Ministry of Health Malaysia

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Academy of Medicine Malaysia

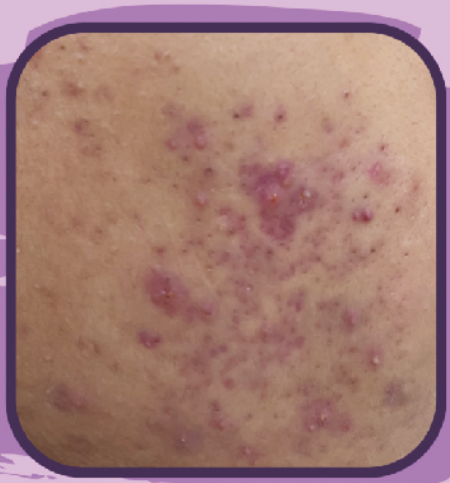
CLINICAL PRATICE GUIDELINES

2022

MOH/P/PAK/496.22(GU)-e

MANAGEMENT OF ACNE VULGARIS

(SECOND EDITION)



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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

UPDATING THE CPG

These guidelines were issued in 2022 and will be reviewed in a minimum period of four years (2026) or sooner if new evidence becomes available. When it is due for updating, the Chairperson of the CPG or National Advisor of the related speciality will be informed. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed, and the latest systematic review methodology used by MaHTAS will be employed.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which will be the definitive version at all times. This version can be found on the websites mentioned above.

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LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention; dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

FORMULATION OF RECOMMENDATION

In line with current development in CPG methodology, the CPG Unit of MaHTAS is in the process of adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size is carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG Development Group as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

DIAGNOSIS AND INVESTIGATIONS

- Microbiological and endocrinological investigations may be performed to rule out other conditions that may mimic acne vulgaris.

ASSESSMENT OF SEVERITY

- Comprehensive Acne Severity Scale may be used for grading of acne severity in clinical practice.

TREATMENT

a. Topical treatment

- Topical benzoyl peroxide monotherapy or in combination with other topical therapy should be given in mild to moderate acne vulgaris.
- Topical retinoids (e.g. tretinoin and adapalene) monotherapy should be used in non-inflammatory acne vulgaris or in combination with other therapies in inflammatory acne.
- Topical antibiotics (e.g. clindamycin) should not be used as monotherapy in acne vulgaris to prevent bacterial resistance.
- Topical azelaic acid may be used in acne vulgaris, especially in patients with post-inflammatory hyperpigmentation.
- Combination topical therapy should be given in moderate acne vulgaris.

b. Systemic treatment

- Oral doxycycline, tetracycline or erythromycin should be used for moderate to severe acne vulgaris.
  - Response to these antibiotics should be evaluated at 6 - 8 weeks.
  - Target duration of therapy should not exceed 3 - 4 months to reduce resistance.
- Isotretinoin should be prescribed for nodulocystic or severe acne vulgaris and treatment-resistant moderate acne vulgaris.
  - It should only be prescribed by dermatologists.

c. Physical treatment

- Chemical peels may be used as an adjunct in the treatment of acne vulgaris.
  - The preferred choices are salicylic acid and glycolic acid peels.

COSMECEUTICALS

- Cosmeceuticals may be used as an adjunct in the management of acne vulgaris.

TREATMENT IN SPECIAL GROUP

a. Pregnant and lactating women

- Hormonal therapy, tetracyclines, co-trimoxazole and isotretinoin should be avoided in the treatment of acne vulgaris in pregnant and lactating women.

b. Adolescents

- Topical benzoyl peroxide and topical retinoids (tretinoin and adapalene) may be used safely in adolescents with acne vulgaris.
- Oral tetracycline derivatives (e.g. tetracycline, doxycycline and minocycline) should not be used in patients aged <8 years with acne vulgaris.
- Oral isotretinoin can be used safely in patients aged ≥12 years with severe acne vulgaris.

QUALITY OF LIFE

- Assessment for quality of life may be considered in the management of patients with acne vulgaris.

REFERRAL

- Patients with moderate to severe acne vulgaris (e.g. nodulocystic acne) should be referred early to a dermatologist.
- Patients with acne vulgaris who exhibit suicidal behaviour should be referred urgently to a psychiatrist.

GUIDELINES DEVELOPMENT AND OBJECTIVES
GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these Clinical Practice Guidelines (CPG) were from the Ministry of Health (MoH), Ministry of Higher Education and private sector. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A systematic literature search was carried out using the electronic databases mainly Medline via Ovid and Cochrane Database of Systemic Reviews and others e.g. PubMed and Guidelines International Network (refer to **Appendix 1** for **Example of Search Strategy**). The common search was limited to literature published on humans, all adults (19 plus years)", publications from the year "2012 to Current" and English language. In addition, the reference lists of all retrieved literature and guidelines were searched and, experts in the field were contacted to identify relevant studies. All searches were conducted from 29 May 2020 to 10 Sep 2020. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 10 February 2022 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were also made to other CPGs on acne vulgaris e.g.:

- Acne Vulgaris: Management [National Institute for Health and Care Excellence (NICE), 2021]
- Acne Management Guidelines by the Dermatological Society of Singapore (2019)
- Guidelines of Care for the Management of Acne Vulgaris (American Academy of Dermatology, 2016)

These CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references.

A total of 14 clinical questions (CQ) were developed under different sections. Members of the DG were assigned individual questions within these sections (refer to **Appendix 2** for **Clinical Questions**). The DG members met 31 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed at each DG meeting. All statements and recommendations formulated were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. This CPG was developed largely

based on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines were graded using the US/ Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was done using the principles of GRADE (refer to the preceding page). The writing of the CPG follows strictly the requirement of AGREE II.

On completion, the draft of the CPG was reviewed by external reviewers. It was also posted for a month on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the Health Technology Assessment and CPG Council MoH Malaysia for review and approval. Details on the CPG development methodology by MaHTAS can be obtained from the Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at http://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf?mid=634).

OBJECTIVES

The objectives of the CPG are to provide recommendations on the management of acne vulgaris on the following aspects:

i. risk and aggravating factors
ii. clinical diagnostic criteria and severity grading
iii. treatment
iv. psychosocial impact and quality of life
v. indications for referral to dermatologists

CLINICAL QUESTIONS

Refer to **Appendix 2**.

TARGET POPULATION

Inclusion Criteria

- Adolescents and adults with acne vulgaris

Exclusion criteria

- Acne variants for example acne conglobata, acne fulminans, acne cosmetica, drug-induced acne and chloracne
- Rosacea
- Folliculitis

TARGET GROUP/USERS

This document is intended to guide health professionals and relevant stakeholders in primary and secondary/tertiary care of both public and private sectors in the management of acne vulgaris including:

i. medical professionals
ii. allied health professionals
iii. trainees and medical students
iv. patients and their advocates
v. professional societies
vi. policy makers

HEALTHCARE SETTINGS

Primary, secondary and tertiary care settings

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The draft guidelines were reviewed by a panel of experts. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

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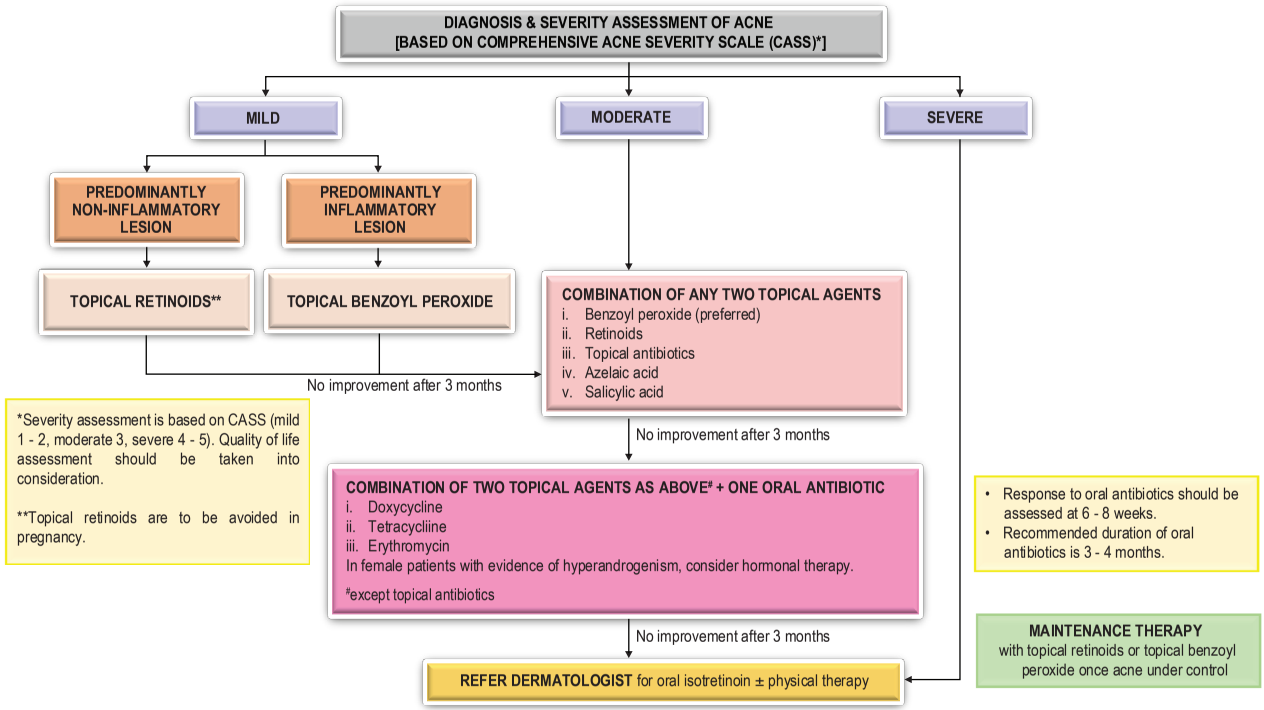
ALGORITHM ON THE MANAGEMENT OF ACNE VULGARIS



1. INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous units, characterised by the formation of non-inflammatory (open and closed comedones) and inflammatory (papules, pustules, nodules and cysts) lesions. Commonly affected areas are the face and trunk, and it usually affects adolescents and young adults. A common misconception by the public is that acne vulgaris is a self-limiting teenage skin problem and thus, does not warrant treatment. However, it has been found to adversely affect the patients' social life, self-esteem and body image. It also has the potential to cause scarring in some patients and may contribute to significant psychological distress, like depression and anxiety, if left untreated.

The pathogenesis of acne vulgaris is multifactorial. Four key pathogenic factors that play an important role in the development of acne vulgaris are increased sebum production, altered follicular keratinisation leading to comedones formation, follicular colonisation by *Cutibacterium acnes (C. acnes)*, previously known as *Propionibacterium acnes*, and inflammation around pilosebaceous unit. There has been recent evidence that microbiome and its interactions with the innate immune system plays a factor in the development of acne vulgaris.[1, level III] In acne vulgaris, the resident microbiome includes *C. acnes* and *Staphylococcus epidermidis*, whereas the transient microbiome includes *Staphylococcus aureus*. Microbial imbalance or 'dysbiosis' has been suggested to be involved in the pathophysiology of inflammatory acne. The loss of balance between the different *C. acnes* phylotypes, together with dysbiosis of the skin microbiome resulted in acne development, rather than *C. acnes* hyperproliferation. The loss of diversity of *C. acnes* phylotypes acts as a trigger for innate immune system activation, leading to cutaneous inflammation. *C. acnes* phylotype IA1 predominance has been observed, with a more virulent profile in acne than in normal skin. Recent studies also showed that the gut microbiome is involved in acne, through interactions with the skin microbiome.[1, level III]

The Global Burden of Disease Study 2019 evaluated the trend of acne vulgaris in 204 countries and territories from 1990 to 2019. Globally, the number of incident cases of acne vulgaris increased by 47.9% from 79.7 million in 1990 to 117.4 million in 2019. On the other hand, the number of prevalent cases also increased globally from 156.7 million in 1990 to 231.2 million in 2019. The age-standardised prevalence rate (ASPR) of acne vulgaris was highest in the high sociodemographic index region across all years from 1990 to 2019. Western Europe, high-income Asia Pacific and East Asia were among the top three regions with the highest ASPR in 2019 (from 41.1/1000 people to 55.8/1000 people). In contrast, the regions with the lowest ASPR were Central

Europe, Tropical Latin America and Central Asia (from 17.2/1000 people to 20.5/1000 people). The ASPR of acne vulgaris in women was 1.3 times higher than in men in 2019 (34.9/1000 people vs 26.8/1000 people). The age-specific burden rate of acne vulgaris was highest in adolescents aged 10 - 19 years, which dropped sharply after the age of 20 years.[2, level III]

There is a wide variation in the prevalence of acne vulgaris among various countries, depending on the study design and patient characteristics. It is estimated that 35% to close to 100% of adolescents have acne vulgaris at some point in their life.[3, level III] Among Asian countries, the prevalence of acne vulgaris was reported to be 88% in Singapore adolescents aged 13 - 19 years old. Another study in Singapore reported higher acne prevalence among both female and male secondary school students (92% - 95%). The prevalence was also high at 91.4% among females aged 15 - 16 years old in Sri Lanka. However, the prevalence was low (36.2%) in younger students (aged 7 - 12 years old) in South Korea. In China, the prevalence of acne vulgaris ranged from 51.3% - 62.7% in different population age groups.[3, level III] Similar overall adjusted prevalence of 57.8% was found in an online, self-reported survey involving seven European countries (Belgium, Czech Republic, Slovak Republic, France, Italy, Poland and Spain).[4, level III]

The prevalence of acne vulgaris in a Malaysian population-based study among adolescents aged 13 - 17 years old, which was published in 2009, was 67.5%.[5] Another recent cross-sectional study involving secondary schools students reported a prevalence of acne vulgaris at 64.7%.[6, level III] This concurred with two local studies among university students with a prevalence of 60.7 - 68.1%.[7-8, level III]

Variation in practice in the management of acne vulgaris warrants an evidence-based guidelines to guide healthcare providers on the issue. This is especially so when cosmeceutical products can be easily bought over the counter by the patients. Advancement in the diagnosis and treatment in acne vulgaris necessitate related updates to be addressed in the new edition of the CPG. Thus, the updated version also addresses the latest treatment modalities in the management of acne vulgaris. It is hoped that the new CPG is helpful for healthcare providers from any level of care to properly manage patients with acne vulgaris.

2. RISK AND AGGRAVATING FACTORS

A number of risk and aggravating factors for acne vulgaris have been described in the literature. The studies included are those with acceptable quality and the results are summarised below:

a. Age

A cross-sectional study showed that subjects aged 15 - 16 and 17 - 18 years old groups were associated with an increased risk of acne (OR=2.38, 95% CI 1.95 to 2.92) and (OR=1.59, 95% CI 1.26 to 2.01) respectively. Older adolescents (aged 17 - 18 years old) were significantly associated with acne severity.[9, level III]

b. Gender

Inconsistent associations have been found between gender and likelihood of acne. A local study found males are more likely to develop acne compared to females (OR=4.734, 95% CI 2.276 to 8.222). They are also found to have a higher risk of developing moderate to severe acne (p=0.001).[8, level III]

A more recent study however found females are more likely to have acne compared with males with a prevalence ratio of 1.16 (95% CI 1.05 to 1.25).[10, level III]

Personal history of acne during adolescence is associated with adult female acne (OR=5.44, 95% CI 3.43 to 8.61).[11, level II-2]

c. Family history

The role of genetics as a risk factor for acne vulgaris has been proposed although the exact mode of inheritance remains unknown. A significant positive family history of acne has been demonstrated where acne is found in twins, mother, first degree relatives and multiple family members.[5]

Two local studies revealed that family history was associated with acne vulgaris among adolescents and young adults:

- family history of acne (p<0.001)[12, level II-2]
- history of acne among father (OR=1.852, 95% CI 1.072 to 3.201), mother (OR=1.752, 95% CI 1.058 to 2.902) and both parents (OR=3.056, 95% CI 1.153 to 8.094)[8, level III]

In addition, a case-control study showed a history of acne in first-degree relatives of either parent (OR=3.02, 95% CI 1.80 to 5.06) or siblings (OR=2.40, 95% CI 1.46 to 3.94) was also associated with adult female acne.[11, level II-2]

However, family history was not found to be an aggravating factor for acne severity.[8-9, level III]

d. Body Mass Index

Obesity is closely related to hyperandrogenism, hence individuals with high body mass index (BMI) are at risk of developing acne vulgaris.[5] There are several physiologic factors that potentially link obesity to acne e.g. release of adipokine-driven inflammatory cytokines.[13, level III] However, there is limited good evidence to show the association between high BMI and acne vulgaris. The available evidence is also not consistent to draw any association between BMI and acne vulgaris.

A cross-sectional study showed that being overweight (BMI >25 kg/m^2) increased the risk of acne vulgaris (OR=2.56, 95%, CI 1.55 to 4.24).[9, level III] Another study also showed overweight and obese teenagers were more likely to have acne vulgaris with a prevalence ratio of 1.15 (95% CI 1.02 to 1.26) and 1.14 (95% CI 1.02 to 1.23) respectively.[10, level III]

In a nationwide, population-based study, overweight and obesity in young adults were inversely associated with acne vulgaris.[13, level III]

However, two studies found that obesity was not a risk factor for acne vulgaris or its severity.[8, level III; 14, level III]

e. Diet

It is postulated that dietary habits play some role in relation to acne development or exacerbation. The following are studies showing the association:

- **High glycaemic diet**

Glycaemic index is a measure of the impact on blood glucose of digestible carbohydrates of foods while the glycaemic load is an important extension of the glycaemic index concept which makes allowance for the quantity of available carbohydrates (net carbs) in the consumed portion size of food.

A cohort study showed diet of patients with acne vulgaris had significantly higher glycaemic load value (175 ± 35) compared with those without acne (122 ± 28). The risk was 25 times higher in those consuming diet with a glycaemic load value of ≥175 compared with <175.[15, level II-2]

- **Dairy products**

Two local studies showed that milk consumption was associated with acne occurrence. Daily intake of ≥2 glasses (OR=2.19, 95% CI 1.04 to 4.65)[12, level II-2] or ≥1 weekly consumption of milk (OR=3.99, 95% CI 1.39 to 11.43) increased the risk of developing acne vulgaris.[15, level II-2]

A large cross-sectional study in France also showed the consumption of milk was associated with current acne (OR=1.12, 95% CI 1.00 to 1.25).[16, level III]

However, the two local studies above found contradicting findings in relation to chocolate and ice cream intake with acne vulgaris.

- One study demonstrated that chocolate intake had resulted in the occurrence of acne vulgaris (OR=2.4, 95% CI 1.08 to 5.33)[12, level II-2] while the other study showed no significant association between them.[15, level II-2]
- In a study, consumption of ice cream ≥1/week elevated acne vulgaris risk (OR=4.47, 95% CI 2.44 to 19.72).[15, level II-2] However, no significant association was found in the other study.[12, level II-2]

Yogurt and cheese consumption had not been found to be associated with acne vulgaris.[12, level II-2; 15, level II-2] There was also no association between the consumption of low-fat milk and acne vulgaris.[10, level III]

- **Sweetened beverages and food**

A study among Chinese adolescents with moderate to severe acne vulgaris found increased risk of acne vulgaris with the following sweetened beverages (sweetened tea, fruit-flavoured and carbonated drinks):[14, level III]

- consumption of sweetened beverages (≥7/week) with sugar intake ≥100 g/day (OR=3.12, 95% CI 1.80 to 5.41)
- consumption of sweetened tea (OR=2.52, 95% CI 1.43 to 4.43) or fruit-flavoured drinks (OR=1.90, 95% CI 1.18 to 3.07)
- consumption of sweetened carbonated drinks (OR=1.61, 95% CI 0.96 to 2.72)

Another cross-sectional study also showed unhealthy sugar intake resulted in increased acne vulgaris occurrence (OR=1.30, 95% CI 1.05 to 1.60). Frequent indulgence of pastries and cakes was also associated with increased risk of acne vulgaris (OR=1.20, 95% CI 1.01 to 1.43).[9, level III]

In another recent large cross-sectional study, there was also a significant association between current acne and consumption of fatty and sugary products (OR=1.54, 95% CI 1.09 to 2.16) and sugary beverages (OR=1.18, 95% CI 1.01 to 1.38).[16, level III]

However, no significant association was found between acne vulgaris and carbonated drinks or sweets in a local study.[12, level II-2]

- **Unhealthy fat intake**

A Turkish study showed increased risk of acne vulgaris among adolescents who had the following dietary habits:[9, level III]

- unhealthy fat intake (OR=1.39, 95% CI 1.06 to 1.82)
- frequent consumption of sausages and burgers (OR=1.24, 95% CI 1.03 to 1.48)

However, another study in Kuwait showed no association between consumption of chips/fried food and acne vulgaris.[10, level III] A local study also showed no significant association between potato chips and acne vulgaris.[12, level II-2]

- **Nuts**

Nuts intake has not been found to be associated with acne vulgaris.[12, level II-2; 15, level II-2]

- **Fibre**

A large cross-sectional study showed that consumption of <5 portions of fruits and vegetables intake/day marginally increased risk of acne.[9, level III] A case-control study also showed that lack of fruits and vegetables intake (≤3 days/week) increased acne occurrence (OR=2.33, 95% CI 1.20 to 4.53).[11, level II-2]

However, another study in Kuwait showed no association between the amount of fruit consumption and acne vulgaris.[10, level III]

- **Fish**

Lack of fresh fish intake (≤3 days/week) is associated with acne vulgaris (OR=2.76, 95% CI 1.31 to 5.81).[11, level II-2]

Refer to the Malaysian Dietary Guidelines 2020 on the principles of healthy eating (available at: https://nutrition.moh.gov.my/MDG2020/mobile/index.html#p=150). Consider referring patients to the dietitian for proper counselling on healthy eating with regards to the management of acne vulgaris.

f. Lifestyle

A cross-sectional study highlighted lifestyle factors with adult female acne occurrence which were:[11, level II-2]

- being an office worker (OR=2.24, 95% CI 1.24 to 4.06).
- no previous pregnancies (OR=1.71, 95% CI 1.06 to 2.78)
- high or very high level of reported psychological stress during the last month (OR=2.95, 95% CI 1.57 to 5.53)

Another study among adolescents aged 13 - 18 showed face washing ≥3/day (OR=0.68, 95% CI 0.48 to 0.99) and living in urban area (OR=0.67, 95% CI 0.56 to 0.79) were associated with decreased risk for acne. However, living in semirural population had been shown to aggravate acne severity ($p<0.05$).[9, level III]

There is a lack of retrievable evidence on smoking and alcohol consumption as risk or aggravating factors for acne vulgaris. A local study showed no significant association between acne vulgaris and smoking.[12, level II-2]

g. Other risk and aggravating factors

Hirsutism is associated with adult female acne (OR=3.50, 95% CI 1.42 to 8.60).[11, level II-2] while oily skin type is significantly associated with acne severity.[9, level III]

- Healthy lifestyle which includes healthy eating is advised as part of the management in acne vulgaris. List of food based on glycaemic index is listed in **Appendix 3**.

3. DIAGNOSIS AND INVESTIGATIONS

Acne vulgaris is diagnosed clinically based on the presence of:

- non-inflammatory lesions (NIL) – open **(Figure 1)** and closed comedones **(Figure 2)**
- inflammatory lesions (IL) – papules, pustules **(Figure 3)**, nodules and cysts **(Figure 4)**

The lesions are usually located on the face and trunk. Untreated or poorly-treated acne may result in scars (hypertrophic, keloid, ice-pick, boxcar and rolling scars).

Investigations are rarely needed in the diagnosis of acne vulgaris. They are only required to rule out other diseases which may be associated with acne e.g. polycystic ovarian syndrome (PCOS), Cushing's syndrome or androgen-secreting tumour. Microbiology and/or endocrinology testing may be offered to exclude these conditions and discussed below.

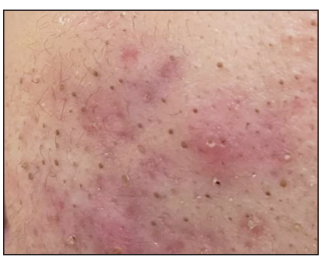


Figure 1: Open comedones

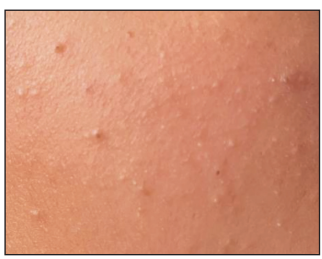


Figure 2: Closed comedones

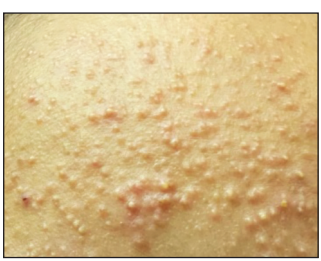


Figure 3: Papules & pustules

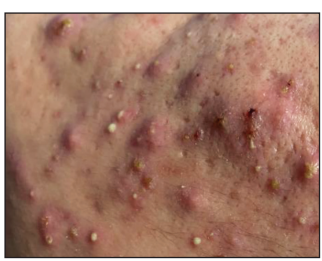


Figure 4: Pustules, nodules and cyst

a. Microbiology test

C. acnes (previously known as *Propionibacterium acnes*), a Gram-positive anaerobic rod, is the primary bacterium implicated in acne vulgaris. However, routine microbiologic testing for the bacteria is not recommended in the diagnosis of acne vulgaris.[17]

Microbiologic testing with a swab culture may be useful to exclude certain infections that may exhibit acne lesions:[17]

- *Staphylococcus aureus* cutaneous infection
  - may appear similar to acne vulgaris particularly in cases of acute eruptions
- Gram-negative folliculitis
  - presents as uniform and eruptive pustules usually at the perioral and perinasal regions
  - implicated bacteria are various e.g. Klebsiella and Serratia
  - unresponsive to many conventional acne treatments
- Pityrosporum folliculitis
  - prominent truncal involvement or monomorphic appearance
  - caused by fungal infection

b. Endocrinology test

Most acne patients have normal hormone levels. Recalcitrant acne vulgaris may be seen in patients with androgen excess. Endocrinology evaluation is indicated in patients with clinical features or a history of hyperandrogenism:[17]

- in prepubertal children, these features include acne, early-onset body odour, axillary or pubic hair, accelerated growth, advanced bone age and genital maturation
- in postpubertal females, clinical signs are infrequent menstruation, hirsutism, androgenetic alopecia, infertility, polycystic ovaries, clitoromegaly and truncal obesity

PCOS is the most common cause of elevated androgens of ovarian origin.[17-18] Referral to a gynaecologist for hormonal assessment and pelvic ultrasound may be helpful in confirming PCOS.

In patients whom there is a suspicion of androgen excess, the following hormonal tests may be considered and a referral to an endocrinologist for further evaluation is warranted:[17]

- oestrogen
- progesterone
- free and total testosterone
- luteinizing hormone
- follicle-stimulating hormone
- sex-hormone binding globulin
- androstenedione
- dehydroepiandrosterone sulfate
- prolactin
- cortisol
- growth hormone
- insulin-like growth factor

Recommendation 1

- Microbiological and endocrinological investigations may be performed to rule out other conditions that may mimic acne vulgaris.

4. ASSESSMENT OF SEVERITY

There are two broad approaches to the assessment of acne severity which are global acne severity grading and lesion counting. Both have some subjectivity involved. More objective methods for assessing the severity of acne vulgaris include photography and advanced imaging technologies.[19, level III]

There are at least 25 different acne severity grading systems, comprising of both global grading and lesion counting.[19, level III] Global severity gradings are usually based on comparisons of descriptive texts or photographic standards. For acne lesion counting method, the number of NIL (open and closed comedones), IL (papules, pustules and nodules) and total lesions (TL) are counted. Currently, there is no universally accepted grading system for acne.[17]

The South-East Asia Study Alliance (SASA) adopts the American Academy of Dermatology Acne Consensus Conference (ACC) grading system for acne severity. The ACC classification of acne severity is based on the number and types of lesions, which is further classified into three groups, which are mild, moderate and severe.[20] The Dermatological Society of Singapore[18] and the first edition of Malaysian MoH CPG on Management of Acne[5] advocate the use of Comprehensive Acne Severity Scale (CASS) for evaluating acne severity. CASS [modification of an Investigator Global Assessment (IGA) of Acne Severity] is a validated tool. It correlates strongly with the Leeds technique for face (r=0.82), chest (r=0.85) and back (r=0.87).[5] It is also simple to use in clinical practice.

In a clinical research setting, lesion counting is better suited than grading. Counts can distinguish between even small differences in therapeutic response. The reliability of lesion counting has been evaluated and shown intraclass correlation coefficients (ICCs) of 0.68 for NIL, 0.72 for IL and 0.65 for global grading. For intra-rater reliability, the ICCs are 0.83, 0.79 and 0.69 for NIL, IL and global grading respectively. These results suggest that lesion counting is more reliable than global grading.[19, level III]

Recognising the concerns with existing measures of acne severity and inadequate appraisals of acne severity scales to date, a review was conducted on original published acne scales to formally evaluate their quality against a set of predetermined criteria. The maximum quality score was 13. The highest score of 6 was achieved by three measures, which are the Leeds Revised Acne Grading (LRAG), The Global Acne Severity Scale (GEA) and The Escala de Gravedad del Acné Española (EGAE). CASS received a score of 5.[21, level III]

Semi-automated or automated methods based on computational imaging techniques have been used for acne severity assessment.[22, level III] Computational assessment is a more objective method, which can reduce inter- and intra-rater variations. However, such techniques have limitations e.g. high cost, use of complex and sophisticated apparatuses, and time-consuming imaging process.

Table 1 shows the comparison among common Acne Severity Grading Techniques based on the core psychometrics criteria.

Table 1: Comparison Among Common Acne Severity Grading Techniques

Grading technique	Type of assessment	Validity	Inter-rater reliability	Intra-rater reliability	Sensitivity to change
The Global Acne Severity Scale (GEA Scale)[23, level III]	6-point photo-numeric scale with descriptive text	No evidence	Strong	Strong	No evidence
Leeds Revised Acne Grading Scale (LRAG) [24-25, level III]	Photo-numeric scale with 13 categories	Weak	Weak	No evidence	Weak
Leeds Grading Technique [26, level II-1; 27, level III]	11-point scale, supported by black and white images; assessment in situ	No evidence	Strong	Strong	No evidence
Comprehensive Acne Severity Scale (CASS) [28, level III]	6-point scale with text description of each category; assessment in situ	Strong	No evidence	No evidence	Strong
Investigators Global Assessment Scale (IGA) [27, level III; 29, level III]	5-point severity scale with descriptive text	No evidence	Strong	No evidence	No evidence
Cook Acne Grading Severity Scale[30, level II-1]	Photographic standard 8-point scale supported by text description, and five black and white photographs; remote assessment	No evidence	Strong	No evidence	Weak

Grading technique	Type of assessment	Validity	Inter-rater reliability	Intra-rater reliability	Sensitivity to change
Global acne grading system (GAGS) 31, level III	5-point scale based on most prominent lesion in any of six regions, multiplied by a factor of 1, 2 or 3 to achieve a global score	No evidence	No evidence	No evidence	No evidence

Modified: Agnew T, Furber G, Leach M, et al. A Comprehensive Critique and Review of Published Measures of Acne Severity. J Clin Aesthet Dermatol. 2016;9(7):40-52

The CPG DG advocates the use of CASS for the assessment of acne severity as it is simple to be used in clinical setting. **Table 2** below describes CASS assessment where inspection is done at a distance of 2.5 metres away for acne on the face, chest and back.

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 metre away. A few scattered comedones, few small papules and very few pustules.
Mild	2	Easily recognisable; 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 cyst.
Very severe	5	Highly inflammatory acne covering the affected area, with nodules and cyst present.

Refer to **Appendix 4** for **Clinical Images According to CASS Grading**.

Recommendation 2

- Comprehensive Acne Severity Scale may be used for grading of acne severity in clinical practice.

5. TOPICAL TREATMENT

Treatment of acne vulgaris is based on the grade and severity of acne. Its goals include resolution of lesions, reduction of psychological morbidity and prevention of scars. Early intervention is important to prevent complications. The treatment can be divided into pharmacological and physical therapies.

Pharmacological treatment is the first-line management for acne vulgaris. It can be divided into topical and systemic treatment. Refer to **Appendix 7** on **Medication Dosage and Adverse Events**. The availability of these treatments in Malaysia is also stated in the appendix.

5.1 Topical Benzoyl Peroxide

Benzoyl peroxide (BPO) is an oxidising agent that has bactericidal, mild anti-inflammatory and comedolytic properties. It is available in concentrations of 2.5%, 5% and 10%.

A large Cochrane systematic review involving 120 randomised controlled trials (RCTs) on 29,592 participants with acne vulgaris looked into the effectiveness and safety of topical BPO and its combination. Topical BPO monotherapy was more effective than placebo or no treatment at long-term (>8 weeks) in:[32, level I]

- reduction of TL count (MD= -16.14, 95% CI -26.51 to -5.78)
- reduction of IL count (MD= -6.12, 95% CI -11.02 to -1.22)
- reduction of NIL count (MD= -9.69, 95% CI -15.08 to -4.29)
- achievement of ‘clear’ or ‘almost clear’ on the IGA-rated scale of acne severity (RR=1.77, 95% CI 1.37 to 2.28)

Topical BPO with add-on treatment was also more effective in acne vulgaris at long-term in the following comparisons:[32, level I]

- BPO/adapalene vs placebo or no treatment
  - achievement of ‘clear’ or ‘almost clear’ rating on IGA scale (RR=2.45, 95% CI 2.07 to 2.9)
- BPO/clindamycin vs placebo or no treatment
  - achievement of ‘clear’ or ‘almost clear’ rating on IGA scale (RR=2.29, 95% CI 1.79 to 2.93)
- BPO/adapalene vs adapalene
  - achievement of ‘clear’ or ‘almost clear’ rating on IGA scale (RR=1.65, 95% CI 1.42 to 1.93)
- BPO/clindamycin vs clindamycin
  - reduction in TL count (MD= -7.25, 95% CI -11.05 to -3.45)
  - reduction in IL count (MD= -1.03, 95% CI -1.88 to -0.18)
  - reduction in NIL count (MD= -3.97, 95% CI -5.81 to -2.13)
  - achievement of ‘clear’ or ‘almost clear’ rating on IGA scale (RR=1.45, 95% CI 1.31 to 1.61)

- BPO/clindamycin vs adapalene/clindamycin
  - achievement of 'clear' or 'almost clear' rating on IGA scale (RR=1.45, 95% CI 0.95 to 2.23)

However, there was no significant difference between topical BPO monotherapy vs topical adapalene or topical clindamycin monotherapy in IGA rated scale of 'clear' or 'almost clear' for acne severity at long-term.[32, level I]

There was also no difference in the effectiveness of topical BPO of various concentrations (2.5%, 5% and 10%) and in various vehicles (alcohol, water, acetone, gel or lotion).[5]

In terms of safety, topical BPO monotherapy or with add on treatment had higher percentage of any adverse events (AEs) compared with their comparators at long-term as listed below:[32, level I]

- BPO monotherapy vs placebo or no treatment (RR=1.46, 95% CI 1.01 to 2.11)
- BPO/adapalene vs placebo or no treatment (RR=4.60, 95% CI 2.42 to 8.75)
- BPO/adapalene vs adapalene (RR=1.38, 95% CI 0.98 to 1.95)
- BPO vs clindamycin (RR=1.27, 95% CI 0.98 to 1.64)
- BPO/clindamycin vs clindamycin (RR=1.48, 95% CI 1.02 to 2.16)

However, topical BPO monotherapy or with add on treatment had less AEs in the following comparisons:

- BPO vs adapalene (RR=0.77, 95% CI 0.48 to 1.25)
- BPO/clindamycin vs adapalene/clindamycin (RR=0.55, 95% CI 0.42 to 0.71)

When comparing the different concentrations of topical BPO, the frequency of AEs was higher in BPO 10% compared with BPO 2.5% and 5%.[5]

Most of the above AEs were mild to moderate. The most common ones across trials included skin dryness, erythema, skin irritation, peeling, stinging/burning sensation and pruritus.[32, level I]

On quality assessment, the included trials in the review were/had high or unclear risk of bias, small sizes, inconsistent results and possible publication bias.[32, level I]

- Practical advice on topical BPO:
  - Start at a lower concentration of 2.5% and titrate gradually to 5 - 10% if no improvement
  - Apply once a day on the affected areas only
  - If skin irritation develops, withhold treatment and restart on alternate days once the AE has subsided
  - Concomitant use of moisturiser may improve tolerability
  - Bleaching of clothes may occur and the patient should be advised accordingly

Recommendation 3
- Topical benzoyl peroxide monotherapy or in combination with other topical therapy should be given in mild to moderate acne vulgaris.

5.2 Topical Retinoids

Topical retinoids, synthetic derivatives of vitamin A, are used in the treatment of both inflammatory and non-inflammatory acne. They help normalise follicular keratinisation and decrease keratinocyte cohesiveness, thus reducing follicular occlusion and comedones formation. Topical retinoids include tretinoin, adapalene, tazarotene and isotretinoin. A new agent that has been recently approved is trifarotene. In Malaysia, only topical tretinoin and adapalene are currently available.

5.2.1 Topical tretinoin

Topical tretinoin/retinoic acid was the first topical retinoid used in the treatment of acne. It is available in various concentrations (0.01% to 0.1%) and formulations.

A large systematic review of 54 clinical trials looked into the effectiveness of topical tretinoin, adapalene and tazarotene, either as monotherapy or combination therapy. At 12 weeks of assessment, the following comparisons involving tretinoin showed:[33, level I]

- tretinoin gel microsphere (TGM) 0.04% and TGM 0.1% had no significant difference in effectiveness based on modified Global Acne Grading System (mGAGS)
- tretinoin 0.05% was more effective than adapalene 0.3% and 0.1% in reducing TL counts ($p<0.001$)
- tretinoin 0.04% and tazarotene 0.05% had no significant difference in NIL, IL and TL counts, and IGA scale rating
- combination therapy (tretinoin 0.025%/clindamycin 1.2%) was more effective than clindamycin 1.2% monotherapy, tretinoin 0.025% monotherapy and vehicle in terms of:
  - reduction in NIL, IL and TL counts ($p<0.05$)

- achievement in 2-point reduction in Investigator's Static Global Assessment (ISGA) ($p<0.001$)

5.2.2 Topical adapalene

Topical adapalene is a naphthoic acid derivative which is a receptor-selective retinoid analogue. It is available in two concentrations, 0.1% and 0.3%, but only 0.1% is currently available in Malaysia.

In the same systematic review as above, the following comparisons at 12 weeks involving adapalene showed:[33, level I]

- adapalene 0.1% was more effective than vehicle in:
  - achievement of 2-point reduction in IGA ($p<0.001$)
  - reduction of NIL, IL and TL counts ($p<0.001$)
- adapalene 0.1% was non-inferior than tazarotene 0.1% in reduction of TL counts
- adapalene 0.3% and tazarotene 0.1% had no significant difference in NIL and IL counts
- adapalene combination therapy (adapalene/BPO) was more effective than vehicle in:
  - achievement of 'clear' or 'almost clear' rating on IGA scale ($p<0.05$)
  - reduction in NIL and IL counts ($p<0.05$)

Comparison of effectiveness between various concentrations and formulations of adapalene at week 12 showed that:

- adapalene 0.3% gel was superior to 0.1% in reduction of IL count ($p=0.015$).[5]
- microsphere adapalene 0.1% and conventional adapalene 0.1% had no significant difference in NIL, IL and TL counts.[33, level I]

5.2.3 Topical tazarotene

Topical tazarotene is a receptor-selective retinoid. It is available as gel or cream in concentration of 0.05% and 0.1%.

In the same systematic review as above, the following comparisons at 12 weeks involving tazarotene showed:[33, level I]

- tazarotene 0.1% was more effective than vehicle in:
  - achievement in 2-point reduction in ISGA ($p<0.001$)
  - achievement of 'clear' or 'almost clear' rating on ISGA scale ($p<0.001$)
  - reduction in NIL, IL and TL counts ($p<0.001$)
- tazarotene combination therapy (tazarotene 0.1% + dapsone 5%) and tazarotene 0.1% monotherapy had no significant difference in IL counts

There is no retrievable evidence of superiority between both concentrations and preparations of tazarotene.[5]

5.2.4 Topical isotretinoin

Topical isotretinoin is not available in Malaysia. There is no recent retrievable evidence on its effectiveness and safety.

5.2.5 Topical trifarotene

Topical trifarotene is a new gamma-selective retinoid cream that is suitable for acne vulgaris on the face and trunk. It has comedolytic, anti-inflammatory and anti-pigmenting properties which is available in 50 µg/g strength.

Two similar RCTs, PERFECT 1 and PERFECT 2 involving 1208 and 1212 participants respectively showed that trifarotene was significantly more effective than placebo for acne vulgaris at 12 weeks in:[34, level I]

- improvement of IGA-rated scale
- reduction in mean IL and NIL count

Similarly, a single arm study demonstrated that 65.1% of participants on trifarotene showed improvement in IGA rating for facial acne vulgaris at 52 weeks.[35, level II-3]

5.2.6 Summary of effectiveness and safety of various topical retinoids

Based on the same large systematic review of 54 clinical trials that looked into the effectiveness of topical tretinoin, adapalene and tazarotene, either as monotherapy or combination therapy, all three topical agents were effective. It was however difficult to rank the various topical retinoids based on the limited number of comparative trials.[33, level I]

Limitations of the systematic review included small clinical trials, lack of blinding, potential investigator grading bias and different duration of clinical trials.

Topical retinoid is recommended as monotherapy in primarily comedonal acne and as combination therapy with BPO or topical/oral antimicrobials in mixed or primarily inflammatory acne lesions.[17-18]

In terms of safety, topical adapalene, tretinoin and tazarotene showed mostly mild to moderate severity of treatment-related AEs which were transient. Both adapalene and tretinoin had similar AEs like skin irritation and erythema, while topical tazarotene was associated with more scaling, stinging and burning sensation.[33, level I] On the other hand, topical trifarotene was associated with erythema, scaling, dryness and stinging/burning.[34, level I; 35, level II-3]

- Practical advice on topical retinoids:
  - It can cause photosensitivity, thus should be applied at night
  - Apply a thin layer on the affected areas or the entire face
  - If skin irritation develops, withhold treatment and restart on alternate days once the AE has subsided
  - Concomitant use of moisturiser may improve tolerability
  - Adequate sun protection (e.g. using broad-spectrum sunscreen, umbrella or hat) is advisable

Recommendation 4
- Topical retinoids (e.g. tretinoin and adapalene) monotherapy should be used in non-inflammatory acne vulgaris or in combination with other therapies in inflammatory acne.

5.3 Topical Antibiotics

Topical antibiotics are useful in the treatment of mild to moderate inflammatory acne. Topical clindamycin and erythromycin are the most widely prescribed antibiotics. The use of topical antibiotics as monotherapy should be avoided to prevent bacterial resistance.[5, 17] A new topical antibiotic (topical minocycline foam 4%) has recently been approved for moderate to severe acne vulgaris. The only topical antibiotic available for the treatment of acne vulgaris in Malaysia is clindamycin.

5.3.1 Topical clindamycin

Topical clindamycin is effective in reducing both NIL and IL counts.[5]

A large network meta-analysis of 40 clinical trials involving 18,089 participants showed that clindamycin monotherapy or in combination was more effective than vehicle in:[36, level I]

- improving Patient Global Assessment for:
  - clindamycin alone (OR=1.56, 95% CI 1.13 to 2.16)
  - clindamycin + BPO (OR=2.98, 95% CI 2.22 to 4.01)
  - clindamycin + tretinoin (OR=1.71, 95% CI 1.12 to 2.62)
- reducing TL count for:
  - clindamycin alone MD= -8.18, 95% CI -11.11 to -5.25)
  - clindamycin + BPO (MD= -12.69, 95% CI -15.92 to -9.47)
  - clindamycin + tretinoin (MD= -7.44, 95% CI -11.90 to -2.97)
- improving IGA for:
  - clindamycin alone (OR=2.00, 95% CI 1.19 to 3.37)
  - clindamycin + BPO (OR=3.12, 95% CI 1.82 to 5.37)
  - clindamycin + tretinoin (OR=1.87, 95% CI 0.94 to 3.72)

In a large Cochrane systematic review, topical clindamycin with add-on treatment was also more effective in acne vulgaris at long-term (12 weeks) in the following comparisons:[32, level I]

- clindamycin + BPO vs placebo or no treatment
  - 'Clear' or 'Almost clear' rated on the IGA scale of acne severity (RR=2.29, 95% CI 1.79 to 2.93)
- clindamycin + BPO vs clindamycin
  - reduced TL count (MD= -7.25, 95% CI -11.05 to -3.45)

The AEs of clindamycin, e.g. erythema, peeling, dryness, scaling, stinging, burning and itching, were mild and transient.[5; 32, level I]

5.3.2 Topical erythromycin

Topical erythromycin is effective in reducing both NIL (25% to 74%) and IL (42% to 74%) at 6 to 12 weeks of treatment.[5]

However, in a large network meta-analysis mentioned above, topical erythromycin in combination with tretinoin or zinc were not more effective than vehicle.[36, level I]

AEs of topical erythromycin, e.g. dryness, itching, burning, erythema, scaling and dermatitis, were localised, mild and transient.[5; 36, level I]

5.3.3 Topical minocycline

Two large RCTs showed that topical minocycline foam 4% was more effective than vehicle in moderate to severe acne vulgaris at 12 weeks in terms of:

- reduction in IL count
  - 13.79 vs 10.94 (LSM difference=2.97, 95% CI 1.44 to 4.49][37, level I]
  - 16.93 vs 13.40 (LSM difference=3.65, 95% CI 2.46 to 4.83)[38, level I]
- reduction in NIL count
  - 14.76 vs 8.64 (LSM difference=6.14, 95% CI 2.47 to 9.82)[37, level I]
  - 18.80 vs 15.89 (LSM difference=2.90, 95% CI 0.51 to 5.30)[38, level I]
- improvement in IGA
  - 11.51% vs 6.34% (RR=1.81, 95% CI 1.10 to 2.98)[37, level I]
  - 30.8% vs 19.6% (RR=1.58, 95% CI 1.32 to 1.88)[38, level I]

In terms of safety, the AEs were mainly mild to moderate. Reported AEs included headache and skin-related changes (application site discolouration and discomfort and yellowing of nails). No treatment-related hyperpigmentation was noted.[37-38, level I]

Recommendation 5

- Topical antibiotics (e.g. clindamycin) should not be used as monotherapy in acne vulgaris to prevent bacterial resistance.

5.4 Topical Azelaic Acid

Topical azelaic acid (AA) is an aliphatic dicarboxylic acid which has both antimicrobial and anticomedonal properties. It is available in various strengths (5 - 20%) and formulations (cream, gel and lotion). It also inhibits tyrosinase, thus effective for post-inflammatory hyperpigmentation (PIH).

A Cochrane systematic review which included 18 studies on AA at various formulations and concentrations for the treatment of acne vulgaris showed the following outcomes at long-term:[39, level I]

- significant reduction in NIL, IL and TL counts for AA compared with placebo/no treatment
- no significant difference in participants' global self-assessment of acne improvement (PGA) scale of acne severity for AA monotherapy vs clindamycin and tretinoin monotherapy
- AA monotherapy was less effective than BPO in PGA scale of acne severity (RR=0.84, 95% CI 0.74 to 0.96)

In terms of safety, there was no significant difference in total minor AEs between AA monotherapy with clindamycin, tretinoin and BPO monotherapies. Most AEs reported, e.g. pruritus, burning, stinging and tingling, were mild and limited to the application sites.[39, level I]

AA has also been shown to improve PIH in acne vulgaris.[40, level III]

Recommendation 6

- Topical azelaic acid may be used in acne vulgaris, especially in patients with post-inflammatory hyperpigmentation.

5.5 Topical Salicylic Acid

Topical salicylic acid (SA) is an O-hydroxybenzoic acid which has keratolytic and comedolytic effects. It is available in most over-the-counter acne preparations in various concentrations (0.5 - 3.0%) and formulations (facial cleanser, cream and lotion).

In the similar Cochrane systematic review as above that also evaluated 18 studies on SA at various formulations and concentrations, there was significant reduction in NIL, IL and TL counts for SA compared with placebo/no treatment. In terms of safety, the AEs were mild and limited to erythema, burning, peeling and itching.[39, level I]

5.6 Topical Dapsone

Topical dapsone has both antimicrobial and anti-inflammatory properties. It is currently not available in Malaysia.

In a pooled analysis of two RCTs in mild-to-moderate acne vulgaris, dapsone gel 7.5% was effective and safe when compared with vehicle at 12 weeks as shown below:[41, level I]

- improvement of global acne assessment score (GAAS) (29.8% vs 21.1%, p<0.001)
- reduction of NIL count (-20.7 vs -18.0, p<0.001), IL count (-15.8 vs -13.9, p<0.001) and TL count (-36.5 vs -32.0, p<0.001)
- comparable AEs (18.3% vs 18.8%); with commonest symptoms being application site reactions, e.g. dryness, pruritus and pain, which were mild to moderate in intensity

5.7 Topical Sulphur

Topical sulphur has long been used in the treatment of acne vulgaris. It has anti-inflammatory and mild keratolytic properties. Sulphur-containing preparations vary in concentrations from 1 - 10%, and available in the form of soap, foam, cream, ointment and lotion.

In a Cochrane systematic review, there was no significant difference between topical sulphur and placebo or no treatment in PGA score for acne at eight weeks. Commonest reported AEs included skin dryness and itchiness.[39, level I]

5.8 Topical Clascoterone (Androgen Receptor Inhibitor)

Clascoterone (cortexolone 17 α-propionate) is a novel, steroidal anti-androgen chemical that competes with dihydrotestosterone (DHT) receptor in the skin, leading to reduction of sebum production and proinflammatory cytokines. It is currently not available in Malaysia.

In a meta-analysis which included five RCTs comprising 2457 subjects with acne vulgaris, topical clascoterone cream 1% was more effective than vehicle at 12 weeks in:[42, level I]

- improving IGA-rated scale (RR=2.87, 95% CI 2.11 to 3.89)
- decreasing NIL counts (MD= -5.64, 95% CI -8.41 to -2.87)

It is well tolerated and showed no significant difference in the incidence of drug-related AEs.

5.9 Topical Olumacostat Glasaretil (Sebum Controlling Agent)

There is no retrievable evidence on this agent.

5.10 Comparison of Various Topical Preparations for Mild to Moderate Acne Vulgaris

A recent network meta-analysis on monotherapies of adapalene, tretinoin, BPO, clindamycin and AA, and combination therapies of adapalene + BPO, clindamycin + BPO, clindamycin + tretinoin, erythromycin + tretinoin and erythromycin + zinc showed that all topical treatments were more effective than vehicle. Amongst them, combination therapy of adapalene + BPO was the most effective with the following results:[36, level I]

- reduction in TL count (MD= -20.96, 95% CI -25.02 to -16.90)
- improvement of IGA score (OR=3.83, 95% CI 2.40 to 6.10)
- improvement of Patient Global Assessment (OR=3.65, 95% CI 2.58 to 5.15)

However, adapalene + BPO combination had a slightly higher incidence of withdrawal due to AEs (OR=2.93, 95% CI 1.69 to 5.08).

5.11 Topical Fixed Combination Therapy

Topical combination therapies can be prescribed as two separate products or as a fixed combination. The available topical fixed combination therapy includes clindamycin/BPO, adapalene/BPO, erythromycin/BPO and clindamycin/tretinoin.

Combination preparations with topical BPO, retinoids or antibiotics are more effective than either agent used alone.[5; 32, level I] However, there is no evidence to demonstrate that combination therapy as separate product is superior or inferior to a fixed combination.[32, level I] Topical fixed combination therapy may improve compliance because of convenience and faster speed of onset.[43, level III]

- Topical agents are the mainstay of treatment in mild to moderate acne vulgaris.
  - There is a variety of preparations available.
  - The commonly used agents are topical BPO, retinoids, antibiotics and fixed combination preparations.
- Combination treatment with either topical BPO, topical retinoid or topical antibiotic is more effective than monotherapy in acne vulgaris.

Recommendation 7

- Combination topical therapy should be given in moderate acne vulgaris.

6. SYSTEMIC TREATMENT

Refer to **Appendix 7** on **Medication Dosage and Adverse Events**. The availability of the treatments in Malaysia is stated in the appendix.

6.1 Oral Antibiotics

The effectiveness of oral antibiotics has long been established due to their anti-inflammatory effects and antibacterial action against *C. acnes*. Oral antibiotics are indicated for moderate to severe papulopustular/ inflammatory acne vulgaris.

Antibiotics must be used judiciously as recent decades have seen increasing emergence of resistant strains of *C. acnes*. Resistance can manifest as reduced response, no response or relapse. Limiting the duration of antibiotic therapy and adequate patient education to enhance compliance are paramount to reduce the risk of resistance while achieving a satisfactory outcome. Topical retinoid, BPO or AA should be used after discontinuation of antibiotic.[44, level III]

There are several antibiotics used in the treatment of acne vulgaris namely tetracycline class, macrolides and trimethoprim-sulfamethoxazole. The effectiveness and safety of the antibiotics are discussed below.

6.1.1 Tetracycline class

The tetracycline class of antibiotics are considered first-line therapy in moderate to severe acne, except where contraindicated (e.g. pregnancy, lactation, age <8 years or allergic to tetracyclines). It inhibits protein synthesis by binding the 30S subunit of the bacterial ribosome and has multiple anti-inflammatory properties, mainly reduction of neutrophil chemotaxis with inhibition of proinflammatory cytokines and matrix metalloproteinases.

a. Doxycycline

Doxycycline is the first tetracycline derivative to be introduced and remains one of the most commonly used antibiotics in the treatment of acne vulgaris.

Doxycycline is effective in reducing both inflammatory and non-inflammatory lesions.[5] It is given at a dose of 100 - 200 mg daily.[18] In a systematic review, two RCTs showed that 100 mg OD doxycycline had higher success rate (percentage of subjects scored ‘clear’ or ‘almost clear’) after 12 weeks and 20 mg BD doxycycline reduced TL count after 6 months of treatment compared with placebo.[45, level I]

In an RCT on subantimicrobial dosing, doxycycline 20 mg BD significantly reduced the number of IL, NIL and TL counts compared with placebo at 12 weeks. While another RCT showed that modified-release doxycycline 40 mg daily was significantly more effective than placebo in mean reduction of IL and, median percentage reduction in IL and TL counts.[45, level I]

The side effects of doxycycline were photosensitivity (dose-dependent), gastrointestinal (GI) disturbance (nausea, vomiting and/or diarrhoea, pill oesophagitis), vaginal candidiasis and pseudotumour cerebri.[45, level I]

- To reduce the side effects of doxycycline, patients should be advised to:[18]
  - take medication after meal with plenty of water
  - practise adequate sun protection

b. Tetracycline

Tetracycline is prescribed at doses ranging from 500 to 1000 mg/day and in two divided doses. In an RCT involving 51 patients with acne vulgaris, oral tetracycline showed higher percentage of clinical improvement compared with placebo after six weeks ($p<0.01$) and at completion of three month of therapy ($p<0.01$).[45, level I]

Food and dairy products reduce the absorption of tetracycline; therefore, the medication should be taken before food. Tetracycline should be used with caution in patients with renal or hepatic impairment.[18]

The common side effects of tetracycline are GI disturbance (dyspepsia, vomiting, diarrhoea), photosensitivity, pseudotumour cerebri, yellow staining of developing teeth and vaginal candidiasis.[18; 45, level I]

c. Minocycline

Of the tetracycline group, minocycline is the most lipophilic, resulting in increased penetration and accumulation in the sebaceous gland, where *C. acnes* colonises. This also allows minocycline to be taken with food and utilised at low doses. The recommended dose is 50 - 100 mg once to twice daily.

In a Cochrane systematic review, minocycline was more effective than placebo in reducing TL counts (MD=9.84, 95% CI 4.84 to 14.84) and improving Investigator Global Severity (RR=1.89, 95% CI 1.26 to 2.82). However, there was no evidence that it was superior to other commonly used oral antibiotics (oxytetracycline, doxycycline, lymecycline, roxithromycin and faropenem). The RCTs were generally small and low quality.[46, level I]

In another systematic review, two RCTs compared extended-release minocycline 1 mg/kg daily and placebo in acne vulgaris. The antibiotic group had higher percentage of treatment success based on Evaluator's Global Severity Assessment scale ($p<0.001$). In a dose-ranging RCTs, the dose of 1 mg/kg showed significant decrease in IL count compared with placebo after 12 weeks.[45, level I]

In terms of safety, 17.4% of participants treated with minocycline had experienced at least one AEs. Common AEs were blue-gray cutaneous pigmentation (dose dependent), vestibular toxicity (vertigo, dizziness), GI disturbances, lupus-like syndrome and hepatitis.[45, level I] There was no significant difference in AEs between minocycline and its comparators.[45-46, level I]

d. Lymecycline

Lymecycline is a semisynthetic antibiotic which is converted to tetracycline in the GI tract.

An RCT showed that lymecycline 300 mg daily was more effective in reducing IL ($p=0.0005$) and TL ($p<0.0007$) counts compared with placebo at 12 weeks. Treatment with lymecycline has the advantages over other tetracyclines, including a less frequent occurrence of GI and dermatological side effects.[45, level I]

e. Sarecycline

Sarecycline is a novel tetracycline-derived oral antibiotic with a narrow antibacterial spectrum. It was Food and Drug Administration (FDA) of United States of America approved in October 2018 for treatment of non-nodular inflammatory moderate to severe acne vulgaris in patients ≥9 years of age.

Two RCTs showed that oral sarecycline 1.5 mg/kg per day for 12 weeks was significantly more effective than placebo in terms of IGA success and mean reduction in percentage of IL count for facial and truncal acne. AEs were mainly GI side effects, nasopharyngitis and headache.[47, level I]

Although sarecycline might be the preferred treatment of choice in children aged 9 to 12 years, it comes with the same warnings of tooth discolouration and impaired bone growth as other tetracycline derivatives.[48, level III]

6.1.2 Macrolides

Macrolide is another antibiotic group commonly used in the treatment of moderate to severe acne vulgaris. It is safe to be used in pregnancy and lactation.

a. Erythromycin

Erythromycin has bacteriostatic activity by binding to the 50S subunit of the bacterial ribosome causing inhibition of RNA-dependent protein synthesis. It also exhibits anti-inflammatory properties. Erythromycin is available in two different formulations which is erythromycin ethyl succinate (EES) (recommended dose 400 - 800 mg twice daily) and erythromycin stearate (recommended dose 250 - 500 mg twice daily).[5] However, widespread antibiotics resistance has rendered erythromycin less useful in recent years.

In an RCT, there is no difference in effectiveness between erythromycin and tetracycline at week 12 of treatment.[45, level I]

In view of increased risk of bacterial resistance, usage of erythromycin should be limited to those in whom tetracyclines are contraindicated (pregnant women or children <8 years of age).[17]

The common AEs of erythromycin are diarrhoea, nausea, abdominal discomfort, cardiac conduction abnormalities and hepatotoxicity.[45, level I] Potential drug interactions with carbamazepine, theophylline and cyclosporine have also been reported.[18]

b. Azithromycin

Azithromycin is a derivative of erythromycin. The long half-life is conducive to less frequent dosing which might improve compliance. It has better bioavailability when taken on an empty stomach.

Numerous dosing regimens have been recommended, from three times a week to four days a month. In a systematic review, an RCT with different doses in patients with papulopustular acne vulgaris concluded that azithromycin total dose of 4.5 g in seven weeks was significantly less effective in decreasing the total of lesions and change over time than total dose of 6.0 g in 10 weeks or 7.5 g in 13 weeks.[45, level I]

In the same systematic review, three RCTs showed comparable effectiveness in lesion count and/or acne vulgaris severity between different pulsed doses of azithromycin and doxycycline in moderate inflammatory acne vulgaris.[45, level I]

A recent local RCT compared the effectiveness of azithromycin 250 mg three times a week plus BPO 5% and doxycycline 100 mg daily plus BPO 5% in patients with moderate to severe acne vulgaris. The effectiveness was comparable in both groups as assessed by improvement of CASS score and lesion counts at week 12. There were no significant differences in the incidence of diarrhoea and abdominal pain, and none of the patients in the azithromycin group experienced nausea.[49, level I]

In terms of safety, azithromycin can cause GI disturbances but at a lower incidence than erythromycin. However, it had been associated with cutaneous hypersensitivity reactions.[45, level I]

6.1.3 Trimethoprim-sulfamethoxazole (Co-trimoxazole)

Sulfamethoxazole is bacteriostatic by blocking bacterial synthesis of folic acid which is necessary for cell division, while trimethoprim is a folic acid analog that inhibits the enzyme dihydrofolate reductase.

In a systematic review, an RCT demonstrated a significant reduction in acne scores after five weeks of therapy with trimethoprim/sulfamethoxazole (400/80 mg once daily) compared with placebo. In another RCT, trimethoprim 100 mg (three times per day for four weeks, then twice daily for four weeks) was found to be as effective as oxytetracycline 250 mg (three times per day for four weeks, then twice daily for four weeks) in reducing lesion count.[45, level I]

The AEs of this antibiotic include GI upset, photosensitivity and the potential for serious AEs e.g. Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), bone marrow suppression,[18] fulminant hepatitis necrosis and respiratory hypersensitivity.[45, level I] It is contraindicated among individuals who are glucose 6 phosphate dehydrogenase (G6PD)-deficient.[45, level I]

Co-trimoxazole should only be used when other antibiotics have failed or are contraindicated because of its potential serious AEs.

6.1.4 Antibiotic resistance

Increase in *C. acnes* resistance has been reported in all major regions of the world. Seven studies explored the pattern of antibiotic resistance and the results are summarised as below in **Table 3**.

Table 3: Resistance Rate of Antibiotics in Acne Treatment

Antibiotics	Resistance rate (%)
Doxycycline	0 - 22
Tetracycline	0 - 22
Minocycline	0 - 10
Erythromycin	10.6 - 64
Clindamycin	6.1 - 62.7
Trimethoprim-sulfamethoxazole (Co-trimoxazole)	6.7 - 26.3

Source:
1 Moon SH, Roh HS, Kim YH, et al. Antibiotic resistance of microbial strains isolated from Korean acne patients. J Dermatol. 2012;39(10):833-7
2 Laochunsuwan A, Taweechotipatr M, Udompataikul M. In vitro Study of Antibiotic Susceptibility of *Propionibacterium acnes* Strains Isolated from Acne Vulgaris Patients. J Med Assoc Thai. 2017;100(10):24.
3 Yang SS, Long V, Liau MM, et al. A profile of Propionibacterium acnes resistance and sensitivity at a tertiary dermatological centre in Singapore. Br J Dermatol. 2018;179(1):200-201
4 Zhang N, Yuan R, Xin KZ, et al. Antimicrobial Susceptibility, Biotypes and Phylotypes of *Clinical Cutibacterium* (Formerly *Propionibacterium*) *acnes* Strains Isolated from Acne Patients: An Observational Study. Dermatol Ther. 2019;9:735-746
5 Mendoza N, Hernandez PO, Tyring SK, et al. Antimicrobial susceptibility of *Propionibacterium acnes* isolates from acne patients in Colombia. Int J Dermatol. 2013;52(6):688-92
6 Schafer F, Fich F, Lam M, et al. Antimicrobial susceptibility and genetic characteristics of *Propionibacterium acnes* isolated from patients with acne. Int J Dermatol. 2013;52(4):418-25
7 Biswal I, Gaind R, Kumar N, et al. In vitro antimicrobial susceptibility patterns of *Propionibacterium acnes* isolated from patients with acne vulgaris. J Infect Dev Ctries. 2016;10(10):1140-1145

Refer to **Appendix 6** on **Clinical Characteristics of Acne Patients in Studies on Antibiotic Resistance** and **Resistance Rates of Systemic Antibiotics Used in Acne Vulgaris**.

Oral antibiotic therapy should not exceed 3 - 4 months and that minimum duration of 6 - 8 weeks is required to see clinical improvement in acne vulgaris.[18]

- Oral antibiotic in combination with other topical treatment e.g. BPO, retinoid and AA is advocated as it prevents development of bacterial resistance, achieves faster resolution of lesions and targets multiple pathogenesis of acne.

Recommendation 8
- Oral doxycycline, tetracycline or erythromycin should be used for moderate to severe acne vulgaris.
  - Response to these antibiotics should be evaluated at 6 - 8 weeks.
  - Target duration of therapy should not exceed 3 - 4 months to reduce resistance.

6.2 Oral Isotretinoin

Isotretinoin or 13-cis retinoic acid is the only acne therapeutic agent that counteracts all four pathogenesis of acne vulgaris. It is converted to all-trans retinoic acid, which penetrates the cell nucleus and binds to

two nuclear receptors which are Retinoic Acids Receptors (RARs) and Retinoids X Receptors (RXRs). Isotretinoin reduces sebaceous glands activity and size markedly, normalises follicular keratinisation, indirectly inhibits *C. acnes* growth in hair follicle and exerts an anti-inflammatory action.

In a Cochrane systematic review, three low quality RCTs assessed the effectiveness of oral isotretinoin vs oral antibiotic plus topical agent. However, heterogeneity of regimens and doses in the studies precluded meta-analysis. There was no clear evidence that isotretinoin improved acne vulgaris severity based on total IL count in the following comparisons:[50, level I]

- isotretinoin vs oral minocycline plus AA in severe acne vulgaris after 24 weeks
- isotretinoin vs oral doxycycline plus adapalene/BPO gel in severe acne vulgaris after 20 weeks
- isotretinoin vs tetracycline plus topical adapalene in moderate to severe acne vulgaris after 24 weeks

Numerous discussions have been raised in recent years regarding optimal dosing and duration of treatment for isotretinoin. In the same systematic review, three RCTs assessed the different doses/therapeutic regimen of isotretinoin. However, heterogeneity between the doses made comparisons of the studies impossible.[50, level I]

- In the first RCT on severe acne vulgaris, decrease in total IL count was 79%, 80% and 84% for 0.05 mg/kg/daily, 0.1 mg/kg/daily and 0.2 mg/kg/daily of oral isotretinoin after 20 weeks.
- A second RCT compared three different doses of isotretinoin in moderate acne vulgaris i.e. daily low dose (0.25 to 0.4 mg/kg/day), daily conventional dose (0.5 to 0.7 mg/kg/day) and intermittent dose (0.5 to 0.7 mg/kg/day, first week in every four weeks) regimens for 24 weeks.
    - Mean IL counts were lower in the daily low dose (MD=3.72 lesions, 95% CI 2.13 to 5.31) and daily conventional dose (MD=3.87 lesions, 95% CI 2.31 to 5.43) compared with the intermittent dose group.
    - One year after the end of therapy, intermittent oral isotretinoin had higher mean values of GAGS scores than either daily low dose (MD=6.35, 95% CI 1.52 to 11.18) or daily conventional dose (MD=7.93, 95% 3.33 to 12.53) groups.
    - One year after the end of treatment, relapse rates were 13% in conventional dose, 18% in low dose and 56% in intermittent dose groups.
- The third RCT on severe acne vulgaris showed 95% improvement in total IL count on the face and trunk at 58%, 80% and 90% with isotretinoin at doses of 0.1 mg/kg/day, 0.5 mg/kg/day and 1 mg/kg/day respectively after 20 weeks.

In a longitudinal study on the effectiveness of isotretinoin at a dose of 0.37 ± 0.11 mg/kg/day in acne vulgaris, a decrease in GAGS score was noted after 6 - 8 weeks of treatment ($p<0.001$).[51, level II-3]

An evidence-based guidelines recommends that low-dose isotretinoin can be used effectively to treat acne vulgaris, and also reduce the frequency and severity of medication-related AEs. This is based on evidence of patients with treatment resistant or relapsing moderate acne vulgaris where low-dose isotretinoin (0.25 - 0.40 mg/kg/day) was effective and comparable to conventional dosing. Intermittent dosing of isotretinoin is not recommended.[17] As such, the CPG DG recommends starting isotretinoin at a lower dose of 10 - 20 mg/day and titrating the dose accordingly if there is no improvement after one to two months of treatment.

Conventionally, a course of isotretinoin has been prescribed until a total cumulative dose of 120 - 150 mg/kg is achieved.[52] However, based on the CPG DG's experience and clinical judgement, isotretinoin may be discontinued earlier (4 - 8 weeks after clearance of skin lesion). Acne vulgaris may relapse after treatment discontinuation. Factors that have been implicated as a higher risk for relapse include severe seborrhoea, young age, family history of acne, prepubertal acne and truncal acne.[44, level III]

Acne flare may occur after starting oral isotretinoin. Consider adding a short course of oral prednisolone to reduce the inflammation.[52] Prednisone can be given in doses of 0.5 - 1 mg/kg/day to prevent the systemic and cutaneous manifestations of isotretinoin-induced acne fulminans-like eruptions.[17] It can be tapered slowly over 4 - 6 weeks.

Isotretinoin is highly lipophilic and is best absorbed when taken with food. Patients should be instructed to take isotretinoin with meals.[17]

AEs includes mucocutaneous (cheilitis, xerosis, erythema, pruritus, desquamation, dryness of nasal mucosa, epistaxis, worsening or triggering atopic dermatitis and telogen effluvium), musculoskeletal (arthralgia and muscular cramps) and ophthalmic (dry eyes and inflammation of the eyelids) systems. With standard courses, these AEs are temporary and resolve without sequelae after discontinuation of the drug.[17]

The causal link between isotretinoin and depression is controversial with rates ranging from 1 - 11%, which are similar with the rates in oral antibiotic control groups. Patients should be screened for symptoms of depression before and during treatment.[18]

Liver function tests and serum lipids should be checked before and 6 - 8 weeks after medication initiation or earlier if necessary.[18] Laboratory abnormalities include elevations of serum aspartate, alanine transaminases and hypertriglycerides which all return to normal after discontinuation of therapy.[5]

Isotretinoin is a teratogenic drug and should not be used in female patients who are or may become pregnant. Contraception should be discussed with the patients when considering isotretinoin. Female patients who can become pregnant must be on contraception while on isotretinoin and until one month after discontinuation of the treatment. There is an extremely high risk that severe birth defects may result if pregnancy occurs while taking isotretinoin. These include external abnormalities e.g. skull abnormality, ear abnormalities (anotia, micropinna, small or absent external auditory canals), eye abnormality (microphthalmia), facial dysmorphia and cleft palate. Documented internal abnormalities include central nervous system abnormalities (cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit), cardiovascular (CV) abnormalities, thymus gland abnormality and parathyroid hormone deficiency. There is also an increased risk of spontaneous abortion and premature birth. If pregnancy occurs during treatment, isotretinoin must be discontinued immediately and patient should be referred to an obstetrician for further evaluation and counseling.[53, level III]

All patients on isotretinoin should also be counselled not to donate blood while taking the medication and for at least one month after the last dose.[53, level III]

Guidelines has recommended the usage of oral isotretinoin in nodulocystic or severe acne vulgaris, treatment-resistant moderate acne vulgaris and acne causing physical scarring or psychosocial distress.[17-18; 44, level III]

Due to the teratogenicity and other AEs related to isotretinoin, adequate counselling and patient consent are required prior to its treatment. It should be used with caution and prescribed only by dermatologists.

- Isotretinoin is teratogenic and strict contraceptive practice is required for females who may become pregnant.

Recommendation 9

- Isotretinoin should be prescribed for nodulocystic or severe acne vulgaris and treatment-resistant moderate acne vulgaris.
  - It should only be prescribed by dermatologists.

6.3 Oral Hormonal Therapy

Hormonal therapy is a treatment option for managing acne vulgaris in women. This option can be considered in women with hyperandrogenism e.g. PCOS.

6.3.1 Combined oral contraceptive

Several mechanisms are postulated on acne improvement with combined oral contraceptive (COC), like decrease free testosterone levels, increase sex hormone-binding globulin and prevent the conversion of free testosterone to DHT.

A Cochrane systematic review of 31 RCTs supported the effectiveness of COCs in reducing inflammatory and non-inflammatory facial acne lesions. The following are the important results of the review:[54, level I]

- levonorgestrel-containing COC was more effective than placebo in:
  - decreasing TL count (MD= -9.98, 95% CI -16.51 to -3.45)
  - decreasing IL count (MD= -2.95, 95% CI -4.97 to -0.93)
  - decreasing NIL count (MD= -6.75, 95% CI -12.56 to -0.94)
  - improving clinician assessment of “clear” or “almost clear” lesions (OR=1.56, 95% CI 1.13 to 2.18)
  - improving participant self-assessment of improved acne lesions (OR=2.13, 95% CI 1.47 to 3.09)
- norgestimate-containing COC was more effective than placebo in:
  - reducing TL count (MD= -9.32, 95% CI -14.19 to -4.45)
  - reducing NIL count (MD= -3.44, 95% CI -5.43 to -1.44)
  - reducing comedones counts (MD= -5.81, 95% CI -9.77 to -1.85)
  - improving clinician assessment on improved acne lesions (OR=3.86, 95% CI 2.31 to 6.44)
- drospirenone-containing COC was more effective than placebo in investigator’s assessment of “clear” or “almost clear” skin (OR=3.02, 95% CI 1.99 to 4.59)

Evidence of effectiveness comparing different COCs were scarce and less clear.

There was no strong evidence showing the superiority of cyproterone acetate COC over other progestins, although it had been traditionally used for acne treatment. COCs that contained chlormadinone acetate or cyproterone acetate improved acne better than those with levonorgesterol and desogestrel, but this apparent advantage was based on limited data or conflicting results.[54, level I] The poor quality and heterogeneity of primary papers in the review make interpretation of the results difficult.

AEs of oral hormonal therapy include nausea, vomiting, breast tenderness, headaches, menstrual disturbances and venous thrombosis.[5]

- Combined oral contraceptives may be beneficial in the treatment of acne vulgaris in female patients, particularly in those with hyperandrogenism.

6.3.2 Spironolactone

Spironolactone is an anti-androgen and aldosterone antagonist. It competes with DHT for androgen receptors in the skin.

In a systematic review on the effectiveness of spironolactone in adult female with acne:[55, level I]

- one RCT showed spironolactone was more effective than placebo in reduction of at least 50% IL count (RR=3.75, 95% CI 1.51 to 9.34)
- another RCT showed that spironolactone plus desogestrel-containing COC vs cyproterone acetate-containing COC had similar effectiveness in reducing acne severity score
- a 3-arm RCT compared spironolactone plus norgestimate-containing COC with norgestimate-containing COC and cyproterone acetate-containing COC plus 10 mg/day additional cyproterone acetate demonstrated no significant difference in the Burke and Cunliffe acne grading system between the three arms after 12 months

The commonest reported AE was menstrual irregularities which was dose related. Quality of the primary papers was very low.[55, level I]

In another recent randomised, double-blinded, placebo-controlled trial of low-dose spironolactone (25 mg and 50 mg daily) and topical BPO in adult female acne:[56, level I]

- the proportion of patients who achieved a “clear/almost clear” grade and at least a 2-grade improvement as measured by the Adult Female Acne Scoring Tool at week 12 was higher in the 50 mg spironolactone group compared with placebo (75% vs 30% for both rates, OR=7.0, 95% CI 5.6 to 8.3)
- patients who received 50 mg spironolactone had a higher rate of menstrual irregularities (p=0.013) and dizziness (p=0.039) compared with placebo
- other AEs e.g. breast tenderness, breast enlargement, fatigue and weight gain were non-significant between groups

6.3.3 Metformin

Metformin, an oral antihyperglycaemic agent, enhances peripheral tissue sensitivity to insulin, hence reducing androgenic hormones and insulin-like growth factor-1 levels.

A meta-analysis evaluated the effectiveness of metformin for treatment of PCOS-related acne. Metformin at doses of 500 - 2,000 mg daily as an adjuvant therapy to conventional treatment of acne vulgaris led to greater improvement of acne scores compared with conventional treatment (SMD= -0.256, 95% CI -0.439 to -0.074).[57, level I] However, quality of primary papers was low.

A systematic review examined the use of metformin as an adjunct therapy on moderate and severe acne in patients not diagnosed with PCOS or androgen excess. Three RCTs showed that metformin was effective as an adjunct therapy:[58, level I]

- One RCT comparing a group with metformin (500 mg twice daily), hypocaloric diet and symptomatic anti-acne treatment vs symptomatic anti-acne treatment alone showed that GAGS significantly decreased in the metformin group.
- Another RCT evaluating metformin (500 mg thrice daily) as an adjunct to lymecycline (300 mg once daily), adapalene and BPO gel showed significantly higher mean reduction rates of TL and IL counts in the metformin group compared with the group without metformin.
- A local trial evaluated metformin (850 mg daily) as an adjunct treatment to topical BPO and oral tetracycline (200 mg twice daily) showed significantly higher percentage of patients with Global Assessment Score of 0 or 1 or improvement of two grades from baseline in the metformin group compared with the group without the adjunct treatment.

However, there was no quality assessment reported in the review.

- Metformin may be beneficial as an adjuvant treatment in acne vulgaris.

A summary on the role of various topical and systemic acne vulgaris treatment based on the pathogenic factors is described in **Table 4**.

Table 4: Mode of Action of Topical and Systemic Treatments in Acne Vulgaris

Medication	Pathogenic factors			
	Abnormal sebum production	Abnormal keratinisation	*C. acnes* follicular colonisation	Inflammation
Topical BPO		✔	✔	✔
Topical retinoid		✔		✔
Topical antibiotic		✔	✔	✔
Topical azelaic acid		✔	✔	
Topical salicylic acid		✔		
Topical sulphur		✔		✔
Topical androgen receptor inhibitor (clascoterone)	✔			✔
Oral antibiotics		✔	✔	✔
Oral isotretinoin	✔	✔	✔	✔
Oral hormonal therapy	✔		✔	✔

7. PHYSICAL TREATMENT

7.1 Intralesional Corticosteroids Injection

In the first edition of Malaysian MoH CPG on the Management of Acne Vulgaris, intralesional corticosteroids injection was recommended to be used selectively for acne nodules/cysts without replacing the conventional treatment.[5] It is recommended to use intralesional triamcinolone acetonide at a dose of 10 mg/ml and may be diluted with sterile normal saline to 5 or 3.3mg/ml for nodular acne.[17]

Systemic absorption leading to adrenal suppression has been reported following higher doses of intralesional corticosteroids injection of >15 mg per session. The suppression persists for 2 - 3 days with 20 - 35 mg dose and at least for five days with 50 mg dose. Local AEs include skin atrophy, pigmentary changes, telangiectasia, haematoma and infection.[5]

7.2 Comedones Extraction

Physical therapy e.g. comedones extraction can provide immediate clinical improvement and patient satisfaction. However, there is no latest published evidence on the effectiveness and safety of comedones extraction.

In the first edition of Malaysian MoH CPG on the Management of Acne, comedones extraction using Shamberg or Saalfeld comedones extractor was effective in superficial acne but not in cystic acne. Another method using cautery and standard dissecting forceps for closed macrocomedones >3 mm in diameter showed that all patients tolerated the procedure and judged the cosmetic results as very good. The disadvantages of comedones extraction include incomplete extraction, tissue damage and recurrence.[5]

- Intralesional triamcinolone acetonide may be used for acne nodules/cysts.
- Comedones extraction may be used in the treatment of NIL in acne vulgaris.

7.3 Chemical Peels

Chemical peels have been used in the management of active acne vulgaris both as an adjunct to medical therapy or as maintenance therapy after improvement or clearance has been achieved. They are classified based on the depth of penetration:[59, level III]

- superficial (epidermis-papillary dermis)
- medium (papillary to the upper reticular dermis)
- deep (mid-reticular dermis)

SA, glycolic acid (GA), Jessner's solution (JS), resorcinol and trichloroacetic acid (TCA) peels are the most commonly used superficial peels in the treatment of active acne lesions.[60, level I] However, in recent years, other peels have emerged proving to be useful in the management of active acne of various clinical severity e.g. AA, pyruvic acid (PA) and combination peels.

a. Salicylic acid peel

SA is a beta-hydroxy acid used for superficial peeling due to its strong keratolytic and comedolytic properties. It is available at a concentration range of 20 - 30%. It promotes the shedding of epidermal cells and due to its lipophilic properties, it can penetrate comedones and pores to prevent clogging and neutralise bacteria.

A systematic review on RCTs looked into the effectiveness of chemical peel for treating acne vulgaris. Three RCTs compared different concentrations of SA with other treatments in mild to moderate acne vulgaris:[61, level I]

- 20% or 30% SA vs 5% or 10% lipohydroxy acid
  Both peels applied once every two weeks for 12 weeks were equally effective in reducing comedones. They were well tolerated but the global tolerance was better for the SA peel (p=0.028).
- 30% SA vs 50% PA
  The two peels done every two weeks for five sessions had similar effects for reducing comedones, papules and pustules. The achievement of an excellent or good improvement in all lesions was comparable for both SA and PA peels (66.7% and 60% respectively). In terms of safety, the burning sensation was seen in >85% in both peels with no significant hyperpigmentation between them.
- 10% SA vs phototherapy
  There was no difference between both treatments given once every week for a total of 10 sessions in the reduction of comedones and papules. However, the number of pustules reduction was higher in the phototherapy group (MD= -7.00, 95% CI -10.84 to -3.16).

In a recent RCT, 30% SA peel was compared with 45% mandelic acid (MA) peel (applied every two weeks for a total of six application) in mild to moderate acne vulgaris and showed the following findings at week 12:[62, level I]

- comedones reduction was higher in SA peel compared with MA peel (73.4% vs 59.7%, p=0.044)

- papule reduction was higher in MA peel compared with SA peel (86.0% vs 76.9%, p=0.004)
- no difference between both peels in pustule reduction and Michealson Acne Score (MAS) reduction

The two peels were well tolerated. Post-peel burning and stinging sensation were the commonest AEs which were higher in SA peel.

- The following are advised on the use of SA peels in patients with acne vulgaris:[17]
  - Very superficial: 20% SA
  - Superficial: 30% SA
  - Applied for 2 - 4 minutes depending on the intensity of clinical response
  - Treatment with isotretinoin should be avoided within the last six months
  - Patients should not have an active infection or open wounds (e.g. herpes simplex, excoriations or open acne cysts)

b. Glycolic acid peel

GA is available at a concentration of 20 - 70%. It is widely used as a superficial peeling agent owing to its exfoliative properties. Exposure of skin to GA leads to reduced corneocyte adhesion, correction of abnormal keratinization in the infundibulum, decreased keratinocyte plugging and ultimately decreased follicular occlusion.

In the same systematic review, three RCTs studied the effectiveness of GA with the following results:[61, level I]

- 40% GA vs placebo in moderate to severe acne vulgaris
  The two treatments applied every two weeks for five sessions showed a significant reduction in the NIL, IL and TL counts with good improvement in all lesions (RR=2.30, 95% CI 1.40 to 3.77) in the GA group. The GA group had less mild dryness but an increase in flare-up which was not significant.
- 20 - 70% GA vs 20 - 60% amino fruit acid in mild to moderate acne vulgaris
  Both treatments done every two weeks for 12 weeks showed comparable effectiveness in reduction of IL and NIL acne lesions. Oedema was more common for the GA peel (RR=1.83, 95% CI 1.21 to 2.78) but no significant difference in the incidence of frosting noted between the two groups. All patients reported discomfort which negatively affected their daily life with the GA peel.
- 30% GA vs 30% SA in mild to moderate acne vulgaris
  Both treatments were done every two weeks for six sessions and showed no significant difference in good or fair improvement in total number of lesions at one month. However, the mean number

of all lesions was significantly higher on the GA-treated side after a two-month follow-up with no treatment. Both peels were safe and well tolerated and the most common AEs were scaling, peeling and erythema.

- 70% GA vs JS in mild to moderate acne vulgaris
  Both GA and JS done every two weeks for three sessions had similar effects in improvement of acne scores by ≥0.5 and self-reported by the patient. Erythema was common for both peels. JS showed a significantly increased degree of exfoliation compared with GA.

- The following are advised on the use of GA peels in patients with acne vulgaris:[17]
  - Very superficial peel: 30 - 50% applied for 1 - 2 minutes
  - Superficial: 50 - 70% applied for 2 - 5 minutes
  - Medium depth: 70% applied for 3 - 15 minutes
  - Dosing interval: Once every 15 days for 4 - 6 months
  - Treatment with isotretinoin should be avoided within the last six months
  - Patients should not have an active infection or open wounds (e.g. herpes simplex, excoriations or open acne cysts)
- In local setting, a lower percentage of 20 - 35% GA for 2 - 5 minutes is advisable in patients of skin of colour to reduce the risk of PIH.

c. Jessner's solution

JS is a combination of 14% resorcinol, 14% SA, 14% lactic acid and ethanol. The strength of the peel is determined by the number of layers of the solution applied and is used in combination with other peels to increase the depth of the overall peel. It is a useful peel for patients with acne because of its SA and resorcinol components.

A local RCT comparing JS peel with SA 30% peel applied every two weeks for three sessions in mild to moderate acne vulgaris showed that both peels were equally effective in reducing the total NIL and IL at eight weeks ($p<0.001$). However, SA peel showed an earlier reduction of total IL at week 2 ($p=0.036$). Both groups also showed reduction of MAS as early as week 2 ($p<0.001$) The AEs in both groups were burning and stinging followed by exfoliation. The majority of the exfoliation was reported as mild in both peels.[63, level I]

In an RCT of the systematic review on mild to moderate acne vulgaris, 30% SA peel was significantly more effective in reduction of comedones and mean MAS compared with JS peel applied every two weeks for a total of six sessions. In terms of safety, both peels were tolerated well. However SA induced more but non-significant burning and stinging sensation.[61, level I]

d. Trichloroacetic acid

TCA is a self-neutralising peel that is used either as a superficial, medium or deep peel depending on the concentration used. It causes coagulation of epidermal and dermal proteins, and necrosis of collagen up to the upper reticular dermis. The clinical effects of TCA are due to the resultant increase in the dermal volume of collagen, glycosaminoglycans and elastin.

Two RCTs on mild to moderate acne vulgaris in a systematic review showed the following comparisons:[61, level I]

- 25% TCA vs 30% SA
  Both peels done every two weeks for four sessions showed no significant difference in the percentage of TL, NIL and IL count reduction. There were no AEs in the SA group but four patients in the TCA group reported hyperpigmentation which lasted for 3 - 4 weeks.
- TCA peel vs non-purpuric pulsed dye laser
  The two treatments applied every two weeks for a total of six sessions showed a non-significant difference in reduction of mean acne severity score and clinical response. However, the mean remission period was longer in the laser group (MD= -1.60 months, 95% CI -1.85 to -1.35). There were no severe AEs and both treatments were well tolerated.

e. Azelaic acid peel

AA is a naturally occurring saturated dicarboxylic acid which has anti-inflammatory and antibacterial properties.

A single-arm study using 30% AA peel, applied six times every two weeks, on mild to severe acne vulgaris patients showed significant reduction of total acne lesions, acne severity based on the IGA scale and seborrhoea using the sebumeter.[64, level II-3]

In an RCT, both AA and PA peels applied every two weeks for six sessions had comparable effectiveness in the treatment of mild to moderate papulopustular acne vulgaris. Both peels were able to reduce acne severity and desquamation compared with baseline ($p<0.001$). The peels were also able to reduce the level of oiliness in the skin with the PA peel showed a greater reduction of the oil level in the skin by using the Nati Analyzer ($p<0.05$).[65, level I]

f. Combination peels

Combination peels allow clinicians to use lower concentrations of single-ingredient peels. The high therapeutic response achieved could be attributed to the synergistic action of the combined peels that enhances the depth of peel without using a higher concentration of single peeling agent. Various combinations have been used in the management of acne vulgaris.

In a systematic review, an RCT compared 20% SA plus 10% MA and 35% GA peel applied every two weeks for six sessions in mild to moderate acne vulgaris. The combination peel was significantly more effective than GA peel in reducing total acne score, comedones, papules and pustules. There was no significant difference between these two intervention groups in burning or stinging sensations, skin dryness and acne flare-up. However, the combination induced more visible desquamation (RR=2.00, 95% CI 1.12 to 3.57).[61, level I]

A split-face RCT using various combination of peels grouped into three comparisons on mild to moderate acne vulgaris patients with Fitzpatrick skin type III and IV demonstrated better effectiveness in combination peel than single peel as shown below:[66, level I]

- Modified JS plus 20% TCA vs 30% TCA
  - reduction in MAS score (p=0.0001) and sustained on follow-up (p=0.001)
  - more favourable patient satisfaction (p=0.004)
- 20% SA plus 10% MA mixture vs 30% SA
  - reduction in MAS score (p=0.006)
  - more favourable patient satisfaction (p=0.009)

In the third comparison, there was no significant difference between Modified JS plus TCA 20% vs 20% SA plus 10% MA mixture in MAS score and patient satisfaction. In terms of safety, the reported side effects were burning sensation, erythema and exfoliation but this were well tolerated by all the patients. This RCT did not report on randomisation and blinding of the patient.

Recommendation 10

- Chemical peels may be used as an adjunct in the treatment of acne vulgaris.
  - The preferred choices are salicylic acid and glycolic acid peels.

7.4 Energy-based Devices

Recently, there has been an increased used of energy-based devices (EBD) in the treatment of active acne. The modalities include light therapy, laser and radiofrequency (RF) devices. Examples of light therapies are photodynamic therapy (PDT), intense pulsed light (IPL), blue light, red light, mixed blue-red light and cool white light. Laser has been an established treatment for acne scar. However, at present, there is an increased usage of laser therapy in the treatment of active acne. They include erbium glass laser, neodymium-doped yttrium aluminium garnet (Nd:YAG), pulsed dye laser (PDL) and non-ablative fractional laser (NAFL). Another recent modality that has been used to treat active acne is RF device which utilises electric current to generate heat instead of optical sources like laser and light devices.

7.4.1 Light-based therapy

a. Visible light sources

i. Blue light therapy

Blue light therapy has a shorter wavelength (407 - 420 nm) compared with red light. It has a bactericidal effect on *C. acnes* via excitation of bacterial porphyrins (coproporphyrin III and protoporphyrin IX) leading to the release of singlet oxygen and reactive free radicals.

A meta-analysis on 14 RCTs involving 698 participants evaluated the effectiveness and safety of blue light therapy in mild to severe acne vulgaris. The blue light was compared with placebo, topical agents (e.g. retinoids, BPO or antibiotics), oral antibiotics or isotretinoin. There was no difference in:

- mean number of NIL at weeks 4, 8 and 10 - 12 with overall MD of 3.47 (95% CI -0.76 to 7.71)
- mean number of IL at weeks 4, 8 and 10 - 12 with overall MD of 0.16 (95% CI -0.99 to 1.31)

In terms of safety, AEs were generally mild and favoured blue light or did not significantly differ between groups. They were skin irritation, erythema, dryness, tightness, peeling, itching, burning, acne flare-ups and changes in pigmentation. Most of the trials in the meta-analysis were small, of short duration (<12 weeks) and with high risk of bias.[67, level I]

ii. Red light therapy

Red light with a wavelength of 630 - 640 nm can penetrate deeper tissues e.g. sebaceous gland and stimulate macrophages to release various cytokines. This can lead to anti-inflammatory reaction and promote skin repair.

A recent large meta-analysis of 13 RCTs involving 422 participants with moderate to severe acne vulgaris on red light vs placebo and combinations of red light with aminolevulinic acid (ALA), methyl aminolevulinate (MAL), blue light, topical 1% SA and fractional erbium glass laser showed no significant difference in IL and NIL counts. Most of the AEs, e.g mild pain and erythema, were tolerable and recovered rapidly.[68, level I] The primary papers were of moderate quality and small in size.

b. Photodynamic therapy

PDT uses light-activated cream (photosensitiser) which is absorbed into the pilosebaceous unit to amplify the response to light therapy. Commonly used photosensitisers include ALA and MAL.[5]

A large Cochrane systematic review compared light therapies, including PDT, with placebo, no treatment, topical treatment or other comparators in moderate to severe acne. Three primary outcomes assessed were as below.[69, level I]

- Participant's global assessment of improvement
  - An RCT showed no significant difference between 20% ALA-PDT (activated by blue light) and vehicle plus blue light at six weeks post-treatment.
  - Another RCT demonstrated no significant difference between ALA-PDT (activated by red light) of 20% and 15%. However, ALA-PDT 20% was more effective than ALA-PDT of 10% and 5% at 24 weeks post-treatment. The NNTB was 6 (95% CI 3 to 19) and 4 (95% CI 2 to 6) for ALA-PDT 20% when compared with ALA-PDT of 10% and 5% respectively.
- Investigator-assessed changes in lesion counts
  - Three RCTs showed that MAL PDT (activated by red light) vs placebo cream plus red light had no significant difference in lesion count and percentage change in count for both IL and NIL.
- Investigator-assessed severe AEs
  - There was no report on severe AE. Blistering had been reported with the use of IPL, infrared light and PDT.

Studies comparing the effects of other interventions were inconsistent or had small samples and high risk of bias.

c. Intense pulsed light

IPL therapy, which uses broadband light, creates short thermal pulses that activate porphyrins synthesised and stored by *C. acnes* resulting in production of free oxygen radicals. This reaction directly damages sebaceous glands and destroy the blood supply which lead to decrease in sebum output.

In the above Cochrane systematic review, conclusion on the effectiveness and safety of IPL could not be derived due to limitations in methodological quality and heterogeneity of the evidence.[69, level I]

A single-arm study on a novel IPL with dual-band (400 - 600 nm and 800 - 1,200 nm) filter (five sessions, 4-weekly) in inflammatory acne patients showed its effectiveness rate of 76.19% based on 5-point scale of investigator's assessment, reduction in Hayashi acne grades ($p=0.022$) and reduction on IL count ($p=0.031$) at one-month post follow-up. Minimal reversible AEs included transient PIH which resolved within one month.[70, level II-3]

In a split-face RCT, combination of IPL (400 - 720 nm cut-off filter, four sessions every two weeks) with topical cream (licochalcone A, L-carnitine and decanediol applied twice daily for 10 weeks) demonstrated significantly better effectiveness than IPL alone plus vehicle in mild to severe acne vulgaris patients as shown below:[71, level I]

- reduction of IL at one month after fourth treatment
- reduction of NIL at three evaluation time points

- reduction of melanin index at one month after fourth treatment

The treatment was well tolerated with no serious AEs.

An RCT compared combination of IPL (420 nm, biweekly session for four weeks) plus isotretinoin (0.5 - 0.75 mg/kg/day for eight weeks) and isotretinoin alone in facial acne vulgaris graded 2 - 4 based on Global Evaluation Acne scale. Topical adapalene 0.1% gel was also added into both groups. The combination group was significantly more effective in improvement of acne severity based on Global Evaluation Acne scale, reduction of both TL and IL counts, and percentage of TL and IL reduction. Main AEs in intervention group were pain during IPL treatment and dry and/or irritation of the skin. Dryness or irritation, lips peeling and allergic reactions to adapalene 0.1% gel were present in both groups with no significant difference.[72, level I]

7.4.2 Laser therapy

Mechanism of laser therapy in active acne is by photocoagulation/ photothermal injury, which is thought to have bactericidal effect on *C. acnes* as well as reducing the size of sebaceous gland.

a. Erbium glass laser

In a split-face RCT, 1,550-nm erbium glass laser, given every two weeks for a total of four sessions, was compared with no treatment. It was significantly effective in reducing mean number of papules, pustules and nodules based on the Burton scale on acne lesion counts at the end of treatment and one year follow-up. Complete clearance of all lesions after treatment and during follow-up was observed in 70.8% of patients.[73, level I]

AEs noted were acute pustular reaction in two patients, which cleared within three days, and erythema in all patients which faded spontaneously within 2 - 24 hours.[73, level I]

b. Neodymium-doped yttrium aluminium garnet laser

A split-face RCT comparing 1,064-nm Nd:YAG and IPL treatment given monthly for three sessions in mild to severe acne showed non-significant difference in acne severity (Cunliffe's grading) and lesion count at one month after treatment completion.[74, level I] No AE was reported.

However, in another RCT, shorter treatment interval (2-weekly for three sessions) of Nd:YAG (with higher energy fluence) and IPL showed different outcomes. Nd:YAG was more effective in reducing NIL ($p=0.0099$) and TL ($p<0.014$) count of acne lesions at one month post-treatment. There was no significant difference in erythema, oedema and PIH except in crust formation.[75, level I]

c. Pulsed dye laser

An RCT compared combination of isotretinoin (0.25 mg/kg/day) and PDL (5 sessions, biweekly), and isotretinoin monotherapy (0.5 mg/kg/day) in moderate to severe facial acne. The combination treatment was more effective in terms of acne severity improvement (p=0.04), Cardiff Acne Disability Index (CADI) score (p=0.016) and erythema grading (p=0.031) at six months. It also had less side effects which were mild pain during the sessions and erythema that subsided within a few days. No hyperpigmentation or scarring was reported.[76, level I]

d. Non-ablative fractional laser

In a split-face RCT on moderate to severe acne vulgaris comparing 1,550-nm NAFL (monthly for three months) with low-dose isotretinoin (10 mg/day) and control, the intervention group had significantly lower Leeds score and mean NIL count at three months. Patients also reported discomfort after NAFL treatment i.e. pain (100%), sensation of heat (100%), erythema (94.5%) and oedema (88.9%) which resolved spontaneously within three days.[77, level I]

A split-face RCT on moderate to severe acne vulgaris compared combination of low-dose isotretinoin (10 mg/day) with 1,550-nm NAFL (monthly for three months) and without NAFL. It demonstrated that the combination treatment had significantly lower Leeds score and mean NIL count at three months. Patients reported discomfort after NAFL treatment i.e. pain, heat sensation, erythema and oedema which resolved spontaneously within three days.[77, level I]

7.4.3 Radiofrequency treatment

RF device delivers high energy causing thermal injury to deep dermis which leads to destruction of sebaceous glands. There are three major types of RF treatments i.e. unipolar, bipolar and fractional RF.

An RCT comparing fractional microneedle radiofrequency (FMR) and fractional carbon dioxide laser showed no significant difference in Global Improvement scale, papules and pustules counts, and sebum decrement at three months. However, FMR had milder AEs while fractional carbon dioxide laser had longer duration of erythema and higher pain score.[78, level I]

In a split-face RCT, FMR compared with bipolar radiofrequency (BR) reduced acne severity based on Cunliffe's grading system (p=0.02) and IL counts (p=0.001) at four weeks. It also reduced NIL counts at day 28 (p=0.005) and reduced sebum excretion level at day 56 (p<0.001). At the final visit (day 84), NIL count was further significantly reduced in FMR-treated side. Apart from that, there was more acne grading 1 compared with BR-treated (90% vs 25%). In terms of safety, FMR resulted in slight increase in Epithelization Scale at day 1 but became

comparable with BR-treated side at day 28. There was also consistent elevated redness in FMR compared with BR. However, there was no serious AEs reported besides mild pain and oedema.[79, level I]

- Laser may be used as an adjunct treatment in acne vulgaris. There is insufficient evidence to support the use of visible light and radiofrequency treatment in acne vulgaris.

8. COSMECEUTICALS

Cosmeceuticals refers to cosmetics that contain non-medicinal ingredients which is able to elicit functional effects on the skin. The term cosmeceuticals are used interchangeably with dermocosmetics and they are non-prescription items. In acne vulgaris, cosmeceuticals target various etiopathogenic factors by having antibacterial, anti-inflammatory and sebum controlling properties. Examples of cosmeceuticals include cleansers, moisturisers and sunscreen. These products contain a wide variety of ingredients which can be classified into corneolytics, sebum controller with anti-inflammatory properties, anti-bacterials and anti-oxidants.

8.1 Cosmeceutical Products

a. Cleanser

Cleansers are used to remove makeup, oil, dirt, dead skin cells and bacteria. They improve acne by removing the hair follicle plugs and preventing the obstruction of hair follicles. Cleansers come in various forms e.g. gels, liquids or creams which can be highly foaming or rinseable. In patients with oily acne-prone skin, gentle cleansers that are easily rinsed are generally preferred.

A systematic review on washing and cleansers in acne vulgaris showed the following findings:[80, level I]

- An RCT on frequency of facial washing in mild to moderate facial acne vulgaris showed that washing with a facial cleanser twice daily for six weeks reduced open comedones and NIL counts ($p=0.03$). On the other hand, once daily facial washing was associated with increased lesion counts ($p=0.01$) while washing four times daily demonstrated no change in lesion counts.
- In another RCT on grade I or II inflammatory acne vulgaris, synthetic detergents (syndets) reduced IL count whereas true soaps increased the count ($p<0.0001$).
- Gentle cleansers
  - An RCT on grade I to II facial acne showed that the usage of cleanser alone twice daily or in combination with a moisturiser with or without skin tonic resulted in no significant reduction in papules count at week 12.
  - A 4-week, single-arm trial on mild to moderate facial acne vulgaris showed improvement in acne lesion counts in patients who used a cleanser which contained surfactant sodium acyl glutamate along with an aqueous lotion and moisturising gel ($p<0.001$).
  - An open-label study on mild-to-moderate facial acne showed that usage of a liquid cleanser formulated with sodium laureth carboxylate and alkyl carboxylate improved clinician-assessed acne severity throughout the face after 28 days of facial cleansing ($p<0.01$).

- **Antiseptics**

A small RCT on mild to moderate facial acne vulgaris showed both 5% BPO leave-on formulation and Hibiclens (4% chlorhexidine gluconate) significantly reduced acne vulgaris counts compared with vehicle but no significant difference between the two at week 12.[80, level I]

- **Cleanser containing BPO**

Three single arm studies showed that cleanser containing BPO reduced *C. acnes* colony counts. However, two RCTs demonstrated conflicting clinical effectiveness of BPO cleansers when used with other topical treatment for acne vulgaris at 12 weeks.[80, level I]

- **Cleanser containing alpha-hydroxy acids (AHA)**

A 6-week single arm study of a 1% GA cleanser reported a decrease in mean Leeds score and severity grade of the face, back and chest ($p<0.001$) in acne vulgaris patients.[80, level I]

- **Cleanser containing salicylic acid (SA)**

A crossover trial on acne vulgaris showed that 2% SA cleanser reduced lesion counts by week 2 ($p<0.01$) and slight worsening following two weeks of BPO treatment ($p<0.05$). Subjects who underwent the reverse regimen had opposite results with no significant improvement following two weeks of BPO wash treatment first but improved only after switching to SA cleanser ($p<0.05$).[80, level I]

b. Sonic cleansing device

Sonic cleansing devices have been developed to be combined with cosmetic products to improve the cleansing process. These brushes cleanse via oscillatory movements which may lead to deeper cleansing of facial pores.[80, level I]

A split-face clinical trial showed no significant difference 90 minutes after facial cleansing between manual and sonic cleansing in sebummetry values, transepidermal water loss (TEWL) values, and thermography and high frequency ultrasound evaluated parameters.[81, level I]

c. Moisturiser

Moisturiser is important in the treatment of acne vulgaris. Its use improves tolerability of topical acne vulgaris treatment (e.g. retinoids and BPO) by decreasing the dryness and stinging sensation associated with barrier disruption. This could improve patients' compliance to their topical treatment.

An RCT on mild to severe acne showed that when compared to not using a moisturiser, usage of a heparinoid containing moisturiser as an adjunct to adapalene resulted in:[82, level I]

- improved adherence to adapalene treatment ($p<0.001$)
- reduced skin dryness in adapalene treatment ($p=0.0018$)

- reduced dropouts whilst on adapalene treatment (p=0.04)
- no significant difference in comedones number reduction

d. Sunscreen

Sun exposure contributes to exacerbation of acne vulgaris. Ultraviolet B (UVB) rays cause inflammation, increase sebum production and proliferation of keratinocytes.

An RCT comparing application of a UV-selective face cream vs placebo in acne vulgaris patients with greasy skin and 10 - 25 comedones per half face for eight weeks showed:[83, level I]

- no significant difference in number of comedones
- significant reduction in TEWL and sebum production in UV-selective face cream group
- more patients reported improvement of their acne in UV-selective face cream group (36% vs 2%)
- no AEs in both groups

e. Hydrocolloid acne patches

Hydrocolloid acne patches have been gaining popularity over the recent years. Being skin coloured, many consumers find them cosmetically acceptable. These patches also protect against touching of the acne lesions.

In a split-faced RCT, compared with hydrocolloid acne patch, water-soluble herbal acne patch application for 11 days resulted in:[84, level I]

- shorter median time to resolution of inflammatory acne (HR=1.68, 95% CI 1.31 to 2.15)
- greater reduction of IL count ($p<0.05$)
- greater reduction in mean diameter of IL ($p<0.05$)
- greater reduction in erythema score ($p<0.05$)

8.2 Active Ingredients in Cosmeceutical for Acne Vulgaris

a. Corneolytics

In acne patients, follicular hyperkeratinisation causes dead skin cells to clog the pilosebaceous glands, leading to formation of comedones. Follicular hyperkeratinisation is caused by an increased rate of keratinocyte proliferation, as well as reduced separation of the ductal corneocytes. This theory supports the use of corneolytic agents in acne as they target abnormal keratinisation.[85, level III] Topical corneolytics induce comedolytic effect and may also facilitate skin absorption of topical drugs. Examples include retinaldehyde, retinol, AHA (e.g. GA), beta-hydroxy acids (e.g. SA) and polyhydroxy acids (e.g. lactobionic acid and gluconolactone)

An RCT on mild to moderate acne vulgaris showed that a combination cosmeceutical product containing 0.03% retinol compared with 0.1%

adapalene gel had no significant difference at 12 weeks in:[86, level I]

- NIL, IL and total lesion counts (TLC)
- acne grading (severity)
- physician-assessed global improvement
- patient self-assessment

There was significantly fewer erythema, scaling, burning and pricking at week 2 but no significant difference at the end of study.

In another RCT, 10% GA containing oil-in-water emulsión compared with placebo in mild acne vulgaris showed improvement in Leed's score at day 45 (p=0.0004) but not at day 90 (p=0.078). There was no significant difference of AEs between the groups.[87, level I]

b. Sebum controller with anti-inflammatory properties

Increased sebum production is a key factor in acne vulgaris pathogenesis. Sebum controlling agents have been shown to absorb and retain sebum, mattify the skin and decrease formation of comedones and inflammatory acne lesions. An example is nicotinamide.

In an RCT on mild to moderate acne vulgaris, topical 4% nicotinamide had no significant difference with 1% clindamycin at eight weeks in reduction of facial papules/pustules, reduction of acne grade and frequency of AEs. However, in subgroup analysis of patients with oily skin, greater improvement in Cook's acne grading was seen in nicotinamide compared with clindamycin.[88, level I]

In women, premenstrual exacerbation of acne is most often linked to increased sebum secretion and a change in its lipid composition after ovulation. This results in alteration in the skin microbiome, triggering activation of the innate immunity, leading to formation of papular inflammatory lesions. An RCT (half-face trial) on women with Grade 2 or 3 acne with premenstrual flare-up using a combination cosmeceutical containing nicotinamide plus lipohydroxyacid (SA derivative) and piroctone-olamine (antifungal) for a month showed:[89, level I]

- reduced IL compared with placebo (p=0.01) and the difference was most apparent with number of papules (p<0.01)
- reduced number of papules (p=0.002) and closed comedones (p=0.01) at the end of the luteal phase of the interventional phase compared with observational phase
- tolerance of the cosmeceutical formulation was rated as good or excellent (96 - 100% by investigators and 88 - 94% by patients)

In a recent RCT on mild to moderate acne vulgaris, compared with BPO 2.5%, a cream containing combination of herbal extracts (onion, lavandula, mangosteen, aloe vera, paper mulberry and tea tree) and 4% niacinamide for 12 weeks resulted in:[90, level I]

- non-inferiority in mean percent reductions of comedones, inflammatory and total lesions

- non-significant difference in mean change in Dermatology Life Quality Index (DLQI) scores
- non-significant difference in patients' satisfaction with effectiveness
- less glazing with peeling and cracking (12.82% vs 28.95%) and erythema with minimal oedema or papular response (0% vs 7.89%)

c. Antibacterial agents

Antibacterial resistance in *C. acnes* has stimulated the discovery of novel ingredients with antimicrobial properties to target this bacteria.[91, level III] A number of these novel ingredients have since been incorporated into many cosmeceutical products. Examples include tyrothricin, tea tree oil, aloe vera, propolis, licochalcone A and cedar.

An RCT comparing topical tyrothricin 0.1% (antimicrobial peptide) against active comparator for 25 days in mild to severe acne papulopustulosa showed:[92, level I]

- tyrothricin was less effective in reducing IL (p=0.038), NIL (p=0.022) and TL (p=0.011) count compared with clindamycin + BPO 5%
- tyrothricin was less effective in reducing NIL (p=0.018) and TL (p=0.045) count compared with BPO 5% but showed no significant difference in reduction of IL count

In dermal tolerability and safety assessments, local intolerances (scaling, erythema, itching, burning and stinging) was found in 62.5% in tyrothricin 0.1%, 75.0% in clindamycin + BPO 5% and 91.7% in BPO 5% groups.

The essential oil of *Melaleuca alternifolia*, also known as tea tree oil or Melaleuca oil, has been used medicinally for more than 80 years. It is known to possess broad spectrum antibacterial activity. In an RCT involving patients with mild to moderate acne vulgaris, compared with erythromycin cream, a cream containing combination of propolis, tea tree oil and aloe vera for 30 days resulted in significant reduction in:[93, level I]

- erythema scars (p=0.003)
- acne severity index (ASI) (p=0.0368)
- total lesion count (p=0.001)

An RCT on mild to severe acne vulgaris demonstrated that compared with adapalene gel, topical gel of tea tree oil nanoemulsion containing adapalene for 12 weeks resulted in significantly greater reduction in:[94, level I]

- mean TLC reduction (MD= -8.832 ± 1.5189, p<0.001)
- mean NIL count reduction (MD= -5.473 ± 1.1429, p<0.001)
- mean IL count reduction (MD= -3.282 ± 0.5989, p<0.001)
- mean ASI reduction (MD= -5.79 ± 1.020, p<0.001)

AEs were more in the tea tree oil nanoemulsion containing adapalene gel group.

Licochalcone A is an oxygenated chalcone isolated from the roots of Chinese plant liquorice.[95, level III] It is known to have potent anti-inflammatory effects. In a split-faced RCT, moisturiser containing Licochalcone A in combination with decanediol, L-carnitine and SA for 12 weeks led to a significantly reduction in mean NIL, IL and TL counts compared with placebo.[96, level I]

Cedar *(Ziziphus spina-christi)* has been used topically for the treatment of skin problems in Persian Medicine. Apart from having antibacterial and anti-inflammatory effects against *C. acnes*, it also contains flavonoid which is an antioxidant. An RCT comparing the use of cedar solution vs placebo in combination with topical 1% clindamycin amongst mild to moderate acne vulgaris patients for eight weeks showed a significantly reduction in mean TLC, NIL counts, IL counts and ASI in the intervention group.[97, level I]

d. Antioxidant

Oxidative stress contributes to the pathogenesis of acne vulgaris. *C. acnes* release chemotactic factors which leads to neutrophils accumulation. These neutrophils then release reactive oxygen species that attack deoxyribonucleic acid (DNA) and/or membrane lipids, causing oxidation of these lipids. Lipid peroxidation products are pro-comedogenic and have been found to be highly concentrated in open and closed comedones. These suggest the possibility of using antioxidants in order to improve acne.

Green tea, from fresh leaves of *Camelia sinensis* contains several polyphenols of the catechin family. Green tea extract (GTE) has been postulated to have anti-bacterial and anti-inflammatory effects, and their benefits have been demonstrated in numerous skin diseases including photo-inflammation, skin aging and skin cancer.

In a systematic review on oral and topical GTE compared with placebo in acne vulgaris:[98, level I]

- topical GTE reduced
  - IL count (MD= -11.39, 95% CI -15.91 to -6.86)
  - NIL count (MD= -32.44, 95% CI -39.27 to -25.62)
- oral GTE showed
  - minimal IL reduction (MD= -1.40, 95% CI -2.50 to -0.30)
  - non-effectiveness in reducing NIL (MD=0.20, 95% CI 0.00 to 0.40)

Even though this systematic review showed favourable results with topical GTE, the formulations of GTE in individual studies were highly heterogeneous. Therefore, the CPG DG is unable to give any recommendation with regards to its use in treating acne vulgaris.

Vitamin C, also known as ascorbic acid, is a potent antioxidant that has been utilised extensively in cosmetic dermatology. In a small RCT on patients with mild to moderate acne vulgaris, sodium L-ascorbyl-2-phosphate, a stable Vitamin C derivative, significantly improved IGA score, reduced IL and NIL counts, and improved Subjects' Global Assessment Score from baseline. However, there was no result comparing sodium L-ascorbyl-2-phosphate and vehicle. In terms of safety, four subjects in sodium L-ascorbyl-2-phosphate and four subjects in vehicle reported mild treatment-related AEs.[99, level I]

- The existing studies on cosmeceuticals are small in sample sizes and low in quality.
- They are also highly heterogenous in terms of ingredients.
- Some studies involve products that contain combination of ingredients which leads to possible overestimation of the effectiveness of a certain ingredient.
- Thus, stronger evidence is warranted before cosmeceuticals can be recommended.

Recommendation 11

- Cosmeceuticals may be used as an adjunct in the management of acne vulgaris.

9. COMPLEMENTARY AND ALTERNATIVE MEDICINES

Complementary and alternative medicines (CAMs) have been practised throughout the world including Malaysia. Examples of CAMs that have been used locally to treat acne vulgaris include turmeric, cinnamon and rice powder/water ("bedak sejuk"). However, there is no retrievable strong evidence on their effectiveness in the treatment of acne vulgaris.

a. Herbal medicine and acupuncture

A large Cochrane systematic review of 35 trials of low quality on acne vulgaris showed:[100, level I]

- lack of evidence to support the use of herbal medicine, acupuncture or wet cupping therapy
- tea tree oil and bee venom significantly reduced total skin lesions compared with placebo
- potential AEs reported from
  - herbal medicines were nausea, diarrhoea and stomach upset
  - acupuncture were itchiness, redness and pain
  - tea tree oil were itchiness, dryness and flaking of the skin

In a meta-analysis of 10 RCTs with low methodological quality, external application of herbal medicines in acne vulgaris showed improvement in global assessment (MD= -2.62, 95% CI -4.84 to -0.40), IL count (MD= -1.25, 95% CI -1.68 to -0.83) and NIL count (MD= -1.32, 95% CI -1.75 to -0.90) compared with placebo. No severe AEs were found.[101, level I]

Combination of medical-grade kanuka honey with 10% glycerine to standard antibacterial soap treatment is not effective than antibacterial soap alone in the treatment of acne vulgaris based on ≥2 improvement in IGA score at week 12.[102, level I]

b. Prebiotics and probiotics

Supplementation with probiotics is increasingly being explored as a potential treatment strategy for skin disorders. Both gut-skin axis and dysregulation of insulin signalling have been implicated in the pathogenesis of acne vulgaris.

Probiotics contain live microorganisms intended to maintain or improve the normal microflora in the body whereas prebiotics act as food for human microflora. *Lactobacillus acidophilus, Bifidobacterium bifidum* and *Lactobacillus rhamnosus* are examples of different strains used as probiotic for acne vulgaris.

An RCT comparing probiotics, minocycline and combination of probiotics (*Lactobacillus acidophilus*, *Lactobacillus delbrueckii* subspecies *bulgaricus* and *Biftdobacterium bifidum*) with minocycline

showed significant improvement in NIL, IL and TL counts in the group at 12 weeks.[103, level I]

Another RCT showed an improvement in investigator's global improvement rating of adults with active inflammatory acne on probiotic strain L*actobacillus rhamnosus* compared with placebo (OR=28.4, 95% CI 2.2 to 411.1).[104, level I]

Probiotic may become an important adjuvant therapy in the management of acne vulgaris. However, there is currently lack of strong scientific evidence to support this finding.

c. Zinc

A meta-analysis which compared zinc and other comparators (topical clindamycin with BPO, topical BPO, topical erythromycin, topical minocycline and tea extract) showed a reduction in the number of acne papules in oral zinc compared with comparators (MD=3.489, 95% CI 1.048 to 11.617) at 6 - 12 weeks. However, there was not significance difference between topical zinc and its comparator.[105, level I]

d. Omega-3 acid and γ-linoleic acidne

An RCT showed that mean IL count, NIL count and acne severity were significantly reduced in the omega-3 and γ-linoleic acid (GLA) groups compared with control.[106, level I]

e. Vitamins

A meta-analysis found that serum vitamin D level was lower in patients with acne vulgaris compared with controls, indicating the possible role of vitamin D deficiency in acne pathogenesis. However, that precise role still remain unclear.[107, level I]

There is no retrievable evidence to support the usage of oral vitamin C and E supplements in the management of acne vulgaris.

- There is insufficient evidence to recommend the use of CAMs in acne vulgaris.

10. TREATMENT IN SPECIAL GROUP

10.1 Pregnancy and Lactation

The treatment of acne vulgaris in this special population requires consideration for safety in both the mother and foetus/infant. Hormonal therapy, tetracyclines, co-trimoxazole, and both oral and topical retinoids should be avoided.[18]

A meta-analysis comparing a total of 654 pregnant women exposed to topical retinoids and 1,375 unexposed pregnant women did not detect increases in rates of major congenital malformation (OR=1.22, 95% CI 0.65 to 2.29), spontaneous abortion (OR=1.02, 95% CI 0.64 to 1.63), low birthweight (OR=1.01, 95% CI 0.31 to 3.27) or prematurity (OR=0.69, 95% CI 0.39 to 1.23). However, the statistical power of this meta-analysis was not adequate to justify the use of topical retinoids during pregnancy. The results of this study may be used primarily to reassure pregnant women who were inadvertently exposed to topical retinoids during their pregnancy.[108, level II-2]

The safety of various topical, systemic and physical treatments in pregnancy and lactation are summarised in **Table 5** and **Table 6**.

Table 5. Safety of various acne treatments in pregnancy and lactation

TREATMENT	FDA PREGNANCY CATEGORY[1]	LACTATION (LACTMED)[2]
TOPICAL TREATMENT		
Benzoyl peroxide	C	Low risk
Topical retinoids		
- tretinoin	C	Low risk
- adapalene	C	Low risk
- tazarotene	X	No study on use in breastfeeding; if used, avoid ingestion/ direct contact between infant's skin and treated maternal skin
- trifarotene	No information	No information
Topical antibiotics		
- erythromycin	B	Low risk
- clindamycin	B	Low risk
- minocycline	D	No risk
Azelaic acid	B	Low risk
Salicylic acid	C	Safe to use
Dapsone	C	No study on use in breastfeeding; manufacturer states not to be used during nursing

TREATMENT	FDA PREGNANCY CATEGORY[1]	LACTATION (LACTMED)[2]
Sulphur in petrolatum[3]	Safe to use	Sulphur 5% to 10% in a petrolatum base is safe for topical use in nursing mothers
Clascoterone	No information	No information
SYSTEMIC TREATMENT		
Oral antibiotics - doxycycline - tetracycline - minocycline - sarecycline - lymecycline[4] - erythromycin - azithromycin - trimethoprim-sulfamethoxazole (co-trimoxazole)	 D D D No information Avoid use B B D	 Avoid use Avoid use Avoid use No information Avoid use Low risk – monitor infant for possible effects on GI flora Low risk – monitor infant for possible effects on GI flora Low risk in healthy, full-term infant; avoid use in G6PD-deficient infant
Isotretinoin	X	No information available; alternative topical treatments are preferred
Hormonal therapies - combined oral contraceptives - spironolactone	 X C	 Avoid in <6 weeks post-partum Low risk
Metformin	B	Should be used with caution while nursing newborn and premature infants, and those with renal impairment
Oral corticosteroids (prednisolone – short-term)	C	Low risk
PHYSICAL TREATMENT		
Intralesional corticosteroids injection (triamcinolone acetonide)	C	No information available; would not be expected to cause adverse effects in breastfed infants
Chemical peel[5] - salicylic acid - glycolic acid - lactic acid - jessner's solution - trichloroacetic acid - azelaic acid	 C; Avoided or use with caution Safe to use Safe to use Avoided or use with caution Avoided or use with caution No information	 Generally safe Generally safe Generally safe Generally safe Generally safe No information
Intense pulse light[5]	Safe to use	Generally safe
Laser treatment[5]	Safe to use	Generally safe
Photodynamic therapy - aminolevulinic acid - methyl aminolevulinate	 C C	 No information available No information available

Source:

1. United States Food & Drug Administration (US FDA) categorisation of risk of drug use in pregnancy.
2. LactMed, Drugs and Lactation Database, National Library of Medicine (U.S.).

3. Salavastru CM, Chosidow O, Boffa MJ, et al. European guideline for the management of scabies. J Eur Acad Dermatol Venereol. 2017;31:1248-1253.
4. Package Leaflet: Information for The User. 300 mg Hard Capsules Lymecycline.
5. Trivedi MK, Kroumpouzos G, Murase JE. A review of the safety of cosmetic procedures during pregnancy and lactation. Int J Womens Dermatol. 2017;3:6-10.

Table 6. Summary of U.S. Food and Drug Administration categories for medication use in pregnancy

Category	Description
A	Controlled studies in women fail to demonstrate a risk to the foetus in the first trimester (and there is no evidence of a risk in later trimesters) and the possibility of foetal harm remains remote.
B	Either animal-reproduction studies have not demonstrated a foetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that is not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
C	Either studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal or others) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the foetus.
D	There is positive evidence of human foetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
E	Studies in animals or human beings have demonstrated foetal abnormalities or there is evidence of foetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Source: Monthly Index of Medical Specialities (MIMS). Safety of Drugs in Pregnancy. (Available at: https://www.mims.com/pregdef).

In summary, the treatment choices that are safe in pregnant and lactating women are listed in **Table 7**.

Table 7. Treatment options in pregnant and lactating women

Type of treatment	Medication
Topical treatment	Benzoyl peroxide
	Topical antibiotics (clindamycin)
	Azelaic acid
	Salicylic acid
Systemic treatment	Macrolides (erythromycin, azithromycin)
Physical treatment	Chemical peel (glycolic acid, lactic acid)
	Light-based therapy (intensed pulsed light, blue- or red-light phototherapy)

Recommendation 12
- Hormonal therapy, tetracyclines, co-trimoxazole and isotretinoin should be avoided in the treatment of acne vulgaris in pregnant and lactating women.

10.2 Adolescents

Acne vulgaris is common in adolescents, defined by World Health Organization (WHO) as individuals between ages 10 and 19. The majority of clinical trials for acne treatment are conducted in patients aged 12 years or older.

The safety of the various acne vulgaris treatments in adolescents is summarised below:[109, level III]

- Topical treatments
  - Topical BPO at various concentrations is safe and effective treatment.
  - Topical retinoid
    - Tretinoin gel 0.05% is FDA-approved in patients aged ≥10 years.
    - Fixed combination therapy of adapalene and BPO gel 0.1%/2.5% is safe in patients aged ≥9 years.
  - Topical antibiotics (e.g. clindamycin)
    - Safety and effectiveness in patients aged <12 years have not been established.[110, level III]
    - Topical 5% dapsone gel is FDA-approved in patients aged ≥12 years.
  - Topical clascoterone cream 1% is FDA-approved in patients aged >12 years.[111, level III]

- Systemic treatments
  - Oral antibiotics
    - Tetracycline derivatives (e.g. tetracycline, doxycycline and minocycline) should not be used in patients aged <8 years.
    - Lymecycline is FDA-approved in patients aged >12 years.[112, level III]
    - Sarecycline is FDA-approved in patients aged ≥9 years.[113, level III]
    - Erythromycin is safe to be used in adolescents.
  - Oral isotretinoin is safe to be used in patients ≥12 years old but may be used in younger patients at physician's discretion.
  - Hormonal therapy
    - Norgestimate/ethinyl estradiol (EE) is FDA-approved for females aged >15 years.
    - Norethindrone acetate/EE is FDA-approved for females aged >15 years.
    - Drospirenone/EE is FDA-approved for females aged >14 years.

Recommendation 13
- Topical benzoyl peroxide and topical retinoids (tretinoin and adapalene) may be used safely in adolescents with acne vulgaris.
- Oral tetracycline derivatives (e.g. tetracycline, doxycycline and minocycline) should not be used in patients aged <8 years with acne vulgaris.
- Oral isotretinoin can be used safely in patients aged ≥12 years with severe acne vulgaris.

11. COMPLICATIONS

Acne vulgaris is a chronic inflammatory skin condition which causes not only profound psychosocial impact but also clinically relevant sequelae, e.g. post-acne erythema (PAE), PIH and scarring. Acne and acne-related complications can have detrimental impacts on the QoL and lead to feelings of embarrassment and low self-esteem. These complications are frequently considered cosmetically unacceptable and can have a lasting impact on the patients.

- **Post-acne erythema**

PAE is a common sequelae of acne vulgaris. It clinically presents as telangiectasia and erythema post-acne treatment. Although PAE lesions may improve over time, some remains and causes undesirable aesthetic effects to the patients.

- **Post-inflammatory hyperpigmentation**

PIH is a common problem affecting acne vulgaris patients with a prevalence of 45.5 - 87.2%. The commonest site involved is the cheeks (67.9 - 81.2%)[114, level II-2; 115-116, level III] while a total of 69.5% patients had moderate severity.[114, level II-2] PIH may last for >1 year duration in 65.2% of patients.[115, level III] It may result in psychosocial impact, e.g. embarrassment, in more than half of patients (54%) while up to 46% of patients reported to use make-up daily to camouflage the lesions. This was more prominent among the females (88% of women used make-up vs 18% of men; $p<0.001$).[117, level III] The frequency of PIH was also noted to be higher among acne vulgaris patients with melasma compared with those without it (66.8% vs 24.1%; $p<0.001$).[116, level III]

- **Acne scars**

A cross-sectional survey reported that acne scars were present in 73% of acne vulgaris patients and 55% of them were located on the face.[118, level III] Acne scars can be divided into atrophic, hypertrophic or keloid scars. The sub-types of atrophic scars are icepick, rolling and boxcar scars (refer to **Figure 5** and **Table 8**).

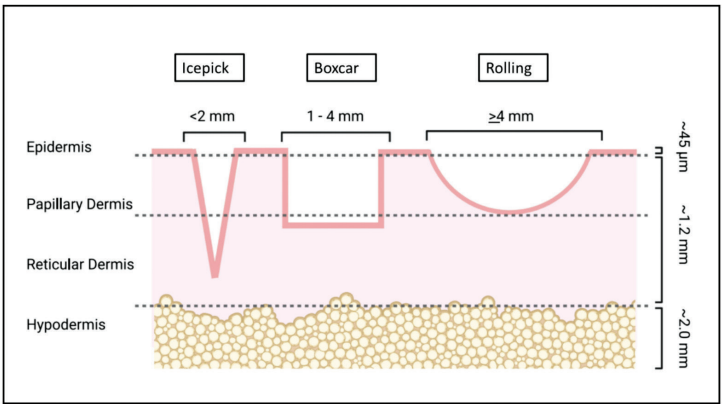


Figure 5. Types of Atrophic Acne Scars and its Depth

Source: Kravvas G, Al-Niaimi F. A systematic review of treatments for acne scarring. Part 1: Non-energy-based techniques. Scars Burn Heal. 2017; 3:2059513117695312

Table 8. Atrophic Acne Scar Subtypes Characteristics

Atrophic Acne Scar Subtypes	Description
Icepick	<2 mm and narrow Tapers as extends to deep dermis
Rolling	4 - 5 mm wide Sloped and shallow borders Caused by dermal tethering of otherwise normal skin
Boxcar	1.5 - 4 mm wide Round to oval depressions with sharply demarcated vertical edges Can be shallow (0.1 – 0.5 mm) or deep (≥0.5 mm)

Modified: Boen M, Jacob C. A Review and Update of Treatment Options Using the Acne Scar Classification System. Dermatol Surg. 2019;45(3):411-422

Refer to **Appendix 5** for images on **Complications of Acne Vulgaris**.

The scope of this CPG does not include the treatment of acne vulgaris-related complications.

12. QUALITY OF LIFE

Acne vulgaris is a chronic disease which may result in profound negative psychological and social effects on the quality of life (QoL) of the patients. Due to the visibility of acne and the potential to cause scarring in some patients, significant psychological distress may develop if acne vulgaris is left untreated.

There are various tools available for the assessment of QoL in patients with acne vulgaris, which can be divided into general and acne specific assessment tools. Example of a general assessment tool is DLQI and acne specific tools are CADI (refer to **Appendix 8**) and Acne Quality of Life (AQOL).

- Acne vulgaris can affect QoL and the assessment tools which can be used are DLQI, CADI and AQOL.

a. Impairment of QoL

In a local study on mild to severe acne vulgaris patients in a dermatology clinic, CADI score was related with depression (p=0.012), anxiety (p=0.015) and stress (p=0.001).[119, level III]

A cross-sectional study conducted locally in secondary schools assessing the perception and psychosocial impact of acne vulgaris among students using the CADI showed that majority had mild QoL impairment based on CADI score with a mean of 3.5±2.5. When individual CADI domain with score ≥1 was analysed, 79.5% perceived acne as a problem, 76.4% were concerned, depressed and felt miserable while 69.4% had some degree of feeling aggressive, frustrated and embarrassed due to acne vulgaris.[6, level III]

In another cross-sectional study on students with mild to severe acne vulgaris using different tools, perceived stigma was associated with health-related QoL (p<0.001), psychological distress (p<0.001) and somatic symptoms (p<0.001).[120, level III]

There is increasing evidence regarding the role of difficulties in emotion regulation (DER) in acne vulgaris patient, thus psychological well-being assessment is recommended. A cross-sectional study showed that DER was significantly higher in acne vulgaris patients than controls. It was also associated with anxiety and depressive symptoms based on the Hospital Anxiety and Depressive scale (p<0.01) and impaired QoL based on AQOL (p<0.01).[121, level III]

In a recent large meta-analysis of 42 observational studies, acne vulgaris was significantly correlated with depression (r=0.22, 95% CI

0.17 to 0.26) and anxiety (r= 0.25, 95% CI 0.19 to 0.31).[122, level II-2] There was no report on the quality of primary papers.

b. Predictive factors of QoL

Factors that have been identified in the impairment of QoL in acne vulgaris in several observational studies are discussed below.

- **Severity of acne vulgaris**

There was a significant correlation between the impairment of QoL and the severity of acne vulgaris:

  - r=0.51 between CADI score and acne severity based on lesion count[123, level III]
  - ρ=0.550 on objective severity and ρ=0.620 on subjective severity in relation to DLQI[124, level III]
  - r=0.13 for relationship, r=0.21 for avoidance behaviours and r=0.16 for perception of acne on patient's QoL and acne severity based on Global Echelle de Cotation des Lésions d'Acné score.[125, level III]

- **Gender**

Females with acne vulgaris had a higher risk of depression which was linked with the significantly higher usage of concealers to camouflage their spots.[117, level III; 126, level III]

- **Age**

University students with acne vulgaris experienced a higher impact of acne vulgaris on their life based on CADI than school students ($p<0.05$) especially among the female gender ($p<0.01$).[127, level III]

- **Acne relapse**

The CADI score was higher among patients of >20 years old who had relapse than those without relapse ($p<0.01$). Based on multivariate analysis, acne relapse was a significant determinant of absenteeism/ productivity loss.[128, level III]

Recommendation 14

- Assessment for quality of life may be considered in the management of patients with acne vulgaris.

13. REFERRAL

The urgency for referral of patients with acne vulgaris is divided into the following categories:[5]

- urgent: within 24 hours
- seen early: within 2 weeks
- non-urgent: based on available appointment date

a. Urgent referral

Refer patients urgently to a dermatologist if the patient is suspected to have acne fulminans.[52] Acne fulminans is a rare skin disorder. It presents as an acute, painful, ulcerating, and haemorrhagic form of acne and, may be associated with systemic symptoms e.g. fever and polyarthritis. It may also cause bone lesions and laboratory abnormalities.

Urgent referral to a psychiatrist should also be made if the patient has major depression or exhibiting suicidal behaviour.[5, 52]

b. Seen early[5]

i. Moderate to severe acne (e.g. nodulocystic acne)
ii. Severe social or psychological problems including a morbid fear of deformity (dysmorphophobia)

c. Non-urgent[5]

i. Diagnostic uncertainties, examples:
   - Suspected rosacea
   - Suspected drug-induced acne
   - Suspected occupational causes
   - Suspected underlying endocrinological cause (e.g. PCOS) requiring further assessment
   - Suspected Staphylococcus folliculitis, pityrosporum folliculitis or gram-negative folliculitis
   - Rare variants of acne e.g. acne excoriae and chloracne

ii. Dermatologist consultation and services:
   - Failed oral antibiotic therapy
   - Resistance or intolerance to current treatment
   - Scarring or pigmentary changes
   - Pregnancy with moderate and severe acne vulgaris
   - Indication for specialised physical treatment (e.g. incision, drainage of cysts and laser)

Recommendation 15

- Patients with moderate to severe acne vulgaris (e.g. nodulocystic acne) should be referred early to a dermatologist.
- Patients with acne vulgaris who exhibit suicidal behaviour should be referred urgently to a psychiatrist.

14. IMPLEMENTING THE GUIDELINES

The implementation of this CPG is the responsibility of the healthcare providers. The management of acne vulgaris should be guided by evidence-based approach in order to provide safe and optimum care for the patients. The following are the factors that may influence the implementation of the recommendations in this CPG:

14.1 Facilitating and Limiting Factors

The facilitating factors in implementing this CPG are:

i. wide dissemination of the CPG (soft- and hardcopies) to healthcare providers
ii. annual dermatology update course for primary care doctors

The limiting factors in the implementation are:

i. availability and cost of treatment
ii. variation in treatment practice and preferences

14.2 Potential Resource Implications

Acne vulgaris may be seen as not important compared with other medical diseases and thus not given priority in provision of medications as recommended by the CPG. It has to be noted that, as emphasised by the CPG, inadequately treated acne vulgaris may lead to various physical and psychological complications that affect QoL of the patients.

Assessment of the severity of acne vulgaris is important as it determines the appropriate medications to be prescribed. The use of assessment tool e.g. CASS requires training to the healthcare providers. This may cause small resource implication. Another important issue related to resource implication is the availability of recommended treatment in the healthcare facilities. It has to be pointed out that even simple medications like topical BPO which is strongly recommended in CPG is not easily available in the health clinic.

To enhance the utilisation of this CPG on Management of Acne Vulgaris (Second Edition), the following clinical audit indicators for quality management are proposed:

$$\text{Percentage of patients with mild to moderate acne vulgaris treated with topical BPO as monotherapy or in combination with other topical therapy} = \frac{\text{Number of patients with mild to moderate acne vulgaris treated with topical BPO as monotherapy or in combination with other topical therapy in a period}}{\text{Total number of patients with mild to moderate acne vulgaris in the same period}} \times 100\%$$

Percentage of patients with moderate to severe acne vulgaris treated with oral antibiotics (doxycycline, tetracycline or erythromycin)

$$= \frac{\text{Number of patients with moderate to severe acne vulgaris treated with oral antibiotics (doxycycline, tetracycline or erythromycin) in a period}}{\text{Total number of patients with moderate to severe acne vulgaris treated in the same period}} \times 100\%$$

Implementation strategies will be developed following the approval of the CPG by MoH which include launching of the CPG, Quick Reference and Training Module.

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Appendix 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: What are the effective and safe topical treatments for acne vulgaris?

1. ACNE VULGARIS/
2. acne.tw.
3. acne vulgaris.tw.
4. pimple*.tw.
5. comedone*.tw.
6. 1 or 2 or 3 or 4 or 5
7. BENZOYL PEROXIDE/
8. (benzoyl adj1 peroxide).tw.
9. RETINOIDS/
10. retinoid*.tw.
11. CLINDAMYCIN/
12. clindamycin.tw.
13. clindamycin hydrochloride.tw.
14. ERYTHROMYCIN/
15. erythromycin.tw.
16. erythromycin a.tw.
17. (erythromycin adj1 (lactate or phosphate)).tw.
18. SALICYLIC ACID/ (7108)
19. (salicylic adj1 acid*).tw.
20. SULFUR/
21. sulfur.tw.
22. DICARBOXYLIC ACIDS/
23. (dicarboxylic adj1 acid*).tw.
24. azelaic acid.tw.
25. (clindamycin adj3 benzoyl peroxide).tw.
26. (benzoyl peroxide adj3 adapalene).tw.
27. olumacostat glasaretil.tw.
28. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 6 and 28
30. limit 29 to (english language and humans and yr=”2020 -Current” and “all adults (19 plus years)”)

Appendix 2

CLINICAL QUESTIONS

1. What are the risk factors for acne vulgaris?
2. What are the aggravating factors for acne vulgaris?
   - smoking
   - diet
   - stress
   - skin care routine e.g. facial treatment
   - hormonal changes
3. What is the diagnostic criteria for acne vulgaris?
   - laboratory investigations to exclude other associated conditions
4. How is acne severity graded?
5. What are the effective and safe topical treatments for acne vulgaris?
   - benzoyl peroxide
   - retinoid
   - topical antibiotic
   - salicylic acid
   - sulphur
   - azelaic acid
   - dapsone
   - combination treatment
     - clindamycin and benzoyl peroxide
     - benzoyl peroxide and adapalene
   - topical sebum controlling agents: olumacostat glasaretil
   - topical androgen receptor inhibitor (clascoterone)
6. Is fixed combination preparation superior than monotherapy in acne vulgaris treatment?
7. What are the effective and safe systemic treatments for acne vulgaris?
   - oral antibiotic
   - oral hormonal therapy
   - oral isotretinoin
   - others: spironolactone and metformin
8. What are the effective and safe physical treatments for acne vulgaris?
   - intralesional corticosteroids injection
   - comedones extraction
   - chemical peel
   - laser therapy
   - light-based therapy
   - photodynamic therapy
   - radiofrequency treatment

9. Is traditional and complementary therapy safe and effective for acne vulgaris?
    - turmeric/honey/rice water etc
10. Are the following cosmeceuticals safe and effective for acne vulgaris?
    - cleanser
    - scrub
    - skin cleansing device
    - facemasks
    - toner
    - moisturiser
    - sunscreen
    - antibacterial agents
    - corneolytics (alpha hydroxy acids, salicylic acid, polyhydroxy acid, retinaldehyde and retinol)
    - niacinamide
11. What are the complications of acne vulgaris?
12. What are the safe and effective treatments for adolescents, pregnant and lactating women with acne vulgaris?
13. How does acne vulgaris affect quality of life?
14. What are the referral criteria for acne vulgaris?
    - urgent referral
    - non-urgent referral

Appendix 3

GLYCAEMIC INDEX CLASSIFICATION OF FOOD

Category	Low Glycaemic Index (<55)	Intermediate Glycaemic Index (55 - 70)	High Glycaemic Index (>70)
Rice	Barley	Basmati rice Brown rice Parboiled rice Red rice	Glutinous rice Jasmine rice White rice Instant porridge Sago
Bread and cereal products	All bran breakfast cereals Muesli Wholegrain bread varieties	*Chapatti* *Idli* Oatmeal Wholemeal pita bread Wholemeal barley flour bread	Cornflakes Rice crackers Sardine sandwich *Roti canai* White flour bread Whole wheat flour bread
Noodle and pasta	Lasagna pasta sheets Spaghetti - white, boiled Spaghetti - wholemeal, boiled	Spaghetti - white, durum wheat semolina Udon noodles - plain Wheat noodles	Fried macaroni Fried *meehoon* Fried rice noodles Rice noodle (*kway teow*)
Bakery products and snacks	Banana cake Sponge cake - plain Chocolate High calcium cracker	Pastry Popcorn Potato crisps Doughnut	Pretzel Waffle Scones Pancake
Traditional *kuih*	Curry puff (potato) *Kuih bakar* *Roti jala* *Seri muka*	*Cucur bilis* *Cekodok pisang* *Keropok lekor* *Popia goreng* *Wajik*	*Popia basah*
Milk and dairy products	Full fat milk Low fat milk Skim milk Soymilk (without added sugar) Yogurt	Ice cream Sweetened condensed milk	*Teh tarik*
Beverages	Fruit juices - freshly made, unsweetened	Soft drink Cordial drink 3 in 1 beverages	-
Sugar	Fructose	Sucrose Honey	Glucose
Fruits	Apple Mango Orange Plum	Banana Dates Papaya Pineapple Raisin	Lychee Watermelon

Category	Low Glycaemic Index (<55)	Intermediate Glycaemic Index (55 - 70)	High Glycaemic Index (>70)
Nuts	Cashew nuts Peanuts	-	-
Legumes	Baked beans Chickpeas Lentils Mung beans	-	-
Tubers	Cassava - boiled Sweet potato - boiled	Pumpkin - boiled Sweet corn - boiled	Potato - boiled
Vegetables	Carrot - boiled Broccoli Cauliflower	-	-

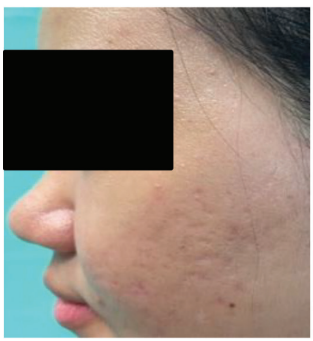
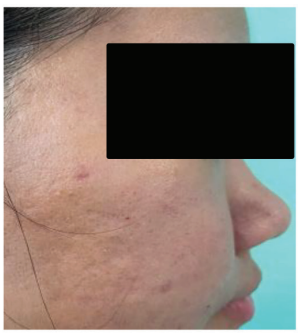
Source:

1. Ministry of Health Malaysia. Management of Acne. Putrajaya: MoH Malaysia; 2012.
2. Ministry of Health Malaysia. Management of Type 2 Diabetes Mellitus (Sixth Edition). Putrajaya: MoH Malaysia; 2020
3. Osman MH, Mohd Yusof BN, Ismail A. Glycaemic index and glycaemic load of foods and food products in Malaysia: a review. Int Food Res J. 2021;28(2):217-229

Appendix 4

CLINICAL IMAGES ACCORDING TO CASS GRADING

CASS 0

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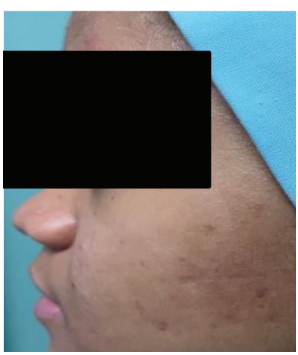
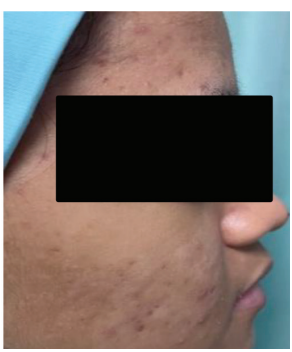

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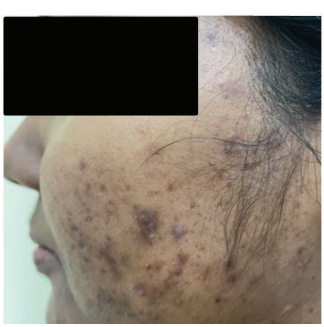
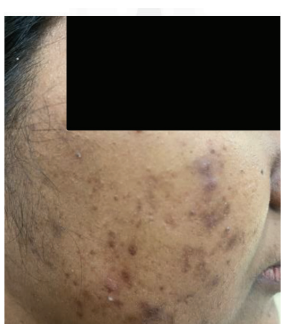

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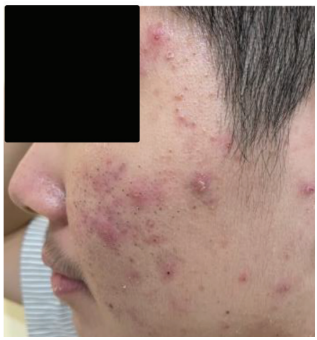
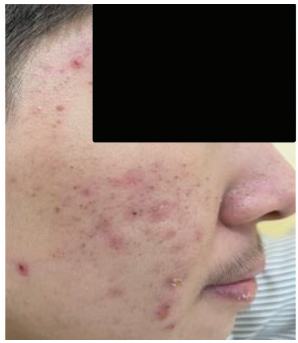
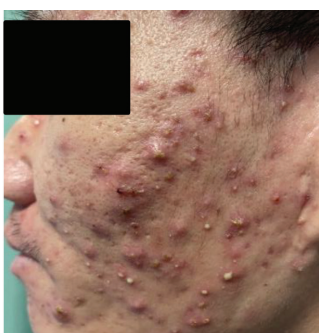
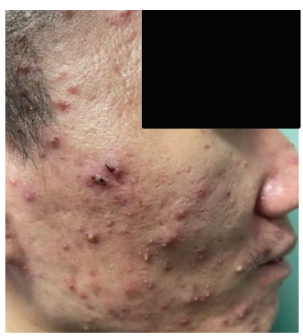
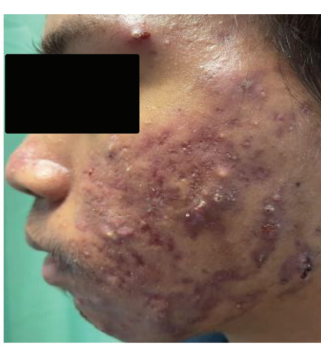
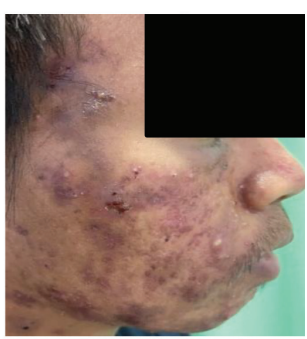



CASS 4

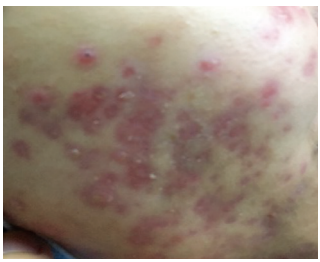
CASS 5

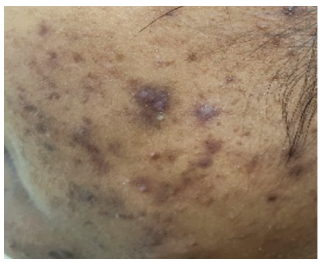
* Photos published with patient's permission

Appendix 5

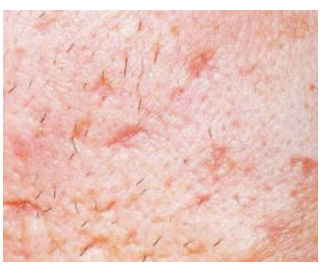
COMPLICATIONS OF ACNE VULGARIS



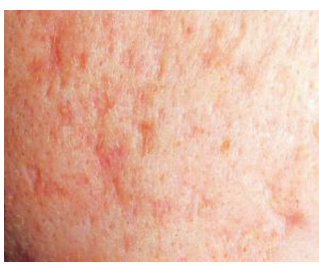
Post-inflammatory erythema



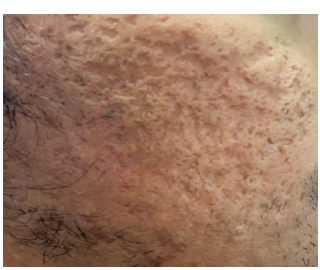
Post-inflammatory hyperpigmentation



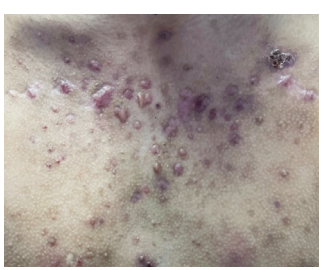
Icepick scar



Rolling scar



Boxcar scar



Hypertrophic and keloid scars

ANTIBIOTIC RESISTANCE

A. Clinical Characteristics of Acne Vulgaris Patients in Studies on Antibiotic Resistance

No.	Authors/year of publication/country	No. of study subjects	Study period	Prior antibiotic usage	Characteristic of patients (including severity of acne vulgaris)	Overall resistance rate of *C. acnes*
1.	Moon SH et al., 2012, South Korea	100	March - September 2011	73 patients had been previously treated with antibiotics and 27 patients were treatment naive	Age ranged 10 - 40 years old 54% patients were females and 46% patients were males. 67 patients had acne more than two years. 68 patients had Korean Acne Grading System (KAGS) grade 1 or 2, and 32 patients had KAGS grade 3 or 4.	36.7%
2.	Laochunsuwan A et al., 2017, Thailand	95	October 2016 - February 2017	62.1% received acne treatment with antibiotics and 37.9% with no prior antibiotic treatment	72.6% patients were females and 27.4% patients were males. Age ranged from 18 - 44 years old. Duration of acne ranged from 1 - 12 years. 69.5% had mild acne, 25.3% moderate acne and 5.2% severe acne according to Leeds revised acne grading system.	No information available

No.	Authors/year of publication/country	No. of study subjects	Study period	Prior antibiotic usage	Characteristic of patients (including severity of acne vulgaris)	Overall resistance rate of *C. acnes*
3.	Yang SS et al., 2018, Singapore	149	April - December 2014	No information available	Age ≥21 years old. Acne severity score of 0 - 3 (U.S. FDA investigator's 5-category global assessment scale).	33%
4.	Zhang N et al., 2019, China	100	October 2016 - March 2017	31 patients received oral antibiotics and 28 used topical antibiotics	Age >18 years old. 57.1% were males and 42.9% females. Mean course of disease was 13.1 ± 1.1 months. According to the Pillsbury grading system, grade I was noted in 5 patients, grade II in 16, grade III in 23 and grade IV in 19.	No information available
5.	Mendoza N et al., 2013, Colombia	100	Jan 2005 - May 2006	73% of patients received oral antibiotics or isotretinoin	53% were males and 47% were females. Age ranged 12 - 27 years old. 49% had moderate acne, 41% mild acne and 10% severe acne.	40%
6.	Schafer F et al., 2013, Chile	83	June 2008 - January 2009	66.3% had prior oral antibiotics (doxycycline being the most common) and 65% used topical antibiotics	58% were males and 42% were females. Average age was 19.1 ± 4.6 years old.	33.7%

No.	Authors/year of publication/country	No. of study subjects	Study period	Prior antibiotic usage	Characteristic of patients (including severity of acne vulgaris)	Overall resistance rate of *C. acnes*
					Acne severity (Leeds revised acne grading system) grade I (6.2%), grade II (41.3%), grade III (35%) and grade IV (17.5%).	
7.	Biswal I et al., 2016, India	102	2010 - 2012	14% had history of previous anti-acne treatment	Age 11 - 29 years old. According to Pillsbury grading, 32% of patients were grade 1, while 26%, 30% and 12% were grades 2, 3 and 4 respectively.	34.8%

B Resistance Rates of Systemic Antibiotics Used in Acne Vulgaris

No.	Authors/year of publication/country	Resistance Rates of Systemic Antibiotics (%)						
		Doxycycline	Tetracycline	Minocycline	Erythromycin	Clindamycin	Trimethoprim-sulfamethoxazole (Co-trimoxazole)	Others
1	Moon SH et al., 2012, Korea	6.7	3.3	10.0	30.0	26.7	6.7	Levofloxacin 0
2	Laochunsuwan A et al., 2017, Thailand	0	1.3	NA*	64.0	62.7	NA*	Amoxicillin 0
3	Yang SS et al., 2018, Singapore	22.0	22.0	0	31.0	33.0	0	
4	Zhang N et al., 2019, China	NA*	0	0	49.2	28.6	NA*	Metronidazole 100
5	Mendoza N et al., 2013, Colombia	9.0	8.0	1.0	35.0	15.0	NA*	
6	Schafer F et al., 2013, Chile	0	0	NA*	12.5	7.5	26.3	
7	Biswal I et al, 2016., India	NA*	9.2	0	10.6	6.1	NA*	Ciprofloxacin 3 Penicillin 6.7

*NA: Not available

Source:

1. Moon SH, Roh HS, Kim YH, et al. Antibiotic resistance of microbial strains isolated from Korean acne patients. J Dermatol. 2012;39(10):833-837
2. Laochunsuwan A, Taweechotipatr M, Udompataikul M. In vitro Study of Antibiotic Susceptibility of *Propionibacterium acnes* Strains Isolated from Acne Vulgaris Patients. J Med Assoc Thai. 2017;100(10):24.

3. Yang SS, Long V, Liau MM, et al. A profile of *Propionibacterium acnes* resistance and sensitivity at a tertiary dermatological centre in Singapore. Br J Dermatol. 2018;179(1):200-201
4. Zhang N, Yuan R, Xin KZ, et al. Antimicrobial Susceptibility, Biotypes and Phylotypes of Clinical *Cutibacterium* (Formerly *Propionibacterium*) *acnes* Strains Isolated from Acne Patients: An Observational Study. Dermatol Ther. 2019;9:735-746
5. Mendoza N, Hernandez PO, Tyring SK, et al. Antimicrobial susceptibility of *Propionibacterium acnes* isolates from acne patients in Colombia. Int J Dermatol. 2013;52(6):688-692
6. Schafer F, Fich F, Lam M, et al. Antimicrobial susceptibility and genetic characteristics of *Propionibacterium acnes* isolated from patients with acne. Int J Dermatol. 2013;52(4):418-425
7. Biswal I, Gaind R, Kumar N, et al. In vitro antimicrobial susceptibility patterns of *Propionibacterium acnes* isolated from patients with acne vulgaris. J Infect Dev Ctries. 2016;10(10):1140-1145

MEDICATION DOSAGE AND ADVERSE EVENTS

A. Topical Treatments

Drug	Recommended Dosage	Common Adverse Events	Contraindications	Special Precautions
Benzoyl peroxide (BPO) (2.5 - 10%)	Apply once to twice daily	Increased sensitivity to sunlight, skin peeling, erythema, swelling, dryness, mild burning sensation, contact dermatitis	Hypersensitivity to BPO	Avoid contact with eyes, eyelids, lips and mucous membranes May bleach fabrics or hair
Tretinoin (0.025 - 0.05%)	Apply once at night or before bedtime	Initial exacerbation of acne vulgaris, skin irritation, stinging, oedema, blistering, crusting, erythema, scaling, photosensitivity, transient hypo/hyperpigmentation	Hypersensitivity to tretinoin, eczema, broken or sunburned skin, personal or family history of cutaneous epithelioma, pregnancy	Avoid: • contact with eyes, mouth, angles of nose, mucous membranes and open wounds • concomitant use of topical keratolytic agents • exposure to sunlight or UV light • use of topical preparations with high concentration of alcohol, menthol, spices and lime • facial scrub

Drug	Recommended Dosage	Common Adverse Events	Contraindications	Special Precautions
Adapalene (0.1%)	Apply once at night or before bedtime	Mild skin irritation, scaling, erythema, dryness, stinging, burning, pruritus	Hypersensitivity to adapalene, pregnancy	Avoid: • contact with eyes, lips, angles of nose and mucous membranes • use on cuts, abrasions, eczematous skin or sunburned skin • exposure to sunlight or UV light
Tazarotene* (0.1%)	Apply once at night or before bedtime	Pruritus, burning, stinging, erythema, skin peeling or irritation, rash, dryness, localised oedema, desquamation, contact dermatitis, skin discolouration, photosensitivity	Hypersensitivity to tazarotene, eczema, broken or sunburned skin, pregnancy	Avoid: • contact with eyes, mouth and other mucous membranes • exposure to sunlight or UV light Women of child-bearing potential should use adequate contraception when tazarotene is used
Trifarotene* (0.005%)	Apply once at night or before bedtime	Erythema, scaling, dryness, stinging/burning, sunburn	Hypersensitivity to trifarotene, pregnancy	Avoid: • use on cuts, abrasions, eczematous or sunburned skin • exposure to sunlight or UV light
Clindamycin (1%)	Apply twice daily	Skin irritation, dryness, stinging, erythema, contact	Hypersensitivity to clindamycin or lincomycin, ulcerative colitis, antibiotic-	Alcohol base solution may cause burning and irritation of eyes especially in atopic

Drug	Recommended Dosage	Common Adverse Events	Contraindications	Special Precautions
		dermatitis	related colitis	individuals Discontinue use if significant diarrhoea occurs
Erythromycin* (2 - 4%)	Apply once to twice daily	Dryness, erythema, burning, pruritus	Hypersensitivity to erythromycin	Avoid contact with eyes and other mucous membranes
Minocycline* (4%)	Apply once at night or before bedtime	Headache, photosensitivity, erythema, dryness, hyperpigmentation, peeling, pruritus	Hypersensitivity to tetracycline group	Avoid exposure to sunlight or UV light
Azelaic acid (20%)	Apply twice daily	Skin irritation, mostly burning or pruritus, occasionally erythema and scaling, photosensitivity	Hypersensitivity to propylene glycol	Avoid: • use on broken skin, mouth, eyes and other mucous membranes • exposure to sunlight or UV light
Salicylic acid (2%)	Apply twice to thrice daily	Skin irritation, sensitivity, excessive dryness	Hypersensitivity to salicylic acid	Avoid: • use on broken skin, mouth, eyes and other mucous membranes • prolonged use in high concentrations and over large areas of the body
Dapsone* (5 - 7.5%)	5%: Apply twice daily 7.5%: Apply once daily	Dryness, erythema, oiliness, peeling	Hypersensitivity to dapsone, pregnancy and lactation	G6PD deficiency, methaemoglobinaemia, Haemoglobin M

Drug	Recommended Dosage	Common Adverse Events	Contraindications	Special Precautions
Sulphur and its combinations (1 - 8%)	Apply once to twice daily	Skin irritation, contact dermatitis	Hypersensitivity to sulphur, infant <2 months	Avoid contact with eyes, mouth and other mucous membranes May stain the skin black and emit foul smell when applied concomitantly with mercurial compounds
Clascoterone* (1%)	Apply twice daily	Pruritus, burning, erythema, peeling	None	Avoid: • contact with eyes, mouth and other mucous membranes • use on cuts, abrasions, eczematous or sunburned skin Hypothalamus-pituitary-adrenal axis suppression may occur during or after treatment
Adapalene + BPO (0.1%/2.5% & 0.3%/2.5%*)	Apply once daily	Skin irritation, dryness, contact dermatitis, burning	None	Avoid exposure to sunlight or UV light
Clindamycin + BPO (1.2%/5%)	Apply once at night or before bedtime	Erythema, peeling, dryness, burning	Hypersensitivity to clindamycin, BPO, or lincomycin, regional enteritis, ulcerative colitis or antibiotic-associated colitis	Avoid exposure to sunlight or UV light Discontinue use if significant diarrhoea occurs

*Currently not available in Malaysia

B. Systemic Treatments

Drug	Recommended Dosage and Duration	Common Adverse Events	Contraindications	Special Precautions
Tetracycline	500 - 1000 mg daily in 2 divided doses for 3 - 4 months	GI disturbances, discolouration of teeth and nails, photosensitivity, visual disturbances	Hypersensitivity to tetracyclines, children ≤8 years old, pregnancy, lactation, severe renal impairment	Should be administered with plenty of water, while sitting or standing, 1 hour before or 2 hours after meals to avoid oesophageal ulceration Absorption is impaired by food, milk, dairy products, iron salts and antacids Use with caution in myasthenia gravis, systemic lupus erythema (SLE), hepatic and renal impairment Avoid co-administration with oral retinoids to prevent idiopathic intracranial hypertension
Doxycycline	100 - 200 mg daily in 1 - 2 divided doses for 3 - 4 months	GI disturbances, photosensitivity, hypersensitivity, permanent staining of teeth, rash	Hypersensitivity to tetracyclines, children ≤8 years old, pregnancy, lactation	Should be taken after meals with plenty of water to avoid oesophageal ulceration Use with caution in venereal disease,

Drug	Recommended Dosage and Duration	Common Adverse Events	Contraindications	Special Precautions
				myasthenia gravis, SLE, hepatic and renal impairment Avoid co-administration with oral retinoids to prevent idiopathic intracranial hypertension
Minocycline	50 - 100 mg once to twice daily for 3 - 4 months	GI disturbances, vestibular disturbances, abnormal hyperpigmentation, photosensitivity, teeth discolouration in children	Hypersensitivity to tetracyclines, children ≤8 years old, pregnancy, lactation	Use with caution in myasthenia gravis, SLE, hepatic and renal impairment Avoid co-administration with oral retinoids to prevent idiopathic intracranial hypertension
Sarecycline*	33 - 54 kg: 60 mg once daily 55 - 84 kg: 100 mg once daily 85 - 136 kg: 150 mg once daily for 3 - 4 months	Nausea, photosensitivity, light-headedness, dizziness, vertigo	Hypersensitivity to tetracyclines, children ≤8 years old, pregnancy, lactation	Should be administered with plenty of water, while sitting or standing, 1 hour before or 2 hours after meals to avoid oesophageal ulceration Avoid co-administration with oral retinoids to prevent idiopathic intracranial hypertension Avoid exposure to sunlight or ultraviolet (UV) light

Drug	Recommended Dosage and Duration	Common Adverse Events	Contraindications	Special Precautions
Lymecycline*	408 mg once daily (equivalent to 300 mg of tetracycline base) for 3 - 4 months	Headache, nausea, diarrhoea, abdominal pain, photosensitivity	Hypersensitivity to tetracyclines, overt renal insufficiency, children ≤8 years old, pregnancy, lactation	Should be administered with plenty of water, while sitting or standing, 1 hour before or 2 hours after meals to avoid oesophageal ulceration Use with caution in myasthenia gravis, SLE, hepatic impairment Avoid co-administration with oral retinoids to prevent idiopathic intracranial hypertension Avoid exposure to sunlight or UV light
Erythromycin	Erythromycin Ethyl Succinate (EES): 400 - 800 mg twice daily for 3 - 4 months Erythromycin Stearate: 250 - 500 mg twice daily for 3 - 4 months	GI disturbances, rash, urticaria, headache, dizziness	Hypersensitivity to erythromycin, prolonged QT interval, uncorrected hypokalaemia or hypomagnesaemia, clinically significant bradycardia	Use with caution in hepatic and renal impairment, concomitant therapy with colchicine (toxicity) and simvastatin (rhabdomyolysis)
Azithromycin	Various regimens ranging from 500 mg thrice weekly to four	Neutropaenia, hearing impairment, vertigo, GI disturbances, abnormal	Hypersensitivity to azithromycin or other macrolides, hepatic	Use with caution in severe renal and hepatic disease, myasthenia gravis,

Drug	Recommended Dosage and Duration	Common Adverse Events	Contraindications	Special Precautions
	consecutive days in a month for 3 - 4 months	liver function, rash, angioedema	dysfunction, jaundice	prolonged QT interval and cardiac repolarisation
Trimethoprim-sulfamethoxazole (Co-trimoxazole)	1 tablet daily (trimethoprim 80 mg and sulfamethoxazole 400 mg) for 3 - 4 months	GI disturbances, skin rashes, hepatitis, dizziness, headache, erythema multiforme Potentially serious AEs - Stevens-Johnson syndrome, toxic epidermal necrolysis	Hypersensitivity to sulfonamides or trimethoprim, severe renal and hepatic impairment, megaloblastic anaemia due to folate deficiency, pregnancy	Use with caution in haematological disorders, elderly, G6PD deficiency, folate deficiency
Isotretinoin	0.1 - 1 mg/kg/day Suggested starting dose of 10 - 20 mg/day Treatment should be given until acne clearance and continued for another 4 - 8 weeks (estimated duration up to 6 months)	Dryness of skin or mucosa, exanthema, pruritus, facial erythema/ dermatitis, hair thinning, photosensitivity, muscle and joint pain, headache, dyslipidaemia Potentially serious AEs - Stevens-Johnson syndrome, toxic epidermal necrolysis, suicide ideation	Hypersensitivity to isotretinoin or any of its components, pregnancy due to teratogenicity, lactation, hypervitaminosis A, hyperlipidaemia, co-administration with tetracyclines and vitamin A (including dietary supplements)	Use with caution in history of depression or other psychiatric disorders, increased intracranial pressure and seizures Avoid blood donation during treatment and within one month after treatment cessation
Chlormadinone + ethinyl estradiol (EE) (2mg/0.03mg)	1 tablet daily for 21 days, followed by 7 days of tablet free period, for 6 - 12 months	Breakthrough bleeding, spotting, headache, breast discomfort, depressed mood, nervousness, irritability, dizziness,	Hypersensitivity to EE and chlormadinone or any of its excipients, known or suspected malignancies, hepatic impairment,	Use with caution in patients with risk of venous and arterial thromboembolism, obesity, diabetes mellitus, hypertriglyceridaemia,

Drug	Recommended Dosage and Duration	Common Adverse Events	Contraindications	Special Precautions
		migraine, visual disturbance, nausea, vomiting, sensation of heaviness, vaginal discharge, dysmenorrhea, amenorrhoea, lower abdominal pain, fatigue, oedema, weight gain, increased blood pressure	pregnancy and lactation, presence or risk of thromboembolic events, severe depression, porphyria, unexplained genital bleeding	renal insufficiency
Cyproterone acetate + EE (2mg/0.035mg)	1 tablet daily for 21 days, followed by 7 days of tablet free period, for 6 - 12 months	GI disturbances, headache, depression, breast tenderness, weight changes	Hypersensitivity to EE and cyproterone acetate or any of its excipients, hepatic impairment, genital tract or breast carcinoma, pregnancy and lactation, thromboembolic events	Use with caution in patients with risk of venous thromboembolism, hypertriglyceridaemia, acute or chronic disturbances of liver function
Desogestrel + EE (0.15mg/0.02mg or 0.15mg/0.03mg)	1 tablet daily for 21 days, followed by 7 days of tablet free period, for 6 - 12 months	Menstrual disturbances, breast tenderness, pain, nausea, vomiting, headache, migraine, depression, fluid retention, weight changes	Hypersensitivity to EE and desogestrel or any of its excipients, suspected oestrogen dependent neoplasms, pregnancy and lactation, thromboembolic events	May increase risk of breast cancer, glucose intolerance and thromboembolism Use with caution in familial defects of lipoprotein metabolism, CV or renal impairment
Drospirenone + EE (3mg/0.02mg or 3mg/0.03mg)	1 tablet daily for 28 days, for 6 - 12 months	Emotional lability, depression, migraine, nausea, breast pain, menstrual disturbances, suspected sex-steroid influenced malignancies, undiagnosed vaginal bleeding	Hypersensitivity to EE and drospirenone or any of its excipients, severe hepatic disease, pregnancy and lactation, thromboembolic events	Use with caution in patients with risk of venous and arterial thromboembolism, depression, diabetes mellitus, hypertriglyceridemia

Drug	Recommended Dosage and Duration	Common Adverse Events	Contraindications	Special Precautions
Levonorgestrel + EE (0.1mg/0.02mg or 0.15mg/0.03mg)	1 tablet daily for 21 days, followed by 7 days of tablet free period, for 6 - 12 months	GI and menstrual disturbances, headache, dizziness, breast tenderness, weight changes, fluid retention, depression	Hypersensitivity to EE and levonorgestrel or any of its excipients, hepatic impairment, genital tract or breast carcinoma, arterial disease, undiagnosed vaginal bleeding and porphyria, pregnancy and lactation, thromboembolic events	Use with caution previous ectopic pregnancy, functional ovarian cysts, history of CV or renal impairment, diabetes mellitus, depression
Norgestrel + estradiol valerate (0.5mg/2mg)	Start on the 5th day of menstrual cycle - 1 tab daily for 21 days, then stop for 7 days, for 6 - 12 months	Weight changes, headache, abdominal pain, nausea, rash, pruritus, uterine/ vaginal bleeding including spotting (usually subside during continued treatment)	Hypersensitivity to estradiol and norgestrel or any of its excipients, undiagnosed vaginal bleeding, known or suspected sex-steroid influenced malignancies, severe hepatic disease, severe hypertriglyceridaemia, pregnancy and lactation, thromboembolic events	Use with caution in patients with risk of venous thromboembolism, hypertension, hypertriglyceridaemia, obesity, diabetes mellitus, hepatic impairment, depression
Spironolactone	50 mg - 200 mg daily, for up to 10 months	Hyperkalaemia, gynecomastia, hyperchloraemic metabolic acidosis, worsened renal function, nausea, vomiting	Hyperkalaemia, anuria, acute renal insufficiency, severe renal impairment	Use with caution in fluid or electrolyte imbalance, diabetes mellitus, porphyria, menstrual abnormalities or breast enlargement, renal and hepatic impairment, co-administration with other potassium sparing diuretics or potassium supplements, best to avoid in pregnancy

Drug	Recommended Dosage and Duration	Common Adverse Events	Contraindications	Special Precautions
Metformin	500 mg - 2000 mg daily	Diarrhoea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort, headache, vitamin B12 deficiency, lactic acidosis (potentially fatal)	Hypersensitivity to metformin, acute/chronic metabolic acidosis, acute conditions which may alter renal function (e.g. dehydration, severe infection, shock), severe renal impairment	Use with caution in patients with risk factors for lactic acidosis, stable heart failure, dehydration, pre-renal azotaemia, mild to moderate renal impairment, hepatic impairment Not indicated for use in patient with type 1 diabetes mellitus or with diabetic ketoacidosis

*Currently not available in Malaysia

Sources:

1. Monthly Index of Medical Specialities (MIMS) Malaysia Online (Available at http://www.mims.com/malaysia)
2. Ministry of Health Medicines Formulary (Updated April 2019) (Available at: https://www.pharmacy.gov.my/v2/en/apps/fukkm)
3. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74(5):945-973.e33
4. Yen H, Chang YT, Yee FJ, et al. Metformin Therapy for Acne in Patients with Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis. Am J Clin Dermatol. 2021;22(1):11-23.
5. Product Package Insert

Appendix 8

THE CARDIFF ACNE DISABILITY INDEX

1. As a result of having acne, during the last month have you been aggressive, frustrated or embarrassed?	☐ ☐ ☐ ☐	(a) Very much indeed (b) A lot (c) A little (d) Not at all
2. Do you think that having acne during the last month interfered with your daily social life, social events or intimate personal relationships?	☐ ☐ ☐ ☐	(a) Severely, affecting all activities (b) Moderately, in most activities (c) Occasionally or in only some activities (d) Not at all
3. During the last month have you avoided public changing facilities or wearing swimming costumes because of your acne?	☐ ☐ ☐ ☐	(a) All of the time (b) Most of the time (c) Occasionally (d) Not at all
4. How would you describe your feelings about the appearance of your skin over the last month?	☐ ☐ ☐ ☐	(a) Very depressed and miserable (b) Usually concerned (c) Occasionally concerned (d) Not bothered
5. Please indicate how bad you think your acne is now:	☐ ☐ ☐ ☐	(a) The worst it could possibly be (b) A major problem (c) A minor problem (d) Not a problem

CADI score	Severity
0 - 5	Mild
6 - 10	Moderate
11 - 15	Severe

Source: Abdelrazik YT, Ali FM, Salek MS, et al. Clinical experience and psychometric properties of the Cardiff Acne Disability Index (CADI). Br J Dermatol. 2021;185,711-724.

LIST OF ABBREVIATIONS

AA	azelaic acid
ACC	American Academy of Dermatology Acne Consensus Conference
AE(s)	adverse event(s)
AGREE	Appraisal of Guidelines for Research and Evaluation
AHA	alpha-hydroxy acids
ALA	aminolevulinic acid
AQOL	Acne Quality of Life
ASI	acne severity index
ASPR	age-standardised prevalence rate
BMI	body mass index
BPO	benzoyl peroxide
BR	bipolar radiofrequency
C. acnes	*Cutibacterium acnes*
CADI	Cardiff Acne Disability Index
CAMs	complementary and alternative medicines
CASS	Comprehensive Acne Severity Scale
CI	confidence interval
CPG	Clinical Practice Guidelines
CQ	clinical questions
COC	combined oral contraceptive
CV	cardiovascular
DER	difficulties in emotion regulation
DG	Development Group
DHT	dihydrotestosterone
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
EBD	energy-based devices
EE	ethinyl estradiol
EES	erythromycin ethyl succinate
EGAE	The Escala de Gravedad del Acné Española
FDA	Food and Drug Administration
FMR	fractional microneedle radiofrequency
GA	glycolic acid
GAAS	global acne assessment score
GAGS	Global Acne Grading System
GEA	Global Acne Severity Scale
GI	gastrointestinal
GRADE	Grading Recommendations, Assessment, Development and Evaluation
GTE	green tea extract
G6PD	glucose 6 phosphate dehydrogenase
HR	hazard ratio
ICCs	intraclass correlation coefficients
IGA	Investigator Global Assessment
IL	inflammatory lesions
IPL	intense pulsed light
ISGA	Investigator's Static Global Assessment
JS	Jessner's solution
KAGS	Korean Acne Grading System
LRAG	Leeds Revised Acne Grading

LSM	least squares mean
MA	mandelic acid
MAL	methyl aminolevulinate
MAS	Michealson Acne Score
MD	mean difference
mGAGS	modified Global Acne Grading System
MoH	Ministry of Health
NAFL	non-ablative fractional laser
Nd:YAG	neodymium-doped yttrium aluminium garnet
NICE	National Institute for Health and Care Excellence
NIL	non-inflammatory lesions
NNTB	'number needed to treat' for an additional beneficial
OR	odd ratio
PA	pyruvic acid
PAE	post-acne erythema
PCOS	polycystic ovarian syndrome
PDL	pulsed dye laser
PDT	photodynamic therapy
PGA	participants' global self-assessment of acne improvement
PIH	post-inflammatory hyperpigmentation
QoL	quality of life
RARs	retinoic acids receptors
RC	Review Committee
RCTs	randomised controlled trials
RF	radiofrequency
RR	relative risk
RXRs	retinoids X receptors
SA	salicylic acid
SASA	South-East Asia Study Alliance
SJS/TEN	Stevens-Johnson syndrome/toxic epidermal necrolysis
SMD	standardised mean difference
SLE	systemic lupus erythema
TCA	trichloroacetic acid
TEWL	transepidermal water loss
TGM	tretinoin gel microsphere
TL	total lesions
TLC	total lesion counts
UV	ultraviolet
UVB	ultraviolet B
WHO	World Health Organization

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