

(REVIEW ARTICLE)



Systematic literature review of acne vulgaris, its sophisticated treatment approaches, types, treatment and their side effects.

Aisha Maqbool ¹, Jibran Ikram ², Syed Aftab ³, Syed Farooq Shafiq ⁴, Sanaullah ⁵, Abid Ali ⁶, Muhammad Nouman ⁷, Mian Atif Sardar ⁸, Sami Ullah ⁴, Muhammad Huzaifa ⁹, Osama Khan ¹⁰, Muhammad Awais Khan ¹¹ and Furqan Ul Haq ^{12,*}

¹ Department of Nephrology, PIMS Hospital Islamabad, Pakistan.

² Department of Internal medicine, Rehman medical institute Peshawar, Pakistan.

³ Department of General Medicine, Cork University, Cork Ireland.

⁴ Department of Medicine lady reading hospital Peshawar, Pakistan.

⁵ Department of Medicine, Hayatabad medical complex Peshawar, Pakistan.

⁶ Department of Medicine, Saidu Teaching Hospital Swat, Pakistan.

⁷ Department of Medicine, Khyber Teaching Hospital Peshawar, Pakistan.

⁸ department of Medical, Roshan medical center, Swat Pakistan.

⁹ Department of General Medicine, Niazi medical college Sargodha, Pakistan.

¹⁰ Department of Oncology, Shifa International hospital Islamabad, Pakistan.

¹¹ Department of Medicine, Combined Military hospital Abbottabad, Pakistan.

¹² Department of Radiation oncology, Shifa International hospital Islamabad, Pakistan.

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Abstract

Background: Acne formation can be controlled effectively but it heals slowly and has numerous interactions with neuropeptides. Once gone another one pops up. Sometimes it can be filled with pus. Its size varies and can cause anxiety, depression, stress and social withdrawal. The mechanism is hyper secretion of sebaceous glands.

Introduction: Acne vulgaris is a condition when hair follicles are accumulated with oil, dead cells and bacteria from skin. It can lead to formation of blackhead, whitehead, oily skin, pimples and scarring eventually. Patients have raised sebum level and thus skin is more prone to acne formation; triggered by propionibacterium, genetics, environment and food. Most commonly occurring on the face, upper limb and trunk between teen to middle age. Sebum contains wax esters, cholesterol, and triglyceride.

Objectives:

- To extensively explain the etiology of acne vulgaris, hormonal, bacterial causes and UV light.
- To write comprehensive review on treatment of AV conventional, topical, retinoid and antibiotics based treatment.
- Write a comprehensive review on its complications and its management.

Methodology: In this research article we have explained systematic review, as well as we have described the systematic literature review of Acne Vulgaris, We did a literature search using electronic bibliographic databases and Journals : such as ELSEVIER, British Medical Journals, MEDLINE (Ovid SP and PubMed), EMBASE, The Cochrane Library (Cochrane Database of Systematic Reviews (CDSR), and Cochrane Central Register of Controlled Trials (CENTRAL), as well as

* Corresponding author: Furqan Ul Haq

annual meetings abstracts from inception till Oct 2024. The literature search has focused mainly on randomized clinical trials, Meta-analysis, phase II/III, and retrospective studies.

Results and Conclusion: The review included 45 studies with a total of 12000 participants. Acne vulgaris affects 9% of the population worldwide, 85% are between 12-24 years. Characters such as age and sex may vary among different studies. Many papers demonstrate the effect of demographic factors. Reaching late teenage can decrease its prevalence, and eruption is higher in females compared to male. Topical retinoid and benzoyl per oxide were effective in reducing inflammatory and non-inflammatory lesions. For mild to moderate acne pharmacological treatment, chemical, antibiotic and photodynamic therapy are among most effective. Oral antibiotics while effective, have raised concerned about resistance. For moderate to severe, the most effective one is oral Isotretinoin and photodynamic treatment. Most of us already know too much about this topic. Its 8th commonest disease known globally. It has many treatments. It's the cause of social withdrawal and depression. In this case it is important to know about the causes that shift non inflammatory to inflammatory ones. Dermatologists are trying their best in combination of multiple therapies to treat it successfully. Personalized treatment plans considering patient-specific factors, such as acne severity, patient preference and risk of adverse effects, are essential for optimal management.

Keywords: Acne Vulgaris; Treatment; Isotretinoin; Clindamycin; Photodynamic therapy; Laser; Hormonal therapy; Pharmacological treatment; Doxycycline

1. Introduction

Acne vulgaris AV is a dermatological disorder mostly affecting teenagers, it is among most commonly occurring skin diseases ¹. Arises during any age but mostly during puberty worsens in adolescence. Apart from excessive sebum production, abnormal follicular differentiation, genetics, micro bacterial colonization, increased inflammation can lead to activation of the immune system. Acne can have various types e.g. acne le vulgaris, acne rosacea, acne fulminant, acne mechanical. Pharmacological treatment is always desirable but not always suitable all the time e.g. during pregnancies as one of its products is teratogenic and even antibiotic resistance can even develop². Side effects vary among different products. Non pharmacological treatments are also available such as Chinese herbal, massage and acupuncture. Severe acne includes cyst, nodule and open lesions. Non-inflammatory as also called closed comedones, open comedones². It can be inflammatory as inflammation is seen and occurs due to allergy or bacterial invasion some scar formation can also occur. It always occurs with symptoms itching, burning, scar, erythema, pus and pain. Although pharmacological treatment is available, results are always never fruitful. Treatment can though reduce the inflammatory and non-inflammatory lesion, reoccurrence, minimize scarring, appearance. Systemic products are retinoid, Isotretinoin, antibiotics or oral contraceptive pills. People also use some alternative medicine such as herbal medicine, dietary modification, acupuncture, and Chinese medication, manual healing therapies and some other traditional and folk therapies are also available³. Reporting and methodological quality limitations in the studies may exist. Many bacteria including e coli, klebsiella, proteus, enterobacter. Girls must be aware of increasing chances of acne by cosmetics products. Certain chemical products are endocrine disruptors such as parabens, triclosan. Soft drink increases risk as well³.

1.1. Epidemiology

Its affecting percentage among teenagers is 80%. It can be due to bacterial invasion, emotional distress, normal maturation process or endocrine system disorder. About 60% use non-prescribed medication while the remaining 40% have been prescribed. It's more common in Caucasian population as compared to rest mostly occurring in girls in 18-19years old. 20% of patient's complaints of scarring as well. Obesity and overweight or PCOS, high glycemic index, high calorie intake, junk or oily food, snacks, cheese, fried things, high fats, noodles increases chances of occurrence. 50% of women developing acne do not have high androgen levels. 60% of women have it due to increased inflammatory lesions in the menstrual cycle. Heritable chances are almost 10%. More commonly occurring during pregnancy⁴.

1.2. Etiology

It can occur due to genetics, environmental variables such as pollution, environment change, temperature, humidity, mineral oil, nutrition, Stress, smoking, androgens, cosmetics, bacteria, steroids, halogens and pregnancy. It can cause discomfort, emotional stress and can even lead to scar formation. A multifactorial process in which excess sebum production occurs and hyper proliferation of bacteria (propionibacterium acne) occurs which can cause abnormal hyperkeratinization and inflammatory mechanisms. Here are four causing agents and factors in bacterial growth⁵.

1.2.1. Increase in sebum production:

It can occur due to hormonal changes such as androgen production, testosterone or insulin growth hormone. There is a clear correlation between acne formation and sebum production.

1.2.2. keratinization follicles in a patient:

follicles the hyper keratinization process occurs it accumulates which together with the lipid causes acne.

1.2.3. Hyper proliferation of *Propionibacterium acne*:

Plays an important role in inflammatory acne formation it is the causing agent as it's the anaerobic gram positive bacteria which colonize in sebaceous follicle and lead to the large amount production of sebum that is excellent habitat for bacterial growth. *Propionibacterium* secrete lipase enzymes that metabolize triglyceride of sebum into glycerol and fatty acid which lead to inflammation of skin. When the immune system detects p .acne the inflammatory process starts and neutrophil, macrophages and lymphocytes agents are released which damages the dermis layer of skin and can lead to formation of ulcers and non-inflammatory lesions can occur as well. Neutrophils produce reactive oxygen species which damage epithelium and cause acne formation and consequently follicular substances are released into the dermis.

1.2.4. DNA methylation:

Environmental stress ,some modifications of genetics can express and change DNA.DNA methylation is one of the example that is increasing in the society which can the production of inflammatory diseases such as cancer. Cancerous disease plays an important role in the formation of psoriasis and other inflammatory diseases.

- **Role of acne:** C acne is widely considered prominent within pilosebaceous follicles. It can trigger innate and adaptive immunity and causes inflammatory responses. It stimulates the pro-inflammatory cascade, specifically TH17 cells. These cells secrete cytokines such as interferon gamma and interleukin. Inflammation occurs. Resistance strain has seen as well. It stimulates the innate immune system as well, resulting in activation of toll-like receptors on macrophages triggering more cytokine release and neutrophil attraction⁶.
- **Diagnosis:** diagnosis is done on the basis of physical examination under room or day light. History and physical examination helps in diagnosing. Differential diagnosis of acne include folliculitis, dermatitis, seborrheic dermatitis, and rosacea. Hormonal profile not usually prescribed for regular menstrual cycle. Pelvic ultrasound can be done as well for polycystic ovaries. Older women with new onset of acne and androgen excess should be tested for measurement of testosterone, dehydroepiandrosterone, FSH, LH, androgen.in hormonal suspect following tests should be done have been discussed in table no 1.

Table 1 Hormonal tests and their results

Series	Hormones	Results
1-	Testosterone	Elevation<200 ng/dl are suggesting ovarian or adrenal tumor
2-	PROLACTIN	Suggests hypothalamic or pituitary tumor
3-	Luteinizing hormone	>2 suggests PCOS
4-	Serum cortisol	Higher levels suggests adrenal hyperplasia
5-	Fasting and postprandial insulin	Shows PCOs

1.3. Treatment

1.3.1. Convention methods

Primary management includes controlling sebum production, abnormal hyperkeratinization and propionibacterium infection. Main treatment includes antibacterial, anti-inflammatory, phototherapy, cryotherapy, comedone extraction. Following is it

1.3.2. Topical treatment

They are effective and usage is worldwide by dermatologists. Retinoid and antibiotics are used. Skin erythema or irritation can occur and topical treatment can take days to years. They have minimal systemic absorption and are the most preferred one. Retinoids are preferred systemic treatment, its vitamin A derivative and suppresses acne for long

term. Used in treatment of severe or inflammatory acne. It is used in oral form. Isotretinoin is the type of retinoid and it causes sebaceous gland differentiation to decrease sebum production and decreases colonization of bacteria⁷. It's teratogenic and the period of administration is 16-24 weeks. Different Retinoid types are given below in table no 2.

Table 2 Types of Retinoids

Medications	Properties	Mechanism of action	Side effects
Tretinoin Retinoid	Vitamin A derivative, anti-inflammatory	Reduce sebum production	Headache, erythema, itching, hair loss.
Tazarotene Retinoid	Second line drug after tretinoin, combined with antibiotic or benzoyl peroxide	Reduces hyperkeratinization	Irritation, erythema.
Adapalene Retinoid	First line therapy for AV	Reduces inflammation and hyperkeratinization	Irritation, erythema.

1.4. Antibiotics

When applied it reduces colonization of bacteria and inflammation. It is used to reduce moderate to severe acne. Antibiotics suppress inflammatory mediator's production⁸, it has the capability to reach pilosebaceous follicles in the dermis, some examples of antibiotics are given below in table 3.

Table 3 Antibiotics and other therapies

Antibiotic	Mechanism
Erythromycin	Topically applied on skin, helps to reduce colonization of Propionibacterium.acne it is 60% resistance
Clindamycin	Topical antibiotic used for treatment of acne. Topical monotherapy should Be avoided and combinational is encouraged
Tetracycline	Include minocycline, doxycycline, widely used anti-inflammatory and anti-bacterial because they cause less GI discomfort. It has lesser resistance than macrolides
Azithromycin	used as anti-inflammatory
Benzoyl peroxide	Topical antibacterial, for acne. Produces oxygen which degrades bacterial protein and its adverse effects are redness, itching.
Salicylic acid	Antibacterial, anti fungicidal, anti-inflammatory. It exfoliates skin, it causes skin irritation, redness. It is the active ingredient of face wash.
Niacin amide	It is a form of vitamin B3 lessen which is anti-inflammatory in nature and the sebum production it is used in serums and face washes.
Azelaic acid	It is anti keratolytic and anti-oxidative. It is used to treat skin whitening and hyperpigmentation
Depose	Its mode of action is unknown but it is antibacterial. It is not first line agents

2. Hormonal therapies

Alternate best option for treating acne, it can be used to treat androgen effect on sebaceous glands. These are mostly derivatives of oral contraceptive pills. As oral contraceptive pills inhibit sebum production as is stimulated by testosterone. It decreases testosterone in female bodies and increases Sex hormone binding globulin. Acnes can be treated with oral contraceptive pills or in combination with other treatments. Spironolactone is an androgen receptor blocker in combination with oral contraceptive pills.

Recent scientific advances are trying their best to inhibit the mechanistic pathway of acne formation⁹. Receptors, chemokine, inflammatory mediators, are targeted to reduce their released discussed in table 4

Table 4 Different drugs available in commercial for acne treatment

Brand name	Drug class	Acne treated	Intake	Side effects of drug used
Accutane	Isotretinoin	Severe Acne	Oral	Loss of hair, dryness of lips
Benzamycin	Erythromycin and benzoyl peroxide	Mild to moderate acne	Topical Gel	Eye and skin irritation, stinging,
Differin	Adapalene-Retinoids	Mild to moderate acne	Topical gel form	Erythema, dryness
Isotin	Isotretinoin	Mild acne	Topical gel	Loss of hair, erythema
Vibramycin	Tetracycline, antimalarial	Acne	Oral	Rash decrease appetite

Managing complications in acne vulgaris involves various approaches to address specific issues that may arise. Here are some common complications and their corresponding management strategies:

Table 5 Management of Complications

Serial no.	Type of complication	Medical Management
1	Postinflammatory hyperpigmentation	Retinoids, Azelaic acid, Hydroquinone
2	Postinflammatory erythema	Tranexamic acid
3	Ice-pick scars	Trichloroacetic acid
4	Rolling scars	Lasers ablation
5	Boxcar scar	Filler injection
6	Hypertrophic scar or keloid	Bleomycin, cryotherapy, 5 fluorouracil

2.1. Differential diagnosis

- Rosacea
- Periorbital dermatitis
- Folliculitis
- Facial angiofibroma
- Pseudofolliculitis
- Sebaceous hyperplasia
- Adnexal tumor

Acne prevention: Relation between acne and diet is highly interlinked. Several studies have shown the link. Some dietary factors are milk, chocolate, glycemic load, fatty food, dietary fiber antioxidant, zinc, vitamin A, iodine. Milk >2 glasses per day is associated with mild to moderate acne. No significant relation between skimmed daily product and acne, similarly for cheese/ yogurt. Highly contents of iodine can lead to sudden eruption of acne. following nutrition can affect

Chocolate intake: Chocolate intake can lead to pro-inflammatory mediators such as cytokines, TNF, interleukin and such more. It further worsens acne. According to some researchers avoiding milk, chocolate and meat can improve it

Glycemic index: Nutrition related lifestyle factors can play an important role as highly glycemic index can proliferate acne formation. A low glycemic index and load can IGF-1 concentration thus formation of acne elevates. Fast food and soda increases calories, carbohydrates, fats. Processed food can elevate it as well¹⁰.

Dietary fiber: Improves skin condition. Eliminates toxins from the body. Fruits, vegetables, and lentils beans are good sources. Gastrointestinal dysfunction can lead to disease of sebaceous gland, and hence proper diet improves acne. High fiber diets increase healthy bacterial growth and microflora. Over abdominal bloating is 37% associated with it.

Antioxidant: Poly phenol is an antioxidant contained in nuts, fruits, chocolate, and wine tea. It has anti-microbial and anti-inflammatory activity and anti-neoplastic activity. It reduces sebum content. Apple polyphenol inhibits lipid production and expression of enzymes that cause fatty acid synthesis¹¹. Vitamin A and E also affect improvement.

Cleansing and sun protection: Cleansers reduce inflammatory and non-inflammatory acne lesions. In addition to these it also contains dye and perfumes causing skin irritation and exacerbating acne. These cleansers are too harsh and result in excessive dryness, leading to overcompensation by excess oil production. Matching skin type is essential for the right cleanser to choose. Soap free cleanser has a PH of 5.5 more suitable for acne. Lowering PH reduces inflammatory mediators and functions to strengthen bacterial barriers¹².

Avoid stress and drug intake: It's a contributing factor to acne formation, several neurological factors can interact with it. Increased cortisol in several conditions, stress, and sleep deprivation has an important effect on hypothalamic pituitary. Direct correlation between smoking and acne. Smokers face has specific features of micro and macro comedones. Sebaceous gland is sensitive to nicotine hence 2-6% acne occurrence is increased¹³.

3. Result

We have included observation and conclusion for mild to moderate acne treatment best among all was pharmacological which is a combination of retinol is and benzoyl peroxide, 95% is the credible interval in it. Salicylic acid or Mandelic acid has a credible interval of 95%. Phytochemicals such as red or blue light have further lesser results. Antibiotics and hormonal contraceptives do not appear to be effective in treatment. For moderate to severe treatment effective one is retinoid and clindamycin in combination and then Isotretinoin, photodynamic therapy together with benzoyl peroxide, topical retinoid and tetracycline. Bias chases are more in photodynamic treatment. Combined retinoid and benzoyl peroxide has 95% credible interval, chemical peels have 95% as well. Oral pharmacological treatments do not appear to be effective after bias. Benzoyl peroxide and retinoid are less tolerated than placebo.

3.1. Prognosis

Overall it's very good when appropriate treatment is followed. Acne is never life threatening but it has long lasting psychological effects. Anxiety and depression is common. Its treatment can be challenging. Some studies show an increase in chances of prostate cancer in boys having acne in teenagers¹⁴.

4. Conclusion

For mild to moderate acne pharmacological treatment, chemical, antibiotic and photodynamic therapy are among most effective. For moderate to severe, the most effective one is oral Isotretinoin and photodynamic treatment. Most of us already know too much about this topic. Its 8th commonest disease known globally. It has many treatments. It's the cause of social withdrawal and depression. In this case it is important to know about the causes that shift non inflammatory to inflammatory ones. Dermatologists are trying their best in combination of multiple therapies to treat it successfully. Antibiotics resistance is still a challenge for them. Acne vulgaris affects 9% of the population worldwide, 85% are between 12-24 years. Characters such as age and sex may vary among different studies. Many papers demonstrate the effect of demographic factors. Reaching late teenage can decrease its prevalence, and eruption is higher in females compared to male. Low computer usage and late marriage has a declining factor. Two case control studies were excluded from studies but the result is still in line with observed. Larger odd ratio 2.6 is observed if both parents have acne compared to single one. Oily skins show more association to sebum production and has been associated with increased risk. Personalized treatment plans considering patient-specific factors, such as acne severity, patient preference and risk of adverse effects, are essential for optimal management.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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