the Canadian health care system.

The last acne treatment guidelines for Canada were published in 2000[1].

The direct application of British, American, or European guidelines to the Canadian environment would not adequately address the variation in available treatments or the differing circumstances of the healthcare environment. Thus, there was an unmet need for a systematically developed Canadian acne CPG.

I.2 Impact of acne

I.2.a Prevalence and Epidemiology of Acne

Acne is one of the most burdensome global diseases due to its high prevalence and chronicity.[2] Acne is a common condition that affects primarily teenagers and young adults, but it can persist beyond young adulthood.[3-5] It has been estimated to affect almost 85% of those aged 12 to 24 years, 64% of those aged 20 to 29 years, and 43% of those aged 30 to 39.[6] Acne occurs in individuals of all races and ethnicities.[3-5] No Canadian data is available, but the estimated prevalence of acne in the Canadian population is 4.5 million based on extrapolation from the US National Health and Nutrition Examination Survey (NHANES).[7] A survey of Canadian acne patients referred to dermatologists found that 50% had acne for more than 3 years and that many had previously been treated with prescription topicals (68%), oral antibiotics (44%), or other therapies without disease resolution.[8] In that survey, the distribution of severity of facial acne was comedonal in 6%, mild-to-moderate papulopustular in 78%, and severe or extremely severe in 13%.[9] For extrafacial sites, 44% had mild-to-moderate papulopustular and 1% severe or extremely severe acne at chest, while the corresponding figures for the back were 58% and 3%, respectively. These results are likely more severe than those of the general population, as this study investigated individuals referred for specialist care. It would be reasonable to assume that a large majority of patients have a

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milder spectrum of severity and may obtain self-care or are treated by primary health care providers.

I.2.b Grading Acne Severity: Pathophysiology and Psychosocial Impact

In clinical practice, global acne grading (comprising a gestalt of acne severity which includes lesion type, number, extent, distribution and intensity of inflammation) is more likely to be used than counting of individual lesional types of acne. However, despite the presence of 18 global acne grading scales, there is no single global scale that is validated and universally applied for acne severity grading.[10] Nevertheless, there is a trend to convergence of these scales to a global standard developed for regulatory drug approval comprising the following categories: clear/almost clear, mild, moderate, and severe.[11]

For congruence with these commonly accepted categories and with the *European Evidence-based (S3) Guidelines for the Treatment of Acne* (ES3) from which this clinical practice guideline (CPG) is adapted,[12] we have applied the following categories to this Canadian Acne CPG:

1. Comedonal: comprised of small white (closed comedones) or grey/white (open comedones) papules due to complete or partial ductal occlusion, respectively, and sebum accretion;
2. Mild-to-moderate (papulopustular): inflammatory lesions that are mostly superficial with small papules, pustules;
3. Severe (papulopustular and nodular): deeper and larger papules, pustules and/or nodules, which may be painful and extend over large areas.

Acne has been associated with a variety of psychosocial issues such as anxiety, depression, embarrassment, psychosomatic symptoms, suicidal ideation, and social inhibition.[13] The incorporation of such patient reported outcomes in combination with physician-rated acne severity scores can provide a rationale for treatment escalation if psychosocial impact is extensive. At present, clinical grading scales of acne severity do not feature integrated measurements of psychosocial impact and the vast majority of quality of life instruments for acne are lengthy and research-oriented, making them largely impractical for clinical use. Two brief instruments, the four-item Acne-Q_4 and the five-item Cardiff Acne Disability Index (CADI) are shorter and potentially more practical.[14-16] These instruments may provide patients with a means to express the impact of their acne on psychosocial domains that are otherwise not apparent to clinicians without direct inquiry.

I.2.c Sources of Care

There are multiple potential sources of care for those with acne, including self-care from public domains such as the internet and over the counter products. In Canada, medical sources of care include nurse practitioners, pharmacists (in some Canadian provinces, pharmacists can prescribe treatment for acne) and physicians (pediatricians, general practitioners, obstetrician/gynecologists, internists, endocrinologists, and dermatologists). Delivery of dermatological care in Canada is a challenge due to the size of the country, dispersion of the population, and a relative undersupply of dermatologists who are localized disproportionally in larger urban centers. Furthermore, despite a universal health care system in Canada, availability of medications and dermatologic care may differ by province and those in lower socioeconomic groups have been shown to be significantly less likely to access dermatological care for acne management, emphasizing the importance of other health care sources for acne management.[17] This document will attempt to address the needs of this diverse group of care providers.

I.3 Overall Objectives

The overall objectives of this Canadian Acne CPG are to:

- Assist Canadian health care providers in diagnosis of acne vulgaris including investigations where appropriate
- Provide updated information on the pathogenesis of acne
- Outline methods for evaluating acne severity
- Recommend treatment for acne based on severity
- Provide evidence-based guidance on treatment for acne vulgaris

These objectives will be addressed with treatments available in Canada and within the context of the Canadian healthcare system. Expected goals of these guidelines are the efficient and effective diagnosis and treatment of acne vulgaris in the affected population. This includes improved patient outcomes through successful management of active acne and possible mitigation of sequelae, such as scarring, dyspigmentation, and adverse psychosocial impact.

The intended audience for this CPG are health care providers for Canadian acne patients, specifically nurses, pharmacists, family physicians, pediatricians, obstetricians/gynecologists, and dermatologists.

I.4 Selection of Key Issues

The focus of this CPG is on evidence-based management of the spectrum of active acne vulgaris through dietary modifications, prescription medications, procedural treatments, and adjunctive therapy. These guidelines will specifically address the diagnosis, severity classification, and treatment recommendations for acne.

Specific questions addressed in this document include:

1. What is the role of prescription topical therapy in acne management (retinoids, benzoyl peroxide (BPO), antibiotics, fixed-dose combination products, dapsone, and azelaic acid)?
2. What is the role of oral antibiotics in acne management?
3. What is the role of combined oral contraceptives (COCs) in acne management?
4. What is the role of oral isotretinoin in acne management?
5. What is the role of dietary manipulation and dairy reduction in acne management?
6. What is the role of procedural treatments in acne management?
7. What is the role of adjunctive therapy in acne management?
8. Which treatments are recommended for comedonal acne?
9. Which treatments are recommended for mild-to-moderate papulopustular acne?
10. Which treatments are recommended for severe acne?
11. Which considerations should be made for special situations/populations (in particular children, pregnant women and women who are breastfeeding)

I.5 Results of Delphi Surveys

Three online Delphi surveys were conducted to establish consensus, pre-defined as two-thirds of the expert panel of 9. The first survey established the treatment recommendation categories and the second and third sought consensus on specific treatment recommendations.

I.5.a Establishing Treatment Recommendation Categories

In ES3, the tables of treatment recommendations had the following six categories of recommendation based on evidence for efficacy and safety, as well as patient acceptance[18]:

1. high strength (strongly recommended)
2. medium (can be recommended)
3. low (can be considered)
4. negative (due to insufficient evidence for efficacy or less favorable benefit:harm profile)

5. not to be used under any circumstances (harmful intervention with very unfavorable benefit:harm profile)
6. open (due to lack of evidence, insufficient data from trials, and/or promising case reports or positive expert opinions)

The initial round of this Delphi survey achieved consensus to remove the category "may not be used under any circumstances". The rationale was to avoid potential distraction from positive recommendations which should be the focus of these tables. Furthermore, it was felt that items in this category could be numerous and impractical to list, may connote legal implications if any were neglected, and that many were based on basic knowledge of treatment mechanisms and safety.

I.5.b Establishing Treatment Recommendations

Prior to the online Delphi voting process, a meeting of the expert panel was convened (Montreal, Quebec; 22 September 2013) to review recommendation categories, review updated and new literature evaluations, and to prepare the panel of the online voting process. The expert panel was presented with all literature evaluations and rationale for recommendations for treatments not included in ES3 or where changes to the recommendations of ES3 were proposed. Canadian wholesale costs for medications were provided but no specific methodology was provided to the panel for integration of this information into placement in recommendations. Relative costs of recommended treatments are given in Appendix 4.

The online Delphi process was started on 2 November 2013 and completed 5 February 2014. Consensus was achieved on all items on the first Delphi survey. An updated search performed on July 14, 2015 did not find any new research that required revisiting the Delphi process.

The consensus recommendations for acne treatment are shown in Tables 1-3.

Table 1 Comedonal Acne Recommendations

High strength of recommendation (strongly recommended)
None
Medium strength of recommendation (can be recommended)
Topical retinoids†
Benzoyl peroxide (BPO)
Fixed-dose combination clindamycin and BPO
Fixed-dose combination adapalene and BPO
Low strength of recommendation (can be considered)
Clindamycin-tretinoin gel
Combined oral contraceptives*
Negative Recommendation (not recommended)
Topical antibiotics alone
Systemic antibiotics
Oral isotretinoin
Open recommendation (a recommendation for or against cannot be made currently)
Visible light as monotherapy, lasers with visible wavelengths and lasers with infrared wavelengths, with intense pulsed light (IPL) and photodynamic therapy (PDT)
Topical dapsone
Azelaic acid §
Chemical peels
† Adapalene and tazarotene preferred; * Recommended only for females; § 15% strength gel formulation

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Table 2 Mild-to-moderate Papulopustular Acne Recommendations

High strength of recommendation (strongly recommended)
Fixed-dose combination adapalene and benzoyl peroxide (BPO) Fixed-dose combination clindamycin and BPO
Medium strength of recommendation (can be recommended)
BPO Topical retinoids† Systemic antibiotics in combination with BPO +/- topical retinoid ‡ Combined oral contraceptives*
Low strength of recommendation (can be considered)
Clindamycin-tretinoin gel Blue light monotherapy Oral zinc
Negative Recommendation (not recommended)
Topical antibiotics alone Systemic antibiotics alone
Open recommendation (a recommendation for or against cannot be made currently)
Azelaic acid § Fixed-dose combination erythromycin and tretinoin # Topical dapsone Red light, IPL, Laser or PDT Spironolactone Low glycemic index diet Chemical peels
† Adapalene and tazarotene preferred; ‡ Best evidence for fixed-dose BPO-adapalene; * Recommended only for females; § 15% strength gel formulation; # No evidence available in public domain for product available on the Canadian market

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Table 3 Severe Acne Recommendations

High strength of recommendation (strongly recommended)
Oral isotretinoin monotherapy
Medium strength of recommendation (can be recommended)
Systemic antibiotics in combination with benzoyl peroxide (BPO) +/- topical retinoid †
Low strength of recommendation (can be considered)
Combined oral contraceptives*
Negative Recommendation (not recommended)
Topical antibiotics alone Oral antibiotics alone All light therapy alone Chemical peels
Open recommendation (a recommendation for or against cannot be made currently)
IPL and laser Photodynamic therapy
† Best evidence for fixed-dose BPO-adapalene; * Recommended only for females

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II Diagnosis

II.1 Pathophysiology of Acne

Acne vulgaris is a chronic inflammatory skin disease of the pilosebaceous unit[19] initiated by hormonal and microbial changes leading to subclinical inflammation, ductal blockage, increased sebum production, and proliferation of *Propionibacterium acnes (P. acnes)* (see Figure 2). These consequently result in the formation of comedones, papules, pustules, and nodules.[19, 20] *P. acnes* present in sebaceous follicles colonize and proliferate in acne-prone areas in response to increased sebum production.[19-21] Studies examining the onset of acne in relation to sexual maturation, *P. acnes* colonization, and sebaceous gland activity have demonstrated that a surge in dehydroepiandrosterone sulfate (DHEAS), a harbinger of puberty, is associated with the acne onset.[22] Comedonal acne generally precedes other external signs of puberty and elevated DHEAS levels predict more severe acne.[23, 24] In a longitudinal study, it was demonstrated that the number of follicles excreting sebum increases with age and pubertal stage. Furthermore, children who develop acne had greater sebum production as well as a greater density of *P. acnes* in these areas.[25]

Recent research on acne pathophysiology suggests that acne vulgaris is an inflammatory skin disease rather than solely a keratinocyte/hyperproliferative disorder.[19] Inflammatory events precede microcomedo formation and the development of ductal hyperkeratinization may be influenced by subclinical inflammation induced by *P. acnes*.[12, 19, 26]

The genome for *P. acnes,* decoded more than a decade ago, has subsequently been classified into three different phylotypes, with type IA being associated with inflammatory acne.[27, 28] *P. acnes* contributes to inflammation through direct release of enzymes, by activation of the innate and adaptive immune systems, and by activation of complement pathways.[29-32] *P. acnes* form an extracellular layer of secreted proteins and polysaccharides, known as a biofilm, which may contribute to acne pathogenesis.[33, 34]

Androgens - from gonadal, adrenal, and locally produced epidermal/sebaceous sources - are crucial in the pathogenesis of acne leading to sebogenesis and ductal occlusion. Androgens and peroxisome proliferator-activated receptors (ligand activated transcription factors) regulate the production of sebum and may be important in the development of acne.[29, 35-39] A deficiency of linoleic acid, which has been noted in the sebum of acne patients, may increase hyperkeratinization of the epidermis and enhance the inflammatory reaction. [29, 36-38]

In summary, the pathophysiology of acne is complex and involves skin microbiota including *P. acnes* phylotypes, biofilms, androgen activity, immunological and inflammatory responses, and regulation of steroidogenesis and sebogenesis in the skin.

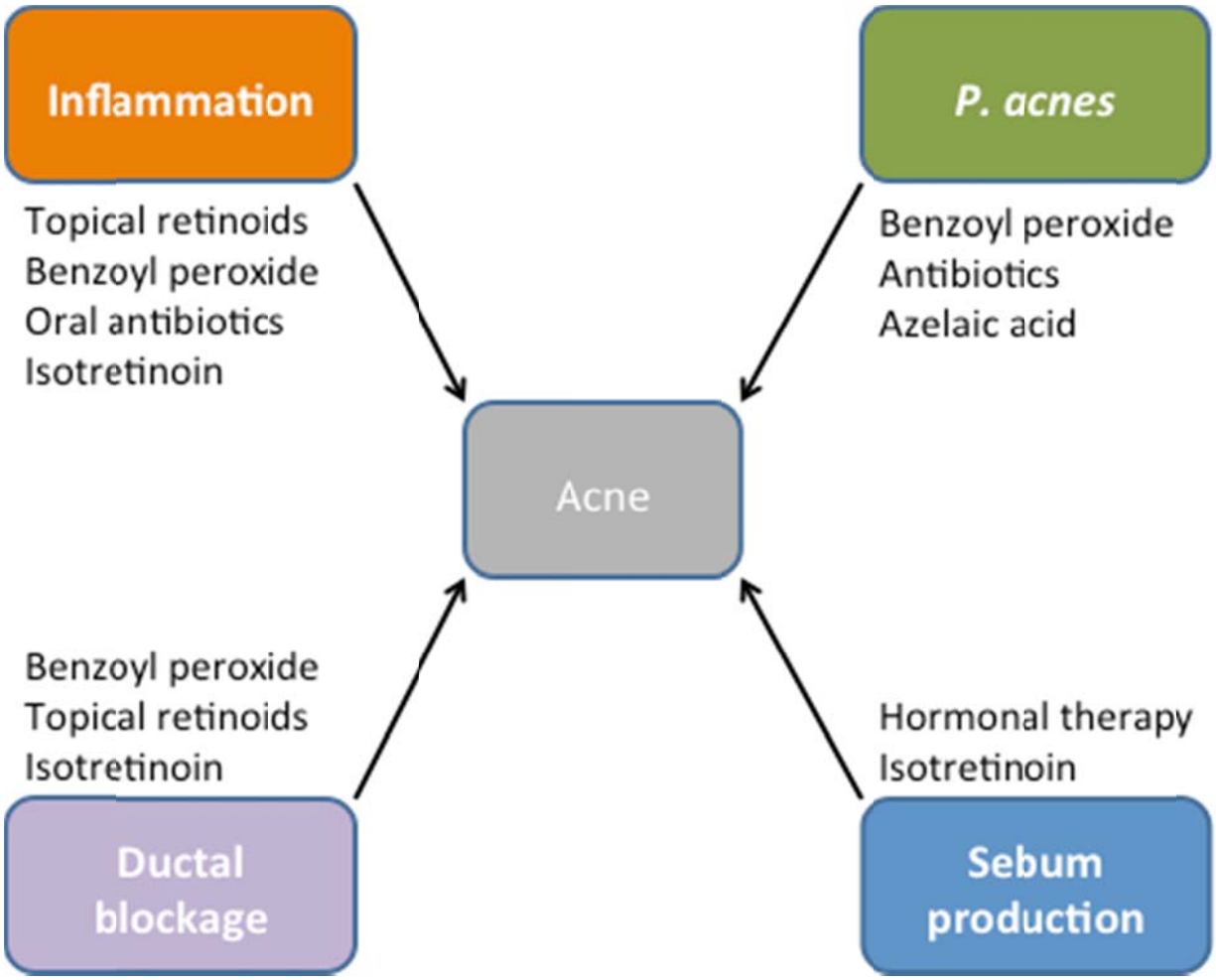

Figure 2 Acne medications and pathogenic factors in acne

II.2 Differential Diagnosis of Acne Vulgaris

Acne vulgaris can generally be easily identified by its distribution (commonly the face and possibly torso) and presence of open comedones (known as “blackheads”), closed comedones (“whiteheads”), papules, pustules and nodules (Table 4). The differential diagnosis of acne vulgaris includes variants with distinct pathogeneses, as well as acne-like dermatoses that are morphologically similar to acne vulgaris.

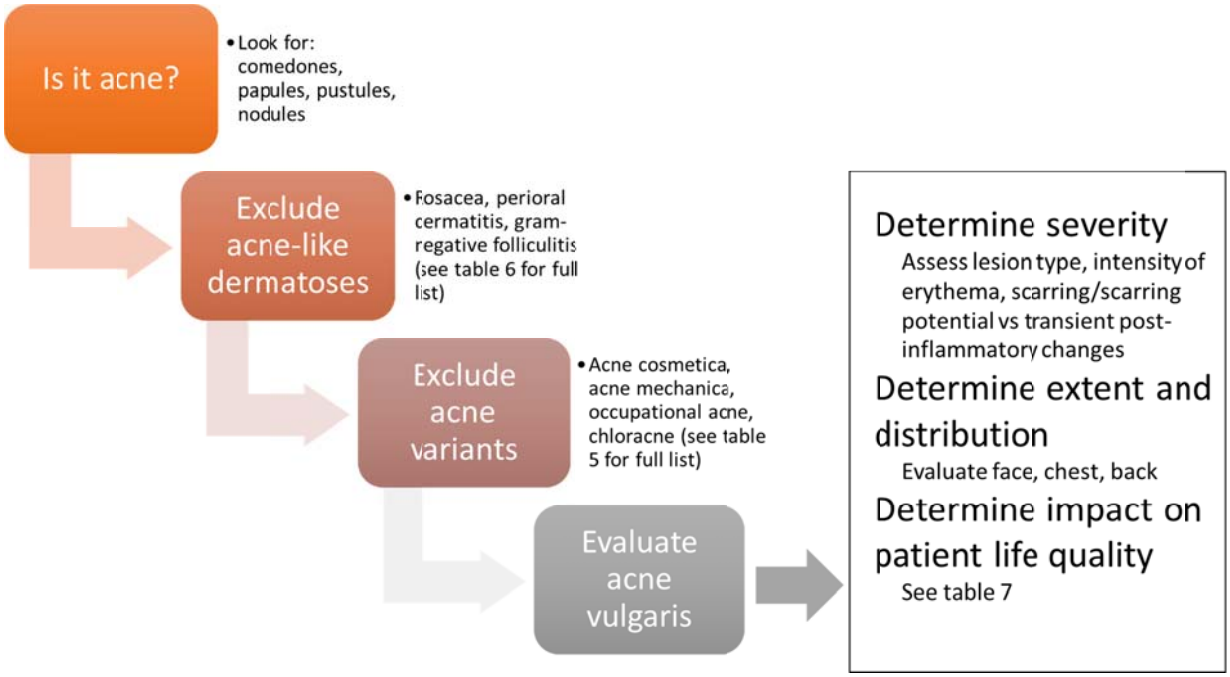

Figure 3 Clinical assessment of acne patients

II.2.a Acne Variants

Acne cosmetica and pomade acne develop due to application of occlusive cosmetics, skincare products, and hair styling products. They present abruptly with extensive monomorphous comedones. Exposure to certain chemicals and compounds, such as cutting oils, petroleum-based products, chlorinated aromatic hydrocarbons, coal-tar derivatives, and iodine- and bromine-containing chemicals may also result in an acne-like eruption. The latter may be differentiated from acne by their abrupt onset following exposure. The presence of an acute eruption of acneiform nodules, friable hemorrhagic plaques, fever, and arthralgia suggests a diagnosis of acne fulminans (Table 5). This condition requires a prompt diagnosis and urgent medical management.

Acne can be seen in association with specific syndromes including the SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) and PAPA syndrome (sterile pyogenic arthritis, pyoderma gangrenosum, and acne). Acne that is associated with systemic features warrants urgent referral to a dermatologist. Hyperandrogenism from a variety of causes may also be associated with acne and is further addressed in section II.4.c.

Table 4 Acne classification

Class	Type	Description
1	Comedonal acne	Comedones result from complete or partial ductal occlusion and sebum accretion leading clinically to small white (closed comedones) or grey/white (open comedones) papules.
2	Mild to moderate papulopustular acne	Both comedones and inflammatory lesions (IL) are present. Superficial inflammatory lesions include papules and pustules (5 mm or less in diameter).
3	Severe	IL comprised of larger or more extensive papules, pustules and/or presence of nodules. Nodules have depth and are > 5 mm diameter. Conglobate acne is characterized by extensive IL including suppurative nodules, which may coalesce into sinus tracts. Extensive and disfiguring scarring may ensue.

II.2.b Acne-like Dermatoses

Several non-acne dermatoses may present with morphology similar to that of acne vulgaris (Table 6). Certain medications and exposure to extreme heat or sunlight, for example, can trigger inflammatory eruptions that may mimic acne, and ionizing radiation causes acute dermatitis with comedo-like papules as it resolves. Acne rosacea is a common inflammatory dermatosis of the face that can be distinguished from acne vulgaris by the absence of comedones, the later age of onset (30 to 50 years), and persistent erythema on the central face with telangiectasias and occasional flares of inflammatory papules and pustules.

Table 5 Differential diagnoses of acne vulgaris: Acne variants

Variant	Etiology	Differentiating Features
Acne cosmetica Pomade acne Acne mechanica Acne detergicans	Cosmetics or skin products Hair products Clothing or sports equipment Too-frequent washing with comedogenic soaps, rough cloths, or abrasive pads	Abrupt onset; primarily extensive monomorphous open comedones
Occupational acne	Cutting oils, petroleum-based products, and coal-tar derivatives	Abrupt onset; comedones, papules, pustules, and cysts
Chloracne	Chlorinated aromatic hydrocarbons	Small cystic papules and nodules on the cheeks, neck, behind the ears, under the arms, and in the groin region; may heal with significant scarring
Acne fulminans	Immunologic, in rare cases systemic isotretinoin can precipitate an acne fulminans-like eruption	Acute eruption of inflammatory nodules and friable plaques with hemorrhagic crusts associated with fever, arthralgias, leukocytosis, an elevated erythrocyte sedimentation rate, proteinuria, and osteolytic lesions

Folliculitis, inflammation of the hair follicle, is typically due to infection with: fungus, such as yeast (*Malassezia* folliculitis, also known as *Pityrosporum* folliculitis) or dermatophytes (*trichophyton mentagrophytes, t. verrucosum, t. rubrum*); bacteria, such as in hot-tub folliculitis (*Pseudomonas aeruginosa),* Barber's itch (*Staphylococcus*), and gram-negative folliculitis; or virus (herpetic folliculitis). Folliculitis can be distinguished from acne vulgaris by monomorphous lesions and the absence of comedones. Of these, gram-negative folliculitis is the most likely to be mistaken for acne, and should be considered in cases of persistent acne resistant to standard therapy.

Pseudofolliculitis is perifollicular inflammation due to ingrown hairs, often resulting from intra-cutaneous hair penetration from regrowth after shaving, waxing, or plucking. It is particularly problematic in those with curly or coarse hair. The ingrown hairs result in inflamed papules and/or pustules and can be distinguished from acne vulgaris by the absence of comedones and localization at sites of epilation or depilation. Pseudofolliculitis barbae and acne keloidalis nuchae present in men and typically appear as inflammatory papules and pustules of the beard, back of the neck, and occipital scalp that may result in keloidal scarring.

Finally, various benign tumours present as flesh-coloured papules on the face. These may be manifestations of rare genetic conditions with systemic sequelae[40] and can be distinguished from acne by their monomorphous presentation and lack of inflammatory lesions. For example, the angiofibromas of tuberous sclerosis, a rare, multisystem genetic disorder that usually appears in childhood, appear as persistent pink or red papules across the nose and cheeks.[41, 42]

II.3 Types of Acne Not Included in this CPG

Disorders not covered by this CPG include:

1. neonatal, infantile and late onset acne;
2. acne fulminans;
3. acne inversa (hidradenitis suppurativa);
4. acne variants such as gram-negative folliculitis, rosacea, demodicidosis, pustular vasculitis, mechanical acne, oil/tar acne, and chloracne.

These were excluded due to different pathogenic mechanisms and to maintain congruence with the source guideline for adaptation, ES3.[12]

Table 6 Differential diagnosis of acne vulgaris: Non-acne dermatoses

Dermatosis	Features
Drug-induced acne	Abrupt onset of monomorphous inflammatory papules and pustules on the face, neck, and torso; typically occurs with use of corticosteroids, androgens, lithium, epidermal growth factor receptor (EGFR) inhibitors, and other tyrosine kinase inhibitors
Tropical acne	Large inflammatory nodulocysts on the trunk and buttocks after exposure to environmental or occupational extreme heat
Acne aestivalis (Mallorca acne)	Eruption of multiple monomorphous, uniform, erythematous, pruritic papules following sun exposure; variant of polymorphous light eruption
Rosacea	Late age of onset; persistent erythema on central face with telangiectasias, papules, and pustules but no comedones
Periorificial dermatitis	Small, grouped erythematous papules and pustules around the mouth, nose, or eyes; spares the vermilion border of the lip; typically affects females
Folliculitis	Inflammatory monomorphous lesions caused by infection of hair follicles; absence of comedones
Pseudofolliculitis	Inflammatory papules and pustules caused by ingrown hairs; absence of comedones
Keratosis pilaris	Follicular prominence and roughness ranging from flesh-coloured to red; usually occurs on the back of arms but may resemble acne when it involves the cheeks
Favre-Racouchot syndrome	Open and closed comedones on the upper cheek and under the eyes due to sun damage; typically appears in older adults

II.4 Clinical Presentation, Classification, and Assessment of Acne

II.4.a Classification

For application of the treatment recommendations within this CPG, acne is assessed on its clinical presentation and by evaluation of disease activity and severity (see Figure 2). During examination the skin should be free of make-up and assessed with adequate lighting. Visual assessment may be complemented by palpation to assist in determination of lesional elevation and depth.[12]

Evaluation of acne of the face, as well as chest and back, should be performed to provide an overall perspective of lesional type, extent, and distribution. It may be useful to grade acne severity using a scale; one such scale developed for regulatory approval of acne interventions comprises the following grades: *clear/almost clear; mild; moderate; severe/extremely severe*.[11] A version of this scale has been validated and shown to be of practical value when applied to each of the face, chest and back, providing separate regional severity for the major sites of acne involvement.[9] Such a scale would provide for determination of change over time whereby a change of at least 2 severity grades or attainment of *clear/almost clear* would be the ultimate goal.

While assessing acne severity on presentation, inquiry should be made regarding past and present treatments as these may affect subsequent treatment recommendations. In the event of partial efficacy, subsequent treatment should be appropriate for the original grade rather than the milder grade that resulted from treatment.

II.4.b Scarring and Scarring Potential

Other aspects to be assessed in acne patients are scarring and post-inflammatory discoloration (dyspigmentation). Scarring is common in patients with highly inflammatory nodules and papules. Less severe acne also has a risk of insidious scarring. Scars may present as increased tissue (hypertrophic scarring) or tissue loss (atrophic scarring).[43] When increasing numbers of scars due to active acne are observed, prompt initiation of aggressive treatment is indicated to mitigate further scarring.[1] In the absence of treatment, scars are considered to be long-term and persistent. In contrast, post-inflammatory changes in skin color after resolution of acne lesions (red, brown or pale) tends to be transient and are distinguished from scars by absence of changes in tissue volume or texture.

In a survey of Canadian acne patients, clinically relevant scarring increased with duration of acne and was observed on the face in 55%, back in 24% and chest in 14%.[9]

II.4.c Laboratory Investigations

In the vast majority of cases, no investigations are required to diagnose acne as it is a clinical diagnosis based on examination of distribution (face, chest, back) and morphology (comedones, inflammatory papules, pustules and/or nodules). When the diagnosis is in doubt, a swab for bacterial culture of pustule contents can serve to exclude bacterial infections such as gram-negative folliculitis or staphylococcal folliculitis. Rarely, a skin biopsy may be required for patients whose acne is unresponsive to therapy. The biopsy may reveal an unsuspected diagnosis such as follicular mucinosis, *Malassezia* folliculitis, or demodicidosis, all of which can mimic acne.

If hyperandrogenism is suspected from the history or physical examination of a female with acne, further testing is appropriate. Signs and symptoms suggesting hyperandrogenism include acne associated with primary or secondary amenorrhea, irregular periods, infertility, hirsutism, androgenetic alopecia, central obesity and/or acanthosis nigricans. Clitoromegaly, voice deepening, and increased libido may also be signs.

It is also prudent to measure serum androgens in females with sudden, severe, or late onset acne and in those whose acne is unresponsive to therapy. This also applies to cases where acne has relapsed shortly after completing a course of systemic isotretinoin.

Recommended blood tests for hyperandrogenism include total and free testosterone or free androgen index (depending on the laboratory used), DHEAS, androstenedione, 17-hydroxyprogesterone, sensitive thyroid stimulating hormone (sTSH) and prolactin. Further testing could include an adrenocorticotropic hormone (ACTH) stimulation test, a pelvic ultrasound to evaluate for ovarian cysts, 24 hour urine for cortisol, or referral to an appropriate specialist.

Blood tests are rarely ordered in males with acne but should be done in cases were an endocrine disorder is suspected.

II.4.d Quality of Life Aspects

Acne vulgaris can adversely affect self-esteem, emotional wellbeing, and socialization and has been associated with psychosomatic symptoms, anxiety, depression, social avoidance, and suicide.[44-51] Of particular relevance to health care providers is that clinically observed

severity is not closely related to psychosocial, emotional, or psychiatric impact. Therefore, inquiry of the latter dimensions is important to inform illness impact in addition to observation of clinical acne severity. Thus, a means of inquiry for quality of life (QoL) impact would be of value in assessments as it provides a patient perspective on acne severity. Acne quality of life questionnaires seek to assess the patient's symptoms, self-perception, as well as emotional and social effects of their acne. However, currently available QoL questionnaires are largely designed for research purposes and may be excessively lengthy and impractical for routine use in clinics.

Table 7 Acne QoL Questionnaires

Scale	Item	Score
Acne-Q4[15]	1. Dissatisfied with appearance 2. Feeling upset 3. Concerns about meeting new people 4. Concern about scarring	Score 0-6: extremely (0), very much (1), quite a bit (2), a good bit (3), somewhat (4), a little bit (5), not at all (6)
CADI[16]	1. As a result of having acne, during the last month have you been aggressive, frustrated or embarrassed? 2. Do you think that having acne during the last month interfered with your daily social life, social events or relationships with members of the opposite sex.' 3. During the last month have you avoided public changing facilities or wearing swimming costumes because of your acne? 4. How would you describe your feelings about the appearance of your skin over the last month? 5. Please indicate how bad you think your acne is now:	1. (a) Very much indeed; (b) A lot; (c) A little; (d) Not at all 2. (a) Severely, affecting all activities; (b) Moderately, in most activities; (c) Occasionally or in only some activities; (d) Not at all 3. (a) All of the time; (b) Most of the time; (c) Occasionally; (d) Not at all 4. (a) Very depressed and miserable; (b) Usually concerned; (c) Occasionally concerned; (d) Not bothered 5. (a) The worst it could possibly be; (b) A major problem; (c) A minor problem; (d) Not a problem

Studies evaluating self-rated severity scales in response to single questions regarding the *occurrence of pimples over the prior week* (4 item response range of no, a little, a lot and very much) or have *acne or pimples been a problem for you?* (4 items response range of hasn't been a problem, not too bad, really bad, and terrible) have shown that positive responses to either of

the 2 items on the positive spectrum of the response scales were associated with a higher risk of anxiety, mental health problems, suicidal ideation and suicidal attempts.[52, 53]

Thus, clinicians may wish to consider direct inquiry of the impact of acne as above or consider the use of two shorter QoL instruments available that may be useful for practice: the Acne-Q4 and the CADI (Table 7).[15, 16]

III Treatment

The recommendations and evidence provided by the ES3 guidelines were reviewed by panel members.[12] Based on the outcome of the review, information on products available in Canada, and the results of an additional updated literature search, recommendations were developed for treatment of Canadian acne patients. Changes from the ES3 recommendations made during adaptation are listed in Table 8 and the end of Section III.

For details on literature search methodology, please refer to the accompanying Methodology for Development of the Canadian Acne Clinical Practice Guidelines manuscript.

III.A Topicals

III.A.1 Topical Therapies in Canada

Topical therapies are an important treatment modality in the management of acne vulgaris as they can provide anatomically targeted therapy with minimal risk of systemic adverse events. These include topical antibiotics, retinoids, BPO, dapsone, azelaic acid and fixed-dose combinations of topical agents. Vehicle choice is an important consideration; individuals with dry or sensitive skin may prefer creams or lotions, which tend to be less drying, while those with oily skin may prefer a less greasy formula, such as a gel, while lotions are best suited for otherwise neutral skin.

III.A.2 Mechanism of Action

Topical acne therapies have different modes of action. The four main aspects of acne pathogenesis include follicular hyperkeratinisation, bacterial proliferation, inflammation, and increased sebum production (see Figure 2).

Retinoids such as tretinoin, adapalene, and tazarotene are anticomedogenic and comedolytic. The retinoids act by decreasing follicular hyperkeratinisation and inflammation,[54] and they also have direct immunomodulatory effects.[55]. Benzoyl peroxide possesses antimicrobial[56] and keratolytic properties[58]. Benzoyl peroxide also has an anti-inflammatory action, which may arise from its ability to kill polymorphonuclear leukocytes (PMN cells) in the pilosebaceous follicles and so prevent their release of reactive oxygen species (ROS) such as peroxides which enhance tissue inflammation.[57] This allows it to target three of the four mechanisms in the pathogenesis of acne. Topical dapsone exhibits anti-inflammatory and possibly antimicrobial effects.[59] Azelaic acid possesses antimicrobial and keratolytic activity. [60] Topical antibiotics, such as clindamycin or erythromycin, suppress *P. acnes* proliferation.[61, 62]

Currently no topical products are available that affect sebum production, likely due to the depth of the sebaceous gland. However, topical products may be used alone or in combination to target the three other pathogenic pathways.

III.A.3 Efficacy

III.A.3.a Comedonal acne

Clinical evidence for the treatment of solely comedonal acne is sparse as studies typically include patients with both comedonal and inflammatory lesions (IL).[12] Therefore, the effect on comedone counts in these studies are used to inform treatment of comedonal acne.

Topical retinoids Topical retinoids have been found to be superior to placebo for comedones (LE 1).[12] Monotherapy with topical retinoids have been shown to reduce formation of microcomedones and comedones.[12, 60] Of the available topical retinoids, adapalene and tazarotene have the strongest evidence for efficacy. Adapalene appears more efficacious than tretinoin.[12] Tazarotene is superior to vehicle for comedones (LE 1) and has been found to be equivalent (4 grade B studies)[63-66] or superior to adapalene (1 grade B study). Like adapalene, tazarotene is superior to tretinoin when treating comedonal lesions (2 grade B studies).[67, 68] Tretinoin has superior efficacy compared to azelaic acid, and is comparable or superior to BPO for comedones.[12] Topical retinoids receive a medium strength recommendation for comedonal acne, with tazarotene showing equivalent or superior efficacy to adapalene.

Benzoyl peroxide Topical BPO has been found to be superior to placebo for comedonal acne, (LE 1) and is superior to all topical antibiotics assessed (clindamycin and erythromycin).[12] Benzoyl peroxide products have a fast onset of action[69], are readily available over the counter, and should thus be considered for initial treatment. Benzoyl peroxide monotherapy receives a medium strength recommendation for comedonal acne and has been found to be equivalent to adapalene for comedonal acne (LE 1).[12] There is insufficient data to compare BPO formulations of different concentrations and vehicles.

Topical antibiotics Topical clindamycin has been found to be superior to placebo for comedones (LE 1).[12] All topical antibiotics evaluated are inferior to BPO when used as monotherapy.[12] Topical clindamycin is inferior to BPO (LE 1) and to tretinoin (LE 3) for treatment of comedones.[12] Topical antibiotics alone are given a negative recommendation for comedonal acne due to presence of more efficacious treatments and the potential for selection of antibiotic resistant bacteria.

Fixed-dose combination therapy Fixed-dose clindamycin-BPO is equivalent to BPO alone (LE 1) and superior to clindamycin alone (LE 4) in comedonal acne.[12, 70] Fixed-dose adapalene-BPO is equivalent or superior to BPO alone (LE 3) and adapalene alone (LE 3) for treatment of comedonal acne.[12, 71] Fixed-dose adapalene-BPO and fixed-dose clindamycin-BPO combination therapies appear to have similar efficacy (LE 4)[12] and receive a medium strength recommendation for comedonal acne.

Clindamycin-tretinoin gel is efficacious for comedonal acne compared to vehicle and is superior to topical 1.2% clindamycin alone (1 grade A study).[72] It is superior to tretinoin 0.025% monotherapy[72] (1 grade A study) and trended toward superiority in one grade B study.[73] A grade B study addressing adherence found equivalent overall efficacy for clindamycin-tretinoin gel compared to clindamycin 1% gel in the morning and tretinoin 0.025% cream nightly, although adherence was higher for the fixed-dose combination therapy.[74] Although evidence for efficacy was present, the paucity of studies led to an assignment of LE3 and fixed-dose combination clindamycin-tretinoin gel was given a low strength of recommendation for comedonal acne.

Topical dapsone There are few studies available for evidence of efficacy of topical dapsone in acne vulgaris. The largest study analyzed two randomized controlled trials together, and found an 8% improvement in comedones after 12 weeks of topical dapsone[75] (1 grade A study). While the difference was statistically significant, this level of improvement did not reach the threshold of clinically significant effect defined by ES3: “treatment should achieve at least a 10% greater reduction in the number of lesions to demonstrate superior efficacy.”[12] The remaining studies on dapsone topical gel were observational,[76] evaluated safety,[77, 78] or addressed use of topical dapsone in addition to topical retinoids or BPO.[79, 80] As such, topical dapsone receives an open recommendation for comedonal acne due to insufficient data (LE4).

Azelaic acid Azelaic acid has been shown to be superior to placebo in the treatment of comedonal acne.[81] The majority of the data in support of the low level recommendation in the ES3 guidelines for azelaic acid used the 20% formulation available in Europe. The only commercial formulation of azelaic acid on the Canadian market is 15% gel. There is only one study available on this product for acne[12, 82]; it is approved in Canada only for the treatment in papulopustular rosacea. Azelaic acid is given an open recommendation for comedonal acne (LE4).

III.A.3.b Mild-to-moderate Papulopustular Acne

Topical therapy plays an important role in the treatment of mild-to-moderate papulopustular acne. Despite the general belief that systemic antibiotics are more efficacious than topical therapy, studies have found that topical BPO and retinoids have comparable efficacy to systemic antibiotics.[12]

Topical retinoids All topical retinoids evaluated in the ES3 guidelines were superior to placebo or vehicle in the treatment of papulopustular acne (LE 1).[12] The efficacy of adapalene is equivalent to BPO and tretinoin for the treatment of IL.[12] Tazarotene is superior to vehicle for inflammatory lesions (1 grade A, 2 grade B studies; LE3)[83, 84] and has been found to be equivalent to (4 grade B studies; LE 2)[63-66] or superior to adapalene (1 grade B study).[68] While tazarotene appears superior to tretinoin for comedonal lesions, it is equivalent for IL (2 grade B studies; LE3).[67, 68] The panel gave topical retinoids a medium strength recommendation for mild-to-moderate papulopustular acne.

Benzoyl peroxide Benzoyl peroxide is more efficacious than vehicle in the treatment of papulopustular acne (LE 1)[12] and has a fast onset of action.[69] It is equivalent to adapalene (LE 2) and conflicting evidence exists regarding its equivalence to tretinoin (LE 4) for the treatment of IL.[12] BPO receives a medium strength recommendation for mild-to-moderate papulopustular acne.

Topical antibiotics Although topical antibiotics exhibit superior efficacy compared to placebo in the treatment of inflammatory acne,[85] their use as monotherapy is not recommended due to the risk of bacterial resistance.[12] Benzoyl peroxide has the advantage of reducing emergence of antibiotic resistance,[86] which has led to its use in combination with topical antimicrobial therapies in acne. Concerns over antibiotic resistance were raised by panel members regarding the absence of BPO in the fixed-dose combination of clindamycin and tretinoin gel. A small, 6-week split-face study investigating combination tretinoin 0.025% and clindamycin 1.2% gel found a decrease in clindamycin-resistant P. acnes compared to clindamycin gel alone. This suggests that topical retinoids could possibly mitigate development of antibiotic resistant strains in the presence of a topical antibiotic; however this requires further investigation.[87]

Topical antibiotics alone receive a negative recommendation as monotherapy for mild-to-moderate papulopustular acne.

Fixed-dose combination therapy Fixed-dose clindamycin-BPO is more efficacious than BPO alone for papulopustular acne (LE 1).[12] Both clindamycin-BPO (LE 4) and adapalene-BPO

(LE 1) are superior to adapalene monotherapy, and these two fixed-dose agents are equivalent in efficacy for papulopustular acne (LE 4).[12] Both are given a high strength recommendation for mild-to-moderate papulopustular acne.

Fixed dose erythromycin-tretinoin available in Canada does not have evidence accessible in the public domain; a different formulation available on the European market has been given low-level recommendation by the ES3 guidelines, and there is no data available comparing its efficacy to other topical mono- and combination therapies.[12] It is, thus, given an open recommendation for mild-to-moderate papulopustular acne.

Fixed dose clindamycin-tretinoin gel is efficacious for IL; it is superior to vehicle, topical 1.2% clindamycin alone, and tretinoin 0.025% alone[72] (1 grade A study). A smaller grade B comparison study with nighty tretinoin 0.025% monotherapy found superiority of clindamycin-tretinoin gel for IL.[73] Overall efficacy of clindamycin-tretinoin gel compared to clindamycin 1% gel in the morning with nightly tretinoin 0.025% cream appears equivalent, although adherence may be higher for fixed-dose therapy[74] (1 grade B study). All of these trials were no longer than 12 weeks and clindamycin resistance was not evaluated. Clindamycin-tretinoin gel is given a low strength recommendation for mild-to-moderate papulopustular acne (LE3).

Topical dapsone As discussed above in Section III.A.4.a, there is little evidence available for the efficacy of topical dapsone in acne vulgaris (LE4). A large grade A study found a statistically significant 6% improvement for IL in subjects on topical dapsone versus vehicle,[75] which did not meet the pre-determined ES3 guidelines criteria for clinical superiority.[12] Therefore, topical dapsone is given an open recommendation for mild-to-moderate papulopustular acne.

Azelaic acid Azelaic acid is superior to placebo in the treatment of papulopustular acne (LE 1)[12, 81] and equivalent to BPO (LE 2) and adapalene (LE 4)[12] though inferior to systemic tetracycline (LE 3).[12] The majority of the data in support of the moderate strength of recommendation in the ES3 guidelines for azelaic acid used the 20% cream formulation available in Europe. However, in Canada, the only commercial formulation of azelaic acid is 15% gel. Only one study is available on the 15% concentration of azelaic acid[12, 82], which is approved in Canada only for the treatment in papulopustular rosacea. Accordingly, this product is given an open recommendation for mild-to-moderate papulopustular acne (LE4).

III.A.3.c Severe Acne

If oral isotretinoin, the treatment of choice for severe acne, is contraindicated or refused, topical therapy may have an adjunctive role in patients with severe acne. Topical retinoids and BPO may be used in combination with systemic antibiotics, with the best evidence in support of fixed-dose adapalene-BPO with doxycycline (LE 3).[12] Topical products alone are not recommended for management of severe acne.

III.A.4 Adverse Events

The most common adverse events related to all topical acne therapies are dryness, redness, burning, irritation, and peeling. The frequency in most studies is generally less than 10%, although this may vary depending on the products used. Individuals living in drier climates or with more sensitive skin may experience more irritation. Practical advice to patients who experience dryness and irritation may include decreasing the amount of product used, reducing the frequency of application, and avoiding application of product immediately after face washing.[88] Short-contact application of retinoids (minutes to a few hours) have been found to be efficacious,[84] which may be an option for individuals who have significant irritation with topical products. It is important to note that many patients overuse prescribed topical products or also use harsh cleansers, scrubs or astringents - avoidance of these should be discussed.[54] Non-comedogenic topical emollients may also be helpful. Allergic contact dermatitis is an uncommon adverse event but should be considered in cases of recalcitrant dermatitis with use of topical agents. As discussed in the ES3 guidelines, it is difficult to compare the safety and tolerability of topical products with systemic treatments.[12]

Topical retinoids Local cutaneous irritation is the primary adverse event for topical retinoids. Some patients on retinoids may report photosensitivity and patients should be advised about photoprotection.[89] Similar to systemic use of isotretinoin, physical depilation or procedures such as waxing or laser hair removal are not advised while on topical retinoids due to skin fragility. Generally, more adverse skin reactions are seen with tazarotene compared to the other retinoids.[64-68] Some studies reporting equivalency of irritation between tazarotene and other retinoids evaluate tazarotene cream with comparator gels; gels are inherently more drying than creams and prescribing therapy in an appropriate vehicle may be a factor for avoiding irritation. There is indirect evidence for patient preference for adapalene, but studies are limited. Overall, adapalene and tretinoin appear to be the best tolerated.[12]

Systemic absorption of tretinoin is less than 1-2% and less than 0.01% of a topically applied dose of adapalene is absorbed.[90] Tazarotene is rated pregnancy category X and is contraindicated for use in pregnant women. In a study examining application under occlusion, the maximum absorption of an applied dose was 6%.[90] Although other retinoids are listed as pregnancy category C, topical retinoids should be avoided in pregnancy.[88] The safety of topical retinoids use by breastfeeding mothers has not been studied; however, due to their poor absorption, they are considered to pose a low risk to the nursing infant.[91] However, caution should be exercised if used over large surface areas of the body (20-30%).[92] Addition of topical retinoids to regimens of systemic antibiotics does not seem to increase side effects or increase dropout rates.[12]

Topical retinoids, alone and in combination with BPO, have been found to be safe in children.[93] Adapalene and tazarotene are indicated for patients ≥ 12 years of age[94] while no age limitation is given for tretinoin.[95]

Benzoyl peroxide Due to its lipophilic nature, BPO concentrates in the lipid-rich sebaceous follicles.[96] Less than 2% is absorbed systemically.[97] The most common side effect of BPO is cutaneous irritation and it has a tolerability profile similar to topical retinoids; lower concentrations tend to be better tolerated.[12] Patients should be careful to avoid contact of BPO products with fabrics as bleaching and/or discoloration may result. Rarely, BPO can induce allergic contact dermatitis[98], reported to occur in up to 2.5% of patients.[90] Benzoyl peroxide is a pregnancy category C product but is considered safe in pregnancy when used on limited areas.[99] The addition of BPO and adapalene to systemic doxycycline has a similar safety profile to systemic doxycycline alone.[12]

BPO is safe and effective for use, alone or in combination, for the treatment of acne in children.[93]

Topical antibiotics Topical 1% clindamycin is minimally absorbed, with a range varying from undetectable in serum to 4-5% of the topically applied dosage.[90] There are two case reports of pseudomembranous colitis associated with topical clindamycin use from the 1980s[100, 101] and some authors suggest avoidance of this medication in individuals with a history of enteritis, ulcerative colitis or antibacterial associated colitis[90]. Topically administered erythromycin is not detectable in the plasma.[102, 103] The topical antibiotics clindamycin and erythromycin are minimally absorbed, well tolerated, and safe to use in pregnancy (Pregnancy category B) and by breastfeeding mothers.

Antibiotic monotherapy should be avoided as it is associated with bacterial resistance. Combinations with BPO and with or without retinoids are safe for use in children.[93]

Antibiotic resistance Resistance of *P. acnes* to clindamycin and erythromycin[104] was first reported in 1979 and the first report of tetracycline resistance followed in 1983.[105] Since then, the incidence of antibiotic resistant *P. acnes* had increased dramatically to greater than 60% in certain populations.[106] Combined resistance to clindamycin and erythromycin is more common than resistance to tetracyclines.[107]

There is evidence that the use of topical antibiotics, the most commonly prescribed being erythromycin and clindamycin, has contributed to the emergence of antibiotic resistance.[108] Monotherapy with clindamycin was found to select for the outgrowth of resistant strains within 12 weeks of treatment[109] and the incidence of resistant *P. acnes* was elevated among close contacts of those that had undergone antibiotic treatment.[108, 110]

Clinically, the increase in incidence of antibiotic resistance of *P. acnes* has correlated with a reported decrease in the efficacy of erythromycin for the treatment of acne.[111-113] Furthermore, treatment of acne with either topical or systemic antibiotics can lead to emergence of resistance in microbial flora other than *P. acnes*, such as staphylococci and streptococci,[104, 114-117] at body sites distant from the treated area.[112, 118, 119] Thus, physicians may be left with fewer therapeutic options in case of infection, such as with methicillin-resistant *S. aureus*, in patients with a history of antibiotic treatment for acne.[112]

The ES3 acne guidelines have highlighted the need for treatment guidelines to restrict the use of topical antibiotics in order to limit the selection for resistant strains.[12] Selection for resistance may be mitigated during acne treatment by avoiding antibiotic monotherapy and combining topical antibiotics with BPO and/or topical retinoids; this has been demonstrated to improve efficacy and reduce the emergence of resistant strains.[112] It is also recommended that the duration of antibiotic treatment be limited.[12]

Fixed-dose combination therapy The safety of combination products, including during pregnancy or breastfeeding, is dependent on the constituents of the combination. Please refer to the appropriate section for more information regarding the safety of individual components of fixed-dose combination therapies.

Clindamycin-BPO fixed-dose combination therapy is similar in side-effect profile to BPO monotherapy, but may be more irritating than clindamycin alone.[12] Adapalene-BPO combination therapy is more irritating than BPO alone, but is comparable to adapalene

monotherapy.[12] For fixed-dose clindamycin-tretinoin, side-effects of the combination do not appear to be greater than the individual components alone.[72]

Fixed-dose combination medications are acceptable for use in children, given that their constituents have been demonstrated safe. Adapalene-BPO is indicated in patients as young as 9 years old[120] while clindamycin-BPO is indicated for patients ≥ 12 years old.[121]

Topical dapsone Dapsone gel is a topical sulfone with minimal systemic absorption and good tolerability.[75] Systemic dapsone use is associated with the risk of methemoglobinemia and hemolytic anemia. In one safety study of topical 5% dapsone, no methemoglobinemia or hemolytic anemia was observed even if oral trimethoprim sulfamethoxazole, an antibiotic that may exacerbate these adverse events, was given.[77] A twelve-month observational study found no changes in hemoglobin associated with topical dapsone.[76] Specific investigation of individuals with deficiency in glucose-6-phosphate dehydrogenase (G6PD), who are at high risk of hemolytic anemia secondary to dapsone, found no clinically significant effects on hemoglobin in these individuals.[78] Sulfones are structurally distinct from sulfonamides and, hence, are not contraindicated in sulfonamide allergic patients.[122] Safety in pregnancy has not been established.

Dryness, erythema, sunburn and contact dermatitis have been reported with topical dapsone use.[76] One study investigating topical dapsone use with BPO and adapalene found similar dropout rates in patients using combination therapy versus dapsone alone, but adverse effects were more common in the dapsone-BPO group.[79] In a second study of combination therapy with retinoids, there were more adverse events in individuals using topical dapsone and tazarotene compared to tazarotene alone.[80] Dapsone is pregnancy category C and its use is not recommended in pregnant women. Dapsone is secreted into breast milk and a case of hemolytic anemia has been reported in a breastfed infant whose mother was taking dapsone[123]; Thus, topical dapsone is not recommended during breastfeeding.[92]

Dapsone has been shown to be safe and effective in children as young as 12 years old.[93]

Azelaic acid Azelaic acid may have a superior safety profile than topical retinoids and BPO.[12] The main adverse effect of azelaic acid is irritation, which tends to be mild. It is approximately 5% bioavailable and is classified as pregnancy category B.[99] Its safety during breastfeeding has not been studied but as topical administration results in low absorption it is considered a low risk to a nursing infant.[91]

Azelaic acid is approved in Canada for rosacea; its safety has not been evaluated in children and its use is not recommended.

III.B Systemics

III.B.1 Introduction

Systemic treatments are generally recommended when there is an extensive inflammatory component and/or affects areas where topical application is impractical. While there are four classes of systemic options, only three are generally used for acne in Canada (excludes zinc):

1. Oral antibiotics
    a. tetracyclines: doxycycline, minocycline, tetracycline
    b. macrolides: erythromycin, azithromycin
    c. clindamycin
    d. trimethoprim
2. Hormonal therapy
    a. combined oral contraceptives (COCs)
        i. Ethinyl estradiol (EE) 0.035 mg / cyproterone acetate (CPA) 2 mg
        ii. EE 0.020 mg / levonorgestrel 0.1 mg
        iii. EE 0.035 mg / norgestimate (NGM) 0.018, 0.215, 0.250 mg
        iv. EE 0.030 mg / drospirenone (DRSP) 3 mg
        v. EE 0.020 mg / drospirenone (DRSP) 3 mg
    b. Spironolactone
3. Oral isotretinoin
4. (Oral zinc)

III.B.2 Mechanism of Action

Antibiotics The primary mechanism by which antibiotics provide therapeutic benefit in acne is through antibacterial activity against *P. acnes*, which colonizes pilosebaceous units and can lead to inflammation. There is also evidence for an anti-inflammatory, non-antimicrobial role for antibiotics, specifically for the tetracyclines. Studies of subantibacterial doses of doxycycline showed significant benefit in acne, although no effect on *P. acnes* or other skin microflora was detected.[124] This effect may be mediated by a reduction in neutrophil chemotaxis and an inhibitory effect on cytokines and matrix metallopeptidase-9 (MMP-9).[125] This is consistent with the observation that oral tetracyclines continue to be efficacious despite an increase in antibiotic-resistant strains of propionibacteria.[126]

Hormonal therapy The estrogenic and progestogenic constituents of combined oral contraceptives (COC) confer anti-androgenic effects by several mechanisms: (1) reduction of pituitary gonadotrophin secretion with consequential reduction in ovarian androgen production, (2) direct inhibition of androgenesis by ovaries, adrenals and possibly at pilosebaceous units, (3) hepatic production of sex hormone binding globulin (SHBG) thereby reducing bioavailable testosterone (4) inhibition of 5-α reductase activity, reducing conversion of testosterone to the more potent dihydrotestosterone (DHT), and (5) competitive antagonism of androgens at receptor sites.[127]

Spironolactone, a synthetic steroidal agent, has mineralocorticoid and androgen inhibiting activities. Its presumed mechanism of action includes competitive inhibition of androgen binding to receptors in skin and sebaceous glands. Other mechanisms of action relevant to acne include increase in SHBG levels, enhanced clearance of testosterone, and reduction in 5-α reductase activity.[128]

Oral isotretinoin Isotretinoin is a member of the retinoid class of compounds related to retinol (vitamin A). Isotretinoin itself has low affinity for endogenous retinoic acid receptors but undergoes intracellular conversion to metabolites that are agonists for RAR and RXR nuclear receptors[129]; as such, isotretinoin likely acts as a pro-drug.[130] Isotretinoin exerts effects on all the factors involved in the pathogenesis of acne: reduces sebaceous gland activity and suppresses sebum production[131], which in turn reduces the bacterial population.[132] Isotretinoin is anti-inflammatory and also decreases hyperkeratinisation.[133, 134]

Oral zinc Zinc effects on inflammation in acne may be through inhibition of chemotaxis of inflammatory cells, inhibition of 5-α reductase activity, reduction in tumor necrosis factor-alpha, and induction of superoxide dismutase.[110]

III.B.3 Efficacy

III.B.3.a Comedonal acne

As comedonal acne is generally milder, topical treatments are preferred over systemic therapies due to their superior safety profiles. ES3 did not evaluate systemic treatments for solely comedonal acne; however, a Cochrane review found that COCs were effective at reducing comedones (LE 3) and are, thus, given a low strength recommendation for treatment of comedonal acne.

III.B.3.b Mild-to-moderate papulopustular

Antibiotics

Tetracyclines The efficacy of tetracyclines (doxycycline, tetracycline and minocycline) compared to placebo has been previously demonstrated in systematic reviews (evidence level A; equivalent to LE 1 – 2);[92,100] however, there is insufficient evidence for superiority of any one agent or dose.[135] Six of seven trials comparing the various tetracyclines found no difference lesion reduction.[135]

Though evidence is limited, tetracycline appears to be comparable or superior to oral clindamycin[136, 137] and erythromycin.[138-140] Minocycline[141] and tetracycline[142] both show greater efficacy than oral zinc (LE3). Minocycline was comparable in efficacy to EE/CPA (LE 4).[143] However, EE/CPA was superior to tetracycline (LE 3).[144] A combination of EE/CPA plus tetracycline was superior to tetracycline alone (LE 3).[144]

Macrolides While erythromycin has been efficacious in treatment of acne (evidence level B;[92] equivalent LE 2-3), there has been a trend to lower efficacy over time,[92,] [111] possibly due to the emergence of antibiotic resistant *P. acnes*. Two small studies comparing azithromycin to tetracyclines found equivalent efficacy for the treatment of papulopustular acne.[145, 146]

Although efficacy of clindamycin in acne has been demonstrated (evidence level B; equivalent LE 2-3)[136, 137, 147] the potential for *Clostridium difficile*-associated enteritis should temper its use in acne.[148]

Trimethoprim and trimethoprim/sulfamethoxazole Evidence of efficacy of these agents is lower than other antibiotics in treatment of acne (evidence level C; equivalent LE 3-4). Their use should be restricted in acne to failures in treatment with more conventional options.[149]

Systemic antibiotics in combination with other therapies The highest evidence for systemic antibiotic plus topical treatment in mild-to-moderate papulopustular acne is for the combination of oral doxycycline plus topical fixed dose adapalene-BPO (demonstrating superiority over doxycycline alone; LE 3)[150]; and doxycycline plus adapalene (superior to doxycycline alone; LE 4).[151]

In comparison to oral isotretinoin, minocycline combined with azelaic acid was found to have comparable efficacy (LE 4),[152] while tetracycline plus adapalene was inferior (LE 4).[12, 153]

Oral anti-androgens in combination with oral antibiotics may be considered for the treatment of severe papulopustular acne. There is low level evidence for superiority of EE-CPA plus tetracycline over tetracycline alone (LE 3).[12]

Hormonal therapy

Combined oral contraceptives (COCs) In Canada, the following COCs are indicated for treatment of acne in females: ethinyl estradiol 0.035 mg / cyproterone acetate 2 mg (EE-CPA), ethinyl estradiol 0.020 mg / levonorgestrel 0.1 mg (EE-LNG), ethinyl estradiol 0.035 mg /norgestimate 0.018, 0.215, 0.250 mg (EE-NGM), ethinyl estradiol 0.030 mg / drospirenone 3 mg (EE3-DRSP), and ethinyl estradiol 0.020 mg / drospirenone 3 mg (EE2-DRSP). These official indications were based on results of placebo-controlled trials [154, 155] [156, 157] [122, 123] [158, 159] with the exception of EE-CPA, which was based on comparative and open label studies.

Of the few comparative trials evaluating comparative efficacy between COCs: EE3-DRSP was similar in efficacy to EE-LNG and to EE-CPA in 2 non-inferiority trials (LE 3) while EE-CPA was superior to EE-LNG (LE 2).[160]

COCs receive a medium strength recommendation for the treatment of mild-to-moderate papulopustular acne in females.

Spironolactone There is sparse evidence regarding spironolactone for the treatment of acne. Three small placebo-controlled trials with spironolactone in acne have been reported but are flawed by shortcomings in trial design, loss to follow up, outcome reporting, and/or statistical analysis.[161-163] The conclusion of a recent Cochrane review was that there is presently no high quality evidence to support the efficacy of spironolactone in acne[164]; thus, spironolactone is given an open recommendation for mild-to-moderate papulopustular acne.

Oral isotretinoin For inflammatory lesions of papulopustular acne, oral isotretinoin was comparable in efficacy to minocycline plus azelaic acid[152] (LE 4) but superior to tetracycline plus adapalene[153] (LE4).

The conventional isotretinoin dose of 1-2 mg/kg/day is extremely efficacious for severe acne. However, the benefit: harm profile for its use in moderate acne should be tempered by the potential for adverse events and teratogenicity. Two studies of isotretinoin dose regimens found lower doses (20 mg every alternate day or 0.25-0.4 mg/kg/day) were as efficacious as higher doses for reducing IL. [165, 166]

Oral zinc Zinc shows some effect against IL but not against comedones.[110] Zinc is less effective than minocycline.[167] The ES3 guidelines give zinc a low strength recommendation for the treatment of mild-to-moderate papulopustular acne (LE4).[12]

III.B.3.c Severe acne

Clinical evidence for the treatment of solely nodular or conglobate acne is sparse; therefore, studies of patients with severe papulopustular acne were selected which evaluated the percentage reduction of nodules and cysts.[12]

Antibiotics In papulopustular acne, the addition of adapalene or fixed dose adapalene-BPO to oral doxycycline was superior to doxycycline alone (LE 4 and 3, respectively) while oral minocycline plus azelaic acid was equivalent to oral isotretinoin (LE 4). In nodular/conglobate acne, equivalent efficacy was observed for oral isotretinoin compared to oral tetracycline and topical adapalene (LE 4). One grade A study found that doxycycline hyclate combined with a fixed-dose combination of adapalene and BPO compared favourably with isotretinoin in severe nodular acne, wherein the former showed composite success (75% reduction of nodules and absence of medically relevant adverse events) in 63.9% of cases compared to 54.9% for isotretinoin.[168] However, isotretinoin had significantly greater improvement from baseline in lesion counts at the study end (20 weeks) and the potential for acne remission with doxycycline and adapalene/BPO is considered unlikely.

Accordingly, a combination of a systemic antibiotic combined with BPO with or without adapalene was given a medium strength recommendation for severe acne.[12, 55]

Due to concerns regarding antibiotic resistance, monotherapy with systemic antibiotics is given a negative recommendation for severe acne.

Hormonal therapy Evidence for the efficacy of hormonal therapy in severe acne is lacking. In Canada, EE/CPA is officially indicated for the treatment of severe acne unresponsive to systemic antibiotics and other available treatments. However, there was only one study demonstrating the superiority of EE-CPA over another COC, EE-LNG (LE 2).[12] Of COCs indicated for acne in Canada, there is otherwise no clear evidence to suggest that any specific COC was superior to another. [160] Thus, COCs are given a low strength recommendation for the treatment of severe acne.

Oral isotretinoin Oral isotretinoin has been the standard treatment of severe acne for over three decades since its efficacy was initially demonstrated in a small study of 14 patients with conglobate acne published in 1979.[169]

There is a sole placebo-controlled randomized trial of oral isotretinoin in 33 subjects with severe acne which demonstrated dramatic improvement with a mean dose of 1.2 mg/kg/day for 4 months (LE 4).[170] These results are consistent with subsequent active comparator and mechanistic studies.[12, 171-179]

Oral isotretinoin is recommended for the treatment of severe acne or for moderate acne that has failed to respond to conventional antibiotic therapies.[12]

In active comparator studies, systemic isotretinoin demonstrated comparable efficacy for inflammatory nodules/cysts or deep inflammatory lesions compared to oral minocycline and topical azelaic acid (LE 4), and to oral tetracycline and topical adapalene; isotretinoin was superior to oral minocycline (LE 4) and to oral tetracycline (LE 3) alone.[12]

Eight trials have been published using different dosage regimens of systemic isotretinoin.[12, 171-180] ES3 reported a mean reduction of 70% of nodules/cysts was achieved dosing at 0.5 mg/kg bodyweight.[12, 171-180] A study on patients with nodular/conglobata acne showed better efficacy for systemic isotretinoin treatment compared to tetracycline.[174] Systemic isotretinoin demonstrated better efficacy against nodules／cysts compared to systemic minocycline or systemic tetracycline.[174] Greater efficacy was not obtained by addition of topical clindamycin and topical adapalene to systemic isotretinoin (LE 4).[178]

A study of four dosing regimens for oral isotretinoin found that, although lower doses appear to be equally efficacious in mild-to-moderate papulopustular acne, the conventional dose of 1 mg/kg/day was more efficacious for severe acne than lower doses or intermittent therapy.[165]

Isotretinoin is lipid soluble and must be taken with food to be efficiently absorbed. A new isotretinoin-Lidose formulation became available in Canada at the beginning of 2013 which has been demonstrated to reduce the requirement that isotretinoin be taken with a fatty meal.[181]

Oral isotretinoin is given a high strength recommendation for the treatment of severe acne.

III.B.4 Adverse Events

Antibiotics Tetracyclines are generally well tolerated but can cause mild gastrointestinal disturbances.[182, 183] In addition to nausea, diarrhea and stomach upset, doxycycline is associated with dose-dependent photosensitivity and esophageal erosion.[183] Minocycline has been associated with a number of rare but severe side-effects, including hypersensitivity reactions and auto-immune disorders, such as lupus-like syndrome, autoimmune hepatitis, arthritis, thyroiditis, and polyarteritis nodosa.[184, 185] ES3 refers to a systematic review of

adverse events reported for minocycline and doxycycline between 1966 and 2003. Minocycline was found to be associated with a greater number and higher severity of adverse events than doxycycline.[183] Due to questions over minocycline's safety, as well as its high cost, its use as a first-line acne medication is not justified.[185] Tetracycline, a pregnancy category D product, is contraindicated during pregnancy due to risk of maternal hepatitis, brown discoloration of deciduous teeth, and the inhibition of bone growth.[186] Tetracycline use during lactation should be limited to less than 3 weeks as prolonged use may lead to dental staining.[92]

Macrolide antibiotics are also associated with gastrointestinal side effects. Systemic clindamycin has been associated with greater incidences of adverse events compared to erythromycin; therefore, topical application, which results in minimal systemic absorption, is preferred.[187] Pseudomembranous colitis has been reported with multiple bacterial agents but is most closely associated with clindamycin ranging in severity from mild-to-life-threatening, when administered orally or parenterally.[136] Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, caution should be taken when using clindamycin containing products with neuromuscular blocking agents.[188] Azithromycin, erythromycin, and clindamycin are pregnancy category B products.[188] Azithromycin and erythromycin are considered safe during breastfeeding but short term use is recommended as there is an unconfirmed association with hypertrophic pyloric stenosis in the breastfed infants of mothers taking macrolide antibiotics.[91, 92] Clindamycin is deemed safe during lactation;[92] however, its use may adversely affect the infants intestinal flora.[91]

Antagonism has been reported between clindamycin and erythromycin. Products containing clindamycin or erythromycin are contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

Adverse effects for trimethoprim include bone marrow suppression, thrombocytopenia, anemia, hyperkalemia and a drug exanthema (4%).[188] Trimethoprim is rated pregnancy category C; studies in rats showed an increased risk of cleft palate at very high doses and use near delivery is associated with an elevated risk of hyperbilirubinemia. Trimethoprim induces folate depression at high doses or in folate-depleted individuals.[186] Trimethoprim should be avoided during pregnancy. Trimethoprim is present in low levels in breast milk and is likely safe; however, avoidance is cautioned in premature infants or neonates with hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficiency.[92]

Antibiotic resistance As with topical antibiotics, there is increasing concern regarding the emergence of antibiotic resistant bacteria, including *P. acnes,* associated with antibiotic therapy for acne. The molecular basis of resistance to erythromycin and clindamycin versus tetracyclines is via mutations in genes encoding different subunits of ribosomal RNA (rRNA).[189, 190] Combined resistance to clindamycin and erythromycin is more common than resistance to tetracyclines.[107]

The use of both topical and systemic antibiotics can lead to resistance in commensal flora, including *Streptococcus pyogenes,* at all body sites.[115] Resistance is a concern for patients with acne and may manifest as a reduced response, no response, or relapse. Resistance is more common in patients with moderate to severe acne and in countries with high outpatient antibiotic sales.[113, 126, 191] There is a gradual decrease in the efficacy of topical erythromycin noted in clinical trials on acne, which is thought to be related to the development of antibiotic-resistant *P. acnes*.[111, 113] However, there has been no evidence to date for reduced efficacy of oral tetracycline or topical clindamycin in the last few decades.[111, 135, 153]

As with topical antibiotics, the ES3 acne guidelines have highlighted the need for treatment guidelines to restrict the use of antibiotics in order to limit the emergence of resistant strains.[12] The recommendation is that systemic antibiotics should not be used as monotherapy and that the duration of treatment be limited. Other recommendations include stricter cross-infection control measures when assessing acne in the clinic and combining any topical/systemic antibiotic therapy with broad-spectrum antibacterial agents, such as BPO.[12, 26, 126, 192] Subantibacterial doses of tetracycline antibiotics may also be considered, although evidence for efficacy at low doses has only been demonstrated for doxycycline. A low oral dose (20 mg twice daily) of doxycycline was found to reduce IL and NIL counts with no detectable selection for resistance.[124]

Hormonal therapy Based on the studies included in ES3 and our extended systematic review, no clear comparison of the safety/tolerability profiles of COCs with other systemic treatments can be made.[12] An assessment to compare the safety profile of the different COCs was beyond the scope of ES3 and this guideline.[12] Relevant safety aspects, including the risk of deep venous thrombosis, have to be considered when prescribing COCs.

COCs must be avoided during pregnancy. COC risks may outweigh benefits within the first 4 weeks postpartum.[91] The optimal time thereafter for reinstitution of COC will depend on the

judgment and experience of the family physician and obstetrician/gynecologist in addressing pregnancy risk and treatment of other conditions including acne.

Spironolactone is generally well tolerated with the most common side-effects reported being diuretic effects, menstrual irregularities, and breast tenderness.[193] Though not strictly contraindicated in men, caution should be exercised due to the risk of gynecomastia, reduced libido, erectile dysfunction, and testicular atrophy. Spironolactone is a pregnancy category D product and should be avoided during pregnancy because it may increase the risk of hypospadias and feminization of a male fetus.[186] Concomitant contraceptive use should be advised during treatment. The active metabolite of spironolactone, canreone, is detectable in breast milk but at only 0.2% of maternal dose. Spironolactone is considered to be compatible with lactation though there is a possibility of a suppression of milk supply.[92]

Oral isotretinoin Isotretinoin has many side-effects including cheilitis, xerosis, epistaxis, dry eyes, impaired night vision, joint pain, and fatigue. Elevated aspartate aminotransferase, alanine aminotransferase, cholesterol, and triglycerides as well as cytopenia may also be side-effects and should be the subject of laboratory monitoring.[194, 195] Isotretinoin-induced hypertriglyceridemia may be associated with pancreatitis.[196] Most side-effects are temporary and resolve after reduction or withdrawal of the drug.[197] Low-dose and intermittent-dose regimens are associated with lower frequency and severity and delayed onset of side-effects.[165, 166]

There is no reliable information available on how long oral isotretinoin may be used or how many courses an individual can safely undergo. Randomized controlled trials using this medication at doses of 1.0mg/kg/day have typically been conducted over 20 weeks[180, 198] and longer durations are expected when using low-dose therapy (0.2-0.5mg/kg day), which is often done to increase tolerability. Concerns have been raised regarding duration of therapy and the likelihood of skeletal sequelae, such as diffuse skeletal hyperostosis, osteophyte formation, and premature epiphyseal closure, which have been reported in individuals undergoing high-dose, long-term systemic retinoid use with etretinate for disorders of cornification. However, several small studies looking at individuals treated with isotretinoin at 1.0mg/kg/day for 16-20 weeks, or for a total dose of 120mg/kg for a duration of 4-6 months, found no evidence of difference in bone mineral density or bone turnover markers.[199-201]

Safety risks can be mitigated by adherence to standard guidelines, which suggest monitoring of liver enzymes, complete blood count, fasting lipid profile, renal function, and conducting serum pregnancy tests (in women only) for the first 3-6 months. If laboratory results remain normal

and the dose remains unchanged, regular testing other than pregnancy tests may be discontinued after 2 months for a 20 week course of isotretinoin.[202]

The available evidence on comparative safety and tolerability of isotretinoin is scarce and was considered insufficient to be used as a primary basis to formulate treatment recommendations.[12] The ES3 guidelines concluded from its systematic review that no clear comparison of the safety and tolerability profiles of isotretinoin with other systemic treatments could be made.

Isotretinoin is a teratogen and is pregnancy category X. The relative risk of congenital malformation associated with isotretinoin exposure during pregnancy is 26%. The described embryopathies include craniofacial, cardiac, thymic, and central nervous system malformations.[203, 204] Because of the teratogenic effects of isotretinoin, risk management and pregnancy prevention programs for isotretinoin are essential to ensure safe use of the drug. Patient counseling, monthly visit reminders, and monitoring for pregnancy prevention in women of childbearing potential contemplating the use of oral isotretinoin should be conducted prior to, during, and at least 1 month after use of this medication. Indeed some authors have suggested consideration of patient-independent contraceptive methods and restricting abstinence only to women who have never been sexually active to reduce isotretinoin-exposed pregnancies.[205]

Isotretinoin is highly lipophilic and passes readily into breast milk presenting a risk of toxicity to the nursing infant. Isotretinoin should be avoided during lactation.[92]

Psychological side-effects, such as suicide and depression, have been reported in studies but a causal relationship has not been demonstrated[206] and suicidal ideation has been correlated with acne severity.[53] The treating physician should monitor for signs and symptoms of psychiatric disturbance among acne patients before, during, and after isotretinoin therapy.[206]

There have been several recent publications investigating the relationship between the isotretinoin and development of inflammatory bowel disease (IBD).[207-212] While the majority of publications do not document an association, the debate continues and is complicated by the undefined relationship between severe acne and IBD.[210]

An underlying relationship between IBD and acne could also explain the association found in one study of tetracycline use with IBD[213] Inquiry about IBD symptoms and family history thereof, along with discussion of the controversy, would be prudent prior to initiating therapy with isotretinoin.

Isotretinoin is indicated for acne in patients aged 12 years and older.[214]

Oral zinc Zinc is generally well tolerated and may be taken in summer as it does not cause photosensitivity. Side-effects include abdominal discomfort and nausea.[110] Long term treatment with oral zinc can lead to hypocupremia by preventing copper reabsorption[215] which can lead to anemia, leukopenia, and neutropenia.[216]

III.C Devices and Procedural Therapies

III.C.1 Devices and Procedural Therapies in Canada

There is growing evidence for light therapy improving acne. [217] Several therapeutic devices have been introduced including visible light, photodynamic therapy (PDT), lasers of various wavelengths, and intense pulsed light sources.

III.C.2 Mechanism of Action

Visible light While the mechanism of action for visible light in acne is unknown, a role for *P. acnes* is central to the current hypothesis. *P. acnes* residing in facial sebaceous glands produce two photosensitizing molecules, coproporphyrin III and protoporphyrin IX. The former acts as a natural photosensitizer for blue light absorbing energy in the UVA and blue region of the spectrum with maximum absorption near 415 nm (the Soret band, indigo colour).

UVA and blue light may have antibacterial and anti-inflammatory activity by decreasing cytokine-induced production of IL-1α and intracellular adhesion molecule-1.[218, 219] However, there is no evidence that exposure to blue light alone significantly reduces colonization by *P. acnes*.[220]

Photodynamic therapy Photodynamic therapy requires the pre-application of a photosensitizer directly to the skin. The pre-treated area is then irradiated with visible light in the presence of oxygen. Commercially available photosensitizers are aminolevulinic acid (ALA), a precursor of heme synthesis, and methyl aminolevulinate (MAL), a more lipid-soluble derivative hydrolysed into ALA by tissue esterases.

When applied to the skin in excess, ALA increases synthesis of porphyrins (mainly protoporphyrin IX, an active photosensitizer) which accumulate preferentially in sebaceous glands. Visible light transforms porphyrins into an unstable triplet state that interacts with oxygen producing reactive oxygen species (ROS). Accumulation of ROS leads to damage and destruction of sebaceous glands.[221]

Various sources of light are used for PDT including red light, blue light, pulsed dye laser, intense pulsed light, and bipolar radiofrequency.

It has been proposed that PDT may have an antibacterial effect on *P. acnes*[222]; however, no significant decrease in *P. acnes* counts was observed in clinical studies with PDT.[223-225]

Other possible mechanisms of action of PDT include reduction of follicular obstruction and hyperkeratosis,[226] local and systemic immunosuppression by decreasing the number of epidermal Langerhans cells,[227] and increased expression of TLR-2.[228]

Lasers and intense pulsed light devices Various lasers have been used for acne treatment including infrared diode, pulsed dye laser (PDL), and potassium titanyl phosphate (KTP), as well as intense pulsed light (IPL).

The relatively long wavelength of the 1450 nm infrared diode laser is absorbed by water, penetrates to mid-dermis, and leads to thermal damage and shrinkage of sebaceous glands,[229] which may result in reduced sebum production.[230]

The mechanism of action for PDL (585nm) on acne lesions is poorly understood; it does not reduce *P. acnes* colonization nor does it reduce sebum production.[231] However, it may stimulate collagen remodeling and reduce inflammation through increase in transforming growth factor (TGF)-beta1.[231] Since PDL targets blood vessels it may reduce erythema associated with IL.

KTP (532nm) may induce non-specific collateral thermal injury to sebaceous glands.[232]

Unlike a laser, intense pulsed light (IPL) is a polychromatic non-coherent (500 to 1200 nm) light that can be modified by filters. Its use has been reported for acne alone and as a light source for PDT. The mechanism of action is unknown but may involve selective photothermolysis of blood vessels that supply sebaceous glands, reducing sebum production.[233]

III.C.3 Efficacy

III.C.3.a Comedonal Acne

Visible light There is inadequate evidence for treatment of comedones with light sources. Treatment with visible light is given an open recommendation for comedonal acne.

Photodynamic therapy There are inadequate PDT studies addressing comedonal acne. Thus, this modality is given an open recommendation.

Lasers Due to lack of evidence for laser treatment in comedonal acne, an open recommendation is given.

III.C.3.b Mild-to-moderate Papulopustular Acne

Visible light Combined red-blue light phototherapy was superior to BPO and to white light and equivalent to blue light alone.[12, 234] Blue light reduced inflammatory lesions compared to control.[235] Blue light was efficacious in reducing acne compared to no treatment.[236]

Based on these studies and the demonstrated efficacy of blue light therapy in reducing IL and total lesions (TL) (LE3), it was recommended as low strength, in agreement with ES3.

Due to conflicting evidence regarding the efficacy of red light compared with placebo[12] it was rendered an open recommendation.

Photodynamic therapy PDT treatment methodology is not standardized and several different approaches are used in treatment of acne. Differences in skin preparation, photosensitizer (ALA vs. MAL), duration of application, light source, and light treatment parameters may all influence outcomes of PDT treatment.

One additional trial subsequent to ES3 was identified which found no difference in lesion counts between treated and untreated sides ($p > 0.05$)[237] (grade C; LE4).

In view of the paucity of evidence and lack of treatment standardization and optimization, PDT was given an open recommendation for mild-to-moderate papulopustular acne, similar to ES3.

Lasers

1450nm In one study, treatment with the 1450nm diode laser reduced lesion counts and sebum production.[238] However, in a subsequent study, improvement was observed for both the treated and untreated sides of the face (grade C).[239]

Pulsed dye laser PDL treatment reduced lesion counts and acne grade compared with sham treatment[231]; however, no additional benefit was observed by addition of PDL to clindamycin-BPO treatment[240] (1 grade B study).

KTP (532nm) KTP laser treatment was reported to result in short-term improvement of acne with minimal side effects (1 grade C study).[241, 242]

Intense pulsed light IPL and IPL with PDT reduced comedone counts compared to untreated control but did not significantly reduce IL.[243] A grade C study reported a short-term reduction of comedones and IL in Asian patients (skin types 3-4) after IPL treatment.[244]

The overall level of evidence for laser/IPL therapy in acne demonstrates variable efficacy and is based on small studies with potential risk of bias (LE4).

In the absence of higher quality clinical trials, treatment with IPL and laser in mild-to-moderate papulopustular acne is given an open recommendation.

III.C.3.c Severe Acne

Visible light There have been no studies on visible light alone in severe acne. In view of the potential risk of sequelae with severe acne and finding of worsening of nodulocystic acne with blue light monotherapy,[236] this modality was given a negative recommendation.

Photodynamic therapy One study reported complete clearance after PDT with ALA activated by long-pulsed PDL in patients that had failed oral isotretinoin therapy.[245]

In the absence of high quality clinical trials and treatment protocol standardization, PDT is given an open recommendation (LE4).

Lasers Due to a lack of evidence, an open recommendation is given for laser treatment of severe acne.

III.C.4 Adverse events

Light therapy for the treatment of acne tends to be well tolerated and side-effects are generally mild. No significant side-effects were reported for treatment with visible light,[234-236] though one study found that nodulocystic lesions tended to worsen after treatment.[236]

In the case of PDT, reported side-effects include pain, erythema, edema, blistering, acute acneiform eruptions and post-inflammatory hyperpigmentation.[246]

Side-effects of PDL include pain, erythema, purpura, and post-inflammatory hyperpigmentation.[240]

Side-effects of IPL were reported to be mild and included mainly erythema, burning and stinging.[244]

III.D Adjunctive Therapies

III.D.1 Adjunctive Therapies in Canada

Although chemical peels and diet were not reviewed in the ES3 guidelines, they were added to the present guidelines due to widespread interest as potential adjunctive therapies for acne. The evidence for these interventions is currently poor but the publication of a small number of recent studies in this area merits discussion.

Diet There has long been an anecdotal link between diet and acne and, accordingly, it has been reported that acne does not occur among two native tribal communities (Kitavan Islanders in Papua New Guinea and Ache peoples in Paraguay) who consume a high fibre, low fat diet with no added sugars and no significant introduction of Western foods.[247] Patients with acne commonly question their physicians regarding the possible role of dietary modification in acne therapy.

Chemical peels Chemical peels, usually utilizing salicylic or glycolic acid as a peeling agent, have been in use for many years as adjunct therapy for acne. As these are not medications, they are not typically covered by drug plans but they are relatively affordable and convenient and seem to be well tolerated.

This section will examine evidence for these interventions in acne.

III.D.2 Mechanism of Action

Diet

Glycemic index A high glycemic index (GI) diet promotes hyperinsulinemia, which in turn trigger hormonal elevations including insulin-like growth factor 1 (IGF-1). These hormones may induce both increased androgen-induced sebum production and follicular epithelial keratinization.[247]

Dairy Milk contains hormones, such as IGF-1, 5-alpha-reduced steroids, and alpha-lactalbumin, which affect the pilosebaceous unit.[248] Furthermore, milk consumption has been shown to increase IGF-1 production.[249]

Chemical peels The most commonly used peeling agents are salicylic acid and glycolic acid. These agents act through direct and indirect enzymatic activation, reducing cohesion of corneosomes and keratinocytes which leads to exfoliation of the superficial skin layer. In addition, salicylic acid may also have anti-inflammatory properties.[250] Glycolic acid belongs to an alpha-hydroxy acid (AHA) family that includes several other organic acids naturally found in fruits and sugar cane such as lactic, malic, tartaric, and citric acids. In contrast, salicylic acid is the only beta-hydroxy acid used in dermatology. In contrast with glycolic acid and other alpha-hydroxy acids, the benzoyl group of salicylic acid is more lipophilic and may perform better in areas rich in sebaceous glands.

Complementary topicals

A recent Cochrane review found low quality evidence for tea tree oil and purified bee venom for treatment of acne.[251] Tea tree oil has been described to have antimicrobial and anti-inflammatory activities, which may contribute to its purported efficacy.[252-254]

III.D.3 Efficacy

III.D.3.a Comedonal Acne

Diet A systematic literature review concluded that there is evidence supporting the role of dairy products and high glycemic index foods in acne prevalence and severity, though the majority of studies assessed were observational, had methodological limitations, and did not specify the type or severity of acne in their results.[255] Thus, there is insufficient evidence to make a recommendation regarding diet in comedonal acne.

Glycemic index A grade C case-control study reported an association between high glycemic load and the prevalence of acne, though acne type or severity was not reported.[256] A small, grade B, interventional study found that patients assigned to a low GI diet showed significant reduction of comedones, as well as improvement of histological parameters, compared to those instructed to follow the control diet.[257] In two additional grade B trials of mild-to-moderate acne that examined only total acne lesions, both found a significant improvement in those counselled to have a low glycemic index diet compared to those on control diet.[258, 259] However, in one of these studies, individuals counselled to have a high glycemic index diet also improved by the end of the study and there was no significant difference between the low and the high glycemic index diets[259]; this study may have been underpowered. A Cochrane review of complementary therapies for acne found no clear evidence for a reduction of NIL with a low GI diet.[251]

Dairy There are no randomized controlled trials regarding the influence of dairy on acne. Three grade C case-control studies have found frequency of milk and/or dairy product consumption associated with acne vulgaris; however these studies had methodological issues including selection bias, recall bias and confounding.[256, 260, 261] The remaining publications are case series[262] or from analysis of cohort studies whose data was collected for other applications.[263-265] These papers also do not indicate type of acne (comedonal, papulopustular or severe). Therefore there was insufficient evidence to make a recommendation regarding dairy consumption in comedonal acne (LE4).

Chemical peels A systematic review of the efficacy of chemical peels for treatment of acne showed an average reduction of comedones by approximately 35%; however, published studies

had sample size or design limitations.[250] Peels using 30% glycolic acid peels have similar efficacy to 30% salicylic acid peels[266] (1 grade B study); 70% glycolic acid was not significantly different from Jessner's solution (14% resorcinol, 14% lactic and 14% salicylic acid in an alcohol base)[267]; however, another study found 30% salicylic acid performed better than Jessner's solution for comedones[268] (1 grade B study). Two other studies compared glycolic acid and salicylic acid, respectively, with peeling agents not available in Canada.[269, 270]

Evidence is lacking for the efficacy of peels; however, peels are relatively safe and inexpensive and are, thus, given an open recommendation for comedonal acne (LE4).

Complementary topicals

In one study, graded as low quality[271], tea tree oil was superior to vehicle for the reduction of comedones and improvement of acne severity index.[251, 272]

One low quality study reported that purified bee venom resulted in significantly greater improvement of acne severity, determined by the Korean Acne Grading System (KAGS), compared to vehicle.[251, 273]

III.D.3.b Mild-to-moderate Papulopustular Acne

Diet

Glycemic index A small interventional study found that patients assigned to a low GI diet showed significant reduction of comedones and IL, as well as improvement of histological parameters, compared to the control group[257] (1 grade B study). Two small randomized controlled trials found an improvement in total acne lesions in those individuals on a low glycemic index diet compared to those on the control diet[258, 259]; no information on morphology or severity of lesions was given (2 grade B studies).

Based on review of the available literature, a low glycemic index diet for acne is given LE3 for mild-to-moderate papulopustular acne (3 grade B studies; LE3).

Dairy As discussed in III.D.3.a, there was insufficient evidence to make a recommendation regarding dairy consumption in papulopustular acne (LE4).

Chemical peels There is conflicting evidence regarding the efficacy of chemical peels for papules and pustules.[250] One grade B study found both 30% salicylic acid and Jessner's solution were effective for IL.[268] Some studies have reported an initial flaring of IL but continued treatment was reported to result in the reduction of both papules and pustules.[250, 274-276]

Due to scarcity of evidence and the presence of conflicting evidence regarding the efficacy of chemical peels for papules and pustules, chemical peels are given an open recommendation for mild-to-moderate papulopustular acne.

III.D.3.c Severe acne

Diet There was insufficient evidence for the panel to make a recommendation regarding the role of diet in severe acne.

Chemical peels Though one study found a delayed improvement in nodulocystic lesions, most studies have found little to no effect of chemical peels on nodulocystic acne.[250]

Due to lack of evidence for efficacy for severe acne, and the risk of scarring or adverse psychosocial effects of delaying effective treatment, chemical peels are given a negative recommendation for severe acne.

III.D.4 Adverse events

Chemical peels Chemical peels are generally well tolerated. Reported adverse events include transient erythema, dyspigmentation, and mild peeling. There may also be a risk of reactivation of herpes simplex. Flares of IL occur in some cases, but these were reported to clear with continued treatment.[250] Salicylic acid is a pregnancy category C product and its application over a large surface area could result in absorption and salicylism. Its use should, thus, be avoided during pregnancy. Due to a lack of controlled trials addressing the safety of salicylic acid and other chemical peel products during pregnancy, definitive recommendations on the safety of their use in pregnant women cannot be made.[277] Therefore, it is advisable to delay chemical peel procedures until completion of the pregnancy.

Complementary topicals

Despite reports of sensitization, which may be exacerbated by oxidation[278, 279], topical tea tree oil-containing gel had a similar frequency of adverse events to vehicle alone; reported side-effects were minimal pruritus, burning sensation, and minimal scaling of the skin.

The safety of purified bee venom has not been assessed.[273]

III.D.6 Adjunctive Therapies Not Covered by this CPG

Treatments such as comedone extraction, electrocautery, and intralesional steroid injection of inflammatory papules and nodules have a legacy of use in dermatology. These may have a role in appropriately selected patients with lesions unresponsive to standard treatments. While

many practitioners have experience with these treatments, there is insufficient evidence from well-designed trials regarding their efficacy to substantiate a formal recommendation in these evidence-based guidelines.

III.E General Considerations for Treatment

A supportive and positive approach of the health care provider to acne patients along with a treatment program supported by evidence based outcomes can enhance patient satisfaction and treatment outcomes. In addition, engaging patients in providing information about the impact of acne on their lives and discussion of their values and preferences in treatment can establish trust and therapeutic rapport. Adherence to the treatment regimen is an important determinant of treatment outcome for all the medications discussed in this CPG. Counselling of patients, including addressing their concerns about treatment, dispelling myths, providing instruction for proper use, and timely follow-up to gauge progress has been demonstrated to enhance adherence.[280]

Upon initiation of treatment, some clinical improvement should be expected within 8 to 12 weeks. A change in medication should be considered if no improvement is observed. In some patients, acne may be a chronic condition.[281] In such cases, acne variants and acne-like dermatoses, such as those discussed in section II.2, should be excluded. Long-term management, including ongoing or maintenance therapy and lifestyle modification, may be required.

Table 8 Changes in recommendations during adaptation from ES3

Treatment	ES3	CA-CPG	Rationale for change
Tazarotene			ES3 favoured adapalene, CA-CPG voted to give tazarotene equal strength
Comedonal	NA	Medium	
Mild-to-mod.	NA	Medium	
Benzoyl peroxide			8 grade A and 2 grade B studies support its efficacy for comedonal acne (LE 1)
Comedonal	Low	Medium	
Fixed-dose comb.			Evidence for comedone reduction (LE 1); equal or superior to BPO or adapalene alone
Comedonal	NA	Medium	
ERY-tretinoin			No evidence for formulation available in Canada
Mild-to-mod. Pap.	Low	Open	
Clinda-tretinoin			Evidence for efficacy on NIL and IL (LE 3) but not BPO raises risk of resistance
Comedonal	NA	Low	
Mild-to-mod.	NA	Low	
Dapsone			Lack of evidence showing topical dapsone superiority to vehicle (LE 4)
Comedonal	NA	Open	
Mild-to-mod.	NA	Open	
Azelaic acid			Lack of evidence for 15% formulation available in Canada
Comedonal	Low	Open	
Mild-to-mod.	Medium	Open	
Systemic antibiotics + adapalene-BPO			Doxycycline + adapalene-BPO superior to doxycycline alone (LE 3) and doxycycline-adapalene (LE 4)
Mild-to-mod.	Low	Medium	
Systemic antibiotics + azelaic acid			Lack of evidence for 15% formulation of azelaic acid available in Canada
Mild-to-mod.	Low	NA	
COC			Evidence for reduction of comedones and IL; Limited evidence for efficacy of COC in severe acne
Comedonal	Negative	Low	
Mild-to-mod.	Negative	Medium	
Severe	NA	Low	
COC + topicals			Insufficient evidence that addition of topicals to COC is superior to COC alone
Severe	Low	NA	
Low GI diet			Some evidence of association of low GI diet with improved acne symptoms (LE 3)
Comedonal	NA	Open	
Mild-to-mod.	NA	Open	
Chemical peels			Some evidence of efficacy but studies suffer from methodological limitations (LE 4); not recommended as sole therapy for severe acne
Comedonal	NA	Open	
Mild-to-mod.	NA	Open	
Severe	NA	Negative	

BPO: benzoyl peroxide; Clinda: clindamycin; COC: combined oral contraceptives; ERY: erythromycin; GI: glycemic index; IL: inflammatory lesions; Mild-to-mod.: Mild-to-moderate papulopustular acne; NIL: non-inflammatory lesions; NA: not assessed;

IV Applicability

IV.A Facilitators and barriers to application

There are multiple potential providers and points of care for people with acne in Canada. Beyond publication in the Canadian Medical Association Journal, facilitation of these guideline recommendations will be by announcements and press releases to relevant stakeholders including professional health care organizations and media within Canada including but not limited to the Canadian Dermatology Association, Canadian Dermatology Nurses Association, Canadian Skin Patient Alliance, Acne and Rosacea Society of Canada, Canadian Family Physician Association, Skin Therapy Letter, and national press services. Presentations based on these guidelines will be conducted for the Canadian Dermatology Association, Canadian Dermatology Nurses Association and other associations based on invitation.

Abridged summaries will be developed for the Canadian Dermatology Association, the Acne and Rosacea Society of Canada and other medical, nursing, and pharmacy professional organizations invited to review these guidelines. Furthermore, medical education materials will be developed to facilitate dissemination.

To enhance dissemination, the authors also plan to develop specific presentations on these guidelines that can be accessed in a live or virtual environment.

Cost of treatments across Canada, including coverage on provincial/territory drug plans, is presented in Appendix 4.

Current barriers to application include the current lack of a French translation.

IV.B Advice on how recommendations can be put in practice

Treatment recommendations can be initiated at time of initial visit and modifications thereafter based on clinical and patient-reported outcomes on follow-up visits. Specific advice on strengths of recommendations, clinical follow-up, and treatment escalation is provided in Figure 1 *Summary schematic for management of acne*.

Tools on implementation are based on Figure 1 *Summary Schematic for management of acne* and Tables 1-3 in these guidelines. These can be printed out for use as handouts, counseling aids, or posters in examination rooms.

Further tools including photographic examples of varying acne severity levels are in development.

IV.C Resource implications of applying the recommendations

These guidelines provide evidence-based treatment recommendations along with cost information, given in Appendix 4. We anticipate that this aggregate information will provide prescribers a means of rationalizing treatment for individual patients with varying values and preferences.

Cost implications of guideline recommendations are fully detailed in an upcoming publication, currently in preparation. (Czilli T, Tan J, Knezevic S. Costs of medications recommended by the Canadian acne clinical practice guidelines; in preparation). Results are briefly presented here and are based on referencing to a standardized 3 month treatment course. Costs for longer durations can be extrapolated mathematically. The highest level of recommendation for comedonal acne is medium - comprising topical retinoids, benzoyl peroxide (BPO), fixed dose BPO-clindamycin and BPO-adapalene. Associated 3 month costs based on assumed daily facial application of 0.5 g/d were $14.40 – 70.65, $6.75, $40.95 - 44.10, and $70.65, respectively. For mild-moderate acne, BPO-clindamycin and BPO-adapalene were high strength recommendations with corresponding 3 month costs as noted above. Medium strength recommendations comprised BPO, topical retinoids, systemic antibiotics plus BPO +/- topical retinoids, and combined oral contraceptives (COCs). For oral antibiotics, 3 month costs ranged from $25.20 (tetracycline) to $97.20 (minocycline) while for COCs, the range was $28.98 for ethinyl estradiol (EE) 0.020 mg / levonorgestrel 0.1mg to $104.58 for EE 0.035 mg / cyproterone acetate (CPA) 2 mg. Addition of topical therapies or systemic antibiotics to these regimens would correspondingly increase costs. For severe acne, oral isotretinoin was the sole high strength recommendation– with three month costs for a 70 kg patient ranging from $393.96 to $478.80 depending on formulation and dosing. Additional costs with oral isotretinoin include more frequent physician evaluations and laboratory testing.

The monitoring of adverse effects of these medications is within the current scope of practice and no additional resource implications are anticipated in this regard with these guideline recommendations.

IV.D Monitoring or auditing criteria

Monitoring and audit criteria include use of appropriate clinical and patient-reported outcomes for acne severity, effectiveness, satisfaction with therapy, and adverse effects during initial and follow-up visits.

A potential set of auditing criteria may include some or all of the following elements:

I. Initial assessment:

A. Evaluation of acne severity

B. Evaluation of acne scar severity

C. Evaluation of acne extent (face, chest and back)

D. Evaluation of impact of acne

E. Appropriate selection of treatment(s) based on acne severity (see recommendations)

F. Treatment counseling

a. medication administration, application, potential adverse events

b. if oral isotretinoin also include informed consent form, pregnancy prevention program, counseling on management of potential adverse events

G. Appropriate follow-up for monitoring: within 2-3 months (monthly for oral isotretinoin)

II. Ongoing management

A. Evaluation of acne severity

B. Evaluation of acne scar severity

C. Evaluation of acne extent (face, chest and back)

D. Evaluation of impact of acne

E. Evaluation of treatment satisfaction

F. Evaluation of patient perceived improvement (or not)

G. Inquiry into possible adverse events

H. Treatment modification if inadequate effectiveness or adverse event development

V Conflicts and Editorial Independence

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Conflict of interest declarations:

- Y. Asai has served on an advisory board for GSK.
- A. Baibergenova has served on an advisory board for Galderma, Valeant, and Astellas.

- M. Dutil has received honoraria for speaking from Galderma, Valeant, GSK, and L'Oreal.
- P. Hull - none
- S. Humphrey has served as a speaker and consultant to Galderma, GSK, Johnson & Johnson, Procter & Gamble and Valeant and as an investigator for Galderma.
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