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ACNÉ

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SUMMARY

Acne is the most traumatic and globally annoying chronic inflammatory skin disease. Its prevalence is highest among patients aged 12-24 years, at a frequency of 85%, although it can persist into adulthood, despite treatment. Its effect involves emotional and physical aspects (presence of marks), in addition to its effect on quality of life. Its clinical presentation ranges from the presence of comedones to mixed comedogenic acne with inflammation (1)(2). The face is the most affected area in most cases, and the trunk is affected in 61% of patients. The lesions caused by this can range from scarring to the presence of post-inflammatory hyperpigmentation. Stimulation of the immune system by hypercolonisation of Propionibacterium acnes is thought to be the possible cause (3).

The aim of this literature review is to communicate to the scientific community the different measures and treatments for this disease, which, as will be analysed, has not only personal impacts, but also psychological and social implications. In fact, this work is based on a dissemination of studies and reviews from 5 years ago, which means that we have all the most up-to-date information possible on this subject.

KEYWORDS: ***Acne, scars, benzoyl peroxide, comedones, sebaceous glands.***

INTRODUCTION

Hereditary factors have also been attributed in the pathogenesis of acne, where severe cases of acne have been found to have a family history of acne. A large-scale genetic study in the UK compared the genes of patients with severe acne with those of a control group; and provided information on how to predict who is prone to acne by establishing the loci of the genes that can cause it (4).

Within the pathophysiological development of acne, we have 4 factors:

- Abnormal follicular hyperproliferation of keratinocytes, leading to the formation of follicular

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plugs.
- Increased sebaceous production in the sebaceous follicles.
- Proliferation of microorganisms in the retained sebum.
- inflammation

RELATED CAUSATIVE FACTORS

Extreme dietary programmes have not proven to be of any value; rather, a balanced, healthy diet has been shown to be appropriate. Studies have found that diet can exacerbate acne. Carbohydrates, milk and other dairy products, saturated fats, including trans fats, along with deficiency of omega-3 and polyunsaturated fatty acids can promote acne. Diet-induced insulin and insulin-like growth factor-1 (IGF-1) overlap with elevated IGF-1 levels during puberty and affect sebaceous gland homeostasis. Some researchers believe that patients should consume an adequate calorie balance and restriction of refined carbohydrates, milk, dairy, nutritional supplements, saturated fats and trans fats. They recommend a diet rich in vegetables and fish. Clinical features include comedones, pustules, nodules, cysts and scars. The comedones that are generated can range from closed to open. Open comedones are also called blackheads, due to oxidation of the keratin. Closed comedones are called blackheads. Pustules occur when follicular inflammation is such that a collection of neutrophils is produced. Cysts are keratin-filled structures with follicular lining that dilate. Nodules occur when these become more inflamed. These are clinically red, with a palpable lesion. Scarring may be the end result once resolved. These scars can be: icepick (narrow and deep), hypertrophic (stacked and smooth), and atrophic (flat and depressed) with a thin epidermal surface. Keloids and hypertrophic scars extend beyond the original site of inflammation. This is an effect that occurs in severe forms of acne, and once present, they are permanent (5)(6). Increased leptin levels increase inflammation. Regular exercise can help with weight control, but can cause alterations in stress hormone regulation, depending on the intensity and timing of the activity, along with increases in adrenal hormones and testosterone. The sebaceous glands play an important role in the generation of acne, due to the response of stress hormones and neuropeptides, as well as promoting the release of enzymes that increase the production of hormones and cytokines (7).

SOCIAL IMPACT

Acne has a major impact on appearance, which is related to self-esteem, self-perception and daily activities. Furthermore, it has been strongly associated with depression, suicidal thoughts, school absenteeism, unemployment, along with relationship problems (impairment with social interaction and public presence) and reduced employability. Influencing factors include decreased sexual attractiveness, relationships with family and friends, people's opinions, stigmatisation, stress, and fear of scarring or persistence of the condition. As a result, treatment has been shown to improve their quality of life. One of the most significant stressors is stress. This can lead to excoriations and itchy lesions that can cause increased inflammation, scarring, hyperpigmentation and anxiety. The stress response is due to hypothalamic-pituitary-adrenal activation, with subsequent adrenergic and cholinergic stimulation, leading to susceptibility of the skin to infection and the ability of the bacteria responsible to adhere to the skin and proliferate (7)(8).

ADHERENCE TO TREATMENT

Adherence to treatment is low, due to several factors, including early improvement, perceived worsening of acne, adverse effects of medication (especially topicals). Oral isotretinoin treatment and treatment satisfaction has been linked to increased treatment adherence in adolescents, suggesting that simplification of treatment (usually monotherapy), patient selection and increased acne severity, together with the use of isotretinoin, have contributed to increased treatment adherence. In contrast, the prescription of multiple treatments, topical retinoids and the prescription of more products has been associated with non-adherence in adolescents; a challenge considering that guidelines suggest starting treatment with topical retinoids and not using monotherapies (8).

THERAPEUTIC MODALITIES

Combination topical and oral antibiotic therapies are not recommended because of increased bacterial resistance. Benzoyl peroxide is a broad-spectrum bactericidal agent, to which bacterial resistance has not been reported (8).

TOPICAL RETINOIDS

These drugs are a diverse group of vitamin A derivatives that modulate gene expression. The US Food and Drug Administration (FDA) has approved the use of this medication for acne vulgaris with products such as: adapalene, tretinoin and tazarotene, preventing the formation of comedones and regulating keratinocyte proliferation, along with anti-inflammatory effects. Topical retinoids are the treatment of choice, especially for maintenance therapy for all types of acne, reducing comedogenic and inflammatory acne lesions. They also have the benefit of preventing and reducing the appearance of atrophic scarring and hyperpigmentation. Due to the effects of skin dryness and irritation, always start with low doses of adapalene or tretinoin, and escalate until tolerated. Adapalene has been studied to be the least effective and best tolerated, while tazarotene is the most effective and least tolerated (8).

TOPICAL AND ORAL ANTIBIOTICS AND BENZOYL PEROXIDE

Topical antibiotics can be used first-line in the treatment of acne vulgaris and have anti-inflammatory effects; however, they should not be used as monotherapy because of the rapid and high development of antibiotic resistance after weeks or months. High rates of resistance are due to erythromycin and clindamycin, leading to decreased efficacy. Decreased resistance rates have been shown with concomitant use of benzoyl peroxide, probably due to non-selective bactericidal activity. Therefore, the use of topical antibiotics with benzoyl peroxide is recommended. Oral antibiotics are indicated for the treatment of moderate to severe acne or inflammatory acne that does not improve with topical therapy. They should also be used in combination with topical retinoids and/or benzoyl peroxide; monotherapy is not recommended.

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Long-term therapies (3-6 months) should be avoided to prevent antibiotic resistance. The first line of oral antibiotics are tetracyclines, such as doxycycline and minocycline, which have anti-inflammatory properties and are considered the first line. Sarecycline is a new tetracycline for moderate to severe acne in patients aged 9 years and older. In cases of contraindication to erythromycin, Azithromycin is suggested. The use of other antibiotics (trimethoprim/sulfamethoxazole, penicillins, cephalosporins) is rejected because of limited scientific support (8).

HORMONAL THERAPY AND CONSIDERATIONS

There are 4 types of combined oral contraceptives approved by the FDA for the treatment of moderate acne in postmenarcheal women: ethinylestradiol and norgestimate; ethinylestradiol, norethindrone acetate, and ferrous fumarate; estradiol and drospirenone; and ethinylestradiol, drospirenone, and levomefolate. This medication is used for its anti-androgenic effect, generated by decreasing the size and function of the sebaceous glands, in addition to its effect in decreasing comedones and inflammation; in general, for the use of this medication, it is important to consider the acne-generating effects of progesterone-based contraceptives, such as medroxyprogesterone and the etonogestrel implant. In a 2018 study, they show that inflammatory acne can be exacerbated by the use of levonorgestrel intrauterine devices. The potassium-sparing diuretic, Spironolactone, has been used by dermatologists in doses of 50-200 milligrams per day and is well tolerated in moderate to severe hormonal acne; however, it has not been approved by the FDA (8).

ISOTRETINOIN

Isotretinoin is an oral retinoid, generally safe and well tolerated, despite having negative connotations. The FDA has approved its use for the treatment of severe recalcitrant acne vulgaris, in addition to moderate treatment-resistant acne, for acne that causes scarring or significant psychosocial distress. Although this drug is considered safe, isotretinoin has embryotoxic and teratogenic effects; therefore, women who are at risk of pregnancy should use contraception (recommended 1 month before pregnancy, during and 1 month after completion of treatment with this drug) or sexual abstinence before taking this drug. In addition, pregnancy testing counselling is always required for all female patients (8)(9).

New modalities under study for the treatment of acne have included studies with a new antibiotic called Sarecillin, a new tetracycline, approved by the FDA and currently in use. Tazarotene 0.1% was re-launched on the market; this formulation attempts to impart moisturising effects to counteract potential irritation. Another drug currently on the market is topical Minocycline, which optimises the therapeutic effect while reducing systemic effects (10). Treatment involving supplementation with essential omega fatty oils, vitamins A and E has been shown to assist in the generation of the skin lipid barrier and keep the skin moisturised. In the case of vitamin C, it is used as anti-inflammatory formulations or as a nutritional component; however, its individual efficacy has not been well studied (11).

TREATMENT ASSESSMENT

There is an Acne Severity Scale (CASS), which can be used as an indicator of severity based on the presence of inflammatory and non-inflammatory lesions, in addition to assessing response to treatment. Aggravating factors, such as comedogenic products, medication, stressors, diet, smoking, obesity, occupation, lifestyle; or systemic disorders, such as Cushing's syndrome, androgen-secreting tumours, along with previous acne treatments, adverse effects, adherence problems should be evaluated beforehand. In women, possible signs of hyperandrogenism should be evaluated (12).

TABLE 2. Comprehensive Acne Severity Scale (CASS)

CONDITION		DESCRIPTIÓN
Clean	0	No lesions evident, not very noticeable, very few comedones and scattered papules. scattered.
Almost clean	1	Visible from 2.5 metres distance; few scattered comedones and few small papules and very few papules and very few pustules..
Mild	2	Easily recognisable, less than half of the affected area is involved, a few comedones, papules and pustules.
Moderate	3	More than half of the affected area involved; numerous comedones, papules and pustules. pustules.
Severe	4	Entire area involved; covered with comedones, numerous pustules and papules, few nodules and cysts.
Very severe	5	Extensively inflamed, covering the affected area, presence of nodules and cysts. cysts.

Source: Oon HH, Wong SN, Aw DCW, Cheong WK, Goh CL, Tan HH. Acne Management Guidelines bythe Dermatological Society of Singapore. *J Clin Aesthet Dermatol*. 2019;12(7):34-50.

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TABLE 3. Summary of treatments for atrophic scars	
NIVEL Y GRADO	**DESCRIPCIÓN**
Level 2, Grade D	Chemical peels, such as 40% glycolic acid, have been found to significantly improve moderate acne and are safe and effective in Asian patients. Asian patients.
Level 2, Grade D	Photodynamic therapy with topical 5-ALA (aminolevulinic acid) and intense pulsed light (blue or red light) is effective for moderate to severe acne.
Level 2, Grade D	As monotherapy, Intense Pulsed Light Therapy (blue or red light) is less effective than Photodynamic Therapy, but can be tried if the side effects of Photodynamic Therapy are not tolerable.
Level 2, Grade D	Combined blue-red LED phototherapy, for which home devices are available, is safe and effective for the treatment of mild to moderate acne, with good adherence.
Level 2, Grade D	The erbium glass laser is an effective treatment for active acne. Laser therapy may be necessary for 1 to 4 sessions.
Source: Oon HH, Wong SN, Aw DCW, Cheong WK, Goh CL, Tan HH. Acne Management Guidelines by the Dermatological Society of Singapore. *J Clin Aesthet Dermatol*. 2019;12(7):34-50.	

There is a study that shows that the use of fractional mycoplasma radiofrequency on atrophic scars, marks, open pores, UV damage, significantly improves scars after 3 treatments with this method. Eighty-six patients were studied, with 15 patients showing 75% improvement, 57 patients showing 50-75% improvement and 14 patients showing 25-50% improvement (13). In another study, the use of 0.3% adapalene gel with 2.5% benzoyl peroxide was shown to prevent and reduce atrophic scarring within 6 months (14). Jessner's microneedling and chemical peel therapies (mixture of 14% resorcinol, 14% salicylic, 14% lactic acid and ethanol) have shown significant improvement; this method uses microneedling in several sessions followed by placement of atrophic scars. Its effect lies in the creation of micro-slits from the epidermis to the papillary dermis. Jessner's solution, on the other hand, produces thinning and exfoliation of the epidermis and dermis, accelerating the skin repair process (15). Another review showed that hyaluronic acid injection improves the appearance of moderate-severe atrophic scars, leading to improved self-perception. The treatment effect, however, developed gradually over time and the highest improvement was at the end of the study (16). There are other modalities that have evolved over the past decade and are still in use today, such as: subcision, injection of fillers, chemical peels, the use of dermabrasion, and the application of microneedles. Each of these with variable results (17).

Table 4. Practical Recommendations

Key practical recommendations (18)		
Clinical Recommendations	***Evidency Level***	***Comments***
Topical retinoids should be used as monotherapy in mild acne and in combination with other agents (topical or oral) for moderate to severe acne.	B	Limited evidence from randomised controlled trials and expert consensus.
Topical retinoids should be used for maintenance therapy once targets have been completed and oral agents should be discontinued.	C	Expert consensus and narrative reviews.
Systemic antibiotics should be used for the treatment of moderate to severe acne.	B	Systematic review of heterogeneous studies.
Oral isotretinoin should be used in the treatment of severe nodular acne or refractory acne in adults and adolescents.	B	Systematic reviews and meta-analyses of non-randomised trials.
Combined oral contraceptives should be considered in menarche unresponsive to treatment or intolerance to past therapies, due to their association with acne flares with menstruation or in women with signs and symptoms of hyperandrogenism (acne, hirsutism, oligomenorrhoea).	A	Cochrane reviews or randomised controlled trials with consistent evidence.

Source: Oge' LK, Broussard A, Marshall MD. Acne Vulgaris: Diagnosis and Treatment. *Am Fam Physician*. 2019;100(8):475-484

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RECOMMENDATIONS FOR TOPICAL THERAPIES

Benzoyl peroxide or combinations with erythromycin or clindamycin are effective for the treatment of acne and are recommended as monotherapy for mild acne or in combination with systemic antibiotic therapy for moderate to severe acne. It is effective in avoiding antibiotic resistance to antibiotic treatment (systemic or oral). Topical antibiotics as monotherapy are not recommended due to the presence of antimicrobial resistance (19)(20).

RECOMMENDATIONS FOR SYSTEMIC ANTIBIOTIC THERAPY

Recommended in the management of moderate to severe acne, as well as forms of inflammatory acne that are resistant to topical treatments. Doxycycline and minocycline are more effective than tetracycline, but neither is superior to the other. Erythromycin, Azithromycin and trimethoprim/sulfamethoxazole may be effective, but their use is limited to those who cannot use tetracyclines (pregnant women or children under 8 years of age). Erythromycin and trimethoprim/sulfamethoxazole should be restricted due to increased risk of bacterial resistance. Benzoyl peroxide should always be used with antibiotic and maintenance therapies after completion of antibiotic treatment (19)(20).

RECOMMENDATIONS FOR USE OF HORMONAL AGENTS

Combined oral contraceptives (with estrogen) are effective and recommended in the treatment of inflammatory acne in women.

Spironolactone is useful in the treatment of acne in specific women.

In patients with adrenal hyperandrogenism, low doses of corticosteroids are recommended in the treatment of acne (19)(20).

RECOMMENDATIONS FOR THE USE OF ISOTRETINOIN

Isotretinoin is recommended for use in severe nodular acne. It is appropriate for the treatment of moderate acne that is refractory to treatment or for the management of acne that causes psychosocial disturbances.

Low doses of isotretinoin can be used to treat acne and reduce the frequency and severity of adverse effects.

INTERMITTENT DOSES OF ISOTRETINOIN ARE NOT RECOMMENDED.

Routinely monitor liver function, cholesterol and triglycerides.

Women of childbearing age taking isotretinoin should be advised about various methods of contraception.

Patients should be monitored frequently for inflammatory bowel disease and depressive symptoms.

Explain to patients about the potential risks of isotretinoin (19)(20).

CONCLUSIONS

The management of acne will continue to undergo continuous development and research. Increasingly, there will be more and more elements leading to optimal therapy. As has been seen, medication recommendations are quite clear and approved from 2000 to the present. However, non-pharmacological strategies are equally important, as this would avoid the indiscriminate use of medication and possible adverse effects, ranging from skin conditions to depression or antibiotic resistance. New therapies based on the application of lasers and dermabrasion are still being investigated, so there is still faith that this pathology, so traumatic for those who suffer from it and for those who have sequelae, has an effective treatment, of short duration and without major adverse effects.

FINAL STATEMENT

This review is based on an article by Santiago Vintimilla called “Acné, un enfoque actualizado”, whose author authorized the translation and rewriting from the Spanish language version to the english language version.

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