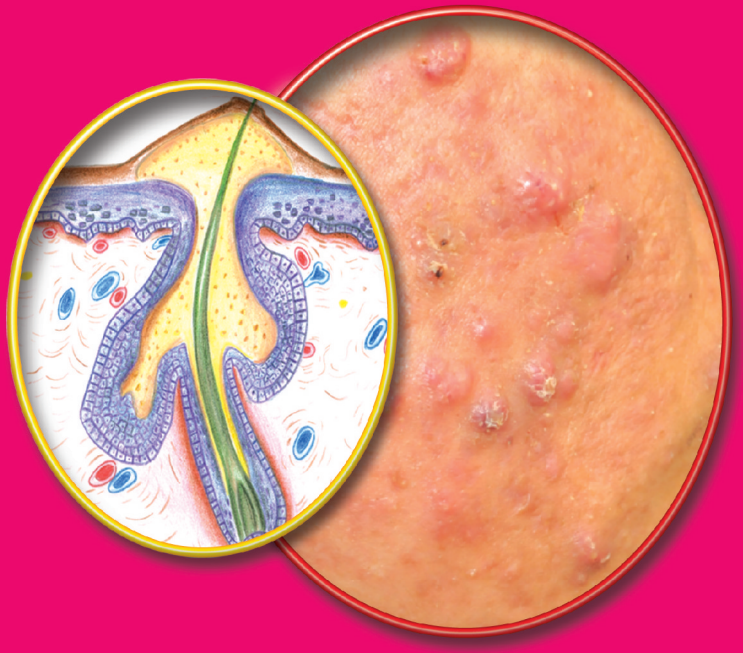
CLINICAL PRACTICE GUIDELINES

JANUARY 2012

MOH/P/PAK/234.12(GU)

MANAGEMENT OF ACNE



Ministry of Health Malaysia

Dermatological Society of Malaysia

Academy of Medicine Malaysia

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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.

These guidelines are issued in 2012 and will be reviewed in 2015 or sooner if new evidence becomes available.

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http://www.moh.gov.my
http://www.acadmed.org.my

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

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and / or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)

Note: The grades of recommendation relate to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The development group (DG) for this Clinical Practice Guidelines (CPG) comprised of members from the Ministry of Health (MOH) and Ministry of Higher Education. This consists of dermatologists, family medicine specialists, a public health physician, a pharmacist, a dietitian and a psychologist. There was active involvement of a multidisciplinary review committee (RC) during the process of developing these guidelines.

Literature search was carried out using the following electronic databases: Guidelines International Network (G-I-N); Pubmed; Cochrane Database of Systemic Reviews (CDSR) and Journal full text via OVID search engine; International Health Technology Assessment websites (refer to **Appendix 1** for Search Terms). In addition, the reference lists of all retrieved literature and guidelines were searched to identify relevant studies. Experts in the field were also contacted to identify further studies. Literature search was officially conducted between 8 July 2009 and 31 December 2010. It was repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published until 31 July 2011 to be considered. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from CPG Secretariat.

Reference was also made from other guidelines on acne such as American Academy of Dermatology (2007) – Guidelines of care for acne vulgaris management. These CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) prior to use.

A total of 27 clinical questions were developed under three main sections. Members of the DG were assigned with individual questions within these sections (refer to **Appendix 2** for Clinical Questions). The DG members met for a total of 24 times throughout the development of these guidelines. All the literature retrieved were appraised by at least two DG members, presented in evidence tables and further discussed during DG meetings. All statements and recommendations were formulated and agreed by both the DG and RC. In areas where the evidence was insufficient, recommendations were made based on consensus agreement of the DG and RC.

These guidelines are largely based on the findings of systematic reviews, meta-analyses and clinical trials, taking into consideration the local practices.

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 modified from grades of recommendation of the Scottish Intercollegiate Guidelines Network (SIGN).

Upon completion, the draft of this guidelines was sent to external reviewers for review. The draft was also posted 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 HTA and CPG Council MOH Malaysia for review and approval.

OBJECTIVES

The aim of these guidelines is to assist clinicians and other healthcare providers in making evidence-based decisions about the appropriate management and treatment of acne i.e. to address:-

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

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

a. Inclusion criteria

Adolescents and adults presenting with acne ranging from mild, moderate to severe

b. Exclusion criteria

Patients with the following conditions:

- Acne variants for example acne conglobata, acne fulminans, acne cosmetic, drug-induced acne and chloracne
- Acne scar
- Post inflammatory hyperpigmentation
- Rosacea
- Folliculitis

TARGET GROUP/USER

These guidelines are applicable to any healthcare providers such as:-

i. Medical Officers
ii. General Practitioners (GPs)
iii. Family Medicine Specialists
iv. Specialists from other disciplines
v. Pharmacists
vi. Dietitians
vii. Nutritionists
viii. Paramedics
ix. Dermatologists
x. Policy makers

HEALTHCARE SETTINGS

Outpatient, inpatient and community settings

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REVIEW COMMITTEE

The draft of these guidelines were reviewed by a panel of independent expert referees, from both public and private sectors, who mainly looked at the comprehensiveness and accuracy in interpretating the evidence which support the recommendations in these guidelines.

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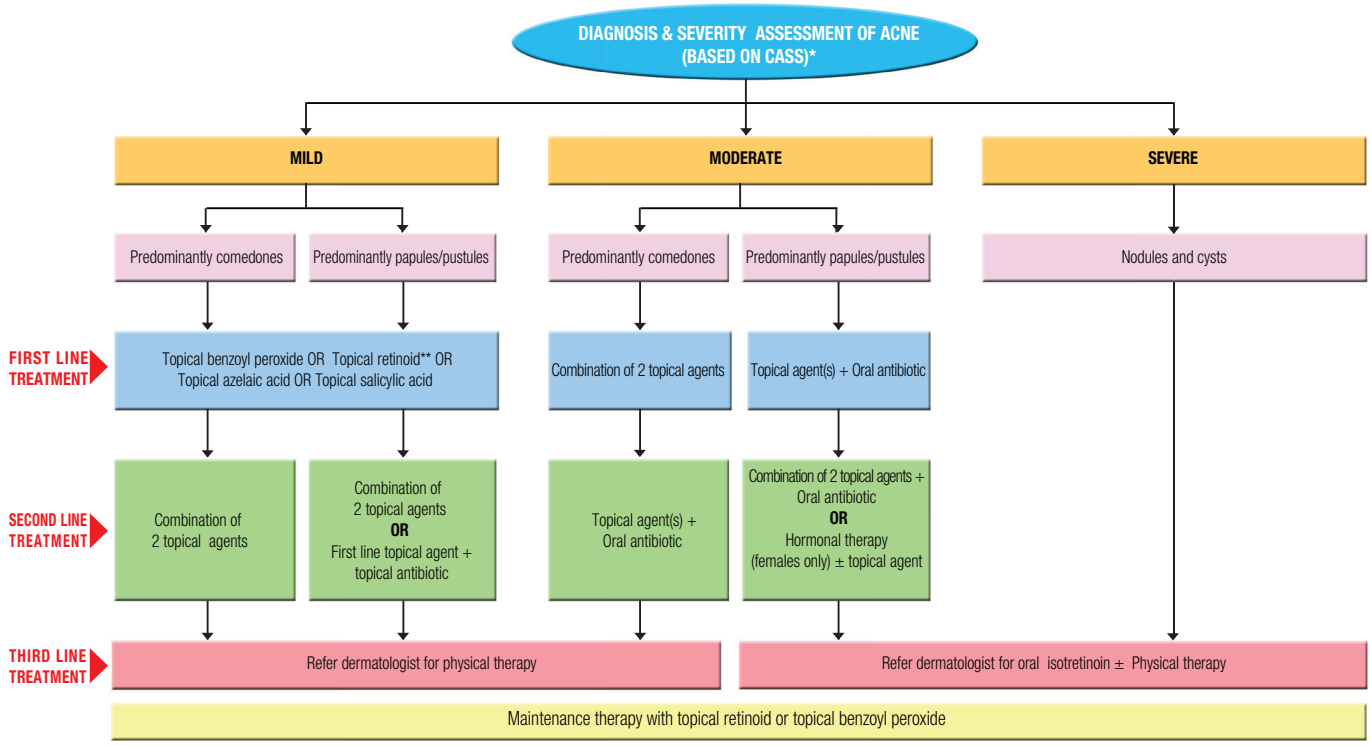
MANAGEMENT OF ACNE



* Severity assessment is based on CASS (mild 1 - 2, moderate 3, severe 4 - 5). Quality of life should be taken into consideration. ** Topical retinoids are to be avoided in pregnancy.

†If there is no improvement in 3 months, consider the next line of treatment. ‡Oral antibiotic is recommended to be used for 4 - 6 months.

1. INTRODUCTION

Acne is a common problem among adolescents and young adults. There are different beliefs as to what causes acne especially in a multiracial country with different cultural practices. As acne is a medical disease, medical treatment by healthcare providers is required. If left untreated, acne may have a profound psychological and emotional impact.

Embarrassment and complications may or may not be an important factor as every individual perceives acne differently at various stages of life. The medical attention provided is very much dependent upon the individual's initiative to seek treatment.

Acne presents with different spectrums of disease severity and there are numerous treatment options currently available. All these factors along with variable exposure to dermatology in medical schools result in a wide variation in prescribing patterns. Hence, there is a necessity to assess acne and its treatment options in a more objective manner.

The aim of these Clinical Practice Guidelines (CPG) is to provide an evidence-based guidance for primary care physicians and other healthcare providers to identify the appropriate management of acne.

2. EPIDEMIOLOGICAL CHARACTERISTICS

There is a wide variation in the prevalence of acne among various countries. However, these population based studies were done among different age groups. The prevalence was 17.3 % among children of 6 - 11 years old in Taiwan,[1, level III] 9.8% among children (6 - 12.5 years old) and adolescent (12.5 - 21 years old) in Hong Kong[2, level III] and 67.5% among adolescent (13 - 18 years old) in two small district secondary schools in Malaysia.[3, level III] A recent study in China showed a prevalence of 10.5% among children (10 - 14 years old), 38% among adolescent (15 - 19 years old), 36% in young adults (20 - 24 years old) and 31% in those above 25 years old in China.[4, level III] The peak age for acne was between 12.5 to 18 years and this represented 85% of the total number of students with acne.[2, level III] While another study showed almost similar result with a peak age between 15 to 24 years (81.3% of total study population).[4, level III] There was a high prevalence of 82.1% among children of 10 - 12 years old in Portugal.[5, level III] In a study among adults (>25 years old) in United Kingdom, the prevalence was 54% in women and 40% in men.[6, level III]

The earliest appearance of comedones is by age of 7 years[1, level III] and papulopustules by 10 - 11 years.[7, level III] Although there is no gender difference in the prevalence of acne,[2 - 5, level III; 8, level III] it tends to be more severe in males.[5, level III] There is also no difference in acne severity among age and ethnic groups.[8, level III] The most commonly affected site of acne is the face followed by the trunk.[5, level III; 9 - 10, level III]

3. PATHOPHYSIOLOGY

The pathogenesis of acne is multifactorial. Acne vulgaris can be divided into non-inflammatory (open and closed comedones) and inflammatory (papules, pustules and nodules) lesions. The most important factors involved are:

a. Increased sebum production
b. *Propionibacterium acnes* proliferation
c. Altered follicular keratinisation
d. Inflammation

a. Increased Sebum Production

i. Androgen Mediated Sebum Production

Sebum production is increased,[11 - 12, level III] either by overstimulation of the gland by high levels androgens or by hypersensitivity of normal levels androgens.[12, level III] Androgens, such as testosterone, dehydroepiandrosterone sulfate (DHEAS) and dihydrotestosterone (DHT), are known to regulate genes responsible for sebaceous gland growth and sebum production.[13, level III] There is a possibility of increased androgen production within the pilosebaceous follicle. The pilosebaceous unit possesses the steroid metabolising enzymes that convert DHEAS to testosterone and DHT.[14, level III] Testosterone is also converted to the more potent androgen i.e. DHT by the enzyme 5α-reductase.[12, level III; 14 - 15, level III] It is not known whether androgens act alone or in combination with growth factors, such as fibroblast growth factor, epidermal growth factor or insulin like growth factor.[14, level III]

ii. Peroxisome Proliferator-Activated Receptors (PPARs)

Sebaceous lipids are at least partly regulated by PPARs and sterol response element binding proteins. PPARs act in concert with retinoid X receptors to regulate epidermal growth and differentiation, and lipid metabolism.[13, level III; 15. level III] Lipid production is increased in sebocytes treated with agonists of the PPARs, which are the transcription factors involved in regulating lipogenic genes.[12, level III; 16, level II-2]

b. *Propionibacterium (P) acnes* Proliferation

Propionibacterium acnes is the main organism and a normal anaerobic resident of pilosebaceous unit that colonises acne prone areas of the skin (in sebaceous hair follicle).[11, level III] The proliferation of these bacteria is responsible for the initiation of inflammation. *P. acnes* releases many enzymes such as proteinases, lipases and hyaluronidases which break down sebum to free fatty acids and peptides. It also releases chemotactic factors which are integral to the inflammatory cascade. These factors contribute to the inflammatory nature of acne by inducing monocytes to secrete proinflammatory cytokines such as TNF-α, interleukin (IL)-1β and IL-8.[17, level III] The inflammatory response to the bacterium and these metabolic by products leads to the formation of papules, pustules, and nodules.[18, level III]

P. acnes also stimulates the host's innate immune response by activating Toll-Like Receptors. This in turn leads to the activation of nuclear factor (NF-kB) which promotes expression of genes responsible for the production of chemokines, cytokines and adhesion molecules. *P. acnes* also activates Toll-Like Receptor-2, resulting in increased levels of IL-8, IL-12, tumour necrosis factor-α and IL-1β.[11, level III; 17, level III]

c. Altered Follicular Keratinisation

In patients with acne, the rate of keratinocyte desquamation at the follicular infundibulum is altered. The keratinocytes accumulate and become interwoven with monofilaments and lipid droplets. This accumulation of cells and sebum results in the formation of microcomedones, the microscopic precursor to all acne lesions.[19, level III] There is also the presence of 5α-reductase activity in the infrainfundibular segments of sebaceous follicles which increases androgen production and subsequent follicular hyperkeratosis.[12, level III]

d. Inflammation

Cellular products from *P. acnes* stimulate the recruitment of CD4 lymphocytes and subsequently neutrophils. These inflammatory cells penetrate the follicular wall, causing disruption of the follicular barrier. This leads to the release of lipids, shed keratinocytes and *P. acnes* into the surrounding dermis, inciting further recruitment of inflammatory cytokines and neuropeptides including substance P.[19, level III]

Linoleic acid has also been found to regulate IL-8 secretion and reduce the inflammatory reaction.[20, level III] Hence, deficiency of linoleic acid may increase hyperkeratinisation of the epidermis.[14, level III]

4. RISK AND AGGRAVATING FACTORS

a. Risk Factors

The role of genetic factors influencing acne has been established. However the exact mode of inheritance is yet to be determined. Obesity is closely related to hyperandrogenism and hence those with high BMI may be prone to develop acne. But there are very few good studies to demonstrate this fact. The following risk factors have been identified for the development of acne:-

i. A significant positive family history of acne has been demonstrated especially when acne is found in:
   - twins (p<0.0001)[21, level III]
   - mother (OR=2.8, 95% CI 1.8 - 4.5)[22, level III]
   - first degree relative [(OR=4.0, 95% CI 3.4-4.7) [23, level II-2] and (OR=3.9, 95% CI 2.7 - 5.5)[24, level II-2]]
   - multiple family members (p<0.0005)[22, level III]

ii. A significant association between obesity and acne in children (p<0.001)[25, level III]

There is no retrievable evidence regarding gender as a risk factor for acne.

b. Aggravating Factors

A number of factors have been postulated to aggravate acne. However, the evidence is limited. The following factors have been shown to aggravate acne:-

i. Smoking [(OR for male smokers=2.3, 95% CI 1.4 - 3.8)[26, level III] and (OR for active smokers=2.0, 95% CI 1.4 - 2.9)[27, level III]]
   - A dose dependent relationship has also been shown (p=0.001).[27, level III] However, another study does not support this finding.[28, level III]

ii. Stress [(r=0.23, p=0.029)[29, level II-2] and (r=0.61, p<0.01)[30, level II-2]]

iii. Facial therapy or salon facial massage.[31, level III]

5. ROLE OF DIET AND SUPPLEMENTS

a. Diet

The following are the dietary factors that may exacerbate acne:

i. Glycaemic Load Diet

Low glycaemic load diet significantly reduces total acne lesion count (-23.5 ± 3.9) compared to high glycaemic load diet (-12.0 ± 3.5) in individuals aged 15 - 25 years (p=0.03).[32, level I] In a local study conducted in individuals aged 18 - 30 years, the risk of acne increased significantly with the increment of dietary glycaemic load at the 50th and 75th percentiles (p<0.01).[33, level II-2]

The glycaemic load (GL) concept describes the quality (the glycaemic index [GI] of the food) and quantity (the amount) of carbohydrate in a meal or diet. The GL of a typical serving of food is the product of the amount of available carbohydrate in that serving and the GI of the food.[34] Dietary GL is the sum of the GLs for all foods consumed in the diet.

The dietary GL can be reduced either by choosing a carbohydrate food from a low GI variety, reducing the amount of carbohydrate intake or both.

The GI is a numerical system used to classify carbohydrate food based on the impact they produce on the postprandial blood glucose level. The higher the GI value of the food, the greater the blood glucose response.[35] In general, most refined carbohydrate devoid of fibre is high in GI while intact carbohydrate (whole grains products), legumes, milk (and milk products), fruits and vegetables are low GI foods.

Calculation of GL

GL = $\sum$ (GI for food item x its carbohydrate content in g/100)

Refer to **Appendix 3** for a food list according to GI classification.

ii. Milk and Milk Products

There is a weak association between all types of milk with worsening of acne among adolescent girls (9 - 15 years old); whole milk (OR=1.19, 95% CI 1.06 to 1.32), low fat milk (OR=1.17, 95% CI 1.04 to 1.31) and skimmed milk (OR=1.19, 95% CI 1.08 to1.31).[36, level III] However, there is only a weak association between skimmed milk consumption and acne among boys (OR=1.19, 95% CI 1.01 to 1.40).[37, level III]

A local study showed that the risk of acne increased by:-

- four-fold when milk intake frequency increased from less than once a week to daily consumption (OR=4.0, 95% CI 1.4 to 11.4)
- seven-fold when ice cream intake frequency is between less than once a week to daily consumption compared to no consumption (OR=7.0, 95% CI 2.4 to 19.7)

No significant differences were found in frequencies of other milk products (yogurt and cheese) consumption between acne patients and controls (p>0.05).[33, level II-2]

iii. Sugar, Fibre and Fat

There is no acne occurrence among two non-western communities (Kavitan in Papua New Guinea and Ache in Paraguay) who consume non-western diet consisting of high fibre and low fat content with negligible added sugars.[38, level III]

iv. Chocolate, Oily Foods and Nuts

There is no good evidence for oily foods in the pathogenesis of acne. In a local study, no significant differences were found in the frequency of chocolate and nuts intake between acne patients and controls (p>0.05).[33, level II-2]

RECOMMENDATION

- A low glycaemic load diet and high fibre diet should be encouraged for acne patients. **(Grade B)**

b. Dietary Supplements

There is no conclusive statement on the effectiveness of zinc supplement in acne.[39, level III] In addition, there is no retrievable evidence on the efficacy of vitamin A, vitamin C, vitamin E and omega-3 fatty acids in the management of acne.

6. PATTERN OF ANTIBIOTIC RESISTANCE

Antibiotic therapy has been the mainstay in the treatment of acne for many years. However prolonged usage may lead to antibiotic resistance resulting in treatment failure.

There was one systematic review (SR) and eight primary papers retrieved on the pattern of antibiotic resistance in acne treatment. The resistance pattern differs with different antibiotics (**Appendix 4**).[40-48, level III] Resistance rates to erythromycin was the highest in majority of the studies. This was followed by clindamycin (**Table 1**).

Table 1: Resistance Rate of Different Antibiotics in Acne Treatment

Antibiotics	Resistance Rate
Erythromycin	4.0 - 92.0%
Clindamycin	4.0 - 95.0%
Tetracycline	0 - 29.9%
Minocycline	0 - 0.6%
Doxycycline	0 - 9.5%
Co-trimoxazole	0 - 21.7%

7. PRINCIPLES OF MANAGEMENT

The aims of acne management are:-

- to induce clearance of lesions
- to maintain remission and prevent relapse
- to prevent physical and psychological complications

Management of acne is based on acne severity and the predominant lesions (refer to **Section 7.1** on **Grading Acne Severity**). Modalities of treatment consist of pharmacological and non-pharmacological measures. This is summarised in the algorithm on **Management of Acne** (page xiii).

7.1 Grading Acne Severity

Grading of acne severity can be done by using grading scale, lesion counting and photographic methods. Leeds technique grading scale is accurate, reproducible, rapid and suitable to be used in the clinic.[49, level III] Counting technique is more suitable for clinical trials.[49, level III; 50, level I]

Photographs may be obtained to establish accurate and achievable records of subjects. However small, non inflammed lesions can be difficult to detect.[51, level II-1]

Various techniques have been used for grading of acne severity (**Table 2**).

Table 2: Comparison among Acne Severity Grading Techniques

Grading Technique	Type of Assessment	Reproducibility	Inter-rater Reliability	Intra-rater Reliability
Leed's Technique[49, level III]	Grading scale and lesion counting	Yes	Yes	Yes
Investigator Global Assessment[50, level I]	Grading scale and lesion counting	Yes	Yes	Not available
Cook Acne Severity Grading scales[51, level II-1]	Grading scale and photographic method	Yes	Yes	Not available
Comprehensive Acne Severity Scale[52, level III]	Grading scale and counting lesion	Yes	Yes	Yes

A new grading system named Comprehensive Acne Severity Scale – CASS (modification of an Investigator Global Assessment [IGA] of Acne Severity) is a validated tool which significantly correlates with the Leeds technique for face (r=0.82), chest (r=0.85) and back (r=0.87). It is simpler to use in clinical practice.[52, level III] Refer to **Table 3** for grading using CASS.

Table 3: 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.

*These guidelines recommend using the CASS for grading of acne severity in clinical practice.

Inspection is done at a distance of 2.5 meters away for acne on face, chest and back.

Chest area defined as:

- Anterior torso superiorly defined by suprasternal notch extending laterally to shoulders and inferiorly by a horizontal line defined by the xiphoid process.

Back area defined as:

- (Is dermacated by the) superior aspects of the shoulders extending to the neck and inferiorly by the costal margins.

RECOMMENDATION

- Comprehensive Acne Severity Scale (CASS) may be used for grading of acne severity in clinical practice. **(Grade C)**

7.2 Treatment

Acne treatment can be pharmacological and non-pharmacological. As acne is a chronic disease, pharmacological treatment can be divided into two phases:-

- Induction therapy
- Maintenance therapy

Non-pharmacological treatment includes physical therapy such as laser, phototherapy, chemical peels and comedone extraction. However, these are not the mainstay of acne treatment.

7.2.1 Induction Therapy

This phase of treatment aims to induce acne remission which can be achieved using topical or systemic agents.

a. Topical Treatment

Topical therapy is the mainstay of treatment for mild acne. It is also useful for moderate acne where comedones are predominant. It plays an important role in induction of remission and maintenance phases of the treatment.

There are a variety of preparations available. The commonly used agents are topical benzoyl peroxide (BPO), retinoids and antibiotics. Newer agents available are fixed combination preparations of these agents.

i. Topical Benzoyl Peroxide (BPO)

BPO is an organic peroxide agent which functions as an effective bactericidal, keratolytic, and anti-inflammatory agent. The use of this agent has not been associated with the development of bacterial resistance [53, level III]

Topical BPO is effective in reducing both inflammatory and non-inflammatory lesions.[54 - 55, level I] The lesion reduction rates achieved with 8 to 12 weeks of therapy are between 42% and 58% for inflammatory lesions ($p<0.05$) and between 30% and 58% for non-inflammatory lesions ($p<0.05$).[54, level I; 56 - 55, level I]

Topical BPO of various concentrations (2.5%, 5% and 10%) and in various vehicles (alcohol, water, acetone, gel or lotion) are equally effective.[57, level I] BPO 2.5% and 5% gel are equally effective in reducing inflammatory lesions at 2, 4, 6 and 8 weeks.[58, level II-1]

The adverse effects of topical BPO such as erythema, dryness, peeling, stinging/burning and itching are usually mild and transient. However, frequency of the adverse effects is higher for BPO 10% compared to BPO 2.5% and 5%.[58, level II-1]

ii. Topical Retinoids

Topical retinoids are synthetic derivatives of vitamin A (retinol). They bind to retinoic acid receptors and have anti-comedogenic, comedolytic and anti-inflammatory properties. They are effective in the treatment of mild to moderate acne vulgaris for both inflammatory and non-inflammatory lesions.

- ***Topical Tretinoin***

  Topical tretinoin/retinoic acid was the first topical retinoid used in the treatment of acne.

  The lesion reduction rates achieved with 8 to 12 weeks of topical tretinoin therapy are between 42% and 72% ($p<0.05$) for inflammatory lesions and between 33% and 70% (**$p<0.05$**) for non-inflammatory lesions.[59 - 60, level I]

  Topical tretinoin is available in various concentrations (0.025%, 0.05% and 0.1%) and formulations. However, evidence that higher concentrations confer better efficacy is controversial.[57, level I; 61, level I]

Topical tretinoin is as effective as topical adapalene, BPO and azelaic acid in reducing both inflammatory and non-inflammatory lesions.[57, level I; 62 - 60, level I; 63, level I] However, compared to adapalene gel 0.1%, tretinoin gel 0.025% was shown to be less well tolerated in a meta-analysis of five randomised controlled trials (RCTs) with $p<0.001$. It was associated with significantly higher occurrence of burning and erythema.[60, level I]

The adverse effects of topical tretinoin such as erythema, dryness, peeling, stinging/burning and itching are usually mild and transient. Incidence of moderate to severe local adverse effects of tretinoin 0.025% gel in a meta-analysis of five RCTs ranged from 6.5% to 38%.[60, level I] Tretinoin 0.1% cream is poorly tolerated[57, level I] while tretinoin microsphere gel (both 0.04% and 0.1%) preparations are well-tolerated.[61, level I]

- ***Topical Adapalene***

Topical adapalene is a naphtoic acid derivative which is a receptor selective retinoid analogue.

The lesion reduction rates achieved with 3 to 12 weeks of topical adapalene therapy are between 47% and 75% for inflammatory lesions ($p<0.05$), and between 50% and 74% for non-inflammatory lesions ($p<0.05$).[54, level I; 62 - 60, level I; 64 - 66, level I]

Topical adapalene demonstrates dose-dependent effect, where 0.3% gel is superior to 0.1% in reduction of inflammatory lesions (62.5% vs 57.8% at week 12; $p=0.015$).[64, level I]

Topical adapalene is as effective as topical tretinoin, isotretinoin and tazarotene in reducing both inflammatory and non-inflammatory lesions.[60, level I; 63, level I; 65 - 69, level I]

Topical adapalene is also as effective as topical BPO in treating inflammatory and non-inflammatory acne lesions. However, BPO 4% gel has an earlier onset of action compared to topical adapalene 0.1% gel.[54, level I]

The adverse effects of topical adapalene are erythema, dryness, peeling, stinging/burning and itching. Most adverse effects are mild. Topical adapalene is better tolerated compared with topical tretinoin,[60, level I] topical isotretinoin,[65, level I] and topical tazarotene.[67 - 68, level I] In a recent RCT, adapalene microsphere formulation was better tolerated than conventional gel formulation with significantly less incidence of erythema and dryness ($p<0.01$).[70, level I]

- ***Topical Isotretinoin***

Topical isotretinoin (13 cis-retinoic acid) is a non receptor-selective synthetic retinoid. It is available as 0.05% cream or gel and 0.1% cream.

The lesion reduction rates achieved with 12 weeks of topical isotretinoin therapy are between 57% and 77% for inflammatory lesions, and between 68% and 78% for non-inflammatory lesions.[65, level I; 71, level I] Topical isotretinoin 0.05% and 0.1% are equally effective.[57, level I]

Topical isotretinoin is as effective as topical retinoic acid and topical adapalene in treating both non-inflammatory and inflammatory acne lesions.[65, level I] However when compared to topical BPO, it is equally effective for non-inflammatory acne lesions but less effective for inflammatory lesions ($p<0.01$).[72, level I]

Adverse effects of topical isotretinoin are generally mild such as erythema, scaling, burning and pruritus. The incidence of adverse effects is similar to topical BPO and retinoic acid but significantly higher than topical adapalene ($p<0.05$).[65, level I; 71 - 72, level I]

- ***Topical Tazarotene***

  Topical tazarotene is a receptor selective retinoid. It is available as gel or cream in concentration of 0.05% or 0.1%. There is no retrievable evidence to show superiority in terms of efficacy in these two concentrations and preparations.

  The lesion reduction rates achieved with 4 to 12 weeks of topical tazarotene therapy are between 37% and 70% for inflammatory lesions ($p<0.05$), and between 37% and 75% for non-inflammatory lesions ($p<0.05$).[73- 76, level I]

  Topical tazarotene is as effective as topical adapalene and tretinoin in reducing inflammatory and non-inflammatory lesions.[67, level I; 73, level I] However, a recent RCT showed that tazarotene 0.1% cream is more effective than adapalene 0.3% gel in reducing total lesion counts and decreasing post-inflammatory hyperpigmentation, while having comparable tolerability.[77, level I]

  Adverse effects of topical tazarotene are generally mild, consisting of erythema, dryness, peeling, burning and pruritus. There is no significant difference in incidence of adverse effects between tazarotene 0.1% cream and adapalene 0.1% cream.[75, level I]

iii. 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 as these are effective and relatively well tolerated. The use of topical antibiotics as monotherapy should be avoided to prevent bacterial resistance.[78, level III] The anti-bacterial properties of these antibiotics are found to inhibit the colonisation of pilosebaceous glands by *Propionibacterium acnes* and have limited anti-comedogenic effect.[79, level I]

- ***Topical Clindamycin***

Topical clindamycin is effective in reducing both inflammatory and non-inflammatory lesions. A Health Technology Assessment (HTA) of eight clinical trials showed that clindamycin was superior to placebo.[57, level I] Rizer RL *et al.* reported that topical clindamycin effectively reduced inflammatory lesions by 54.9% (p=0.015) and non-inflammatory lesions by 26.4% (p=0.043) at week 12 of treatment.[79, 2001, level I]

In the same HTA mentioned above, five clinical trials showed that topical clindamycin was as effective as topical erythromycin.[57, level I]

Various combination (fixed and non-fixed) preparations of clindamycin with either BPO, tretinoin or adapalene show superiority over clindamycin alone (p<0.05).[57, level I; 80. level I; 81, level II-1]

Comparison of daily versus twice daily application of topical clindamycin does not show any significant differences in the reduction of both inflammatory (p=0.810) and non-inflammatory lesions (p=0.184).[79, level I]

The efficacy of topical clindamycin is similar whether the vehicle used is a gel, lotion or solution.[57, level I]

The adverse effects of clindamycin such as erythema, peeling, dryness, scaling, stinging, burning and itching are mild and transient.[57, level I; 79 - 81, level II-1; 82, level I; 83, level II-1]

- ***Topical Erythromycin***

Topical erythromycin is effective in reducing both inflammatory and non-inflammatory lesions.[57, level I; 84 - 85, level II-3; 86, level I; 87, level II-1; 88 - 89, level I]

Significant lesion reduction rates achieved with 6 to 12 weeks of therapy are between 42% and 74% for inflammatory lesions and between 25% and 74% for non-inflammatory lesions.[57, level I; 84 - 85, level II-3; 86, level I; 87, level II-1; 88 - 89, level I]

Topical retinoic acid 0.05% and BPO 10% are superior to topical erythromycin in reducing non-inflammatory lesions but not in inflammatory lesions.[84, level II-3]

Addition of zinc in topical erythromycin (topical zineryt) is more efficacious compared to erythromycin alone in reducing papules and pustules ($p<0.001$).[86, level I]

Adverse effects of topical erythromycin such as dry skin, itching, burning, erythema, scaling and dermatitis are localised, mild and transient.[85, level II-3; 86, level I; 87, level II-1; 88; level I]

iv. Topical Azelaic Acid (AA)

AA is a naturally occurring dicarboxylic acid which has comedolytic, antimicrobial and anti-inflammatory properties.

Topical AA causes reduction in total lesion count by 60.6% and Acne Severity Index by 65.2% in six weeks.[90, level I] A systematic review (SR) and two trials showed that it was effective in reducing both inflammatory and non-inflammatory lesions.[57, level I; 90 - 91, level I]

Topical AA is as effective as topical BPO and adapalene in reducing both inflammatory and non-inflammatory acne lesions.[91, level I]

Topical AA reduces sebum production by an average of 13.9% on the forehead and 14.2% on the cheek. Its therapeutic activity, however, does not depend on its capacity in sebum reduction.[91, level I]

Adverse effects of topical AA are generally mild and transient, with an overall incidence of approximately 3%. These include pruritus, burning, stinging and tingling.[90, level I]

v. Topical Salicylic Acid (SA)

SA is a keratolytic agent which has been shown to be effective for mild to moderate acne. It has both comedolytic and antimicrobial properties.[92, level I]

Topical salicylic acid effectively reduces both inflammatory and non-inflammatory acne, with reduction rates of 44% and 19% respectively at week 12 (p<0.001).[92, level I]

Salicylic acid of 1.5% and 2% concentrations are effective compared to placebo.[57, level I]

Adverse effects of salicylic acid such as pruritus, burning, tingling, desquamation and erythema are mild and transient.[57, level I; 92, level I]

vi. Topical Sulfur and Its Combination

Sulfur has long been used in the treatment of acne. It has anti-inflammatory and mild keratolytic properties. There is no sufficient evidence to support the use of sulfur alone.[57, level I] However, the combination of sulfur with other agents is effective in treating mild to moderate acne.[93, level II-3]

Combination therapy of 5% sulfur and 10% sulfacetamide is effective in reducing 78% of total lesions and 82.9% of inflammatory lesions in women with mild to moderate acne at week 12 (p<0.001).[93, level II-3]

Combinations of sulfur (2% to 6%) in calamine lotion have long been used in the treatment of facial and truncal acne.[94, level III] However, there is no retrievable clinical study demonstrating its efficacy.

Adverse effects include transient mild dryness and pruritus.[93, level II-3]

vii. Topical Dapsone

Topical dapsone is assumed to have similar mechanisms of action on acne as oral dapsone. It has antimicrobial (bacteriostatic) and anti-inflammatory properties.

Topical dapsone is effective in the treatment of mild to moderate acne, reducing both inflammatory and non-inflammatory lesions. Significant reduction rates achieved with 12 weeks of therapy are between 30% and 49% for inflammatory lesions ($p<0.001$), and between 5% and 32% for non-inflammatory lesions ($p<0.001$). Its onset of action on inflammatory lesions occurs as early as four weeks.[95-96, level I; 97, level II-3] Sustained effectiveness was demonstrated in a 12-month study showing lesion reduction of 58% for inflammatory lesions ($p<0.001$) and 19.5% for non-inflammatory lesions ($p=0.002$).[97, level II-3] However, there is no head-to-head study comparing the efficacy of topical dapsone with other topical agents.

Topical dapsone is well tolerated for up to 12 months. Adverse effects, reported in 14 - 38% of patients, are mostly mild or moderate. Common effects include dryness, rash, sunburn, burning sensation, erythema and pruritus.[95, level I; 97, level II-3] Topical dapsone is safe for use in Glucose-6-phosphate dehydrogenase (G6PD) deficient patients with acne for up to 12 weeks, with no significant increase in the incidence of hemolysis.[95, level I; 98, level I] No studies have been done in pregnancy and children aged less than 12 years.[99, level III]

viii. Topical Fixed Combination

Fixed combination therapies are new anti-acne treatment. Combination preparations with topical benzoyl peroxide, retinoids or antibiotics are more effective than either agent used alone.[100]

- ***Topical Clindamycin/BPO (CBP)***

  CBP is effective in reducing both inflammatory and non-inflammatory lesions when compared to vehicle ($p<0.05$), clindamycin ($p<0.05$) and BPO ($p<0.05$) alone.[101, level I; 102, level I; 103, level I]

  The lesion reduction rates achieved at week 2 to 12 weeks of CBP therapy are between 30% and 60% for inflammatory lesions ($p<0.05$) and between 10% and 43% for non-inflammatory lesions ($p<0.05$).[101, level I; 102, level I; 103, level I]

  There is no statistically significant difference between the local irritant effects of combination preparation compared to either agent on its own. However, treatment with either CBP or BPO resulted in higher frequency of peeling than clindamycin alone.[103, level I]

  The preparations currently available are clindamycin 1% in combination with 2.5% BPO or 5% BPO.

- ***Topical Adapalene/BPO (ABP)***

  ABP is effective in reducing inflammatory and non-inflammatory lesions when compared to vehicle ($p<0.05$), adapalene ($p<0.05$) and BPO ($p<0.05$) alone.[104 - 105, level I]

  Success rates (clear to almost clear) at week 12 are 27.5% to 38% with ABP compared to adapalene 15.5% to 22% and BPO 15.4% to 27% ($p< 0.05$).[104 - 105, level I]

  Adverse effects are mild to moderate in severity without any residual effects.

  The preparation currently available is adapalene 0.1% in combination with 2.5% BPO.

- ***Topical Erythromycin/BPO (EBP)***

  EBP is effective in reducing both inflammatory and non-inflammatory lesions. However, this effect was slower in the latter.[57, level I]

  Reduction rates achieved at week 4 and week 10 are between 50% and 75% for inflammatory lesions ($p<0.05$) while at week 8 and week 10, they are between 50% and 53% for non-inflammatory lesions ($p< 0.05$).[106, level I]

  Adverse effects such as scaling and skin tightness had been reported.[57, level I]

- ***Topical Clindamycin/Tretinoin***

  Topical clindamycin (1%)/tretinoin (0.025%) in hydrogel demonstrates superior efficacy to clindamycin, tretinoin and vehicle alone ($p<0.05$). The reduction rates at week 12 are 53.4% for inflammatory lesions and 45.2% for non-inflammatory lesions. Adverse effects are minor and well tolerated.[107, level I]

Practical tips on topical agents

- Apply a thin layer to the entire susceptible areas
- Topical retinoids are to be avoided during pregnancy.
- Topical azelaic acid may be useful in acne patients with hyperpigmentation
- Topical antibiotics should not be used as monotherapy to minimise antibiotic resistance

RECOMMENDATION

- Topical benzoyl peroxide, topical retinoid, topical antibiotics, topical azelaic acid or topical salicylic acid are indicated for mild to moderate acne. **(Grade A)**
- Topical sulfur combinations can be used in for mild to moderate acne. **(Grade C)**
- Benzoyl peroxide should be initiated at a concentration of 2.5% or 5%. **(Grade A)**
- Topical fixed combination such as clindamycin and benzoyl peroxide or adapalene and benzoyl peroxide can be used as an option for the treatment of mild to moderate acne. **(Grade A)**

b. Systemic Treatment

i. Oral Antibiotics

Oral antibiotics have been widely used for moderate to severe acne vulgaris. The anti-*Propionibacterium acnes* properties found in antibiotics are able to inhibit the colonisation of pilosebaceous glands by the bacteria and prevent further inflammation. Tetracycline antibiotics have also been shown to exert direct anti-inflammatory effect by inhibiting chemotaxis and matrix metalloproteinases. However, prolonged use of oral antibiotics may be associated with bacterial resistance.

- ***Oral Tetracycline***

  Tetracycline has been widely used in the management of moderate to severe acne. It has antimicrobial and direct anti-inflammatory properties. However, its use is contraindicated in children aged less than eight, pregnancy and lactation. Absorption of tetracycline from the gastrointestinal tract is impaired by food, milk, dairy products, iron salts and antacids. Hence it should be taken one hour before or two hours after meals with a full glass of water, in upright position. A SR of 18 trials showed that oral tetracycline in doses ranging from 250 to 500 mg twice daily for 8 to 24 weeks was effective for both inflammatory and non-inflammatory lesions in mild to moderate acne. Lesions reduction rates were between 19% and 84% for inflammatory lesions and between 25% and 63% for non-inflammatory lesions.[108, level I]

  There is lack of retrievable evidences to show any difference in efficacy among different dosages of oral tetracycline. However, there is no statistical difference between the available tetracyclines preparations in terms of the efficacy in reducing inflammatory (p=0.898) and non-inflammatory lesions (p=0.429).[108, level I]

  Majority of the adverse events are mild and transient. Common adverse effects are nausea, vomiting, diarrhoea, cramping, erythema, abdominal pain, esophagitis, oral candidiasis and vaginal candidiasis.[57, level I; 109, level II-1; 110, level II-3]

- ***Oral Doxycycline***

  Doxycycline is a tetracycline derivative. In contrast to tetracycline, the absorption of doxycycline is less affected by food. It is contraindicated in children aged less than eight, pregnancy and lactation.

Oral doxycycline 50 to 100 mg daily is effective in reducing both inflammatory and non-inflammatory lesions. The lesion reduction rates achieved with three months treatment of oral doxycycline were between 14% and 50% for non-inflammatory lesions ($p<0.05$), and between 30% and 75% for inflammatory lesions ($p<0.05$).[57, level I; 111, level I; 112, level II-1; 113, level II-2; 114, level I]

A sub-antimicrobial dosage of oral doxycycline 20 mg BD for six months was found to exert a 50% reduction in inflammatory lesions ($p<0.04$) and 54% reduction in non-inflammatory lesions ($p<0.01$).[115, level I]

Common adverse effects are mainly gastrointestinal such as diarrhoea, nausea, vomiting, dyspepsia and abdominal pain. Less common adverse effects are headache, photosensitivity, photo-onycholysis and rash.[57, level I; 111, level I; 112, level II-1; 113, level II-2; 114 - 115, level I]

- ***Oral Erythromycin***

Erythromycin is a macrolide antibiotic. It exerts direct anti-inflammatory activities by reducing neutrophil chemotatic factors and reactive oxygen species.

Oral erythromycin is effective in reducing both inflammatory and non-inflammatory lesions. In a study by Greenwood R *et al.*, oral erythromycin 250 mg twice daily for four months showed 21 - 45% improvement in Leed's acne severity grading in patients with moderate to severe acne ($p<0.05$). Facial acne responded better than truncal acne, giving an acne severity reduction of 66.5% and 51.5% respectively ($p<0.05$).[116, level II-1]

In similar study, doubling the dose of erythromycin from 500 mg daily to 1 g daily significantly increased the response from 47% to 79% after six months (p<0.001). The relapse rate (defined as a return of the acne to >50% of original severity) with erythromycin 1g daily was lower compared to 500 mg daily i.e. 35% vs 72%.[116, level II-1]

Treatment with erythromycin-base 333 mg three times a day for four weeks followed by 333 mg once daily for eight weeks produced lesion reduction rates of 67% for inflammatory and 22% for non-inflammatory lesions.[117, level I]

A SR of three clinical trials comparing the use of oral erythromycin and oral tetracycline showed that both were equally effective.[57, level I]

Common adverse effects of erythromycin are mainly gastrointestinal such as nausea and diarrhoea. Other adverse effects such as headache, dizziness and rashes are mild and transient.[116, level II-1; 117, level I; 118, level II-1] Doubling the dose of erythromycin from 500 mg daily to 1g daily does not cause an increase in the incidence of adverse effects.[57, level I; 116, level II-1]

- ***Oral Minocycline***

Minocycline is a tetracycline antibiotic that has been used in the treatment of moderate to severe acne vulgaris. It is contraindicated in children aged less than eight, pregnancy and lactation. Compared to the first-generation tetracyclines, it only needs to be taken once or twice a day and can be taken with food. However, it is more expensive.[119, level I]

A Cochrane SR of 27 RCTs found that the RCTs were generally small and of poor quality. The efficacy of minocycline relative to other acne therapies could not be reliably determined due to the poor methodological quality of the trials and inconsistent outcome measures. In the same SR, there was no evidence to support the benefits of minocycline in acne which is resistant to other therapies.[119, level I]

Minocycline was shown to have comparable efficacy with tetracycline, doxycycline and lymecycline.[109, level II-1; 114, level I; 120 - 121, level I]

Dose regimes of minocycline used in the above studies were 50 mg to 100 mg once to twice daily. However, there are no studies which compare different dose regimes of the medication.[119, level I]

There is concern about its safety. Overall, 11% of patients experienced adverse reactions that are attributed to the therapy. Of these, 2.9% were severe enough to warrant in therapy withdrawal. These include moniliasis, abnormal pigmentation, vertigo, urticaria, renal failure and fixed drug eruption.[57, level I; 109, level II-1; 114, level I; 119-120, level I] There is evidence to suggest that the risk of minocycline-induced pigmentation increases with cumulative dose especially above 100 g.[119, level I]

- ***Oral Azithromycin***

Azithromycin is a macrolide antibiotic. It has a long half-life of 68 hours and therefore can be given three times a week.

Pulse treatment of oral azithromycin at a dose of 500 mg three times a week is effective in reducing both inflammatory and non-inflammatory lesions in patients with moderate to severe acne. [112, level I; 113, level II-1; 122, level I; 123, level II-3]

The lesion reduction rates achieved with three months treatment of oral azithromycin are 50% for non-inflammatory lesions (p<0.05) and 70% for inflammatory lesions (p<0.05).[112, level I] Overall improvement of more than 80% is seen in 52% to 53% of patients.[112, level I; 113, level II-1; 123, level II-3]

Common adverse effects include gastrointestinal intolerances such as diarrhoea, minor gastric discomfort and nausea. Majority of the adverse effects are mild and transient.[112, level I; 113, level II-1; 122, level I; 123, level II-3]

- ***Oral Co-trimoxazole and Trimethoprim Alone***

Co-trimoxazole is a combination of trimethoprim and sulfamethoxazole. It should be avoided in patients with hypersensitivity to sulfonamides. Trimethoprim has also been used alone.

In a RCT, oral co-trimoxazole one tablet daily (trimethoprim 80 mg and sulfamethoxazole 400 mg) for three months was found to reduce acne severity in 81% patients and was comparable to oxytetracycline 250 mg daily (p>0.01). A further reassessment after a month of treatment cessation found no significant difference in the rate of relapse (p>0.1).[124, level I]

Trimethoprim 100 mg three times a day achieved lesion reduction rates of 60% for inflammatory lesions (p<0.01) and 18% for macules (p<0.01) at eight weeks. These findings are comparable to oxytetracycline given 250 mg three times a day.[125, level I]

Adverse effects are mainly flatulence, abdominal pain, dizziness, headache, macular erythema and desquamation.[57, level I; 125, level I] Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis are uncommon but potentially serious adverse effects.

Practical tips on oral antibiotics

- Oral tetracycline, doxycycline, minocycline or co-trimoxazole are contraindicated in pregnancy.
- Sulfonamide antibiotics have been reported to cause severe adverse drug reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis.
- Oral antibiotics should not be prescribed continuously for more than six months.

RECOMMENDATION

- Oral tetracycline, oral doxycycline, oral erythromycin or oral minocycline may be used as treatment for moderate to severe acne. **(Grade A)**

ii. Oral Hormonal Therapy

Hormonal therapy is an alternative treatment for managing acne in women. This option may be particularly valuable for those requiring contraception or with signs of hyperandrogenism.

- ***Combined Oral Contraceptive (COC)***

COCs are thought to reduce acne by several mechanisms. COCs decrease free testosterone levels, increase sex hormone-binding globulin and prevent conversion of free testosterone to DHT.

COCs containing different progestins and oestrogen dosages are prescribed for acne. In a Cochrane SR, five RCTs showed that COCs significantly reduced inflammatory and non-inflammatory facial lesions counts, severity grades and self-assessed acne when compared to placebo.[126, level I]

Comparison on the effectiveness of different COCs was less clear. COCs that contained chlormadinone acetate (CMA) or cyproterone acetate (CPA) improved acne better than those with levonorgesterol and desogestrel, although this apparent advantage was based on limited data or conflicting results. Studies comparing COC containing levonorgestrel and desogestrel also showed conflicting results.[126, level I]

Adverse events include nausea, vomiting, breast tenderness, headaches, menstrual disturbances and venous thrombosis.[126, level I]

- ***Spironolactone***

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

Spironolactone is not effective for acne although there is some evidence on its effectiveness in the treatment of hirsutism.[57, level I; 127, level I]

- ***Other Anti-Androgens***

Flutamide, a potent non-steroidal anti-androgen, is usually prescribed for prostatic cancer and also effective for women with idiopathic hirsutism and polycystic ovarian syndrome. Low dose flutamide (250mg/day) and CPA were effective in reducing acne scores from baseline ($p<0.01$).[128, level I] However, flutamide should be used with caution as it can potentially cause liver failure.

Finasteride, a specific inhibitor of 5-α reductase, has been shown to be less effective for the treatment of acne in hyperandrogenic women when compared to flutemide and cyproterone acetate (p<0.05).[128, level I]

Cimetidine, a H_2 receptor antagonist drug used mainly for inhibition of gastric acid secretion, is also noted to have anti-androgenic property but there is no evidence to show that it improves acne.[57, level I]

RECOMMENDATION

- Combined oral contraceptives may be used in the treatment of acne in females patients with moderate acne, particularly in those who require concomitant contraception and/or those with hyperandrogenism. **(Grade A)**

iii. Oral Isotretinoin

Oral isotretinoin (13-cis-retinoic acid) is a retinoid compound commonly used for the treatment of nodulocystic and severe acne. It targets all pathophysiologic factors in acne. It decreases the size and secretion of sebaceous glands, normalises follicular keratinisation, indirectly inhibits *P. acnes* growth in hair follicle and exerts an anti-inflammatory action.

Isotretinoin is teratogenic. Strict contraceptive practice is required for female patients and isotretinoin should only be prescribed by dermatologists.

Oral isotretinoin is effective in the treatment of nodulocystic acne as evident by a placebo-controlled clinical trial showing reduction in nodules and cysts by 17% after one month (p<0.001) and 32% after two months (p<0.008). The average maximum dose received was 1.2 mg/kg/day (range of 0.5 to 3.2). The mean time for complete clearance with one course of therapy was six months. Those who cleared completely were in remission for 38 months in average.[129, level I]

Various doses of oral isotretinoin have been used. A study comparing 0.1, 0.5 and 1 mg/kg/day doses in the treatment of nodulocystic acne showed significant clinical response to treatment with all three doses (p<0.01) without significant difference between doses. However, relapse rates were higher in the lower dose groups (0.1 and 0.5 mg/kg/day). With a dose of 0.5 mg/kg/day, 20% needed to be re-treated while those on 0.1 mg/kg/day, 42% needed to be re-treated during the three month post-therapy follow up.[130 - 131, level I] A cumulative dosage of 120 mg/kg is associated with a lower relapse rate.[78, level III]

Low-dose oral isotretinoin has been used to treat mild to moderate acne unresponsive to conventional therapy. However, there was marked heterogeneity in the dosing regimens making it difficult to compare between them:-

- A dose of 0.5 mg/kg/day for one week each month over a period of six months significantly reduced both total acne grades and inflamed lesion count with 88% resolution (p<0.0001). Twelve months after completing treatment, 61% of those who responded remained significantly improved (p<0.0001).[132, level II-3]

- A dose of 0.5 - 0.75 mg/kg/day for one week each month over a period of six months resulted in 82.9% complete and 11.6% partial healing. This study however did not monitor for relapses.[133, level II-3]

- A dose of 20 mg/day for six months showed complete or almost complete remission in 94.8% of patients aged 12 - 20 years old and 92.6% aged 21 - 35 years old. Failures of treatment were 5.2% and 7.4% respectively. Within the four-year follow up period, relapses occurred in 3.9% aged 12 - 20 years old and 5.9% aged 21 - 35 years old.[134, level II-3]

- A RCT studied intermittent and conventional dosing of isotretinoin where 66 patients were randomised to three groups [Group 1 (0.5 mg/kg for first 10 days of the month for six months), Group 2 (0.5 mg/kg every day for one month, then first 10 days for five months) and Group 3 (0.5 mg/kg per day everyday for six months)]. No statistically significant differences were obtained among the treatment protocols in patients with moderate acne. However, there was a significant difference in severe acne between Groups 1 and 3 at the end of follow up period (p=0.013). The frequency and severity of isotretionin-related side effects were found to be lower in Groups 1 and 2 compared with Group 3.[135, level I]

- A RCT compared the effectiveness of isotretinoin in conventional dose (0.5 - 0.7 mg/kg daily), low-dose (0.25 - 0.4 mg/kg daily) and intermittent dose (0.5 - 0.7 mg/kg daily for 1 week out of every 4 weeks) in moderate acne. The conventional and low-dose regimens were superior to the intermittent dose regimens in the improvement of Global Acne Grading System (GAGS) scores with p<0.001 and p =0.044 respectively. There was no significant difference between conventional and low dose regimens. One year after the end of treatment, the relapse rates were 13% in the conventional group, 18% in the low dose group and 56% in the intermittent group.[136, level I]

  Side effects are dose-dependent, mostly limited to the skin and mucous membrane, and well tolerated and reversible. Common side effects include cheilitis, dermatitis, conjunctivitis, xerosis and dryness of the nasal mucosa with nosebleeds. Other rare side effects are arthralgia, decreased appetite and fatigue. Laboratory abnormalities are limited to elevations of serum aspartate, alanine transaminases and hypertriglycerides which all return to normal after discontinuation of therapy.[129 - 131, level I] There is no consensus yet on depression and suicide from the use of oral isotretinoin. However, caution is advised in patients with history of depression and mood swings.[78, level III]

RECOMMENDATION

- Oral isotretinoin can be used for nodulocystic or severe acne. **(Grade A)**
- Oral isotretinoin may also be used for moderate acne as third line therapy. **(Grade B)**

7.2.2 Maintenance Therapy

Recurrence of acne lesions after successful treatment is common. Hence, maintenance therapy is an important modality as part of a comprehensive management of acne. The mainstay of maintenance treatment is topical therapy.

i. Topical Adapalene

Following an induction therapy (BPO 2.5% and adapalene gel 0.1%) for eight weeks, maintenance therapy for 12 weeks with adapalene gel 0.1% daily or alternate day led to a further reduction of microcomedones count in mild to moderate acne compared to vehicle.[137, level I]

In another study on moderate to moderately severe acne, after 12 weeks of maintenance therapy with adapalene gel 0.1% once daily, there were further reduction in total (p=0.049) and non-inflammatory (p<0.001) lesions compared to vehicle.[138, level I]

Zhang *et al.* reported a reduction in total, inflammatory and non-inflammatory lesions after 12 weeks of maintenance therapy in moderate to moderately severe acne with adapalene gel 0.1% monotherapy as compared to control group.[139, level I]

ii. Topical Tazarotene

Leyden *et al.* compared three maintenance regimens in patients with moderately severe to severe acne. Tazarotene 0.1% gel plus placebo, vehicle plus oral minocycline and tazarotene gel plus oral minocycline were associated with sustained improvement in both non-inflammatory and inflammatory lesions during the 12-week maintenance phase. However, there was no statistically significant difference between the maintenance regimens.[140, level I]

iii. Topical Azelaic Acid (AA)

Maintenance therapy with topical 20% AA monotherapy showed improvement after three months in both inflammatory and non-inflammatory lesion counts in severe acne.[141, level I]

iv. Topical Adapelene-Benzoyl Peroxide

A fixed combination gel of adapelene 0.1% and BPO 2.5% (adapelene-BPO) is an effective maintenance therapy agent. It prevents relapse and continues to reduce disease symptoms during six month maintenance therapy in severe acne.[142, level I]

There is no retrievable evidence on the use of topical antibiotics as maintenance therapy.

However, the Global Alliance recommends BPO or BPO-antibiotic combination with topical retinoid, such as adapalene gel 0.1% and tazarotene, as effective maintenance therapy.[13, level III]

RECOMMENDATION

- Maintenance treatment of acne should be commenced after an initial successful induction therapy to sustain remission. **(Grade A)**
- Topical retinoid monotherapy should be considered for maintenance therapy in patients with acne. **(Grade A)**
- Combination therapy of adapalene-benzyl peroxide gel may be considered for maintenance therapy in severe acne. **(Grade A)**

7.2.3 Intralesional Corticosteroid Injection

Intralesional corticosteroid injection is indicated for the treatment of acne nodules and cysts.[143, level III] It is a simple and useful technique in rapidly reducing inflammation and resolving lesions in order to minimise scarring.[143 - 144, level III]

Corticosteroids should be injected at the lowest effective dose, which can be determined by individual doctor's experience with the types of lesions and the patient's response. Intralesional triamcinolone acetonide 2.5 to 5 mg/ml is commonly used.[143, level III]

There is evidence of systemic absorption following intralesional corticosteroid injection. Adrenal suppression occurs in doses of more than 15 mg per session. Suppression persists for 2 to 3 days with 20 - 35 mg and at least 5 days with 50 mg dose.[145, level II-3]

Local adverse effects include skin atrophy, pigmentary changes, telangiectasias, haematoma and infection.[143 - 144, level III]

A combination of intralesional triamcinolone 2.5 mg/ml and lincomycin hydrochloride 75 mg/ml was shown to be superior over intralesional triamcinolone alone in the treatment of nodulocystic lesions of acne.[146, level II-3]

Intralesional corticosteroid injection should be used with caution due to potential local and systemic adverse effects.

RECOMMENDATION

- Intralesional corticosteroid injection may be used in the treatment of selected acne cases (acne nodules/cysts) but cannot replace conventional treatment. **(Grade C)**

7.2.4 Physical Therapy

Physical therapy can be used as an adjunct or alternative treatment in acne. However, it is not widely available and can only be provided by trained personnel.

i. Comedone Extraction

Physical removal such as comedone extraction by a variety of techniques can provide immediate clinical improvement and patient satisfaction. However, published article describing the use of comedone extraction is sparse.[147, level III] Comedone extraction using Shamberg or Saalfeld comedone extractor is effective in superficial acne but not in cystic acne.[148, level III]

In a study by Kaya TI *et al.* using cautery and standard dissecting forceps for closed macrocomedones >3 mm in diameter, all patients tolerated the procedure and judged the cosmetic results as very good.[149, level III]

The disadvantages of comedone extraction include incomplete extraction, tissue damage and recurrence.

ii. Chemical Peels

Chemical peels are used as adjuvants in the treatment of facial acne. Various chemical preparations are used for epidermal exfoliation. Commonly used peeling agents include glycolic acid and salicylic acid.

- ***Glycolic Acid***

Glycolic acid, an α-hydroxy acid, is a hydrophilic compound often used in chemical peels due to its desquamating properties. Desquamation reduces corneocyte cohesion and keratinocyte plugging. This enables the extrusion of contents which prevent comedone formation.

Both 70% glycolic acid and Jessner's solution twice a week on mild to moderate acne for six weeks were effective in the treatment of facial acne. Improvement was noted after three treatment sessions. However, there were no significant differences between the two solutions. Both solutions resulted in erythema which resolved within four days. Jessner's solution caused more significant exfoliation compared to glycolic acid ($p < 0.01$).[150, level I] In another study, Atzori *et al.* reported that 70% glycolic acid peel improved comedones more rapidly than papulo-pustules and nodulo-cystic lesions.[151, level III]

In moderate to moderately severe acne, glycolic acid peel (35% or 50%) for four sessions at 3-weekly intervals together with pre- and post-treatment use of 15% glycolic acid at home peel resulted in significant resolution of comedones, papules and pustules.

Physician's assessment at week 11 showed a 50% improvement in about one third of patients with comedones or papules and one fifth in those with pustules.[152, level II-3] Grover *et al.* reported that glycolic acid (10 to 30%) at fortnightly interval significantly reduced the number of comedones and papulo-pustules in patients with mild to moderate acne.[153, level III]

The most common side effect is erythema. Other reported side effects include post- inflammatory hyperpigmentation, local herpes simplex infection and mild skin irritation.[151, level III; 152, level II-3]

- ***Salicylic Acid (SA)***

SA, a lipophilic β-hydroxy acid, reduces corneocyte cohesion and acts well on sebaceous areas of the face. It has excellent keratolytic effect and is useful against comedones. It is also effective against inflammatory lesions.

In mild to moderately severe acne, both 30% salicylic acid and 30% glycolic acid were noted to be effective after two treatments ($p<0.05$). At two months post-treatment, salicylic acid was able to sustain its effectiveness ($p<0.01$). However some patients were also on topical retinoid, oral antibiotics and other topical acne therapy at enrollment which could have confounded the results.[154, level I]

Lee HS *et al.* reported that 30% salicylic acid at 2-weekly intervals for five sessions were effective in both non-inflammatory and inflammatory acne lesions. The mean acne grading reduction by Leed's grading system from baseline to week 12 was 1.29 with a range of 1.67 to 0.38 ($p<0.01$).[155, level II-1]

Adverse events include peeling, redness and scaling which are highest in first two sessions.[154, level I; 155, level II-1]

RECOMMENDATION

- Chemical peel with glycolic acid or salicylic acid may be used as adjuvant treatment for acne. **(Grade B)**

iii. Phototherapy and Photodynamic Therapy

Phototherapy and photodynamic therapy are alternative therapeutic options for patients who either fail or unable to tolerate other standard acne therapies. These are specialised procedures and should be carried out by dermatologists. The development of light-based therapies was based on the observation that sunlight exposure may improve acne.

The proposed mechanisms of action are photothermal heating of sebaceous glands and photochemical inactivation of *P. acnes*. Porphyrins which may be produced by *P. acnes* can absorb light at a peak of 415 nm to form singlet oxygen radicals that kill the bacteria.

- ***Phototherapy***

  These include pulsed dye laser, potassium titanyl phosphate laser, infrared diode laser, intense pulse light and broad spectrum continuous wave visible light sources such as blue and blue-red light. Many studies have been published with varying qualities and results.

  - ***Pulsed Dye Laser (PDL)***

    A SR of two RCTs evaluated the efficacy of PDL vs placebo and untreated control on facial acne with ambiguous results.

Seaton ED *et al.* reported 49% improvement in PDL on inflammatory acne lesions vs 10% improvement in the placebo at 12 weeks after one treatment (p=0.007). However, Orringer JS *et al.* found no significant differences in inflammatory or non-inflammatory lesions in a split-face study comparing one or two PDL treatments vs no treatment.[156, level I]

Adverse effects following PDL treatment are minimal which include pain, erythema, purpura and post-inflammatory hyperpigmentation.[156, level I]

- ***Potassium Titanyl Phosphate (KTP) Laser***

Improvement in total acne lesion scores by 35% at one week (p<0.01) and 21% at four week (p=0.09) after KTP laser treatment was observed compared to no improvement with placebo.[156, level I]

- ***Infrared Diode Laser***

A SR of four RCTs evaluated the efficacy of infrared lasers at 1320 nm or 1450 nm vs control (untreated or cryogen). Treatment with 1320 nm laser showed 27% reduction of open comedones vs 12% deterioration in the untreated control at one week post-treatment. The 1450 nm laser showed improvement up to six months after four treatments on the upper back (mean reduction 98%) vs cryogen alone (mean reduction 6%) in the same period.[156, level I]

Another study involving 26 patients with inflammatory facial acne using 1450 nm diode laser (four treatments) at three to four weeks interval reported reduction of mean acne lesions by 29% (p<0.01) and 40% (p<0.03) after four weeks and six months respectively.[157, level II-3]

Noborio R *et al.* reported reduction in mean acne grading from 3.9 to 1.4 in inflammatory acne using 1450 nm diode laser within 5 to 10 sessions at 2 - 4 week intervals ($p<0.01$).[158, level II-3]

o *Intense Pulse Light (IPL)*

A SR showed that IPL by itself was not beneficial. The efficacy of IPL was evaluated in one RCT and two clinical trials, involving a total of 59 patients. The trials evaluated the efficacy of IPL vs IPL assisted PDT in two and three treatment sessions with topical 5-aminolaevulinic acid (ALA) and in four treatment sessions with topical methyl aminolaevulinate (MAL).[156, level I] IPL-assisted PDT with topical ALA or topical was more effective than placebo in inflammatory acne (reduction of 87.7% vs 66.8%; $p<0.05$) after 12 weeks. In a split-face trial, there was no statistical difference between treatment with BPO as monotherapy and BPO with IPL treatment. Side effect of IPL was mild with minimal erythema for a few hours after treatment.[159, level I]

o *Visible Light Sources*

There were two SR comprising eight RCTs for this comparison. The devices studied were 532 nm pulsed laser (green light), 585 nm pulsed laser (yellow light), 405 - 420 nm (blue light), 635 - 670 nm (red light) and 415 nm with 600 nm laser (blue-red light). Below were the results:-[156, level I; 159, level I]

- Blue and blue-red light treatment showed significant moderate to large improvement when compared to controls. Blue-red light was significantly more effective than blue light alone in the short term, but by 12 weeks there was no difference between the two treatments.

- Red light treatment showed significant improvement but the study was not blinded.
- Green light had either no difference or a small to moderate improvement.
- Yellow light showed either no difference or a moderate improvement.

In a local study on mild to moderately severe acne receiving blue light twice a week for 10 sessions, reduction of comedones (50.2 %), papules (73.1%) and pustules (61.5%) was observed at five weeks. Inflammatory lesions responded better than comedones.[160, level III]

Side-effects included moderate pain during the procedure, itch, erythema and swelling which resolved within hours. Few patients had postinflammatory hyperpigmentation which resolved within three months.[156, level I; 159, level I]

- ***Photodynamic Therapy (PDT)***

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. Porphyrin photoexcitation occurs optimally within the Soret band (360 – 405 nm) with four smaller peaks between 500 nm and 635 nm.

A SR involving five RCTs, 12 clinical studies and two case reports showed that topical ALA or MAL at 2 - 4 week intervals for a total of two to four treatments produced greatest clinical effect. In all Fitzpatrick skin types, papulopustular acne responded better compared to non-inflammatory acne. However, patients with darker skin types had a higher risk of post- inflammatory hyperpigmentation.[161, level I]

In another SR by Hamilton FL *et al.*, the following findings were noted:[159, level I]

- PDT was superior to light therapy or placebo. However, the number of participants in each trial was small.
- No significant differences between red light with MAL or ALA were observed. More pronounced adverse effects (such as stinging, burning, erythema and oedema) were seen with ALA than with MAL except for pain scores.
- Comparison with three different light sources (600 - 850 nm IPL, 580 - 980 nm IPL and bipolar radiofrequency, and blue light) showed the best improvement in lesion count occurred with blue light but was not statistically significant.

Side effects of PDT include varying degree of erythema, oedema, blistering, acute acneiform eruptions and post inflammatory hyperpigmentation. These side effects are often severe enough for patient to discontinue treatment.[159, level I]

RECOMMENDATION

- Phototherapy and photodynamic therapy may be used as an alternative therapeutic options for patients who fail or unable to tolerate other standard acne therapies. **(Grade B)**

7.2.5 Complementary and Alternative Medicines (CAMs)

CAMs are commonly used to treat acne vulgaris. However, there is insufficient evidence on these therapies.

A SR listed a broad range of CAMs available for the management of acne. However, the primary papers in this review were generally of poor methodology with no strong evidence to show the efficacy of these therapies.[162, level I]

Five percent topical tea tree oil gel had been shown to be an effective treatment option for mild to moderate acne vulgaris in one RCT. Compared to the placebo, there was a greater reduction in mean total lesion count by 43.6% versus 12.0% after six weeks of treatment ($p<0.001$). Adverse effects of this treatment included pruritus, burning and scaling.[163, level I]

Ayurverdic formulations have also been used for the management of acne vulgaris with different efficacy. 'Sunder Vati' shows significant clinical improvement in the severity of both inflammatory and non inflammatory acne. However, the exact mechanism of action remains unknown.[164, level I] In addition, there were methodological flaws in this study in terms of randomisation.

There is insufficient evidence to recommend any specific CAMs for the treatment of acne.

8. QUALITY OF LIFE (QoL)

QoL refers to the patient's ability to enjoy a normal life. Acne vulgaris affects patients' perceptions of themselves which may limit goals, standards, and expectations in everyday activities.

A review on medication adherence among acne patients found that in general, patients with better QoL impact were more adherent to treatment. Study results among acne patients in community-based dermatologists found a similar pattern, where adherence was significantly positively correlated with QoL impact.

Patients with better QoL are more adherent to treatment.[165, level III] A local study in Sarawak showed a positive correlation between QoL and adherence to treatment (r=0.24, p=0.003).[166, level III] Another local study looking at acne prevalence among secondary school children in Muar, Johor, found considerable impact on QoL among study subjects.[3, level III]

QoL is important as it may affect treatment adherence and subsequent treatment outcomes.

a. Impairment of QoL

In a study conducted among university students in Hong Kong, the majority of acne sufferers (81.8%, 95% CI 78.1 to 85.6) indicated that their QoL was impaired by acne in terms of psychological and social consequences, and subjective assessment of acne severity.[167, level III]

Negative effects of acne on patient's QoL were found in their symptoms and feelings, daily activities, leisure, work and study, personal relationships and treatment. In addition, when compared to a non-acne group, acne patients had significantly higher scores on psychological issues such as obsession (p=0.01), sensitivity (p=0.001), depression (p=0.001), anxiety (p=0.01), paranoid ideation (p=0.02), and psychoticism (p=0.001).[168, level III]

The QoL of acne patients with psychological distress significantly affects activities of daily living (p=0.033), social activities (p=0.016), performance at work or at school (p=0.003), feelings (p=0.0002), and overall mental health (p=0.0001).[169, level III]

In a local study in Sarawak, more than two-thirds (66.5%) of acne patients from government clinics reported QoL impairment, with symptoms and feelings as the main domain affected.[170, level III]

In patients with mild to moderate acne, treatment improved QoL in domains of symptoms (p<0.01), emotions (p<0.01) and function (p<0.01), in addition to improvement in acne severity.[171, level III]

b. Predictive Factors of QoL

Identified factors predicting QoL impairment are:

i. Severity of acne

Studies found significant correlation between severity of acne and QoL impairment.[167 - 168, level III; 170 - 171, level III]

ii. Gender

Three studies identified that females in all categories of acne severity had significantly higher QoL impairment compared to males.[167, level III; 171 - 172, level III] This is contrary to the findings of a study by Abdel-Hafez *et al.* where males were more affected.[168, level III]

iii. Duration of acne

Significant positive correlation was found between the duration of acne and impairment of QoL.[168, level III; 172, level III]

iv. Age

Older patients have worse acne related QoL.[171 - 172, level III]

Various tools were used for QoL assessment in the above studies, out of which only three measured acne-specific QoL namely Skindex, Cardiff Acne Disability Index (CADI) and Acne Quality of Life (Acne-QoL). However, none of these tools have been validated locally.

RECOMMENDATION

- Quality of life assessment may be considered in the management of patients with acne. **(Grade C)**

9. REFERRAL

The urgency for referral is dependent upon various factors. It should follow accepted guidelines based on acuteness of severity and psychological impact. The urgency for referral is divided into the following categories:

Urgent : Within 24 hours
Seen Early : Within one to four weeks
Non-urgent : Based on available appointment date

a. Urgent referral (to a psychiatrist)

Major depression or any suicidal behaviour

b. Seen Early

i. Severe acne or nodulocystic acne that may need isotretinoin[173 - 178, level III]
ii. Severe social or psychological problems including a morbid fear of deformity (dysmorphophobia)[173, level III; 176, level III] and depression[174, level III; 175, level III]

c. Non-urgent

i. For diagnosis

- Suspected rosacea[176, level III]
- Suspected drug-induced acne[176, level III]
- Acne beginning or persisting outside the normal age range for the condition or late onset acne[176, level III]
- Suspected occupational causes[176, level III]
- Suspected underlying endocrinological cause (such as Polycystic Ovarian Syndrome) requiring further assessment[173 - 174, level III; 177, level III]

- Rare variants of acne such as acne excoriae, chloracne and acne fulminans[177, level III]
- Suspected Demodex folliculitis[177, level III]
- Pityrosporum folliculitis[177, level III]
- Gram negative folliculitis

ii. Specialist services

- Resistance or intolerance to current treatment[174, level III]
- Moderate or severe acne[174, level III; 176, level III]
- Possible scarring or failure to achieve adequate response[174, level III]
- Failed oral antibiotic therapy[177, level III; 179, level III]
- Pregnancy with moderate and severe acne[177, level III]
- Acne requiring surgery (such as incision and drainage of cysts)[178, level III]
- For specialised physical treatment

If patient exhibits suicidal behaviour, an urgent referral to psychiatry is warranted.

10. IMPLEMENTING THE GUIDELINES

To assist healthcare providers on appropriate management for acne, it is important to develop valid guidelines by a sound methodology and to ensure the implementation of evidence-based recommendations.

a. Facilitating and Limiting Factors

The facilitating factors in implementing these CPG are:-

i. Wide dissemination of these CPG to healthcare providers (hard copy & soft copy)
ii. Annual dermatology update course for primary care doctors

The limiting factors in the implementation are:-

i. Cost and availability of treatment
ii. Variation in treatment practice and preferences

b. Potential Resource Implications

In implementing recommendations in these CPG, the possible resource implications are:-

i. Expensive topical medications in the primary care setting
ii. Insufficient financial and human resource in conducting training

To enhance the utilisation of these CPG on Management of Acne, the following clinical audit indicators for quality management are proposed:-

Percentage of acne patients treated with topical antibiotic as monotherapy = $\frac{\text{Number of acne patients treated with antibiotic as monotherapy for 12 weeks}}{\text{Total number of acne patients receiving treatment in the same period}}$ x 100%

Percentage of acne patients referred to specialist = $\frac{\text{Number of acne patients referred to dermatologist/ plastic surgeon/psychiatrist}}{\text{Total number of acne patients receiving treatment in the same period}}$ x 100%

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Appendix 1

SEARCH TERMS

The following MeSH terms or free text terms were used either singly or in combination:

"acne vulgaris"[MeSH], acne, "nodulocystic acne", "epidemiology"[Mesh], pathophysiology, "risk factors"[MeSH], age, "sex"[Mesh], gender, genetics"[MeSH], "obesity"[MeSH], "body mass index"[MeSH], BMI, "hormones"[MeSH], "pituitary tumor", adrenal, "ovarian tumor", "polycystic ovarian syndrome", "smoking"[MeSH], stress, "cosmetics"[MeSH], "facial therapy", "diet"[MeSH], diary, "milk"[MeSH], chocolate, sugar, "glycemic index"[MeSH], "glycaemic index", "glycemic load", "glycaemic load", "clinical presentation", "diagnosis"[Mesh], "physical examination"[Mesh], "biopsy"[Mesh], "skin biopsy", "histology"[Mesh], "microbiology"[Mesh], "microbiological techniques"[Mesh], "microbiologic testing", "microbial sensitivity tests"[Mesh], "laboratory techniques and procedures"[Mesh], "folliculitis"[Mesh], "infective folliculitis", "clinical diagnosis", "clinical response", "treatment response", "drug resistance, microbial"[Mesh], "antibiotic resistance", "diagnostic criteria", grading, severity, "classification"[Mesh], "global assessment", "grading system", "Leeds grading system", "Leeds technique", "therapeutics"[Mesh], treatment, efficacy, response, "treatment failure"[Mesh], "administration, topical"[Mesh], gel, cream, lotion, "benzoyl peroxide"[MeSH], "retinoids"[Mesh], "tretinoin"[Mesh], adapalene, tazarotene, "isotretinoin"[MeSH], "clindamycin"[Mesh], "erythromycin"[Mesh], "salicylic acid"[Mesh], "sulfur"[Mesh], "sulfacetamide"[Mesh], "hydrocortisone"[Mesh], azelaic acid, "dapsone"[Mesh], "administration, oral"[Mesh], "anti-bacterial agents"[Mesh], antibiotics, "oral anitibiotics", "tetracycline"[Mesh], "oxytetracycline"[Mesh], "doxycycline"[Mesh], "erythromycin stearate", "zinc acetate"[Mesh], "azithromycin"[Mesh], "minocycline"[Mesh], "lymecycline"[Mesh], "fusidic acid"[Mesh], diane, "doxycycline"[Mesh], "trimethoprim-sulfamethoxazole combination"[Mesh], cotrimoxazole, bactrim, "oxytetracycline"[Mesh], "maintenance therapy", "remission induction"[Mesh], monotherapy, combination, "drug therapy, combination"[Mesh], "contraceptives, oral"[Mesh], "combined oral contraceptives", "spironolactone"[Mesh], "flutamide"[Mesh], "finasteride"[Mesh], "cimetidine"[Mesh], "oral isotretinoin", "13-cis retinoic acid", "injections, intralesional"[Mesh], corticosteroid, "intralesional corticosteroid", "photochemotherapy"[Mesh], "photodynamic therapy", "laser therapy"[Mesh], "chemical peel", "trichloroacetic acid"[Mesh], "glycolic acid", "alfa-hydroxyacid", "beta-hydroxyacid", "fatty acids, omega-3"[MeSH], fibre, "herbal therapy", "traditional therapy", "phytotherapy"[MeSH], "quality of life"[Mesh], "referral and consultation"[Mesh], referral, "physician referral"

Appendix 2

CLINICAL QUESTIONS

1. What are the epidemiological characteristics of acne?
2. What is the pathophysiology of acne?
3. What are the risk factors for acne?
4. What are the aggravating factors for acne?
5. What is the role of diet in acne?
6. What is the role of supplements in acne?
7. What is the resistance pattern to oral antibiotics?
8. How is acne severity graded?
9. Is maintenance therapy after induction of remission effective in the treatment of acne?
10. Is combination therapy, compared to monotherapy, more effective in maintenance phase of acne treatment?
11. Is topical benzoyl peroxide effective in the treatment of acne?
12. Is topical retinoid effective in the treatment of acne?
13. Is topical antibiotic effective in the treatment of acne?
14. Is topical salicylic acid effective in the treatment of acne?
15. Is topical sulphur effective in the treatment of acne?
16. Is topical azelaic acid effective in the treatment of acne?
17. Is fixed combination preparation compared to monotherapy more effective in acne treatment?
18. Is oral antibiotic effective in the treatment of acne?
19. Is oral hormonal therapy effective in the treatment of acne?
20. Is oral isotretinoin effective in the treatment of acne?
21. Is intralesional corticosteroid injection effective in the treatment of acne?
22. Is photodynamic therapy or laser therapy effective in the treatment of acne?

23. Is chemical peel effective in the treatment of acne?
24. Is comedone extraction effective in the treatment of acne?
25. Is alternative therapy or complement therapy (herbal, traditional or complementary) effective in the treatment of acne?
26. How does acne affect the quality of life?
27. When should acne patient be referred to a dermatologist or plastic surgeon?

FOOD LIST ACCORDING TO GLYCAEMIC INDEX (GI) CLASSIFICATION

Classification of GL

Low : ≤10
Moderate : 11 - 19
High : ≥20

Categories of GI (based on glucose as the reference)

Low : <55
Medium : 55 - 70
High : >70

Foods/ Drinks	Low GI		Medium GI		High GI	
	Example	GI	Example	GI	Example	GI
Rice	Rice, parboiled	48	Brown rice, boiled Basmati, white, boiled	68 58	White rice, boiled Glutinous rice, white	73 98
Bread	Whole grain bread Chapatti	51 52	Pita bread	57	Whole meal bread White bread Sardine sandwich	74 75 73
Breakfast cereals	Oat bran, raw	50	Instant porridge, oats	66	Cornflakes Cocoa-flavoured puffed rice	81 77
Pasta and noodles	Spaghetti, whole meal, boiled	37	Rice noodles, dried, boiled	61	Fried meehoon Fried macaroni	99 74
Tubers	Yam	51	Sweet potato, boiled Potato, French fries	63 63	Potato, boiled	78

Foods/ Drinks	Low GI		Medium GI		High GI	
	Example	GI	Example	GI	Example	GI
Legumes	Kidney beans Lentils Soya beans	24 32 16				
Vegetables	Carrots, boiled Broccoli Cauliflower	39 15 15			Pumpkin	75
Fruits	Apple, raw Orange, raw Banana, raw	38 43 51	Pineapple, raw	59	Watermelon, raw	76
Dairy products and alternatives	Milk, full fat Milk, skim Ice cream, low fat Yogurt Low-fat yogurt, fruit, sugar. Soy milk	27 32 50 36 33 32	Ice cream	61		
Snack products	Chocolate	40	Popcorn Soft drink/soda Potato crisps	65 59 56		
Sugars	Fructose	19	Sucrose Honey	68 61	Glucose *Teh tarik*	99 78

Source:

1. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr. 2002 Jul;76(1):5-56
2. Nik Shanita S. Development and determination of glycaemic index and types of carbohydrate in endurance athletes' food choices. Final Report UKM N14/2000 grant. Universiti Kebangsaan Malaysia, Kuala Lumpur, 2006 (unpublished document)

CLINICAL CHARACTERISTICS OF ACNE PATIENTS IN STUDIES ON ANTIBIOTIC RESISTANCE

No.	Authors / year of publication / country	No. of studies / study subjects*	Study period	Prior antibiotic usage	Characteristic of patients (including type of severity)	Overall resistance rate of P. Acne
1.	Cooper AJ, 1998, UK and USA[40, level III]	SR of 12 studies	Primary papers published between January 1976 & January 1997	Not mentioned	3,049 respondents (selected four key studies)	20% in 1978 - 62% in 1996
2.	Coates P *et al.*, 2002, UK[41, level III]	4,274 patients	Data collected between 1991 & 2000	All received prior antibiotic therapy	2,173 males, age: 6 months to 86 years old 2,101 females, age: 1 to 77 years old	Ranges from 31.5 - 64% in 10 years period
3.	Zandi S *et al.*, 2011, Iran[42, level III]	100 patients	March - December 2008	Not mentioned	36 males & 64 females, >14 years old, moderate to very severe acne	Overall resistance to at least one antibiotic: 31%
4.	Dumont-Wallon G *et al.*, 2010, France[43, level III]	273 patients	Not mentioned	Numbers undetermined	39% males & 61% females, ≥12 years old, moderate acne (no nodules, <40 comedones & at least 25 papules &/or pustules)	• Erythromycin = 75% • Tetracycline = 9.5% • Resistance to doxycycline (in those resistance to tetracycline) = 100%
5.	Oprica C *et al.*, 2004, Sweden[44, level III]	130 patients	March 1999 - May 2000	100 patients (on oral antibiotic last 2 - 6 months)	Age: 12 - 45 years old, moderate to severe inflammatory acne	39% among treated group, only 3% in untreated group OR=3.8 (95% CI 2.1 to 6.7)

No.	Authors / year of publication / country	No. of studies / study subjects*	Study period	Prior antibiotic usage	Characteristic of patients (including type of severity)	Overall resistance rate of P. Acne
6.	Bettoli V *et al.*, 2006, Italy[45, level III]	1,206 patients	April 2000 - June 2004	Not mentioned	Age: 12 - 42 years old	(mean prevalence of resistance) • Erythromycin = 49.8% • Clindamycin = 40.9% • Tetracycline = 1.8% • Minocycline = 0.6%
7.	Ross JI *et al.*, 2003, UK, Italy, Sweden, Hungary, Greece, Spain[46, level III]	644 patients	October 1999 -February 2001	Numbers undetermined	Age: ≥12 years old	50.8 - 93.6% (lowest in Hungary & highest in Spain)
8.	Kurokawa I *et al.*, 1999, Japan[47, level III]	50 patients	November 1994 - August 1995	17 patients	19 males & 31 females, Age: 11 - 34 years old Had acne for 1 week to 15 years	• 2 (4%) strains resistant to erythromycin • 2 (4%) strains resistant to clindamycin • 1 (2%) strain each to doxycycline & tetracycline
9.	Tang JJ, 2010, Malaysia[48, level III]	100 patients	January - June 2010	Not mentioned	≥12 years old	15.1% of positive isolates

*All attended dermatology clinic

RESISTANCE RATES OF SYSTEMIC ANTIBIOTICS USED

No.	Authors / year of publication / country	Erythromycin	Clindamycin	Tetracycline	Doxycycline	Minocycline	Others
1.	Cooper AJ, 1998, UK, USA[40, level III]	20.0 - 72.5% Cross-resistance		34.2 - 35.6% Cross-resistance		<1%	Trimethoprim (17.5%)
2.	Coates P *et al.*, 2002, UK[41, level III]	57.6%**	50.0%**	NA	NA	NA	NA
3.	Zandi S *et al.*, 2011, Iran[42, level III]	12.1%	10.3%	0%	0%	NA	• Co-trimoxazole (24.1%) • Azithromycin (0%)
4.	Dumont-Wallon G *et al.*, 2010, France[43, level III]	75.1%	NA	9.5% Cross-resistance		NA	NA
5.	Oprica C *et al.*, 2004, Sweden[44, level III]	19.9%	27.4%	NA	NA	NA	Co-trimoxazole (0%)
6.	Bettoli V *et al.*, 2006, Italy[45, level III]	mean - 49.8%	mean - 40.9%	NA	NA	mean - 0.6%	NA
7.	Ross JI *et al.*, 2003, UK, Italy, Sweden, Hungary, Greek, Spain[46, level III]	47 - 92%***	43 - 95%***	NA	NA	NA	NA
8.	Kurokawa I *et al.*, 1999, Japan[47, level III]	4.0%	4.0%	2.0%	2.0%	0%	NA
9.	Tang JJ, 2010, Malaysia[48, level III]	7.5%	15.1%	5.7%	5.7%	0%	NA

NA = Not available

**highest prevalence in 10 years duration

***approximate percentage from the figures in the study

SUGGESTED MEDICATION DOSAGES AND SIDE EFFECTS

Drug	Recommended Dosage	Common Adverse Effects	Contraindications	Special Precautions
Topical benzoyl peroxide	Apply once to twice daily	Contact dermatitis, dryness, skin discolouration, skin rash, peeling, transient local oedema	Hypersensitivity to benzoyl peroxide	Avoid contact with eyes, eyelids, lips and mucous membranes. May bleach fabrics or hair.
Topical tretinoin	Apply once in the evening before retiring	Initial exacerbation of symptoms, skin irritation, stinging, oedema, blistering, crusting of skin, erythema, scaling, photosensitivity, temporary hypo/hyperpigmentation	Hypersensitivity to tretinoin, pregnancy, lactation, eczema, sunburn conditions	Avoid concomitant use of topical keratolytic agents. Avoid exposure to sunlight or ultraviolet (UV) light. Avoid contact with eyes, mouth, angles of nose, mucous membranes and open wounds. Avoid facial scrub. Avoid use of topical preparations with high concentration of alcohol, menthol, spices or lime.
Topical adapalene	Apply once daily to affected areas after washing in the evening before retiring	Mild skin irritation, scaling, erythema, dryness, stinging, burning, pruritus	Hypersensitivity to adapalene	Avoid contact with eyes, lips, angles of nose and mucous membranes. Avoid cuts, abrasions, eczematous skin or sunburned skin. Minimise exposure to sunlight.

Drug	Recommended Dosage	Common Adverse Effects	Contraindications	Special Precautions
Topical tazarotene*	Apply once in the evening before retiring	Pruritus, burning, stinging, erythema, skin peeling, irritation, rash, dryness, localised oedema, desquamation, contact dermatitis, discolouration of skin, photosensitivity	Hypersensitivity, pregnancy, lactation, eczema, sunburn conditions	Avoid contact with eyes, mouth and mucous membranes. Avoid exposure to sun or UV light. Women of child bearing potential should take birth control measures. Negative pregnancy test to be obtained within 2 weeks prior to initiation and start therapy during normal menstrual period.
Topical isotretinoin	Apply once daily in the evening before retiring	Stinging, burning, slight irritation, erythema, peeling	Pregnancy, lactation, personal or family history of cutaneous epithelioma	Avoid lips, mouth, eyes, mucous membranes, angles of nose, broken, eczematous and sunburned skin. Avoid exposure to sunlight.
Topical clindamycin	Apply twice daily	Irritation, dryness, stinging, erythema, contact dermatitis	Hypersensitivity to clindamycin or lincomycin, ulcerative colitis, antibiotic-related colitis	Alcohol base solution may cause burning and irritation of the eyes especially in atopic individuals.
Topical erythromycin	Apply twice daily	Dryness, erythema, burning, pruritus	Hypersensitivity to erythromycin	Avoid contact with eyes and other mucous membranes.
Topical salicylic acid	Apply once to thrice daily	Irritation, sensitivity, excessive dryness	Hypersensitivity to salicylic acid	Avoid prolonged use in high concentrations and over large areas of the body. Avoid broken skin, mouth, eyes and mucous membranes.

Drug	Recommended Dosage	Common Adverse Effects	Contraindications	Special Precautions
Topical sulfur and its combinations	Apply once to twice daily. Initiate with once daily, then increase gradually.	Skin irritation, dermatitis	Hypersensitivity to sulfur, children less than 2 years old	Avoid contact with eyes, mouth and other mucous membranes. May stain the skin black and emit foul smell when applied concomitantly with mercurial compounds.
Topical azelaic acid	Apply twice daily	Skin irritation, mostly burning or itching, occasionally erythema and scaling	Hypersensitivity to propylene glycol	Avoid broken skin, mouth, eyes and mucous membranes.
Topical dapsone*	Apply twice daily	Dryness, erythema, oiliness and peeling	Hypersensitivity to dapsone, pregnancy and lactation	G6PD deficiency, methaemoglobinaemia, Hemoglobin M.
Oral tetracycline	500 mg - 1 g daily in 2 divided doses	Gastrointestinal disturbances, discolouration of teeth and nails, photosensitivity, visual disturbances	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. Absorption is impaired by food, milk, dairy products, iron salts and antacids.
Oral doxycycline	50 - 100 mg once to twice daily	Gastrointestinal disturbances, photosensitivity, hypersensitivity, permanent staining of teeth, rash	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.

Drug	Recommended Dosage	Common Adverse Effects	Contraindications	Special Precautions
Oral erythromycin	Erythromycin Ethyl Succinate (EES): 400 - 800 mg twice daily Erythromycin Stearate: 250 - 500 mg twice daily	Gastrointestinal disturbances, rash, urticaria, headache, dizziness	Hypersensitivity to erythromycin	Hepatic and renal impairment, prolonged QT interval, concomitant therapy with colchicine (toxicity) and lovastatin (rhabdomyolysis)
Oral azithromycin	500 mg thrice weekly[112, 113, 122, 123]	Neutropenia, hearing impairment, vertigo, gastrointestinal disturbances, abnormal liver function, rash, angioedema	Hypersensitivity to azithromycin or other macrolides, hepatic dysfunction, jaundice	Severe renal and hepatic disease, myasthenia gravis, prolonged QT interval and cardiac repolarisation
Oral minocycline	50 - 100 mg once to twice daily	Gastrointestinal disturbances, vestibular disturbances, abnormal hyperpigmentation, photosensitivity, teeth discolouration in children *Potentially serious adverse reactions - autoimmune hepatitis, drug-induced lupus erythematosus	Hypersensitivity to minocycline and other tetracyclines, children ≤8 years old, pregnancy, lactation	Hepatic and renal impairment, concomitant use of isotretinoin
Oral co-trimoxazole	1 tablet daily (trimethoprim 80 mg and sulfamethoxazole 400 mg)[124]	Gastrointestinal disturbances, skin rashes, hepatitis, dizziness, headache, erythema multiforme *Uncommon but serious adverse reaction - Stevens-Johnson syndrome, toxic epidermal necrolysis	Hypersensitivity to sulfonamides or trimethoprim, severe renal and hepatic impairment, megaloblastic anaemia due to folate deficiency, pregnancy, lactation	Haematological disorders, elderly, G6PD deficiency, folate deficiency

Drug	Recommended Dosage	Common Adverse Effects	Contraindications	Special Precautions
Oral trimethoprim	100 mg thrice daily[125]	Gastrointestinal disturbances, pruritus, rash, dizziness, headache, erythema multiforme *Uncommon but serious adverse reaction - Stevens-Johnson syndrome, toxic epidermal necrolysis	Hypersensitivity to trimethoprim, megaloblastic anaemia due to folate deficiency	Hepatic and renal impairment, folate deficiency
Oral isotretinoin	0.5 - 1 mg/kg/day	Dryness of skin or mucosa, exanthema, pruritus, facial erythema/dermatitis, hair thinning, photosensitivity, muscle and joint pain, headache, dyslipidaemia	Hypersensitivity to isotretinoin or any of its components, pregnancy due to teratogenicity, lactation, hypervitaminosis A, excessively elevated blood lipid values	History of depression or other psychiatric disorders, increased intracranial pressure and seizures. Avoid blood donation during treatment and within 1 month after treatment cessation.
Oral cyproterone acetate 2 mg, ethinyl estradiol 35 mcg	1 tablet daily for 21 days, followed by 7 days of tablet-free period	Gastrointestinal disturbances, headache, depression, breast tenderness, weight changes	Hypersensitivity to ethinyl estradiol and cyproterone acetate or any of its excipients, history of severe liver impairment, genital tract or breast carcinoma, pregnancy and lactation, presence of thromboembolic events	Risk of venous thromboembolism, hypertriglyceridaemia, acute or chronic disturbances of liver function

Drug	Recommended Dosage	Common Adverse Effects	Contraindications	Special Precautions
Oral chlormadinone acetate*	1 - 2 mg/day	Gastrointestinal and menstrual disturbances, weight changes, fluid retention, allergic skin rashes, urticaria, depression, breast tenderness	Hypersensitivity to chlormadinone, history of severe liver impairment, genital tract or breast carcinoma, arterial disease, undiagnosed vaginal bleeding and porphyria, pregnancy and lactation	History of cardiovascular or renal impairment, diabetes mellitus, asthma, epilepsy, migraine, depression
Oral levonorgestrel + ethinyl estradiol	1 tablet daily for 21 days, followed by 7 days of tablet-free period	Gastrointestinal and menstrual disturbances, headache, dizziness, breast tenderness, weight changes, fluid retention, depression	Hypersensitivity to ethinyl estradiol and levonorgestrel or any of its excipients, history of severe liver impairment, genital tract or breast carcinoma, arterial disease, undiagnosed vaginal bleeding and porphyria, pregnancy and lactation, presence of thromboembolic events	Past ectopic pregnancy, functional ovarian cysts, history of cardiovascular or renal impairment, diabetes mellitus, depression

Drug	Recommended Dosage	Common Adverse Effects	Contraindications	Special Precautions
Oral desogestrel + ethinyl estradiol	1 tablet daily for 21 days, followed by 7 days of tablet free period	Menstrual disturbances, breast tenderness, pain, nausea, vomiting, headache, migraine, depression, fluid retention, weight changes	Hypersensitivity to ethinylestradiol and desogestrel or any of its excipients, suspected oestrogen dependent neoplasms, pregnancy and lactation, presence of thromboembolic events	May increase risk of breast cancer, glucose intolerance and thromboembolism Familial defects of lipoprotein metabolism Cardiovascular or renal impairment
Oral flutamide	250 mg daily[128]	Breast tenderness, hot flushes, decreased libido, impotence, diarrhoea, nausea, vomiting	Hypersensitivity to flutamide, hepatic impairment, pregnancy and lactation	Monitor liver function test

*These medications are currently not available in Malaysia

Sources:

1. MIMS Malaysia (internet communication, 28 June 2011 at http://www.mims.com/)
2. Thomson Reuters. Micromedex®1.0 (Healthcare Series). Greenwood Village Thomson Reuters; 2011
3. Product Package Insert

Disclaimer:

- The outline of drug dosage and administration is intended as a general guide to therapy.
- The adverse effects listed are not exhaustive.
- Caution is advised when prescribing for patients with other medical problems or on multiple drugs.

LIST OF ABBREVIATIONS

AA	Azelaic acid
ABP	Adapalene/BPO
ALA	5-aminolaevulinic acid
BPO	Benzoyl peroxide
CAMs	Complementary and alternative medicines
CASS	Comprehensive acne severity scale
CBP	Clindamycin/BPO
CI	Confidence interval
CMA	Chlormadinone acetate
COC	Combined oral contraceptive
CPA	Cyproterone acetate
CPG(s)	Clinical Practice Guidelines
DG	Development group
DHEAS	Dehydroepiandrosterone sulfate
DHT	Dihydrotestosterone
EBP	Erythromycin/BPO
g	Gram
G6PD	Glucose-6-phosphate dehydrogenase
GI	Glycaemic index
GL	Glycaemic load
HTA	Health Technology Assessment
IPL	Intense pulsed light
IL	Interleukin
kg	Kilogram
KTP	Potassium titanyl phosphate
MAL	Methyl aminolaevulinate
mg	miligram
MOH	Ministry of Health
OR	Odds ratio
P. acnes	*Propionibacterium acnes*
PDL	Pulsed dye laser
PDT	Photodynamic therapy
PPARs	Peroxisome proliferator-activated receptors
QoL	Quality of life
RC	Review Committee
RCT(s)	Randomised controlled trial(s)
SA	Salicylic acid
SR	Systematic review
UV	Ultraviolet
vs	Versus

ACKNOWLEDGEMENT

The members of development group of these guidelines would like to express their gratitude and appreciation to the following for their contributions:

- Panel of external reviewers who reviewed the draft
- Ms Sin Lian Thye (Nursing Matron) and Ms Loong Ah Moi (Nursing Sister)
- Technical Advisory Committee for CPG for their valuable input and feedback
- All those who have contributed directly or indirectly to the development of the CPG

DISCLOSURE STATEMENT

The panel members of both Development Group and Review Committee had completed disclosure forms. None held shares in pharmaceutical firms or acts as consultants to such firms. (Details are available upon request from the CPG Secretariat)

SOURCES OF FUNDING

The development of the CPG on Management of Acne was supported financially in its entirety by the Ministry of Health.