CONSENSUS GUIDELINES

Acne Management Guidelines by the Dermatological Society of Singapore

by HAZEL H. OON, MD, MRCP, FAMS; SU-NI WONG, MBBS, MMED, FRCP, FAMS; DERRICK CHEN WEE AW, MBBS, MRCP, FAMS; WAI KWONG CHEONG, MBBS, MRCP, FRCP; CHEE LEOK GOH, MD, MMED, FRCP, FAMS; and HIOK HEE TAN, MBBS, MRCP, FRCP, FAMS

Drs. Oon and Goh are with the National Skin Centre in Singapore. Dr. Wong is with Dr. SN Wong Skin, Hair, Nails & Laser Specialist Clinic in Singapore. Dr. Aw is with Sengkang General Hospital in Singapore. Dr. Cheong is with Specialist Skin Clinic and Associates in Singapore. Dr. Tan is with Thomson Specialist Skin Centre in Singapore.

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ABSTRACT

Due to the multiethnic patient population with varying skin types in Singapore, clinicians often find the management of acne in their patients to be challenging. The authors developed these guidelines to provide comprehensive advice on individualized acne treatment and to provide a reference guide for all doctors who treat patients of Asian descent. Unique features of acne in Singapore are highlighted. We address concerns such as diet, special population needs, and the benefits, side effects, risks, and cost-effectiveness of currently available acne treatments. These treatment guidelines outline recommendations for the diagnosis, grading, and treatment of children, adolescents, and adults with acne of varying severity, and include advice pertaining to the use of cosmeceuticals and management of scars.

KEYWORDS: acne vulgaris, topical therapy, systemic therapy, benzoyl peroxide, retinoid, antibiotics, fixed combination, diet, hormonal therapy, laser therapy, light therapy, contraceptives, *Propionibacterium acnes*, acne scar, irritation, adjunctive therapy, cosmeceuticals, Singapore, treatment guidelines

Acne is a chronic inflammatory disease of the pilosebaceous units, characterized by the formation of comedones, erythematous papules, pustules, and/or nodules (i.e., pseudocysts) that can be accompanied by scarring.[1] Acne affects the face more than the trunk and is most common in individuals aged 15 to 24 years, with a typical onset in adolescence or early adulthood.[2,3]

In a community-based study in Singapore, acne was found in about 88 percent of adolescents aged 13 to 19 years.[4] In another study, 41 percent of adults treated at the National Skin Centre in Singapore had experienced acne since adolescence, although the majority presented with adult-onset acne. Comedonal acne is more prevalent in adolescents, while cystic acne is seen more often in adults.[5] Additionally, adolescent acne is more common in men (61%), while postadolescent acne is more common in women (69%) (Figure 1).[5,6] Pruritus is common (70%) in patients with acne and negatively affects mood in about 55 percent of these patients.[7] Postacne scarring and dyspigmentation are also prevalent in patients with acne. In a cohort of 40 patients, 58 percent of patients with mild acne had macular erythema or hyperpigmentation; in those with moderate acne, 54 percent had postacne scarring and 14 percent had hypertrophic/keloid scars.[8] Acne is also likely to be a significant contributor to psychological distress, particularly in adolescents. About half of patients reported that they are "rarely" or "never" comfortable with their acne. Twenty-eight percent of these patients reported self-esteem concerns related to their acne, while more than 25 percent reported that they felt "depressed." A majority (60%) shared feelings of concern due to scarring caused by acne.[4] These statistics highlight the importance of effective and timely treatment of acne.

Similar to the general population, the course of acne in Singaporeans is influenced by hormonal and genetic factors, although exogenous elements (e.g., physical, chemical, environmental, dietary) can precipitate flares.[9] *Propionibacterium acnes* (*P. acnes*) is central to inflammation (Figure 2).[9–12]

METHODS

The Dermatological Society of Singapore (DSS) Acne Advisory Board members represent various institutions and the private sector in Singapore and were nominated by the DSS Executive Committee for a period of one year. Patient views were sought informally from

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CORRESPONDENCE: Hazel H. Oon; Email: hazeloon@nsc.com.sg

patients, relatives, friends, and staff of the board members.

Management recommendations were developed based on the Appraisal of Guidelines for Research and Evaluation (AGREE) II. The references include meta-analyses and current guidelines (e.g., S3, Canadian, Global Alliance for Acne, South-East Asia Study Alliance [SASA], Malaysia and Philippine Guidelines, and the National Skin Centre Management Guidelines for Acne).[13–18] A literature search was conducted on PubMed to identify relevant research from the date of its inception until December 31, 2014. These recommendations were appraised based on the United Kingdom National Institute for Health and Clinical Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines (Table 1).

Disclaimer. While these guidelines are evidence-based, they cannot be substituted for clinical judgement, and patients should be assessed and managed on an individualized basis. These recommendations were derived from critically appraised data at the time of this document's preparation. While a "user pays" healthcare system allows for more flexibility in implementing these guidelines in clinical practice, it also poses a barrier to patients who are cost-conscious. As costs varies, these guidelines will not address costs specifically, but rather provide general recommendations regarding the costs of laboratory investigations, medications, and cosmeceuticals.

DIAGNOSIS AND ASSESSMENT

The Comprehensive Acne Severity Scale (CASS) can be used to qualitatively estimate acne severity by assessing inflammatory and noninflammatory lesions, as well as to evaluate patient response to treatment (Table 2).[19] Aggravating or causative factors (e.g., acnegenic products, occlusion-causing agents, medications, stress, diet, smoking, obesity, occupation, sports, and other lifestyle habits) and systemic disorders (e.g., Cushing syndrome, androgen-secreting tumors) should be assessed. In women, clinicians should assess for signs of hyperandrogenism (i.e., menstrual irregularity, hirsutism, and androgenetic alopecia).[20–22] Previous acne treatments and response, as well as specific adverse effects and adherence issues, should

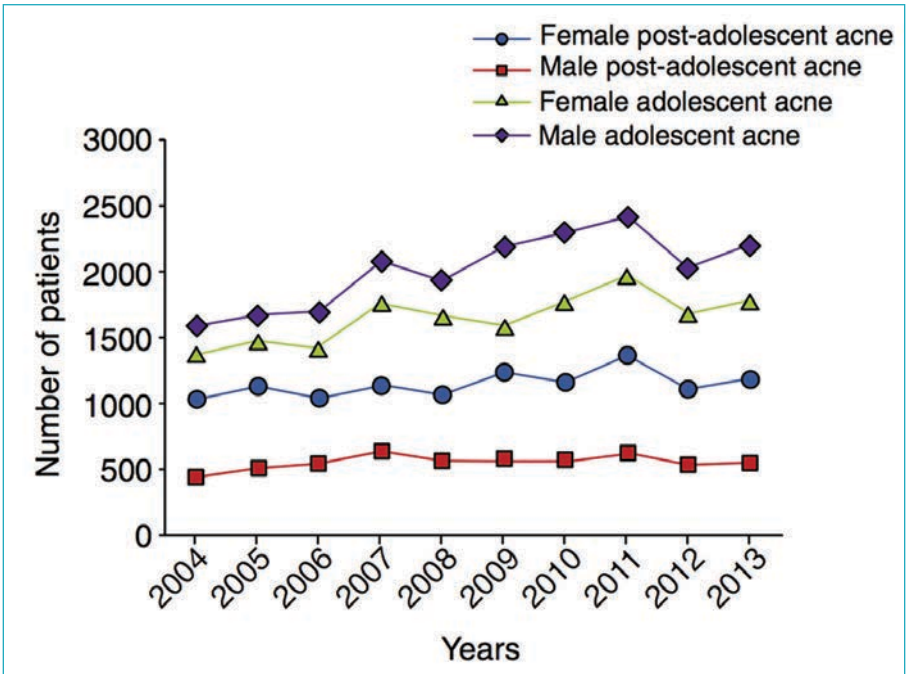

FIGURE 1. Year-on-year comparison of male and female adolescent and male and female postadolescent patients with acne
Source: Han XD, Oon HH, Goh CL. Epidemiology of post-adolescence acne and adolescence acne in Singapore: a 10-year retrospective and comparative study. *J Eur Acad Dermatol Venereol.* 2016;30(10):1790–1793.

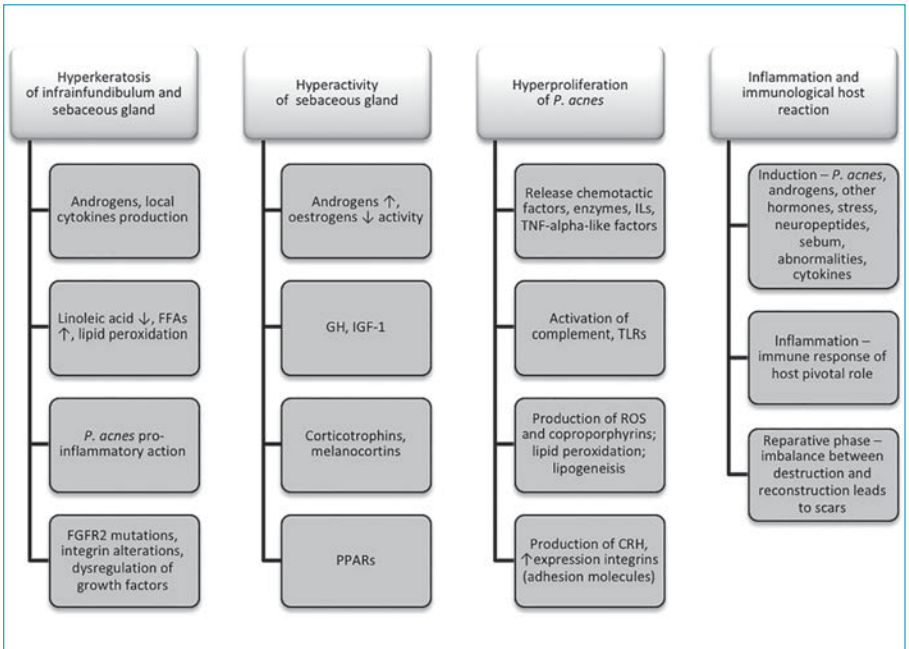

FIGURE 2. Factors contributing to acne[9–11]
FFA: free fatty acids; FGFR2: fibroblast growth factor receptor 2; IL: interleukin; TNF: tumor necrosis factor; GH: growth hormone; IGF-1: insulin-like growth factor-1; TLR: toll-like receptor; ROS: reactive oxygen species; CRH: corticotropin-releasing hormone; PPARs: peroxisome proliferator-activated receptors.

TABLE 1. Basis for level of evidence and strength of recommendation

LEVEL OF EVIDENCE	DESCRIPTION
1++	High-quality meta-analyses or high-quality systematic reviews of clinical trials with very little risk of bias
1+	Well-conducted meta-analyses, systematic reviews of clinical trials, or well-conducted clinical trials with low risk of bias
1–	Meta-analyses, systematic reviews of clinical trials, or clinical trials with high risk of bias
2++	High-quality systematic reviews of cohort or case and control studies; cohort or case and control studies with very low risk of bias and high probability of establishing a causal relationship
2+	Well-conducted cohort or case and control studies with low risk of bias and moderate probability of establishing a causal relationship
2–	Cohort or case and control studies with high risk of bias and significant risk that the relationship is not causal
3	Nonanalytical studies, such as case reports and case series
4	Expert opinions
STRENGTH OF RECOMMENDATION	**DESCRIPTION**
A	At least one meta-analysis, systematic review or clinical trial classified as 1++ and directly applicable to the target population, or a volume of scientific evidence comprising studies classified as 1+ that are highly consistent with each other; evidence drawn from a NICE technology appraisal
B	A body of scientific evidence comprising studies classified as 2++, directly applicable to the target population and highly consistent with each other, or scientific evidence extrapolated from studies classified as 1++ or 1+
C	A body of scientific evidence comprising studies classified as 2+, directly applicable to the target population and highly consistent with each other, or scientific evidence extrapolated from studies classified as 2++
D	Level 3 or 4 scientific evidence, or scientific evidence extrapolated from studies classified as 2+, or formal consensus
D (GPP)	A good practice point (GPP) is a recommendation for best practice based on the experience of the Advisory Board members

NICE: United Kingdom National Institute for Health and Clinical Excellence
* Studies with a "–" level of evidence were not used for making a recommendation. For Level 4 evidence, 80% consensus of the Advisory Board was required to generate a consensus. These guidelines will be updated every five years.

TABLE 2. Comprehensive Acne Severity Scale (CASS)

GRADE		DESCRIPTION
Clear	0	No lesions to barely noticeable ones; very few scattered comedones and papules
Almost clear	1	Hardly visible from 2.5 meters away; a few scattered comedones and a few small papules; and very few pustules, comedones, and papules
Mild	2	Easily recognizable; less than half of the affected area is involved; many comedones, papules, and pustules
Moderate	3	More than half of the affected area is involved; numerous comedones, papules, and pustules
Severe	4	Entire area is involved; covered with comedones, numerous pustules and papules, a few nodules and cysts
Very severe	5	Highly inflammatory acne covering the affected area, nodules and cysts present

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be evaluated. While assessing patient awareness, obtaining previous treatment history and psychosocial effects data are essential. The use of validated questionnaires (e.g., Acne-specific Quality of Life) might be advantageous, but are not essential.[23]

DIET, OBESITY, AND ACNE

Diet modification as an adjunct to acne treatment should be based on good-quality evidence ti avoid unnecessary prohibitions that might lead to nutritional deficiency.[24] Due to strong biochemical, histopathologic, and clinical evidence, a low glycemic index (GI) diet is encouraged for patients with acne (Level 2, Grade B). The GI ranks food according to the effects of its carbohydrate content on blood glucose level. For instance, high-GI food (GI>70) results in rapid rise in blood glucose, while low-GI food causes little change (Table 3).[15,25–29]

Factors that influence GI include amount of soluble fiber (high fiber has lower GI); fat and protein content; type of sugar (e.g., fructose has a lower GI and glucose has higher GI); type of starch; amount of cooking/processing (i.e. cooking/processing increases GI); food form (e.g., small particle size is more quickly digested and absorbed); and acidity (delays absorption).

Chocolate and oily/fatty foods are commonly implicated in acne. Recent studies have shown a correlation between chocolate consumption and acne, and thus chocolate should be avoided (Level 2–, Grade D). However, there is generally insufficient evidence supporting the withdrawal of oily or fatty food.[30–32] Observational studies suggest that milk, particularly skim milk, exacerbates acne.[33–35] Whey has also been associated with new onset or exacerbation of acne. This effect was more prominent in women and in individuals without current acne and/or no family history of acne.[36] Further clinical trials are required before any restrictions on whey consumption can be recommended.[37]

Obesity is associated with acne, particularly inflammatory acne. School children with a body mass index (BMI) of less than 18.5kg/m^2 had a lower prevalence of acne, while those with a BMI-for-age in the 95th percentile or above had a significantly higher rate of acne development. This is most likely due to the peripheral hyperandrogenism that accompanies obesity.[38]

TABLE 3. Glycemic index values of common food items in Singapore[15,28,29]

FOOD GROUP	LOW GI (<55)	MEDIUM GI (55–70)	HIGH GI (>70)
Rice and rice alternatives	• Long grain rice, boiled • Semolina • Wild rice, boiled	• Basmati rice, boiled • Brown rice, boiled • Quinoa • Couscous, rehydrated with water	• Jasmine rice, boiled • White rice, boiled • Glutinous rice
Cereals	• Rolled oats, raw • Oat bran, raw	• Natural muesli • Instant oat porridge • Bran cereal • Muesli bar	• Rice bubbles • Corn flakes, cocoa-flavoured puffed rice • Other sweetened cereals
Bread	• Whole grain bread • Multigrain bread • Sourdough bread • Rye bread • Wheat tortilla	• Wholemeal bread • White bread with fiber • Pita bread • Muffin • Pancake • Chapatti	• White bread • Sweetbreads • Donut
Pasta and noodles	• Wholemeal spaghetti, boiled • Spaghetti, white, boiled • Lasagna	• Rice noodles/ vermicelli, boiled • Various pasta, boiled • Buckwheat noodles, udon, instant noodles • Fried beehoon, Singapore-style	
Vegetables and legumes	• Baked beans in tomato sauce • Carrots, raw • Yam, boiled • Lentils/chickpeas/kidney beans/peas, boiled • Hummus	• Potatoes, boiled • Tapioca, boiled • Sweet potato, boiled • Sweet corn, boiled • Cocoyam	• Pumpkin • French fries • Mashed potato
Fruits	• Mango, raw • Pear, raw • Apple, raw • Orange, raw • Banana, raw • Grapefruit, raw • Strawberries, raw • Prunes, pitted • Grapes, raw	• Most fruits eaten whole (with fiber) • Pineapple, raw • Cherries, raw • Blueberries, raw • Lychee, raw • Rock melon, raw • Papaya, raw • Raisins, dried • Cranberries, dried	• Watermelon, raw • Canned fruit in syrup • Dried fruit
Dairy products and alternatives	• Milk, full fat • Milk, skim • Yogurt • Soy milk	• Ice cream	
Drinks	• Boiled barley • Water • Orange or apple juice, unsweetened* • Carrot juice, fresh	• Sugar (sucrose) • Sucrose-containing drinks (e.g., orange cordial, reconstituted) • Carbonated soft drinks • Honey	• Glucose-containing drinks (e.g., energy drinks) • Teh tarik

*While retention of fruit pulp and not adding sugar lowers the GI of fruit juices, they are still considered a source of excessive sugar. In general, fresh fruit is preferred over juice in the context of a healthy diet.

TOPICAL THERAPIES

Topical antimicrobial therapy. *P. acnes* has shown a growing antibiotic resistance in Singapore.[4,18,39] Worldwide, the highest rates are seen in those who previously used topical erythromycin and clindamycin.[40] Antibiotic resistance in *P. acnes* confers a potential reduction in treatment efficacy, and transfer of resistant organisms through close contact is possible. Additionally, antibiotic resistance (*P. acnes*) can potentially promote resistance within other bacterial pathogens. *De novo* antibiotic resistance is an ongoing problem; thus, topical antibiotic monotherapy is not recommended.

Combination therapy is preferred, not only because monotherapy is less effective, but because topical antibiotic monotherapy is associated with rapid antibiotic resistance.[41,42] Consider alternative antibacterials, such as BPO, salicylic acid, or dermocosmetics.

Topical BPO (2.5%, 5%) is effective against *P. acnes* and efficacious in inflammatory acne. Its use is encouraged over topical antibiotics to reduce development of antibiotic resistance, but widespread use is limited by irritation. The combination therapy of BPO and adapalene is more effective than adapalene or BPO alone.[43] A summary of recommendations regarding topical therapies is provided in Table 4.

Topical retinoids. Topical retinoids are an effective first-line therapy against comedonal and inflammatory acne.[44] These agents have demonstrated, *in vivo,* anti-inflammatory activity.[45] They reduce microcomedones and mature comedones, promote desquamation of follicular epithelium, and reduce inflammatory and noninflammatory lesions.

Prescription retinoids (e.g., tretinoin) have established rejuvenation effects; skin texture is improved via activation of retinoid receptors.[46] OTC retinoid esters (e.g., retinol, retinyl palmitatem, retinyl propionate) also demonstrate the same effects but to a lesser extent. These products are not available in some countries.

TABLE 4. Summary of recommendations for topical therapies

Topical antibiotic monotherapy is highly discouraged. *Level 1+, Grade A*
Combination topical therapy is preferable and more effective than topical antibiotic alone. *Level 1+, Grade A*
Consider alternative antibacterial agents, such as benzoyl peroxide, salicylic acid, or dermocosmetics. *Level 4, Grade D, GPP*
Addition of BPO to adapalene is significantly more effective than adapalene monotherapy or BPO monotherapy. *Level 1+, Grade A*
Topical retinoids are effective first line therapy against both comedonal and inflammatory acne. *Level 1++, Grade A*
Fixed-combination therapy of BPO and adapalene provides significantly greater efficacy for the treatment of acne vulgaris as early as week one relative to monotherapies, with a comparable safety profile to adapalene. *Level 1+, Grade A*
Topical retinoids are recommended for maintenance in acne after successful treatment of acne. *Level 1+, Grade A*
Antibiotics do not prevent the development of microcomedones and should be discouraged as maintenance. *Level 4, Grade D, GPP*

Regarding sensitivity, adapalene has the least irritating effect.[47] There was more erythema, desquamation, dryness, stinging, pruritus, and transepidermal water loss with tretinoin than adapalene. Tolerability was lowest among Chinese patients, followed by Indian, Malay, and Caucasian patients.[48]

Fixed-combination BPO and adapalene. Fixed-combination BPO and adapalene provides significantly greater efficacy as early as the first week of treatment, relative to monotherapies, with a comparable safety profile to adapalene alone.[43]

In three 12-week trials in patients 12 years of age or older with moderate acne, success rates were significantly higher with adapalene 0.1%/BPO 2.5% gel than with adapalene 0.1% gel or BPO 2.5% gel alone, and combination therapy had an earlier onset of action. A rapid onset of action was observed using this combination treatment, reducing lesions from the first week. Additionally, this combination therapy clears both inflammatory and non-inflammatory lesions, targets three out of four pathogenic causes of acne, is antibiotic-free (removing the risk of antibiotic resistance) and has shown long-term efficacy and tolerability.[49]

TABLE 5. Strategies for improving tolerability of topical agents

DOSING AND TITRATION	FORMULATION AND ADJUNCTIVE AGENTS
Initiating low dose therapy	Use of cream and nonalcohol-based vehicles, when possible
	Concomitant use of moisturizer
	Use of gentle cleansing agents
Initiating every-other-day dosing with titration upward slowly as needed *Level 4, D, GPP*	Avoid astringents and toners
	Avoid overly drying soaps and cleansers
	Level 4, D, GPP

Maintenance treatment. Acne typically recurs soon after cessation of active treatment, making maintenance treatment necessary. About 28 percent of sections of normal-appearing skin from patients with acne show histologic features of microcomedones, the subclinical precursors to both inflammatory and noninflammatory acne lesions, and biopsy of papules demonstrates the presence of microcomedones in 52 percent of patients with acne.[50] Maintenance anticomedogenic agents have been shown to effectively control acne and prevent relapses and minimize sequelae.[50]

Retinoids are recommended for maintenance.[51–53] Antibiotics do not prevent the development of microcomedones and should not be used for maintenance.

Topical therapy-induced skin irritation. The most common side effect of these therapies is irritation, including dryness, erythema, scaling, stinging/burning, and itching. These result from the disruption of the skin barrier due to external (e.g., inflammatory process, harsh cleansing) and internal factors (e.g., sebum overproduction, altered ceramides/free fatty acids/cholesterol). To mitigate irritation, the skin barrier should be restored.[54,55] Dosing, titration, formulation strategies, and adjunctive agents can be employed to improve tolerability of topical agents(Table 5).

Miscellaneous. Topical dapsone is not currently available in Singapore. Cases of methemoglobinemia that have resulted in hospitalization were reported in association with twice-daily use of dapsone 5% gel in postmarketing surveys.[56] This occurs frequently in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, a condition that is common in Singapore.[57]

SYSTEMIC ANTIBIOTICS

Systemic antibiotics are indicated for moderate-to-severe papulopustular acne, in conjunction with the appropriate topical agents (Table 6). Antibiotics work by reducing *P. acnes* levels, inhibiting of bacterial lipases, and anti-inflammatory activities. Among the spectrum of activities are inhibition of neutrophil leukotaxis, reduction in cytokine secretion, and decrease in matrix metalloproteinase activity.[58–60] The evidence for their efficacy is extremely well-established and, thus, additional elaboration will not be provided.[13,61–63]

In Singapore, there has been a reported increase in resistance rates of *P. acnes* from eight percent in 1999 to 14.9 percent in 2007.[4,39] Further, Tan et al[4] documented resistant *P. acnes* in school-attending adolescents who had not been previously treated for acne. The concern over antibiotic resistance warrants judicious use. Patient education and adherence are essential to ensure good outcomes while minimizing the risk of resistance.

TABLE 6. Summary of recommendations for systemic antibiotics

Doxycycline, tetracycline and erythromycin are recommended as first line oral antibiotics. The absorption of tetracycline is restricted by food and dairy products. Erythromycin can be used to treat acne in pregnancy. *Level 1+, Grade A*
Minocycline is considered as a second-line antibiotic for acne due to evidence of more severe adverse events in comparison to doxycycline. *Level 1+, Grade A*
Cotrimoxazole is recommended only as a third-line antibiotic, when other treatments have failed. *Level 2++, Grade B*
Systemic antimicrobials should not be used together with topical antibiotics or as monotherapy. *Level 4, Grade D, GPP*

TABLE 7. Prescribing information for systemic antibiotics[61]

DRUG		DOSAGE	ADVERSE EFFECTS	COMMENTS
First-line antibiotics	Erythromycin	500–1,000mg/day	• GIT upset	• Potential drug interactions with carbamazepine, theophylline, cyclosporine among others
	Doxycycline	100–200mg/day	• GIT upset • Oesophagitis • Photosensitivity	• Taken with meals • Take with large glass of water to decrease dyspepsia • Safe in renal impairment • Most likely of all tetracyclines to induce photosensitivity, patients should be cautioned and encouraged to use sun protection.
	Tetracycline	500–1,000mg/day	• GIT upset (diarrhea, vomiting, dyspepsia) • Yellowish staining of forming teeth[66]	• Taken on an empty stomach • Decreased absorption if taken with iron, calcium, or other dairy products • Avoid in renal and hepatic disease
Second-line antibiotics	Minocycline	100–200mg/day	• Vestibular toxicity (i.e., vertigo, dizziness) • Blue-gray cutaneous pigmentation • Lupus-like syndrome • Hepatitis	• Taken with meals • Expensive • Some authorities suggest screening ANA and LFT in young women on long term treatment
Third-line antibiotics	Cotrimoxazole	2–4 tablets daily, with each tablet containing 400mg of sulfamethoxazole and 80mg of trimethoprim	• Rashes • SJS/TEN • Bone marrow suppression	• Screen for G6PD • Useful for gram-negative folliculitis

GIT: gastrointestinal tract; SJS: Stevens–Johnson syndrome; TEN: toxic epidermal necrolysis; ANA: antinuclear antibody; LFT: liver function test; G6PD: glucose-6-phosphate dehydrogenase

There is a general consensus that oral antibiotic therapy should not exceed 3 to 4 months and that a minimum duration of six weeks is commonly required to see clinical improvement. Oral antibiotics should not be used as a single agent or with another topical antibiotic and should be combined with other recommended topical agents. The characteristics of systemic antibiotics commonly used in acne are seen in Table 7.

First-line antibiotics. Doxycycline and erythromycin are recommended first-line oral antibiotics.[13,61,63] Doxycycline is contraindicated in children under eight years of age and in pregnant and lactating women. Erythromycin is as effective as tetracycline in the treatment of inflammatory acne and is effective and safe for use in younger patients. Erythromycin can also be considered for the treatment of severe acne in pregnancy.[64] Tetracycline can be used as an alternative to doxycycline; however, tetracycline must be taken on an empty stomach and in the absence of dietary iron and calcium, and is therefore not generally considered for use as first-line therapy.[13,65,66]

Second-line antibiotics. Studies have shown that minocycline is as effective as tetracycline and doxycycline in the quantitative reduction of inflammatory acne.[67] Early research has indicated that minocycline tends to produce a more rapid clinical improvement when compared to tetracycline. However, subsequent controlled trials did not support the superiority of any one of these agents above the rest.[62] The rationale for recommending minocycline as second-line therapy is based on a systematic review of case reports that showed more severe adverse events occurring with minocycline treatment.[63] Minocycline is associated with more central nervous system side effects and has been linked to lupus and autoimmune hepatitis.[68]

Third-line antibiotics. Cotrimoxazole is recommended only as a third-line treatment when other options have failed.[61,69,70] It is effective, but has the potential for serious adverse events (e.g., Stevens-Johnson syndrome/toxic epidermal necrolysis, bone marrow suppression).[61,70] It is also contraindicated among individuals who are G6PD-deficient.[61] The potential risks versus benefits should be discussed with the patient.

Currently, long-term use of other systemic antibiotics for acne, such as penicillin and clindamycin, is not favored by the Advisory Board. One particular complication of long-term systemic antibiotic therapy with tetracyclines or erythromycin is the development of gram-negative folliculitis resulting from an overgrowth of lactose-fermenting gram-negatives. Its management involves shifting to an antibiotic specific to gram-negative bacteria, such as amoxicillin clavulanate or ciprofloxacin.

Overall, the current best practice regarding the use of systemic antibiotics is an individualized approach. When choosing oral antibiotics, factors such as cost, patient preference, efficacy of the medication, and risk-benefit profile must be taken into account. Physicians should also use the recommended nonantibiotic topical agents (e.g., retinoids, BPO). Systemic and topical antimicrobials should not be used together or as monotherapy.[71]

SYSTEMIC ISOTRETINOIN

The efficacy of oral isotretinoin in cases of severe acne has been established (Table 8). However, treatment regimens are highly variable among expert groups. Systemic isotretinoin is indicated for use in severe nodulocystic acne, severe acne after having failed 6 to 8 weeks of oral antibiotics in combination with topical retinoids and BPO, and in patients with severe scarring or

TABLE 8. Summary of recommendations for systemic isotretinoin

Oral isotretinoin is recommended for the treatment of severe acne that has not responded to conventional therapy. *Level 1++, Grade A*
Referral to a dermatologist is recommended in cases of severe nodulocystic acne or conglobate acne. *Level 4, Grade D, GPP*
An acceptable high-dose isotretinoin therapy of nodulocystic acne is 120 to 150mg/kg cumulative dose. *Level 1+, Grade A*
For non-nodulocystic or moderate acne, a 0.3 to 0.5mg/kg dose for six months might be sufficient. *Level 1+, Grade A*
Low-dose maintenance for adult persistent acne can be considered, but with caution due to potential adverse events. *Level 2+, Grade C*
Pregnancy is an absolute contraindication to systemic isotretinoin. Sexually active female patients should be made aware of the risk of teratogenicity and must be screened for pregnancy. *Level 4, Grade D, GPP*
Contraception should be discussed with the patient. The patient must be routinely reminded to avoid pregnancy. *Level 4, Grade D, GPP*
Screen for symptoms of depression before and during treatment and inform the patient of possible risk of depression and suicidal behaviors. *Level 4, Grade D, GPP*
For long-term therapy, monitoring of laboratory parameters (e.g., serum cholesterol, triglycerides, liver function tests) every six months is recommended. *Level 4, Grade D, GPP*
Maintenance with topical retinoids is recommended for at least several months after treatment cessation with oral isotretinoin. Addition of BPO might be required for moderate to severe acne. *Level 1+, Grade A*

psychological and/or physical distress as a result of acne.[13,72]

For severe nodulocystic acne or conglobate acne, referral to a dermatologist is recommended. For high-dose isotretinoin therapy of nodulocystic acne, a 120 to 150mg/kg cumulative dose is acceptable.[13,72] For non-nodulocystic or moderate acne, 0.3 to 0.5mg/kg for six months will likely be sufficient.[13,73–75] A daily dose of 0.25 to 0.5mg/kg can be started and adjusted as tolerated. Pulse therapy (every 1 to 3 weeks) is not recommended due to higher relapse rates.[76] Low-dose maintenance for persistent acne in adults can be considered, but with caution due to the potential for adverse events (e.g., teratogenicity, hepatotoxicity, hyperlipidemia).[77–79] Lastly, combination with oral tetracyclines should be avoided due to the risk of pseudotumour cerebri.[80,81]

Monitoring. *Pregnancy.* Pregnancy is an absolute contraindication to systemic isotretinoin. Physicians must ensure that female patients are not pregnant and are aware of the risk of teratogenicity before starting therapy. Contraception (e.g., hormonal, intrauterine device, sterilization, barrier, or abstinence) should be discussed with female patients when considering systemic isotretinoin. Treatment can be withheld until commencement of the next menstrual period. The administration of a pretreatment pregnancy test is at the doctor's discretion or done in accordance with the region's medical regulations. During follow-up, the patient must be routinely reminded to avoid pregnancy (e.g., by documenting last menstrual period at every visit).

Depression. The causal link between isotretinoin and depression is controversial. Rates range from 1 to 11 percent across trials with similar rates in oral antibiotic control groups (some demonstrated trend towards fewer or less severe depressive symptoms after treatment).[13] Physicians should screen patients for symptoms of depression before and during treatment and inform them of the possible risks of depression and suicidal behavior while taking isotretinoin.

Laboratory testing. Laboratory parameters, such as liver function tests and serum cholesterol and triglycerides should be checked at pretreatment[13,72] and again after medication initiation (e.g., after 6 to 8 weeks of treatment or earlier if necessary).[72] For long-term therapy, monitoring every six months is recommended.

Relapse/recurrence. On average, relapse rates following systemic isotretinoin treatment can vary between 21 and 30 percent.[82] Risk factors for recurrence include male sex, age younger than 16 years, residence in urban areas, cumulative oral retinoid dose greater than 2,450mg, and treatment duration longer than 121 days.[83] Maintenance with topical retinoids is recommended for at least several months after the cessation of oral isotretinoin; the addition of BPO might be required for moderate-to-severe acne.[51,72,84]

HORMONAL THERAPY AND OTHER SYSTEMIC THERAPIES

Combined oral contraceptives. Combined oral contraceptives (COCs) are effective in the treatment of both noninflammatory and inflammatory acne.[85] Evidence comparing COCs with systemic antibiotic therapy is scarce and conflicting. Minocycline shows comparable efficacy to ethinyl estradiol combined with cyproterone acetate (EE-CPA); EE-CPA shows superior efficacy compared to tetracycline; and combining EE-CPA and tetracycline shows no superior efficacy compared to EE-CPA alone.[13]

Although antibiotics appear superior at three months, oral contraceptives are equivalent to antibiotics at six months in reducing acne lesions and might be a better first-line alternative to systemic antibiotics for long-term acne management in women.[86] Indications include moderate-to-severe papulopustular acne in women, signs of hyperandrogenism, need for effective contraception (e.g., during oral isotretinoin use), and as adjuvant therapy to topical and systemic therapies.

Choice of hormonal therapy. The COCs registered in Singapore are listed in Table 9.[87] A Cochrane review of 31 trials of COCs supported their efficacy in reducing inflammatory and noninflammatory facial acne lesions. A few important and consistent differences were found

TABLE 9. Health Sciences Authority list of approved combined oral contraceptives in Singapore.[81]

BRAND	CONTRACEPTIVE AGENTS					
	CYPROTERONE ACETATE (ANTIANDROGEN)	DESOGESTREL	DROSPIRENONE (ANTI-ANDROGEN)	ETHINYLESTRADIOL	LEVONORGESTREL	GESTODENE
Diane–35™	2mg			35mcg		
Estelle-35™	2mg			35mcg		
Gracial™		25mcg (blue) 125mcg (white)		40mcg (blue) 30mcg (white)		
Gynera™				30mcg		75mcg
Marvelon™		150mcg		30mcg		
Meliane™				20mcg		75mcg
Mercilon™		150mcg		20mcg		
Microgynon™				30mcg	150mcg	
Yasmin™			3mg	30mcg		
Yaz ™ (only FDA-approved agent in Singapore)			3mg	20mcg		

between COC types in their effectiveness for treating acne,[88] as follows:

1. A levonorgestrel COC was more effective than placebo in decreasing total, inflammatory, and noninflammatory lesion counts and led to a clinician assessment of "clear" or "almost clear" lesions and participant self-assessment of improved acne lesions.
2. For two combined trials of a drospirenone COC, the investigator's assessment of "clear" or "almost clear" skin favored the drospirenone group versus placebo.
3. In one trial, the drospirenone COC group showed a greater percentage of changes for total, inflammatory, and noninflammatory lesion counts, as well as papule and closed comedone counts compared to the placebo.
4. COCs that contained chlormadinone acetate or cyproterone acetate demonstrated greater improvement in acne than levonorgestrel. Also, a cyproterone acetate COC demonstrated better outcomes than desogestrel COC, but the studies produced conflicting results.
5. Levonorgestrel demonstrated slightly better outcomes in acne than desogestrel, but the results were not consistent.
6. A drospirenone COC appeared to be more effective in treating acne than norgestimate or nomegestrol acetate plus 17β-estradiol, but less effective than cyproterone acetate.

TABLE 10. Contraindications to COCs[89]

ABSOLUTE CONTRAINDICATIONS	RELATIVE CONTRAINDICATIONS
• Lactation less than six weeks postpartum • Age >35 years and smoking >15 cigarettes/day • Hypertension (systolic >160 or diastolic >100) • Coronary artery disease/cerebrovascular disease • Deep venous thrombosis, pulmonary embolism, known thrombogenic mutations • Major surgery with prolonged immobilization • Valvular heart disease with complications (e.g., atrial fibrillation, pulmonary hypertension) • Migraine with aura or no aura if age >35 years • Current breast cancer • Diabetes with complications • Acute viral hepatitis, decompensated liver cirrhosis, liver tumor	• Lactation six weeks to six months postpartum • Age >35 years and smoking <15 cigarettes/day • Hypertension (systolic 140–160 or diastolic 90–100) • Multiple risk factors for cardiovascular disease; hyperlipidemia • Previous breast cancer longer than five years ago with no recurrence • Mild compensated liver cirrhosis, previous COC-induced cholestasis, gallbladder disease, concurrent medication with potential for transaminitis

In a 2012 Cochrane review by Bhate et al,[85] the authors concluded that there was no evidence that COCs containing cyproterone were more effective than other COCs for the treatment of acne. More trials comparing COCs to each other and other acne treatments are needed.

Progestogen-only contraceptives often worsen acne, as they bind androgen receptors, and so should be avoided in women who have no contraindications to estrogen-containing preparations. Third-generation progestogens, such as desogestrel, norgestimate, and gestodene, bind more selectively to the progesterone receptor than do the second-generation progestogens (e.g., levonorgestrel and norethisterone), but at the cost of an increased risk of venous thromboembolism (VTE).

A recent updated Cochrane review on the use of spironolactone* in hirsutism and acne concluded that there is no evidence for its effectiveness in acne. **Addendum dated April 13, 2016: the current DSS guidelines are based on a literature review until December 31, 2014. This updated article now lists spironolactone as an alternative therapy for moderate and severe acne.*[27]

Risks/contraindications. It is necessary to identify risks/contradindications for certain conditions (Table 10) associated with COC use.[89]

Dosing and administration. Dosing should start on the first day of menstrual cycle as follows: one tablet daily for 21 days, stop for seven

TABLE 11. Summary of recommendations for adjunctive procedural therapy

Chemical peels, such as glycolic acid 40% have been found to significantly improve moderate acne and are safe and effective in Asian patients. *Level 2, Grade D*
Photodynamic therapy with topical 5-ALA and IPL (blue or red light) is effective for moderate to severe acne. *Level 2, Grade D*
As monotherapy, IPL (blue or red light) phototherapy is less effective than PDT but may be tried if side effects of PDT are not tolerable. *Level 2, Grade D*
Combination blue–red LED phototherapy, for which home devices are available, is safe and effective for the treatment of mild-to-moderate acne, with good adherence. *Level 2, Grade D*
Erbium-Glass laser is an effective treatment for active acne. Laser therapy of 1 to 4 sessions might be necessary. *Level 2, Grade D*

IPL: intense pulsed light; ALA: aminolevulinic acid; PDT: Photodynamic therapy; LED: light-emitting diode

days, then repeat. The duration of treatment is expected to be within a 6- to 12-month course.[90] There is no increase in efficacy from combining oral antibiotics and oral contraceptives.

Adverse effects. Blood pressure should be documented upon initial consult and monitored at follow-up visits. Adverse effects of COCs include nausea, vomiting, breast tenderness, headaches, menstrual disturbance, fluid retention, and venous thrombosis. The association of VTE and COCs is known, with an estrogen dose-dependent relationship. During a woman's reproductive years, her risk for VTE with ethinyl estradiol is 6 to 8 times higher than in nonusers.[89] The evidence regarding COCs and stroke is unclear. In healthy, young women, the risk of ischemic stroke is low, but concomitant COC use and smoking increases the risk significantly. As for malignancy, the evidence demonstrating a link between breast cancer and hormone exposure is marginal and controversial. For cervical cancer, there might be an association; however, the association is reduced with cessation of a COC, and, by 10 years, the risk of cervical cancer is similar to that of those who have never taken COCs.[89] Recently, the Singapore Health Promotions Board recommended decreasing cervical screenings to once every three years after the onset of sexual activity or beginning at the age of 25.[91] It is acceptable to start COCs with succeeding consultation that includes a Pap smear.

In summary, COCs are effective for noninflammatory and inflammatory acne (Level 1++, A). They may be considered alternatives to systemic antibiotics or systemic retinoids for moderate-to-severe papulopustular acne in women, in combination with topical retinoids with or without BPO. Identifying risk for certain conditions associated with COC use is a necessity, and patients should be advised.

ADJUNCTIVE THERAPY

Adjunctive acne therapy can provide further clinical effect in addition to conventional therapy. Recommendations are summarized in Table 11.

Chemical peels. Chemical peels for acne and acne scars in Asian patients have been shown to be safe and effective.[92,93] More trials with better study designs and higher numbers of subjects are needed to further establish the role of chemical peels in Asian patients with acne.[92] For instance, glycolic acid 40% has been found to significantly improve moderate acne.[93]

Light devices. Photodynamic therapy with topical 5-aminolevulinic acid and intense pulsed light (IPL) and other light sources have been shown to be effective in moderate-to-severe acne.[94,95] In combination with fractional CO_2 laser treatments, IPL has been shown to reduce the inflammatory lesion and atrophic scar scores compared to at baseline. Subsequent fractional CO_2 laser treatments further decreased the atrophic scar score. Around 90 percent of the patients experienced significant or moderate overall improvement, and almost 80 percent patients rated their results as "excellent" or "good." The melanin index (MI), erythema index (EI), and skin sebum level all significantly decreased after IPL treatments, and the EI and sebum level were still low when assessed at the three-month follow-up, although the MI had increased again by this point. The adverse effects of both treatments were transient and bearable.[94,95]

Combination blue–red light-emitting diode (LED) phototherapy at home has been shown to reduce sebum production, attenuate inflammatory cell infiltrations, and decrease sebaceous gland size.[96]

Lasers. Papules, pustules, and nodules respond well to therapy using the 1,550-nm Erbium–Glass laser. The sebaceous gland size decreased significantly, hence the long remission period.[97] Treatment efficacy is due to the antibacterial effect on *P. acnes* and the ablation of sebaceous glands. Although cost might be an issue, laser therapy can induce remission in acne long term. Pain, when present, is tolerable.

Other energy devices. Fractional radiofrequency microneedle therapy has been demonstrated in one trial to have sebosuppressive effects from a single treatment, but its therapeutic efficacy requires further evaluation.[98]

ADJUVANT THERAPY: COSMECEUTICALS/DERMOCOSMETICS

The term *cosmeceutical* is defined as "a topical preparation that is sold as a cosmetic but [which] has performance characteristics that suggest pharmaceutical action."[99] The term is used interchangeably with *dermocosmetics*. In existing resources on dermocosmetics, many use trade names, extrapolate efficacy of single ingredients from studies using proprietary combination products, contain biases, and overstate the efficacy of proprietary products. These methods can leave patients confused. Cosmeceuticals are not always necessary (i.e., the simpler the regimen, the easier it might be for the patient to adhere to it), but can be added as an adjuvant. The role of adjuvant therapy is to help reduce side effects that might be associated with treatment (e.g., irritation and dryness), provide a synergistic effect when used together with conventional treatment, reduce adverse sequelae (e.g., postinflammatory hyperpigmentation [PIH] or scarring), and improve quality of life.[100,101]

The range of cosmeceutical agents for the management of acne is listed in Table 12.[55,102–110] Studies investigating cosmeceutical products tend to involve a combination of agents, making it difficult to provide a level of evidence for a single agent. Hence, only a few cosmeceutical agents are listed and without an associated level of evidence.

TABLE 12. List of adjuvant topical therapies

ADJUVANT THERAPY	EXAMPLE	FUNCTION/EVIDENCE	RECOMMENDATIONS
Cleansers	• Soap-free, nonacnegenic, nonirritating, nonallergenic, oil-control without drying, and pH-balanced	• To remove sebum, dirt, and microorganisms	• Use of gentle soap-free cleansers is preferred especially when used in conjunction with topical retinoids • Twice-daily cleansing is adequate unless there is increased sebum or dirt
Moisturizers	• Lightweight, provide adequate hydration, noncomedogenic, nonacnegenic, might contain substances effective in acne treatment	• Counteracts the effect of acne treatment on the barrier function of stratum corneum and improves clinical outcome	• Acne-specific moisturizers can be used without inducing comedone formation
Topical sebum-controlling agents	• Methacrylate polymers, aluminium starch octenylsuccinate • Zinc gluconate or zinc PCA • Nicotinamide/niacinamide • Triethyl citrate and ethyl linoleate • 2% L-Carnintine • Erthryomycin-zinc formulation	• Mattifying effects of substances • Effect on 5-α-reductase or sebaceous gland activity • Reduction of sebum excretion rate after four weeks of application in Japanese skin[102] • Reduction of sebum production[103] • Reduction of sebum production for three weeks *in-vivo* application[104] • Significant reduction in casual level, sebum excretion rate, and total area of lipid spots compared to control at six and nine weeks[105]	N/A
Corneolytics	• Alpha hydroxy acids, salicylic acid, polyhydroxy acid, retinaldehyde, and retinol • Retinaldehyde/glycolic acid as add-on to treatment or substitute for topical retinoids	• Causes intercorneocyte cell detachment to induce a comedolytic effect • Also improves skin texture • Reduced both inflammatory and comedonal acne in an open-label uncontrolled study among women[106]	N/A
Antimicrobial agents	• Ethyl lactate and phytosphingosine both *in vitro* and *in vivo*[107,108] • Antibacterial adhesive substances (ABA) • Others: tea tree oil, triclosan	• To minimize the emergence of *P. acnes* resistance, topical antimicrobial agents are used alongside topical antibiotics	• More studies are necessary to prove that the product translates to lowered *P. acnes* count in lesional skin
Anti-inflammatory agents	• Nicotinamide 5% , 1% • Triethyl citrate and ethyl linoleate in proprietary lotion	• As effective as clindamycin 2% and 1% gel for women with mild to moderate acne and moderate inflammatory acne, respectively[109] • Statistically superior to placebo in reduction of Leeds grading in mild-to-moderate acne	• Nicotinamide is more effective in oily skin type and clindamycin gel is more effective in non-oily skin types[110]
Antimicrobial agents	• Ethyl lactate and phytosphingosine both *in vitro* and *in vivo*[107,108] • Antibacterial adhesive substances (ABA) • Others: tea tree oil, triclosan	• To minimize the emergence of *P. acnes* resistance, topical antimicrobial agents are used alongside topical antibiotics	• More studies are necessary to prove that the product translates to lowered *P. acnes* count in lesional skin
Sunscreens	• Oil-free preparations, designed for acne	• Photoprotection is important especially in those treated with retinoids, oral contraceptives, or those with postacne hyperpigmentation	• Daily use of an oil-free sunscreen is recommended, together with photoprotective behaviors
Camouflage	• Makeup/concealer that are noncomedogenic	• A technique to minimize or conceal erythema and pigmentary changes associated with acne	• Use an appropriate concealer to help improve the quality of life of patients with acne

N/A: Not applicable

TABLE 13. Summary of management of acne vulgaris

Mild Comedonal	• First choice: topical adapalene, topical tretinoin or topical isotretinoin (Level 1+, Grade A)* • Alternatives: topical BPO or azelaic acid (Level 2+, Grade B)
Mild Papulopustular	• Topical clindamycin-BPO *or* • Adapalene-BPO fixed combination products (Level 1++, Grade A) • Topical antibiotic + BPO + topical retinoid/azelaic acid (Level 1+, Grade A) • Topical retinoid + BPO (Level 1+, Grade A) • Topical antibiotic should never be used as monotherapy
Moderate Papulopustular	• Clindamycin-BPO or adapalene-BPO fixed combination products (Level 1++, Grade A) *or* • Oral antibiotics + topical retinoid + BPO (Level 1+, Grade A) *or* • Oral antibiotics + topical adapalene-BPO fixed combination product (Level 1+, Grade A) *or* • Oral antibiotics + topical azelaic acid + BPO (Level 2+, Grade B) • Alternatives in women: oral anti-androgen + topical retinoid/ azelaic acid ± BPO (Level 1+, Grade A)
Severe Papulopustular	• First-line: oral antibiotics + topical retinoids + BPO (Level 1+, Grade A) *or* • Oral antibiotics + topical adapalene-BPO fixed combination product (Level 1+, Grade A) • Seccond-line: oral isotretinoin *or (in women)* • Oral anti-androgen + topical retinoid/ azelaic acid ± BPO ± oral antibiotics (Level 1+, Grade A) • The use of COCs in women should take into account higher risks of adverse side effects and patient noncompliance with polypharmacy (Level 4, GPP)
Very Severe Nodulocystic	• Oral isotretinoin; suggest referral to dermatologist (Level 1+, Grade A)
Very Severe Conglobate	• Oral isotretinoin; suggest referral to dermatologist (Level 1+, Grade A)
The Advisory Board recommends oral antibiotic treatment duration not exceeding three months (Level 4, GPP)	
Maintenance with topical retinoid	

*Consult your local formularies regarding available preparations and strengths. Avoid sun exposure when using these medications. Stop temporarily when skin is irritated. May consider alternate dosing.

MANAGEMENT OF MILD, MODERATE, AND SEVERE ACNE

These management guidelines draw heavily from pre-existing, evidence-based guidelines and reviews. Expert opinions, particularly those that are relevant to local Singapore patients and conditions, have also been considered. Management options in terms of acne severity are summarized in Table 13.

Mild acne. *Comedonal acne.* Limited data suggest that increasing concentrations of tretinoin cream (i.e., 0.01%, 0.025%, 0.05%, and 0.1%) are associated with increased efficacy but with an increased rate of side effects.[111] In comparison, adapalene 0.1% gel or cream causes less irritation versus tretinoin and is as efficacious as tretinoin cream.[48,112] Topical isotretinoin gel 0.05% application for acne is not associated with any significant systemic levels of the drug and is effective and well-tolerated.[113,114] Topical isotretinoin preparations are not available in some countries.

Azelaic acid 20% is a mild comedolytic with anti-inflammatory activity.[115] It is safe and effective as a treatment and maintenance option for women with adult acne with noninferior efficacy to adapalene (0.1%) in the control of inflammatory acne.[116] It can be used during pregnancy[117] and can be useful in patients with acne and PIH, as it induces hypopigmentation in darker skin.[118] BPO (2.5%, 5%, and 10%) has anti-inflammatory, antibacterial, and mild comedolytic activities and does not induce bacterial resistance.[119] Lower concentrations of BPO (2.5% or 5%) are preferred, as there is increased irritation with increasing concentrations of BPO and without a significant increase in efficacy between the 2.5% and 10% concentrations.[120]

Papulopustular acne. Recommended treatment for mild papulopustular acne includes fixed-combination products containing BPO (with clindamycin or adapalene) with or without topical retinoid/ azelaic acid. BPO should be applied in the morning, and the topical retinoid should be administered at night. It is advised to avoid simultaneous BPO and tretinoin application due to potential oxidation of the tretinoin cream.[121] The topical fixed-combination products are effective in the treatment of mild-to-moderate papulopustular acne and can be used as monotherapy applied once-daily.[122–125] Systematic reviews have noted the superiority of combination products against individual components alone. These options also generally have good tolerability profiles and have now become the standard of care for mild-to-moderate papulopustular acne.[13,72]

Moderate acne (papulopustular). Treatment recommendations for moderate papulopustular acne include fixed combinations of antibiotics and/or adapalene/ BPO and/or topical azelaic acid. The choice of medication depends on several factors, including cost, convenience, adherence, and patient preference. Treatment duration with systemic antibiotics should not exceed 3 to 4 months. At Week 6 of therapy, the patient's response to treatment should be assessed. The use of oral antiandrogens as an alternative second-line treatment might be suitable for some women with moderate papulopustular acne. The various contraindications should always be considered.

Severe acne. *Papulopustular acne.* Treatment recommendations include the use of oral antibiotics, topical retinoid/azelaic acid, BPO, and oral antiandrogen combinations. Topical treatment alone is not recommended. Patients should be followed closely to monitor treatment response, and second-line therapy should be considered when treatment response is inadequate after a suitable amount of time. Some doctors combine oral contraceptives with systemic antibiotics; however, there is insufficient data on the potentially superior efficacy of this approach. Consideration of risks should be included in

clinical decision making before prescribing COCs.

Nodulocystic and conglobate acne. For these types of acne, oral isotretinoin is the recommended treatment and its use should be managed by a dermatologist.

ACNE IN ADULT WOMEN

A large scale international study of 374 women from Europe, the Americas, and Asia evaluated the significance of acne in this population.[126] Adult acne can be defined as the presence of acne lesions after the age of 25 years. It might be an extension or relapse of adolescent acne (persistent acne) or can be a new occurrence (late-onset acne). More than 50 percent of individuals in their 30s reported acne, and late onset is more common in women. There are two distinct clinical presentations of acne in adult women: one is similar to adolescent acne (almost 90%) and the other is a mild, inflammatory/nodular acne localized to the mandibular region. The pathogenesis might be different (i.e., androgens), and recognition of this entity is needed. The majority (93.7%) of women had facial comedones. Scarring occurred in 59.4 percent, and PIH in 50.4 percent of the women in this study. Acne in adult women represents a psychosocial burden and affects quality of life.

Acne in adults is largely mild-to-moderate in severity and can be refractory to treatment.[127] Subgroup analyses of recent large-scale controlled clinical trials have shown that many adult women respond well to standard first-line acne therapy. Refractory cases might require long-term treatment and referral to a dermatologist. Treatment choices are outlined in Table 14.

SPECIAL POPULATIONS

Pregnant/lactating women. Treatment of acne in this population requires safety considerations for both the mother and fetus/infant (Table 15).[117,128–132] As discussed, hormonal therapy, tetracyclines, cotrimoxazole, and both oral and topical retinoids should be avoided. Treatment choices are outlined in Table 16. In cases of mild-to-moderate acne, consider topical antibiotics used in combination with topical acne agents.[133] Topical BPO and adapalene are generally safe. For moderate-to-severe acne, previously mentioned topical agents can be used with oral antibiotics.

TABLE 14. Management of adult female acne, perimenstrual flare

METHOD	MILD ACNE	MODERATE ACNE	SEVERE ACNE
First-line	Topical retinoid or topical retinoid/ BPO	Oral antibiotic + same topicals as first-line for mild acne	Oral isotretinoin
Alternatives	Topical retinoid/antibiotic or topical retinoid/ BPO-antibiotic	COC	Oral isotretinoin + short-course oral antibiotic or oral isotretinoin + COC
Second-line	Oral antibiotic+topical retinoid±BPO	Oral isotretinoin	N/A
Cosmeceuticals	Gentle soap-free pH-balanced cleanser or BPO cleanser, acne-specific moisturizer, sunscreen	Gentle soap-free pH-balanced cleanser, acne-specific moisturizer, sunscreen	Gentle soap-free pH-balanced cleanser, moisturizer, sunscreen, lip balm

BPO- benzoyl peroxide; COC: combined oral contraceptive; N/A: not applicable

TABLE 15. Pregnancy and lactation information on selected anti-acne therapy options

CLASS	PREGNANCY	LACTATION	FDA CATEGORY
Azelaic acid	Has not shown mutagenicity, teratogenicity or embryotoxicity in animals; minimal absorption occurs	Small doses unlikely to pose risk during pregnancy or lactation	B
Benzoyl peroxide	No animal and human reproduction studies.	No adverse reports in lactation	C
Adapalene	Limited safety data; very low systemic absorption; not recommended in pregnancy	Excretion in breast milk unknown; use with caution	C
Oral isotretinoin	Contraindicated in pregnancy; major fetal abnormalities (up to 28%), spontaneous abortion, premature births, low IQ scores reported; embryopathy reported even with single dose; likely not dose-related	Excretion in breast milk unknown; use not recommended	X
Tretinoin	Not recommended in pregnancy; avoid particularly in first trimester due to reported teratogenicity	Minimal amounts found in breast milk; not thought to be harmful to infants	C

TABLE 16. Treatment choices for pregnant and lactating women

	TREATMENT	EVIDENCE LEVEL
First-line	1. Antibiotics (erythromycin, clindamycin) 2. Benzoyl peroxide 3. Azelaic acid 4. Salicylic acid	Level 2– to 3, Grades C to D
Second-line	1. Oral macrolides (azithromycin) 2. Cephalexin	Level 3, Grade D
Third-line	1. Chemical peel (glycolic acid) 2. Light-based therapy (intense pulsed light, blue or red light phototherapy) in addition to topical and/or oral therapies	Level 3, Grade D

TABLE 17. Summary of recommendations for the management of pediatric patients

Topical treatment with benzoyl peroxide is safe and effective and can be used as monotherapy or in topical combination products for mild acne or in regimens of care for acne of all types and severities. *Level 4, Grade A*
Fixed-dose combination topical therapies might be useful in regimens of care for all types and severities of acne *Level 1–, Grade A for adolescents, Grade B for preadolescents and younger*
Oral isotretinoin is recommended for severe, scarring, and/or refractory acne in adolescents and can be used in younger patients *Level 1+, Grade A for adolescents, Grade B for preadolescents and younger*
A low starting concentration (i.e., 2.5% BPO) is recommended as children are more prone to irritation. It might minimize development of antibiotic-resistant *P. acnes* when used with topical or systemic antibiotics *Level 4, Grade D*

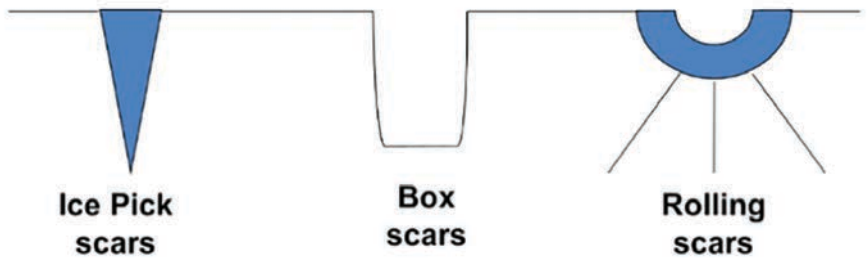

FIGURE 3. Types of acne scars

Although some studies suggest that the use of topical retinoids on a limited body surface area is likely safe, most experts do not recommend the use of topical retinoids in pregnant or lactating patients.[128]

Pediatric patients. For children 1 to 7 years old with significant acne, evaluation for systemic associations is warranted, with referral to a pediatric endocrinologist to rule out a gonadal/ovarian pathology.[134,135] Recommendations are summarized in Table 17. A low starting BPO concentration is recommended, due to increased risk of irritation; this can minimize antibiotic resistance when used with antibiotics.[135] Topical retinoids may be used as monotherapy or in combination products and in regimens of care for all types and severities of acne in children and adolescents of all ages.[135] If topical antibiotic treatment is extended beyond a few weeks, topical BPO should be added or used in combination products.[135]

Oral antibiotics are appropriate for moderate-to-severe inflammatory acne at any age.[135] Tetracycline derivatives can be used once the child has acquired full dentition. Second-generation tetracyclines (e.g., doxycycline, minocycline) are sometimes preferred due to ease of use, fewer problems with absorption, and less frequent dosing.[135] Patient education and monitoring for adverse events should be practiced. Extensive counseling is recommended when using certain agents. Previously mentioned issues regarding the use of isotretinoin and COCs should be discussed. Hormonal therapy with COCs can be useful as second-line therapy in regimens of care in pubertal women with moderate to severe acne. Tobacco use and family history of thrombotic events should be assessed (Level 4, D, GPP).[135]

Pityrosporum folliculitis can complicate acne treatment and has a predilection for adolescents. Both folliculitis and acne can be aggravated by occupation, sports, and the humid tropical climate of Singapore.[136] Retinoid dermatitis or photosensitivity from topical retinoids can be worsened by tropical sun exposure. Such exposure also results in prolonged postacne erythema and increased risk of PIH. Patients with acne should be advised accordingly.

TREATMENT OF ACNE SCARS

Scars refer to the imperfect repair of the skin following skin inflammation. There is dystrophy of the epidermis and dermis that results in focal skin atrophy or hypertrophy. This is in contrast to dyspigmentation due to postinflammation without any skin dystrophy. Such cases present as erythema or PIH and heal spontaneously without leaving any dystrophic scars. This type of dyspigmentation should not be classified as scars and instead referred to as pseudoscars.

Postacne scars cannot be reversed, but can be made less noticeable and more easily covered with makeup. Post-acne scars can be physically disabling and psychologically disturbing.[137]

There are in general three morphologies of acne scars (Figure 3): ice pick, box car, and rolling.[138] Asian skin has peculiar postacne scarring morphologies, in that some patients jawline keloids, or soft papular scars that resemble sebaceous hyperplasia on the nose and chin, and dumbbell or nodular keloids on the chest.[138]

The Qualitative Global Acne Scar Grading[139] can be used for rating of the severity of acne scarring (Table 18). Grade 1 severity (macular dyspigmentation) can cause patient distress but is only temporary and is generally not considered true acne scarring. Hence, DSS has adopted a

TABLE 18. The Qualitative Global Acne Scar Grading system[139]

GRADE	LEVEL	CHARACTERISTICS	EXAMPLES
1	Macular	Erythematous, hyper- or hypopigmented flat marks	Erythematous macules, postinflammatory hyperpigmentation, hypopigmented macules
2	Mild	Mild atrophic/hypertrophic, not obvious at social distance of 50cm away, might be adequately covered	Mild rolling, soft papular
3	Moderate	Moderate atrophic/hypertrophic, visible at 50cm, not easily covered, can be flattened by stretching skin	More significant rolling, shallow box car, mild–moderate hypertrophic/papular scars
4	Severe	Severe atrophic/hypertrophic, visible at 50cm, not easily covered, not able to flatten by stretching skin	Deep box car, ice pick, bridges and tunnels, gross atrophy, dystrophic scars, significant hypertrophy/keloid

TABLE 19. DSS Qualitative Acne Scar Grading (Modified from the Qualitative Global Acne Scar Grading system)

GRADE	LEVEL	CHARACTERISTICS	EXAMPLES
0 (pseudoscars)	Macular dyspigmentation only	Erythematous macules, postinflammatory hyperpigmentation, hypopigmented macules	Erythematous macules, postinflammatory hyperpigmentation, hypopigmented macules
1	Mild	Mild rolling, soft papular	Mild rolling, soft papular
2	Moderate	More significant rolling, shallow box car, mild–moderate hypertrophic/papular scars	More significant rolling, shallow box car, mild–moderate hypertrophic/papular scars
3	Severe	Deep box car, ice pick, bridges and tunnels, gross atrophy, dystrophic scars, significant hypertrophy/keloid	Deep box car, ice pick, bridges and tunnels, gross atrophy, dystrophic scars, significant hypertrophy/keloid

Note: Grades 1 to 3 scars can be erythematous, hyper- or hypopigmented, but grading is based on the extent of atrophy/hypertrophy rather than on color.

modified version of this scale in which macular dyspigmentation is instead considered to be grade 0 (Table 19).

The choice and extent of treatment modalities for acne scars will depend on their morphology and severity. Summary recommendations are enumerated in Table 20. Laser resurfacing is another option and includes ablative laser resurfacing or photothermolysis (AP), nonablative laser resurfacing or photothermolysis (NP), and fractional resurfacing or photothermolysis (FP). A systematic review comparing AP to NP reported a short-term improvement (26 to 83% for AP and 26 to 50% for NP) in acne scars based on both subjective and objective measurements.[140] FP is the current gold standard of laser treatment, due to less downtime. It uses thermally induced coagulation and produces a columnar-shaped microthermal zone with diameters of less than 250µm and covering up to 10 to 43 percent of total skin. There is no significant difference in efficacy between different laser settings despite adjusting fluences or densities.[141] The PIH from FP is usually mild and short-lived, lasting no longer than three months, even in individuals with darker skin types. PIH can be reduced by conservative treatment densities in Fitzpatrick Skin Types IV to VI.[142,143]

A new modality of erbium-doped yttrium aluminium garnet (Er:YAG) laser combining short-pulsed and dual-mode laser was reported to be safe and effective in treating atrophic facial acne scars in Asian patients with darker skin tones.[144] Fractional Er:YAG and CO_2 lasers provided comparable outcomes for scar treatment, but Er:YAG laser was associated with less treatment discomfort.[145]

Fractional radiofrequency (RF) therapy and bipolar RF energy therapy have also been shown to be safe and effective.[146] Fractional RF and fractional erbium-doped glass are similar in effectiveness.[147] Use of fractional laser with RF followed by fractional RF was shown to be safe and effective for treatment of acne scars, with a modest improvement and low PIH rate comparable to other resurfacing techniques in this Asian case series.[148]

ActiveFX fractional CO_2 laser therapy (Lumenis, San Jose, California, USA) is a new technology for the treatment of facial acne scars, using a diffractive lens array and 755-nm picosecond laser.[149] This laser produced improvement in appearance and texture of acne scars at three months after the last treatment, with objective findings similar to those of fractional ablative laser treatments. Histologic findings suggest that improvement in scarring from this treatment goes beyond collagen remodeling.[150]

Microneedling with dermaroller, also known as collagen induction therapy (CIT), is a simple and inexpensive modality for acne scars, demonstrating satisfactory results with little downtime, but with occasional side effects in Asian skin (e.g., PIH, tram-track scarring).[151] Additional studies are needed to confirm their efficacy. In Singapore, microneedling is included under the Ministry of Health List B Aesthetic Procedures and should only be performed as part of a clinical trial. These options are adjunctive and should never be used as first-line therapy.

TABLE 20. Summary recommendation for treatment of acne scars.

Fractional resurfacing is recommended to treat acne scars. *Level 1+, Grade B*
For ice pick scars, it might be necessary to excise or punch out the lesion or perform chemical reconstruction. For box car scar, an excision, punch elevation/excision, or subcision can be performed. For rolling scars, subcision can be performed. *Level 2+, Grade C*

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