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Review Article

**MANAGEMENT OF ACNE**

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<sup>1</sup>Jazan University<sup>2</sup>King Fahad Central Hospital Abu Arish<sup>3</sup>Misr University For Science And Technology<sup>4</sup> King Abdulaziz University<sup>5</sup> King Khalid University<sup>6</sup> Southeast University**Abstract:**

**Introduction:** Acne vulgaris is one of the most important inflammatory skin disease and it is the 8<sup>th</sup> most prevalent disease around the world with a prevalence that can reach 9% of the general population. It affects the teenagers in most cases and specially girls. However, it also can affect the adults. One of the worst complications of acne is the development of scars. As known, severe acne cause a very bad, long lasting scars that can cause psychological problems and social difficulties. Recently, the guidelines for acne treatment have become controversial.

**Aim of work:** In this paper, we will review the most recent evidence on the management of acne vulgaris.

**Methodology:** We did a systematic search for the current and recent advances in management of acne vulgaris using PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>). Our search also looked for presentation, and treatment of acne vulgaris. All relevant studies were retrieved and discussed. We only included full articles.

**Conclusions:** Acne is a chronic inflammatory disease that affects the adolescent population generally and girls specially, it can cause really serious psychological damage and physical scarring without the appropriate treatment. Depression, anxiety and even suicide are found in acne patients. The right early treatment is essential in acne, so in order to effectively and rapidly reduce acne lesions, and avoid scarring, a combination therapy of topical and systemic agents that targets as many of the underlying factors as possible should be considered. The emergence of *P. acnes* resistance requires a combination topical therapy and a low therapeutic threshold to introduce oral isotretinoin, which is a highly effective, well established treatment of acne and the only therapy that targets all of the etiological factors of this disease.

**Key words:** Acne vulgaris, risk factors, clinical features, management.

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**INTRODUCTION:**

Acne vulgaris Is one of the most important inflammatory skin diseases and it is the 8<sup>th</sup> most prevalent disease around the world with a prevalence that can reach 9% of the general population [1]. It affects the teenagers in most cases and specially girls. However, it also can affect the adults [2]. It is an increasing cause for women to visit dermatologists [3]. The exact pathological process of the acne is not clear yet, but some etiologies have been strongly suggested by previous studies. These include: High sebum production induced by high androgen concentration; the infection of hair follicles on face, neck, and chest and back by Propionibacterium acnes; alteration in keratinization; and the presence of chronic inflammation in the skin.

One of the worst complications of acne is the development of scars. As known, severe acne cause a very bad, long lasting scars that can cause psychological problems and social difficulties such as: Social isolation and lack of confidence, which lead to depression and sometimes even thinking of suicide.

There are many different treatments modalities used for acne, some of them are topical, and some are systemic. Oral isotretinoin is the best example for the systemic drugs and it is the most effective one, studies suggest that it plays role in all the known etiologies. However, there is no solid evidence that supports the efficacy of these drugs.

Recently, the guidelines for acne treatment have become controversial. Generally, the old guidelines recommended that in mild to moderate cases we should use only a mixture of topical agents, and in moderate to severe or refractory cases we should use the systemic agents. However, new guidelines are suggested considering the social and psychological problems of the patient, it recommends the application of systemic agent whenever the topical have failed.

In this paper, we will review the most recent evidence on the management of acne vulgaris.

**METHODOLOGY:**

We did a systematic search for the current and recent advances in management of acne vulgaris using PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>). Our search also looked for presentation, and treatment of acne vulgaris. All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Acne vulgaris, presentation, risk factors, recent advances, management, and adverse effects.

**Risk factors:**

The most important suggested risk factor in the acne pathology is diet. A new theory tells that western diets components are possibly associated with acne<sup>4</sup>. Some researches ensure that the manufactured food contains hormones and hormonal mediators' \_ insulin-like growth factor<sup>1</sup> was found in milk\_ and as we mentioned in the introduction, hormones, specially androgen, are a great factors in acne formation [4]. A recent large prospective cohort study which found hormonal components in skim milk in concentrations that are high enough to cause biological problems in teenage males [5].

The association between the acne development and the high level of glucose found in the adolescent western diet has been studied. A randomized controlled trial shows that there was a marked improvement in acne and insulin sensitivity in adolescent boys with acne after involving them in low glucose level diet. But, in fact we need more studies to clarify the pathophysiological mechanisms of the effects of low glucose diet and reducing weight in the management of acne.

Other important risk factors in acne are hereditary factors. Patients who have a positive family history found to have the severe cases<sup>8</sup>. In the other hand, studies of twins show us an evidence of the genetic factor of acne<sup>9</sup>. For the purpose of locating the possible causative genes of acne, a new large scale genetic study has been done in the UK. It gives us information to predict who is suspected to develop acne by comparing the genetics of patient with severe acne with the genetics of people in the control group [6]. This study is the first step to continue research into the genetic basis of acne.

**Clinical features:**

The clinical features of acne are various, they are: seborrhea, pustules; which are inflammatory lesions, comedones; which are non-inflammatory lesions, scarring in various degrees, and nodules and cysts; in very severe cases [7].

The location of acne follows the distribution of the pilosebaceous units, the area with the highest density of it, are the area where the acne locates most, such as the face, the neck, chest and back [8].

The most group likely to be affected is the adolescents around adrenarche, because of the

increased secretion of the sebum from sebaceous glands [9].

### Impact on quality of life:

As we mentioned previously, patients with acne suffer from important psychological and social problems beside the physical symptoms they have. These problems cause a life difficulties and challenges that are somehow as hard as the patients with chronic diseases suffer \_like asthma, epilepsy, diabete, back pain or arthritis<sup>14</sup>. Regardless of the severity of acne, patients are likely to have depression and anxiety if we compare them with normal people. Generally, patient with acne do not recognize the emotional side of their disease from the start, that is why physicians should keep in mind the psychological complications of this disease and pay attention to the psychological symptoms and signs.

### Pathogenesis

Acne an inflammatory disease of the pilosebaceous units, and multiple factors are included in the pathophysiological mechanisms [10]:

- Increased level of sebum secretion caused by the high concentrations of androgen.
- Alteration of keratinisation with the occlusion of the follicle and duct.
- The infection of the pilosebaceous duct by *Propionibacterium acnes*.
- The release of inflammatory mediators into the skin.

The right order of these events and their interaction together is still unknown; but , recent studies suggest that there may be a considerable connection between them [11].

### Treatment:

The essential rule in the treatment of acne is to get rid of the sebum and keep the skin clean so the use of soap-free face wash is the first line, it is also important to use oil-free moisturisers to reduce the side effects of topical treatments, and to avoid the use of triggers. Make up, sunscreens and medications, such as corticosteroids and anabolic steroids, are examples of triggers of acne [12]. The main purposes of pharmacological treatment of acne is stop the causing factors, clear the acne and reduce the scarring. In order to affect more than one of the pathogenic factors and give the biggest efficacy, the joining of multiple topical agents is recommended [13]. The basic topical agents are: antiseptics (benzoyl peroxide), keratinolytics (salicylic acid, sulphur) retinoids and antibiotics.

There are different forms of these drugs in different strengths and different vehicles; so there is an appropriate regimen for almost every type of skin. There are many studies that compare the efficacy of these numbers of topical agents. Recent guidelines depend on specialists' consensus for treatment more than evidence-based treatment and include the Global Alliance to Improve Outcomes in Acne, the European Dermatology Forum, and the guidelines of care from the American Academy of Dermatology.

There is also another difficulty of the treatment of acne that there is no agreed on, clear assessment standard that used worldwide. The assessment of severity of acne backs to the physician and his experience, and it depends on many factors such as (lesion type, number, size, distribution and location) and of course, the effect of acne on the patient's life. (eg, the Dermatology Life Quality Index) [14].

### Benzoyl peroxide (BPO):

BPO is one of the antibiotics that are used in the treatment of acne; it is a strong, over-the-counter, bactericidal agent with no known association with resistance development that also causes peeling of the skin, so it's effective for acne with mild and transient irritation [15].

The Australian guidelines recommend PBO 5% as first line agent for mild to moderate cases of acne <sup>16</sup>, with a combination with other topical antibiotics or topical retinoid. But, unfortunately, PBO is not tolerable for some patients with its side effects: contact urticaria; contact dermatitis; bleaching the clothes; and the most important side effect is that it may cause irritation or dryness of the skin. When the irritation occurs it is suggested to reduce the strength and frequency of the application of BPO to ensure compliance.

Tretinoin, adapalene, isotretinoin and tazarotene, are topical retinoids that are anti-inflammatory drugs and they play role in correcting the abnormal keratinisation leading to open the obstructed follicle and duct [8].

The Australian therapeutic guidelines recommend either adapalene 0.1% in cream or gel topically, or tretinoin 0.025% in cream topically for 6 weeks and then review.

Topical retinoids also have side effects that are local irritation and photosensitivity, in few cases, they may cause a severe cutaneous irritation and when it happens they should be stopped. The gradual

introduction of retinoids in combination with a low irritant, pH balanced, soap-free cleanser can prevent irritation

The current Australian therapeutic guidelines warn that topical retinoids are teratogenic and ensure that they should be avoided in females who are planning to become pregnant, are pregnant or breastfeeding. The regulatory concern of the teratogenic potential of topical tretinoin is contrary to previous human percutaneous absorption studies. A human study that examined the percutaneous absorption of tretinoin in various formulations indicated that it was minimally absorbed and did not affect the endogenous levels of the drug or its metabolites in the subjects studied. There has also been a study that examined the incidence of major congenital anomalies for 215 exposed women versus 430 non-exposed age-matched women, and concluded that topical tretinoin is not associated with increased risk for major congenital disorders.

#### **Antibiotics:**

Topical antibiotics:

Erythromycin and clindamycin are the primary topical antibiotics used for acne treatment and they have the same efficacy. But, there is an increasing concern about *P. acnes* resistance, especially with erythromycin [10], so, it is suggested by the current Australian therapeutic guidelines the use of a combination of BPO and topical retinoid gel (benzoyl peroxide/adapalene 2.5%/0.1%) or clindamycin gel (benzoyl peroxide/clindamycin 5%/1%).

And to avoid using only topical antibiotic; But, in particular cases, if the patient's skin is prone to irritation with other acne treatments, clindamycin alone can be used.

Oral antibiotics:

The primary treatment in moderate to severe acne is the oral antibiotic \_ it works as antimicrobial and anti-inflammatory\_ although there is a big fear of the development of resistance; it is used in combination with benzoyl peroxide and topical retinoid.

When starting the oral antibiotics course, it is necessary to establish a tolerable long term topical treatment to avoid recurrence when course is done.

Doxycycline (50e100 mg orally once daily for 6 weeks) is the first agent of choice, and if it is not tolerated, then minocycline (50e100 mg orally once daily for 6 weeks), and if tetracyclines are contraindicated (eg, pregnancy), then erythromycin (250e500 mg daily for 6 weeks).

Side effects of antibiotic treatment are a concern for both patients and clinicians and, therefore, the choice of antimicrobial agent may vary among dermatologists based on preference and experience. For example, photosensitivity caused by doxycycline may be intolerable or impractical as a first line treatment for some patients.

There are a serious side effects for oral antibiotics specially tetracycline and macrolide antibiotic classes, fortunately they are rare.

For example: minocycline is known to be associated systemic symptoms<sup>30</sup> such as benign intracranial hypertension; vestibular disturbances; pigment deposition in the teeth, skin and mucous membranes<sup>31</sup>; and drug reaction with eosinophilia. Macrolides also have serious adverse effects, with reports of cardiac conduction abnormalities and hepatotoxicity [17].

The efficacy of antibiotic therapy should be reviewed after 6 weeks and if there is no improvement, the antibiotic should be changed. The prolonged use of antibiotics is questionable in light of resistance concerns from the long term use of low dose antibiotics [18].

#### **Antiadrenergics:**

Combined oral contraceptive pill (COCP). Hormonal therapies are useful adjunctive treatment options. A recent Cochrane review reaffirmed the efficacy of COCP for treatment of inflammatory and non-inflammatory acne, but found few differences in efficacy between the different types of COCP that are currently available [19]. The Australian guidelines, however, suggest that the COCP most likely to improve acne is one that contains cyproterone acetate. The benefit from COCP is slow and may not be apparent for 3 months, so a 6 month trial is recommended.

#### **Spirolactone:**

Spirolactone is a diuretic and anti-androgen agent, it blocks the androgen receptors when administered at increased doses. When COCP is contraindicated in a female patient, not tolerated or desired, or insufficient as monotherapy, soironolactone is the choice.<sup>20</sup> It also may be used in male patients, but there is a fear of having the adverse effect of feminisation, as seen in a recent Japanese trial that involved 23 men treated initially with 200 mg spironolactone daily for 8 weeks, but ceased in men prematurely due to the side effect of gynaecomastia. The common side effects of spironolactone are irregular menstrual bleeding breast pain, diuresis, dizziness, headache and fatigue [21].

There is a big risk of defective virilisation of the male fetus if taken by pregnant women. That is why pregnancy should be excluded before starting this therapy. Hyperkalaemia is also an important side effect; but, it is rare in young healthy females and it was recently stated in the American guidelines for the treatment of acne that testing potassium in young healthy females on spironolactone is unnecessary

#### Oral retinoids:

Isotretinoin (13-cis retinoic acid) has been the most effective treatment for acne and the only drug that offers remission since it was introduced in 1982. It targets all four known pathologic mechanisms involved in the development of acne. The standard dose accepted of isotretinoin in severe cases of acne is a starting dose of 0.5 mg/kg/day for the first 4 weeks, increase to 1 mg/kg/day, then continuation until a cumulative dose of 120e150 mg/kg is reached and tolerated by the patient For extremely severe cases, when there is large areas of inflammatory lesions, a course of prednisone 20e40 mg a day and starting at lower doses of isotretinoin to prevent severe flares may also be warranted

in a recent prospective interventional study has examined considerably higher doses of isotretinoin than those used historically, including up to 220 mg/kg, and it was found that there was a significantly decreased risk of relapse and that rash was the only adverse effect in patients. Conversely, a low dose isotretinoin (0.3e0.4 mg/kg/day) treatment has also been found to be a safe and effective management of patients with early recurrent disease [22].

Tetragenic effects of oral isotretinoin are well known so it must be strongly regulated when used, and in many countries it is available only through specialist care.

A recent population-based study of incidence rates of pregnancy, abortions and birth deformities incurred by women on isotretinoin found that the incidence of major malformations while on isotretinoin was 11%, which is lower than what was previously reported [23].

Depression and suicide have been reported and well publicized in patients taking isotretinoin, although a causal relationship between isotretinoin and suicidal thoughts or depression has never been established. In the other hand, there have been studies that showed reduced depression and anxiety in patients with cystic acne after a successful treatment with oral isotretinoin.

#### Adjuvant and newer procedures for acne and acne

#### scarring

Scarring is the worst complication of acne and it must be treated seriously. The psychological effects of acne can be long lasting, and the association between acne and depression and anxiety is independent of the disease severity [24]. That is why, newer treatment forms and adjuvant therapies for acne and scarring, are a growing market in both medical and cosmetic practices although they are expensive. For examples, chemical peels, light, laser and radiofrequency.

As an example of the chemical peels ; salicylic acid (a b-hydroxy acid) and glycolic acid (an a-hydroxy acid) are two chemical peels currently available as an adjuvant treatment for acne affecting the face.<sup>25</sup> Chemical peels cause desquamation , which reduces corneocyte cohesion and keratinocyte blockage, and allow the promotion of normal epidermal differentiation, and at last, reduce the abnormal pattern of keratinisation .<sup>26</sup> A downside to this is that it requires multiple treatments to be efficacious, which is costly and can have side effects of redness and irritation to the skin. Therefore, chemical peels do not replace the existing topical and systemic treatment available for acne.

Lasers and light-based devices for acne have been increasingly used over the past few years. Light therapy, in the form of blue light and blue and red light, can treat active acne causing the destruction of the propionibacteria through targeting the porphyrins produced by these bacteria. Evidence exists that light therapy is a safe and efficacious treatment of acne.

Other examples of new therapies for the treatment of acne and scarring are radiofrequency and photodynamic therapy. While there has been a recent plethora of research on the efficacy of the different modalities, there is no enough long term follow-up to prove their efficacy in the treatment of acne.

#### CONCLUSION:

Acne is a chronic inflammatory disease that affects the adolescent population generally and girls specially, it can cause really serious psychological damage and physical scarring without the appropriate treatment. Depression, anxiety and even suicide are found in acne patients.

The right early treatment is essential in acne, so in order to effectively and rapidly reduce acne lesions, and avoid scarring, a combination therapy of topical and systemic agents that targets as many of the

underlying factors as possible should be considered. The emergence of *P. acnes* resistance requires a

combination topical therapy and a low therapeutic threshold to introduce oral isotretinoin, which is a highly effective, well established treatment of acne and the only therapy that targets all of the etiological factors of this disease. Side effects of these drugs should be considered when medications are prescribed.

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