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REVIEW

Pathological Mechanisms of Acne with Special Emphasis on *Propionibacterium acnes* and Related Therapy

UTA JAPPE[1,2]

[1]*Department of Dermatology and Venereology, University of Heidelberg, Germany and* [2]*Department of Microbiology, University of Leeds, UK*

Acne is a common disease that in cases of extreme disfiguration can have severe consequences for the personality development of young people and is associated with a relatively high prevalence of depression and suicide. Spontaneous regression is common, but acne can extend into the fourth and fifth decades of life. The pathogenesis is still not fully understood. Factors promoting the development of acne are: increased sebum production, ductal cornification, bacterial colonization of the pilosebaceus ducts and inflammation. However, there is evidence that inflammation is not a factor but rather a consequence of the interaction of the other three factors. *Propionibacterium acnes* releases pro-inflammatory cytokines as well as antigens and mitogen(s), with cellular and non-cellular responses to these products triggering inflammation. Treatment is often frustran. Therapeutical strategies are needed based on new understandings of the pathomechanisms involved in acne. The aim of this review is to summarize the data on aetiopathological factors in acne and their contribution to acne pathology and therapy.
Key words: acne therapy; acne vulgaris; mitogen; Propionibacterium acnes.

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Uta Jappe, Department of Dermatology, University of Heidelberg, Vosstraße 2, D-69115 Heidelberg, Germany. E-mail: Uta_Jappe@med.uni-heidelberg.de

Acne vulgaris is one of the most common diseases of the skin and in cases of extreme disfiguration can sometimes have severe consequences for the personality development of young people, with ensuing social and economic problems. Adolescents suffering from acne show higher levels of anxiety and greater social inhibition and aggression compared to non-affected individuals. Among skin diseases, acne vulgaris is the second highest cause of suicides (1).

Acne is an exclusively human disease and a unique condition of human sebaceous follicles of the face, chest and back that begins in the prepubertal child. Spontaneous regression is common, but in about 5% of cases acne persists beyond the age of 25 and extends into the fourth and fifth decades of life (2). The earlier the symptoms start, the more severe is the course of the disease. The prevalence of the disease does not reflect any preference for male or female, but usually the course is more severe in males. There seems to be a familial trait with an autosomal-dominant mode of inheritance with different expression.

AETIOLOGY OF ACNE

Factors promoting the development of acne are: increased sebum production, ductal cornification, bacterial colonization of the pilosebaceus ducts and inflammation (Fig. 1). Although the severity of acne vulgaris is associated with seborrhoea, the disease is one of the follicular infundibulum. In mild acne, the keratinocytes of the infundibulum hypercornify, hyperkeratinize and hypodesquamate to produce comedones. In severe acne the infundibulum ruptures to introduce sebum into the dermis, where it is highly inflammatory.

Sebum production and androgens

Seborrhoea is significantly more common in patients with acne than in controls and contributes to lesion formation (3, 4). The sebaceous gland is an androgen target organ, stimulated to produce sebum at puberty and beyond by androgens. Sebaceous glands present the highest androgen receptor density in human skin (5, 6). The most important androgen is testosterone, which is converted to the more potent dihydrotestosterone (DHT) by the iso-enzyme 5α reductase (type I), the major isotype detected in skin, particularly in sebaceous gland-rich areas (7–10). From cell-culture experiments there is evidence that human sebocytes possess a complete corticotropin-releasing hormone (CRH)-receptor system. CRH is a coordinator for neuroendocrine and behavioural responses to stress. It has been concluded that CRH may function as an important autocrine hormone with a homeostatic pro-differentiation activity (11). Clinical observations suggest an influence of stress on the course of acne, which may be explained via this hormonal pathway.

Fatty acids

Free fatty acids are known to be highly inflammatory and chemotactic (Fig. 1). Exclusive production of irritant fatty acids by the lipases of *P. acnes* acting

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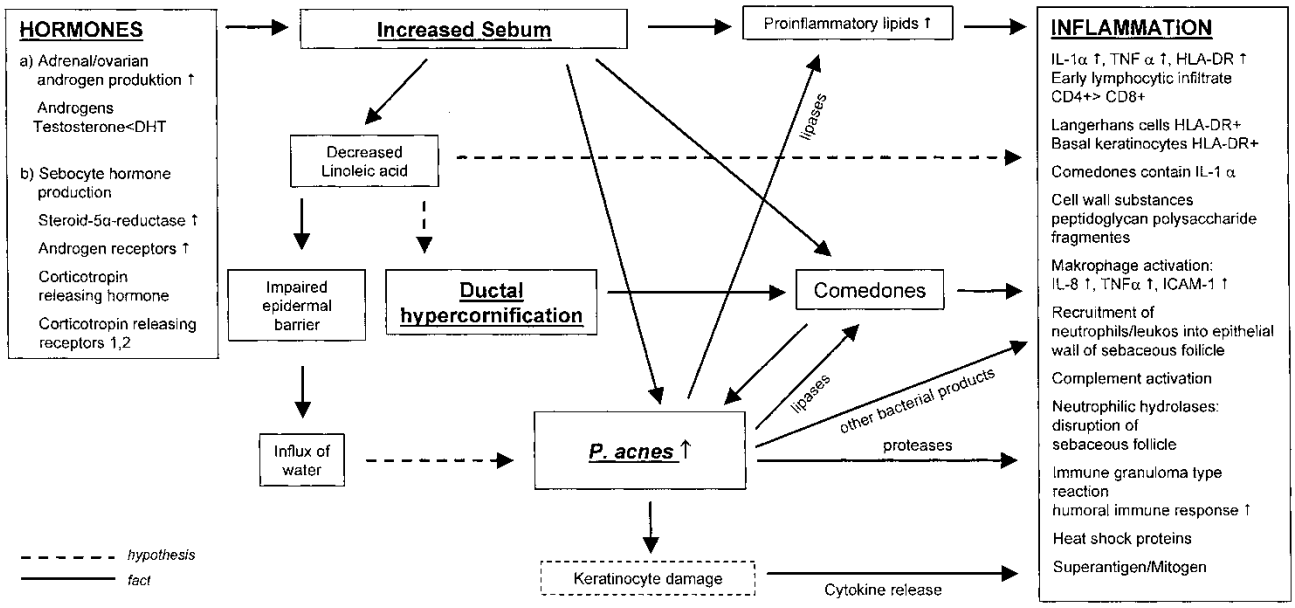

Fig. 1. Synopsis of factors involved in the pathogenesis of acne.

on triglycerides derived from sebocytes was an early hypothesis dashed by Weeks et al. (12), who showed that lipase inhibition induced a reduction of fatty acids on the skin, but failed to treat acne. Pro-inflammatory lipid fractions in sebum produced by other mechanisms than bacterial lipases may be one responsible factor for the development of inflammation in acne.

Linoleic acid deficiency

Linoleic acid is incorporated into sphingolipids in the follicular epithelium, which participates in the formation of the intracellular lipid lamellae. In 1986, it was suggested that linoleic acid deficiency was an important factor in the aetiology of acne (Fig. 1) (13). It was argued that linoleic acid deficiency impaired the follicular epithelium barrier, allowing other free fatty acids, resulting from bacterial lipase activity and/or sebocyte metabolism to enter the epithelium and to induce localized essential fatty acid deficiency. Zouboulis (14) recently showed that linoleic acid is able to regulate interleukin (IL-)8 secretion and, as a consequence, the inflammatory reaction.

Ductal hypercornification

The mechanisms underlying the infundibular changes are still obscure. Prominent hypotheses implicate a local follicular deficiency of linoleic acid, effects of IL-1α and androgens as potential factors involved in follicular hyperkeratinization causing an apparent early cornification of the keratinocytes and scaling (Fig. 1) (15, 16). Il-1α causes an upregulation of cellular retinoic acid binding protein-II and small proline-rich protein 1 in keratinocytes cultures which correlates with keratinocyte differentiation (17).

Oxygen stress and free radicals

Another hypothesis focuses on the importance of reactive oxygen species as an inflammatory mediator released by phagocytes such as neutrophils, which produce these mediators for lysis of invading microorganisms. In 1998, Akamatsu & Horio showed that neutrophil-derived reactive oxygen species are involved in the irritation and destruction of the follicular wall in acne patients (18).

Bacteria

Acne is not an infectious disease and, therefore, not contagious. Among the bacteria species that colonize normal skin as resident flora, only those able to colonize the follicular duct and multiply there can be pathogenic for acne. Only three species of microorganisms could therefore be associated with the development of acne lesions: propionibacteria, coagulase-negative staphylococci, and yeasts of the species *Malassezia*. However, acne did not improve after antifungal treatment, so yeasts could not be associated with the pathogenesis of acne. Staphylococci could also be excluded, because these develop antibiotic resistance during the first weeks of treatment in most patients (19), and the numbers quickly rise. Scientific interest has therefore been focused on propionibacteria.

Propionibacteria are Gram-positive, non-motile, pleomorphic rod-shaped cells that ferment sugars to yield propionic acid as one of the end products in this metabolic process. *P. acnes* is the predominant resident

microorganism on sebaceous gland-rich areas of skin in adults (20). On human skin, propionibacteria can be found from birth until death (21). Bacteriological analysis and sebum production investigated in multiple body areas demonstrated a high association between *P. acnes* levels and sebum production (22).

P. acnes is associated with the development of acne but reports are increasing in number implicating *P. acnes* in other diseases (reviewed in 23) (Table I).

The pathogenicity of propionibacteria is thought to be due to, first, the production of exocellular enzymes and other bioactive exocellular products, which could act as virulence determinants, and, second, on the microorganism's interaction with the immune system. Propionibacteria resist phagocytosis and can persist intracellularly within macrophages for prolonged periods (24).

First significant hints of an influence of *P. acnes* on acne were obtained from *in vivo* studies on the injection of highly concentrated viable propionibacteria into sterile cysts of Steatocystoma multiplex patients; this induced prominent inflammation (25). Intradermal application of dead *P. acnes* cells as well as the injection of viable *Staphylococcus epidermidis* cells were unable to reproduce this effect.

Furthermore, the first use of antibiotics in acne and the clear-cut clinical improvement of acne seen with those agents that reduce *P. acnes*, such as tetracyclines, macrolides, sulfonamides and clindamycin, strengthen the hypothesis that *P. acnes* plays an important role. Likewise the emergence of antibiotic-resistant strains and a concomitant clinical failure further solidifies the importance of *P. acnes* in acne (26). There is evidence that *P. acnes* is involved in invoking an inflammatory response. Although the antigens of *P. acnes* have not been characterized in detail yet, an increased cellular as well as humoral immunity to *P. acnes* could be detected in patients with severe acne. The production of antibodies correlated with the severity of the disease (27, 28). The initial infiltrate into the lesion is lymphocytic, with later progression to a general infiltrate of mixed cell types. CD4+ cells are predominant. CD8+ occur occasionally perivascularly and periductally, and CD1+ cells are present in low numbers (29). Langerhans' cells expressing human leucocyte antigen (HLA)-DR have been observed in close association with perilesional CD4+ T-cells and HLA-DR was shown to be upregulated in the periductal and perivascular infiltrates of acne lesions. Basal keratinocyte expression of HLA-DR has been demonstrated and is indicative of a specific immune response (29).

It is possible that the microorganism and/or its products interact with keratinocytes and sebocytes which then produce cytokines. Cytokines attract lymphocytes non-specifically. Preliminary data suggest that both T-helper 1 (Th1) and Th2 cells play a role in the inflammatory events. Recently it could be demonstrated that *P. acnes* has mitogenic activity. Therefore two mechanisms of lymphocyte activation by *P. acnes* cells are proposed, antigen and mitogen driven (30).

Bacteria and antibiotic resistance

P. acnes is the target of antimicrobial treatments in acne. In 1976, no antibiotic resistance could be detected in *P. acnes* strains from acne patients (31). It was in 1979, when Crawford et al. (32) first described antibiotic resistance of *P. acnes* towards erythromycin and clindamycin in 20% accompanied by therapeutic failure, followed by Eady et al. (26) who reported on resistance to orally applied erythromycin associated with therapeutical failure. The resistance rate increased from 20% in 1978 to 68% in 1996. According to a recent investigation, Mediterranean countries had the highest prevalence of resistance to erythromycin and clindamycin: Spain 91% and 92.4%, respectively; Greece for both erythromycin and clindamycin 75.3%; Italy for both antibiotics 59.5%. A lower resistance rate was detected in northern countries, where it ranged for both substances between 41.5 and 51.4% (33).

Resistance towards minocycline is only 1% (34). Recently, Dreno et al. (35) described a prevalence of bacterial resistance to erythromycin of 95% for *S. epidermidis* strains, 52% for *P. acnes* strains that were colonizing patients with predominantly inflammatory lesions, and 42% of *P. acnes* strains from patients without any previous application of erythromycin. In

Table I. *Diseases (infections/inflammatory conditions) with which* Propionibacterium acnes *has been associated*

Skin manifestation	Ocular manifestation	Others
Acne vulgaris	Acute endophthalmitis	Endocarditis
Periorbital cellulitis	Chronic endophthalmitis	Cerebral absesses
Primary purulent folliculitis	Conjuctivitis	Arthritis
Abscesses	Blepharitis	Osteomyelitis
Kawasaki disease	Keratitis	Meningitis
Sarcoidosis	Canaliculitis, dacryocystitis	Various abscesses (incl. dental)
SAPHO syndrome (acne, palmoplantar pustulosis, osteitis hyperostosis		Dental caries, periodontal disease and gingivitis

Modified from ref. 23

their 10-year surveillance study, Coates et al. (36) showed an increase in antibiotic resistance from 34.5% in 1991 to 64% in 1997. The prevalence then dropped to 50.5% in 1999 and rose again to 55.5% in 2000. Resistance to erythromycin was the most common and most of the strains were cross-resistant to clindamycin. Most patients were colonized with resistant bacterial strains at various sites, including the nares, the latter being difficult to eradicate.

Acne lesions are dominantly colonized by *P. acnes* and *S. epidermidis*. Nishijima et al. (37) isolated *S. epidermidis* and *P. acnes* simultaneously from half of the acne lesions. The application of antimicrobials has to take into consideration that acne lesions are inhabited by both. Therefore, careless administration of antibiotics increases the resistance of several bacteria (34). Nishijima et al. (37) detected antibiotic resistance for more than 30% of *S. epidermidis* strains resistant to erythromycin, roxithromycin, clindamycin. These antibiotics cannot therefore be recommended for long-term (more than 3 months) acne therapy. The ability of *S. epidermidis* to transfer resistance via plasmids to the more pathogenic *S. aureus* has already been observed and taken into consideration (37, 38).

But not only *P. acnes* and *S. epidermidis* develop antibiotic resistance due to acne treatment, and resistance is not only spread among bacteria but resistant bacteria are also spread among patients and their close contacts. Mills et al. (39) have observed that topical treatment with erythromycin can result in a higher carriage rate and dissemination of erythromycin-resistant *S. aureus* from the nares. They observed an increase in the prevalence of erythromycin-resistant coagulase-negative staphylococci from 37% to 88% over the 12-week course of treatment which did not alter in the regression phase, meaning that antibiotic resistance can persist for a considerable time. There is evidence that duration of the treatment period (>6 weeks) has an influence on the persistence of resistant strains. The same study showed that a dissemination of resistant organisms occurred to untreated areas. This implies the transfer of resistant strains to close contacts which has been reported previously (40).

Whereas staphylococci acquire antibiotic resistance very rapidly via plasmids, *P. acnes* develops resistance to tetracyclines, erythromycin and clindamycin over a long period of time via mutational change which is transferred vertically. According to recent results, *P. acnes* antibiotic resistance is commonly associated with mutations in 16S and 23S mRNA, which are present in bacterial isolates from Japan, Australia, U.S.A., and Europe (41). There are additional mechanisms involved which have not yet been characterized (41). The same group found high-level resistant *P. acnes* strains to minocycline in the U.S.A. which is of concern because the resistance may not remain confined to the U.S.A.

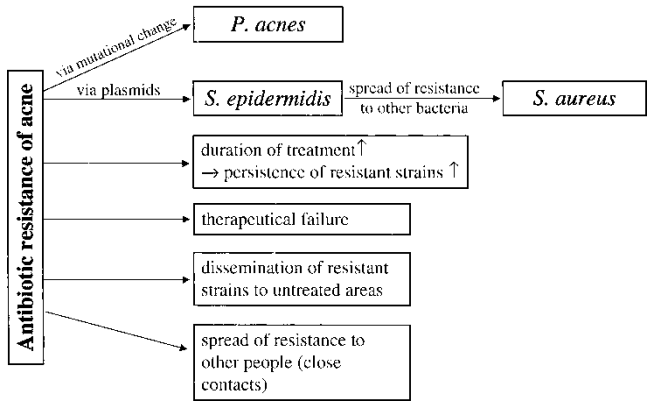

Fig. 2. Consequences of antibiotic resistance in acne. (26, 34, 37–41)

Ross et al. have also discovered a transposon-based macrolide-lincosamide-streptogramin B resistance determinant in cutaneous propionibacteria from six European cities (42). The transposons came from corynebacteria, but the mechanism by which it is transferred into propionibacteria has not been elucidated. The determinant confers a higher degree of resistance than the known 23S rRNA mutations to several macrolide-lincosamide-streptogramin B antibiotics, especially telithromycin and clindamycin, the latter being extensively used in the topical treatment of acne (42).

Further factors

Although early reports and several individual observations indicate that dietary factors, especially chocolate and meat, have an influence on the exacerbation of acne, the association could not be proven. However, there is a significant linear dose-dependent relationship between both acne prevalence and severity and the number of cigarettes smoked daily (43). Cordain et al. (44) reported a very low prevalence of acne in two non-Western societies and observed that the absence of acne is correlated with their diets, which in contrast to a Western diet is significantly less glycaemic. The authors suggest that a diet-induced hyperinsulinaemia elicits endocrine responses that may affect the development of acne through mediators such as androgens, insulin-like growth factor, insulin like growth factor binding protein 3, and retinoid signalling pathways. Further studies on these interactions may be useful in the treatment of acne in Western populations.

DIAGNOSTIC PROCEDURES

The first examination should include inquiries on familiar occurrences, on cosmetics used, menstrual cycle irregularity indicating hyperandrogenism, drugs like vitamin B, lithium, phenytoin, which aggravate acne, further skin diseases and non-skin diseases, particularly endocrinologic and metabolic disturbances. Facing the

growing significance of antibiotic resistance, facial skin swabs should be investigated for *P. acnes* and staphylococci including resistance analysis (reviewed in 45), which has not been introduced as a routine test due to a lack of appropriate facilities for *P. acnes* cultivation in dermatological practice. Female patients with clinical signs for hyperandrogenaemia should be investigated for the concentrations of testosterone, prolactin, sex hormone binding globulin (SHBG), DHEAS, cortisol, estradiol. Patients with a severe course of the disease should additionally be examined for erythrocyte sedimentation rate, C-reactive protein, differential blood count, immunoglobulins, zink and α1-antitrypsin (45).

TREATMENT OF ACNE

The aims of treatments are to improve the disfiguring, the psychological distress, and to prevent scarring. According to the aetiopathological factors in acne, the therapy consists of anticomedogenic, anti-inflammatory and antimicrobial substances. Drugs that reduce comedones are the topical retinoids (tretinoin, tazarotene, adapalene and retinylaldehyde) and oral isotretinoin.

Retinoids

Retinoids do have an effect on cell proliferation and differentiation, are sebostatic and keratolytic but also have anti-inflammatory properties. Isotretinoin given orally induces sebaceous gland size reduction to up to 90% by decreasing proliferation of basal sebocytes, suppressing sebum production and inhibiting sebocyte differentiation *in vivo*. Its unique activity on sebaceous glands is still not clearly understood. However, in 2000, Tsukada et al. (46) reported the mechanism by which 13-*cis* retinoic acid is sebocyte-specific. They provided evidence that the so-called specific antisebotropic activity of 13-*cis* retinoic acid is likely to be mediated by a selective rapid and marked intracellular isomerization of 13-*cis* retinoic acid to all-*trans* retinoic acid in human sebocytes with subsequent binding of all-*trans* retinoic acid to and activation of retinoic acid receptors, supporting a pro-drug/drug relation between the two compounds (46).

It has also been suggested from investigations of biopsy material that retinoids have a direct pharmacological action on neutrophils. Topical tretinoin has been shown to have an inhibitory effect on the release of lysosomal enzymes from polymorphonuclear leucocytes, enzymes playing a key role in follicular wall damage, thereby releasing inflammatory mediators into the dermis (47). Tretinoin and adapalene were shown to inhibit human polymorphonuclear neutrophil lipoxygenase activity (48), the latter being essential for the oxidative metabolism of arachidonic acid, a pathway in the production of inflammatory mediators. The systemic retinoid, isotretinoin, is used for severe cystic and scarring acne, acne that is resistant to oral antibiotics and acne that quickly relapses after antibiotic therapy. Serious side effects like teratogenicity, myalgias, arthralgias have to be considered, and the patient has to sign informed consent. Recently, several cases of psychological depression and even suicide have been reported among patients treated with isotretinoin. However, the causal relationship between isotretinoin therapy and depression has not been clearly established and needs further study (49, 50).

Micronized isotretinoin caused fewer and less intense mucocutaneous adverse events than standard isotretinoin, which may improve patients' quality of life (51).

Similar to other topically applied retinoids, adapalene shows antiproliferative and prodifferentiating effects on keratinocytes but less potential for irritation and a high lipophilicity (52). As to antimicrobial effects, adapalene has no direct influence on *P. acnes* itself. There is evidence that it reduces the inflammatory response to bacterial antigens and mediators. Therefore, it does not support the development of antibiotic resistance in *P. acnes*.

Hormonal treatments

Hormonal treatments of acne consist of the ovarian suppression of androgen production by oral contraceptives, androgen receptor blockers: cyproterone acetate and spironolactone, adrenal suppression of androgen production by corticosteroids and inhibitors of 5-α-reductase. Hormones are not the first choice treatment, only for women with mild acne or signs of hyperandrogenism who ask for contraception. Pills with an extremely low androgenic progestin concentration, or – even more efficient – with a low dose of 2 mg of cyproterone acetate should be used.

Antimicrobial substances

Antibiotics reduce the bacterial colonization of the deeper parts of the follicle. *P. acnes* is sensitive to a wide range of antimicrobials *in vitro*, but only lipophilic drugs penetrate the microcomedo and are bacteriologically and clinically efficient in patients with acne, which is the case for tetracycline, doxycycline and minocycline. These antibiotics have additional anti-inflammatory capacities, particularly minocycline. For topical application erythromycin, gentamycin, tetracycline as well as clindamycin are used. Topical erythromycin is not only well accepted, it also has anti-inflammatory properties, suppresses the chemotaxis of inflammatory cells and decreases pro-inflammatory free fatty acids in sebum indirectly by down-regulating either the *P. acnes* metabolism and/or extracellular lipase production, the latter being also affected by tetracyclines (53–56). However, it is highly advisable not to use topical antibiotics alone because of the risk of the development of antibiotic resistance (57) but instead to combine it

with other topical substances, for example, benzoyl peroxide (BPO), azelaic acid, tazarotene, tretinoin, adapalene, which also have either direct or indirect antimicrobial activity (52, 58). Out of the retinoids retinoic acid, retinol and retinaldehyde, which are currently used in many formulations, retinaldehyde has been shown to have significant direct antibacterial activities upon topical use without the emergence of resistant strains (59). The combination of erythromycin or clindamycin and BPO topically is recommended because the number of aerobic bacteria is reduced without any change in the resistance towards erythromycin or other antibiotics (31, 57, 60). Cunliffe (34) recommended the combination of BPO + Adapalene + topical antibiotic to reduce the resistance rate. Pfannschmidt et al. (61) demonstrated that the combination of topical tretinoin and erythromycin was more effective than either agent used alone. In patients with comedones and papulopustular lesions a therapy with a topical retinoid and either a topical or systemic antibiotic is the preferred approach (62).

New therapeutical strategies

Because most retinoids do not have a direct effect on *P. acnes*, this group of substances is not able to rectify the four major components of acne pathogenesis. Monotherapy, therefore, is mostly not efficient. Nor should topical antibiotics, which apart from antimicrobial activity also have anti-inflammatory properties, be used as monotherapy because of the development of antibiotic resistance. Future strategies for the use of antimicrobial therapy in patients with acne should consist of minimization of antibiotic use, and the combination of antibiotics with other substances. Oral antibiotic treatment should be stopped once control is achieved. Maintenance therapy should consist of either topical retinoids and benzoyl peroxide or benzoyl peroxide and antibiotic (63). And whichever strategy is used, it should be started as early as possible (52).

As to the development of new substances and their introduction into medical practice, a topical antiandrogenic treatment would be an interesting approach. So far it has been disappointing probably because *P. acnes* is able to metabolize androgens applied to the skin, therefore, the development of combinations of antiandrogen and antimicrobial agents should be considered. A relatively new antibiotic is lymecycline, which is as effective as minocycline but has fewer side effects (64).

Zouboulis et al. (65) demonstrated a 70% reduction in inflammatory lesions after 3 months of therapy with a new anti-inflammatory agent that specifically blocks the formation of leukotriene B4. In parallel, these patients showed a reduction in total lipids, hydroperoxides and free fatty acids in sebum. Recently, the efficacy of topical 5-aminolaevulinic acid photodynamic therapy and selectivity of photosensitizer accumulation has been demonstrated in the treatment of both truncal and facial acne (66).

Vaccination

According to a single publication, an oral antigen treatment with heat inactivated lyophilized acne bacteria had been performed in the early 1970s and could be shown to have improved acne in 80% of cases (67). Since there is evidence that *P. acnes* is associated with inflammation in acne and that the microorganism rises a humoral as well as a cellular immune response the idea of a *P. acnes*-based vaccination is tempting. However, the multifactorial character of acne has to be considered.

CONCLUSION

The increasing importance of appearance and the influence of disfiguring on psychologic health confirm the significance of the disease "acne". Although during the past 50 years dramatic progress has been made concerning the development of treatment modalities, the pathomechanism is still not fully understood. Molecular biology combined with molecular immunology and pharmaceutical research is necessary to clarify these issues. The current recommendations for the use of antibiotics in acne is summarized in Table II.

Table II. *Recommendations for the use of antibiotics in acne therapy*

1. Prescribe antibiotics only if necessary.
2. Treatment for as short a time as possible accepting that 6 months is the minimum for oral and 3 months for topical therapy.
3. When further treatment is necessary, re-use the same antibiotic (unless it loses efficacy).
4. Apply benzoyl peroxide (BPO) for a minimum of 5–7 days between antibiotic courses to eliminate resistant organisms from the skin (which unfortunately may persist in the nares).
5. Avoid changes of therapeutic protocols unless necessary.
6. Avoid concomitant use of oral and topical therapy with chemically dissimilar antibiotics.
7. Inform and educate the patient concerning compliance and treatment strategies.
8. Stop antibiotic treatment once control is achieved.
9. Institute maintenance therapy consisting of either topical retinoids and BPO or BPO and topical antibiotic.

Modified from ref. 68

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