



ANNOYING ACNE: WHAT SHOULD WE DO?

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ABSTRAK

Akne vulgaris (AV) adalah peradangan kronis pada unit pilosebacea, yang melibatkan 4 elemen kunci dalam patogenesis, termasuk hiperproliferasi folikel epidermis, produksi sebum, aktivitas *Cutibacterium acnes*, serta respon imun inflamasi. Akne vulgaris terjadi pada 85% populasi dunia dan menimbulkan berbagai dampak negatif pada pasien. Penatalaksanaan AV tetap menjadi tantangan bagi sebagian besar klinisi, karena terdapat beberapa faktor internal dan eksternal yang menyebabkan AV rekalsitran namun cenderung diabaikan. Tinjauan pustaka ini bertujuan untuk memaparkan berbagai faktor yang menyebabkan AV rekalsitran sehingga klinisi dapat mengidentifikasi tantangan ini dan menanganinya dengan tepat. Beberapa strategi untuk menangani AV rekalsitran juga diuraikan.

Kata kunci: akne vulgaris; faktor risiko; pengobatan; rekalsitran

ABSTRACT

Acne vulgaris (AV) is a chronic inflammation of the pilosebaceous unit, involving 4 key elements in the pathogenesis, including hyperproliferation of epidermal follicles, sebum production, *Cutibacterium acnes* activity, and immune inflammatory responses. Acne vulgaris occurs in 85% of the world's population and causes various negative impacts on patients. Management of AV remains a challenge to most clinician, because there are several internal and external factors that cause AV recalcitrant annoying acne but tend to be overlooked. This literature review aims to describe various factors that cause recalcitrant AV so that clinicians can identify these challenges and treat accordingly. Several strategies are needed to manage recalcitrant AV.

Keywords: acne vulgaris; recalcitrant; risk factor; treatment

BACKGROUND

Acne vulgaris (AV) is a chronic inflammation of the pilosebaceous unit, involving 4 key elements in the pathogenesis; hyperproliferation of follicle epidermis, sebum production, *Cutibacterium acnes* (previously *Propionibacterium acnes*) activity, and immune inflammatory responses.¹ This disorder affects about 85% of the world's population.² In various countries, the prevalence of acne vulgaris ranging from 35% to nearly 100% of adolescents.³ In 2014-2018 AV was included in the 10 most common diseases at the Dermatology and Venereology (DV) Outpatient Clinic, Dr. Mohammad Hoesin General Hospital (RSMH) Palembang, with an incidence of 4.5% (116 of 2,364 visits) in 2018.⁴

The clinical features of AV are open and closed comedones, papules, pustules, nodules, and cysts on the face, chest, and back.¹ These lesions cause the patient to experience discomfort, lack of confidence, interfere with work, social life, and cause psychological disorders in the form of anxiety, depression, and schizophrenia.³ In addition, AV lesions can cause significant morbidity include scarring and post-inflammatory hyperpigmentation (PIH).² According to a study in the United States (2019), the estimated financial burden of AV cases is > \$2 million per year.⁵

The objective of this literature review is to summarize the various factors that cause recalcitrant acne vulgaris or annoying acne so that clinicians can identify these challenges and provide strategies to manage recalcitrant acne vulgaris.



DISCUSSION

Factors Causing Recalcitrant AV (Annoying Acne)

There are several factors that can cause AV recalcitrant to the therapy, classified into internal factors and external factors. Internal factors consist of genetic, skin type, and hormonal, while external factors consist of inadequate management, skincare habits, skin microbiome dysbiosis, lifestyle, obesity, diet and other medication.

Internal factors

Genetics

Studies have demonstrated the impact of genetic factors on acne presentation. Reports show that positive family history of AV in parents, siblings, or second-degree relatives were associated with increase AC risk in the patient. The odds ratio for AV with positive history of AV in parents is 2.91, (95% confidence interval 2.58-3.28).³ Moreover, genetic factors also affect the severity of acne. Bhat et al. in a study of twins, showed that individuals with a family history of AV were more likely to have severe AV.⁶

Skin type

Some studies show that skin type can influence acne severity. Oily and seborrheic skin was observed to be associated with severe acne. Similarly, those with more severe acne were more likely to have higher sebum production and high usage of drugs to treat their acne. In line with that, severe AV degrees are more common in late adolescence than early adolescence. This is due to increased sebum production during puberty so that adolescents in late age have higher sebum levels. Higher sebum levels promote the growth of *C. acnes*.³

Hormonal

In adolescent AV, most studies show hormonal factors such as menstrual characteristics and the onset of puberty were not significantly related to the severity of acne.³ Recent research has shown an increase number of adult female acne (AFA) cases, 12-22% women suffer from acne in their adult life⁷ (**Figure 1**). Adult female acne most often occurs due to hormonal imbalance, but can also be caused by psychological stress, use of comedogenic hair and facial products, or side effects of medications. Adolescent acne can progress to AFA.⁸ The etiopathogenesis of AFA is multifactorial, and androgen is one of the trigger. These hormones increase the production of sebum, stimulate follicular hyperkeratinization resulting in microcomedo. A small percentage of women with AFA have hyperandrogenism, including polycystic ovary syndrome (PCOS). In those cases, the presence of other clinical alterations is common, such as hirsutism, alopecia, change of voice timbre, irregularity of menstrual cycle, and infertility.⁷

The use of several types of oral contraceptives containing estrogen is protective against severe AV,³ however, some contraceptives contain androgenic progestins and implants can cause AV.¹ Beside hyperandrogenism, acne can also be part of other various endocrine disorders, such as congenital androgen hyperplasia, and adrenal and ovarian neoplasms.¹

External factors

Inadequate management

Some recalcitrant AV may be caused by inadequate management, overtreatment, and undertreatment. Misdiagnosis is a common cause of inadequate management. Acne vulgaris true acne, in the form of chronic inflammation of pilosebaceous follicles with multifactorial causes, generally occurs in adolescents, is diagnosed clinically, by finding various lesions in the form of

comedones, pustules, papules, and nodules, on the face, back, or chest.¹ Apart from being caused by various hormonal disorders, there are several other diagnoses that are similar to acne vulgaris that need to be recognized because they are caused by different pathogenesis and require different treatment.¹ Inflammatory acne may be similar to bacterial or fungal folliculitis, rosacea, perioral dermatitis. Various other types of acne need to be distinguished from acne vulgaris, such as neonatal acne, infantile acne, midchildhood acne, fulminant acne, conglobata acne, acne with solid facial edema, and acne excoriee. Acneiform eruptions can also be found, for example medication-induced acne, halogen acne, chloracne, acne mechanica, and radiation acne.¹

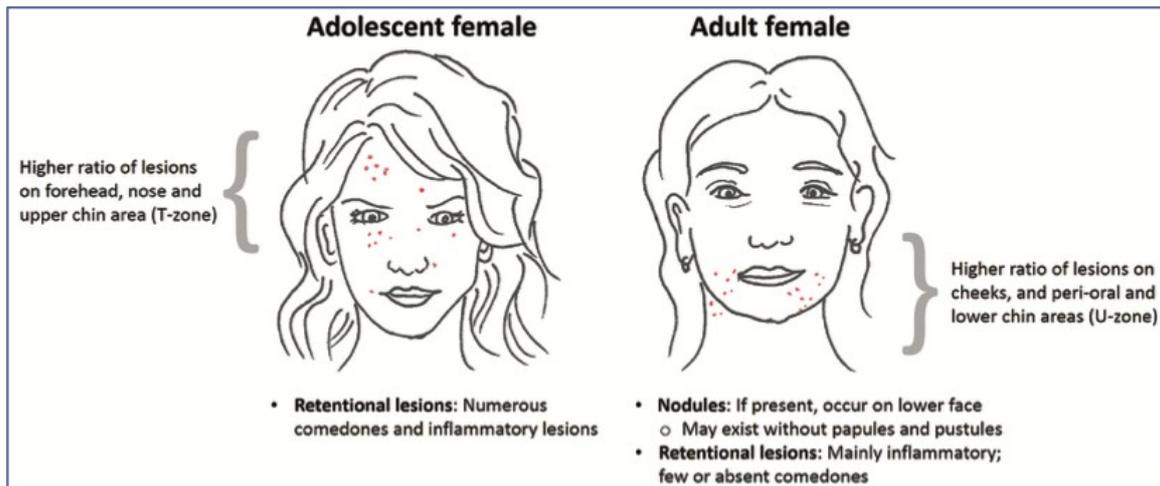


Figure 1. Differences in the morphology of adolescent acne and mature age⁸

Table 1. Classification of acne vulgaris⁹

Degree of severity	Criteria
Mild	<ul style="list-style-type: none"> • Number of blackheads < 20 OR • Inflammatory lesions < 15 OR • No nodules/cysts • Total lesions < 30
Moderate	<ul style="list-style-type: none"> • Number of blackheads 20-100 OR
<ul style="list-style-type: none"> • Inflammatory lesions 15-50 OR • Number of nodules/cysts < 5 • Total lesions 30-125 	
Severe	<ul style="list-style-type: none"> • Number of nodules/cysts > 5 OR • Number of blackheads > 100 OR • Inflammatory lesions > 50 OR • Total lesions > 125

Overtreatment may be found if the diagnosis of patient with AV was not classified according to the current guideline. Classification according to the Indonesian Society of Dermatology and Venereology⁹ (ISDV) based on the degree of severity, consists of mild, moderate, and severe, are presented in **Table 1**. For optimal management, the treatment of moderate and severe AV is very important to be provided by specialists of Dermatology and Venereology.

Moreover, undertreatment can occur in patient with AV. Patient's in adherence to therapy is one of the reasons of undertreatment of AV. Various factors that can affect patient compliance are early improvement, perception that AV is worsening, and adverse effects of treatment causing patients to discontinue treatment. Therefore, anticipation by educating the patient before starting treatment is very important. Treatment with simpler regimens and identification of patient expectations can improve patient compliance. In addition, clinicians need to consider cost as one of the factors that can hinder the continuation of treatment.¹⁰

Skincare habit

A good skincare routine may improve skin condition but some skin care habits may worsen AV. Some social media are referenced for acne treatment consultation especially among adolescents; however, it must be noted that most treatment decision based on social media recommendation do not align with dermatology guidelines. For example, patients tend to choose oral supplements for AV management without sufficient supporting evidence.¹¹ Other habit that can worsen acne including trying new acne treatment every week, using comedogenic products, share makeup or applicators, scrubbing, rubbing, and squeezing AV.¹²

Skin microbiome dysbiosis

Recent studies have shown an association between the skin microbiome and inflammation in AV.^{13,14} *Cutibacterium acnes* and *Staphylococcus epidermidis* are part of the skin microbiome, a complex community of bacteria, viruses, and fungi that live on the epithelial surface and function specifically on the skin. *Cutibacterium acnes* is a skin commensal that prevents colonization and invasion of pathogens by hydrolyzing sebum triglycerides and releasing fatty acids that are antimicrobial, but can also be pathogenic and are associated with the onset of AV.¹⁵ Recent studies have shown that AV is not based on hyperproliferation of *C acnes* but an imbalance in the number and strains of *C acnes* or dysbiosis.¹³ The microbial dysbiosis could be attributed to androgen-mediated seborrhea and dysseborrhea, that select for distinct strains which are genetically better adapted to exploit such an environmental shift.¹⁵ An imbalance in the number and strains of *C acnes* is associated with the inflammatory process in AV pathogenesis, activation of innate immunity and skin inflammation. Both resident and transient bacterial flora also interact with skin inflammatory signals and play a role in the HPI of AV lesions.¹³ In AV lesions, there was a large number of *C acnes* biofilms from the hair shaft to the follicular epithelial wall to the follicular base (Figure 2).¹⁵

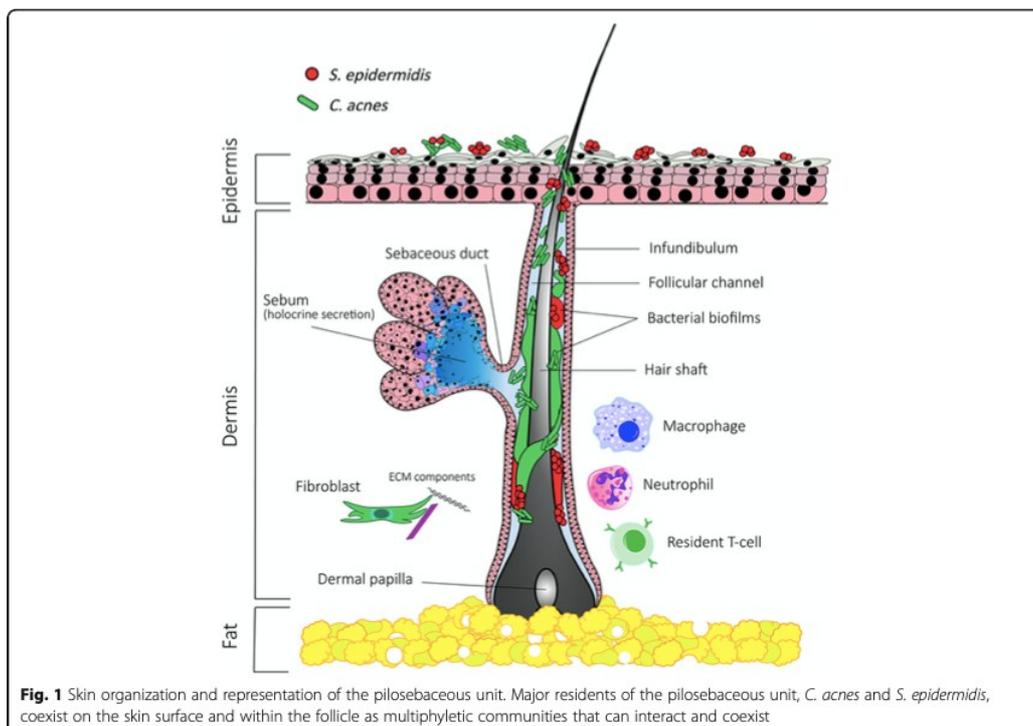


Figure 2. Pilosebaceous units and resident bacteria¹⁵

Lifestyle

Several studies have shown that lifestyle includes insomnia, sun exposure, tobacco, high mental



stress, use of cosmetics are associated with the appearance of AV, whereas frequent washing of the face reduces the risk of AV. Use of cosmetics and high mental stress also increase the severity of AV, while exercise can help reduce the severity of AV.³

Obesity

Most studies have noted increase prevalence of AV in overweight and obese individuals, relative to underweight individuals. Regarding AV severity, overweight and obese body mass index (BMI) may increase the more severe AV.³ Interestingly, Snast et al. in a nationwide study of 600,404 adolescents reported that in youth, overweight and obesity are inversely associated with acne. However, the study did not provide the data concerning AV severity.¹⁶ Dietary factors may confound the effect of BMI.³

Diet

The effect of diet on acne severity is still debated. Some studies show the effect of dairy products including milk, ice cream, yogurt, cheese, does not have a significant impact on acne risk and severity, but other studies show the opposite result. Other studies have hypothesized that sugar and chocolate trigger insulin secretion, affecting signaling pathways leading to increased proliferation and causing acne. Meta-analyses show that large amounts of chocolate consumption increase the risk of AV. The oleic acid present in cocoa butter affects keratinization and promotes the formation of comedones thereby contributing to severe AV. On the other hand, high consumption of fruits and vegetables can reduce the risk of severe AV. However, factory-produced fruit juices do not have this protective effect and increase the severity of acne. Fish consumption may also reduce the risk and severity of AV. Various other diets such as bread, pasta, red meat, spicy food, were found not to be significantly associated with the severity of AV.³

Other medication

Some medications, like vitamin B, corticosteroids, isoniazid, cyclosporine, and anti-cancer targeted therapies, with incidence of 50-85% may cause inflammatory acneiform eruptions.¹⁷

Strategies To Manage Recalcitrant AV (Annoying Acne)

To manage AV, clinician need to identify the internal and external factors described above then some strategies may be applied to manage recalcitrant, including diagnostic approach, education regarding skin care, drug choice, and combination therapy.

Holistic diagnostic approach may be needed in recalcitrant therapy. More detail history taking regarding family history of AV, drug use, diet, lifestyle, skin care habits, smoking can guide further education for the patient. Sebumeter test may be helpful to determine the skin type. Some cases need extraction to find fungal or bacterial etiology of the lesion. In cases when hormonal causes are suspected, hormonal tests and cooperation with Obstetric and Gynecology specialist are important.^{2,8}

Education to patient is the mainstay strategy to manage AV. The patient needs to receive information regarding how AV develop, the causes, and the treatment. Since acne lesion take at least 8 weeks to mature, patient should use a treatment for a minimum 2-3 month before deciding if the treatment is effective. Patient has to be encouraged to wash the face twice daily using gentle nonsoap facial skin cleanser, to not pick or squeeze the acne, and to use sunscreen every day. A noncomedogenic moisturizer may minimize dryness commonly caused by some acne treatment.¹⁸

The approach to selecting treatment modalities is carried out by targeting the four components of AV pathogenesis and tailored to each individual need. Topical retinoids are the treatment of choice and are also used as maintenance because they can reduce comedone lesions, inflammation, prevent and reduce atrophic scars, and dyspigmentation. It should be noted that the side effects of topical retinoids in the form of dry skin, irritation, redness, peeling, so it is



important to start therapy with a low concentration and increase slowly according to patient tolerance.^{10,19}

Topical benzoyl peroxide is a broad-spectrum topical bactericidal agent and bacterial resistance to benzoyl peroxide has not been reported. Benzoyl peroxide can also have a negative impact on the skin barrier with the potential to increase dysfunction. Appropriate vehicle choice and improvement in vehicle technology have mitigate some of these problems. For example, addition of humectants and emollients may help.²⁰

Monotherapy with topical and oral antibiotics is not recommended because it increases the risk of bacterial resistance. Oral antibiotics are indicated for the treatment of severe AV or recalcitrant to topical therapy and should be combined with a topical retinoid and/or benzoyl peroxide. Oral antibiotic therapy is a temporary treatment and is not recommended for long-term (>3-6 months) to avoid antibiotic resistance. The choice of oral antibiotics for severe AV belongs to the tetracycline group, include doxycycline and minocycline, which have anti-inflammatory properties. If tetracycline is contraindicated, macrolides can be used. Other classes of antibiotics, such as trimethoprim and sulfamethoxazole, penicillin, and cephalosporins are not recommended because scientific evidence is limited, unless tetracyclines and macrolides are contraindicated.¹⁰

Conventional therapy not always desirable because of the development of antibiotic resistance and potential risk of adverse effect associated with topical and systemic therapy. Combination therapy with laser and light-based therapy, chemical peels, microneedling, microdermabrasion, and mechanical lesion removal may be added to the treatment regimen, to minimize the risk of adverse effect, boost the effectiveness of the treatment, and relatively safe to use. In a systematic review assessing the efficacy and safety of non-pharmacological therapies in the treatment of acne vulgaris, glycolic acid peels, intense pulsed light (IPL), diode laser, and pulse dye laser (PDL) show good evidence.²¹ Some clinical trial show that low fluence 1064-nm neodymium:yttrium-aluminum-garnet (Nd:YAG) also effective in reducing inflammatory acne lesions.^{22,23}

CONCLUSION

Acne vulgaris is an inflammatory disorder that can have a significant burden on patients, therefore, a holistic approach identifying internal and external factors that may contribute to recalcitrant or annoying acne to treatment is needed. Several strategies including patient education, drug choices, and combination therapy are important in the management of recalcitrant acne vulgaris.

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