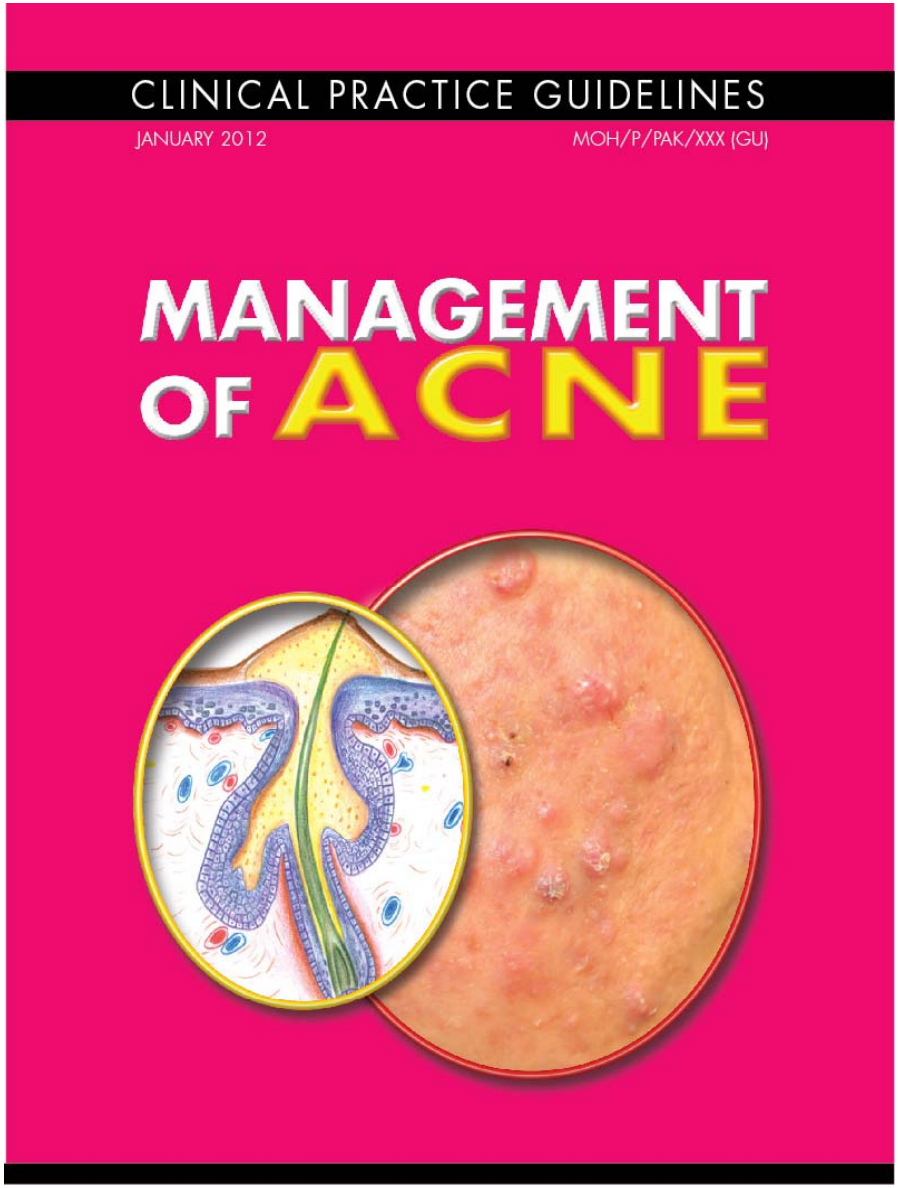

INTRODUCTION, EPIDEMIOLOGY & PATHOPHYSIOLOGY

Clinical Practice Guidelines
Management of Acne
Development Group

Ministry of Health Malaysia

Dermatological Society of Malaysia

Academy of Medicine of Malaysia

Development Group

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INTRODUCTION

- Acne - common problem among adolescents & young adults
- A medical disease - medical treatment by healthcare providers
- May have profound psychological & emotional impact if untreated
  - Embarrassment
  - Complications

Each individual perceives acne differently at various stages of life.

RATIONALE FOR CPG

Acne:

- A wide spectrum of clinical severity
- Different types of treatment modalities
- Healthcare providers may have minimal exposure to dermatology in medical schools
- A wide variation in prescribing patterns

There is a necessity to assess acne & its treatment options in a more objective manner (evidence-based)

DEVELOPMENT OF CPG

OBJECTIVES

To assist clinicians & other healthcare providers in making evidence-based decisions about the appropriate management & treatment of acne:

- pathophysiology
- risk & aggravating factors
- clinical diagnostic criteria & severity grading
- psychosocial impact & quality of life
- appropriate treatment
- indications for referral to dermatologists/plastic surgeons

TARGET GROUP/USER

These guidelines are applicable to any healthcare providers:

- Medical Officers
- General Practitioners (GPs)
- Family Medicine Specialists
- Specialists of other disciplines
- Pharmacists
- Dietitians
- Nutritionists
- Paramedics
- Dermatologists
- Policy makers

TARGET POPULATION

Inclusion criteria

Adolescents & adults presenting with acne ranging from

- mild, moderate to severe

Exclusion criteria

- Acne variants: acne conglobata, acne fulminans, acne cosmetic, drug-induced acne & chloracne
- Acne scar
- Post inflammatory hyperpigmentation
- Rosacea
- Folliculitis

LEVEL 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 RECOMMENDATIONS

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 SIGN

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

EPIDEMIOLOGY

A wide variation in the prevalence of acne among various countries.

Country	Prevalence	Age group
Taiwan	17.3 %	6 – 11 yrs
Hong Kong	9.8 %	6 - 12.5 yrs & 12.5 - 21 yrs
Malaysia (2 small district secondary schools)	67.5 %	13 – 18 yrs
China	10.5 %	10 - 14 yrs
	38 %	15 - 19 yrs
	36 %	20 - 24 yrs
	31 %	> 25 yrs
Portugal	82.1 %	10 – 12 yrs
United Kingdom	54 % in women	>25 yrs
	40 % in men	>25 yrs

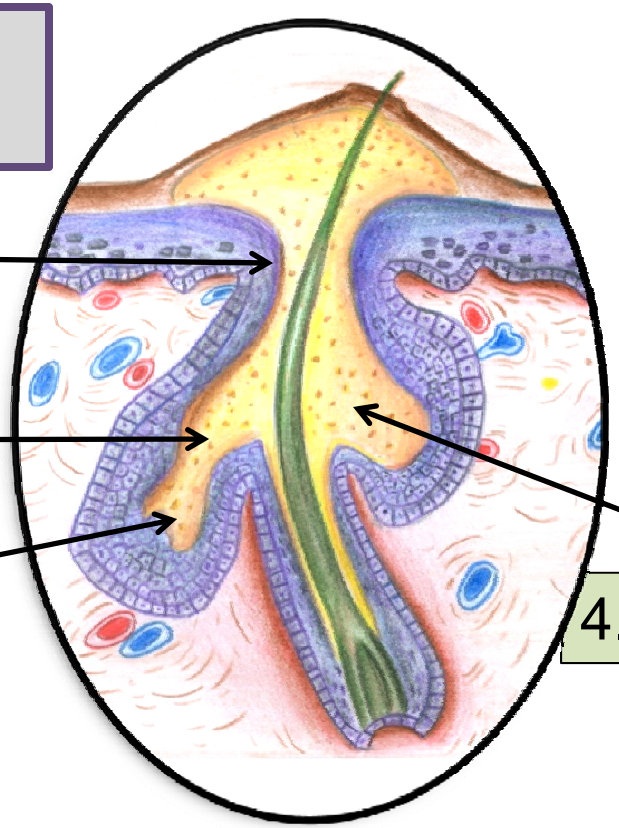
EPIDEMIOLOGY

- Peak age: 12.5 to 18 years old
- Comedones earliest presentation - 7 years old
- Papulopustules earliest presentation - 10 - 11 years old
- Tends to be more severe in males
- No difference in the prevalence of acne between gender & acne severity in different ethnic a & age groups
- Most common affected site – face, followed by trunk

PATHOPYHSIOLOGY-1

- The pathogenesis of acne is multifactorial.
- Acne vulgaris can be divided into:
  i) non-inflammatory (open & closed comedones) lesions
  ii) inflammatory (papules, pustules & nodules) lesions.

The most important factors involved are 1 - 4.



3. Altered follicular keratinisation

2. Propionibacterium acnes proliferation

1. Increased sebum production

4. Inflammation

PATHOPYHSIOLOGY-2

a) Increased Sebum Production

i) Androgen Mediated Sebum Production

ii) Peroxisome Proliferative-Activated Receptors (PPARs)

- Sebum production is increased
  - overstimulation of the gland by androgens at high levels or
  - hypersensitivity to androgens at normal levels
- There is also possibility of increased androgen production within the pilosebaceous follicle
  - The pilosebaceous unit possesses the steroid metabolising enzymes that convert DHEAS to testosterone & DHT

PATHOPYHSIOLOGY-3

a) Increased Sebum Production

i) Androgen Mediated Sebum Production

ii) Peroxisome Proliferative-Activated Receptors (PPARs)

- Sebaceous lipids - partly regulated by PPARs & sterol response element binding proteins.

- PPARs act in concert with retinoid X receptors to regulate epidermal growth & differentiation, & lipid metabolism

PATHOPYHSIOLOGY-4

b) Propionibacterium (P) acnes Proliferation

- *Propionibacterium acnes* - main organism & a normal anaerobic resident of pilosebaceous unit - colonises acne prone areas of the skin (in sebaceous hair follicle)
- *P. acnes* releases:
  - enzymes: proteinases, lipases & hyaluronidases ⟶ break down sebum ⟶ free fatty acids & peptides
  - chemotactic factors - integral in the inflammatory cascade - induce monocytes to secrete proinflammatory cytokines: TNF-α, interleukin (IL)-1β & IL-8
- The inflammatory response to the bacterium & these metabolic by products leads to formation of papules, pustules & nodules

PATHOPYHSIOLOGY-5

c) Altered Follicular Keratinisation

- The rate of keratinocyte desquamation at the follicular infundibulum is altered
- The accumulation of cells & sebum results in the formation of microcomedones, the microscopic precursor to all acne lesions
- Presence of 5α-reductase activity in the infrainfundibular segments of sebaceous follicles ⟶ increases androgen production & subsequent follicular hyperkeratosis

PATHOPYHSIOLOGY-6

d) Inflammation

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

TAKE HOME MESSAGE

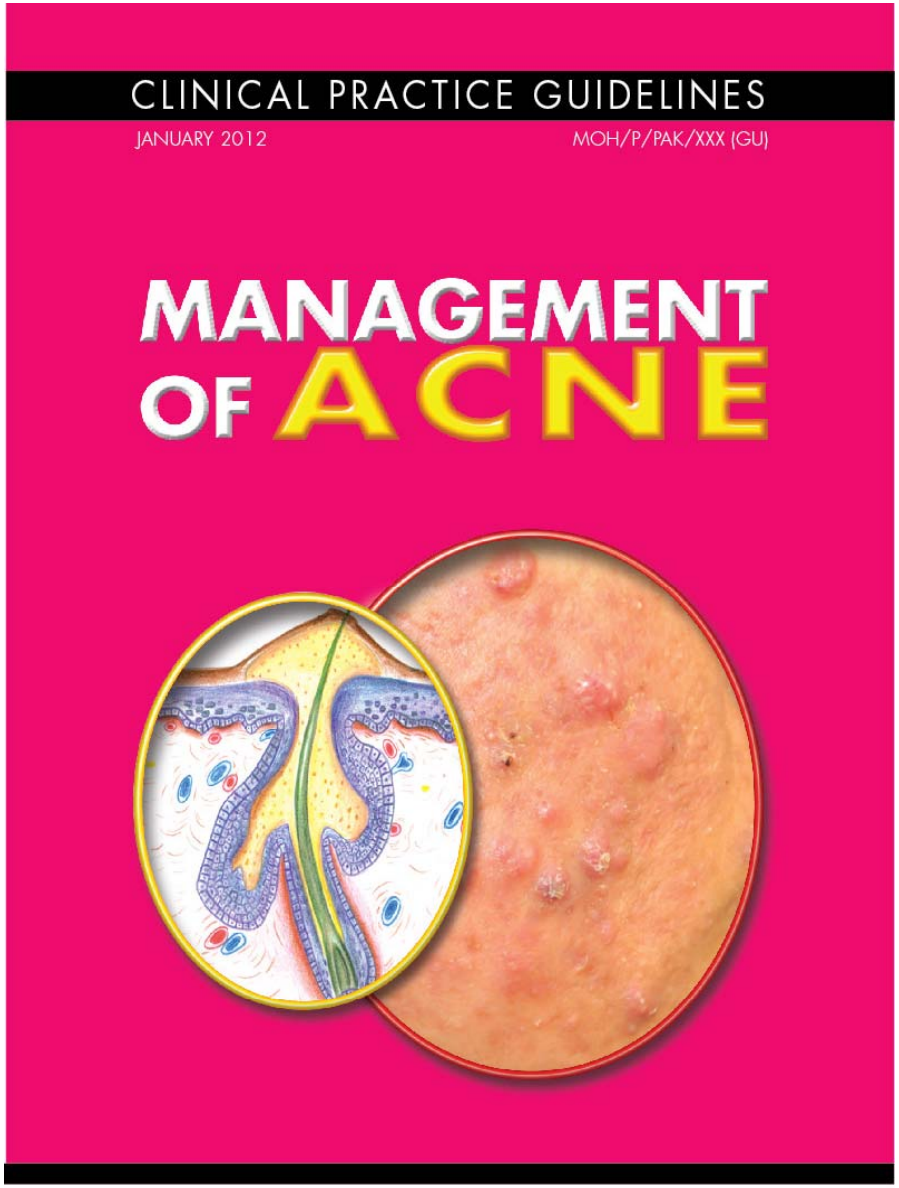
- A medical disease: common among adolescents & young adults
- Untreated: profound psychological & emotional impact
- Acne prevalence can be quite high in Malaysia

The most important factors in the pathogenesis of acne are:

- Increased sebum production
- *Propionibacterium acnes* proliferation
- Altered follicular keratinisation
- Inflammation

With this information, the choice of treatment is better understood

THANK YOU



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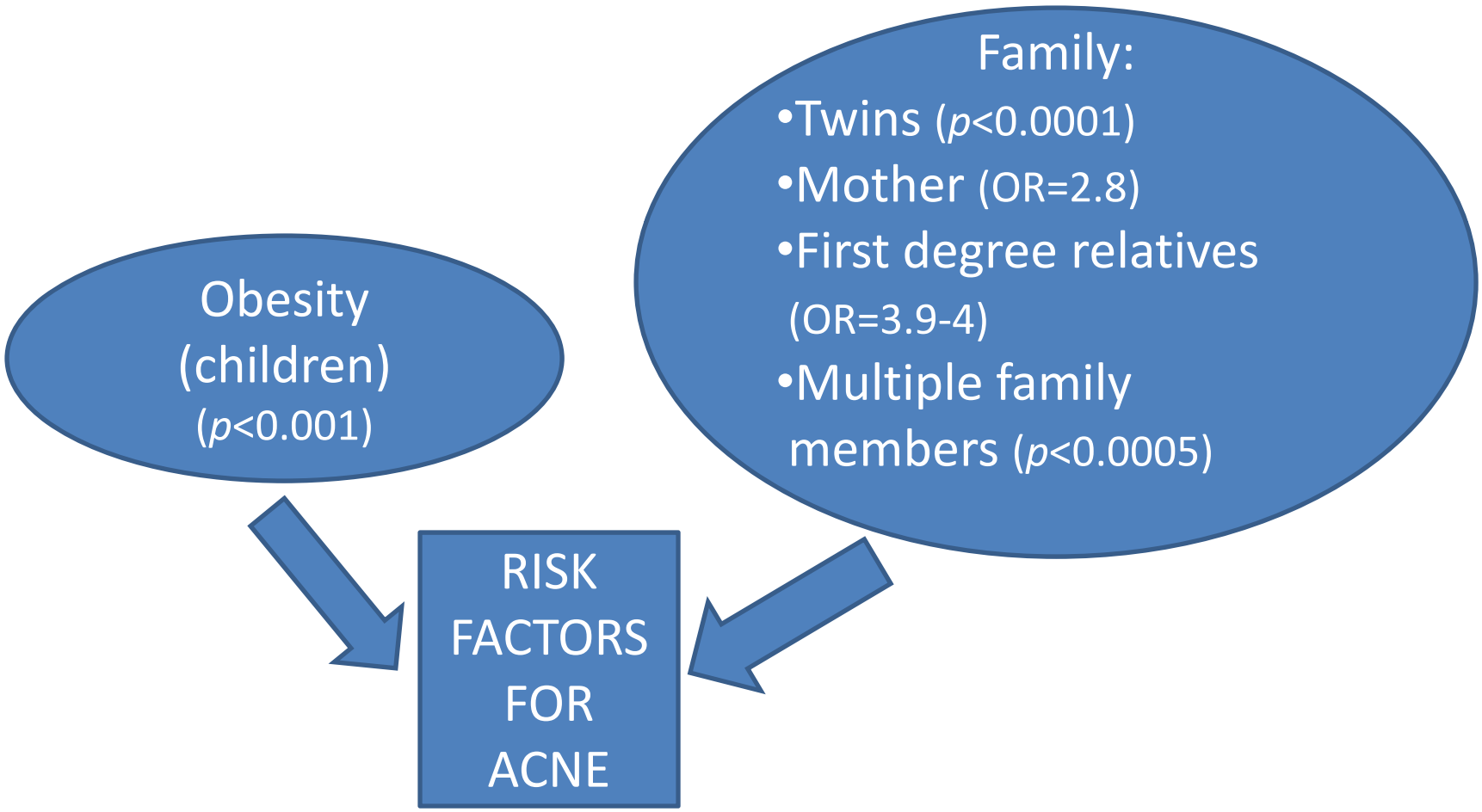
RISK, AGGRAVATING FACTORS , ROLE OF DIET & SUPPLEMENTS

Clinical Practice Guidelines Management of Acne Development Group

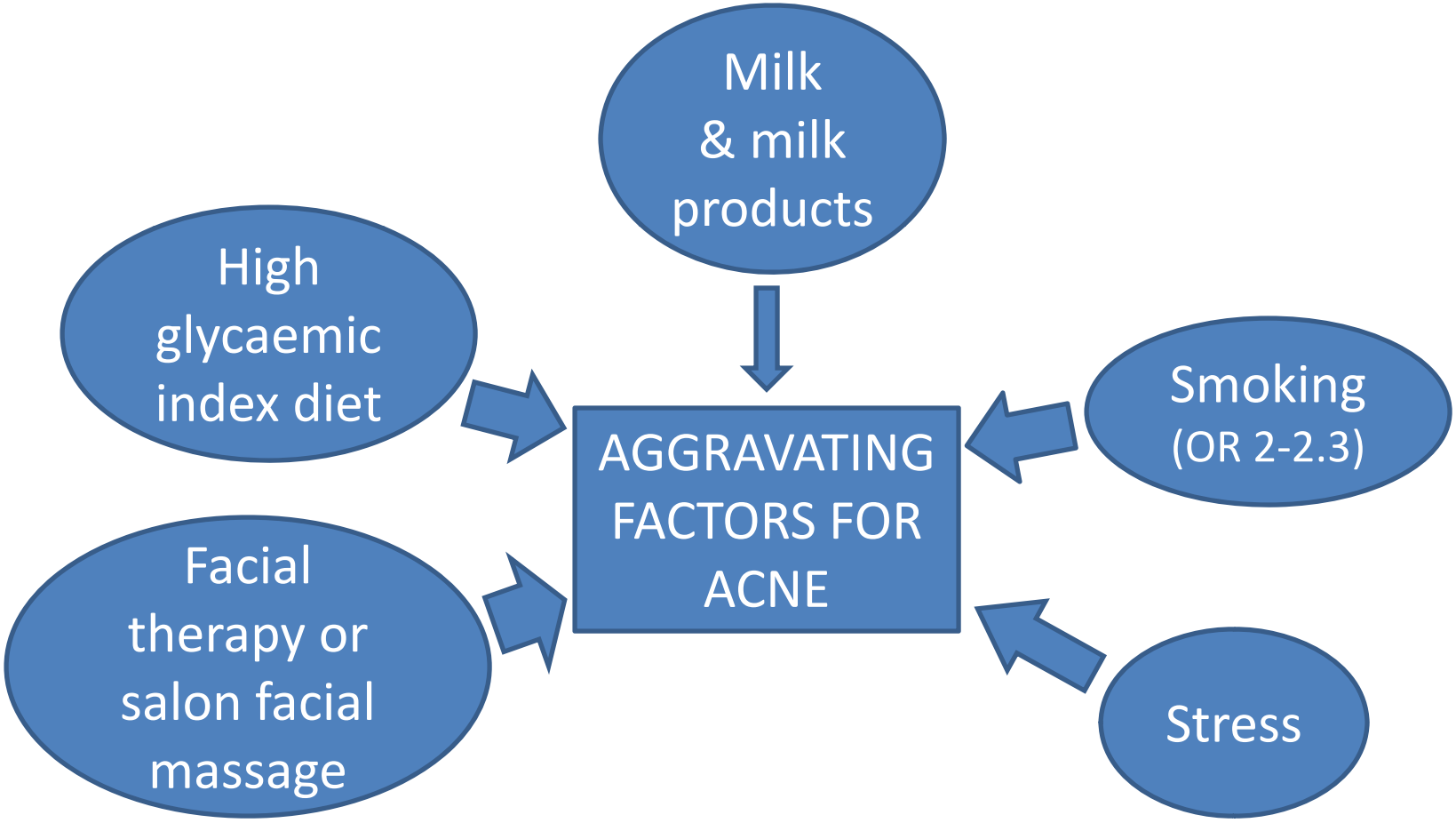
LEARNING OBJECTIVES

- To understand the risk factors for developing acne
- To know the aggravating factors of acne
- To understand the role of diet in acne
- To understand the role of supplements in acne
- To understand the Quality of Life (QoL) of patients with acne

RISK FACTORS



AGGRAVATING FACTORS



Glycaemic Index

- The GI is a numerical system used to classify carbohydrate food based on the impact they produces on the postprandial blood glucose level.

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 Jasmine rice, white, Glutinous rice, white	73 109 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 (Quaker Oats Co)	50	Instant porridge, Quick Oats (Quaker Oats Co)	66	Cornflakes Coco Pops, cocoa-flavoured puffed rice (Kellogg's)	81 77
Pasta and noodles	Spaghetti, whole meal, boiled	37	Rice noodles, dried, boiled	61	Fried *meehoon* Fried macaroni	99 74

SUPPLEMENTS

- No conclusive evidence that zinc supplement is beneficial in acne.

- No evidence of benefit for:
  - Vitamin A
  - Vitamin C
  - Vitamin E
  - omega-3 fatty acids

QUALITY OF LIFE (QoL)

- Acne impairs QoL
- It affects:
  - daily living (p=0.033)
  - social activities (p=0.016)
  - work & school performances (p=0.003)
- Resulting in psychological problems:
  - obsession (p=0.01)
  - sensitivity (p=0.001)
  - depression (p=0.001)
  - anxiety (p=0.01)
  - paranoid ideation (p=0.02)
  - psychoticism (p=0.001)

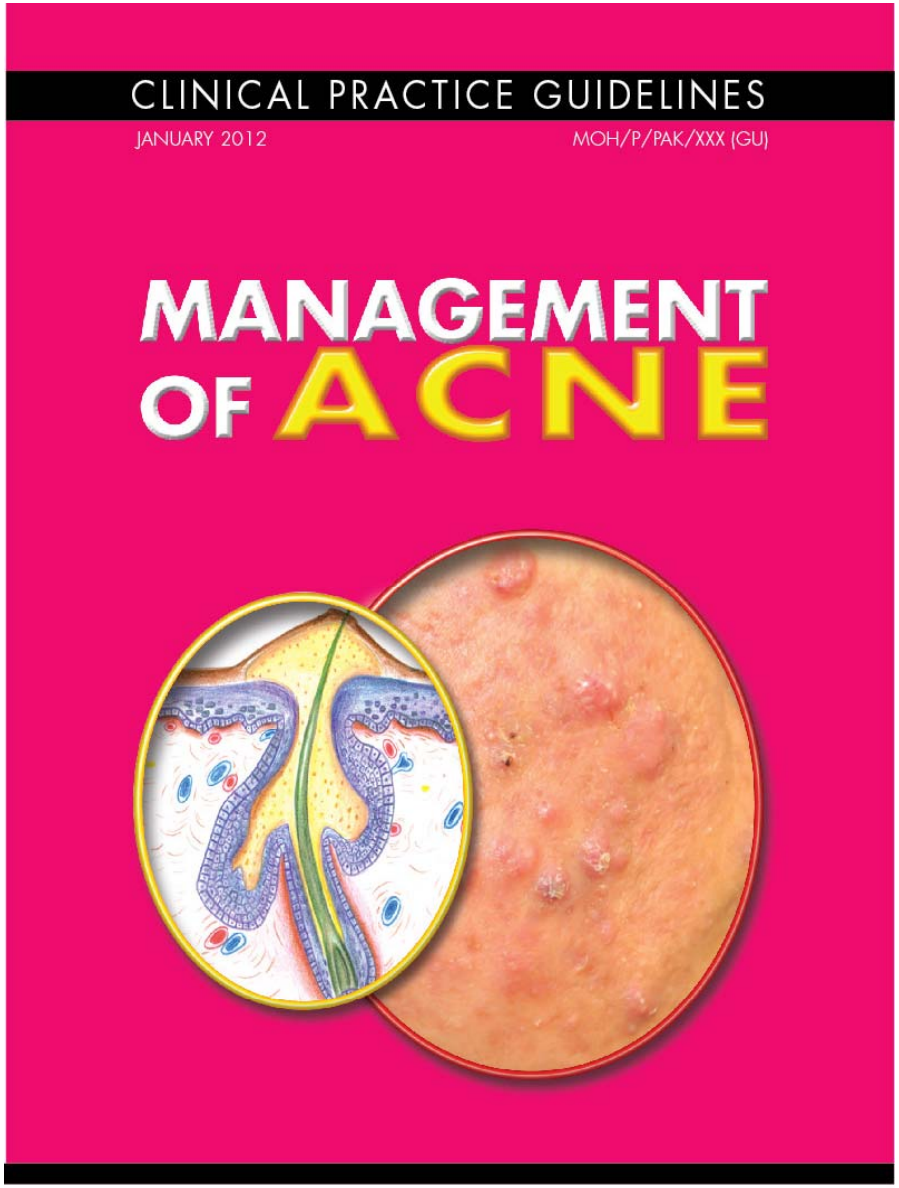
PREDICTIVE FACTORS OF QoL

- Impairment of QoL is associated with:
  - severity of acne
  - duration of acne
  - female gender
  - older age

TAKE HOME MESSAGES

- Familial predisposition & obesity is a risk for developing acne
- Acne is worsened by:
  - smoking
  - facial or beauty salon treatment
  - high glycaemic diet
  - milk & milk products
  - Stress
- Acne impairs QoL
- QoL assessment may be considered in the management of patients with acne

THANK YOU



CLINICAL ASSESSMENT (Algorithm & Grading of Severity)

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LEARNING OBJECTIVES

- To be aware of various techniques available for the assessment of acne severity
- To be familial with the algorithm used for the assessment of acne severity

GRADING OF ACNE SEVERITY-1

- Grading of acne severity can be done by using:

  1. *Grading scale*
  2. *Lesion counting*
  3. *Photographic method*

GRADING OF ACNE SEVERITY-2

- **Leeds technique grading scale**
  - accurate
  - reproducible
  - rapid
  - suitable to be used in clinic
- **Counting technique**
  - more suitable for clinical trials
- **Photographs**
  - may be obtained to establish accurate & achievable records of subjects
  - but difficult to detect small & noninflammed lesions

COMPARISON AMONG ACNE SEVERITY GRADING TECHNIQUES

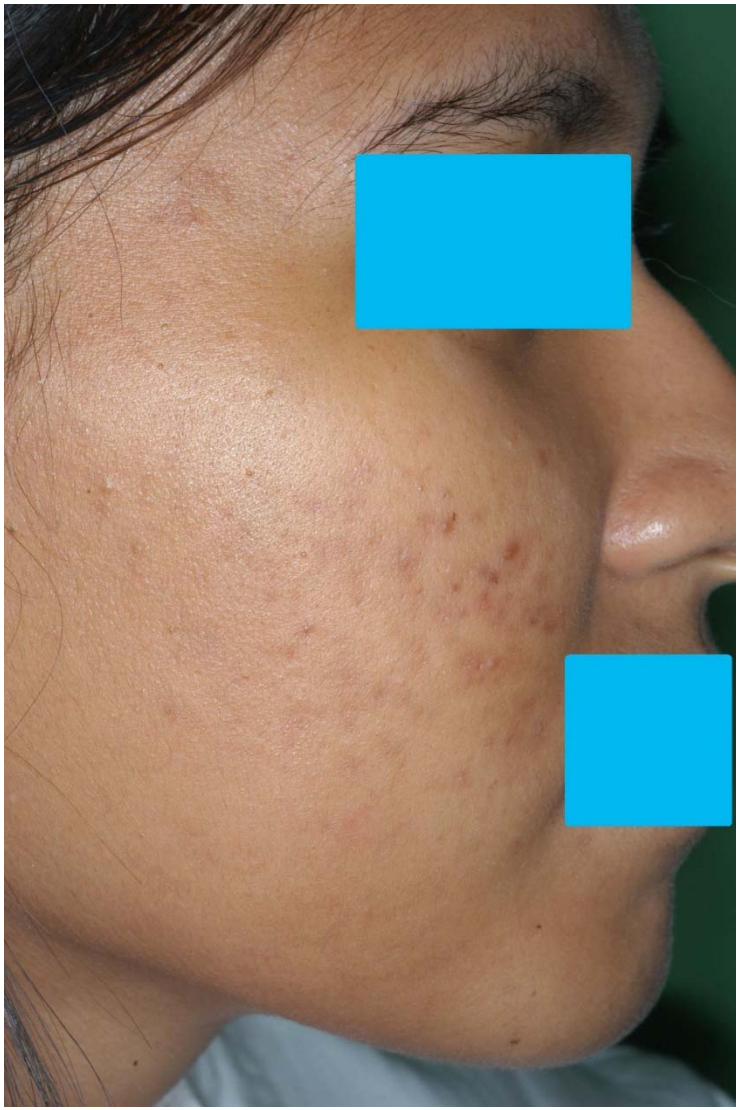
Grading Technique	Type of Assessment	Reproducibility	Inter-rater Reliability	Intra-rater Reliability
Leed's Technique	Grading scale & lesion counting	Yes	Yes	Yes
Investigator Global Assessment	Grading scale & lesion counting	Yes	Yes	Not available
Cook Acne Severity Grading Scale	Grading scale & photographic method	Yes	Yes	Not available
Comprehensive Acne Severity Scale	Grading scale & lesion counting	Yes	Yes	Yes

COMPREHENSIVE ACNE SEVERITY SCALE (CASS)

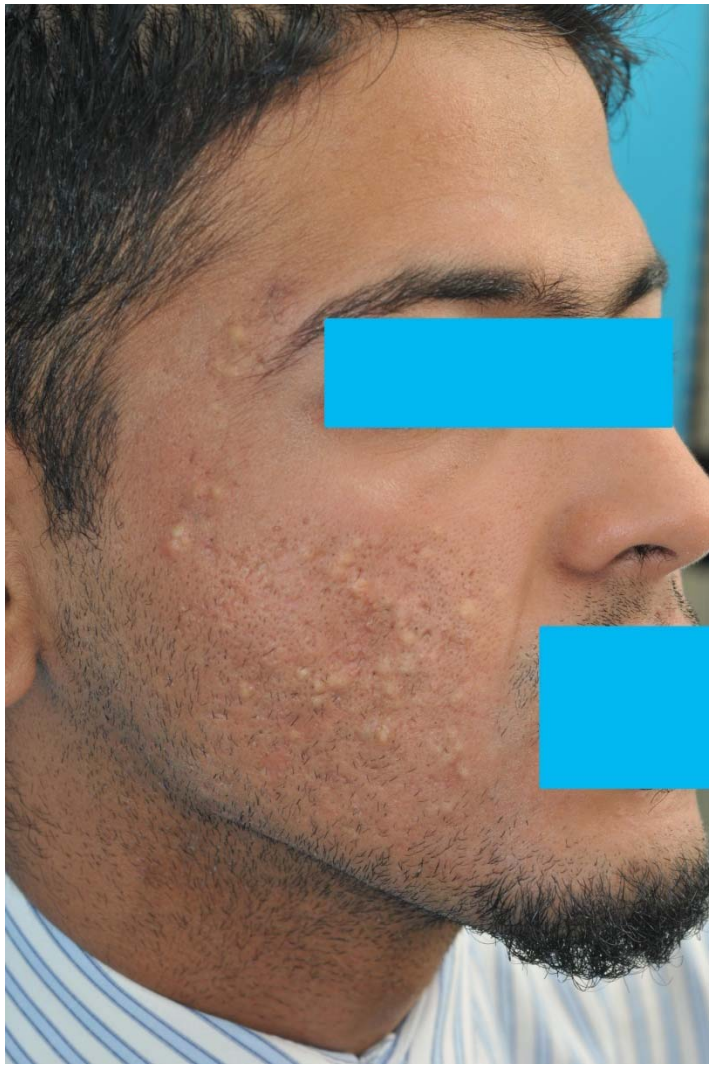
- Modification of Investigator Global Assessment (IGA) of Acne Severity
- Recommended in this CPG: simpler to use in clinical practice

GRADE*		DESCRIPTION
Clear	0	No lesions to barely noticeable ones. Very few scattered comedones & papules.
Almost clear	1	Hardly visible from 2.5 m away. A few scattered comedones, few small papules & very few pustules.
Mild	2	Easily recognisable; less than half of the affected area is involved. Many comedones, papules & pustules.
Moderate	3	More than half of the affected area is involved. Numerous comedones, papules & pustules.
Severe	4	Entire area is involved. Covered with comedones, numerous pustules & papules, a few nodules & cyst.
Very severe	5	Highly inflammatory acne covering the affected area, with nodules and cyst present.

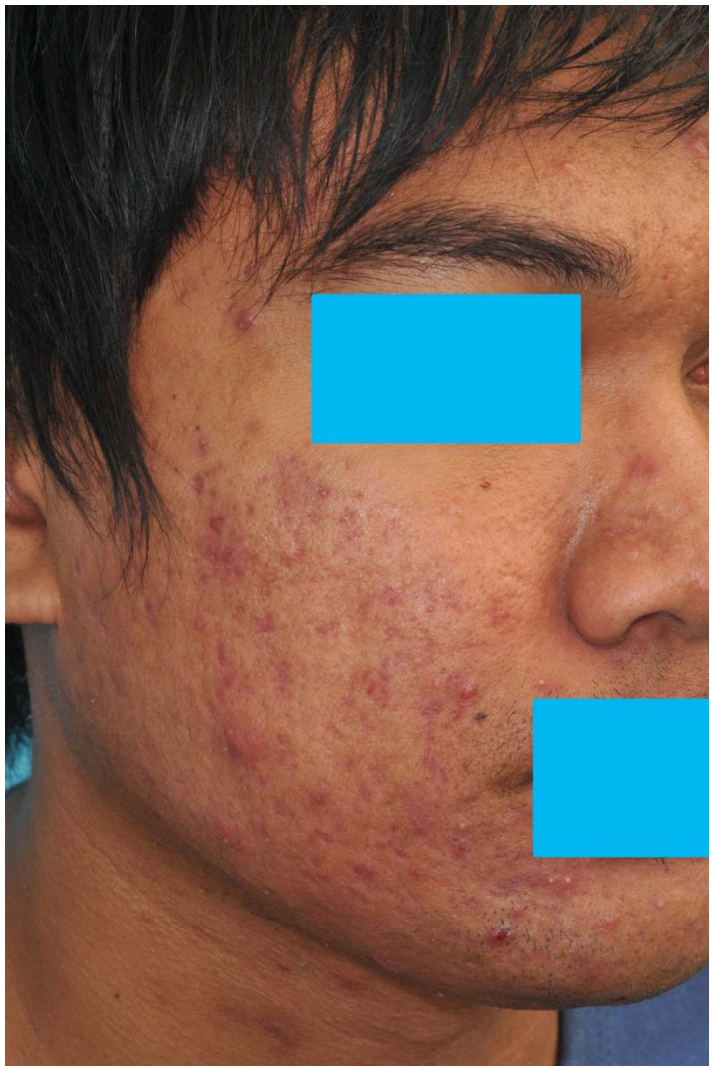
MILD ACNE



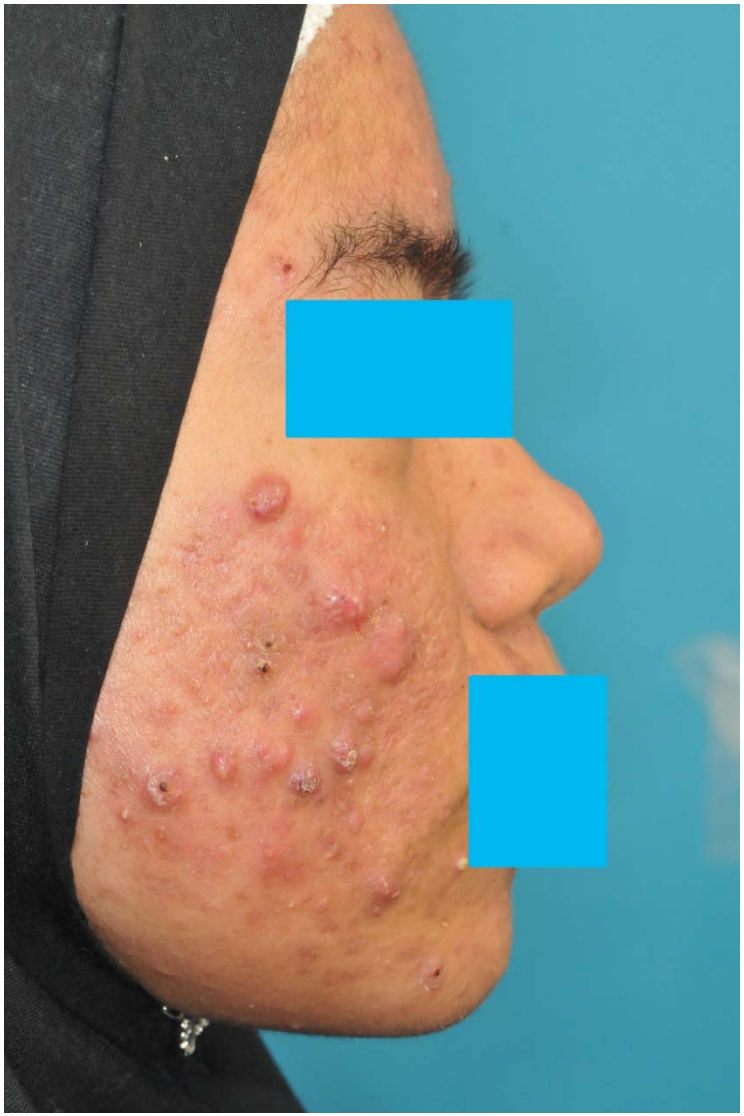
MODERATE ACNE
PREDOMINANTLY COMEDONES



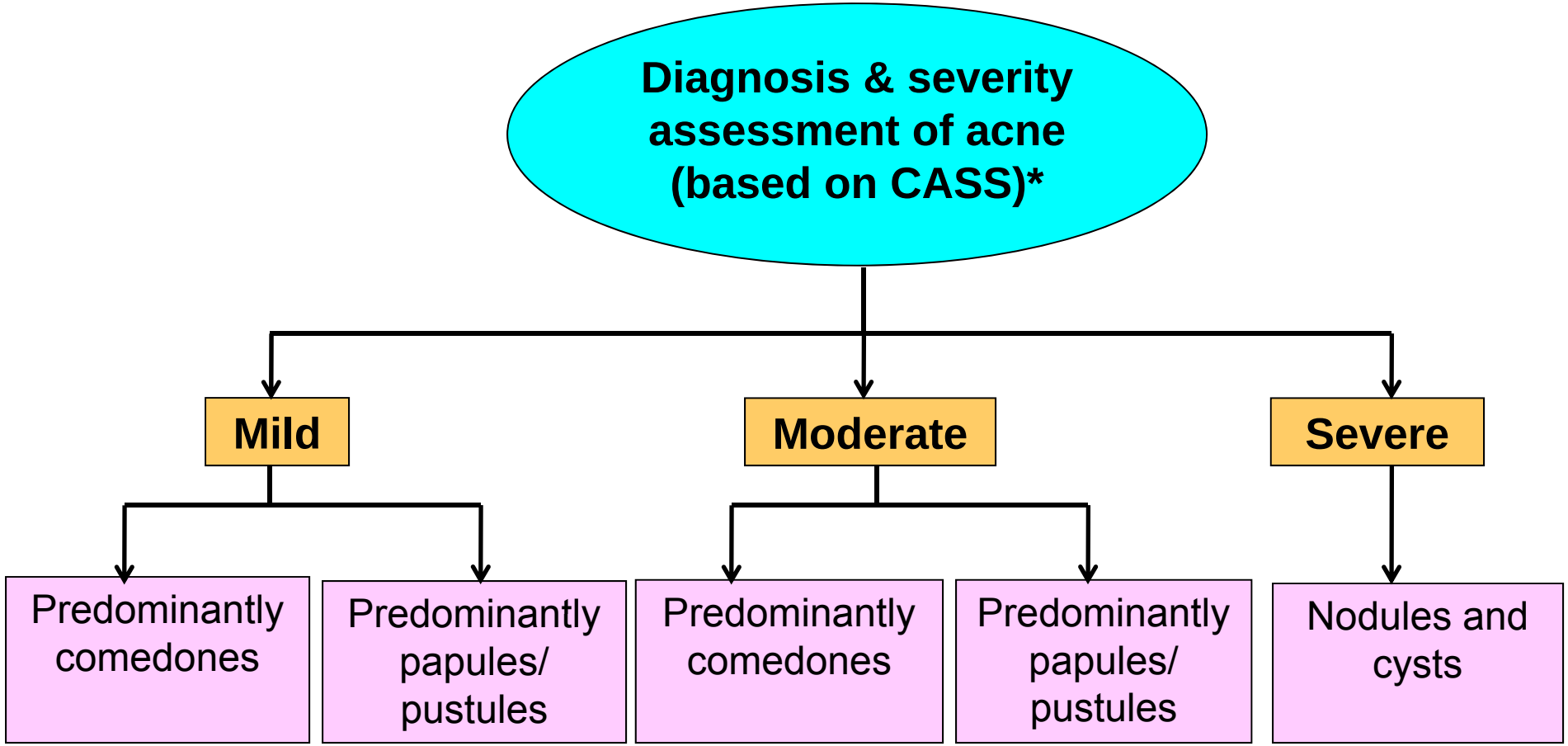
MODERATE ACNE PREDOMINANTLY PAPULES-PUSTULES



SEVERE ACNE



CLASSIFICATION OF ACNE SEVERITY

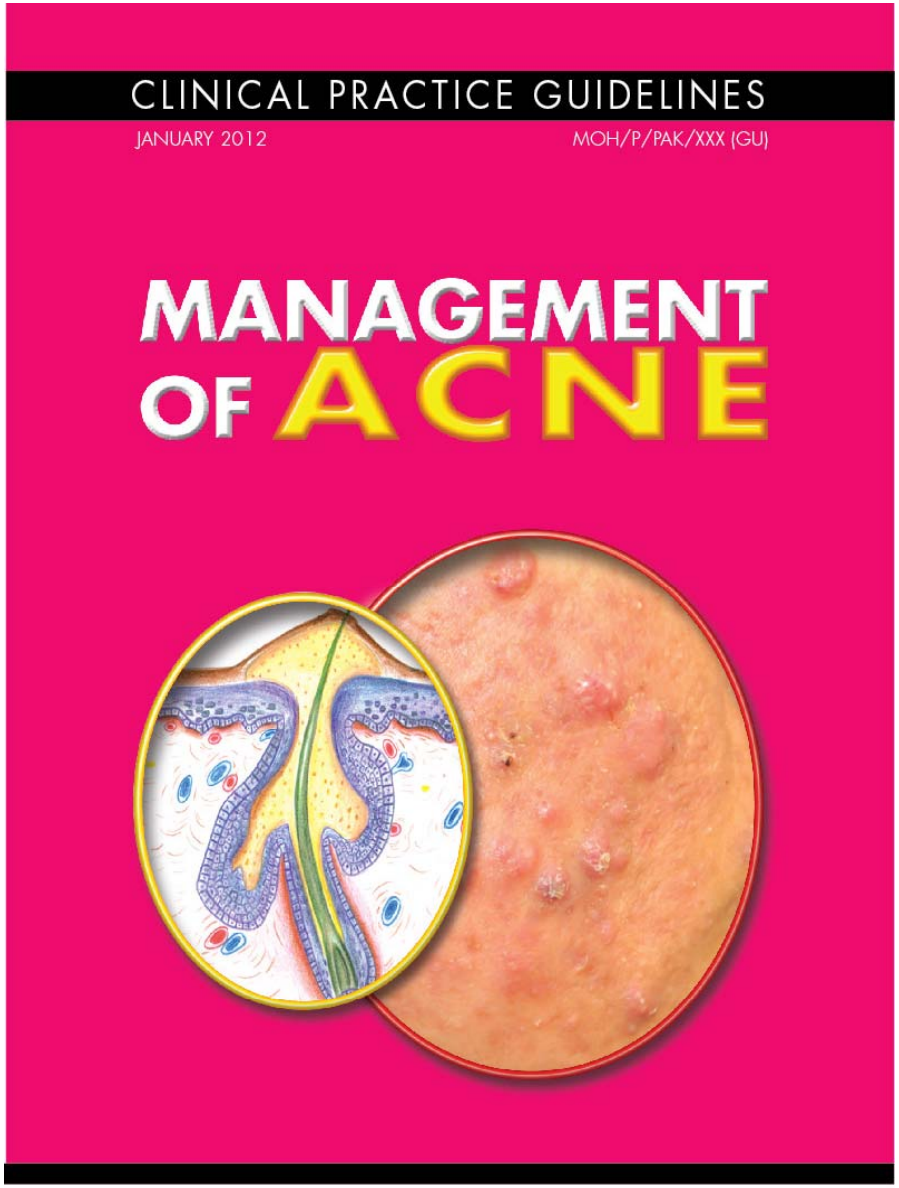


- Severity assessment is based on CASS (mild 1- 2, moderate 3, severe 4 - 5)
- Quality of life should be taken into consideration.

TAKE HOME MESSAGE

- Acne should be graded according to severity
- Comprehensive Acne Severity Scale (CASS) grading is recommended in this CPG

THANK YOU



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TOPICAL THERAPY

Clinical Practice Guidelines
Management of Acne
Development Group

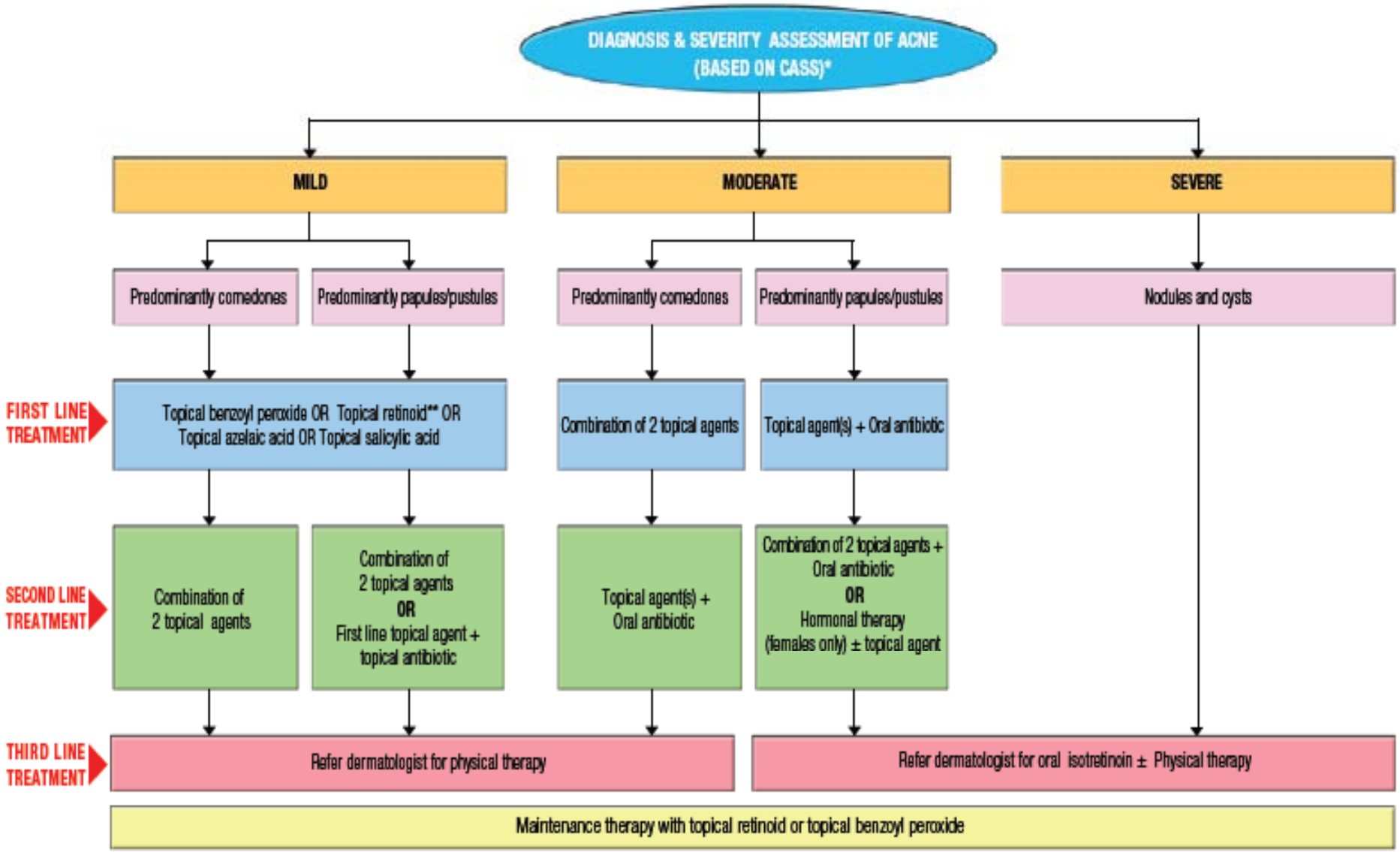
LEARNING OBJECTIVES

- To be able to select appropriate topical therapy to treat mild & moderate acne
- To know the strengths & preparations of the topical therapy
- To know the expected treatment response
- To know the common adverse effects of the topical therapy

INTRODUCTION

- 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 both induction of remission & maintenance phases.

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.

COMMONLY USED TOPICAL AGENTS

- Topical benzoyl peroxide (BPO)
- Topical retinoids
- Topical antibiotics

TOPICAL BENZOYL PEROXIDE-1

- An organic peroxide agent which functions as an effective bactericidal, keratolytic & anti-inflammatory agent
- Its use has not been associated with the development of bacterial resistance
- Available as 2.5%, 5% & 10% gel or cream

TOPICAL BENZOYL PEROXIDE-2

- Effective in reducing both inflammatory & non-inflammatory lesions
- Efficacy: (8 to 12 weeks)
  - inflammatory lesions 42% - 58%
  - non-inflammatory lesions 30% - 58%
- BPO in various concentrations (2.5%, 5% & 10%) & in various vehicles (alcohol, water, acetone, gel or lotion) are equally effective

TOPICAL BENZOYL PEROXIDE-3

- Adverse effects are usually mild & transient
  - Erythema, dryness, peeling, stinging/burning & itching
- Frequency of adverse effects is higher for BPO 10% compared to BPO 2.5% & 5%

TOPICAL RETINOIDS-1

- Synthetic derivatives of vitamin A (retinol)
- Bind to retinoic acid receptors
- Anti-comedogenic, comedolytic & anti-inflammatory properties
- Effective for both inflammatory & non-inflammatory lesions

TOPICAL RETINOIDS-2

- Types of topical retinoids:
  - Topical tretinoin
  - Topical adapalene
  - Topical isotretinoin
  - Topical tazarotene

TOPICAL TRETINOIN-1

- Topical tretinoin (retinoic acid) was the first topical retinoid used in the treatment of acne

- Efficacy: (8 to 12 weeks)
  - Inflammatory lesions 42% - 72%
  - Non-inflammatory lesions 33% - 70%

TOPICAL TRETINOIN-2

- Available in various concentrations (0.01%, 0.025%, 0.05% & 0.1%) & formulations
- Evidence that higher concentrations confer better efficacy is controversial

TOPICAL TRETINOIN-3

- Topical tretinoin is as effective as topical adapalene, BPO & azelaic acid in reducing both inflammatory & non-inflammatory lesions
- Tretinoin gel 0.025% is less well tolerated than adapalene gel 0.1%, with higher occurrence of burning & erythema

TOPICAL TRETINOIN-4

- Adverse effects are usually mild & transient
  - Erythema, dryness, peeling, stinging/burning & itching
- Incidence of moderate to severe local adverse effects ranges from 6.5% to 38%
- Tretinoin microsphere gel (both 0.04% & 0.1%) are better tolerated than tretinoin 0.1% cream

TOPICAL ADAPALENE-1

- Naphtoic acid derivative
- A receptor-selective retinoid analogue
- Efficacy: (3 to 12 weeks)
  - Inflammatory lesions 47% - 75%
  - Non-inflammatory lesions 50% - 74%
- 0.3% gel is superior to 0.1% in reduction of inflammatory lesions

TOPICAL ADAPALENE-2

- As effective as topical BPO, tretinoin, isotretinoin & tazarotene in reducing both inflammatory & non-inflammatory lesions
- However, BPO 4% gel has an earlier onset of action compared to topical adapalene 0.1% gel

TOPICAL ADAPALENE-3

- Most adverse effects are mild
  - Erythema, dryness, peeling, stinging/burning & itching
- Better tolerated compared with topical tretinoin, isotretinoin & tazarotene
- Adapalene microsphere formulation is better tolerated than conventional gel formulation

TOPICAL ISOTRETINOIN-1

- Non receptor-selective synthetic retinoid
- Available as 0.05% cream or gel & 0.1% cream
- Efficacy: (12 weeks)
  - Inflammatory lesions 57% - 77%
  - Non-inflammatory lesions 68% - 78%
- Isotretinoin of 0.05% & 0.1% are equally effective

TOPICAL ISOTRETINOIN-2

- As effective as topical tretinoin & adapalene in treating both non-inflammatory & inflammatory acne lesions
- When compared to topical BPO, it is equally effective for non-inflammatory lesions but less effective for inflammatory lesions

TOPICAL ISOTRETINOIN-3

- Adverse effects are generally mild
  - Erythema, scaling, burning & pruritus
  - Incidence is similar to topical BPO & tretinoin but significantly higher than topical adapalene ($p<0.05$)

TOPICAL TAZAROTENE-1

- Receptor-selective retinoid
- Available as gel or cream in 0.05% or 0.1%
- Efficacy: (4 to 12 weeks)
  - Inflammatory lesions 37% - 70%
  - Non-inflammatory lesions 37% - 75%

TOPICAL TAZAROTENE-2

- As effective as topical adapalene & tretinoin in reducing inflammatory & non-inflammatory lesions
- Tazarotene 0.1% cream is more effective than adapalene 0.3% gel in reducing total lesion counts & decreasing post-inflammatory hyperpigmentation, while having comparable tolerability

TOPICAL TAZAROTENE-3

- Adverse effects are generally mild
  - Erythema, dryness, peeling, burning & pruritus
- No significant difference in incidence of adverse effects between tazarotene 0.1% cream & adapalene 0.1% cream

TOPICAL ANTIBIOTICS-1

- Useful for mild to moderate inflammatory acne
- Effective & relatively well tolerated
- The use of these agents alone can be associated with bacterial resistance
- Inhibit the colonisation of pilosebaceous glands by *Propionibacterium acnes*
- Limited anti-comedogenic effect

TOPICAL ANTIBIOTICS-2

- Topical clindamycin
- Topical erythromycin

TOPICAL CLINDAMYCIN-1

- Effective in reducing both inflammatory & non-inflammatory lesions
- Efficacy: (12 weeks)
  - Inflammatory lesions 54.9%
  - Non-inflammatory lesions 26.4%
- Available as clindamycin 1% lotion
- As effective as topical erythromycin

TOPICAL CLINDAMYCIN-2

- Various combination (fixed & non-fixed) preparations of clindamycin with either BPO, tretinoin or adapalene show superiority over clindamycin alone
- No difference in efficacy between daily versus twice daily application
- Efficacy similar whether the vehicle used is a gel, lotion or solution

TOPICAL CLINDAMYCIN-3

- Adverse effects are mild & transient
  - Erythema, peeling, dryness, scaling, stinging, burning & itching

TOPICAL ERYTHROMYCIN-1

- Effective in reducing both inflammatory & non-inflammatory lesions
- Efficacy: (6 to 12 weeks)
  - Inflammatory lesions 42% - 74%
  - Non-inflammatory lesions 25% - 74%
- Available as 2% lotion or 3% cream or gel

TOPICAL ERYTHROMYCIN-2

- Less effective for non-inflammatory lesions compared with topical retinoic acid 0.05% & BPO 10%

- Addition of zinc in topical erythromycin (topical zineryt) is more efficacious compared to erythromycin alone in reducing papules & pustules

TOPICAL ERYTHROMYCIN-3

- Adverse effects are localised, mild & transient
  - dry skin, itching, burning, erythema, scaling & dermatitis

TOPICAL AZELAIC ACID-1

- A naturally occurring dicarboxylic acid
- Has comedolytic, antimicrobial & anti-inflammatory properties
- Available as 20% cream
- Causes reduction in total lesion count by 60.6% & Acne Severity Index by 65.2% in six weeks
- Effective in reducing both non-inflammatory & inflammatory lesions

TOPICAL AZELAIC ACID-2

- As effective as topical BPO & adapalene in reducing both non-inflammatory & inflammatory acne lesions
- Reduces sebum production by an average reduction of 13.9% on the forehead & 14.2% on the cheek
- Its therapeutic activity, however, does not depend on its capacity in sebum reduction

TOPICAL AZELAIC ACID-3

- Adverse effects are generally mild & transient
  - Overall incidence of approximately 3%
  - Pruritus, burning, stinging & tingling

TOPICAL SALICYLIC ACID-1

- A keratolytic agent
- Effective for mild to moderate acne
- Has both comedolytic & antimicrobial properties
- Efficacy: (12 weeks)
  - Inflammatory lesions 44%
  - Non-inflammatory lesions 19%

TOPICAL SALICYLIC ACID-2

- Salicylic acid of 1.5% & 2% concentrations are effective compared to placebo
- Adverse effects such as pruritus, burning, tingling, desquamation & erythema are mild & transient

TOPICAL SULFUR & ITS COMBINATION-1

- Anti-inflammatory & mild keratolytic
- No sufficient evidence to support the use of sulfur alone
- Combination of sulfur with other agents is effective in treating mild to moderate acne

TOPICAL SULFUR & ITS COMBINATION-2

- 5% sulfur + 10% sulfacetamide (12 weeks):
  - Total lesions 78% reduction
  - Inflammatory lesions 82.9% reduction
- Sulfur (2% to 6%) in calamine lotion have long been used, but there is no retrievable clinical study demonstrating its efficacy
- Adverse effects include transient mild dryness & pruritus

TOPICAL DAPSONE-1

- Assumed to have similar mechanisms of action on acne as oral dapsone
- Antimicrobial (bacteriostatic) & anti-inflammatory properties
- Effective in mild to moderate acne
- Reducing both inflammatory & non-inflammatory lesions
- Efficacy: (12 weeks)
  - Inflammatory lesions 30% - 49%
  - Non-inflammatory lesions 5% - 32%

TOPICAL DAPSONE-2

- Onset of action on inflammatory lesions is as early as 4 weeks
- Sustained effectiveness was demonstrated in a 12-month study showing lesion reduction of 58% for inflammatory lesions ($p<0.001$) & 19.5% for non-inflammatory lesions ($p=0.002$)
- No head-to-head efficacy study comparing topical dapsone with other topical agents

TOPICAL DAPSONE-3

- Well tolerated for up to 12 months
- Adverse effects are reported in 14 - 38% of patients
  - Mostly mild & moderate
  - Dryness, rash, sunburn, burning, erythema & pruritus
- Safe for use in G6PD deficient patients with acne for up to 12 weeks, with no significant increase in incidence of haemolysis
- No studies have been done in pregnancy & children aged <12 years

TOPICAL FIXED COMBINATION-1

- Fixed combination therapies are new anti-acne treatment
- Combination preparations with topical benzoyl peroxides, retinoids or antibiotics are more effective than either agents used alone

TOPICAL FIXED COMBINATION-2

- Topical clindamycin/BPO
- Topical adapalene/BPO
- Topical erythromycin/BPO
- Topical clindamycin/tretinoin

TOPICAL CLINDAMYCIN/BPO

- More effective than topical clindamycin or BPO alone
- Efficacy: (2 to 12 weeks)
  - Inflammatory lesions 30% - 60%
  - Non-inflammatory lesions 10% - 43%
- Topical clindamycin/BPO & BPO cause higher incidence of peeling compared to clindamycin alone

TOPICAL ADAPALENE/BPO

- More effective than topical adapalene or BPO alone
- Success rates (clear to almost clear) at week 12 are 28% - 38%
- Adverse effects are mild to moderate

TOPICAL ERYTHROMYCIN/BPO

- Effective in reducing both inflammatory & non-inflammatory lesions
- Efficacy: (4 to 10 weeks)
  - Inflammatory lesions 50 - 75%
  - Non-inflammatory lesions 50 - 53%
- Adverse effects such as scaling & tightness had been reported

TOPICAL CLINDAMYCIN/TRETINOIN

- More effective than clindamycin or tretinoin alone
- Efficacy: (12 weeks)
  - Inflammatory lesions 53.4%
  - Non-inflammatory lesions 45.2%
- Adverse effects are minor & well tolerated

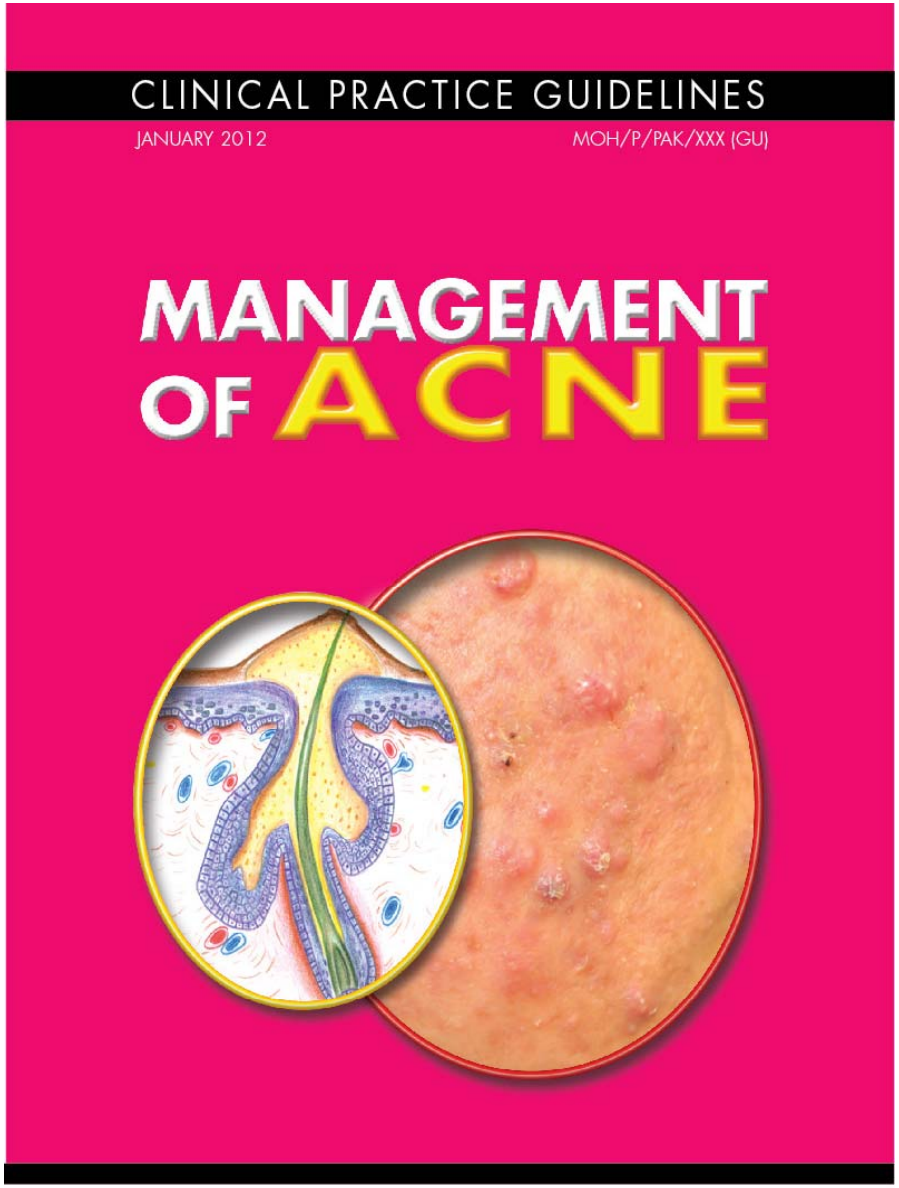
PRACTICAL TIPS

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

RECOMMENDATION

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

THANK YOU



SYSTEMIC TREATMENT AND ANTIBIOTIC RESISTANCE

Clinical Practice Guidelines
Management of Acne
Development Group

Ministry of Health Malaysia

Dermatological Society of Malaysia

Academy of Medicine of Malaysia

LEARNING OBJECTIVES

- To be able to select the appropriate systemic therapy to treat moderate to severe acne
- To know the common dosing regimens for systemic therapy
- To be aware of antibiotic resistance
- To know common adverse effects of systemic therapy

SYSTEMIC TREATMENT

Can be divided into:

- Oral antibiotics
- Hormonal therapy
- Oral isotretinoin

ORAL ANTIBIOTICS

ORAL ANTIBIOTICS

- Used for moderate to severe acne vulgaris
- Mechanism:
  - the anti-*Propionibacterium acnes* properties
  - direct anti-inflammatory effect by inhibiting chemotaxis and matrix metalloproteinases
- Duration of treatment: 4 – 6 months or longer
- Should be combined with topical therapy e.g. BPO to prevent resistance
- Prolonged use of oral antibiotics may be associated with bacterial resistance

Oral antibiotics

- The antibiotics commonly used to treat acne vulgaris
  - Oral tetracycline
  - Oral doxycycline
  - Oral minocycline
  - Oral erythromycin
- Sulfonamide antibiotics is known to cause severe adverse drug reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis
- Oral antibiotics should not be prescribed for more than 6 months

Oral Tetracycline

- Contraindicated in children aged < 8yo, pregnancy and lactation women
- Absorption of tetracycline from GIT ↓food, milk, dairy products, iron salts and antacids
- A SR of 18 trials oral tetracycline in doses ranging from 250 to 500 mg twice daily for 8 to 24 weeks effective for inflammatory and non-inflammatory lesions
- Lesions reduction rates were between 19% and 84% for inflammatory lesions and between 25% and 63% for non-inflammatory lesions
- Common adverse effects are nausea, vomiting, diarrhoea, cramping, erythema, abdominal pain, esophagitis, oral candidiasis and vaginal candidiasis

Oral Doxycycline

- Doxycycline is a tetracycline derivative
- 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 ($p<0.05$)
- Common adverse effects are mainly gastrointestinal such as diarrhoea, nausea, vomiting, dyspepsia and abdominal pain

Oral Erythromycin

- Erythromycin is a macrolide antibiotic
- 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 gave 21 - 45% improvement in Leed's acne severity grading in patients with moderate to severe acne ($p<0.05$)
- A SR of three clinical trials comparing the use of oral erythromycin and oral tetracycline showed that both were equally effective
- Common adverse effects are nausea and diarrhoea. Other adverse effects such as headache, dizziness and rashes are mild and transient

Oral Minocycline

- Minocycline is a tetracycline derivative antibiotic
- 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
- Minocycline was shown to have comparable efficacy with tetracycline, doxycycline and lymecycline
- Dose regimes of minocycline 50 mg to 100 mg once to twice daily
- Adverse reactions include moniliasis, abnormal pigmentation, vertigo, urticaria, renal failure and fixed drug eruption

ANTIBIOTIC RESISTANCE

ANTIBIOTIC RESISTANCE

- Prolonged usage of antibiotics may lead to antibiotic resistance resulting in treatment failure
- The resistance pattern differs with different antibiotics
- Resistance rates to erythromycin was the highest in majority of the studies, followed by clindamycin

Resistance Rate of Different Antibiotics in Acne Treatment

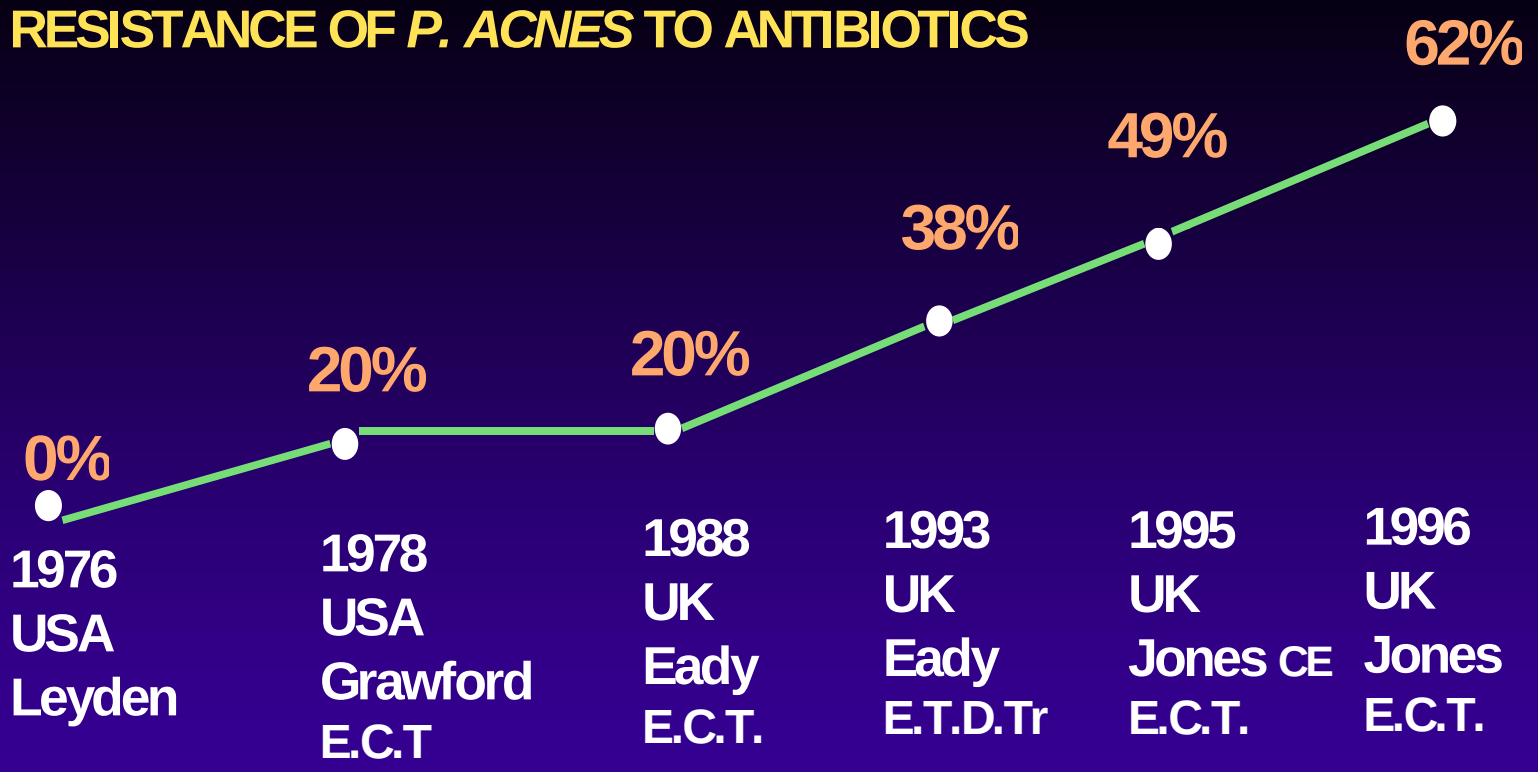
Antibiotics	Resistance Rate
Erythromycin	4.0 - 92.0%
Clindamycin	4.0 - 95.0%
Tetracycline	0 - 29.9%
Minocycline	0 - 0.6%
Doxycycline	0 - 9.5%
Co-trimoxazole	0 - 21.7%

Antibiotics Resistance Rate

Antibiotic	Worldwide	Malaysia Tang JJ, 2010	Singapore Tan HH, 2007
Clindamycin	4 – 95%	15.0%	7.5%
Erythromycin	4 – 92%	7.5%	10.3%
Doxycycline	0 – 9.5%	5.7%	3.4%
Tetracycline	0 – 29.9%	1.9%	1.7%
Minocycline	0 – 0.6%	0%	1.7%
Co-trimoxazole	0 – 21.7%	-	5.7%

Antibiotic Resistance and Acne : The Facts …

↑ RESISTANCE OF *P. ACNES* TO ANTIBIOTICS



E= Erythromycin C= Clindamycin D= Doxycycline Tr= Trimethoprim T= Tetracyclines

Dreno B. 2001.

HORMONAL THERAPY

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
- Common hormonal therapy used is the combined oral contraceptive pills.
- Spironolactone, flutemide and finasteride have little evidence in the effectiveness of treating acne

COMBINED ORAL CONTRACEPTIVE (COC) THERAPY

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

ORAL ISOTRETINOIN

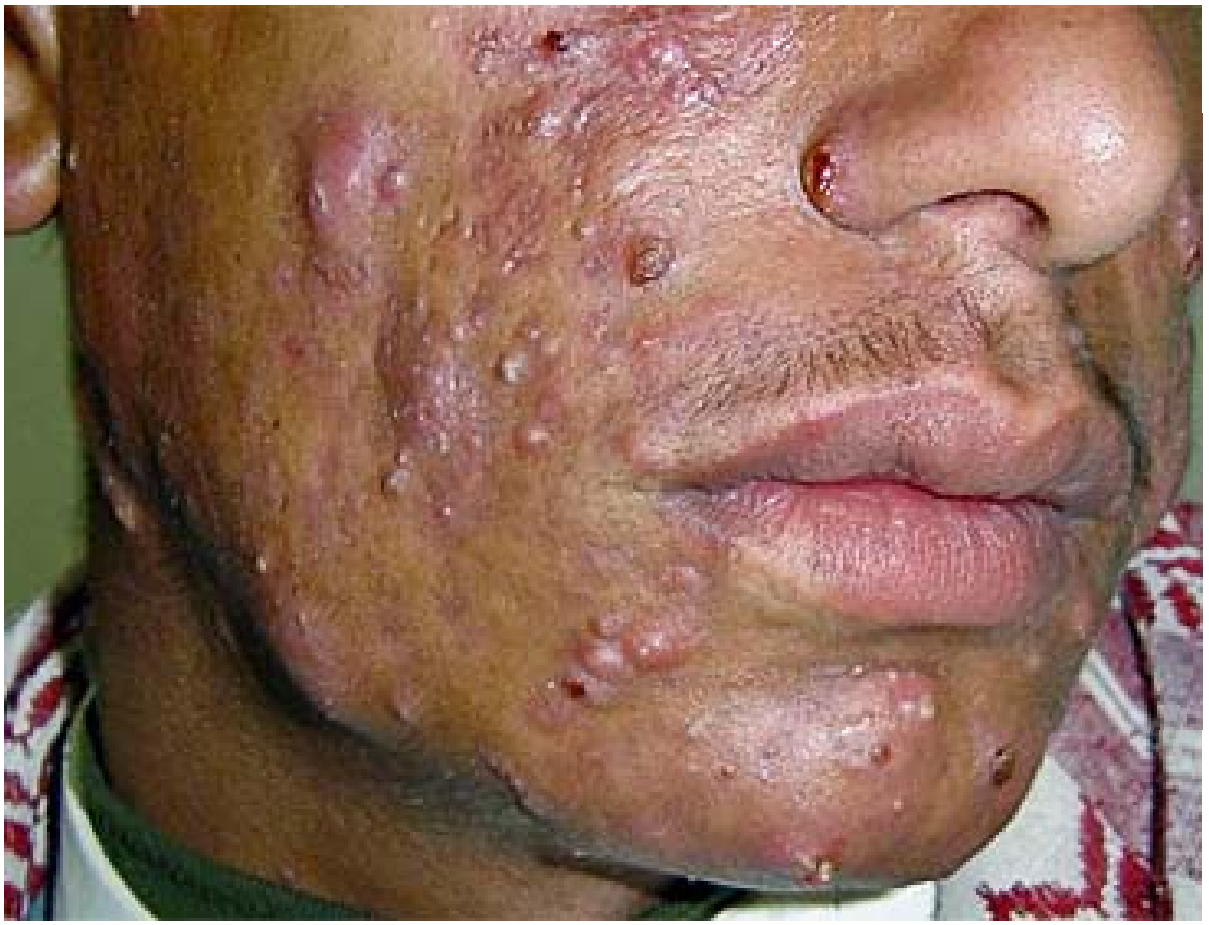
ORAL ISOTRETINOIN

- 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
  - exerts an anti-inflammatory action

ORAL ISOTRETINOIN

- Oral isotretinoin is teratogenic
- Strict contraceptive practice is required for female patients
- Oral isotretinoin **MUST** only be prescribed by dermatologists
- Pregnancy should not be attempted until >1 month after discontinuation of therapy

Nodulocystic Acne



ORAL ISOTRETINOIN

NODULOCYSTIC ACNE

- 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

ORAL ISOTRETINOIN

NODULOCYSTIC ACNE

- A study comparing 0.1, 0.5 and 1 mg/kg/day doses in the treatment of nodulocystic acne showed significant response to treatment with all three doses ($p<0.01$) but no 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/d, 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
- A cumulative dosage of 120 mg/kg is associated with a lower relapse rate

ORAL ISOTRETINOIN

MILD TO MODERATE ACNE

- 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

ORAL ISOTRETINOIN

MILD TO MODERATE ACNE

- 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

ORAL ISOTRETINOIN

SIDE EFFECTS

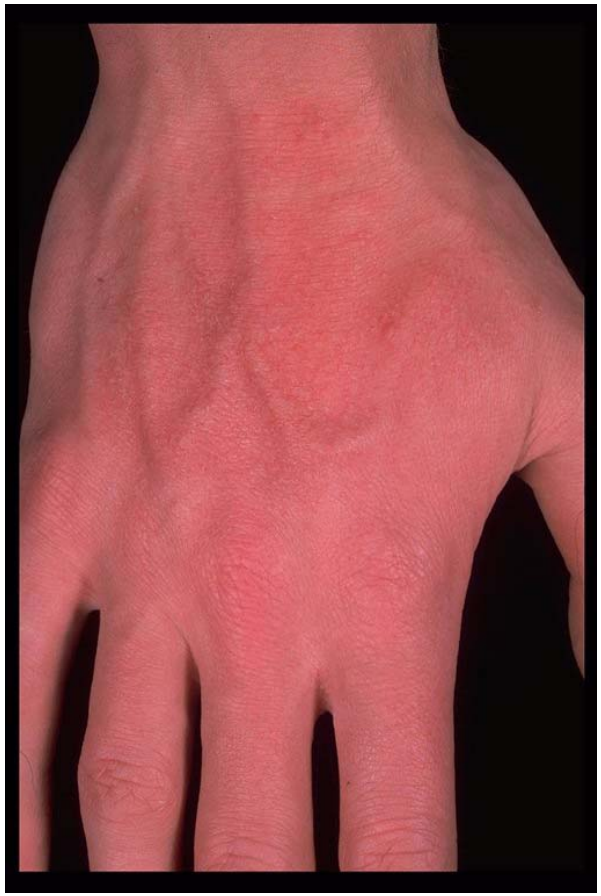
- Side effects are dose-dependent
- Mostly limited to the skin and mucous membrane, and well tolerated and reversible.
- Common side effects include cheilitis, dermatitis, conjunctivitis, xerosis and dryness of the nasal mucosa with nosebleeds.
- Other rare side effects are arthralgia, decreased appetite and fatigue.
- Laboratory abnormalities: elevations of serum aspartate, alanine transaminases and hypertriglycerides which all return to normal after discontinuation of therapy
- 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

ORAL ISOTRETINOIN

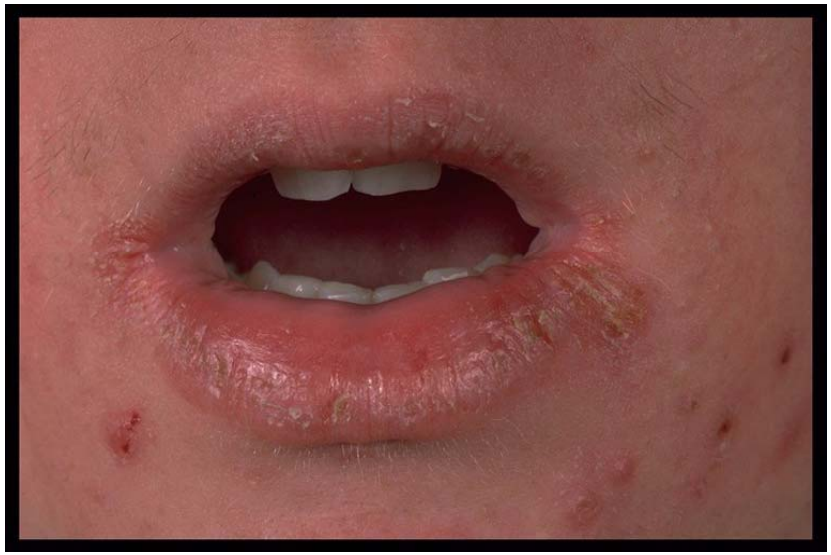
SIDE EFFECTS

- Teratogenicity
- Mucocutaneous/hair:
  - Xerosis, cheilitis, dry mucosae
  - Photosensitivity
  - Retinoid dermatitis
  - Telogen effluvium
  - Pyogenic granuloma
- Systemic:
  - Elevated transaminases, hepatitis
  - Hyperlipidaemia
  - Pancreatitis (rare)
  - Gastrointestinal disturbances
  - CNS: mood swings, depression, suicidal ideation (rare)
  - Hypothyroidism
  - Diffuse interstitial skeletal hyperostosis (DISH) - rare

Side effects of isotretinoin



xerosis

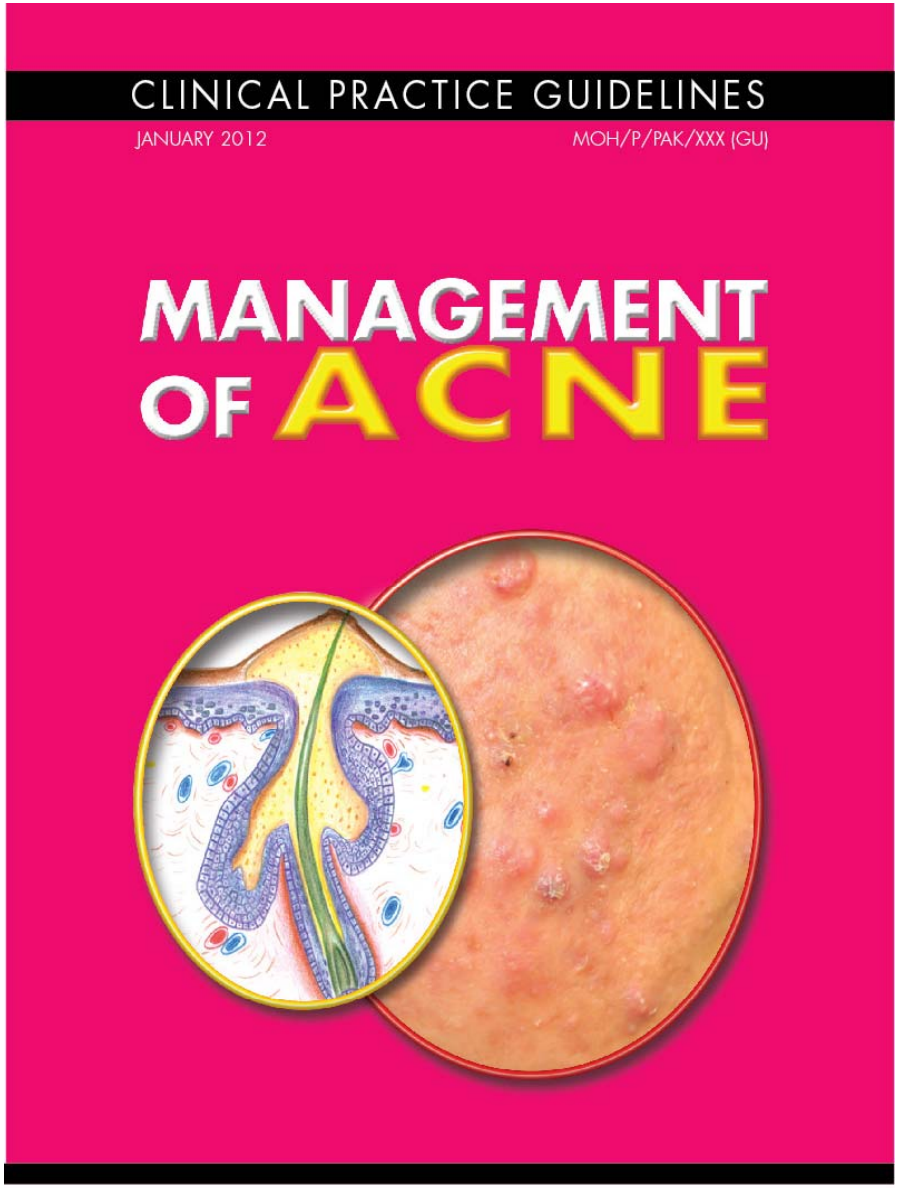


chelitis

TAKE HOME MESSAGE

- Oral tetracycline, oral doxycycline, oral erythromycin or oral minocycline may be used as treatment for moderate to severe acne
- Prolonged usage of antibiotic leads to resistance. Resistance rates to erythromycin was the highest in majority of the studies, followed by clindamycin
- 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
- Oral isotretinoin is recommended for nodulocystic or severe acne. May also be used for moderate acne as third line therapy
- Isotretinoin is teratogenic. Strict contraceptive practice is required for female patients and isotretinoin should only be prescribed by dermatologists

THANK YOU



Ministry of Health Malaysia

Dermatological Society of Malaysia

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Maintenance & Physical Therapy

Complementary & Alternative Medicines

Referral

Clinical Practice Guidelines Management of Acne Development Group

LEARNING OBJECTIVES

- To select appropriate topical treatment for maintenance therapy
- To know the physical therapy, its indication & side effects
- To know the indications for referral

MAINTENANCE THERAPY

- Recurrence of acne lesions after successful treatment is common
  - should be commenced after an initial successful induction therapy to sustain remission
- Mainstay of maintenance treatment is topical therapy
- Topical retinoid monotherapy should be considered for maintenance therapy in patients with acne
- Combination therapy of adapalene-benzyl peroxide gel may be considered for maintenance therapy in severe acne

TOPICAL TREATMENT FOR MAINTENANCE THERAPY

Type of topical treatment	Type of acne	Comparison	Duration	Comments
Adapalene gel 0.1%	Mild to mild moderate	Vehicle	12 weeks	Reduction of microcomedones count
Adapalene 0.1% & BPO 2.5% (adapalene-BPO)	Severe	-	6 months	Reduce disease symptoms
Azelaic Acid 20%	Severe	-	3 months	Improvement after three months
Tazarotene 0.1% gel	Moderately severe to severe	Vehicle + oral minocycline & tazarotene gel + oral minocycline	12 weeks	No statistically significant difference
Topical antibiotics	No retrievable evidence			

INTRALESIONAL CORTICOSTEROID INJECTION

- Useful for treatment of acne nodules & cysts
- Used with caution due to potential local & systemic adverse effects:
  - skin atrophy, pigmentary changes, telangiectasias, haematoma & infection
  - evidence of systemic absorption & adrenal suppression occurs in doses of >15 mg per session
- Should be injected at lowest effective dose
  - triamcinolone acetonide 2.5 to 5 mg/ml is commonly used

PHYSICAL THERAPY

- Adjunctive or alternative treatment in acne
- Not widely available & can only be provided by trained personnel
- Type of physical therapy:
  - comedone extraction
  - chemical peeling
  - phototherapy & photodynamic therapy (PDT)

- Can provide immediate clinical improvement & patient satisfaction
- Lack of published article
- Comedone extraction using Shamberg or Saalfeld comedone extractor was effective in superficial acne but not in cystic acne
- Kaya TI *et al*. reported good result with cautery & standard dissecting forceps for closed macrocomedones >3 mm in diameter

COMEDONE EXTRACTION

- Disadvantages: incomplete extraction, tissue damage & recurrence

CHEMICAL PEELS

- Adjuvants for facial acne
- Various chemical preparations are used for epidermal exfoliation
- Commonly used peeling agents:
  - glycolic acid
  - salicylic acid (SA)

GLYCOLIC ACID-1

- α-hydroxy acid with hydrophilic compound
- Used in chemical peels due to its desquamating properties
- Desquamation reduces corneocyte cohesion & keratinocyte plugging
  - enables extrusion of contents which prevent comedone formation

GLYCOLIC ACID-2

- Both 70% glycolic acid & 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
  - 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

GLYCOLIC ACID-3

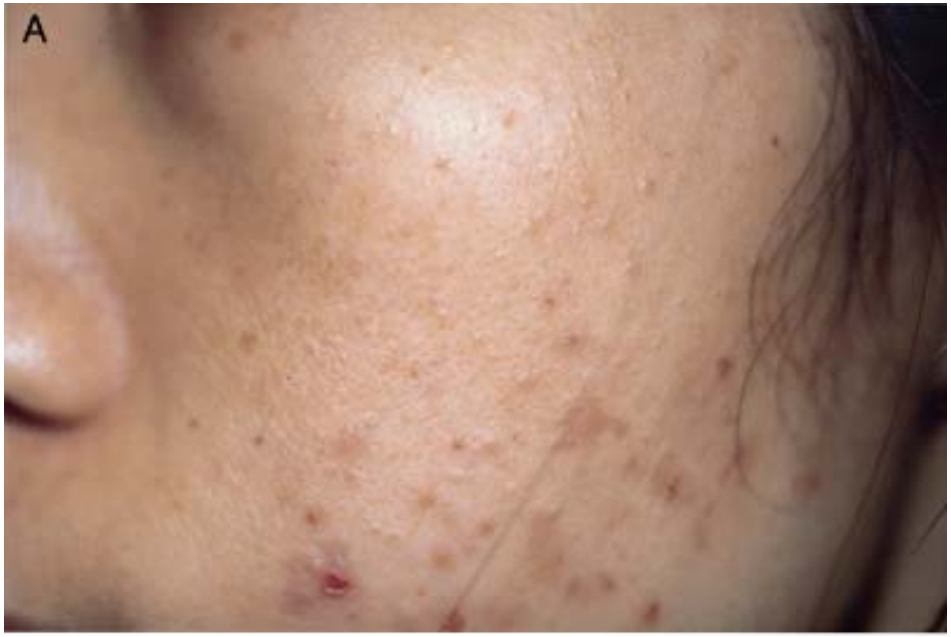
- In moderate to moderately severe acne
  - glycolic acid peel (35% or 50%) for four sessions at 3-weekly intervals resulted in significant resolution of comedones, papules & pustules
- Side effect: erythema, mild skin irritation post- inflammatory hyperpigmentation

SALICYLIC ACID-1

- Lipophilic β-hydroxy acid
- Reduces corneocyte cohesion & acts well on sebaceous areas of the face
- Excellent keratolytic effect
- Useful against comedones & also effective in inflammatory lesions

SALICYLIC ACID-2

- Lee HS *et al*.
  - 30% salicylic acid at 2-weekly intervals for five sessions were effective in both non-inflammatory & inflammatory acne lesions
  - 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 ($p<0.01$)
- Adverse events include peeling, redness & scaling



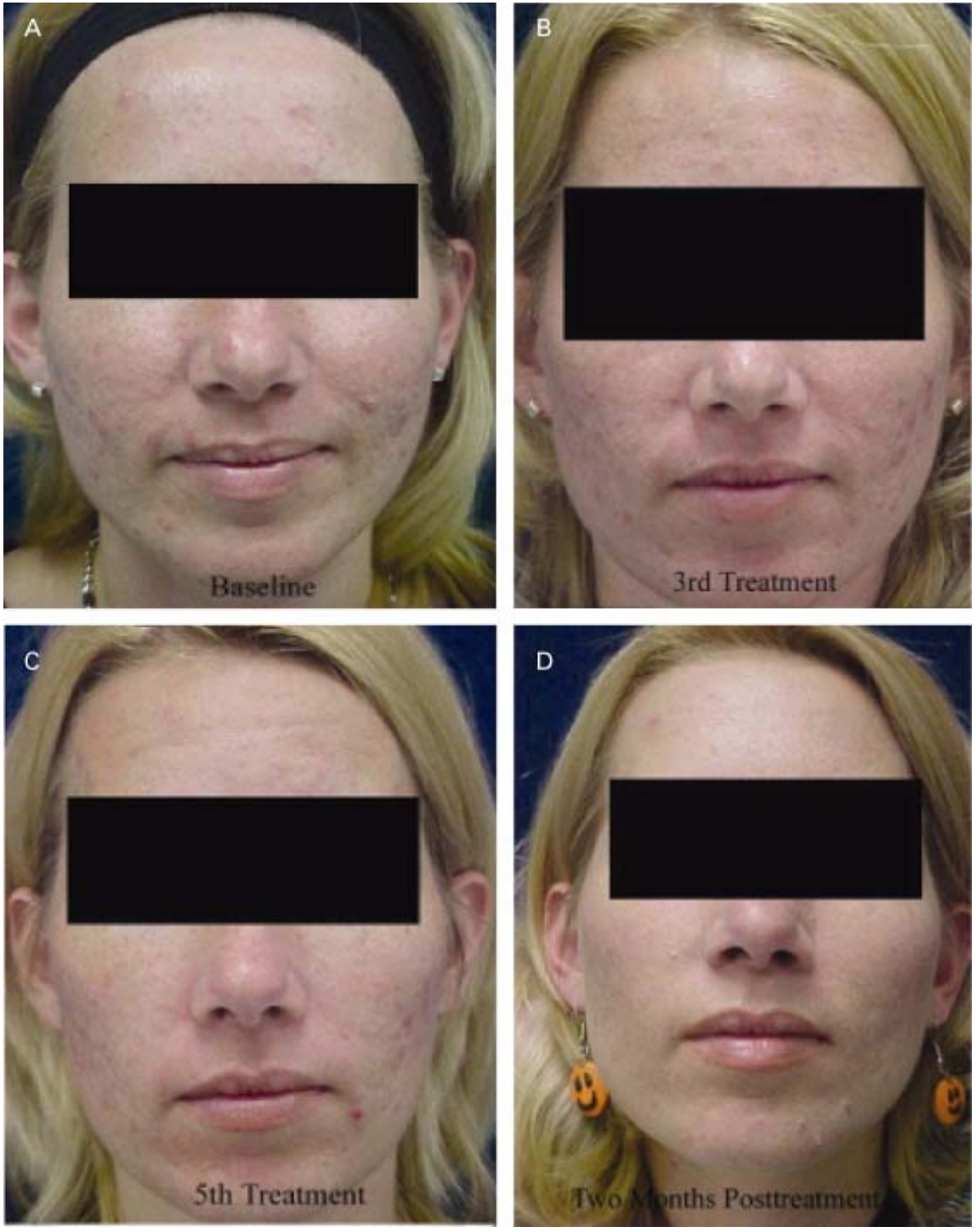
SALICYLIC ACID (SA)-3

- 31-year-old female with acne vulgaris

(A) Before treatment

(B) After five sessions of treatment of 30% SA peel biweekly

Lee HS, Kim IH. Salicylic acid peels for the treatment of acne vulgaris in Asian patients. Dermatol Surg 2003 Dec;29(12):1196-9



30% SA & 30% glycolic acid peel biweekly for 6 treatments

A. Patient at baseline

B. After third treatment

C. After fifth treatment

D. 2-month follow up

Similar degrees of improvement

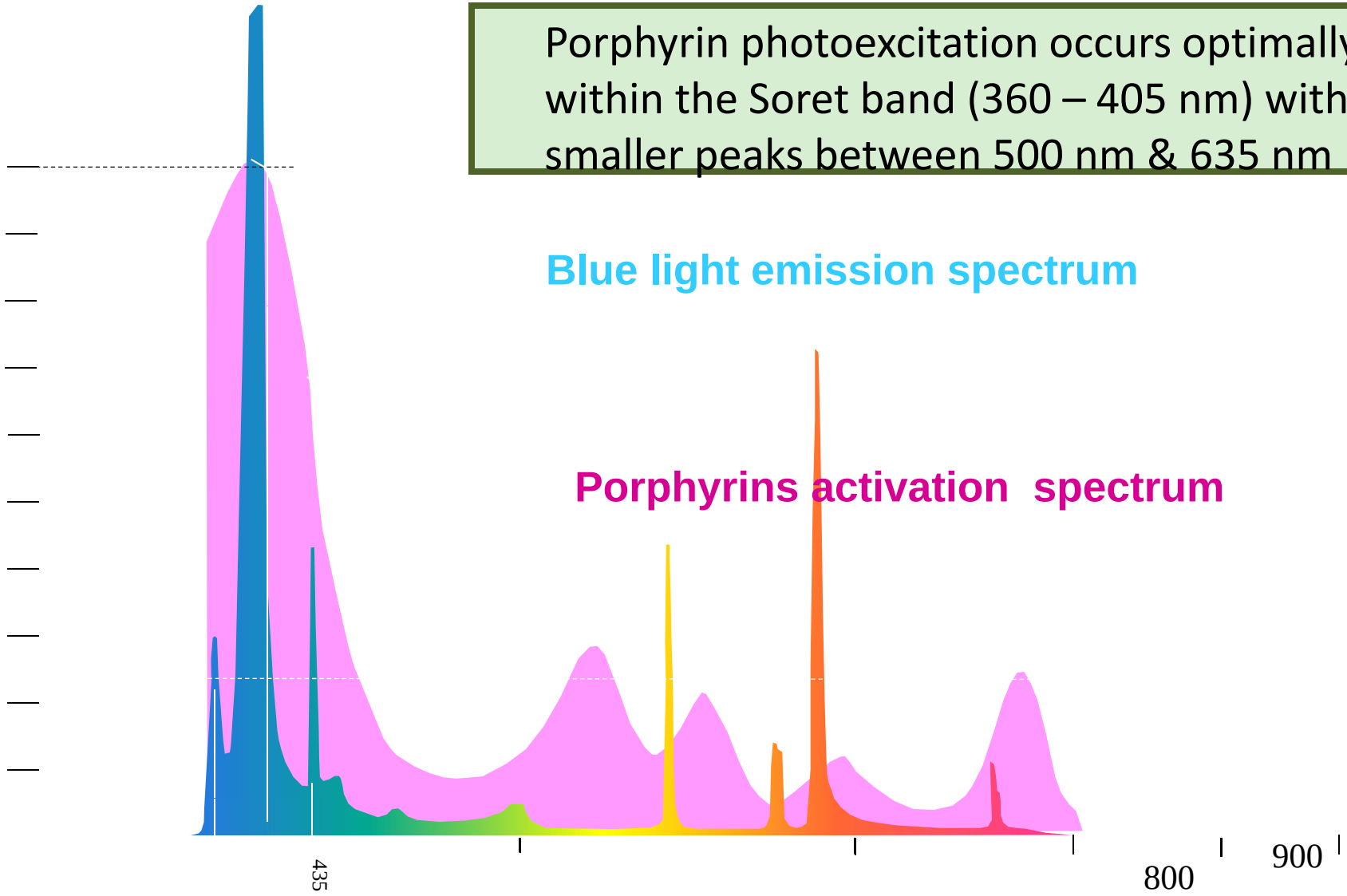
Kessler E, Flanagan K, Chia C *et al*. Comparison of alpha- and beta-hydroxy acid chemical peels in the treatment of mild to moderately severe facial acne vulgaris. Dermatol Surg. 2008 Jan;34(1):45-50

PHOTOTHERAPY & PHOTODYNAMICTHERAPY

- Alternative therapeutic options for patients who either fail or unable to tolerate other standard acne therapies
- Specialised procedures & should only be carried out by dermatologists
- Proposed mechanisms of action are photothermal heating of sebaceous glands & 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

Porphyrin photoexcitation occurs optimally within the Soret band (360 – 405 nm) with 4 smaller peaks between 500 nm & 635 nm



PHOTOTHERAPY-1

- Include pulsed dye laser, potassium titanyl phosphate laser, infrared diode laser, intense pulse light & broad spectrum continuous wave visible light sources such as blue & blue-red light

- Many studies have been published with varying qualities & results

PHOTOTHERAPY-2

Type of phototherapy	Authors	Studies	Duration of study	Improvement
Pulsed Dye Laser (PDL)	Seaton ED *et al.*	RCTs	12 weeks	49% vs 10% in placebo
Pulsed Dye Laser (PDL)	Orringer JS *et al.*	RCTs	12 weeks	No significant differences
Infrared Diode Laser	SR	4 RCTs	1 week	27% reductions of comedones
Intense Pulse Light (IPL)	A SR showed that IPL by itself was not beneficial			
Visible Light Sources	Blue & blue-red light treatment showed significant moderate to large improvement			

Side-effects: moderate pain during the procedure, itch, erythema & swelling

PHOTODYNAMIC THERAPY -1

- Uses light-activated cream (photosensitiser) which is absorbed into the pilosebaceous unit to amplify the response to light therapy.

- Commonly used photosensitisers
  - 20% 5-Aminolevulinic acid (ALA) applied 4 to 6 hours under occlusion
  - MAL (methyl aminolaevulinate) applied 3 hours under occlusion

PHOTODYNAMIC THERAPY-2

- A systematic review (5 RCTs, 12 clinical studies & 2 case reports) showed topical ALA or MAL at 2 - 4 week intervals for a 2 to 4 treatments produced greatest clinical effect

- Side-effects: erythema, oedema, blistering, acute acneiform eruptions & post inflammatory hyperpigmentation
  - often severe enough for patient to discontinue treatment

COMPLEMENTARY & ALTERNATIVE MEDICINES (CAMs)

- Commonly used to treat acne vulgaris
- Insufficient evidence to recommend any specific CAMs due to poor methodology of studies
- Topical tea tree oil gel had been shown to be an effective for mild to moderate acne vulgaris in one RCT
- Ayurverdic formulations have also been used with different efficacy

REFERRAL-1

- Urgency for referral is dependent upon various factors
- Should follow accepted guidelines based on acuteness of severity & psychological impact
- Referral is mainly to a dermatologist. However, patient may be referred to a plastic surgeon who provides physical treatment.
- Divided into :
  - urgent: within 24 hour
  - seen early: 1 to 4 week
  - non-urgent: based on available appointment date

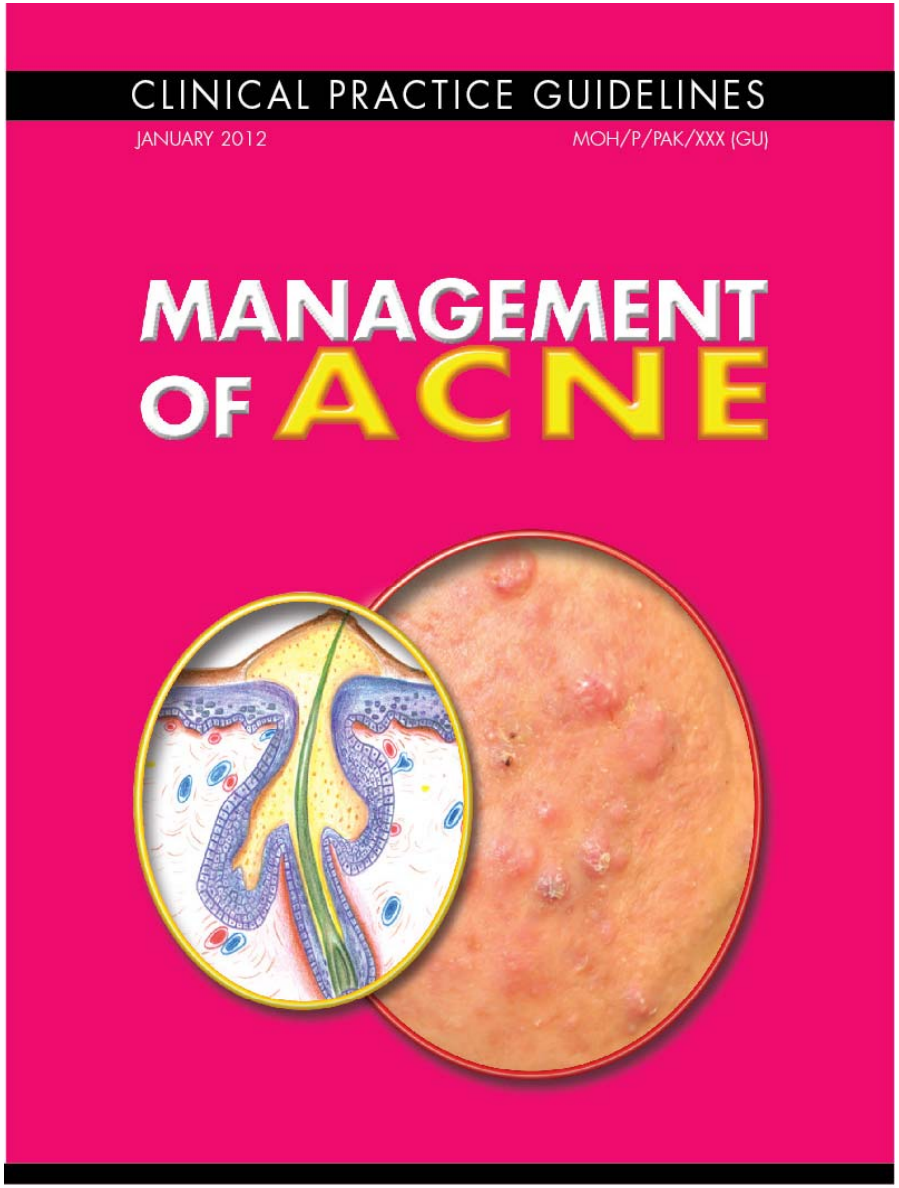
REFERRAL-2

- If patient exhibits suicidal behaviour, an urgent referral to psychiatry is warranted
- Those with severe social & psychological problems, severe acne & nodulocystic acne that may need isotretinoin should be seen early
- Non urgent referral
  - resistance or intolerance to current treatment
  - moderate or severe acne which fail oral antibiotic therapy
  - acne requiring surgery or specialised physical treatment

TAKE HOME MESSAGES

- Maintenance treatment of acne is important
- Intralesional corticosteroid injection should be used with caution due to potential adverse effects
- Glycolic acid or SA peel may be used as adjuvant treatment
- Phototherapy & PDT can be an alternative therapeutic options for patients who fail or unable to tolerate other standard acne therapies
- Insufficient evidence to recommend any specific CAMs for the treatment of acne

THANK YOU



Group Discussion on Management of Acne

Case Discussion 1

A 19-year-old college student complaints of facial acne for the past 2 years for which she has not taken any treatment earlier. However, her friends started commenting on her appearance, which led her to pay more attention on her skin. She tried a cream & cleanser purchased from a pharmacy which did not help much. Hence, she decided to seek further treatment from a medical doctor. Clinically, there are very few papules on her forehead & chin, with open comedones mainly on her nose. Nodules & cysts are absent.

Q1. What are the important issues to obtain from her prior to initiation of therapy?

Q2.

How would you grade acne severity? Which is the preferred tool?

Comprehensive Acne Severity Scale (CASS)

Grade	Score	Descriptive Guide	Grading (✓)
Clear	**0**	No lesions to **barely noticeable ones**. **Very few scattered comedones** & **papules.**	
Almost clear	**1**	Hardly visible from **2.5 meters away**. **A few scattered comedones,** & **few small papules** & **very few pustules.**	
Mild	**2**	Easily recognisable, **< ½ affected area** involved. **Many comedones, papules** & **pustules**	
Moderate	**3**	**> ½ affected area** involved. **Numerous comedones, papules** & **pustules**	
Severe	**4**	**Entire area** involved. Covered with **comedones, numerous papules**, & **pustules** & **few nodules** & **cysts.**	
Very severe	**5**	**Highly inflammatory acne** covering the affected area; with **nodules** & **cysts** present.	

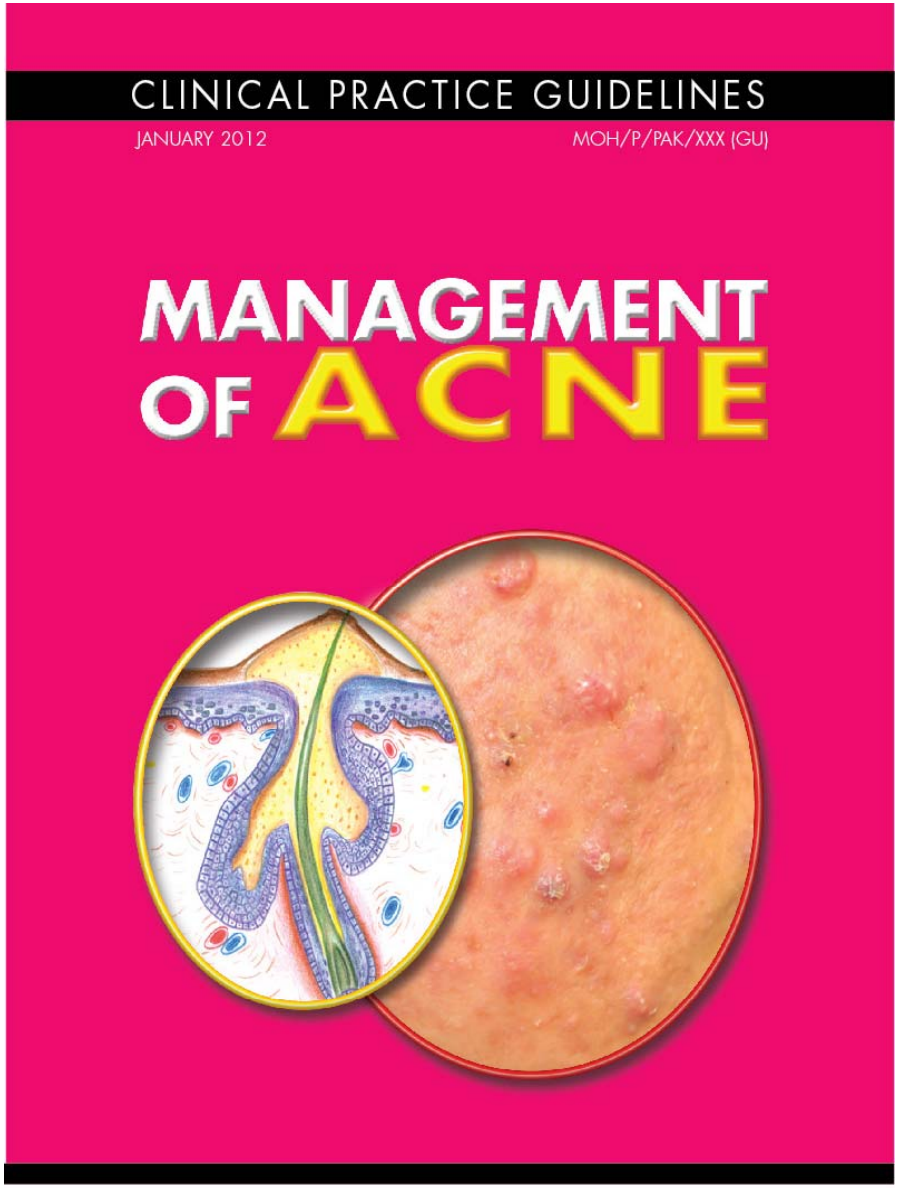
Q3.

Which treatment is suitable for her?

Q4.

She has refrained from eating fried food, seafood & spicy food as she read from a magazine that these foods may worsen her acne. How would you correct her misperception regarding the role food in acne management?

THANK YOU



Group Discussion on Management of Acne

Case Discussion 2

A 24-year-old man has acne on his face for more than 5 years. He had received doxycycline 100 mg daily for 3 months 3 years ago.
Currently, he has numerous new papules & pustules covering about half of his cheek & forehead.
Q1. What is your approach?

A. Restart doxycycline for 6 months
B. Refer to a dermatologist urgently
C. Trial of antibiotic while waiting for dermatology clinic appointment
D. Start on topical antibiotic
E. Start both topical treatment & oral antibiotic

Q2.

Which topical treatment would you give besides the oral antibiotic for the above patient?

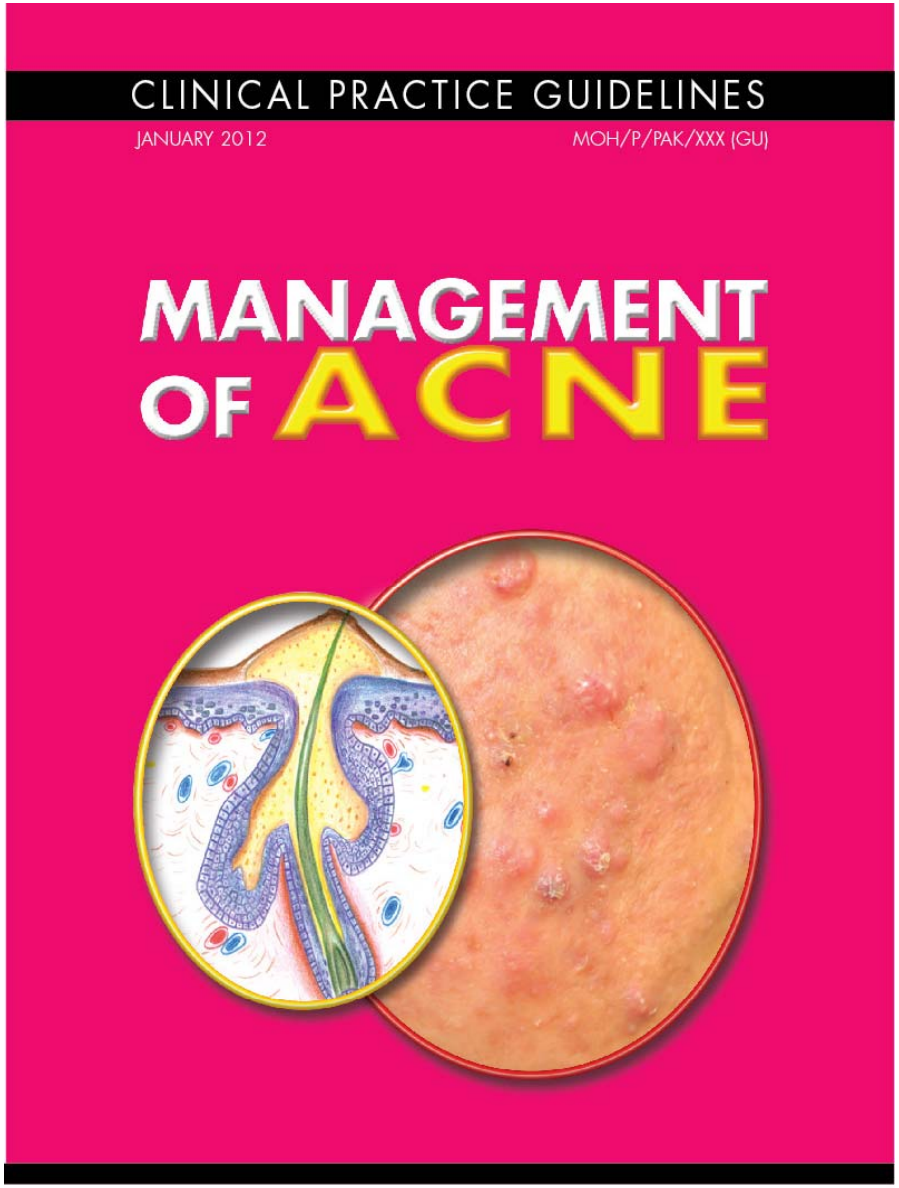
A. Topical clindamycin alone
B. Topical benzoyl peroxide or topical retinoid
C. Topical azelaic acid alone
D. Topical salicylic acid alone
E. Topical azelaic acid & topical salicylic acid

This patient comes back to your clinic 3 months later saying his acne has not improved. He is compliant with the oral antibiotic but has developed local irritation with topical anti-acne & stopped applying it.

Q3. What is your approach?

A. Start oral isotretinoin
B. Refer to dermatologist for laser treatment
C. Continue the oral antibiotic & start another topical therapy after the irritation has settled
D. Change to another oral antibiotic & review in 2 months
E. Stop the antibiotic & start another topical anti-acne

THANK YOU



Group Discussion on Management of Acne

Case Discussion 3

A 19-year-old man has acne nodules on his face & is unhappy with his appearance as he plans to be a steward in the near future.

Q1. What is your approach?

A. Prescribe antibiotic for 3 to 6 months
B. Refer to a dermatologist urgently
C. Trial of antibiotic while waiting for Dermatologist appointment
D. Refer for laser treatment
E. Give a prescription to buy isotretinoin in the pharmacy

Q2.

Are the following clinical assessments important in this patient?

A. Psychological impact
B. Sites of involvement
C. Acne grading severity
D. Future work plan
E. Risk factors
F. Dietary intake

Q3.

Which topical treatment would you give?

Give & discuss your answer.

Q4.

After completing treatment & discharged back to *Klinik Kesihatan*, one nodule on his face is found to be very deep seated & does not resolve with systemic treatment. What will you do?

Give & discuss your answer.

THANK YOU