

Acne



Acne is a common skin disorder. It can severely affect the lives of sufferers, particularly teenagers. Over the years, pharmaceutical research has discovered various treatments for it. Further investigations are set to lead to promising treatments in the future, especially in more severe forms.

What is acne?

Acne is a skin disorder of the pilosebaceous unit, which consists of a hair follicle, sebaceous gland, and a hair. The number of these units is greatest on the face, upper neck, and chest. Sebaceous glands produce sebum, an oily substance which keeps the skin and hair moisturised. During puberty and adolescence, the glands, under the influence of hormones, enlarge and produce more sebum. A bacterium known as *Propionibacterium acnes* is a normal inhabitant of the adult human skin where it resides in sebaceous follicles and feeds on sebum. People with acne have more *P. acnes* in their follicles than people without the disorder. The increased presence of bacteria attracts white blood cells which produce enzymes that damage the wall of the follicle, allowing its content to enter the surrounding tissue. This finally leads to an inflammatory response seen as papules, pustules, and nodules. The bacterium also causes the formation of free fatty acids, which are irritants, increasing the inflammatory process in the follicle.

All acne begins with a basic lesion: the comedo (blackhead), an enlarged hair follicle plugged with sebum and bacteria. With the ongoing sebum production bacteria flourish within the swollen pore. If the plugged follicle stays below the surface of the skin, the lesion is called a closed comedo. Where the clogged follicle pushes through the surface of the skin, one speaks of an open comedo. Both forms of comedones represent forms of non-inflammatory acne.

The mildest form of inflammatory acne is the papule. It appears as a small, firm pink bump and is considered an intermediary step between non-inflammatory and clearly inflammatory lesions. Like papules, pustules are small round lesions; unlike papules, they are clearly inflamed and contain visible pus. Nodules are large and usually painful pus-filled lesions lodged deep within the skin. They develop when the contents of a comedo have spilled into the surrounding skin and the local immune system responds. They often leave deep scars. The rare but serious form of inflammatory acne called *acne conglobata* develops primarily on the back, buttocks and chest. In addition to the presence of pustules and nodules, there often is severe superimposed bacterial infection.

Who does acne affect?

Acne is one of the most widespread medical conditions in the world. Overall life time prevalence is around 90 per cent. Acne is most prevalent in the teens and early adulthood, mainly because of increasing production of the hormone androgen. As more androgen is present in males, teenage boys tend to have more severe acne than teenage girls. Research has shown that genetics play a part in the development and persistence of the disease and people with a family history are prone to develop more severe forms. People with oily skin tend to get more acne. In most cases it will last from six to ten years. Acne usually clears up in early adulthood. However, there are people who have acne throughout their lives and 20 per cent of all cases are adults.

Present treatments:

Present acne treatments achieve one or more of the following: (i) decrease sebum production; (ii) reduce bacterial colonisation with *P. acnes*; (iii) normalise skin shedding; and (iv) eliminate inflammatory reaction.

There are medicines for local use or for oral application. One common ingredient in locally applied products is benzoyl peroxide, which may be combined with other topical or oral treatments. Benzoyl peroxide is an antiseptic and oxidising agent which destroys the bacterium *P. acnes*. The compound does not affect the body's own production of sebum. It must be used over a long period and it takes several weeks before the outward signs begin to disappear.

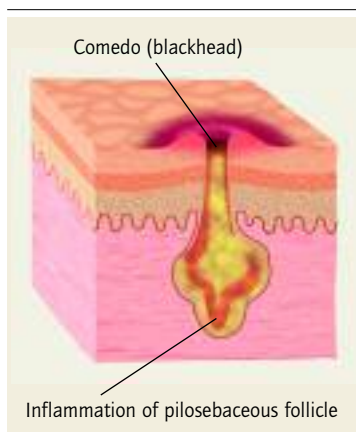
Mild acid solutions, such as salicylic acid and glycolic acid, are also used as topical medications. The approved range of salicylic acid concentrations for acne treatment is between 0.5 per cent and two per cent. The preparations work as keratolytic agents, i.e. they encourage the peeling of the top layer of the skin and the opening of plugged follicles, which supports the re-establishing of the normal skin-cell replacement cycle.

Salicylic acid does not have any effect on the production of sebum or the presence of *P. acnes* bacteria. Like many other locally applied products, salicylic acid must be used continuously, even after acne lesions have healed. Other topical acne preparations with a peeling agent may contain resorcinol or sulphur.

For patients who suffer from moderate to severe acne, dermatologists generally prescribe a combination of topical remedies and low-dose oral antibiotics. The most common antibiotics used to combat bacterial infection are tetracycline preparations and macrolides. There are also antibiotic-containing foams for local application. It takes weeks before first improvements can be seen after the start of low-dose antibiotic treatment.

In some female patients, acne can be caused by excessive production of androgens, especially when the disorder appears in adults for the first time or when there are acne flare-ups preceding the menstrual cycle. Women whose acne has resisted treatment with antibiotics or topical remedies may be candidates for treatment with oral contraceptives. Low doses of estrogen help suppress the androgens produced by the ovaries and the newer progestin agents are less androgenic. In combination with oral contraceptives, anti-androgen medicines may also be given, which inhibit androgen production in the ovaries and adrenal glands and help prevent existing androgens from causing excessive sebum production. Sexually active patients undergoing such therapies therefore have to use some form of birth control.

Small doses of corticosteroids may curb inflammation and suppress the androgens produced by the adrenal glands. In extreme cases, injections of diluted corticosteroids may be injected into nodules and cysts to lessen the local inflammation. Oral corticosteroids are most effective when used in combination with oral contraceptives.



Skin: enlarged follicle plugged with sebum and bacteria

Patients with forms of acne resistant to standard therapies are treated with compounds derived from vitamin A acid or retinoids, especially in severe forms of acne, i.e. in nodular or conglobate acne or acne that risks permanent scarring. Retinoids are the most effective acne treatment available because they work on all four factors that predispose a person to acne – excess sebum production, clogged skin pores, flourishing *P. acnes* and ongoing inflammation. The remissions achieved after a once or twice daily treatment course over 16 weeks usually last from many months to years. For many patients, only one course of therapy is needed. There are formulations for topical treatment and products which are given orally. As vitamin A acid derivatives cause severe birth defects in the unborn, women of childbearing potential who are undergoing therapy have to care for contraceptive measures. Pharmaceutical manufacturers marketing such products in the EU provide educational material to be given to patients by doctors, and those for distribution to pharmacies.

What's in the development pipeline?

A new antibiotic retinoid acne combination product, consisting of a 1 per cent macrolide antibiotic plus 0.025 per cent retinoid has been shown in two Phase 3 trials to be more effective. It performed better than either constituent alone.

The longer-term future:

In July 2004, two European research groups reported that they had unveiled the entire genome sequence of *P. acnes*. The genetic material of this Gram-positive bacterium encodes 2333 putative genes and reveals numerous gene products involved in degrading host molecules, including enzymes such as sialidases, neuraminidases, lipases, and pore-forming factors. The researchers also identified surface-associated factors and others involved with the body's immune system, which might be involved in triggering acne inflammation and other *P. acnes*-associated diseases. Their findings will open new avenues to study the harmful involvement of the bacterium in all forms of acne and to find new ways to get along with this usually harmless organism that lives in the pores of human skin.



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