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# Acne: Pathophysiology and Management

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ABSTRACT

Acne is a common multifactorial inflammatory condition of the pilosebaceous follicle. Topical therapy is the first-line therapy with adjunct systemic therapy if results are unsatisfactory. Oral antibiotic, oral contraception pill or isotretinoin is indicated for inflammatory acne. Since the use topical and systemic treatments might be limited in some patients, several laser and other light sources have been developed to treat acne by decreasing the level of *P. acnes* or decreasing the function of the sebaceous unit. This article reviews the management strategy of acne.

**Keywords:** Acne, laser, *Propionibacterium acne*

ABSTRAK

Akne merupakan kondisi inflamasi multifaktorial dari folikel polisebaseus. Kalsifikasi akne berdasarkan derajat keparahan ringan, sedang, dan berat. Terapi topikal menjadi pilihan utama dengan tambahan terapi sistemik bila hasil belum maksimal. Antibiotik oral, pil kontrasespi atau isotretinoin diindikasikan untuk akne yang disertai inflamasi. Karena beberapa pasien tidak toleran dengan terapi topikal dan sistemik, terapi cahaya dan laser dikembangkan untuk menurunkan jumlah *P. acnes* dan menurunkan fungsi kelenjar sebaseus. Artikel ini membahas strategi penanganan akne. **Elvira. Akne: Patofisiologi dan Tatalaksana**

**Kata kunci:** Akne, laser, *Propionibacterium acne*

## INTRODUCTION

Acne is a chronic inflammatory disease of sebaceous follicles. In Western countries, acne predominantly affects patients during adolescence.[1] The clinical features of acne include non-inflammatory lesions (open and closed comedones) and inflammatory lesions (pustules, papules, or nodules) in pilosebaceous units.[2] Key pathophysiologic mechanisms are known to play roles in the formation of acne lesion: hyperseborrhoea, abnormal follicular keratinization, and *Propionibacterium acnes* proliferation in pilosebaceous unit.[3] Numerous medications have been developed that target one or more pathogenic processes. Acne is associated with social impairment, diminished quality of life, depression, and reduced global self-esteem.[4]

## PATHOPHYSIOLOGY OF ACNE

Key pathogenic factors are increased sebum production (seborrhea), follicular hyperkeratosis, and perifollicular inflammation. Various physiological and exogenous factors act as trigger or modulator, such as: androgens, growth factor (IGF-1), neuroendocrine mediators, propionibacteria, drugs, and dietary habits (high glycemic load and dairy products) (**Diagram 1**).[1] The molecular mechanisms and genetic background are not yet fully understood. Patients with a positive family history tend to exhibit an early disease onset and a severe clinical course. [1]

Sebum production is induced by different receptors in sebaceous gland. Histamine receptor, hormonal DHT receptor, and neuromodulator receptor are expressed by the sebocyte and control sebum production.[3] Newly identified receptors is activated by a dietary substance: peroxisome proliferator-activated receptors are stimulated by free fatty acids and cholesterol, insulin-like growth factor 1 (IGF-1) receptor by sugar and leptin receptor by fat (**Picture 1**). The development of follicular hyperkeratosis is not yet fully understood. Follicular hyperkeratosis might be promoted by inflammatory mediator (IL-1) or by biofilm of *Propionibacterium acnes*.[1]

Elevated systemic androgen levels can trigger seborrhea and acne. Hyperandrogenemia can be caused by androgen-producing tumors, polycystic ovary syndrome, congenital adrenal hyperplasia, iatrogenic administration of androgens or anabolic steroids.[1]

## CLINICAL PRESENTATION

Increased sebum production and follicular hyperkeratosis give rise to microcomedones. Microcomedones developed into skin-color or whitish papules referred to as closed comedones or comedonal acne. Inflamed comedones present as erythematous papules or papulopustules (papulopustular acne). In severe cases (conglobate acne), follicular

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rupture causes foreign body reactions to comedonal components (corneocytes, hairs), giving rise to cysts and fistulae. Conglobate acne associated with systemic vasculitis and arthritic involvement is referred to as acne fulminant.[1] The other acne classification based on the severity are mild, moderate, and severe.[5]

## TREATMENT

Topical, systemic therapeutic agents, and laser have been developed that target one or more pathogenic processes. Current clinical guidelines focus on severity and degree of inflammation to determine the appropriate treatment regiment (**Diagram 2 and 3**).

### Topical Therapy

Topical therapy is the mainstay of treatment for mild to moderate acne. Benzoyl peroxide, salicylic acid, azelaic acid, and retinoids are commonly used to treat mild comedonal acne. Topical antibiotic and bacteriostatic medication are more effective against inflammatory acne. Most topical preparations are available in variety of strength and selection of vehicle. Gels, washes, and solution tend to be more drying than creams, lotions, and ointments. Topical agent has fewer systemic effects than oral agent, but it can cause skin irritation.[2]

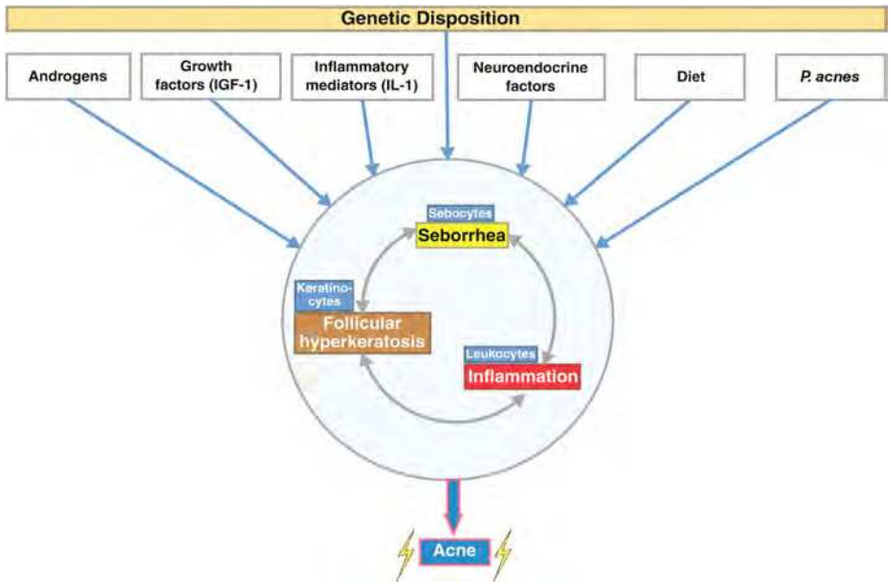
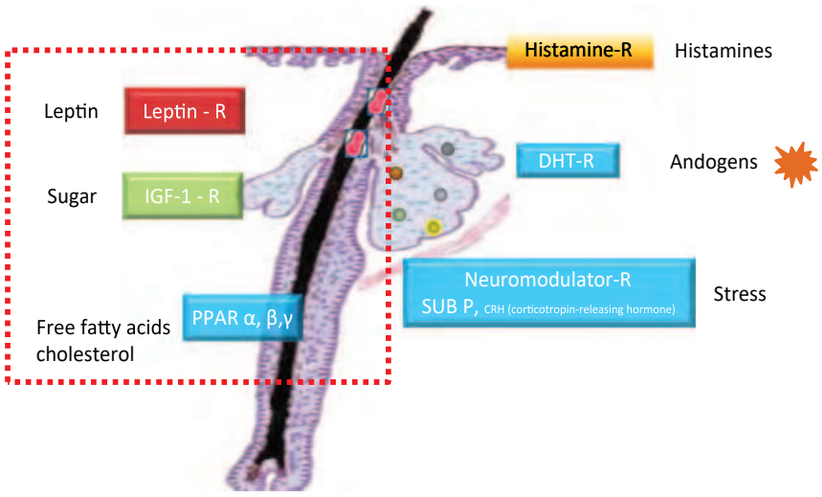



**Diagram 1.** Factors involved in the pathogenesis of acne.[1]




**Picture**. Receptors controlling sebum production.[3]

1. Topical Retinoids

   Retinoids are vitamin A derivatives that act as comedolytic by normalizing desquamation of the epithelial lining, improve differentiation and increase the follicular epithelial turnover.[2,6] Topical retinoids also block inflammatory pathways, such as Toll-like receptors, leukocyte migration, and the AP-1 pathway.[7] Topical retinoids used for acne include tretinoin, adapalene, and tazarotene.[6] They do not directly inhibit *P. acnes* but create an inhospitable environment and limited action on sebum production.[6]

   Tretinoin is the first retinoid used for acne, effective in comedonal and inflammatory mild to moderate acne.[6] Tazarotene is the most irritating of topical retinoids. Adapalene is less irritative and has better tolerability.[2] The efficacy and side effect of retinoids are dose-dependent.[7] Local adverse effects (peeling, erythema, dryness, burning, and itching) are commonly occur, typically in the first few weeks of treatment and then subside.[7] This effects might be increased by ultraviolet light, so daily use of sunscreen is recommended. Irritation can be minimized by reducing the frequency of treatment, applying a small amount of cream, starting with lower strength of the preparation, or switching to a different vehicle.[2] Systemic absorption of topical retinoid medication is low.[8] Both tretinoin and adapalene are pregnancy category C and tazarotene is pregnancy category X.[2]

2. Topical Antibiotic

   Topical antibiotic is mainly used in acne due to antibacterial and anti-inflammatory actions. Indicated for mild to moderate acne and offer limited benefit for treatment of comedonal acne.[2] Erythromycin 2-4% and Clindamycin 1% are commonly available in various topical formulation. Although these topical agents are effective, their widespread use has also been associated with the emergence of resistant strains of *P. acnes*. The combinations of erythromycin and clindamycin with benzoyl peroxide may decrease the risk of bacterial resistance.[9] Localized skin side effect is such as erythema, dryness and burning might be found.[2] Formulation change or reduced

dose can minimize the irritation.

3. Other Topical Agents

Benzoyl peroxide (BPO) is an non-antibiotic that inhibit *P. acnes* by creating reactive oxygen species within the hair follicles and has weak comedolytic and anti-inflammatory effect.[2] Its action on inflammatory lesions appears similar to topical antibiotic, but more effective on non-inflamed lesions. Kawashima et al., report the safety and efficacy of a long-term BPO monotherapy; 2.5% and 5% BPO can decrease the number of lesions from the start of treatment to 12 weeks.[10] A combination of BPO 5% and erythromycin 3% or clindamycin is more effective than either drug alone and reducing risk of antibiotic resistance.[6] The most common adverse effects include local erythema, dryness and peeling.

Salicylic acid (SA) has been used as skin keratolytic and anti-inflammatory. Although the comedolytic activity of SA is less potent than topical retinoid, it is often used if retinoids are not tolerated.[11] SA causes local irritation especially at concentrations over 2%. Glycolic acid is an alpha-hydroxy acid and was the first to be added to cosmetic products; recommended for hyperpigmentation and anti-aging. It is important to wear sun protection during daily use of glycolic acid product, as this topical increases sun sensitivity.[2]

Azelaic acid has antimicrobial, comedolytic and anti-inflammatory properties.[2] No bacterial resistance has been associated with azelaic acid treatment. The other benefit of azelaic acid is reduced post-inflammatory hyperpigmentation.[6]But a randomized, single-blind, parallel-group study demonstrated BPO 3% + clindamycin 1% was more superior than azelaic acid 20% cream at 4 weeks of treatment of moderate acne vulgaris.[6]

Dapsone is a sulfone classified as antimicrobial due to its inhibition of bacterial DNA synthesis and is also an effective anti-inflammatory agent. Topical dapsone may cause mild irritation and dryness. Combination of topical dapsone and BPO may result in orange-brown skin color due to dapsone oxidation.[6] Oral dapsone can cause hemolytic anemia especially in patients with G6PD deficiency.[2]

Nicotinamide provides potent anti-inflammatory properties without the risk of bacterial resistance or systemic side effect. Nicotinamide or niacinamide is a form of vitamin B3. Topical 2% nicotinamide significantly reduce sebum production, protect the natural barrier of the skin against infection and may have bacteriostatic effect on *P. acnes*.[12] Nicotinamide has shown benefit in clinical dermatologic studies but has not yet become a standard treatment option.[12]

4. Chemical Peels

Chemical peels are an effective alternative treatment option for non-inflammatory acne lesions. The most commonly used chemical peels for acne include salicylic acid, glycolic acid, Jessner's solution, resorcinol, and trichloroacetic acid (TCA).[2] Chemical agent causes controlled

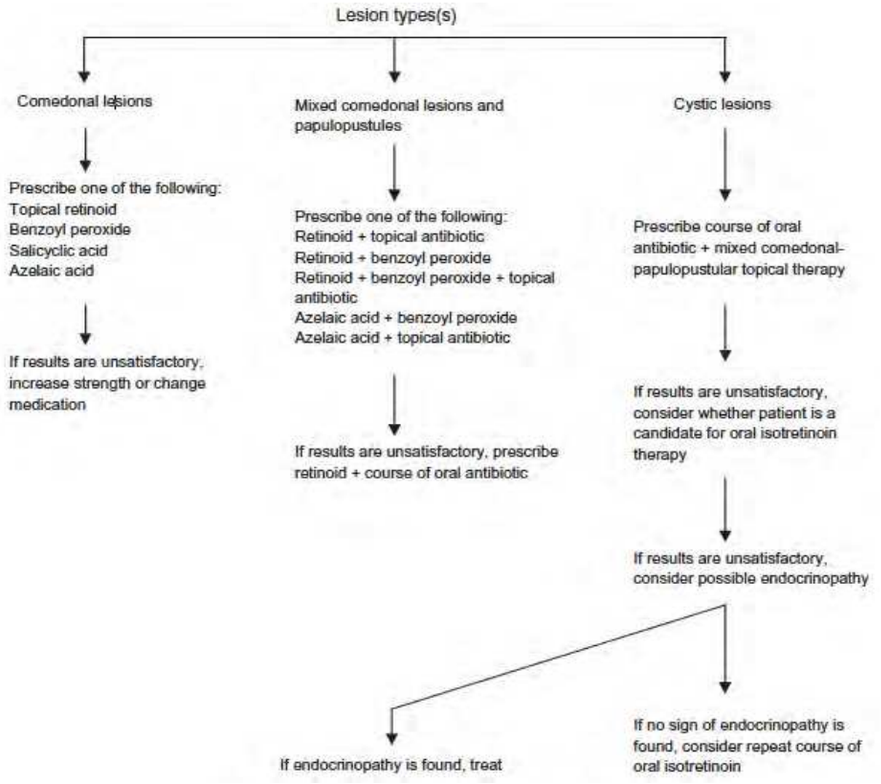



**Diagram 2.** Guideline for acne treatment based on lesion type.[5]

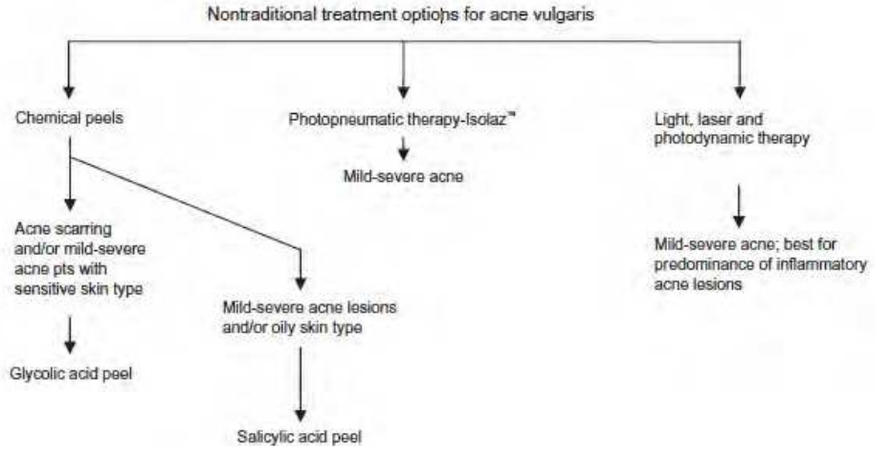



**Diagram 3.** Adjuctive acne treatment algorithm.[5]




destruction of a part or entire epidermis, with or without dermis, leading to exfoliation and followed by regeneration of new epidermal and dermal tissue.[14] More recently, other peels have emerged that been proven useful in management of acne such as lactic acid and salicylic acid-mandelic acid (SM).[13] Jessner's solution (JS) is a combination of 14% resorcinol, 14% salicylic acid, 14% lactic acid in 95% ethanol. Each component of JS has specific effects.[15] TCA can be used as a superficial, medium depth or deep peel depending on the concentration used. When applied to the skin, TCA causes coagulation of epidermal and dermal protein, necrosis of collagen up to the upper reticular dermis. The clinical effect of TCA is due to the resultant increase in dermal volume of collagen, glycosaminoglycan, and elastin.[13]

### Oral Antibiotic

Oral antibiotics are indicated for moderate to severe acne as they exert both anti-microbial and anti-inflammatory effect by inhibiting *P. acnes* proliferation.[2] Because the prevalence antibiotic-resistant *P. acne* is growing worldwide, oral and topical antibiotics are not recommended as monotherapy and should be combined with other topical anti-acne agents. Systemic antibiotic is limited to a treatment period of 3 months.[16] The prevalence of antibiotic-resistant P. acnes is worldwide, with rates varying in different parts of the world, and increasing over the years form 20% in 1979 to 64% in 2000, with the higher rates of resistance noted for clindamycin and erythromycin compared to the tetracyclines.[16]

### Hormonal Agent

Hormonal agent used as adjunct for women with moderate or severe acne. Oral contraceptive pills (OCP) and androgen-receptor blockers can decrease sebum production. All hormonal agents are contraindicated to men and pregnant women due to anti-androgenic effects.[2] Layton et al., revealed a lack of high-quality evidence on the benefits and potential harms of oral spironolactone for managing acne in women.[17]

**Table.** Mechanism and side effect of lasers.[20]

| Type of Light Source | Wavelength | Mechanism |
|---|---|---|
| Intense Pulse Laser | 400-1200 | Bactericidal on *P. acnes*<br>Antiinflammatory effect<br>Alter sebaceous gland function |
| ND Yag | 1064 | Antiinflammatory effect<br>Alter sebaceous gland function |
| Pulse Dye Laser (PDL) | 585, 595 | Antiinflammatory effect<br>Alter sebaceous gland function |
| Infrared Lasers | 1320, 1450, 1540 | Alter sebaceous gland function |
| Blue Light and Red Light | 415; 660 | Bactericidal on *P. acnes* |

### Isotretinoin

Isotretinoin is a vitamin A metabolite thought to target all four pathogenic factor of acne. Isotretinoin is indicated for severe inflammatory acne, nodulocystic acne, or recalcitrant disease.[2] Starting dose is around 0.5 mg/kgBW daily, and this is increased as tolerated by patient, to a goal dose of 1 mg kg/kgBW daily.[18] Because there is an inverse relationship between a patients cumulative dose and risk of relapse, it is recommended that patients reach a cumulative dose of 120-150mg/kg before cessation of therapy.[18] A 6-month course of oral isotretinoin treatment is sufficient for the majority of patients, however relapse can occur and significantly more frequent among patients who are under low-dose therapy. The major adverse effect is teratogenicity. Contraception is mandatory 1 month before, during and 5 weeks post-therapy.[19]The correlation between isotretinoin treatment and depression is still controversial. Isotretinoin treatment does not appear to be associated with risk of depression, treatment acne appear to ameliorate depressive symptoms instead.[20]

### Nontraditional Treatments

The use of oral and topical treatments can be limited in some patients because of ineffectiveness, inconvenience, poor tolerability, or side effects. Several laser and light sources have been developed to treat acne by decreasing the level of *P. acnes* or decreasing the function of the sebaceous unit.[21]Intense pulse light (IPL) sources use a lamp to emit a non coherent, non laser, pulsed, broad spectrum of light with different wavelengths depending on the target therapy.[21]Nd:YAG is an infrared laser causing thermal coagulation of the sebaceous glands and associated with hair follicle.[22] Pulse Dye Laser is used to target vascular lesions and treat atrophic acne scarring.[23]

## CONCLUSION

Acne is predominantly in adolescent and manifest as comedone, papulopustular acne or acne scars. Pathogenic factors are increased sebum production (seborrhea), follicular hyperkeratosis, *Propionibacterium acne*, and perifollicular inflammation. Physiological and exogenous factors might contribute as the trigger. Topical, systemic therapeutic agents and laser have been developed that target one or more of the pathogenic process. Several laser and light sources have been developed to treat mild to severe acne.

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