

Acne Vulgaris in Adults: A Brief Review on Diagnosis and Management

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ABSTRACT

Acne vulgaris is a chronic skin disease with an inflammatory condition of the skin affecting the pilosebaceous glands. Four concepts of pathogenesis lead to the formation of acne vulgaris, such as sebum production, follicular skin, microbial colonization by *Propionibacterium acnes* bacteria, and inflammatory mediators. The diagnosis of acne vulgaris is dependent on the identification of lesions using classification from the American Academy Dermatology. Acne management is exceptionally diverse, including monotherapy or a combination of various agents that have a role in suppressing the anti-inflammatory and antibacterial activities following the multifactorial causes of acne.

Keywords: acne, adults, skin diseases, *Propionibacterium acnes*, management

INTRODUCTION

Acne vulgaris (AV) is a chronic skin disease with an inflammatory condition of the skin affecting the pilosebaceous glands. [1] Acne does not only occur in teenagers but also adults population. [2] The study of the Global Burden of Disease (GBD) reported that AV affects about 85% of young adults aged 12-25 years. [3] In the United States (US), one of the top three most prevalent skin disease is acne vulgaris. [4] Based on a study from Singapore, acne was found dominantly in about 88% of adolescents aged 13 to 19 years. Acne vulgaris is commonly found in adolescent males, while in the post-adolescent period, it is more frequent in females. [5] Sahala et al. reported

that Indonesia is one of the countries with a high prevalence of skin diseases; including AV. [6] Sitohang et al. reported 1,525 new acne cases in outpatient visits from the cosmetic dermatology division of Cipto Mangunkusumo General Hospital, making AV as the second most common skin disease from dermato-venerology outpatient clinics. [7]

Symptoms of AV are known to be affecting the occurrence of depression, leading to a lower quality of life in its patients, especially adolescents. [8] Psychological comorbidities, including depression and anxiety, have been associated with AV. The potential for post-inflammatory hyperpigmentation (PIH) and scarring into adulthood affected later quality of life as well. [8] A previous study by Yentzer et al. reported 8.8% of female patients with depression associated with AV. [9] Thus, more patients are presenting to physicians seeking proper treatment. The objective of this review is to describe the diagnosis and management of AV accurately to prevent further complications.

CONCEPT OF ETIOLOGY AND PATHOGENESIS

Four concepts of pathogenesis lead to the formation of AV, including the increase and alteration of sebum production, alteration of follicular skin keratinization that leads to comedones, colonization by *Propionibacterium acnes*, and inflammatory processes that involve innate and acquired immunity. [10] Bronsnick et al. reported an

association between AV and consumption of milk or low-fat milk product. [11] Melnik et al. also found that high consumption of high glycemic food products and milk are hypothesized to increase the levels of insulin and serum insulin growth factor-1, leading to comedogenesis, sebaceous lipogenesis, follicular inflammation, and androgenic stimulation. All these factors which promote to AV processes pathology. [12]

Sebum Production

The production of sebum is controlled by androgen and testosterone hormones. [9,12] The initial pathology is initially triggered by androgen hormone. [12] In patients with severe acne, an increased level of dehydroepiandrosterone sulfate (DHEAS) but low sex hormone-binding globulin (SHBG) levels were found, which further induce the elevation of the androgen level. Significant elevation of DHEAS, androstenedione, and SHBG level may occur both in female and male patients. Sebum production subsequently plays a role in the pathophysiology of acne to induce the inflammatory process. [13]

Follicular Hyperkeratinization

In acne pathophysiology, there is an essential role of one type of fatty acid known as linoleic acid. The decreased levels of linoleic acid in the skin may cause hyperkeratinization or hypercornification of follicular cells in the skin. Hyperkeratinization occurs when follicular cells undergo cohesion and cannot be shed to the surface of the skin, causing microcomedones that are subsequently forming into acne. [14]

Microbial Colonization by Propionibacterium acnes

Propionibacterium acne has been implicated in the pathophysiology of AV. Genomic observation identifies that P.acne is about 2.5 Mb in size. [15] P.acne is an anaerobic Gram-positive commensal of normal skin. This bacterium contains ribosome-rich cytoplasm and peptidoglycan that build the cell wall layer. The

overgrowth of P.acne is ideal in comedones because of the presence of lipase enzyme that functions to degrade the lipids on the skin follicle and subsequently become their nutritional source. [16] Free fatty acids produced by lipase are secreted from P.acne and activate the comedogenic and acnegenic factors in sebaceous follicles, leading to the irritation of the follicular walls and the surrounding dermis. This process causes follicular rupture, which induces inflammation by releasing low molecular weight chemotactic factors. These factors diffuse through the thinned follicular epithelium and attract neutrophils, creating the local inflammation reaction. [17] Additionally, P.acne also produces protease and hyaluronidase, induces the keratinocyte growth, and activates matrix metalloproteinase-toll like receptor pathway. [18]

Role of Inflammatory Mediators

The fourth and final factor involved in the pathogenesis of acne is the inflammatory reaction. [17] Inflammatory mediators lead to the formation of microcomedones through lymphocytic infiltration mediated by CD4+ T-cells and CD68+ macrophages. Interleukin 1 alpha (IL-1a), Th17 pathway, dendritic cells are also present in the mechanism of AV. [19] Interleukin-1a has been found as an initial inflammatory mediators in comedogenesis. [1] The invasion of neutrophils can also increase the reactive oxygen species (ROS) level as the result of microbial colonization. This condition leads to the lysis of the invaded cell and increases more inflammatory mediators that induce the acne. [20]

DIAGNOSIS AND EVALUATION

The diagnosis of AV is generally established by identifying of quantity and morphology of the lesions. Their morphologies are divided into the non-inflammatory comedones, termed as open (blackheads) or closed (whiteheads) and the inflammatory lesions, termed as papules, pustules, cyst, or nodules. American

Academy Dermatology (AAD) classified the severity of AV into mild, moderate, and severe (See Figure 1). Mild AV is characterized by the presence of a few to several papules and pustules, but no

nodules. Moderate AV is characterized by several papules and pustules, along with a few nodules. Severe AV is characterized by numerous or extensive papules and pustules, as well as multiple nodules. [10]



Figure. 1 Classification of Acne Vulgaris. [21]

DIFFERENTIAL DIAGNOSIS

There are several of differential diagnosis of AV, such as (1) acne rosacea, which is commonly observed in middle age or later in life, (2) folliculitis and boils, which often present with pustular lesions similar to acne, (3) milia, which is a small non-follicular keratin papules that may be confused with whiteheads, and (4) pityrosporum folliculitis, which more predominates on the trunk. [22]

MANAGEMENT

According to the American Academy Dermatology (AAD), the management of AV consists of two principles i.e., the first-line and alternative treatment (Table 1). [23]

Table 1. Consideration of Management of Acne Vulgaris [10, 23]

Type of Treatment	Mild Acne	Moderate Acne	Severe Acne
First-line medication	<ul style="list-style-type: none"> • Topical retinoid; or • Benzoyl peroxide; or • Topical combination therapy* 	<ul style="list-style-type: none"> • Topical combination therapy*; or • Oral antibiotic, topical retinoid, and benzoyl peroxide; or • Oral antibiotic, topical retinoid, benzoyl peroxide, and topical antibiotic 	<ul style="list-style-type: none"> • Oral antibiotic and topical combination therapy*; or • Oral isotretinoin
Alternative medication	<ul style="list-style-type: none"> • Add topical retinoid or benzoyl peroxide (in case one is not used already); or • Consider alternative retinoid; or • Consider topical dapsone 	<ul style="list-style-type: none"> • Consider alternative combination therapy*; or • Consider change in oral antibiotic; or • Add combined oral contraceptive or oral spironolactone (female patients); or • Consider oral isotretinoin 	<ul style="list-style-type: none"> • Consider change in oral antibiotic; or • Add combined oral contraceptive or oral spironolactone (female patients); or • Consider oral isotretinoin

* Topical combination therapy (benzoyl peroxide and antibiotic agent; retinoid and benzoyl peroxide; or retinoid, benzoyl peroxide, and an antibiotic) may be prescribed as a fixed-dose combination product or as separate components. This recommendation for the management of AV was modified from Zaenglein et al. [10]

Topical Agents

The main focus on acne treatment is topical drugs. The most common topical medications for acne include benzoyl peroxide, clindamycin, and retinoids. [23-25]

Benzoyl Peroxide

Benzoyl peroxide (BP) is commonly prescribed topical medications for AV. It

mainly reduces the colonization of *P. acnes* and inflammatory acne lesions. It also has keratolytic and sebostatic effects without a concern for the development of drug-resistant bacteria. Benzoyl peroxide is a bactericidal agent, has stable formulation in treating comedonal acne. It has several concentrations ranging from 2.5%, 5%, and 10%. The Food and Drug Administration (FDA) classified that BP as pregnancy risk category C. [24, 25]

Retinoids

Topical retinoids are effective first-line therapy against comedonal and inflammatory acne. These topical are vitamin A derivatives, and the binding of retinoids to their receptors, these agents may reduce hyperkeratinization and decreases adhesion. [26] Based on in vivo observation, these agents have demonstrated anti-inflammatory activity. Topical retinoids may reduce microcomedones and mature comedos, promote desquamation of follicular epithelium, and reduce inflammatory mediators. [27]

Clindamycin

Another commonly used topical antibiotic regiment for the treatment of AV is clindamycin. It works by targeting the 50s subunit of bacterial ribosomes and interfering with the protein synthesis, thereby exerting antibacterial effects. Clindamycin also has the effect of suppressing inflammation, which can be induced by *P. acnes*. [28] Some studies showed that clindamycin could inhibit the expression of proinflammatory cytokines, such as interleukin 1, interleukin 6, and tumor necrosis factor. Although this regiment has been shown to display considerable success in the treatment of AV, it is rarely used as a monotherapy because of the high risk of resistance. [29]

Other topical agents

Other topical agents include salicylic acid and azelaic acid, which have antibacterial, comedolytic, and anti-inflammatory properties. They are considered as potential first-line monotherapy for female adult patients and a

good choice for maintenance therapy. [30] A potential adverse effect of azelaic acid is hypopigmentation, which might be helpful in treating post-inflammatory hyperpigmentation. Azelaic acid with 15% gel formulation was found to be as effective as topical benzoyl peroxide and clindamycin for patients with mild to moderate acne. [31]

Systemic Agents

Isotretinoin

Oral isotretinoin works by affecting the four pathophysiological pathways of AV and reported to have a permanent remission result on the disease course. It shows a 90% reduction in sebum secretion and an almost 85% cure rate without relapse. [32] Its mechanism of action is done by influencing the G1-S phase of the cell cycle by decreasing DNA synthesis, increasing p21 (encoded CDKN1A) protein expression, and decreasing cyclin D1 protein expression. Oral isotretinoin causes numerous adverse effects, but severe effects rarely occur. Although uncommon, depression is among one of the adverse effects; thus, the use of this regiment should be monitored closely. [33]

Spiroonolactone

Spiroonolactone (SP) is a potassium-sparing diuretic, and selective aldosterone blocker used off-label in dermatology for the treatment of acne. In 1960, it received initial approval by the FDA. [34] The mechanism of action of SP is still unclear, but is expected to affect androgen receptors in the sebaceous glands and reduce sebum production, causing an improvement of AV symptoms. It also reduces the conversion of weaker androgens to more potent androgens in the peripheral tissues. The dose recommendation of SP for acne is 25-200 mg/day divided into one to two doses. The use of 50 mg SP twice a day on days 5 through 21 of women's menstrual cycle showed favorable clinical results with a low incidence of side effects. [35] Salama et al. reported that SP has antiandrogen properties with a promising result in the treatment of acne, especially in female patients.

However, the use of this preparation must be careful because the systemic side effects are often more detrimental than its clinical benefits. [36]

Oral Antibiotics

Systemic antibiotics that are commonly used in AV against P.acne include tetracycline, erythromycin 500 mg twice daily, clindamycin and doxycycline 100 mg twice daily. Unfortunately, the broad spectrum and long-term use of antibiotics over the years have led to the emergence of resistant bacteria. [37] Resistance to tetracycline and cross-resistance to doxycycline are also common and associated with a mutation in the 16S ribosomal rizinform of the small ribosomal subunit in the equivalent base of E. coli 1058 (G-C). Resistance of erythromycin is associated with point mutations in the genes encoding subunit 23S of the ribosomal RNA. [38] Meanwhile, reports of resistance to azithromycin have not yet been found. [37] Azithromycin 500 mg twice weekly for 12 weeks is safe and effective treatment of AV. It reveals more potent efficacy if combined with oral desloratadine. [39,40] Akter reported that the combination regimen of azithromycin and daily topical benzoyl peroxide (4%) is indeed more efficient and safe in the management of AV after 12 weeks of treatment. [41]

Oral Contraceptives

The FDA has approved the treatment of AV related to hormonal pathology since the 1990s. These regimens include the combination of ethinyl estradiol and norgestimate or the combination of norethindrone acetate and ethinyl estradiol. Oral contraceptives manipulate the androgen activity and have the same properties as 25 mg of SP. Although the use of hormonal modification may be helpful for AV, dermatologists need to look for endocrinopathies such as polycystic ovarian syndrome (PCOS) that manifested as having irregular menses, acne, infertility, and obesity. It is recommended that these hormonal therapies may only be considered when first-line therapy failed. [42]

Future Development of Acne Treatment

One of the interesting findings about the future management of AV is the potential use of acne vaccines. As mentioned above, AV is known to have a multifactorial etiology. These vaccines are supposed to induce the host immunity against bacterial toxicity produced by P.acne bacteria. An experimental study done in animals showed a good outcome in improving the immunity reaction in P. acne-associated inflammatory acnes. This vaccine was also found to decrease the release of cytokine production that is involved in acne pathophysiology. [43]

CONCLUSION

This brief review highlights the relevant clinical findings and pathology of acne vulgaris as a chronic inflammatory skin disease affecting the pilosebaceous glands. It has multifactorial causes and manifestations varying from the mild to severe degree. Several highly effective treatments of choice have been proposed as a monotherapy or combination therapy to reduce and prevent the occurrence of acne. Appropriate clinical considerations are needed for clinicians to ensure a comprehensive approach in the management of acne vulgaris.

REFERENCES

1. Rahmayani T, Putra IB, Jusuf NK. Association of serum interleukin-10 (IL-10) with the severity of acne vulgaris. Bali Med J. 2019;8(3):573-6.
2. Thiboutot D, Gollnick H, Bettoli V, et al. New insights into the management of acne: an update from the global alliance to improve outcomes in acne group. J Am Acad Dermatol. 2009;60(5):1-50.
3. Seattle WI. Global Burden of Disease (GBD) Compare. Seattle: University of Washington; 2013.
4. Bhate K, Williams HC. Epidemiology of acne vulgaris. Br J Dermatol. 2013;168(3): 474-85.
5. Oon HH, Wong S, Wee Aw DC, et al. Acne management guidelines by the

- dermatological society of Singapore. *J Clin Aesthet Dermatol.* 2019;12(7):34-50.
6. Sahala MA, Soedarman S, Rizky LA, et al. The prevalence of skin diseases and its association with hygiene behavior and level of education on a Pesantren, Jakarta Selatan 2013. *eJKI* 2016;4(2):119-24.
 7. Sihotang IBS, Fathan H, Effendi E, et al. The susceptibility of pathogens associated with acne vulgaris to antibiotics. *Med J Indones.* 2019;28:21-7.
 8. Gieler U, Gieler T, Kupfer JP. Acne and quality of life-impact and management. *J Eur Acad Dermatol Venereol.* 2015;29:12-4.
 9. Yentzer BA, Hick J, Reese EL, et al. Acne vulgaris in the United States: a descriptive epidemiology. *Cutis.* 2010;86(2):94-9.
 10. Zaenglein AL, Pathyl AI, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2016;74(5):945-73.
 11. Bronsnick T, Murzaku EC, Rao BK, et al. Diet in dermatology: part I. Atopic dermatitis, acne and nonmelanoma skin cancer. *J Am Acad Dermatol.* 2014;71(6):e1-1039.e12.
 12. Melnik BC. Evidence for acne-promoting effects of milk and other insulinotropic dairy products. *Nestle Nutr Workshop Ser Pediatr Program.* 2011;67:131-45.
 13. Ray C, Trivedi P, Sharma V. Acne and its treatment lines. *Int J Res Pharma Sci.* 2013;2(1):1-16.
 14. Tuchayi SM, Makrantonaki E, Ganceviciene R, et al. Acne vulgaris. *Nat Rev Dis Primers.* 2015;1:1-20.
 15. Platsidaki E, Dessinioti C. Recent advances in understanding *Propionibacterium acnes* (*Cutibacterium acnes*) in acne. *F1000Research.* 2018;7:1-12.
 16. Contassot E, French LE. New insights into acne pathogenesis: *Propionibacterium acnes* activates the inflammasome. *J Investig Dermatol.* 2014;134:310-3.
 17. Toyoda M, Morohashi M. Pathogenesis of acne. *Med Electron Microsc.* 2001;34:29-40.
 18. Dessinioti C, Andreas D, Katsambas. The role of *Propionibacterium acnes* in acne pathogenesis: facts and controversies. *Clin Dermatol.* 2010;28:2-7.
 19. Jeremy AHT, Holland DB, Roberts SG, et al. Inflammatory events are involved in acne lesion initiation. *J Investing Dermatol.* 2003; 121:20-7.
 20. Prasad SB. Acne vulgaris: a review on pathophysiology and treatment. *Asian J Pharm Clin Res.* 2016;9(4):54-9.
 21. Thiboutot DM, Dreno B, Abanmi A, et al. Practical management of acne for clinicians: an international consensus from the global alliance to improve outcome in acne. *J Am Acad Dermatol.* 2018:1-24.
 22. Knott L. Acne vulgaris [Internet]. *Patient Info*; 2015 May 11 [2020 May 18]. Available from <http://www.patient.co.uk/doctor/acne-vulgaris>.
 23. American Family Physician. Acne vulgaris: treatment guidelines from the AAD. *American Family Physician.* 2017;95(11):740-1.
 24. Kawashima M, Nagare T, Doi M. Clinical efficacy and safety of benzoyl peroxide for acne vulgaris: comparison between Japanese and Western patient. *J Dermatol.* 2017; 44(11):1212-8.
 25. Kircik LH. The role of benzoyl peroxide in the new treatment paradigm for acne. *J Drugs Dermatol.* 2013;12(6):73-6.
 26. Chien AL, Voorhees JJ, Jang S. *Fitzpatrick's Dermatology in Medicine.* Seventh Edition. New York: McGraw-Hill; 2008.
 27. Hubbard BA, Unger JG, Rohrich RJ. Reversal of skin aging with topical retinoids. *Plast Reconstr Surg.* 2014; 133(4):481e-90e.
 28. Leccia MT, Auffret N, Poli F, et al. Topical acne treatments in Europe and the issue of antimicrobial resistance. *J Eur Acad Dermatol Venereol.* 2015;29(8):1485-92.
 29. Del Rosso JQ, Schmidt NF. A review of the anti-inflammatory properties of clindamycin in the treatment of acne vulgaris. *Cutis.* 2010;85(1):15-24.
 30. Dreno B. Adult female acne: a new paradigm. *J Eur Acad Dermatol.* 2013; 27(9):1063-70.
 31. Gollnick HP, Graupe K, Zaumseil RP, et al. Azelaic acid 15% gel in the treatment of acne vulgaris: combined results of two double-blind clinical comparative studies. *J Dtsch Dermatol.* 2004;2(10):841-7.
 32. Zouboulis CC, Bertoli V. Management of severe acne. *Br J Dermatol.* 2015;172(1):27-36.
 33. Sandoval LF, Hartel JK, Feldman SR. Current and future evidence-based acne

- treatment: a review. *Expert Opin Pharmacother.* 2014;15(2):173-92.
34. Goodfellow A, Alaghband ZJ, Carter G, et al. Oral spironolactone use improves acne vulgaris and reduces sebum excretion. *Br J Dermatol.* 1984;111(2):209-14.
35. Harper JC. Antiandrogen therapy for skin and hair disease. *Dermatol Clin.* 2006;24(2):137-43.
36. Salama A, Badran M, Elmowafy M, et al. Spironolactone-loaded liposomes as potential topical delivery systems for female acne: in vitro appraisal and ex vivo skin permeability studies. *Pharmaceutics.* 2020;12(25):1-17.
37. Kus S, Yucelten D, Aytug A. Comparison of efficacy of azithromycin vs. doxycycline in the treatment of acne vulgaris. *Clin Exp Dermatol.* 2005;30(3):215-20.
38. Ross JI, Eady EA, Carnegie E, et al. Detection of transposon Tn 5432-mediated macrolide-lincosamide-streptogramin B (MLSB) resistance in cutaneous *Propionibacteria* from six European cities. *J Antimicrob Chemother.* 2002;49(1):165-8.
39. Dhaher SA, Jasim ZM. The adjunctive effect of desloratadine on the combined azithromycin and isotretinoin in the treatment of severe acne: randomized clinical trial. *J Dermatol Dermatol Surg.* 2018;22(1):21-5.
40. Fernandez-Obregon AC. Acne treated successfully with azithromycin. *Int J Dermatol.* 2004;43(10):45-50.
41. Akter B. Oral azithromycin pulse therapy and daily topical benzoyl peroxide in the treatment of acne vulgaris: an open clinical trial study. *J Bangladesh Coll Phys Surg.* 2018;36(1):11-5.
42. Mathur R, Levin O, Azziz R. Use of ethinylestradiol/drospirenone combination in patients with the polycystic ovary syndrome. *Ther Clin Risk Manag.* 2008;4(2):487-92.
43. Nakatsuji T, Rasochova L, Huang CM. Vaccine therapy for *P. acnes*-associated diseases. *Infect Disord Drug Targets.* 2008;8(3):160-5.

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