Etiology, Pathophysiology And Treatment of Acne Vulgaris.

[1]Vinanti Dipak Mudgal, [2]Dr. K. B. Burade, [3] Sadhana Mane, [4]Megha Mane, [5]Prajakta Waghamare.

[1]Research student, [2]Principal (Research guide)
Department of pharmaceutics
Government college of pharmacy, karad. Maharashtra, India

ABSTRACT: Acne vulgaris is one of the most frequent dermatological illnesses that affect adolescent skin. Acne vulgaris, also known as acne, is a skin condition that causes scaly red skin, blackheads and whiteheads (comedones), pinheads (papules), big papules (nodules), pimples, and scars. Acne vulgaris is a pilosebaceous unit disease that causes open and closed comedones, papules, pustules, nodules, and cysts to occur. Acne affects skin with a lot of sebaceous follicles, such as the face, chest, and back. Although acne is not life threatening, it can have a negative impact on one's psychological well-being and social activities. The current study focuses on the epidemiology, aetiology, pathophysiology, diagnosis, differential diagnosis, and therapy of acne using oral and topical pharmacological dosage forms. Benzoyl peroxide, antibiotics, antiseborrheic pharmaceuticals, sulphur and sodium Sulpha*cetamide, antiandrogen medications, salicylic acid, hormonal therapies, alpha hydroxy acid, retinoids, azelaic acid, keratolytic soaps, and nicotinamide are some of the medications used to treat acne. Acne is being treated with laser and light equipment, as well as modest subcision surgery.
Index term: Propinobacterium acne – P. acne, Benzoyl peroxide – BP, Retinoic Acid Receptor – RARs,

Introduction :

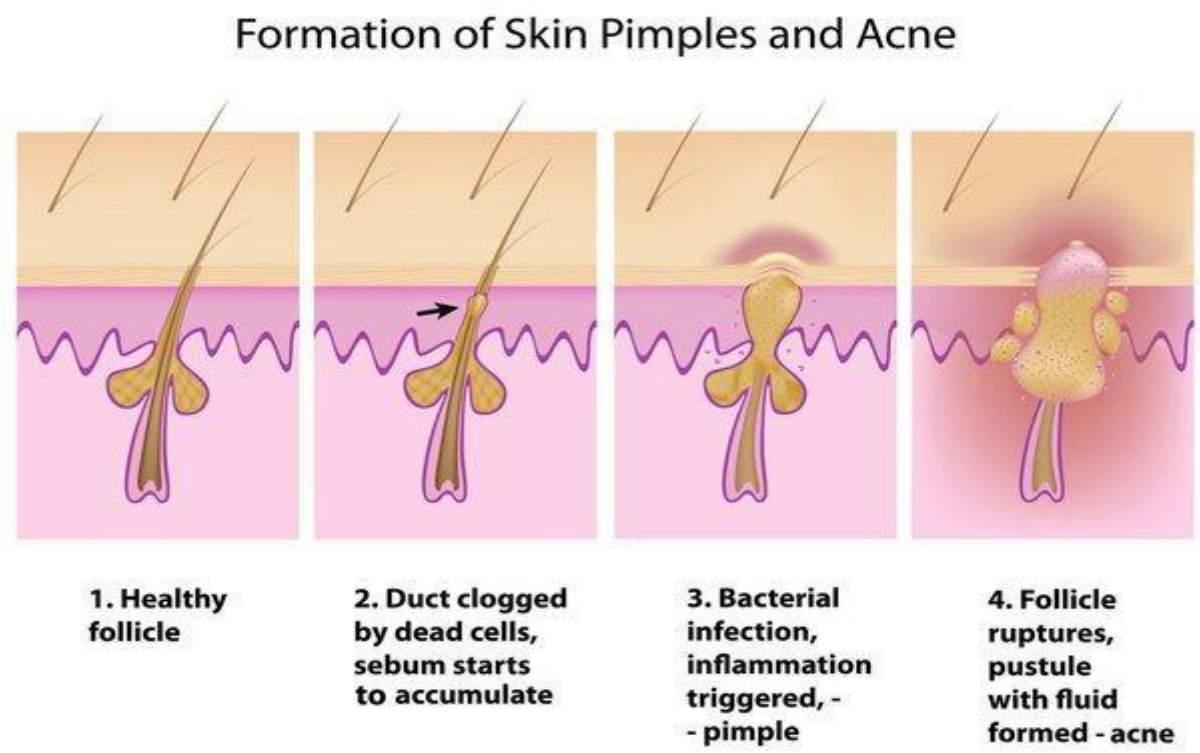
Acne vulgaris is the most common skin disease in adolescents and young adults with a 70–95% prevalence rate. Adult or post adolescent acne occurs in 12–14% of this population and is seen as the continuation of acne from adolescence into adulthood or starts in adult life. [1,2]

Acne vulgaris is an inflammatory disorder of the pilosebaceous unit primarily caused by increased sebum production and follicular plugging. Physical distress is common with acne but every day dermatologists see the devastating effect that acne can have on someone's life. For many people who have acne, the skin disease affects more than their appearance. Acne can take a toll on one's emotional health. [3,4] Which develops depression, anxiety, poor self-image, low self-esteem, feeling of being all alone, and decreased quality of life. This problem is faced by teenagers and also adults.

Fortunately, it is possible to improve the quality of life of patients with successful treatment. Over the past few decades, a large spectrum of local and systemic drugs has been introduced and a lot of efforts have been devoted to reach a consensus on the treatment approach of acne.

Etiology of acne

The underlying cause of acne is excess sebum production in sebaceous glands. One of the 1 st stages of lesion development is blockage of the follicular canal. Follicles plug with sebum & keratin due to increased cohesiveness of corneocytes and hyperkeratosis. Propionibacterium acnes (P. acnes) is the prominent bacteria associated with acne. They are part of the normal skin flora and are an inhabitant of the pilosebaceous follicle. Colonization of follicles by cutibacterium acnes leads to inflammation and irritation associated with acne. Also, Acne triggers greatly contribute to acne vulgaris. [5] Hormones play a major role in the stimulation of sebaceous glands and which leads to development of acne. Sebaceous gland size and metabolic rate are directly stimulated by dihydrotestosterone, a derivative of testosterone also called as sex or androgenic hormone. People faces acne breakout mostly in puberty because during puberty sex hormone production increases. [5,6] Severity of acne often depends on secretion of sex hormone which is highest in mid teenage years. Females also tend to experience a burst in acne about a week before menstruation. Acne can be a result of hyperandrogenism which is seen in female teenagers and adult women having irregular menses, unexplained and sudden weight gain, hirsutism Evaluation for polycystic ovary syndrome. [7,8] Other external reasons include follicle plugging due to comedogenic products such as make up and greasy hair products. Occlusive garments like collars, sports bras, hats, helmets, and chin straps can greatly contribute to acne due to mechanical irritation and occlusion of the follicles. Over washing practice especially with exfoliant also causes mechanical damage to skin. [8]



Pathophysiology of acne

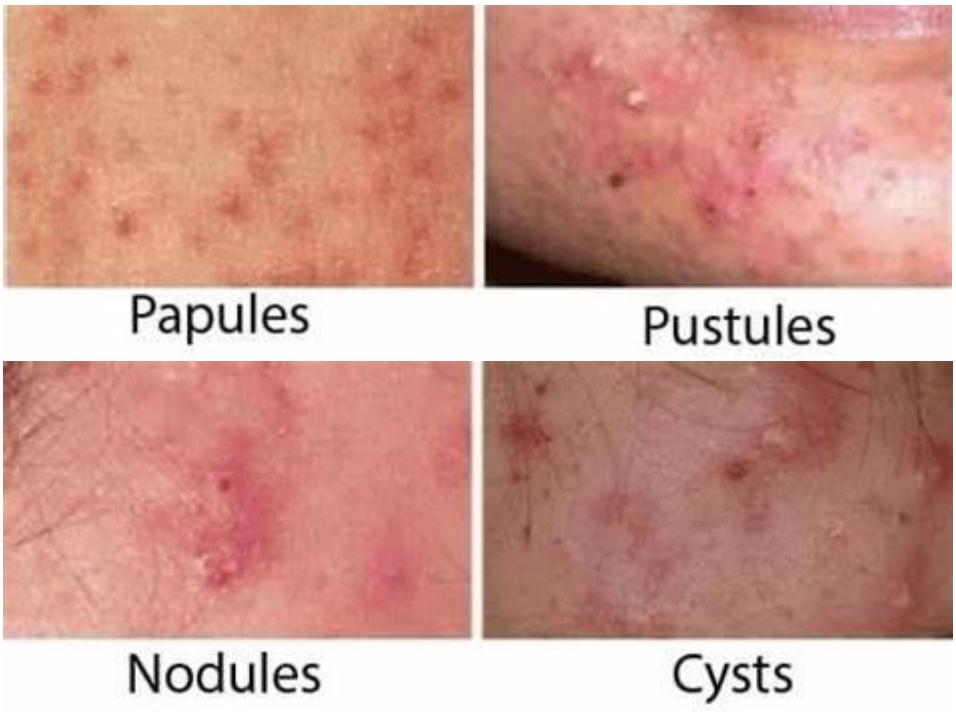
Acne is a skin condition characterized by red pimples on the skin, especially on the face, which may be filled with yellowish fluid. It is a very common skin disorder which can present with inflammatory and non-inflammatory lesions.

Non-Inflammatory i.e. COMEDONES	**Inflammatory i.e. PIMPLE**
1.Blackheads 2.Whiteheads	1.Papules 2.Pustules 3.Nodules 4.Cysts

Table no -1. Classification of Acne vulgaris

Non- Inflammatory Lesions (COMEDONES) - This type of acne forms when keratin, sebum or oil accumulates in the follicle. This creates a plug (comedo) above the sebaceous gland duct. Continuously comedo expands behind a small follicular opening to the skin. This leads to distension of the follicle and formation of a closed comedone i.e., whiteheads (firm, elevated, white or yellow) Open comedones also called as blackheads are the result of pore dilation to the skin surface due to retention of keratosis. They are generally non painful in nature. [1,10,]

Inflammatory (PIMPLE) – The closed comedones are precursors of inflammatory lesions. Large comedones increase force within the follicle resulting in rupture of comedo wall and extrusion of keratin & sebum as well as inflammation to skin. Papules develop when the impurities clogged in pores inflame the hair follicle. A papule is a small red bump. Its diameter is usually less than 5 millimetres. It does not have a yellow or white centre of pus. Pustules are small bumps on skin that contain fluid or pus. They usually appear as white bumps surrounded by red skin. They can grow quite big. Pustules usually contain pus due to an infection to the pore cavity. [1,2] Pustules can become hard and painful. When acne infection goes deep underneath your skin, causing the affected pores to become red and swollen is called nodular acne. Because issues deep within the skin, nodular acne is considered a severe type of acne. Nodules look like small bumps under skin. It may be skin toned, but it can also turn red as the surrounding area gets more inflamed. It doesn't have a "head" like other pimples might. Nodules may persist for weeks or even months, with the result of their contents hardening into deep skin. They are painful to touch. Cystic acne is the stubborn and serious form of nodular acne. It is deep rooted under the skin damaging the layers. This can result from a combination of bacteria, oil, and dry skin cells that get trapped in your pores. Acne cysts develop when contents of blackheads or whiteheads "spill" into the surrounding area of skin. In an effort to fix the situation, the body perceives an attack, and the local immune system responds by producing pus. Cystic acne tends to be the largest in size and looks like a red boil. Also have characteristics like large-pus filled, large white bump, redness, and painful to touch. They are softer than nodule acne. It is the most painful among all types of acne. [1,2]



GENERAL GUIDELINES FOR TREATMENT OF ACNE VULGARIS

The Global Alliance to improve outcomes in Acne group ("Global. Alliance") is an international group of dermatologists with clinical research and research expertise in acne vulgaris, formed in 2003. Reviewing the guidelines on treatment of acne, a recommended common approach is

1. Start with topical treatment if appropriate.
2. Give Systemic treatment when necessary.
3. Limit the use of local & systemic antibiotic concomitantly OR add Benzoyl peroxide. [11]

TOPICAL TREATMENT

Topical therapy includes the use of drugs / products (Agents) available over the counters /via prescription. Treatment is dependent on age of patient, site of involvement, extent of severity of disease & patient preference. Commonly used anti- acne agent

Benzoyl peroxide

BP is a potent antibacterial agent that kills P. acnes by releasing free oxygen radicals & also has mild comedolytic action and anti-inflammatory action as well. Combination of BP antibiotics gives better results and no resistance development. BP is available as topical washes, foams, creams/ gels. BP is available in different strengths ranging from 2-5-5%. Use of BP is limited by concentration-dependent irritation. People with more sensitive skin up to 5% can tolerate it. Benzoyl peroxide + Erythromycin/ clindamycin = Mild acne. The main problem with benzoyl peroxide is its potential for irritation. Some patients using benzoyl peroxide formulation may develop mild, transient erythema and xerosis, while some people cannot tolerate medication at all due to severe erythema and vesiculation. Stronger concentration formulations are better options for chest, back and arms. [13]

Topical antibiotics

Inflammatory papules are often treated with topical antibiotics. Topical antibiotics accumulate in the follicle and give antibacterial effects & also anti-inflammatory mechanisms. Topical antibiotic monotherapy is not used because development of resistance is reported. Currently 1% clindamycin gel is the most preferred agent in acne therapy. Topical erythromycin in concentration of 2% (gel, lotion, creams) are available but it has less efficacy than clindamycin because of the development of resistance of cutaneous staphylococci & P. acnes. They work best when used in combination with BP, which decreases the development of resistance in bacterial strain and increases the efficacy. Fixed combinations are available in markets like erythromycin 3% with BP 5%, clindamycin 1% with BP 3.75%. [15]

Salicylic acid

It is a comedolytic agent available over the counter. 0.5%-2% strengths are used for treatment of acne vulgaris. It is beta hydroxy acid that has both comedolytic and anti-inflammatory properties. All preparations are better tolerated. Mostly used in mild type of acne. [17]

Sulfone agents

Dapsone 5% gel twice daily agent available for acne treatment. Dapsone shows modest to moderate efficacy, primarily reducing the inflammatory lesions. It is recommended with topical retinoid if comedonal components are present to treat mild to moderate inflammatory acne. Its mechanism of action is not clearly understood but generally thought it works as an anti-inflammatory agent. Topical dapsone can be oxidized by the application of BP, causing orange- brown coloration of skin which can be washed off. This agent has less to no skin irritation and it can be a good alternative to BP sensitive/ allergic skin. [19]

Topical retinoids

Retinoids are vitamin A derivatives, preferably used in treatment of acne with multiple mechanisms of action including: decreasing cellular proliferation and differentiation, thereby decreasing the growth rate of follicular keratinocytes; and inhibiting the blockage of follicles and formation of new lesions, including comedones, inflammatory and noninflammatory lesions. It is also thought that the anti-inflammatory mechanism of retinoids is in part due to reducing the release of proinflammatory cytokines. Three topical agents are currently approved by the U. S. FDA. Tretinoin, adapalene, tazorotene. Different retinoids bind to different sets of retinoic acid receptors, thereby conferring slight differences in activity, tolerability & efficacy. The topical retinoids are generally safe and efficacious for the treatment of acne, but also showed that all had common adverse effects of irritation, erythema and dryness.[20,21]

Tretinoin

Tretinoin is a first-generation retinoid that has been used to treat acne for over 30 years. It causes the links between keratinized cells to weaken, allowing the keratin plug to disintegrate and be removed. It has an anti-inflammatory impact in addition to the comedolytic action, but it has no effect on sebaceous gland activity. After migrating to the nucleus, it binds to RARs in the cytoplasm and modulates gene expression. It is capable of binding all three types of RARs: namely α, β, and γ. Tretinoin can be taken on its own or in combination with other medications. It produces a synergistic impact when used in combination with other medications since it improves their penetration. Different formulations of tretinoin molecules have been introduced including 0.025, 0.05, and 0.1% cream, 0.025 and 0.1 gel, 0.05% solution, microsphere gel, and polymer cream. [1,22,23,]

Adapalene

Adapalene is a third-generation retinoid. It is available in 0.1 and 0.3 % gel and 0.1% cream form. It has selectivity towards β, γ types of RARs.[1,2,25]

Tazarotene

Tazarotene is a third-generation retinoid, and tazarotenic acid is its active metabolite. It has the ability to bind all three types of RARs. It exhibits anti-inflammatory characteristics, similar to other retinoids, as well as antiproliferative qualities and normalises Filaggrin expression. As a result, it's also employed in the treatment of psoriasis. It comes in cream forms of 0.05 and 0.1 percent. [20,21,25,]

THE SAFETY PROFILE OF TOPICAL RETINOIDS

Local skin reactions such as erythema, scaling, dryness, burning, and stinging are the most common side effects of topical retinoids; they can also induce pustular eruption in rare cases. Adapalene has a superior tolerability profile than tretinoin in comparative trials due to decreased irritation rates. Tretinoin was not preferred by the patient.[1,23,25]

SAFETY PROFILE OF TOPICAL AGENTS IN PREGNANCY

However, after using local retinoids in the first trimester, congenital problems have been recorded. Only systemic and high dose adapalene has been shown to cause teratogenicity in animals. However, because no trials in pregnant women have been conducted, a potential danger cannot be ruled out. Anophthalmia and abortion on the 22nd week have been documented in a pregnant lady who used adapalene in the 13th week of pregnancy, according to the literature. Tretinoin and adapalene are classified as pregnancy category C, thus they should only be used during pregnancy if the possible benefit outweighs the danger to the fetus. Erythromycin, azelaic acid, and BP, on the other hand, are safe to use during pregnancy, whilst retinoids are not. They should be avoided during lactation because no research has been done on breastfeeding mothers. Tazarotene's pregnancy category is X, hence topical preparations are not recommended. [25,27]

SYSTEMIC TREATMENT

Patients with mild acne can be treated with topical medications, while those with moderate to severe acne will need systemic treatment. The basic systemic therapy for acne is oral antibiotics, hormone medications, and isotretinoin.

Antibiotics

Systemic antibiotics are often considered the next line of treatment when topical medicines are ineffective or not tolerated, particularly in cases of moderate to severe acne, especially when the chest, back, and shoulders are involved. Oral antibiotics usually produce a response after at least six weeks of treatment. [28] Because of the possibility of resistance, systemic antibiotics should not be used to treat mild acne. It's worth thinking about using nonantibiotic topical treatments in addition to oral antibiotics. Topical retinoids combined with oral antibiotics may provide a faster and more effective response than either treatment alone. [29,30] Tetracyclines (tetracycline, doxycycline, minocycline) are the most widely given antibiotics for acne because they have both antibacterial and anti-inflammatory characteristics. Tetracyclines and erythromycin suppress the production of bacterial-induced inflammatory cytokines by reducing P. acnes within the follicles. In addition to reducing leukocyte chemotaxis and bacterial lipase activity, these compounds exhibit anti-inflammatory properties. [21,22] Minocycline and doxycycline also prevent inflammation and tissue degradation by inhibiting cytokines and matrix metalloproteinases. Although P. acnes has a 20% to 60% tetracycline resistance rate, it is unclear whether this is important in the treatment of acne. [22,23] Tetracycline is regarded less effective than doxycycline and minocycline. Erythromycin is reserved for patients who cannot take tetracyclines (for example, pregnant women and children under the age of nine), yet resistance to erythromycin is more common than resistance to other antibiotics. Sulfmethoxazole /trimethoprim (an off-label acne treatment) is also effective, but its link to Stevens-Johnson syndrome makes it a less popular option among doctors. [20] Patients should continue to take antibiotics until they stop developing new lesions. This may usually be done within 2 to 5 months of starting treatment. [24]

Retinoid

Isotretinoin inhibits all of acne's causative mechanisms, changing aberrant follicular keratinization, lowering sebum production by 70%, reducing P. acnes colonisation, and acting as an anti-inflammatory. [25] Scarring disease, severe nodulocystic acne, and less than 50% improvement with oral antibiotics or hormonal treatments after four months are all indications for isotretinoin. Potent teratogenicity, hypertriglyceridemia and pancreatitis, hepatotoxicity, blood dyscrasias, hyperostosis, premature epiphyseal closure, and night blindness are among side effects of isotretinoin medication. [27] It's been linked to serious skin reactions like erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis. Although no causal link has been established, patients should be informed about sadness, suicidal thoughts, and psychosis and constantly monitored. [27,28] A baseline blood test is recommended before a patient begins oral isotretinoin therapy. [26] Serum blood lipid measures, complete blood count and differential, liver enzyme tests, and blood glucose levels (as well as a pregnancy test for women of childbearing age) are all part of this testing. During treatment, these tests should be performed every month. Unless the patient has had a hysterectomy or is sexually abstinent, women of reproductive age should use two kinds of birth control during and for one month after treatment. [29] Isotretinoin has cutaneous adverse effects such as dry eyes, nose, and lips, as well as dermatitis. Artificial tears should be used, as well as plenty of moisturiser on the nose, lips, and skin.

Antiseborrheic drugs

Sulfur is used in concentrations varying from 1 to 10% and act as an antiseborrheic and mild keratolytic but it produces bad odor and the staining of clothes. Alcohol-ether in equal parts and zinc sulfate also act as sebum reducing agents. [30]

Hormonal therapy

Hormonal medications, regardless of underlying hormonal abnormalities, are an effective second-line treatment for acne in women. [31] Antiandrogen medication can be beneficial even if there is no evidence of androgen excess. Deep-seated nodules on the lower face and neck, according to clinical observation, are particularly susceptible to hormone therapy. [2] Oral contraceptives containing oestrogen can be beneficial; the various formulations are thought to lower free testosterone levels by boosting sex-hormone-binding globulin, and they are all considered equally effective. The patient's tolerance and potential side effects should be considered while selecting a combination oral contraceptive. [32] Anti-androgen cyproterone combined with 50 µg of ethinylestradiol is available as Dianette® which is the most effective hormonal intervention. [33] Other estrogen-containing contraceptives (e.g., vaginal rings, transdermal patches) are not known to be effective. Progesterone-only contraceptives may aggravate acne. If oral contraceptives are ineffective, the antiandrogen spironolactone might be added. When taken in larger quantities, spirolactone acts as a 5-reductase inhibitor. [34] Spironolactone has been demonstrated to be useful in treating acne when used alone or as an adjuvant at doses of 50–200 mg/d, however the data is limited. [35] Patients should be informed about the risks, which include hyperkalemia, menstruation abnormalities, and feminization of a male foetus [36]. Antiandrogen medication alone may be effective in less than half of women, and when it is stopped, acne may return. Combination therapy with topical medicines or oral antibiotics yields significantly better results. [36,37]

Table no – 2. Current Medical Treatments of Acne Vulgaris

Administration	Drug or dosage form	Treatment features
Oral	Tetracycline, Doxycycline, Minocycline, Isotretinoin (13-cis-retinoic acid)	Drugs should be taken daily, High patient compliance, Adverse effects limit the use of the drugs
Topical	Benzoyl peroxide, Clindamycin, Erythromycin, Tetracycline, Tretinoin, Tazarotene, Green tea extracts	Local administration of drugs, Ease of termination of drug action, Adverse effects limit the use of the drugs
Particle-based Drug delivery system	Liposomes, Solid lipid nanoparticles, Nanostructured lipid carriers, Micro emulsions Sustained	Sustained release of drugs, More effective than topical gel, Higher flux of drug across the skin, Effective for follicular targeting
Light based therapy**	Endogenous porphyrins (coproporphyrin III), 5-aminolevulinic acid	Fewer adverse effects than systemic/topical administration and Drug delivery system, Light therapy alone or along with liposomal drugs reported, Not a first line therapy for acne vulgaris

* For particle-based Drug delivery system, **This therapy uses either topical drugs or particle based drug delivery systems along with light irradiation.

Procedures

Patients with comedones that have not responded to normal treatment may benefit from comedo extraction. [38] For quick treatment, corticosteroids are injected into the acne comedone.[39] Microdermabrasion has not been proven to be beneficial. [38] The data for light treatment and lasers as of 2012 is insufficient for routine use. [38] Light therapy is a costly treatment that only has a short-term benefit, and there is no long-term data in individuals with severe acne. [38,39] Acne scars can be treated using laser surgery to decrease their appearance. [40] In patients with cystic acne, surgical lancing can be used to eliminate boils.[31] A comparison of alpha-hydroxy (30 percent glycolic acid) with beta-hydroxy (30 percent salicylic acid) peels was done in a double-blind, randomised research, and both peels were found to be equally beneficial for acne therapy. [42] Acne scars are occasionally treated by subcision. Subcision entails inserting a tri-beveled hypodermic needle through a skin surface puncture and moving the needle's edges to break down subcuticular fibrotic strands, allowing the skin to be separated from the underlying connective tissue. It looks to work just as well as collagen filler. [41]

Laser and light devices

Photodynamic therapy, light emitting diode therapy, and a combination of pneumatic energy and light have all been shown to be effective when combined with standard acne treatments. [44] IsolazTM (Aesthera, Pleasanton, CA, USA) is a combined device that employs a vacuum with a broad band light source to treat acne. It has been found to be successful in 11 individuals treated at three-week intervals and reduces inflammatory and noninflammatory lesions. [44]

Conclusion

Acne vulgaris is one of the most frequent skin conditions that affect teenagers. Seborrheic skin, blackheads and comedones, papules, papules, pimples, and scars are all signs of acne vulgaris. The Pillsbury scale, Cook's acne grading scale, and Leeds acne grading approach are all used to grade the severity of acne vulgaris. Benzoyl peroxide, antibiotics such as erythromycin, clindamycin, and tetracyclines, antiseborrheic medications such as sulphur and sodium sulphacetamide, antiandrogen medications such as norgestimate, desogestrel, or drospirenone, Dianette®, Yasmin®, salicylic acid, hormonal treatments, alpha hydroxy acid, retinoids, azelaic Acne is being treated with laser and light equipment, as well as modest subcision surgery. P. acnes bacteriophage (PA6) genome sequencing was recently discovered which could aid in the development of a potential bacteriophage therapy to treat acne.

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