Christos C. Zouboulis · Andreas D. Katsambas
Albert M. Kligman *Editors*

# Pathogenesis and Treatment of Acne and Rosacea

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*In memoriam Dr. Albert Montgomery Kligman, 17.03.1916–09.02.2010.*

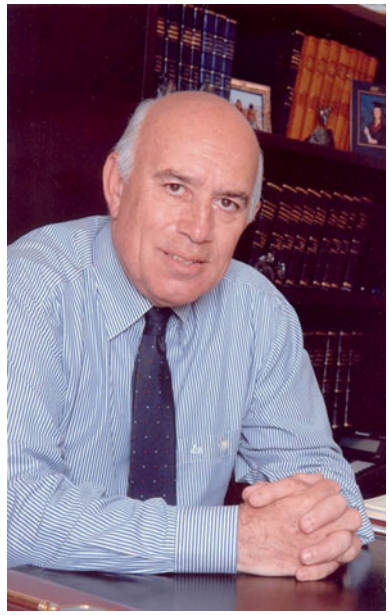
*Dedicated to Gundula, Konstantin and Viktor-Alexander for their enormous love and patience*

# Preface

Christos C. Zouboulis

## The History of this Book

It was a warm day in late July 2002 during the 50th Annual Montagna Symposium on the Biology of Skin when two of us met for the first time. We knew each other longer; the younger part has admired the more experienced part for his pioneer work and great contribution to science, and the latter part was well informed on the scientific work of the younger, but they have simply never met before in person. There, in Snowmass, up on the mountains of Colorado, an invitation to lunch was followed by a long exchange of ideas and scientific arguments in the fields of sebaceous gland, acne, and rosacea that lasted for a few hours. Since then, the two discussants met once a year for lunch during the annual meeting of the Society of Investigative Dermatology and stayed for hours discussing, what else, the developments but also histories on the research of sebaceous gland, acne, and rosacea. They renewed their appointment for the next annual meeting with "a lot of new aspects to elucidate" in between. They even agreed for a common cruise at the islands of Greece in order to have plenty of time for scientific discussions under the inspiration of the plain sun and the magic of white and blue. Unfortunately, this journey never took place.



Andreas D. Katsambas

During one of these annual discussions, the experienced part introduced the idea of a book on, what else, the sebaceous gland, acne, and rosacea and motivated the younger part to overtake the task. The latter felt the load too heavy to be carried on his shoulders, especially with all these giants, Albert M. Kligman, Gerd Plewig, and William J. Cunliffe, having overtaken this responsibility before him. But the most experienced insisted: "This volume will be a classic…This will be a great classic, and I am proud to be a part of it…It's an enormous labor of love for you, but it will do you a great honor when it is finished." So the younger part decided to start the long way, especially with the contribution of a third, politically experienced acneologist, who joined the group and declared: "I have an invitation for a new acne book, would you like us to write it together?" Alea iacta est.

Since then, a few more years have passed; the three editors were accompanied by approximately 100 additional authors from all around the world, hundreds of pages have been written, rewritten, and actualized, and the time for this first edition became mature. It is a great pity that the brain behind the book is not anymore among us to feel proud for the result of the common effort. Dr. Albert Montgomery Kligman died 93-year-old on February 9, 2010, in Philadelphia. He was prophetic regarding the long way to go; the rest two of us can only hope that he will also be prophetic in his prediction that "This volume will be a classic!"

We want to thank all our coauthors for their enormous work and group spirit. We are grateful to Spinger Verlag, especially Mrs. Ellen Blasig, Mrs. Ioanna Panos, and Mr. Sverre Klemp, for their continuous support. We also

Albert M. Kligman

thank Dr. Clio Dessinioti for her tireless contribution. And all three of us are indebted to our families for their patience and love.

Dessau/Berlin, Athens and Philadelphia, 2008–2013

Dessau/Berlin, Germany
Athens, Greece
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# Introduction

Diseases of facial skin have been mentioned repeatedly in medical history, starting with Greek physicians in antiquity. *Hippocrates* of Kos and *Aristotle* in Athens used the term "ίονθοι" (ionthoi, pl.) to describe lesions located on the face as a well-recognised disease appearing during the time when "the first beard grows", most likely corresponding to what we call acne today. Roman physicians and/or scholars such as *Plinius* used the term "vari" or "vari seu ionthi" referring to similar skin lesions located in the face, with peaks of oozing and pain. For management honey, soaps, mineral waters and baths, often containing sulphur, were applied in the ancient Roman Empire for cleaning and drying out the skin, as mentioned by *Celsus* (first century AD) in his "De Medicina", a major source of Greco-Roman medicine. Sulphur-containing ointments were still used for the same purpose in Europe during the last centuries, together with laxatives and various diets.

The word "Acne" is obviously derived from the Greek "Ακμή" (acme) and entered the medical literature to indicate a high point, the peak of development or maturation (of a general condition or disease), as has been used by *Galenos* from Pergamon (129–201 AD), though unrelated to skin. During the following centuries, however, this expression came into use also to express the same for an individual, i.e. the flourishing period of puberty. It seems that the term took its present significance after having been misspelled in "Ακνή" by the Byzantine physician and medical scholar *Aetius Amidanus* (502–575 AD) in writing one of his numerous books (Polybiblia) transferring and commenting the wisdom of *Hippocrates* and *Galenos*. Interestingly, acne is still called "acme" in contemporary Greek medical nomenclature, while the term maintains its original meaning in spoken Greek.

The history of rosacea is less known, although the condition may have been early mentioned by *Theocritos* in the third century BC, and the flushing condition of the face (nose) was later brought in relation to lying and shame. As a medical term "gutta rosacea" was documented by *J. Plenck* (1735–1807), who separated this entity from "vari" or "ionthi" in classifying cutaneous diseases, whereas *R. Willan* (1757–1812) with *Th. Bateman* (1778–1821) linked rosacea to acne; they listed "acne rosacea" in their nomenclature system based on clinical morphology, although they recognised the differences.

It seems that *C.H. Fuchs*, in expressing his disagreement, coined the term "acne vulgaris" ("Die Krankhaften Veränderungen der Haut", Göttingen, 1840), indicating a disease of facial skin affecting young individuals and

leaving pitted scars, aiming to clearly separate the condition from "acne rosacea". The specific denominations of distinctive clinical phenotypes and variants of acne commonly used today, such as comedonic/papulopustular, conglobate, nodulocystic, acne tarda, androgenica, venenata, etc., were compiled by various authors over the last century.

Why such a comprehensive book on acne and rosacea?

In our modern societies skin diseases are most common and due to their visibility and identification with the suffering individual have reached great attention by the medical community and the public. Acne in particular, with all its variants, is a leading diagnosis in the dermatologist's office and has become a hot issue in recent years. In European populations over 70–80 % of all males will experience acne in some point of their lifetime. In the USA acne has been reported to affect an estimated number of over 25 (17–45) million Americans, while spending on topical anti-acne preparations and oral anti acne drugs amounted billions of dollars in recent years.

The presence of acne on the face is visible to all while appearing in early life during a critical phase of individual self-recognition. In addition, some mystery of acne derives from its unclear aetiopathology and its incidence in young boys and girls, obviously in relation with the synthesis of hormones and their precursors in menarche and adrenarche, an imagined relation to sexual activities, and its interaction with the psychological status of the patient during adolescence. Needless to say, there are a series of misconceptions referring to the significance of the disease for life quality, but indisputably, most of the young patients with acne clearly suffer, some of them having the feeling of being inferior and stigmatised. They all look for understanding and treatment.

Over the past decades thorough laboratory investigations on the pilosebaceous unit have been performed and a series of possible acnegenic mechanisms were elucidated in experimental and clinical models. As a result, both the causes and pathogenesis of acne have become increasingly expanding, complicated issues in part, and difficult to overlook. The numerous reasons for developing acne may overlap or even clearly differ from one individual to another. Especially the mechanisms of persisting comedogenesis, the generation of pro- and anti-inflammatory lipids, the consecutive receptor processing and the intriguing pathways leading to transformation of comedonal, non-inflammatory, into inflammatory skin lesions, including the governance of their particular clinical morphology and course, are not fully clarified, being still under ongoing investigation.

The major tissue component involved in the pathogenesis of acne is the sebaceous gland as a mastermind of hormone metabolism and, possibly, hormone synthesis in skin. Hyperseborrhea, hyperkeratinisation of the duct lumina with appearance of microcomedos and insufficient comedolysis, bacterial colonisation and inflammatory tissue response leading to papules, pustules, nodules and cysts are major causes for generating the disease; however, a series of side pathways and the sequence of events involved remain to be elucidated. Hormonal disorders (systemic and/or peripheral hyperandrogenism), inappropriate skin care and hygienic conditions (oily bases and other acnegenic cosmetics), bacteria (*P. acnes,* etc.), various

drugs (anticonvulsants, lithium, androgens, anabolic steroids with resting androgenic properties, corticosteroids), toxic agents (chlorinated polyphenols), halogens (iodine, chlorine, bromides, etc.), nutrition (fats, seafood, chocolate, nuts, milk products, westernised food with high carbohydrates and diverse relation of ω-unsaturated lipids) and stress (neuropeptides) may all have an influence in generating acne lesions, based on genetic predisposition that controls the frequency of inflammatory lesions, and, possibly, their severity. The question arises as far as genuine inflammatory mechanisms are contributory factors in acne, with PPAR and stimulated toll-like receptors being primarily involved in its pathogenesis.

Overall, acne may be regarded as a model of a complex cascade of events, controlled by hormones, leading to inflammation.

Therapy of acne is a challenge in a considerable number of cases, also because disfiguring scars may result and become permanent, if the disease progresses. Individualised treatment is recommended. Therefore, a wide range of anti-acne preparations are of growing significance for the prescription market, both topical remedies and systemic drugs including antikeratinising and antiseborrhoeic agents, antibacterials, antibiotics, retinoids, hormones and hormone-like products and various others. Retinoids in particular have revolutionised the treatment of acne, and after its first introduction into the market in 1982 isotretinoin has been a global frontrunner. It is still today the most successful drug in the treatment of severe acne, and its worldwide sales were a few years ago at the level of one billion dollars, growing by 5–10 % per year. However, although the anti-acne potency of isotretinoin is unsurpassed, its teratogenicity, among other side effects, is a serious risk that limits its oral use requiring continuing contraception. Recently, an assumed relation of isotretinoin to 5-serotonin metabolism suspected to cause depression and suicidal ideation is of additional concern.

Thus, the evolution of acne therapy is still ongoing, and, in addition to further improvement of conventional modalities, new potent anti-acne agents surface, also based on the concept that acne, may represent a genuine inflammatory disorder *per se*. Together with new antibiotics and conventional retinoids, rexinoids, 5α-reductase inhibitors, leukotriene antagonists and 5-lipoxygenase inhibitors are under current investigation. In addition, new therapeutic and managing options are being reported for the practicing dermatologist by using modern technical devices, such as light and UV therapies, photodynamic agents, various types of lasers, etc.

The three editors of this comprehensive book represent three generations of prominent dermatologists with profound and long-lasting experiences on acne and rosacea, covering all related clinical and investigational issues. They faced together the challenge to approach and cover the multifactorial issues in several small and specific chapters written by an international community of colleagues, all experts in their fields. Thus, different aspects and emerging views are presented in this book, summarising our accumulating knowledge. The editorship maintains a red line by having clustered and reviewed the manuscripts. This book has been designed as an indispensable work of reference for all physicians dealing with acne or rosacea and for scientists having specific questions on any relevant issue, including the established theories on

the clinical entities covered, their treatment and pathogenesis, while also referring to new concepts and alternative views.

Acne and rosacea is a most interesting field of expanding dermatological research on a series of intriguing scientific and clinical mechanisms leading to disfiguring skin lesions. Such a comprehensive textbook epitomises our updated knowledge and current understanding on acne and rosacea.

I sincerely hope that it will also stimulate the fantasy and catalyse the vigour of young dermatologists and researchers, in their attempt to present new evidence on this important section of dermatology, following their own visions.

At the end, the patients who suffer will harvest the real benefit.

# Part I

# The Pilosebaceous Unit

# The Sebaceous Gland Through the Centuries: A Difficult Path to Independence

1

Carlo Gelmetti

## Contents



**Core Messages**

- The existence of cutaneous orifices has been observed since ancient times.
- Marcello Malpighi (1628–1694) should be considered the true discoverer of the skin glands.

## 1.1 The Discovery of the Cutaneous Glands

From the Classical Age to date, a lot of progress has been made in Medicine, but skin diseases only reached their autonomy during the eighteenth century. Before this period, cutaneous disorders were only considered as "*materia peccans*," that means a sign of an internal disequilibrium of "humors," which need to be evacuated. Cutaneous pores were seen just as the way by which the body could purify itself.

As a matter of fact, the existence of cutaneous orifices has been observed since ancient times. In the early medical literature, they are usually called "pores." It was also known that the skin had some production of water (sweat) and fat (sebum), but the concept of specific glands was not clear until seventeenth century.

Indeed, the fine anatomy of the skin was not the interest of the early dermatologists as it can be observed in the first books devoted to skin diseases, such as those written by Gerolamo Mercuriale (1530–1606), who wrote the first

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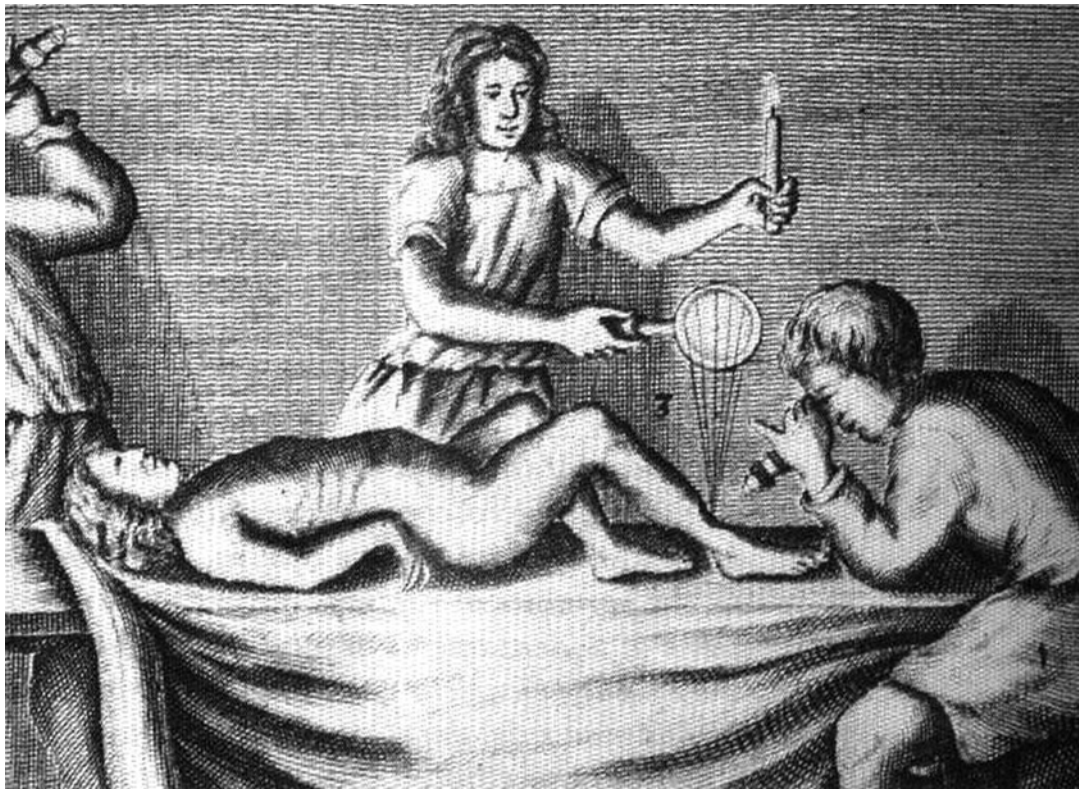

**Fig. 1.1** An old illustration showing one of the first uses of the microscope on the human skin (from: "Opuscula omnia actis omnium eruditorum Lipsiensibus inserta, Venetiis, 1740")

dermatological book ever [1] by Anne-Charles Lorry (1726–1783) who wrote the first French dermatological book [2] or by Joseph Jacob von Plenck (1735–1807), who was the first to classify skin diseases with a rational method. For instance, in his book of dermatology written in 1776, sebum comes on the surface of the skin directly from the hypodermis [3].[1]

To be honest, the discovery of the anatomy and physiology of the skin was the result of the efforts of many anatomists especially from Italian and Dutch school. A powerful input came from the invention of the microscope. The first useful microscope was developed in the Netherlands in the early 1600s or even a few years before. Three different eyeglass makers have been given credit for the invention: Hans Lippershey (1570–1619), Hans Janssen, and his son, Zacharias (1585–1632). The coining of the name "microscope" has been credited to Johann Faber (1574–1629), who gave that name to Galileo Galilei's (1564–1642) instrument in 1625. At this time the magnification was only X3 to X9.

From this period on, the technical improvement of the microscope allowed a more refined anatomy (Fig. 1.1). Indeed, Marcello Malpighi

[1] Cutis Unctuosa

Est cutis splendor unctuosus ac si esset butyro illita.

Causa proxima est pororum glandularium, vel qui ad tunicam adiposam pergunt, laxa amplitudo, quae oleum subcutaneum transudare sinit.

1. Unctuositas vulgaris, curatur roborantibus internis, & externa applicatione aquae frigidae & liquoris adstringentis.

2. Unctuosistas elephantina, quae in elephantiasi observatur, est incurabilis ut elephantiasis

Translation from latin
Oily skin

The skin is shining as it as been treated with butter.

The proximal cause is due to follicular glands communicating with hypodermis, which let the subcutaneous oil appear on the surface because their loose opening.

1. Common oily skin is treated with internal remedies and external applications of cold water and astringent lotion.

2. Elephantine oily skin, as it is observed in elephantiasis, cannot be cured as the underlying disease"


**Fig. 1.2** A classical image of Malpighi in an old print. The text says: "Marcellus Malpighius Medicus Bononenesis Mortuus 29 Novemb. Anno Dom. 1694"


**Fig. 1.3** Giovanni Battista Morgagni represented when he was teaching in Padua. The text says: "Joannes Baptista Morgagnus natuis Forolivii die 25 Februarii anno 1682 in Patavino gymnasio e primaria sede Anatomen ad huc docebat anno 1769"

(1628–1694) (Fig. 1.2) [4] and then Giovanni Battista Morgagni (1682–1771) (Fig. 1.3) [5] in Italy have described the existence of glands inside the skin. Malpighi should be considered the true discoverer of the skin glands that have been described in his *Opera Postuma* (Fig. 1.4) including his famous *Epistola*. The opinion of Malpighi was accepted and adopted by the famous physician Hermann Boerhaave (1668–1738) (Fig. 1.5) who, at that time, was professor of Medicine and Botanics at the University of Leiden in the Netherlands.

In a letter written to the great anatomist Friederick Ruysch (1638–1731) (Fig. 1.6) who sent to him an anatomical specimen prepared from a child's cadaver, Boerhaave stated that:*"… after a long and careful observation, with the help of a powerful microscope, I am of the idea that those papules are indeed the follicles of the most simple skin glands."* In Boerhaave's opinion, the skin glands are small bags ("*utriculi*") and not clusters of small vessels as Ruysch thought after his experiments with the injections of vessels with colored wax. Boerhaave continues his letter stating that Malpighi's opinion was the correct one when he stated that these glands are everywhere even though they are very small.

In the following lines, he continues the description found in the *Opera postuma* of Malpighi, in which the anatomist describes both the simple and composed *("conglobate")* glands. *"But, to help you to imagine with a better clarity, let me present to you this figure that is described in Malpighi's "Opera Postuma". In this (Figure 1.1-ure)* ***a,a,a,a*** *indicate the follicles of the simplest glands;* ***b,b,b,b*** *the single emissary vessels, coming from each gland ("otricina"); these (vessels) take in the common excretory canal;* ***d,c*** *their humors that finally are expelled through the opening* ***c*** *of the canal"* (Fig. 1.7).

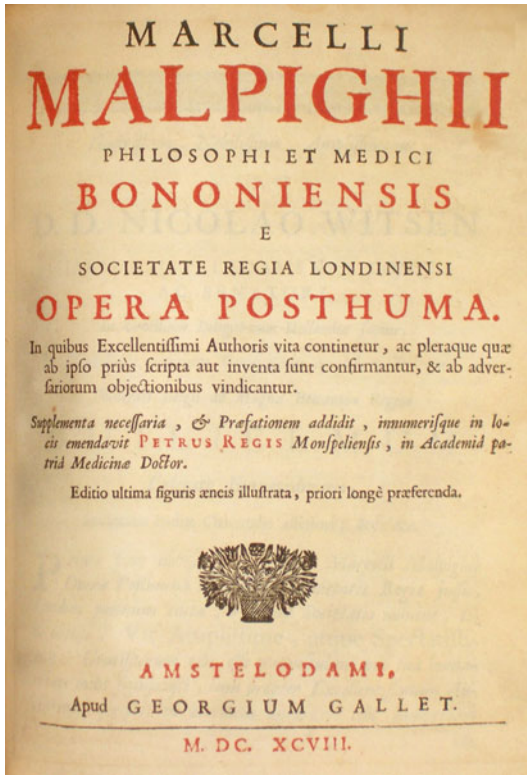
MARCELLI
MALPIGHII
PHILOSOPHI ET MEDICI
BONONIENSIS
E
SOCIETATE REGIA LONDINENSI
OPERA POSTHUMA.
In quibus Excellentiſſimi Authoris vita continetur, ac pleraque quæ ab ipſo priùs ſcripta aut inventa ſunt confirmantur, & ab adverſariorum objectionibus vindicantur.
Supplementa neceſſaria, & Præfationem addidit, innumeriſque in locis emendavit PETRUS REGIS Monſpelienſis, in Academiâ patriâ Medicinæ Doctor.
Editio ultima figuris æneis illuſtrata, priori longè præferenda.
AMSTELODAMI,
Apud GEORGIUM GALLET.
M. DC. XCVIII.

**Fig. 1.4** The first page of Malpighi's Opera Postuma published in Amsterdam in 1698

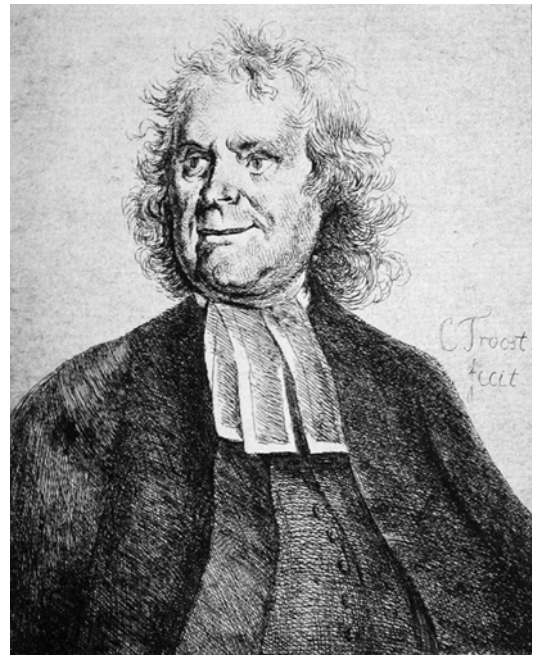

**Fig. 1.5** An image of Hermann Boerhaave, professor of Medicine and Botanics at the University of Leiden in the Netherlands and partisan of Malpighi's ideas

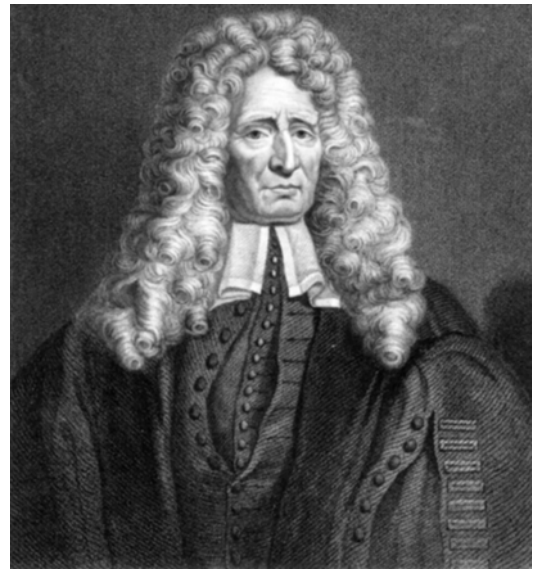

**Fig. 1.6** The great anatomist Friederick Ruysch was contempory with Boerhaave but he did not agree with Malpighi's observations

In opposition with this view, Ruysch answered to his friend and colleague Boerhaave, the 1st of June, 1722 stating that: *" I had to fight, alone, against two great men: Malpighi and you, who both have a deepest knowledge of the anatomy ("fabrica") of the human body and who have almost conspired against me. You, has indeed defended the opinion ("causa") of Malpighi as it was yours. However I am not sorry, because…reading your writing I have learned something; of this I thank you".*

While Govard Bidloo (1649–1713) [6] and Boerhaave [7], following the description of Malpighi, realized the first illustrations of a skin gland, Morgagni, finally, included the term sebaceous glands ("*glandulae sebaceae*") in the index of his famous book (Figs. 1.8 and 1.9).

But the opinion of those authors was not accepted by other experts; some, as Ruysch [8], were not able to demonstrate cutaneous glands and the pores were considered the natural orifices of blood and lymphatic vessels. In his famous book of anatomy written in the second half of the eighteenth century, Antoine Portal (1742–1832) describes the sebaceous glands in brief, but these

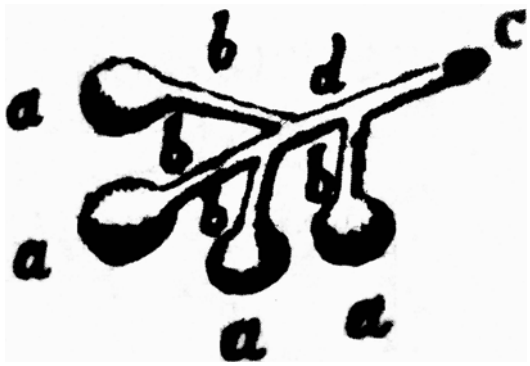


**Fig. 1.7** This drawing comes from Opera postuma of Malpighi, in which the anatomist describes both the simple and composed glands

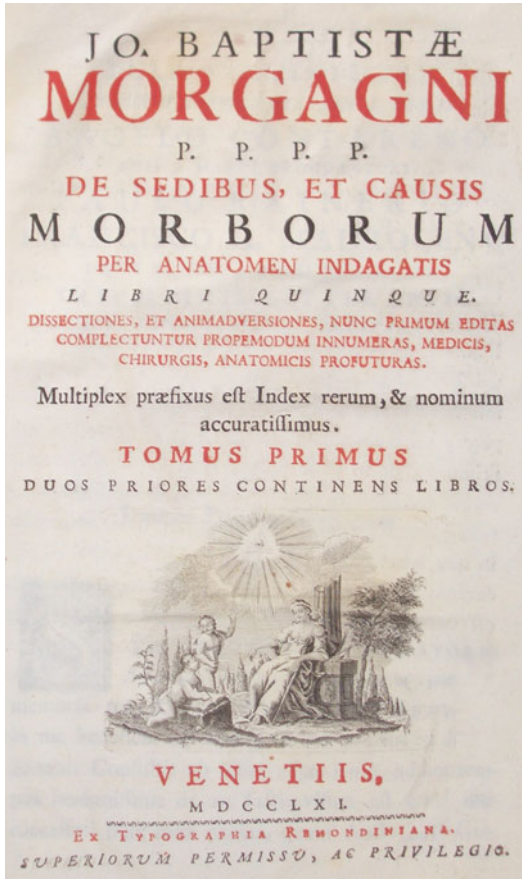
JO. BAPTISTÆ
MORGAGNI
P. P. P. P.
DE SEDIBUS, ET CAUSIS
MORBORUM
PER ANATOMEN INDAGATIS
LIBRI QUINQUE.
DISSECTIONES, ET ANIMADVERSIONES, NUNC PRIMUM EDITAS COMPLECTUNTUR PROPEMODUM INNUMERAS, MEDICIS, CHIRURGIS, ANATOMICIS PROFUTURAS.
Multiplex præfixus eſt Index rerum, & nominum accuratiſſimus.
TOMUS PRIMUS
DUOS PRIORES CONTINENS LIBROS.
VENETIIS,
MDCCLXI.
EX TYPOGRAPHIA REMONDINIANA.
SUPERIORUM PERMISSU, AC PRIVILEGIO.

**Fig. 1.8** The first page of the most famous book of Morgagni: "De sedibus et causi morborum per anatomen indagatis"

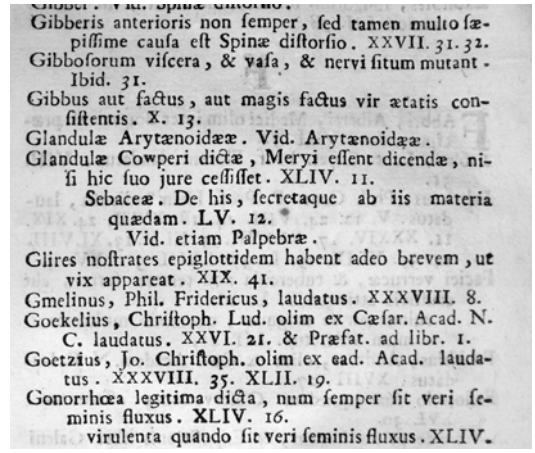
Gibberis anterioris non ſemper, ſed tamen multo ſæpiſſime cauſa eſt Spinæ diſtorſio. XXVII. 31. 32.
Gibboſorum viſcera, & vaſa, & nervi ſitum mutant. Ibid. 31.
Gibbus aut factus, aut magis factus vir ætatis conſiſtentis. X. 13.
Glandulæ Arytænoidææ. Vid. Arytænoidææ.
Glandulæ Cowperi dictæ, Meryi eſſent dicendæ, niſi hic ſuo jure ceſſiſſet. XLIV. 11.
Sebaceæ. De his, ſecretaque ab iis materia quædam. LV. 12.
Vid. etiam Palpebræ.
Glires noſtrates epiglottidem habent adeo brevem, ut vix appareat. XIX. 41.
Gmelinus, Phil. Fridericus, laudatus. XXXVIII. 8.
Goekelius, Chriſtoph. Lud. olim ex Cæſar. Acad. N. C. laudatus. XXVI. 21. & Præfat. ad libr. 1.
Goetzius, Jo. Chriſtoph. olim ex ead. Acad. laudatus. XXXVIII. 35. XLII. 19.
Gonorrhœa legitima dicta, num ſemper ſit veri feminis fluxus. XLIV. 16.
virulenta quando ſit veri ſeminis fluxus. XLIV.

**Fig. 1.9** In the index of the same book, immediately below "Glandulæ Cowperi" you can read "Glandulae sebaceæ"

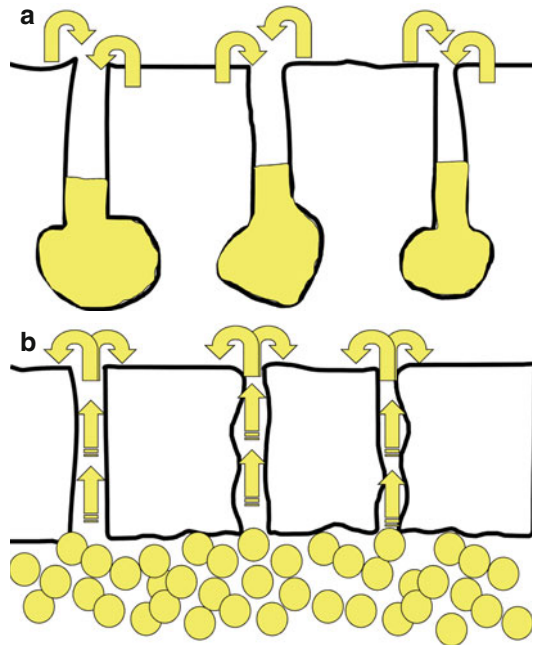


**Fig. 1.10** (**a**) Portal's View: sebum comes out from the skin and fills the follicles as reservoirs. (**b**) Plenck's View: sebum comes out directly from the hypodermis

structures are not interpreted as glands but just as "reservoirs" [9] (Fig. 1.10a), while the Plenck's opinion, as previously quoted, was different but always wrong (Fig. 1.10b). Indeed, after more than one century, wrong ideas were still alive! These discussions were exposed also in the first Belgian edition of Jean Louis Alibert's (1768–1837) textbook [10].

Only in the following decades the sebaceous glands are properly described. From the beginning

and, even more, the half of the nineteenth century, the fine skin anatomy starts to develop and the studies of the physiology of the skin can be interpreted in a more scientific way, abandoning the Hippocratic School. Therefore, the modern dermatology started his contemporary path: the skin glands, including the sebaceous ones, have been studied both from anatomists and from dermatologists more and more carefully. Their size and physiology related to the age of the patient and to the site of the body have been documented in the first part of the twentieth century by various investigators.

## 1.2 Distribution of the Sebaceous Glands

It is a common knowledge that the sebaceous glands of man are distributed in the skin throughout all areas of the body except the palm, soles, and the dorsum of the feet. It is also known that the sebaceous glands are associated almost invariably with hair follicles, with the exception of mucous membranes where they open directly to the surface. Wherever they are found, a great variation is observed in the number of the sebaceous glands per unit area of the skin surface.

Detailed studies on the volume and density of gland distribution have been carried out mostly by Japanese authors. The historic study of Yamada in 1932 [11] calculated the gland volume in different body regions. In a middle-aged adult man, the gland volumes, in descending order of size, were found on the forehead, scalp, back, forearm, upper arm, abdomen, thigh, and calf. In the same period, the Italians Benfenati and Brillanti (1939) [12] studied the distribution of human sebaceous glands. According to these authors, the areas of the body can be divided into two broad categories, i.e., head and other areas. The face, together with the scalp, had the greatest number of sebaceous glands (up to 876 sebaceous glands per square centimeter of skin surface!). In agreement with the earlier Japanese study, these authors found that in all other areas of the body there were <100 and sometimes <50 glands per square centimeter.

Many authors, however, reported a wide variation in the number of glands in any given area from subject to subject. In general, the size of the sebaceous glands tends to be correlated with their density; in other words, the largest glands are usually found in areas where the glands are most numerous. Finally, it should be remembered that there is a wide variation in sebum production from individual to individual and in different ages of the life [13].

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# Embryology of the Pilosebaceous Unit

2

Vladimir A. Botchkarev and Michael Y. Fessing

## Contents



**Core Messages**

- The pilosebaceous unit is formed as the result of a complex interplay of signals between the keratinocyte stem cells and their progenies and mesenchymal cells that form follicular papilla.
- The nature of these signals is just now being elucidated, with many molecular pathways important for the development of pilosebaceous unit also playing roles in its cyclic regeneration.
- Each stage of the development of pilosebaceous unit is regulated by tightly controlled balance of growth-stimulatory and growth-inhibitory signals.
- Key signalling pathways regulating hair follicle development (Wnt, Edar, BMP, Shh, Notch) are also involved in the control of sebaceous gland formation and differentiation of the progenitor cells into lipid-producing sebocytes.
- Additional efforts are required to bridge the gap between the current knowledge of molecular signalling pathways involved in the control of the development of pilosebaceous unit and clinical application of numerous growth regulators for treatment of different types of its pathological conditions.

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## 2.1 Introduction

In mammals, hairs fulfil a number of important functions including thermoregulation, collecting sensory information, protection against environmental stressors, social communication and mimicry [1]. Hairs are produced by the pilosebaceous unit that consists of the hair follicle and associated structures such as sebaceous gland, perifollicular nerve fibres and arrector pili muscle [1, 2]. In humans, hair follicles are distributed throughout the body with exception of the soles, palm and part of the external genitalia and produce two major hair types (terminal and vellus hairs) that show distinct morphology and distribution patterns [3].

Hair follicles are formed during embryonic development, and there is general assumption that adult skin cannot develop new follicles under normal circumstances [4]. During postnatal life, hair follicles show remarkable periodic changes in its activity and transit between phases of the intensive growth and hair shaft production (anagen), apoptosis-driven involution (catagen) and relative resting associated with hair shedding (telogen/exogen) [1, 5, 6]. This activity is regulated by signalling exchange between stem cells and their progenies residing in the epithelial portion of the hair follicle including bulge area and mesenchymal cells that form follicular papilla [7–9].

In this review, we summarize the data on the basic principles and molecular mechanisms that underlie the development of pilosebaceous unit in human embryo with special emphasis on the sebaceous gland, a unique structure that supplies lipids to the skin surface throughout the entire life and protects skin from environmental stressors and ageing [10].

## 2.2 Development and Anatomy of the Pilosebaceous Unit

In human embryo, hair follicle formation begins on the head at about 9–10 weeks of gestation and then moves downward to the remainder of the body. Developing hair follicles form groups of three, in which primary follicles occupy the central position relatively to the peripherally located secondary follicles [4]. The first hairs formed are lanugo hairs, which are non-pigmented, soft and fine. Lanugo hair is typically shed between the 32nd and 36th weeks of gestation although approximately one-third of newborns still retain their lanugo hair for up to several weeks after birth [2, 4, 11].

Hair follicle development results in a formation of the hair bulb, in which keratinocytes rapidly proliferate and differentiate into six distinct cell populations, forming the medulla, cortex and cuticle of the hair shaft, as well as the cuticle, Huxley and Henle layers of the inner root sheath (Fig. 2.1). The inner root sheath separates hair shaft from the outer root sheath, which forms the external concentric layer of epithelial cells in the hair follicle [12]. During hair follicle development, neural crest-derived melanocytes migrate into the hair follicle, differentiate and produce melanin, which is then transported to the hair shaft keratinocytes and determine hair colour [13, 14].

Although hair follicles and hairs all share the same basic anatomy, their growth, size, shape, pigmentation and other characteristics differ widely based on body location and variation among individuals. Many of these characteristics are established during development, but are then profoundly altered by hormonal influences later in life. Within the same follicle, phenotypic changes in size may occur several times throughout life. For example, lanugo hairs subsequently convert into vellus follicles followed by their sex-dependent enlargement and transformation into terminal follicles that generate thick long hairs. On the scalp of genetically predisposed to androgenetic alopecia individuals, terminal follicles miniaturize and transform into the vellus follicles generating very thin and hardly visible hairs [2].

During last decade, a substantial progress has been achieved in delineating molecular mechanisms that control hair follicle development and cyclic activity [15–17]. In particular, it was shown that regulation of hair follicle development in embryo and control of hair follicle growth during postnatal life are highly conserved and both require involvement of the similar molecular mechanisms. Since many of the molecules that control hair follicle development and cycling are also involved in regulating morphogenesis and

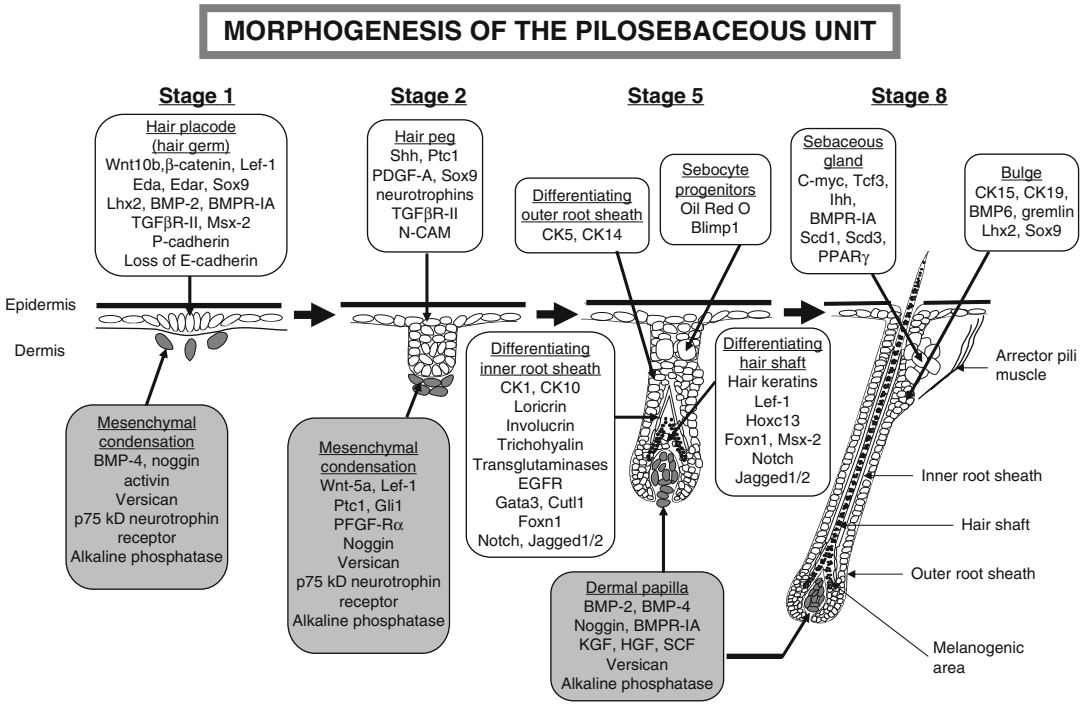


**Fig. 2.1** Molecular control of the development of pilosebaceous unit. The scheme shows the expression of different growth factors, their CI receptors, adhesion and cell matrix molecules, transcriptional regulators in hair follicle epithelium, mesenchyme and sebaceous gland during distinct stages of the development of pilosebaceous unit

postnatal biology of other ectodermal derivatives, such as tooth, feather and mammary gland, basic principles and molecular mechanisms that govern hair follicle development may also be applicable for other developmental systems [18].

## 2.3 Molecular Mechanisms Controlling Hair Follicle Development

Morphologically, a process of hair follicle development has been divided on eight consecutive stages (Fig. 2.1), each of them is characterized by unique expression patterns for growth factors and their receptors, growth factor antagonists, adhesion molecules and intracellular signal transduction components [5, 16, 19]. Below, we briefly summarize data on major mechanisms that drive hair follicle transition through its developmental stages and result in a formation of highly specialized cutaneous mini-organ producing hair.

### 2.3.1 Initiation Stage of the Hair Follicle Morphogenesis

In the human embryo, hair follicles develop from small number of cells or "epithelial placodes", which corresponds to stage 1 of hair follicle development and first appear around 10 weeks gestation (Fig. 2.1). The cells of the hair placode express P-cadherin and become oriented vertically loosing their desmosomes, hemidesmosomes and E-cadherin that decrease their adhesion to their neighbours [20–22]. The epithelial placode then expands to form the "primary hair germ" whose progeny eventually generate the entire epithelial portion of the hair follicle. Dermal cells beneath the hair placode form a cluster, which later develops into the follicular papilla [23, 24].

It is generally believed that hair follicle development is governed by the series of inductive events or "messages" that epidermal keratinocytes committed to hair follicle-specific differentiation and mesenchymal cells that form follicular papilla

send each other to achieve progression to the next developmental stage [23]. An initial signal arises in the mesenchyme (primitive dermis) and instructs the overlying epithelium to form an appendage, indicated by the appearance of regularly spaced placodes. The second signal arises from the epithelial placode and causes an aggregation of cells in the underlying mesenchyme that will eventually form the dermal papilla. Finally, a signal from this primitive dermal papilla initiates proliferation and differentiation of placode cells, ultimately leading to formation of a mature follicle.

Recently, the molecular signature of cells forming hair placode have been characterized, and several transcription factors including Lhx2 and Sox9 have been implicated in regulation of the placode formation [20, 22, 25]. While the roles for large number of genes that show changes in their expression in developing hair placodes remain to be determined, we review here the major signalling mechanisms whose balance play a critical role in the control of hair placode formation.

One of the earliest molecular pathways that positively regulate hair follicle initiation is the WNT/ß-catenin pathway. WNT ligands bind to receptors on the cell membrane and through a series of signals, inhibit the degradation of cytoplasmic ß-catenin followed by its translocation to the nucleus, forming a complex with the LEF/TCF family of transcription factors and resulting in expression of downstream genes [15]. Activation of this ß-catenin pathway appears necessary for establishing epithelial competence—a state in which the epithelial tissue has the potential to form a hair follicle. Normally, the ß-catenin pathway is inactive in the adult epidermis, but by artificially activating ß-catenin in epidermal basal cells of adult transgenic mice, hair follicles develop de novo [26]. Wnt/ß-catenin pathway also contributes to de novo hair follicle formation in large cutaneous wounds [27], while its constant activation in the hair follicle also results in pilomatricomas and trichofolliculomas, two types of benign cutaneous tumours [26, 28].

Ectodysplasin (*EDA*), a molecule related to tumour necrosis factor, and its receptor (*EDAR*) also are part of another major pathway that stimulate early follicle development in both mice and humans [29, 30]. *EDA* gene mutations cause X-linked anhidrotic ectodermal dysplasia, a syndrome associated with decreased numbers of hair follicles, and defects of the teeth and sweat glands [31]. The *EDAR* gene is mutated in autosomal recessive and dominant hypohidrotic ectodermal dysplasias, causing identical phenotypes to those resulting from *EDA* mutations. The mouse *Edar* gene is expressed ubiquitously in the epithelium prior to placode formation, and then becomes restricted to placodes, while the *Eda* gene is ubiquitously expressed even after placode formation [32]. Mice with mutations in these genes have the same phenotype as humans with similar mutations, and mice overexpressing Eda in the epidermis show formation of the "fused" follicles due to the loss of proper spacing between neighbouring hair placodes [32–34] .

In contrast to the Wnt and Edar signalling pathways, which promote hair follicle development, members of the bone morphogenetic protein (BMP) family inhibit follicle formation. BMP signalling inhibits placode formation, while neutralization of BMP activity by its antagonist Noggin promotes placode fate, at least in part via positive regulation of Lef-1 expression [35–37]. Mice lacking Noggin have fewer hair follicles than normal and retarded follicular development [37]. Noggin-mediated inhibition of the BMP signalling also plays an important role in hair cycle initiation: Noggin promotes hair follicle entering into anagen possibly via activation of the epithelial stem cells or their progenies residing in the follicular bulge/secondary hair germ [38–40].

### 2.3.2 Downgrowth of the Developing Hair Follicle into the Dermis

Stage 2 of hair follicle morphogenesis is characterized by downgrowth of the hair placode into the dermis and resulted in a formation of the column of epithelial cells covered at its proximal end by a "cap" of mesenchymal cells [19] (Fig. 2.1). At stage 3, downgrowth of the column of epithelial cells into the dermis becomes more advanced, and epithelial cells begin to cover mesenchymal cells, which form a ball-shaped cluster which will transform into the follicular papilla [19].

Few secreted proteins expressed in the follicular placode play a major role in promoting downgrowth of the developing hair bud and epithelial-mesenchymal signalling: Sonic hedgehog (SHH) and platelet-derived growth factor-A (PDGF-A). Skin from mice lacking Shh has extremely effete hair follicles with poorly developed dermal papillae [41, 42], while PDGF-A null hair follicles show smaller follicular papillae and abnormal connective tissue sheaths [43]. Patched1 (PTC1), the receptor for SHH, is expressed in the germ cells and the underlying dermal papilla, suggesting that SHH may have both autocrine and paracrine inductive properties necessary for hair germ and follicular papilla formation [41, 42]. Interestingly that Shh plays important roles in regulating responsiveness of developing follicular papilla to PDGF-A, since expression of PDGF-Rα is downregulated in cells of mesenchymal condensation of Shh null mice [43].

### 2.3.3 Cell Differentiation in the Hair Follicle and Formation of the Inner Root Sheath and Hair Shaft

Starting from stage 4 of hair follicle development, follicular papilla becomes incorporated into epithelial hair bulb, in which keratinocytes rapidly proliferate, move upward and differentiate into the inner root sheath and hair shaft cells (Fig. 2.1). First morphological signs of cell differentiation are seen in stage 4 hair follicles, where a Henle's layer of the inner root sheath becomes visible as a cone-shaped structure above the dermal papilla [19]. At stage 5, the first sebocytes become visible in the distal part of the hair follicle, while melanin granules and hair shaft are seen above the follicular papilla.

During stages 6–7 of hair follicle development, a tip of differentiating hair shaft reaches the levels of dermis-subcutis border or sebaceous gland, respectively, and hair canal becomes visible at the distal portion of the hair follicle [19]. Finally, at stage 8 of hair follicle development, the hair follicle elongates up to its maximal length, and proximal hair bulb is visible deeply at the subcutis; sebaceous gland and arrector pili muscle are seen in the dermis, while hair shaft emerges through the epidermis [19] (Fig. 2.1).

Knowledge that genes determine specific cell lineages within the follicle is important for further understanding the pathobiology of hair disorders. CDP (Cutl1) and Gata3 transcriptional regulators have been shown to be important in inner root sheath differentiation [44, 45]. Notch1, a membrane protein involved in determining cell fate through cell–cell interactions and intracellular signal transduction, and its ligands Serrate1 and Serrate2, are expressed in matrix cells destined to form the inner root sheath and hair shaft and control their formation [46–48].

As the hair shaft is produced, several signalling pathways are involved in the control of its differentiation. Wnt/β-catenin/Lef-1 signalling plays an important role in hair shaft formation: hair shaft keratin genes contain binding sites for LEF1 and ectopic expression of *Wnt3*; in the hair follicle outer root sheath causes hair shaft fragility [49, 50]. BMP signalling is also essential for proper differentiation of the inner root sheath and hair shaft, since conditional deletion of BMPR-IA in keratinocytes results in profound alterations of the inner root sheath and hair shaft formation [51–53]. Several other putative transcription factors control hair shaft differentiation, including HOXC13 [54] and the WHN gene [55], which is mutated in nude mice and rarely in humans with hair nail and immune defects [56].

## 2.4 Mechanisms Controlling the Development of Sebaceous Gland

Morphologically, first sebocytes become visible as round-shaped cells with Oil Red O-positive cytoplasm in the upper central portion of the developing stage 5 hair follicle [19]. Most recent data suggest that these cells arise from the subset of Sox9-positive placode cells that will form hair follicle stem cell population [25]. Subsequently, Oil Red O-positive sebaceous gland progenitors form the uppermost swelling on the side of the follicles that will further develop into the sebaceous gland [57, 58]. The deeper swelling or bulge serves as the future site of epithelial stem

cells that generate the new lower follicle during hair follicle cycling [59]. However, in the axillae, anogenital region, areolae, periumbilical region, eyelids and external ear canals, a third swelling develops superficially to the sebaceous gland bud and gives rise to the apocrine gland [57, 58].

Sebaceous gland progenitors in the developing stage 5 hair follicle express transcriptional regulator Blimp1 that also label small cluster of sebocytes at the base of the gland in fully developed hair follicle [60]. During more advanced stages of hair follicle development (stages 6–8), sebocytes loose Blimp1 expression, proliferate and begin to express c-myc and peroxisome proliferator-activated receptor γ (PPARγ) [60]. Differentiating sebocytes in fully developed hair follicle also express stearoyl-Coa-desaturases Scd1 and Scd3, Indian Hedgehog (Ihh) and BMPR-IA [38, 61–63] (Fig. 2.2).

Increased evidence of data suggests that major signalling pathways that control hair follicle morphogenesis also contribute to the development of sebaceous gland [17]. However, in contrast to the development of the hair-generating portion of the pilosebaceous unit, inhibition of the Wnt signalling pathway via transgenic expression of the dominant-negative form of Lef1 transcription factor in keratinocytes promotes sebaceous gland development [64, 65]. Also, constitutive activation of the hedgehog signalling via transgenic expression of a mutant isoform of the Shh receptor smoothened results in ectopic sebocyte appearance in the epidermis [66], while treatment of sebocytes with Ihh promotes their proliferation [63]. Interestingly, inhibition of BMP signalling by overexpression of the BMP antagonist Noggin results in ectopic appearance of sebocytes in the outer root sheath [67], while overexpression of the inhibitory component of the BMP signalling pathway Smad7 in keratinocytes results in sebaceous gland hyperplasia [68].

It is unclear how the downstream signalling components of the Wnt, hedgehog and BMP pathways regulate the transcription programme of the developing sebocytes. It has recently been shown that transcriptional repressor Blimp1 inhibits the differentiation program in the developing sebocytes via downregulation of c-Myc [60], the overexpression of which, in turn, results in sebaceous gland hyperplasia [69]. Activation of PPARγ that regulates transcription of genes involved in lipid metabolism promotes sebocyte differentiation and sebum production [70]. Conversely, mutation of the stearoyl-Coa-desaturase Cdc1 involved in fatty acid metabolism results in severe alterations of sebaceous gland development [61].

Recent advances in microarray technology allowed defining the molecular signature and determining age-dependent differences in gene expression in cultured sebocytes [11, 71]. However, the significance of many molecules detected by microarray analysis for the development and differentiation of sebocytes in vivo remains to be determined. Further applications of the laser-capture microdissection approach, which was successfully applied for molecular analyses of distinct hair follicle compartments in situ [72], will help in identification of the molecular signature of the sebocyte progenitors and for establishing signalling network that control their

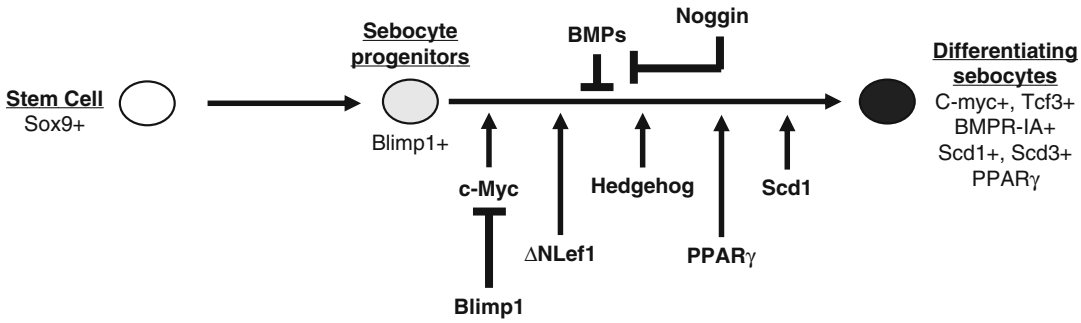


**Fig. 2.2** Involvement of distinct growth regulatory molecules in the control of sebocyte differentiation. Scheme illustrating the expression and roles of distinct growth regulatory molecules in the process of sebocyte differentiation during morphogenesis of the pilosebaceous unit

differentiation towards matured lipid-producing sebocytes.

### Conclusions

During the last decade, a tremendous progress has been achieved in delineating the molecular mechanisms that control the development of pilosebaceous unit. It appears that many growth stimulators and inhibitors involving in the regulation of the hair follicle and sebaceous gland development also control cyclic activity in postnatal hair follicles. However, additional research is required to bridge the gap between our current knowledge of molecular signalling pathways involved in the control of the development of pilosebaceous unit and clinical application of numerous growth regulators for treatment of different types of its pathological conditions. The progress in this area of research would hopefully lead to the development of new treatment strategies for the disorders of pilosebaceous apparatus seen in clinical practice and cosmetology.

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# Molecular Aspects of Sebaceous Differentiation

3

Christos C. Zouboulis, Georgios Nikolakis, and Clio Dessinioti

## Contents



**Core Messages**

- Sebaceous glands arise from the hair follicle.
- The canonical Wnt/β-catenin signaling pathway has been implicated in regulating sebaceous lineage differentiation.
- The level of β-catenin controls lineage selection in the skin, with high levels promoting hair follicle formation and low levels stimulating the differentiation of interfolicular keratinocytes and sebocytes.
- Analysis of transgenic mice with simultaneous activation of c-myc and β-catenin revealed mutual antagonism: c-myc blocked β-catenin formation of ectopic hair follicles and β-catenin reduced c-myc-stimulated sebocyte differentiation.
- Indian hedgehog is expressed in mature sebocytes and could play an important role in regulating proliferation and differentiation of the sebaceous gland in the skin.
- An interplay of the canonical Wnt/β-catenin pathway and the Indian hedgehog signaling has been suggested to control sebaceous gland proliferation and differentiation.
- Several genes/proteins may regulate or are markers of sebaceous differentiation.

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## 3.1 Introduction: Morphogenesis of the Sebaceous Gland

Epidermal progenitor cells give rise to multiple skin lineages: hair follicle, sebaceous gland, and the overlying interfollicular epidermis [1, 2]. The multipotent stem cells reside in the bulge region of the hair follicle. These cells transform into the epidermis (epidermal keratinocytes) as well as its associated structures, sebaceous gland (sebocytes), and cells of the hair follicle (follicular keratinocytes). Sebocytes are the major cells within sebaceous glands (SG) [3]. The human SG is a multiacinar, holocrine-secreting tissue present in all areas of the skin except for the palms and soles. Its development is closely related to the differentiation of the hair follicle and the epidermis. SG develops in the 13–16th weeks of gestation in humans, arising in a cephalocaudal sequence from the hair follicle. In the skin, most sebaceous glands are associated with the upper portion of a hair follicle, forming the pilosebaceous unit. They are located as an outgrowth of the hair follicle outer root sheath, at the level of the middle dermis [4]. Development of the pilosebaceous unit involves an ordered set of developmental processes [5]. During late embryogenesis, developing hair follicles (hair peg stage) display several bulges of which one will give rise to the sebaceous gland and is located just above the hair follicle stem cell bulge and below the infundibulum of the developing follicle [5].

Lipid droplets are seen at the center of the gland at 17 weeks. The future common excretory duct, around which the acini of the SG attach, begins as a solid cord. The cells composing the cord are filled with sebum, and eventually they lose their integrity, rupture, and form a channel that establishes the first pilosebaceous canal [4]. New acini result from buds on the peripheral sebaceous duct wall. The cell organization of the neonatal sebaceous acini consists of undifferentiated, differentiating, and mature sebocytes [6]. In particular, the peripheral cell layer of the SG is undifferentiated, expresses keratin 14, and is mitotically active [7]. SG produce and secrete an oily, waxy material (sebum) via the differentiation and disintegration of fully mature sebocytes, a unique process termed holocrine secretion [3].

Despite continuous differentiation of its cells, the SG can be regenerated by the reservoir of stem cells in the hair follicle bulge. However, retroviral lineage marking has provided strong evidence that the SG can arise and be maintained independently of the hair follicle bulge [8–11]. The different observations can be reconciled if there is a stem cell compartment that normally maintains the SG, but can be replenished, following injury or deletion of the transcription factor PR domain-containing protein 1 (PRDM1) [formerly known as B-lymphocyte-induced maturation protein 1 (BLIMP1)] by stem cells from the bulge [12, 13]. Free sebaceous glands (not associated with hair follicles) secrete their product directly onto the surface. Examples include the Meibomian glands (found in the eyelids), Montgomery's glands (nipples), Tyson's glands (genitals), Fordyce's spots (oral epithelium), and the ceruminous glands (ears) [3, 4].

Molecular networks and signaling pathways balancing epidermal growth and differentiation have been identified [14]. Key molecules include Wnt/β-catenin and the hedgehog pathway [15]. In this chapter, an outline of major molecular aspects involved in sebaceous cell differentiation will be presented.

### 3.1.1 SOX9, PRDM1 (BLIMP-1), c-myc, LRIG1

Several important molecular aspects of SG development have been identified, mostly with the aid of genetically modified mouse lines. The earliest known signal necessary for SG development is *SOX9*, which is in fact essential for the specification of early hair follicle stem cells and therefore for the morphogenesis of both structures [16]. Recent studies indicate that later in embryonic development, a subpopulation of these stem cells expressing PRDM1 (BLIMP1) is established near the entrance of the SG [12]. The existence of a separate stem cell population responsible for the supply of sebocytes has been previously suggested by label-retaining lineage analysis in mouse skin

[17]. PRDM1 (BLIMP-1)-positive cells would represent a resident population of unipotent progenitor cells and the ultimate source for the sebocyte lineage in adult skin [12]. The role of PRDM1 (BLIMP-1)-positive cells as sebocyte progenitor cells has been disputed by Lo Celso et al [7]. with the suggestion that PRDM1 (BLIMP-1) acts as a marker of terminal sebaceous differentiation rather than of progenitor cells [18]. Moreover, Magnúsdóttir et al [19]. suggested that PRDM1 (BLIMP-1) are also involved in terminal keratinocyte differentiation.

Loss of *PRDM1* (*BLIMP-1*) results in increased gene expression of c-*myc* [12], an essential player in SG homeostasis. Overexpression of *c-myc* in transgenic mice results in enlarged and more numerous SG at the expense of the hair follicle lineage [20, 21]. Skin-specific deletion of *c-myc* negatively affects SG development [22].

Activation of *c-myc* stimulates epidermal proliferation without depleting label retaining cells and induces differentiation of sebocytes within the interfollicular epidermis [23]. The effect of myc is somewhat surprising because c-myc is reported to act downstream of β-catenin and to be a direct target gene of canonical Wnt signaling [24, 25]. In skin, c-myc and β-catenin exert opposing effects on sebocyte differentiation (Fig. 3.1). Analysis of transgenic mice with simultaneous activation of c-myc and β-catenin revealed mutual antagonism: c-myc blocked β-catenin formation of ectopic hair follicles and β-catenin reduced c-myc-stimulated sebocyte differentiation [7]. Anatagonizing Wnt/β-catenin signaling constitutes an important prerequisite for normal sebaceous differentiation in postnatal skin tissue.

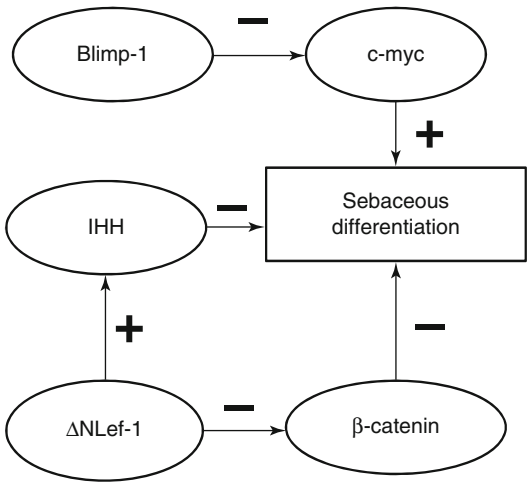


**Fig. 3.1** Simplified scheme of signaling effects on sebocyte differentiation

Stem cells expressing leucine-rich repeats and immunoglobulin-like domain protein 1 (LRIG1), which has been suggested to be multipotent stem cells giving rise to epidermal lineages, can act—under homeostatic conditions—as sebocyte progenitor cells [26–30].

## 3.2 Canonical Wnt/β-Catenin Signaling

Wnt (Wingless) proteins form a family of highly conserved secreted signaling molecules that regulate cell-to-cell interactions during embryogenesis. Insights into the mechanisms of Wnt were based on findings in Drosophila and Caenorhabditis elegans. Mutations in *Wnt* genes or Wnt pathway components lead to specific developmental defects, as well as various human diseases, including cancer. Wnt signals may not only promote cell proliferation and tissue expansion but also control fate determination or terminal differentiation of postmitotic cells. The Wnt pathway has distinct transcriptional outputs, which are determined by the development identity of the responding cell rather than by the nature of the signal. In other words, the majority of Wnt target genes appear to be cell type specific [24]. The recent finding that in transgenic mouse epidermis the same *β-catenin* mutation exerts different effects depending on the cells in which it is expressed underlines the importance of cellular context and microenvironment in the control of tissue renewal and differentiation [31, 32].

Wnt signaling is required for the establishment of the hair follicle. Within the established hair follicle, the Wnt cascade remains crucial throughout life. Wnt signals play a key role in the activation of bulge stem cells to progress toward hair formation, and this signal is mediated by β-catenin (the vertebrate homolog of *armadillo*)

and lymphoid enhancer factor-1 (Lef1) [24]. Indeed, β-catenin and Lef-1 seem to be of major importance for sebocyte development [1, 33]. The level of β-catenin regulates lineage selection by stem cell progeny in mammals. High levels of β-catenin stimulate the formation of hair follicles and low levels that of epidermis and sebaceous glands. When β-catenin levels are elevated by expressing a stabilized, N-terminally truncated form of the protein, there is de novo formation of hair follicles in postnatal interfollicular epidermis. Conversely, when β-catenin is absent, or its activity blocked with dominant negative forms of the downstream transcription factor Lef1, hair follicles are converted into cysts of interfollicular epidermis with associated sebocytes (Fig. 3.1). So, it appears that the level of β-catenin controls lineage selection in the skin, with high levels promoting hair follicle formation and low levels stimulating the differentiation of interfollicular epidermal keratinocytes and sebocytes [1].

Intracellular signaling molecules like transcription factor 3 (Tcf3) and Lef-1, a DNA binding molecule, control differentiation lineage [1]. Overexpression of Lef-1 blocks β-catenin signaling, which may lead to spontaneous sebaceous tumors [34]. Wnt proteins bind to receptors of the Frizzled and LRP families on the cell surface, leading to transduction of the signal to β-catenin, which enters the nucleus and forms a complex with TCF to activate Wnt target gene transcription [24].

Wnt signaling blocks differentiation toward the sebocyte phenotype, since inhibition of Wnt target genes promotes sebocyte development [35, 36]. Inhibition of Wnt target genes during skin development by expression of a dominant negative mutant transcription factor Lef1 (ΔNLef1) under the control of a keratin 14 promoter promotes sebocyte development, while inhibiting differentiation of hair lineage [35, 35]. A high proportion of human sebaceous adenomas and sebaceomas have double nucleotide mutations within the β-catenin binding domain of the lef1 gene. These mutations within the NH2 terminus of Lef1 prevent β-catenin binding and inhibit expression of β-catenin target genes [33]. Accordingly, transgenic mice expressing N-terminally deleted ΔNLef1 in the skin develop spontaneous sebaceous tumors [36]. LEF1 mutations had a positive effect on expression of sebocyte differentiation markers. PPAR-γ, C/EBP-α, keratin 7, Indian hedgehog (IHH), and GLI1 were upregulated in SZ95 cells transduced with ΔNLef1 [33].

The consequences of antagonizing canonical Wnt/β-catenin signaling for sebaceous gland differentiation has been further explored using a different transgenic mouse model exhibiting manipulation of Smad signaling. Induction of β-catenin degradation in the skin of developing mice by forced expression of SMad7, a Smad antagonist, perturbed hair follicle morphogenesis and differentiation but accelerated sebaceous gland morphogenesis [37]. Analyses of these mice pointed to a direct interaction between Smad7 and the Wnt/β-catenin pathway involving the recruitment of the E3 ligase Smurf2, thereby targeting cytoplasmic β-catenin for degradation. This suppression in Wnt/β-catenin signaling activity resulted in an increase in sebocyte differentiation [37]. Interestingly, aged skin often features enlarged sebaceous glands and exhibits upregulation of Smad7 expression associated with reduced β-catenin protein levels [37, 38].

Also, apart from signaling properties, β-catenin has adhesive properties. β-catenin plays a role in simple epithelia, that is, as a component of adherens junctions. It is an essential binding partner for the cytoplasmic tail of various cadherins such as E-cadherin [24].

## 3.3 Hedgehog Signaling Pathway

Another critical determinant of sebocyte fate is the hedgehog pathway. Inhibition of hedgehog signaling blocks sebocyte formation, while activation of this pathway promotes sebocyte development [1, 39]. It includes the secreted protein Sonic hedgehog (SHH), its receptors Patched (PTHC/Ptch) and Smoothened, and downstream transcription factors of the GLI family [1].

Whereas β-catenin levels regulate lineage choice within the epidermis, Hedgehog promotes the proliferation of committed progenitors [1]. SHH is a signaling pathway, which is important in embryos and adults of the regulation of progenitor cells of hair lineage differentiation and proliferation. SHH, which is a controlled member of the Wnt signaling pathway, is required for terminal differentiation of hair lineage [40].

Inhibition of hedgehog signaling in the skin by overexpressing the dominant negative transcription factor GLI2 (K5-GliΔC4) leads to suppression of sebocyte development. In contrast, ectopic hedgehog signaling by overexpression of a gain of function mutant receptor smoothened induced an increase in number and size of the sebaceous glands [41].

Transgenic mice overexpressing SHH under the control of the keratin 14 promoter do not show an enlargement of sebaceous glands [42, 43]. Instead, it has been shown that a different hedgehog ligand, IHH, is expressed in mature sebocytes and could play an important role in regulating proliferation and differentiation of the sebaceous gland in skin [1]. Hedgehog signaling could be a positive regulator of proliferation of progenitor cells. This hypothesis is supported by experiments demonstrating that treatment of human sebocyte cells with cyclopamine, an antagonist of hedgehog signaling, reduces proliferation and stimulates sebocyte differentiation [1]. Whereas SHH promotes proliferation of progenitors of the hair lineages, IHH produced by mature sebocytes promotes proliferation of sebaceous progenitors in a paracrine manner [1]. SHH and IHH appear to signal via common receptors and so specificity would be at the level of the cell type expressing each ligand [44].

IHH is involved in growth and differentiation of sebocytes in normal skin and in the formation of sebaceous tumors of human and mice. IHH is upregulated in the differentiated sebocytes of normal human and mouse epidermis and in sebaceous tumors. It has been proposed that ΔNLef1 and IHH cooperate to control proliferation and differentiation of sebocyte progenitors (Fig. 3.1) [1].

Levels of both PTCH1 and hedgehog were higher in differentiated SZ95 cells than in undifferentiated cells. These data indicate that IHH and its receptor, PTCH1, are upregulated during sebocyte differentiation *in vitro*. The nuclear accumulation of GLI1 in undifferentiated sebocytes in vivo is an indication of active hedgehog signaling [1]. Suprabasal and differentiated cells had cytoplasmic but not nuclear GLI1 and GLI2. Treatment of SZ95 sebocytes with cyclopamine decreased proliferation and stimulated differentiation. Neither ΔNLef1 nor ΔN-β-catenin had any effect on sebocyte differentiation. ΔNLef1 stimulated proliferation of undifferentiated sebocytes compared with control cells. This finding is in contrast to the effects of the constructs on the growth of normal human interfollicular keratinocytes. Expression of ΔNLef1 increases IHH expression in differentiated sebocytes and stimulates proliferation of undifferentiated sebocytes [1].

## 3.4 Interaction Between IHH and β-Catenin Signaling

Interestingly, the canonical Wnt/β-catenin pathway may also be linked to IHH signaling in sebocytes; as overexpression of mutant ΔNLef1 leads to upregulation of IHH in human sebocyte cells in culture (Fig. 3.1) [1, 45]. This suggests that a tight balance of both signaling cascades is crucial for proper sebaceous gland proliferation and differentiation.

It has been suggested that sebocyte fate is governed by the relative level of stimulatory (hedgehog) and inhibitory (Wnt) signals acting on multipotent progenitors. Lef-1 and IHH seem to cooperate to control proliferation and differentiation of sebocyte progenitors [35, 36].

Other molecules are implicated in sebocyte development, including peroxisome proliferator-activated receptors (PPAR) and noggin [41]. Forced expression of the bone morphogenetic protein (BMP) inhibitor noggin in transgenic mice promoted ectopic sebocyte differentiation, indicating that the BMP pathway normally suppresses sebaceous differentiation [46]. Finally,

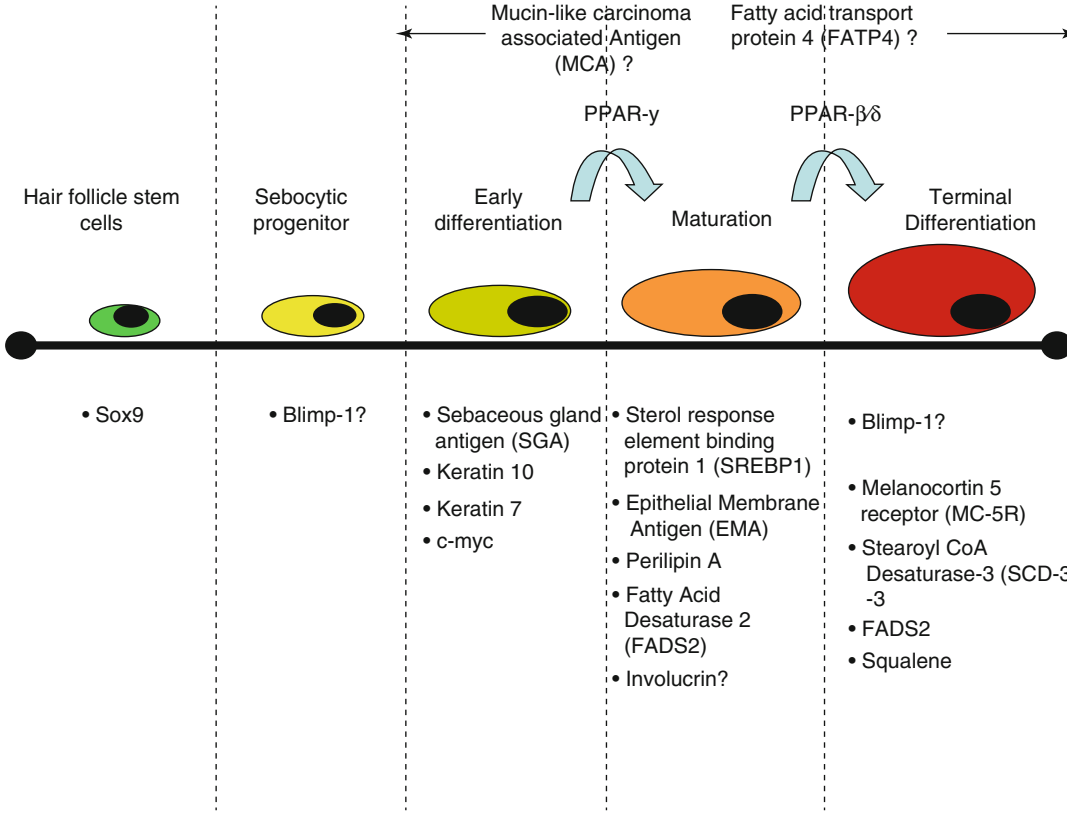


**Fig. 3.2** Outline of genes involved in sebaceous cell differentiation and maturation

PPARγ governs a battery of genes involved in lipid synthesis and therefore plays a central role in sebocyte differentiation and maturation.

Liganded androgen receptor represses β-catenin/T cell factor-mediated transcription [47–49], suggesting a possible synergy between ΔNLef1 and androgens in promoting sebocyte differentiation in addition to the potential synergy between androgens and IHH in stimulating proliferation of sebocyte progenitors [1].

## 3.5 Further Genes Been Involved in Sebaceous Cell Maturation

There are several genes reported to be involved or simply be markers of sebaceous differentiation and maturation (outlined in Fig. 3.2) [3, 12, 16, 18, 50–58].

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# Anatomy of the Sebaceous Gland

4

Fragkiski Tsatsou and Christos C. Zouboulis

## Contents



**Core Message**

- Sebaceous glands are found over the entire surface of the skin except for the palms and soles of the feet.
- They consist of a series of lobules (acini) each with a duct running towards the main sebaceous duct.
- They are holocrine glands; their secretory product, sebum, is produced from complete degeneration of the acini and is released to the skin surface.
- There are two types of sebaceous glands, those associated with a hair follicle forming a pilosebaceous unit or apparatus, and the free sebaceous glands, independent of hair follicles.
- The pilosebaceous unit or apparatus is formed by a sebaceous gland, the arrector pili muscle and the hair follicle.
- Stem cells are thought to exist at the base of the sebaceous gland, except for the follicle bulge and the basal layer of the epidermis.
- The number of sebaceous glands remains approximately the same throughout life, whereas their size and activity varies with age.

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## 4.1 Introduction

Sebaceous glands are skin appendages found over the entire surface of the skin except for the palms and soles of the feet. They are particularly abundant on the face, the scalp, in the midline of the back, the perineum and are concentrated around the orifices of the body. They can number up to 400–900 glands/cm$^2$ on the face [1]; they are most populous and most productive on the face and scalp and largest on the back and forehead [2].

All sebaceous glands are similar in structure and secrete their terminal differentiation product, called sebum, by a holocrine process. However, the nature of this secretion and the regulation of the secretory process seem to differ among the various types of sebaceous glands [1].

### 4.1.1 Types of Sebaceous Glands

Most sebaceous glands are associated with hair follicles in hair-covered areas and are called pilosebaceous glands. They form together with a hair follicle the pilosebaceous unit or apparatus. Sebaceous glands independent of hair follicles also exist as free sebaceous glands at mucosal margins and areas of modified skin [3].

#### 4.1.1.1 Pilosebaceous Gland

The pilosebaceous gland is a small saccular structure lying in the dermis, which occupies the angle between the arrector pili muscle and the hair follicle and forms together with them the pilosebaceous unit or apparatus (Fig. 4.1). Most sebaceous glands are located in association with the upper portion of a hair follicle, as lateral protrusions from the outer root sheath [3]. There is no relationship between the size of the sebaceous gland and the size of the associated hair. For example, in the centre of the face and on the forehead, very large sebaceous glands are associated with small vellus hairs in the pilosebaceous units. These have prominent follicular orifices and are called sebaceous follicles. The sebaceous follicles are found on the face (excluding the beard) and on the upper part of the chest, shoulders and back [2]. The sebaceous glands associated with follicles on the face, scalp and back are large (sebaceous follicles), but on the leg are minuscule [2].

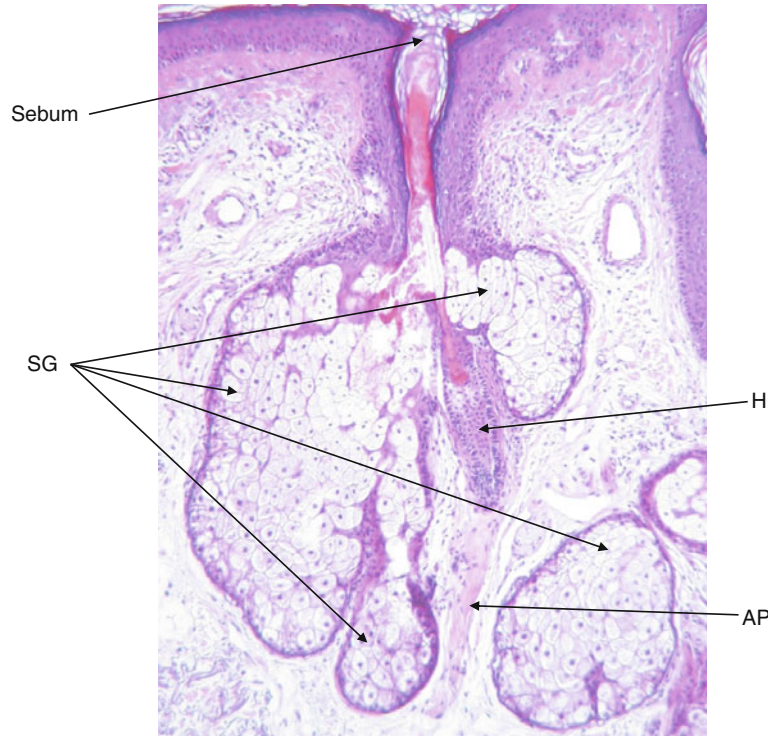


**Fig. 4.1** Cross-section of a pilosebaceous unit: (**a**) hair follicle (HF) surrounded by a (**b**) multilobular sebaceous gland (SG); (**c**) arrector pili muscle (AP); (**d**) sebum and keratin (×20)

#### 4.1.1.2 Free Sebaceous Gland

Although the majority of sebaceous glands are part of a pilosebaceous unit, some can be found as free sebaceous glands independent of hair follicles. These glands are particularly prevalent in transitional zones between the skin and mucous membranes, e.g. the anogenital region, periareolar skin, vermillion border of the lips and eyelids. They are also to be found in the oral mucosa and atypically in other regions of the digestive tract, the respiratory tract, the uterus and the vagina [1].

They are found over the entire surface of the nipple and in Montgomery's areolar tubercles, where several sebaceous lobules are found in association with a lactiferous duct [4]. Free sebaceous glands found on the vermilion border of the lips and on the buccal mucosa are called Fordyce spot or Fordyce's condition. Occasionally, glands can be found on the gums and tongue. Free sebaceous glands are called Meibomian glands and glands of the Zeiss, when found on the eyelids, are evenly spaced in rows at the border of the eyelids and can be seen with the naked eye upon evertion of the eyelids. They are also to be found on the inner aspect of the prepuce, called Tyson's glands, as well as on the labia minora and produce copious amount of sebaceous matter called smegma. They occur very rarely on the glans penis [5].

## 4.2 Structure

All sebaceous glands are basically similar in structure. They consist of a single lobule, the acinus, or series of lobules, the acini, each with a duct running towards the main sebaceous duct [6].

In the case of the pilosebaceous gland, the lobules open into the pilary canal. The short midsection of the hair follicle, called the isthmus, is bounded superiorly by the sebaceous duct and inferiorly by the insertion of the hair-erector muscle. The sebaceous follicle is characterised by a long infundibulum into which feed several sebaceous ducts connected to large lobules of a sebaceous gland. In contrast, the follicles of vellus hairs have relatively short infundibula, fewer associated sebaceous ducts, and smaller lobules of sebaceous glands [2]. The free sebaceous glands have their own duct opening directly to the surface of the skin [1].

The several lobules that comprise a sebaceous gland are enveloped by a thin, highly vascular, fibrous tissue capsule (periadnexal dermis). This connective tissue, called stroma, separates the various acini, is rich in fibroblasts and capillaries, and provides physical support [7].

Apart from meibomian glands, which are well supplied with cholinesterase-rich nerves, sebaceous glands are normally not innervated [1]. Therefore, sebaceous gland secretion is not under direct neural control but depends upon circulating hormones, despite of the presence of minuscule nerves in the vicinity of the larger glands [2].

## 4.3 Histology/Cell Differentiation

The sebaceous gland consists of secretory lobules composed of sebaceous gland cells and a rather short tubular duct composed of sebaceous duct cells, a stratified squamous epithelium. This epithelium is continuous with the wall of the pilary canal in pilosebaceous glands and the surface epidermis [1]. The sebocytes may be classified into:

(1) undifferentiated cells arranged in a single layer facing the basal lamina, comparable to the epidermal basal layer; they represent the germinative cells of the gland, flattened or cuboidal in shape, showing round and densely basophilic nuclei [8]. These bear characteristics of stem cells, since they give rise to a continual flux of proliferating and differentiating cells [9]. Growing towards the centre of the gland lobules, the basal cells gradually differentiate into (2) an early differentiated cell type, (3) an advanced differentiated cell type, (4) a fully differentiated cell type and (5) the mature sebocyte [10].

Mitoses are rare in differentiating sebaceous gland cells and, characteristically, accumulation of lipids in their cytoplasm increases with advanced cell differentiation. As the cells differentiate, there is an increase in smooth endoplasmic reticulum, where lipids are produced, and in Golgi apparatus for packaging of the lipids. The cells become thus loaded with lipid droplets, and their cytoplasmic organelles seem compressed

into a fine vacuolated pattern of lipid material, acquiring a characteristic 'bubbly' cytoplasm. The increase in lipid accumulation can be detected by Oil Red O staining [7]. In routinely processed sections in which lipids have been extracted, the cytoplasm of these cells appears as a delicate network. Lipid stains reveal lipid droplets in the excretory duct, whereas routine stains reveal amorphous material [4].

The proliferation of undifferentiated peripheral cells gradually displaces the more differentiated vacuolated cells towards the centre of the acinus. Finally, the boundaries of these bloated cells become indistinct, the cells disintegrate and the mass of lipid and cellular debris (sebum) is discharged into the sebaceous duct [2].

In fully differentiated and in mature sebocytes, the nuclei become distorted and disintegrated and the cells rupture, thus forming sebum as a holocrine secretory product [11]. Lysosomal enzymes bring about the physiologic autolysis that occurs in the holocrine secretion. As the sebaceous cells become more lipidised, the number of lysosomes increases. Prior to the sudden disintegration of the sebaceous cells, an abrupt conversion of –SH to –S–S linkages occurs in sebaceous glands [4].

Sebocytes preserve characteristics of stem-like cells despite their programming for terminal differentiation, since they present a remarkable potential of bipotential differentiation [12]. It is believed that the epidermal sebaceous gland is maintained by unipotent stem cells that are replenished by multipotent stem cells in the hair follicle bulge [13]. However, it is an emerging view that there might be at least three distinct niches for skin stem cells: the follicle bulge, the base of the sebaceous gland and the basal layer of the epidermis [9, 14].

## 4.4 Mechanism of Sebaceous Gland Secretion

The sebaceous lobules are located in the angular area between the hair follicle and the arrector pili muscle and in the counter-angular area. The mechanism of the sebaceous gland secretion can be divided into an internal mechanism, derived from volume expansion of the sebaceous lobules caused by cellular differentiation, and an external mechanism due to hair erection accompanying arrector pili muscle contraction [15]. The gland's secretion, sebum, drains into the sebaceous duct and is then released into the hair follicle around the hair shaft.

### 4.4.1 Holocrine Secretion

All sebaceous glands secrete their specific end product, sebum [6], via holocrine rupture of individual sebocytes. Increased cell volume, accumulation of lipid droplets in the cytoplasm and nuclear degeneration are phenomena indicating terminal differentiation of human sebocytes followed by holocrine secretion and cell death [16]. The molecular pathways of natural and induced sebocyte elimination remain still unknown [17].

Human sebocytes have also been shown to be naturally eliminated by apoptosis on their way to terminal differentiation before their death and holocrine secretion [17]. Apoptotic events occur in parallel, as signs of nuclear degeneration followed by cell bursting and death [11].

## 4.5 Sebaceous Gland Physiology

Three phases may be distinguished in sebaceous physiology of the hair-associated gland: secretion-production, stocking in the follicular reservoir and excretion. Once secreted, the sebum is colonised by various xenobiotes, whose development is controlled by several defensive humoural mechanisms and by the contact with ambient oxygen. Oxygen and micro-organisms transform "native" sebum, lysis of triglycerides to fatty acids being the most pronounced activity [18].

High rates of sebum production per sebocyte result in low levels of linoleate in the sebaceous esters, subjecting the follicular epithelium to essential fatty acid deficiency and the characteristic hyperkeratosis that results in comedo formation. Suppression of sebum production by drugs elevates sebum linoleate concentration and

relieves follicular hyperkeratosis. Thus, sebum plays a major role in the pathogenesis of acne. Overproduction of sebum, especially during adolescence, is causally related to acne and inflammation [19]. Low levels of sebaceous gland activity, however, are not correlated with the occurrence of dry skin [20].

**Take Home Pearls**

- Sebocytes preserve characteristics of stem-like cells.
- All sebaceous glands secrete sebum via holocrine rupture of individual sebocytes.
- Increased sebum production results in essential fatty acid deficiency, follicular hyperkeratosis and comedo formation, thus playing a major role in the pathogenesis of acne.
- Low levels of sebaceous gland activity are not correlated with the occurrence of dry skin.

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# Sebum and Sebaceous Lipids

5

Apostolos Pappas

## Contents



**Core Messages**

- Human sebum is a mixture of nonpolar lipids, mainly triglycerides, wax esters, squalene, fatty acids, and smaller amounts of cholesterol, cholesterol esters, and diglycerides.
- Elevated sebum excretion is a major factor involved in the pathophysiology of acne.
- The sebaceous gland synthesizes lipid species that cannot be found in other areas of the body.
- Complexity and uniqueness are the two terms that best characterize sebaceous lipids. Δ6 desaturation, wax ester synthesis, and squalene accumulation are examples that manifest the uniqueness of sebaceous lipid biology.
- Genetic knockout animal models of lipid synthesis demonstrate dramatic changes in skin physiology and pathology. Impairment of sebaceous lipid pathways results in severe skin phenotypes.

## 5.1 Introduction

Human sebum is a complex mixture of lipids—triglyceride fats, wax esters, squalene, cholesterol esters, and cholesterol. The triglycerides are largely hydrolyzed by bacteria from the anaerobic environment of the gland by the time the sebum reaches the skin surface, so that about one-third of

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the surface lipids consists of free fatty acids, which are produced without exogenous influence [1].

Cholesterol is not unique to the sebaceous gland; it is found throughout the body since it is a component of cellular membranes. Squalene is not only found in sebum either; increased levels of squalene have been found in the serum of postmenopausal woman with coronary artery disease [2]. Squalene is the linear intermediate in cholesterol biosynthesis and in other tissues is quickly converted to lanosterol and finally to cholesterol. However, the squalene produced in sebaceous cells is not converted to cholesterol.

Some of the lipids contained in sebum have features that are unique. Sebaceous gland fatty acids include species with chain branching or with unusual double-bond positions [3] that are uncommon in other organs. Another aspect that distinguishes sebaceous lipids from other human lipids is the pattern of unsaturation seen in sebaceous lipids. Sapienic acid is the most abundant fatty acid in human sebum and is not present in the sebum of other hair-bearing animals. Sebaleic acid is also thought to be unique to human sebum.

Genetic and hormonal factors cause individual differences in sebaceous lipid composition. Genetic factors seem to influence the proportions of the various types of branched-chain fatty acids [3].

The uptake of circulating lipids in blood is an important step in the production of sebaceous lipids. Palmitic acid is the preferred fatty acid for incorporation into wax esters. The sebaceous gland provides an interesting model to study lipid production that is different from that found in other areas of the body.

Sebaceous lipids are unique and intriguing. As Nicolaides [4] commented: "two key words characterize the uniqueness of skin lipids: complexity and perversity." Human sebum contains mainly nonpolar lipids as triglycerides, wax esters, squalene, fatty acids, and smaller amounts of cholesterol, cholesterol esters, and diglycerides [3, 5, 6]. Depending on the sampling method used, qualitative analysis dramatically differs, particularly if the major components of sebum, the triglycerides, are sampled from the canal before or after modification by bacteria that hydrolyze them to produce free fatty acids [4, 7–10]. The mean weight % that is often cited in the literature is given in Table 5.1.

**Table 5.1** Relative sebum composition, (from Refs [3, 4, 6, 7, 10])

| Lipid class | Range weight, % | Mean weight, % |
|---|---|---|
| Triglycerides | 20–60 | 45 |
| Wax esters | 23–29 | 25 |
| Squalene | 10–14 | 12 |
| Free fatty acids | 5–40 | 10 |
| Cholesterol and sterol esters | 1–5 | 4 |
| Diglycerides | 1–2 | 2 |

Human sebaceous lipids are significantly different in quantity and quality compared to other species [11–13]. The reason for such a unique sebum is not understood; however, one can also consider that human skin is also unique. In addition, acne is also unique to humans, and it seems likely that the unique sebaceous lipids do contribute to this odd disease. Elevated sebum excretion is a major factor involved in the pathophysiology of acne [1, 14, 15].

Otherwise various functions have been attributed to sebum [5, 16]. It offers an additional coat of the fur, which contributes to heat and moisture insulation. Besides being another layer of waterproofing, it has been speculated that it serves as the solvent for pheromones, odor, and volatile molecules that transmit various communication signals [4, 12, 17].

## 5.2 Uniqueness of Sebaceous Lipids

Although the majority of lipids produced by organs of the human body are alike, the sebaceous gland has unique species that cannot be found in other organs of the body.

### 5.2.1 Sapienic Acid

The best example is the most predominant fatty acid of sebum, the sapienic acid (16:1, Δ6), which has its single double bond at the sixth position from the carboxyl end [4, 16]. This particular fatty acid is truly unique to sebum and is not found anywhere else in the human body. In addition, it cannot be obtained from the diet, since only very few plant species have been reported to manufacture

this unusual fatty acid [4, 18]. In nature the abundant and preferred position for the first double bond on long chain fatty acids is the nineth from the carboxyl end. The 16-carbon isomer with one double bond at the nineth position from the carboxyl end is the palmitoleic acid, which is naturally found in many tissues. Almost no other monounsaturated fatty acids with a single double bond in the sixth carbon are found in nature. In particular, the elongation of sapienic acid by two carbons followed by the insertion of an additional double bond between the fifth and sixth carbon yields sebaleic acid (18:2Δ5, 8), and this synthesis takes place only in human sebaceous cells. The levels of sapienic acid are multiple folds higher than any of its derivatives, isomers, or other monounsaturated fatty acids found in sebum (Table 5.2).The potential role of sapienic acid in the etiology of acne is controversial. Thus, it has been argued that its presence in sebum correlates with the elevated sebum levels [19], while others report that it can be potent against bacteria commonly associated with acne [20–22].

The most abundant monounsaturated fatty acid, in most organisms, is the oleic acid. This is the product of a widely expressed desaturase, stearyl coA desaturase (SCD), that inserts a double bond between the Δ9th and Δ10th carbon of stearic acid (18:0) to form oleic acid (18:1, Δ9). The presence of the Δ9 or other double bonds normally precedes any action of the delta 6 desaturase (fatty acid desaturase-2; FADS-2), which further introduces a double bond at the sixth position from the carbonyl end. The delta 6 desaturase has higher affinity for substrates, which are already highly unsaturated [23]. Its prime substrates are linoleic (18:2, Δ9,12) and α-linolenic (18:3, Δ9,12,15) acids. The Δ6 desaturase enzyme converts linoleate and α-linolenate into distinct groups of long-chain polyunsaturated fatty acids, classified as the omega-6 and the omega-3 families, respectively [24]. Many members of these families are bioactive lipids, which serve as ligands of nuclear receptors (e.g., PPARs) or demonstrate potent pro- or anti-inflammatory effects (e.g., prostagladins, leukotriens). These pathways are widely expressed in human sebaceous cells [25–27].

The absence of the Δ9 desaturase in sebaceous cells, in addition to the high expression of Δ6 desaturase, results in a unique biology [23]. The Δ6 desaturase catalyzes a "sebaceous type" reaction of converting palmitic acid into sapienic acid. This reaction does not take place anywhere else in our body [4], since the preferred substrates for the delta 6 desaturase are linoleic and α-linolenic acid [28].

A recent study [29] revealed that linoleic acid undergoes a rapid oxidation and degradation, in sebaceous cells, which makes only palmitic acid available as a substrate to the delta 6 desaturase. Otherwise, the enzyme would have catalyzed the synthesis of more omega-6 derivatives from linoleic acid, since it is the preferred substrate for this reaction. In fact, linoleic acid was the only fatty acid that appeared to be subjected to β-oxidation, and this activity correlated with the ability of sebaceous cells to synthesize wax esters, which is a differentiation marker for the

**Table 5.2** Relative sebum composition, (from Ref [4])

| Fatty acid | Amount, % |
|---|---|
| *Main fatty acids* | |
| 16:0 (palmitic acid) | 25.33 |
| 18:0 (stearic acid) | 2.89 |
| 18:1 (oleic acid) | 1.87 |
| 18:2 (linoleic acid) | 0.53 |
| *Products Δ6 of desaturation* | (*~45 %*) |
| 16:1, Δ6 (sapienic acid) | 21.70 |
| 18:1, Δ8 (elongated derivative of sapienic) | 8.75 |
| 15:1, Δ6 (Δ6 desaturation on odd 15 carbon chain) | 3.96 |
| 18:1, Δ6 (Δ6 desaturation on 18 carbon chain) | 1.87 |
| 17:1, Δ6 (Δ6 desaturation on odd 17 carbon chain) | 1.31 |
| 18:2, Δ5,8 (sebaleic acid derivative of sapienic) | 1.12 |
| 14:1, Δ6 (Δ6 desaturation on 14 carbon chain) | 1.06 |
| (other Δ6 products) | (3–4 %) |

sebaceous cells. Thus, oxidation of linoleic acid is specific to sebaceous cells and correlates with their function and differentiation.

The above study is the only one that used radiolabeled fatty acids substrates as most of the studies to determine lipid synthesis into the sebaceous gland have used radiolabeled acetate, glucose, or amino acids [30, 31]. The majority of the organs receive its lipids through uptake of circulating lipids. Sebaceous glands express at least two different receptors involved in uptake of circulating lipid. The first, FATP4, is a fatty acid transporter, which has been shown to be expressed in sebaceous glands [32]. The second is the LDL receptor that has also been shown to be expressed in sebaceous glands and the human sebocyte cell line SEB-1 [32, 33]. A transgenic mice overexpressing apolipoprotein C1 demonstrated sebaceous gland atrophy [34]. In addition, fasting reduced the incorporation of fatty acids in sebum by 20 %, fact that suggests that circulating lipids could be incorporated by the sebaceous gland [35, 36]. Taken together these results reinforce the notion that uptake of circulating lipids is an important step in the production of sebaceous lipids.

Sebum analysis demonstrates that the essential fatty acids which come strictly form the diet as linoleic acid and its derivatives constitute small amounts in surface lipid samplings [4]. One of the most intriguing studies was performed by Sinclair's group [37, 38]. When guinea pigs were dosed with radioactively labeled linoleic and linolenic acids, skin and fur were the most heavily labeled tissue, suggesting a necessary role for essential fatty acids in sebaceous gland biology. Very little is known about how these essential nutrients are utilized in the human sebaceous cells. However, one study has claimed that many acne patients had a linoleic acid deficiency [39].

Another unusual characteristic of the human sebum is the presence of branched chain fatty acids or fatty acids with odd numbers of carbon atoms or very long chain fatty acids, which are uncommon in other organs [4, 11]. It is possible that these are products of the resident skin micro flora, since they are more common to bacterial metabolism [18]. Another possibility is that they are synthesized from branched precursors, which are products of essential branched amino acid catabolism [3].

### 5.2.2 Wax Esters

Wax esters, like sapienic acid, are unique to sebaceous cells and are not produced by any other cell in the body. They account for approximately 25 % of sebaceous gland lipids, and their production correlates with sebaceous gland differentiation [6, 16]. Animal models demonstrated a strong correlation between impaired wax ester synthesis and atrophic sebaceous gland [40, 41].

Wax ester synthases [42, 43] have only recently been discovered; however, additional recent reports [44, 45] provided evidence that another family of enzymes can also synthesize waxes. Therefore, there is not a unique wax synthase and we can only speculate on the complexity of the wax ester biosynthesis, which is poorly understood in humans. Although waxes that serve as a differentiation marker for sebaceous cells is not clear if they are the cause or the effect of the complex sebaceous differentiation. In vitro, it is the pathway that gets mostly suppressed no matter if explanted sebaceous glands, tissues, cell preps, or transformed cell lines are used.

Age- and sex-related differences have been reported in wax ester synthesis, which always correlate with total sebum output and activity [46–48].

In nature waxes exist as protective layers for leaves, fruits of plants, or on skin, feathers, or fur of animals, in addition to bacteria, algae, and fungi. Waxes are more resistant to oxidation, hydrolysis, and heat than triglycerides. Besides protection they also serve as lubrication aim and seal internal moisture or prevent excessive hydration [49]. In certain instances the packing and physicochemical properties of the wax crystals demonstrate unusual surface self-cleaning properties that repel not only moisture, but together with water any kind of physical or biological invader [50].

### 5.2.3 Squalene

There is nothing unique about synthesizing squalene, which is a precursor of cholesterol. Most of the mammalian cells have the capacity to synthesize cholesterol, which is an essential molecule for membrane fluidity and structure. The uniqueness in human sebum is that this cholesterol precursor accumulates in unusually high levels (12 %), while cholesterol accounts for <2 % of the total sebaceous gland lipids.

Squalene is an unsaturated hydrocarbon which in other tissues is quickly converted to lanosterol and finally to cholesterol [5]. Squalene is produced by the action of squalene synthase and is metabolized further by Squalene epoxidase or monooxygenase. Perhaps in sebum change in the activities of these two enzymes are responsible for the accumulation of squalene. There are more cases where levels of squalene are increased as, for example, in the serum of postmenopausal woman with coronary artery disease [2].

Squalene synthase levels have never been measured in human sebocytes. Studies in other systems have determined squalene synthase mRNA levels in response to anaerobic environment, which approximates the environment found inside sebaceous glands. For example, in yeast the squalene synthase gene ERG9 has decreased expression in anaerobic conditions [51]. Crucial transcription factors for the cholesterol metabolism, the sterol response element-binding proteins (SREBP1a and 2), have been shown to increase transcription of human squalene synthase in the livers of transgenic mice overexpressing SREBPs [52, 53]. SREBP1 is also increased in SEB-1 cultured human sebocytes in response to insulin and IGF [54]. Therefore, the levels of squalene synthase may be affected by factors as hormonal regulation, the function of other glands or even diet [55].

It is also possible that squalene accumulates in sebaceous lipids due to downregulation of the levels and/or activity of the enzymes that process squalene to cholesterol. Squalene monooxygenase requires molecular oxygen for its function, which may be limited in the anaerobic environment of the sebaceous cell. Therefore, this step could become the rate limiting and responsible for the slower conversion of squalene to cholesterol.

Squalene as a long and highly unsaturated hydrocarbon is a natural lubricant and has high penetration efficiency; therefore, its role could be more than just a precursor of cholesterol. Several reports demonstrate possible role of squalene oxidation products on UV protection [56] but also irritation [57]. These products together with unsaturated free fatty acids have been reported as comedogenic [58, 59]. This could be the reason why human sebum also transports other lipophilic compounds as vitamin E [60] and glycerol [61], which play important roles in protecting skin from lipid oxidation and proper barrier function, respectively.

## 5.3 Importance of Sebaceous Lipids and Animal Models

In the last decade, observations in knockout (KO) mice have clearly demonstrated the importance of sebaceous lipids in skin physiology. In these studies, skin and fur abnormalities become the common denominator, once a sebaceous lipid pathway is disturbed.

In 1997 it was demonstrated that knocking out of the melanocortin-5 receptor (MC5-R) resulted in severe defects in water repulsion and thermoregulation due to decreased production of sebaceous lipids [62]. Although the analytical techniques and focus were not to dissect which sebaceous lipids were more suppressed, the effect of the melanocortin receptors on sebaceous lipid metabolism shed more light on a different path, besides the anticipated role that melanocortins have on pigmentation, obesity, or body weight regulation.

In 1999 Zheng at al [63], demonstrated by positional cloning that the dramatic alopecia manifested at the asebia mouse is due to the lack of a functional Stearoyl-CoA desaturase (Scd1). The absence of mature sebaceous glands demonstrated the apparent importance of the SCD1 gene and its products (monounsaturated fatty acids) to normal sebaceous gland function and

their role in hair development. The revelation that asebia's nonfunctional SCD1 is solely responsible for scant to absent hair and hypoplastic to absent sebaceous glands [64] was further supported by the fact that sebaceous glands are scant in certain forms of alopecias [65]. These findings were further confirmed in 2001 by the reverse experiment where the SCD1 KO mice were produced [41].

Examination of either the asebia or the SCD1 deficient mouse substantiates the necessity of the sebaceous lipids. SCD catalyzes the Δ9-cis desaturation of long chain fatty acyl-CoA substrates, and its preferred substrates are palmitoyl- and steraoyl-CoA. The skin of the KO mice has also lower levels of triglycerides, wax esters, as well as monounsaturated fatty acids. In addition to skin, SCD1 is expressed in the liver, eyelid, and white adipose tissue. As these mice also suffer from corneal opacities and hypoplastic meibomian glands, Scd1 appears to be required for normal ocular barrier function.

A similar phenotype was demonstrated in the Acyl CoA:diacylgylcerol acyltransferase 1(DGAT1) KO mouse, where sebaceous gland atrophy and hair loss were profound [40]. DGAT is the primary triglyceride synthase and exists in two forms, DGAT1 and DGAT2, which differ in sequence and localization [66]. DGAT1 is also involved in the synthesis of wax esters, unlike DGAT2 [44], and is expressed in most tissues, including the sebaceous gland [40, 66]. The apparent involvement of DGAT1 in wax ester synthesis is consistent with the observation that there are little to no wax esters in the fur lipids of the DGAT1 KO.

The DGAT2 KO animals [67] similarly to SCD2 KO [68] do not survive due to impaired permeability barrier function in the skin. Interestingly, the DGAT1 deficient mice, when bred onto an obese mouse background, with a genetic deficiency in leptin expression, have normal sebaceous glands and fur. Therefore, it appears that leptin has an effect on the production of wax esters by the sebaceous gland when DGAT is absent [40].

Another animal model, which demonstrated the importance of sebaceous lipids to skin function, is the ELOVL3 KO mouse [69]. The Elovl3 gene product is involved in the formation of very long chain fatty acids and has a distinct expression in the skin that is restricted to sebaceous glands and epithelial cells of hair follicles. Disruption of that gene disrupted the formation of specific neutral lipids that are necessary for skin functions. The Elovl3-ablated mice had sparse hair coats and hyperplastic sebaceous glands with unusual lipid content in monounsaturated fatty acid with 20 carbons. In addition the loss of ELOVL3 activity caused a severe defect in water repulsion and increased trans epidermal water loss.

## Conclusions

Sebaceous lipids seem to contribute in many functions as aging, conditioning, and defense of the health of the skin. However, many may still share the notion that sebum has no use, since the skin of young children does not seem to be adversely affected by a lack of sebaceous lipids. The idea that all these unusual lipids make the skin unfriendly to fungi and bacteria gains more attention. Even if the major component of sebum, the triglycerides, is hydrolyzed by bacteria to nutrients: fatty acids, these are unusual enough to orchestrate together with the other perverse lipids a unique mechanism that will select which organism is an enemy and which is desirable on our skin. Clearly additional studies are required before we have a complete understanding of the roles of sebaceous lipids in skin physiology.

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# Experimental Models of the Sebaceous Gland

6

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## Contents



**Core Messages**

- Seborrhea and acne are exclusively human disorders and sebaceous gland differentiation is species-specific, thus posing the need for human in vitro models.
- Human sebaceous gland cell lines (SZ95 as well as SEB-1, Seb-E6E7) have been used in monolayer cultures as models to study specific functions involved in development, growth, and differentiation of sebaceous gland cells.
- Maintenance of sebaceous gland cells in certain culture conditions has helped to investigate the physiology of the sebaceous gland, including its changes in acne.
- Sebocyte culture models have provided insight in the mechanism of action of acne treatments, including retinoids, anti-androgens, and PPAR ligand antagonists.
- More complex culture systems, including three-dimensional models are under development.
- Sebocyte culture models provide new chances for further research on biologically active ingredients, new pharmaceutical and cosmetic drugs for antiaging, and acne treatment.

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## 6.1 Introduction

Experimental sebaceous gland models are essential for a better understanding of the pathophysiology of human skin disorders involving the sebaceous gland, such as sebostasis, seborrhea, and acne, for thorough research and development of cosmetics and drugs, and for investigation of drug pharmacokinetics. So, the need for an established model for studies of sebocyte differentiation and for pharmacologic assays has led into considerable advances in this field (Table 6.1).

Several attempts were made to cultivate animal [1, 2] or human sebaceous gland cells, using mechanical dissociation of isolated sebaceous glands or enzymatic separation of sebocytes from skin sections with a keratotome [3, 4]. However, seborrhea and acne are exclusively human diseases and sebaceous gland differentiation is species-specific, and no animal model was found to be predictive in assessing antiacne drug effects in humans. So, basic research on human sebaceous gland function and control requires human in vitro models.

Initial studies have been reported on experimental models carried out on whole human skin plugs, either incubated in vitro [5–7] or grafted on to nude mice [8]. However, it was not until the isolation of viable human sebaceous glands and pilosebaceous units [9, 10] and the establishment of the human sebocyte culture model in vitro [11] that fundamental research on human sebocyte activity and its regulation begun [12].

Human sebaceous gland experimental models have shed light on a plethora of functions of the sebaceous gland, highlighting its role in skin homeostasis [13]. Apart from acne, sebaceous glands are involved in embryology, development, and differentiation; in skin protection; and in

**Table 6.1** Reported sebaceous gland experimental models

| Research group | Experimental model |
|---|---|
| [3] | Cultivation of human sebocytes in collagen after enzymatic dissociation of isolated sebaceous glands |
| [4] | Cultivation in monolayers after enzymatic digestion of sebaceous-gland-rich dermal slices obtained with as Castroviejo keratotome |
| [9] | Introduced the maintenance of the sebaceous gland ex vivo. |
| [16] | Modified the technique of Karasek (1986). Removed the top 0.4-mm facial skin section containing the epidermis and some of the dermis and used the second 0.4-mm dermal section as the source of human sebocytes. |
| [11] | In vitro cultivation of human sebaceous gland-derived cells. Human sebocyte monolayer cultures as outgrowths from the periphery of sebaceous gland organ cultures were obtained. |
| [19] | Sebaceous glands were treated with collagenase before cultivating them in serum-free supplemented William's E medium. |
| [33] | Zouboulis et al. modified the culture medium including 2 % human serum, 8 % FCS, and omitting hydrocortisone. |
| [20–22] | Primary sebocyte cultures were obtained by omitting the 3 T3 fibroblast layer, and secondary cultures were grown in a medium supplemented with delipidized serum and serum-free keratinocyte basal medium. |
| [23] | Primary sebocytes were cultured after the technique of Xia et al. (1989) for at least three passages in serum-free KGM without a feeder cell layer. |
| [27] | Generation of an immortalized sebocyte cell line (SZ95) by transfecting human facial sebocytes with Simian virus-40 large T antigen. SZ95 showed similar morphologic, phenotypic and functional characteristics of normal human sebocytes. |
| [30] | Second immortalized human sebaceous gland cell line (SEB-1) by applying the transfection system of Zouboulis et al. (1999) |
| [15] | Third immortalized sebaceous gland cell line (Seb-E6E7) by introduction of HPV16 E6 and E7 genes. |

**Table 6.2** Complex sebaceous gland functions identified by research in experimental sebocyte culture models

| Sebaceous gland function | Mechanism |
|---|---|
| Embryology, development, differentiation | Influence on follicular differentiation<br>Preservation of characteristics of stem-like cells |
| Synthetic activity | Production of sebum |
| Protection | Photoprotection against ultraviolet B radiation<br>Thermoregulation<br>Wound healing<br>Delivery of antioxidants from and to the skin surface |
| Inflammation, immunity | Direct pro- and anti-inflammatory activities<br>Production pro- and anti-inflammatory lipids<br>Toll-like receptor 2-induced upregulation of lipogenesis<br>Synthesis of proinflammatory cytokines in the presence of bacteria |
| Endocrine properties | The sebaceous gland is a steroidogenic organ:<br>• *Expression of all enzymes required for steroidogenesis*<br>• *Regulation of local androgen synthesis*<br>Involvement in skin aging<br>Expression of peptide hormone and neurotransmitter receptors (CRH-R, MC1R, MC5R, VPACR, histamine receptor)<br>Expression of IGF-1 receptor, GH receptor<br>Expression of nuclear receptors: steroid receptors [estrogen, androgen, progesterone, retinoid (RAR, RXR), and vitamin D receptor] and thyroid receptors, PPAR, liver X receptor |

*CRH-R* corticotropin-releasing hormone receptor, *MC1R* melanocortin 1 receptor, *MC5R* melanocortin 5 receptor, *VPACR* vasoactive intestinal polypeptide receptors, *IGF-1* insulin-like growth factor-1, *GH* growth hormone, *RAR,* retoinic acid receptors, *RXR* retinoid X receptors, *PPAR*, peroxisome proliferator-activated receptors

inflammation and immunity and display complex endocrine properties (Table 6.2) [13]. Also, sebocytes, despite their programming for terminal differentiation, preserve characteristics of stem-like cells, as they present a remarkable potential of dual differentiation. The interactions between β-catenin and Sonic hedgehog promote proliferation of progenitors of the hair lineages, while Indian hedgehog stimulates proliferation of sebocytes precursors [14]. Overexpression of myc stimulates sebocyte differentiation, whereas overexpression of β-catenin stimulates interfollicular epidermal differentiation in vitro [15].

## 6.2 Human Experimental Models of the Pilosebaceous Unit

Karasek and Charlton [3, 4] first described the cultivation of human sebocytes in collagen after enzymatic dissociation of isolated sebaceous glands and in monolayers after enzymatic digestion of sebaceous-gland-rich dermal slices obtained with a Castroviejo keratotome. Cells obtained by the first technique exhibited a significant loss of sebocyte characteristics in vitro. The latter method was modified later and further developed by Doran et al. [16] who removed the top 0.4-mm facial skin section containing the epidermis and some of the dermis and used the second 0.4-mm dermal section as the source of human sebocytes.

The first successful human sebocyte culture was introduced in 1989 by Xia et al. [11] with the in vitro subcultivation of human sebaceous gland-derived cells. Intact sebaceous glands were isolated from full-thickness human skin after incubation in dispase and deoxyribonuclease. Human sebocyte monolayer cultures as outgrowths from the periphery of sebaceous gland organ cultures were obtained. The ducts of the glands were removed; the isolated gland lobules were seeded on a 3 T3-cell feeder layer in Dulbecco's modified Eagle's medium and Ham's F 12 medium (3:1) supplemented with fetal calf serum (10 %), L-glutamine, antibiotics, epidermal growth factor (10 ng/ml), hydrocortisone (0.4 μg/ml), and cholera toxin ($10^{-9}$ M), and were

then cultivated in a $CO_2$ incubator at 37° C. After 2–3 weeks, cell outgrowths resulted from the periphery of the gland lobules, and dispersed cells were subcultured thrice with or without 3 T3-cell feeder layer. The cultured cells preserved in vitro morphologic characteristics and differentiation patterns comparable to those described for normal human sebocytes in vivo with a high rate of viable cells. Their labeling pattern with monoclonal antibodies showed close similarities to the pattern of keratinocytes in vivo and in vitro. In their cytoplasm oil red- and nile red-stained droplets were detected, and the observed density and distribution evidenced in vitro lipogenesis. This technique demonstrated the growth of cells originating from intact human sebaceous glands and their long-term differentiation into lipid-producing cells in vitro [11]. Also, sebocyte cultures could be obtained not only from sebaceous-gland-rich skin areas but also from other areas of the human skin [17]. Disadvantages of the method included the fact that the exact separation of glands from the skin was time consuming and required skillful preparation and that the rather low number of proliferating cells in the intact sebaceous gland lobules did not provide optimal conditions for their in vitro growth.

Over the years, modifications of the technique of Xia and al [11]. have improved the culture of human sebocytes in vitro. Zouboulis et al. [18] modified the culture medium including 2 % human serum, 8 % fetal calf serum, and omitting hydrocortisone. Lee [19] treated sebaceous glands with collagenase before cultivating them in serum-free William's E medium supplemented with 10 μg/ml insulin, 10 μg/ml transferring, 10 μg/ml hydrocortisone, 10 ng/ml epidermal growth factor, 10 ng/ml sodium selenite, 2 nmol/l L-glutamine, and penicillin/streptomycin [19]. Primary sebocyte cultures could also be obtained by omitting the 3 T3 fibroblast layer, and secondary cultures could be grown in a medium supplemented with delipidized serum and serum-free keratinocyte basal medium. [20–22]

Fujie et al. [23] cultured primary sebocytes after the technique of Xia et al. [11] for at least three passages in serum-free keratinocyte growth medium without a feeder cell layer. Keratinocyte growth factor, shown to be a mitogen for primary cultures of mammary epithelium alone or combined with epidermal growth factor and/or bovine serum albumin, was found to significantly improve yield rates and proliferation of human sebocytes [24–26].

Human sebocytes however, are predestined to differentiate by accumulating neutral fat droplets until they burst and die. Therefore, adequate cell amounts for large-scale experiments could only be obtained from multiple donors, whereas prolonged experiments were hindered by the short life spans of the cells, as normal human sebocytes could only be grown for 3–6 passages.

These drawbacks were overcome by the generation of an immortalized sebocyte cell line (SZ95) by Zouboulis et al. [27] by transfecting cultured human facial sebocytes from a 87-year old woman with the Simian virus 40 large T antigen. The SZ95 sebaceous gland cell line is nowadays protected by national and international patents as well as priority submissions [28]. SZ95 sebocytes exhibit similar morphologic, phenotypic, and functional characteristics of normal human sebocytes. Several studies have shown that SZ95 sebocytes retain major characteristics of normal human sebocytes, such as progressing differentiation with increasing cell volume and lipid synthesis, expression of markers of sebaceous lineage and terminal sebocyte differentiation, such as keratin 7 and epidermal membrane antigen (EMA), respectively [18], and can subsequently undergo apoptosis [29]. SZ95 sebocytes also express characteristic organ- and function-specific proteins of human sebaceous glands and exhibit expected biological responses to androgens and retinoids [27, 29].

In 2003, Thiboutot et al. [30] applied the transfection system administered by Zouboulis et al. [27] to develop a second immortalized human sebaceous gland cell line, termed SEB-1. SEB-1 was established from sebaceous glands of normal skin of the preauricular area of a 55-year-old male. Like SZ95 sebocytes, SEB-1 sebocytes also express characteristic sebaceous gland proteins and their cytoplasm-induced oil red O-positive lipid droplets. In gene array studies, genes characteristic for the sebaceous gland and

such involved in lipid and steroid metabolism were expressed in SEB-1 sebocytes.

A third immortalized sebaceous gland cell line, Seb-E6E7, has been generated from adult human facial skin following a facelift procedure. Human sebocytes were immortalized by introduction of HPV16 E6 and E7 genes. Seb-E6E7 sebocytes were transduced by coculture with mitomycin C-treated packaging cells in the presence of 3 T3-J2 cells. Seb-E6E7 sebocytes, like SZ95 sebocytes, express both K7 and involucrin. In first experiments, Seb-E6E7 seem to respond to chemicals in a similar manner with SZ95 sebocytes despite their different transfection methods [15].

## 6.3 Acne Treatments Investigated in Experimental Sebocyte Culture Models

Cell culture models, especially the SZ95 sebaceous gland cell line, have advanced in excellent models to investigate new ingredients against seborrhea, acne, and aging skin.

Antiacne therapies investigated in vitro include retinoids, anti-androgens, and zileuton, a potent peroxisome proliferator-activated (PPAR)-α ligand antagonist [31, 32] (Table 6.3). Among these, the most investigated therapy in vitro is 13*cis* retinoic acid. Its mechanism of action has been elucidated by in vitro sebocyte research revealing that 13*cis* retinoic acid and all-trans retinoic acid inhibit the proliferation of cultured sebocytes in a dose- and time-dependent manner [22, 33, 34]. Marked decreases in wax esters, a slight decrease in squalene, and a relative increase in cholesterol level have been measured. It has been shown that 13*cis* retinoic acid undergoes intracellular isomerization to all-trans retinoic acid in human sebocytes, which then exerts its antiproliferative effect on sebocytes via binding to retinoic acid receptors (RAR) [35]. Also, 13*cis* retinoic acid causes cell cycle arrest and induced apoptosis in cultured sebocytes by a RAR independent mechanism [36] and may reduce the mRNA expression of pro-matrix metalloproteinase (MMP)-2, proMMP-9, proMMP-13, which are increased in acne [37].

Anti-androgens have been studied regarding their mechanism of action in acne. Anti-androgens, like spironolactone, inhibit the stimulatory effect of testosterone and 5α-dihydrotestosterone on sebocyte proliferation. They inhibit lipogenesis under the presence of peroxisome proliferator-activated receptor (PPAR) ligands [21]. Cyproterone acetate inhibits the activity of 3β-hydroxy-steroid dehydrogenase and blocks the androgen receptor [38].

Zileuton, the only known potent PPARα ligand antagonist, inhibits leukotriene B4 synthesis, thus

**Table 6.3** Mechanism of action of acne treatments investigated in in vitro sebocyte culture models

| Treatment | Modes of action |
|---|---|
| 13*cis* retinoic acid | • Inhibits proliferation of cultured sebocytes (via intracellular isomerization to all *trans* retinoic acid)<br>• Decreases squalene and wax esters<br>• Modulates keratin expression<br>• Reduces mRNA expression of MMP-2, -9, -13<br>• Causes cell cycle arrest and induces apoptosis in cultured sebocytes by a RAR-independent mechanism |
| Anti-androgens<br>*Spironolactone*<br>*Cyproterone acetate* | • Inhibit androgen metabolism<br>• Block the androgen receptor<br>• Inhibit the action of testosterone and 5α-dihydrotestosterone on sebocyte proliferation<br>• Inhibit lipogenesis (in the presence of PPAR ligands)<br>• Inhibit the activity of 3β-hydroxy-steroid dehydrogenase |
| Zileuton | • A potent PPARα ligand agonist<br>• Reduces lipid synthesis by inhibiting leukotriene B4 synthesis |
| Ectopeptidase inhibitors | • Reduce proliferation<br>• Reduce proinflammatory cytokine production in SZ95 sebocytes<br>• Inhibits the topical activites of human peripheral T cells in vivo and in vitro |

reducing lipid synthesis [31, 32, 39]. Also, ectopeptidase inhibitors reduce proliferation and cytokine production in SZ95 sebocytes as well as the topical function of human peripheral T cells in vivo and in vitro [40].

## Conclusions

Mammal sebocytes and sebocyte-like cells (human, mouse, hamster, rat) and human sebaceous gland cell lines (SZ95, SEB-1, SebE6E7) have been used in monolayer cultures as models to study specific functions involved in development, growth, and differentiation of sebaceous gland cells.

Maintenance of these cells in certain culture conditions has helped investigate the physiology of the sebaceous gland, including its changes in acne. Also, sebocyte culture models provide new chances for further research on biologically active ingredients, new pharmaceutical and cosmetic drugs for antiaging, and acne treatment. More complex culture systems, including three-dimensional models, are under development.

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# Part II

# Acne Vulgaris: Epidemiology

# Acne Epidemiology and Socioeconomic Aspects

7

Christos C. Zouboulis, Clio Dessinioti, and Christina Antoniou

## Contents



**Core Messages**

- The prevalence of adolescent acne is approximately 80 %, varying among different studies (44.1–94.9 %) partly depending on the method of acne classification or due to differences between populations regarding genetic and/or environmental factors.
- Adult acne seems to have gender differences as to its prevalence, impact on the patient's quality of life, treatment choice, and clinical features.
- The prevalence of female adult acne differs (12–50.9 %) according to the criteria used in different studies.
- Acne may have substantial psychosocial sequelae. It has been shown to negatively affect the patient's quality of life similarly with other chronic disabling diseases, such as asthma, epilepsy, diabetes, and arthritis.
- Even mild acne may have an important negative impact on the patient's quality of life, self-esteem, and psychological well-being, depending on the patient's particular environment (personal, social, and occupational).
- These findings have public health implications because they underline the need of appropriate health care for adolescent and adult acne patients in the community.

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## 7.1 Introduction

Acne is the most common skin disease and the leading reason for visiting a dermatologist [1]. It affects approximately 50 million people in the USA, with annual costs for health care in acne exceeding $1 billion in the USA alone [2]. A community-based survey study of acne-related health preferences in adolescents assessed adolescents' acne-related preferences. Adolescents were willing to pay a median of $275 to never have had acne in their lifetime and were willing to pay significantly more for 100 % clearance than for 50 % clearance or 100 % clearance but with scarring ($p<0.001$ for both comparisons) [3].

In the past, acne was thought of as a trivial, "normal" condition; however, acne has been recently redefined to be a chronic disease, as for many patients, acne is characterized by a prolonged course, a pattern of recurrence or relapse, manifestation as acute outbreaks or slow onset, and a psychologic and social impact that affects the individual's quality of life [4] (see Chap. 27).

In this chapter, data regarding epidemiology, economics, and psychosocial effects of adolescent and adult acne are presented.

## 7.2 Adolescent Acne

Acne vulgaris is highly prevalent among teenagers, affecting approximately 80 % of them with similar sex distribution [5]. Most epidemiological acne studies have focused on adolescent age. It has been reported to range from 44.1 % in 1,857 adolescents in Peru [6] and 49.8 % in 317 adolescents in the UK to 67.3 % in 9,570 adolescents in New Zealand [7], 82.1 % in 1,290 adolescents in Portugal [8], 83.1 % in 666 adolescents in Australia [9], 87.9 % in 1,045 adolescents in Singapore [10], 91.3 % in 522 adolescents in China (Hong Kong) [11], and 94.9 % in 594 adolescents in Belgium [12].

A cross-sectional, community-based study in Tehran, Iran, of 1,002 pupils aged $16 \pm 0.9$ years showed an overall acne prevalence of 93.3, with 94.4 % rates for boys and 92.0 % for girls. Moderate to severe acne was observed in 14 %. No association between gender and acne severity was detected. Moderate to severe acne was significantly more prevalent in pupils with a positive family history of acne ($p<0.0005$, OR: 2.3). Also, risk factors for moderate to severe acne were increasing pubertal age, seborrhea, the premenstrual phase, mental stress, and sweet and fatty foods [13].

The prevalence of adolescent acne in different studies varies partly depending on the method of acne classification or due to differences between populations regarding genetic and/or environmental factors (see Chaps. 20, 21, 25, 26). The low acne prevalence in Peruvian adolescents (44.1 % in 1,857 adolescents) [6] might be attributed to distinct nutrition patterns or genetic predisposition [14]. The importance of genetic factors in acne susceptibility is suggested by genetic and ethnic studies and is confirmed by the very high degree of concordance between identical twins (see Chap. 14) [15].

In adolescents, acne can affect self-image, psychological well-being, feelings, personal relationships, sports, social life, and may even precipitate suicide [16]. It has been suggested that it is important to identify adolescents that are affected by their acne early to reduce the future socioeconomic burden of their disease [5]. Acne patients ($n=111$) reported levels of social, psychological, and emotional problems as great as those reported by patients with long-standing disabling diseases, including asthma, epilepsy, diabetes, and arthritis. These findings underline the importance of appropriate management of the acne patient. In this study, quality of life was measured using the Dermatology Life Quality Index (DLQI), Rosenberg's measure of self-esteem, a version of the General Health Questionnaire (GHQ-28), and the Short Form 36 (SF-36). Of note, the deficits found in all quality of life measurements did not correlate with the clinically assessed acne severity, implying that even mild acne may have an important negative impact on the patient's quality of life, self-esteem, and psychological well-being, depending on the patient's particular environment (personal, social, and occupational) [17].

In a questionnaire-based survey of 3,775 late adolescents (18 years old) in Norway, the prevalence of acne was 13 % for girls and 14 % for

boys. For both sexes, acne explained a low sense of pride for girls (OR 1.54 [1.06; 2.24]) and for boys (OR 1.85 [1.18; 2.89]) and poor body image for girls (OR 1.56 [1.11; 2.20]) and for boys (OR 1.66 [1.08; 2.54]) independently of body mass index and depressive symptoms. Only boys showed lower self-attitude because of acne (OR 2.07 [1.10; 3.88]) and only girls showed lower self-worth because of acne (OR 1.88 [1.23; 2.88]) [18].

A recent cross-sectional, questionnaire-based study among 3,775 adolescents aged 18–19 years showed substantial acne in 14 %. Suicidal ideation was noted significantly more often by those with increasingly severe acne ($p$-value for trend <0.01). Suicidal ideation remained significantly associated with substantial acne (odds ratio 1.80, 95 % CI: 1.30–2.50) in a multivariate model including adjustments of symptoms of depression, ethnicity, and family income. Mental health problems, as assessed by the Strengths and Difficulties Questionnaire (2.25, 1.69–3.00), low attachment to friends (1.52, 1.21–1.91), not thriving at school (1.41, 1.12–1.78), never having had a romantic relationship (1.35, 1.05–1.70), and never having had sexual intercourse (1.51, 1.21–1.89) were all associated with substantial acne in a multivariate model [16].

On the other hand, the impact of acne on daily life significantly correlated with its perceived severity ($n=711$) in a French study of young people (12–15 years old) who called a general youth helpline. Severe acne was reported to be a problem in daily life, to affect relations with friends and boy/girlfriend, and to affect leisure. Also, severe acne was perceived as a very important problem [19]. A 12-month cohort study of 209 high-school students did not find an association of the presence of acne with examined measures of psychological and psychiatric morbidity [20].

## 7.3 Adult Acne

Acne in adulthood affects the patient's quality of life and employment chances, with acne patients having a higher unemployment rate than adults without acne [21]. Studies regarding the epidemiology and psychosocial effects of adult acne have included university students and other young adults, while others have focused on female adult patients. The prevalence of adult acne has been reported to be 56.2 % in a study of Saudi medical students [22]. The prevalence of acne was 50.9 % for men and 42.5 % for female nonuniversity young adults in their 20s [23].

A study of 98 medical students (22–35 years old) in Portugal reported a prevalence of acne of 62.2 %. In this study, the prevalence of acne was not significantly associated with gender, family history of acne, smoking, or self-perceived presence of acne. Menstrual regularity was not associated with the presence of female acne. The most important patient-reported causes of acne were hormonal changes (94.9 %), diet (85.7 %), genetic problems (69.4 %), poor skin hygiene (61.2 %), and infections (50 %). The majority thought that acne strongly affects self-image and, to a much lesser extent, personal relationships, academic performance, or recruitment to a job [24].

The prevalence of female adult acne differs according to the criteria used in different studies. In the UK, 18.4 % of 200 adult acne patients (older than 25 years old) were females [25], and in another study of 749 adults, clinical facial acne (grade >0.75) was recorded in 3 % of men and in 12 % of women ($p<0.01$) [26]. Another study in the UK showed that 14 % of women 26–44 years old had acne [27]. An Australian study of 787 adult women showed that 13.6 % had acne [28]. In France, a questionnaire-based study of 3,305 adult women showed that 41 % had late-onset acne [29]. A USA questionnaire-based study reported that among 1,013 individuals aged 30–60 years old, the reported prevalence of acne in women aged 20–29 years old was 50.9 % [30].

Adult acne seems to have gender differences as to its prevalence, impact on the patient's quality of life, treatment choice, and clinical features. A cross-sectional and longitudinal questionnaire study of 60 adult acne patients showed that patients with acne experienced functioning and emotional effects from their skin disease comparable with those of patients with psoriasis. Also, older adults reported more effects of acne on their quality of life than younger adults [21]. It has been suggested that after the teenaged years, women seem to be

more likely to have acne than men [26, 30]. Gender differences in self-reported quality of life of the patient and treatment choice were evaluated in a retrospective study of 211 acne patients (mean age: 21.6 years). Men had significantly more severe acne when compared to women; however, women scored worse in the DLQI than men, indicating a greater impact of acne in their quality of life. Also, there was a significant gender difference in treatment choice as more women were treated with oral isotretinoin, although most of them had moderate acne and the DLQI was not known to the treating dermatologist [31]. Recently, the patient's perspective of his disease has started to be incorporated in the decision making by the clinician in a plethora of skin diseases. Taking into account the particular characteristics of the acne patients, such as gender and impact of acne on his/her quality of life as perceived by the individual patient, may be valuable parameters to incorporate in the treatment approach.

In a study of 89 female acne patients, the acne that developed after the age of 21 showed different clinical features compared with the acne that developed before the age of 21 year, with patients with acne after 21 years of age having significantly less comedones and total number of acne lesions. There were no significant differences in the fluorescence density of *P. acnes* or sebum secretion between the two groups [32]. On the other hand, another study of 226 adult women (25–50 years old) reported comedonal postadolescent acne (CPAA) in the majority of patients (85 %) and inflammatory acne in the remaining 15 %. In this study CPAA was significantly associated with smoking [33] (see Chaps. 21, 32).

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# Part III

# Pathogenesis of Acne: Classical Aspects

# Acne Pathogenesis: What We Have Learned Over the Years

8

Clio Dessinioti

## Contents



**Core Messages**

- Past knowledge is essential for future research and therefore should not be underestimated
- In this chapter we will discuss what we have learned regarding the four major factors that influence acne pathogenesis (increased sebum production, follicular hyperkeratinization, *P. acnes* proliferation, and inflammation) over the years until 2000
- The increased sebum production in acne patients may be due to an hyperresponsiveness of the target organ (the pilosebaceous unit) to androgens
- The culture of sebocytes made it possible to better study the complex pathways of androgen control on the sebaceous gland
- Ductal hypercornification results from an increased rate of keratinocyte proliferation and/or a reduced separation of ductal corneocytes
- Additional factors that may influence comedogenesis include abnormalities of the sebaceous lipids, local androgens, retinoids, comedone cycling, and cytokines (IL-α)
- The exact nature and sequence of events in acne initiation have been a matter of debate. Inflammation has been classically considered as a secondary event

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- *P. acnes* secretes various biologically active molecules like enzymes, proinflammatory cytokines, and chemotactic factors, which play a role in the initiation and perpetuation of the local inflammatory response

## 8.1 Introduction

A better understanding of the pathophysiology of acne has been made possible through years of research in the field. Studies of the past have opened the way for new research ideas and have provided the foundations for further scientific progress.

In this chapter we will summarize what we have learned on acne pathogenesis over the years until 2000. There are four major pathogenetic factors that have been implicated in acne pathogenesis, namely sebaceous gland hyperplasia with seborrhea, altered follicular growth and differentiation, *Propionibacterium acnes* colonization of the pilosebaceous unit, and inflammation [1]. Each factor will be addressed separately in the following sections.

### 8.1.1 Increased Sebum Production

#### 8.1.1.1 The Sebaceous Gland and Sebum Production

Seborrhea had been identified as a sine qua non for acne development as early as 1964, and sebum production was shown to be greater in acne patients compared to matched controls [2, 3].

Sebum is a mixture of lipids, most of which are synthesized de novo by the sebaceous gland, and it provides hydrophobic protection against overwetting and heat insulation in mammals. Sebum composition is remarkably species specific [4, 5]. The unique composition of human sebum has been shown in animal studies by Nikkari [4]. The lipid composition of sebum was investigated and early results showed lower quantities of triglycerides and higher alcohol esters in the surface lipids of acne patients [6] and more squalene and wax esters in acne patients than controls [7], while others have failed to demonstrate any differences in surface lipid composition [8–10]. Differential composition of lipids from different follicles was documented by using skin surface biopsies, in the study of Thielitz et al [11].

Sebum production and sebaceous gland activity is high at birth. Indeed, the neonatal adrenal gland is primarily a "fetal" adrenal gland consisting of an enlarged zona reticularis, the androgen-producing zone, and producing high levels of dehydroepiandrosterone (DHEA). Increased DHEA levels, in turn, stimulate sebaceous glands to produce sebum, until around 1 year of age when DHEA levels disappear following the decrease of the fetal adrenal gland. During adrenarche (at the age of 6–7 years in girls and 7–8 years in boys), the secretion of androgens by the adrenal glands (DHEA, DHEAS) begins to increase, and the reactivation of the sebaceous glands takes place [12].

Prof. J.S. Strauss and Prof A.M. Kligman were among the first researchers who begun working on the basic fundamentals of acne [13, 14]. Strauss and his colleagues developed a technique for measuring sebum excretion rate by absorbent paper [3, 15] and were one of the first to demonstrate the hormonal dependence of the sebaceous gland [14, 16]. Also, the work of Montagna, Ebling, Strauss, Pochi, and coworkers provided evidence that the pilosebacous unit is hormonally controlled [16–20].

The increased sebum production in acne patients may be due to an increased blood level of androgens and/or a hyper-responsiveness of the target organ (the pilosebaceous unit) to androgens [1].

Until 2000, it had been shown that the sebaceous gland possesses all the enzymes required for the conversion of DHEAS into active androgens (dihydrotestosterone, DHT) and estrogens [21–23]. These enzymes include 3β-hydroxysteroid dehydrogenase, 17β-hydrosteroid dehydrogenase, and 5α-reductase.

There are two isoenzymes of 5α-reductase, and the type 1 isoenzyme is predominant in the

sebaceous gland. This enzyme is responsible for the conversion of testosterone to the most potent androgen, DHT [24]. Increased activity of type 1 5α-reductase was shown in sebaceous glands isolated from acne-prone regions of the skin compared with nonacne-prone regions [24]. There is a differential response of sebocytes to androgens in vitro depending on the anatomic localization of their origin [25]. Facial sebocytes exhibit in vitro a stronger 5α-reductase expression than other cultured cells derived from adult skin [26] and their proliferation was stimulated by 5α-dihydrotestosterone [25]. Therefore, regional differences in the activity of this enzyme and consequently in the local production of DHT may be critical for increased sebum production and acne development [24]. Testosterone and DHT then interact with nuclear androgen receptors that have been localized to the basal layer of the sebaceous gland and the outer root sheath keratinocytes of the hair follicle [27, 28]. Moreover, the sebaceous glands of acne patients have increased number of such androgen receptors [29].

Initially, experimental animal models were used to study the pathophysiology of the sebaceous gland [30]. However, since acne is an exclusively human disease and the sebaceous gland differentiation is species specific, human models were necessary [4]. Early studies have been performed on whole human skin plugs, either been incubated in vitro [31–33] or grafted on to nude mice [34]. The isolation of viable human sebaceous glands by Kealey et al [35] and the establishment of the human sebocyte culture model in vitro by Xia et al [36] revolutionized research on sebocyte function. Thus, new insight was provided on sebocyte differentiation and sebocyte markers [37, 38]. Free fatty acids were shown to be synthesized by sebocytes without bacterial influence [37] and to play an active part on sebocyte proliferation [39].

Androgens have been proven to be one of the main factors in acne pathogenesis as they enhance follicular keratosis and influence sebum production [40–42].

The exact mechanisms by which androgens increase the size and secretion of sebaceous glands remain unknown [43]. Nevertheless, the culture of sebocytes made it possible to better study the complex pathways of androgen control on the sebaceous gland. Over the years, modifications of the technique of Xia et al. (1980) facilitated reproducible cultivation of human sebocytes in vitro [25, 26, 44–46]. Human sebocytes, however, could be maintained only for 3–6 subcultures with decreasing numbers of proliferating and increasing numbers of differentiated cells, accumulating neutral fat droplets until they died [36, 47]. This way, multiple donors were necessary in order to obtain adequate cell amounts for laboratory experiments, and even then, the short life span of the cells did not permit prolonged studies. The establishment of a human immortalized sebaceous gland cell line termed SZ95 by Zouboulis et al. overcame these constraints and opened the way for future research on the physiology of the sebaceous gland and its role in acne. The SZ95 cell line was shown to retain the morphologic, phenotypic, and functional characteristics of human sebocytes, including synthesis of the sebaceous lipids squalene, wax esters, triglycerides, and free fatty acids, even after 25–40 passages [47].

Apart from androgens, other hormones including insulin, hydrocortisone, and thyroid-stimulating hormone influence cultured sebocytes [48].

In addition, retinoids were shown to influence sebaceous gland growth and differentiation. Retinoic acid receptors γ and α and retinoid X receptor α have been detected in human sebocytes at the mRNA level [49]. Isotretinoin (13-*cis* retinoic acid) demonstrates an independent regulation of proliferation, lipid synthesis, and terminal differentiation of human sebocytes in vitro [37, 38].

#### 8.1.1.2 The Role of Androgens

The important role of androgens in acne has been substantiated by both clinical and research evidence (Table 8.1) [43].

There are studies of the role of DHEA, the major adrenal androgen, in prepubertal acne. The production of sebum correlated significantly with serum levels of DHEAS in prepubertal boys and girls. Also, the serum levels of

**Table 8.1** Evidence supporting the role of androgens in acne pathogenesis

| |
|---|
| Early acne in prepubertal patients is associated with elevated serum DHEAS |
| Men with androgen insensitivity do not produce adult levels of sebum and do not develop acne |
| Androgen excess due to hyperplasias/carcinomas of the adrenals or the gonads is often associated with the development of acne |
| Androgen excess has been reported in female patients with acne vulgaris, usually associated with other clinical signs of hyperandrogenism such as hirsutism, alopecia, or menstrual disturbances |
| Systemic administration of testosterone and DHEA increases the size and secretion of the sebaceous glands |
| Severe acne may be associated with high serum androgen levels |
| Anti-androgen therapy is beneficial in female acne |

**Table 8.2** Evidence supporting the hyper-responsiveness of the pilosebaceous unit to androgens in acne patients

| |
|---|
| Normal serum levels of testosterone and other androgens are usually found in acne patients |
| Not all sebaceous gland follicles are similarly affected by acne which predominates on the face, chest, and back, despite a constant serum level of androgens |
| The response of sebocytes to DHT and testosterone varies depending on their anatomic localization: sebocytes from the leg have a lower or no response at all to DHT and testosterone, while sebocytes from the face show a dose-dependent increase in proliferation |
| Female patients with clinical and laboratory androgen excess may have no acne |

DHEAS in prepubertal girls with comedonal or inflammatory acne were significantly higher compared with controls [50]. This data indicates that adrenal androgens are a major determinant of sebaceous gland activity during the prepubertal period [51].

Hyperplasia or carcinomas of the gonads or the adrenals, which result in elevated androgen levels, are often associated with the development of acne. Moreover, high androgen levels have been reported in patients with acne vulgaris, usually associated with other clinical signs of hyperandrogenism such as hirsutism, alopecia, or menstrual disturbances [40, 42, 52–58]. Conversely, androgen excess has been found in women with persistent or severe acne without other clinical evidence of hyperandrogenism [54, 59].

Additional evidence supporting the role of androgens in acne includes the findings that androgen-insensitive men (with nonfunctional androgen receptors) do not produce adult levels of sebum and do not develop acne [60] and that the systemic administration of testosterone or DHEA increases the size and secretion of sebaceous glands [61]. Also, anti-androgen therapy is highly successful in the management of female acne, highlighting the key role of androgens in acne etiology [62, 63].

As already mentioned, the increased sebum production in acne patients may be due to an increased blood level of androgens and/or a hyperresponsiveness of the target organ (the pilosebaceous unit) to androgens. There are many studies showing elevation of free testosterone, DHEA, and androstenedione [54, 64–66], although most patients with acne do not suffer from endocrinologic abnormalities. Also, the severity of acne has not been correlated with elevated androgen levels [67]. This raises the question of whether there is an increased local production of androgen within the sebaceous gland of patients with acne, which may then influence sebum production [68]. It was found that skin with acne converted testosterone to DHT at a rate 2–20 times greater than normal skin.

The end-organ sensitivity of the pilosebaceous unit to androgens could explain the normal serum levels of testosterone and other androgens usually found in acne patients (Table 8.2) [13, 68]. Also, not all sebaceous gland follicles are similarly affected by acne which predominates on the face, chest, and back, despite a constant serum level of androgens [69]. What is more, the response of sebocytes to DHT and testosterone varies depending on their anatomic localization. Thus, sebocytes from the leg have a lower or no response at all to DHT and testosterone, while sebocytes from the face show a dose-dependent increase in proliferation [25]. In support of this findings, female patients with clinical and laboratory hyperandrogenism may have no acne [69].

Although the role of androgens in the pathogenesis of acne cannot be refuted, an association

between acne severity and the degree of androgen excess has not been consistently reported. In 1989, Levell et al. showed a weak relationship between total acne count and level of free DHT, but no correlation between other androgens or SHBG levels and acne severity [70]. Walton et al. showed a positive correlation between levels of androstenedione and DHEAS and acne score and a negative correlation between SHBG levels and acne score [71]. Schmidt et al. also showed a positive correlation between androstenedione and acne severity [72]. On the other hand, Sheehan-Dare et al. demonstrated no relationship between clinical markers of androgenicity (excessive body hair, irregular menstrual bleeding, alopecia) and acne severity [73]. Also, the severity of acne in adult women (>17 years old) was not positively correlated with any clinical or laboratory markers of androgenicity in the study of Cibula et al [67].

### 8.1.2 Follicular Hyperkeratinization

Ductal hypercornification may be due to an increased rate of keratinocyte proliferation and/or a reduced separation of ductal corneocytes due to increased cohesion between keratinocytes [13, 74, 75].

The microcomedone is the initial lesion in acne and may be present in normal-appearing skin of acne patients, as has been demonstrated by biopsies [76]. Keratinocyte hyperproliferation of both comedones and microcomedones compared with normal follicles has been demonstrated immunohistochemically by the use of the antibody Ki-67. Also, cellular proliferation was greater in normal follicles from acne-affected areas (acne-prone follicles) compared with areas not affected by acne (not acne prone) [74].

Ductal hypercornification centers on the interplay of various factors, including local androgens, retinoids, local cytokines, abnormalities of the sebaceous lipids, and comedone cycling.

Certain sebaceous lipids, such as squalene oxide and free fatty acids, are higher in acne patients than controls and may contribute to comedone formation [77, 78]. Similarly, a deficiency of linoleic acid may be an additional comedogenic factor [79, 80]. In addition, local cytokines may play a role, and interleukin-1α (IL-1 α) has been shown in vitro to cause comedone formation, while this process was inhibited by the addition of IL-1α receptor antagonist to the growth medium. It was suggested that changes in sebum excretion or composition may result in the production of IL-1 by follicular corneocytes, thus influencing comedogenesis [81]. These findings provide some evidence for the involvement of endogenous inflammation processes in acne initiation [5].

The potential role of androgens in controlling ductal hyperproliferation has been studied. It has been reported that keratinocytes are capable of converting testosterone to DHT, as 5α-reductase type 1 activity was demonstrated in infrainfundibular segments of follicles. Activity of this enzyme varies within regions of the pilosebaceous unit. Infrainfundibular keratinocytes demonstrate greater activity of this enzyme compared to interfollicular epidermal cells, thus showing greater capacity for producing androgens compared with the epidermis. Androgens in turn may influence follicular hyeprkeratinization [82, 83]. This data is supported by the clinical observation that anti-androgen therapy with combined oral contraceptives reduces the number of comedones [84].

Both oral and topical retinoids suppress comedogenesis by 98 and 60 %, respectively, after 4 months of treatment [85–87].

Comedo cycling may be an important factor in the development and resolution of comedogenesis and it provides an explanation to the clinical observation that many open and closed comedones resolve spontaneously [85]. Pilosebaceous follicles and comedones have showed different expression of cycling cells and proliferation markers, suggesting that the duct may also undergo cycling like the hair follicle [88].

There was no convincing evidence until 2000 to support a role for *Propionibacterium acnes* (*P. acnes*) in comedogenesis; formalin-killed *P. acnes* cells did not induce normal human keratinocytes to produce IL-1α in vitro [89, 90].

### 8.1.3 *Propionibacterium acnes* and Inflammation

*Propionibacterium acnes* (*P. acnes*) is a Gram-positive anaerobic bacterium found in the normal human cutaneous flora. When it was first isolated in 1896, it was thought to be the direct cause of acne. However, in the early 1960s the role of *P. acnes* in causing acne was refuted as it was shown that it also resides on normal human skin and that surface *P. acnes* levels were similar between patients with acne and controls [91, 92]. Also, numbers of viable *P. acnes* within follicles do not correlate with the severity of inflammation and some inflamed lesions do not contain viable bacteria [93]. A possible explanation was offered as early as 1978; it was proposed that specific changes in the follicular microenvironment may allow follicular colonization by *P. acnes* [94]. Later, a key role was attributed to *P. acnes* in acne pathogenesis when antibiotics that reduced skin surface *P. acnes* (such as erythromycin and clindamycin) were shown to clinically improve acne [92, 94]. Moreover, the fact that clinical failure of oral erythromycin was associated with the presence of resistant *P. acnes* strains in some patients delineated the key role of this bacterium in acne [95, 96]. Nevertheless, antibiotics possess anti-inflammatory properties that may, at least in part, account for their effectiveness in acne [97]. The aforementioned evidence suggested that *P. acnes* is not the direct cause of acne, but a significant contributing factor to the inflammatory stages of the disease.

*P. acnes* secretes various biologically active molecules like enzymes and chemotactic factors, which play a role in the initiation and perpetuation of the local inflammatory response. Also, it stimulates monocytes to produce proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-1β, and IL-8 [98].

The exact nature and sequence of events in acne initiation has been a matter of debate. Inflammation has been classically considered as a secondary event. Evidence published until 2000 supported that inflammatory lesions arise from non-inflamed comedones, which are the clinical manifestation of abnormal ductal hypercornification [99]. However, as already mentioned, a role of the proinflammatory cytokine IL-1α in comedone formation has been demonstrated in vitro [81]. In vivo, comedones contain enough IL-1α activity to initiate a nonspecific inflammatory response if released into the dermis [100]. This data raises the question of whether inflammatory events occur pre- or post-hyperproliferation.

Another controversial issue is whether the initial cellular infiltrate is neutrophilic or lymphocytic.

In 1974, Kligman's study demonstrated that the initial infiltrate consisted of neutrophils and was followed by microscopic rupture of the follicle wall and subsequent formation of clinically apparent inflammatory lesions [13, 76]. *P. acnes* produces neutrophil chemoattractants that diffuse through the follicle wall and trigger the inflammation process. Moreover, it was proposed that inflammation results from a type IV hypersensitivity reaction to *P. acnes* or other comedonal components after the release of reactive oxygen radicals and enzymes by neutrophils and rupture of the sebaceous follicle wall [101, 102].

On the other hand, studies investigating early inflammatory events in acne lesion showed an initial CD4+ lymphocytic infiltrate as a primary inflammatory event [99, 103]. Also, a 1998 study concluded that the inflammatory cell and cytokine profile in papules is that of a delayed cellular reaction to an antigen or antigens, the nature of which is yet uncertain [103].

Until 2000, although several lines of evidence support the direct role of *P. acnes* in acne, little is still known about the mechanism by which this microorganism contributes to the pathogenesis of the disease.

## 8.2 The Role of Cutaneous Neuropeptides: Neurogenic Inflammation

Up to 2000, there is increasing evidence that the cutaneous sensory nervous system innervates multiple cell types and plays an important role in inflammation [104, 105]. After the activation of peripheral nerve endings by various stress-sensing stimuli, neuropeptides are released and result in

changes collectively termed as neurogenic inflammation [106, 107]. Neuropeptides, such as substance P, are produced from sensory neurons or from keratinocytes and mast cells in the skin [107].

Also, the presence and activity of proopiomelanocortin, corticotropin-releasing hormone, and corticotropin-releasing hormone receptor genes has been demonstrated in human skin and sebaceous glands [108, 109].

### Conclusion

Fascinating new data elucidating the pathophysiology of acne has recently been published and will be discussed in detail elsewhere in this book. However, none of these achievements would have been possible without the work done by predecessors.

Many questions on acne pathogenesis and resolution still remain unanswered. As history can teach us many lessons and techniques, both in the clinic and the laboratory, the profound knowledge of the past is a prerequisite for research and advancement in the future.

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# The Role of Hyperkeratinization

9

Ichiro Kurokawa

## Contents



**Core Message**

- Hyperkeratinization is the initial event in comedogenesis.
- Microcomedones originate from hyperkeratinization of the infundibulum and sebaceous duct.
- Interleukin (IL)-1α may contribute to hyperkeratinization.
- Disorder of terminal differentiation of infundibular keratinocytes, hormonal factors, and *Propionibacterium acnes* products may be responsible for abnormal keratinization.
- Retinoids control local cytokine modulation in acne vulgaris.

A crucial factor of comedogenesis is hyperkeratinization in the infundibulum and sebaceous duct. The initial event (early phase) in acne vulgaris is hyperkeratinization in the infundibulum. Although there have been many intensive studies of the pathogenesis of hyperkeratinization in infundibulum and sebaceous duct, the process of hyperkeratinization remains unclear. The mechanism of this hyperkeratinization is described in its clinical, histological, and etiological aspects below.

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## 9.1 Clinical Significance of Hyperkeratinization in Acne Vulgaris

"Normal" looking skin at acne sites is affected subclinically by microcomedones [1]. The microcomedone is defined as an early distension of the follicular walls by corneocytes. In clinically not affected skin in acne-prone patients, skin biopsy demonstrates microcomedones in 28 % of the follicles [1]. Consequently, microcomedones precede visible closed comedones.

The comedone is the initial primary lesion of acne and is an impaction of horny material within the sebaceous follicles. In acne vulgaris, only the infrainfundibulum is involved in comedo formation, resulting in closed comedone as the initial comedone. Blockage of sebum flow and progressive enlargement of microcomedones give rise to visible closed comedone with closed follicular orifice partially followed by open comedone with dilated follicular orifice [2]. During comedogenesis, two distinct factors are considered: abnormal cellular differentiation and passive diffusion of lipids from sebaceous follicles.

## 9.2 Histological Findings in Normal Skin and Acne Vulgaris

### 9.2.1 Normal Pilosebaceous Unit and Microcomedo

To understand the pathogenesis of acne, it is important to be familiar with the anatomical structure of the pilosebaceous unit. Plewig and Kligman [3] have classified hair follicles into three types:

1. Vellus hair follicles: tiny short hairs with small sebaceous gland
2. Sebaceous follicles: tiny short hairs with multi-lobulated large sebaceous glands and dilated large follicular channels
3. Terminal hair follicles: thick firm long hairs with small sebaceous glands

Acne usually develops in sebaceous follicles and, therefore, the usual regions of acne vulgaris are the face, breast, and upper back where sebaceous follicles are abundant. The sebaceous glands connect to a long infundibulum with profound depth. In addition, the follicular wall of the sebaceous follicles is thin, suggesting that it is very permeable. The infundibulum is divided into two portions: acroinfundibulum and infrainfundibulum. The acroinfundibulum is continuous to the interfollicular epidermis and has identical characteristics with the interfollicular epidermis. The infrainfundibulum has decreased desmosomes and tonofilaments, and the granular layers and horny layers are thinner [3]. Cohesion between the corneocytes is loose and there is a tendency to shed into follicular channels. Anatomically, the infundibulum and sebaceous duct are classified into three types of cells: superficial cells facing the follicular channels, intermediate cells, and basal cells [4].

Histologically, hyperkeratinization in the infrainfundibulum is first observed in microcomedones [3, 4]. Peculiar changes in infundibular keratinization result in comedone formation. The epithelium is acanthotic with hypergranulosis and producing laminated corneocytes. Decreased dehiscence of corneocytes causes them to stick together tightly like bricks and form a solid compact wax [3]. Occasionally, the sebaceous duct is also hyperkeratotic [3]. In addition, dedifferentiating sebaceous lobules are observed, the sebaceous acini may regress, and sebaceous glands may disappear [3].

### 9.2.2 Closed and Open Comedone

#### 9.2.2.1 Light microscopy

Light microscopy reveals multilaminated, sticky, coherent keratinocytes in the infundibulum [5]. Hyperkeratinization of the follicle is believed to be due to hyperproliferation of infundibular and ductal keratinocytes and reduced desquamation (a reduced separation of infundibular or ductal corneocytes). The pattern of keratinization is retention hyperkeratosis. The process

of desquamation is altered. Dense colonies of *Propionibacterium acnes* (*P. acnes*) are present. The horny squamae are densely packed. The hyperkeratinization may be different in closed and open comedones.

#### 9.2.2.2 Electron microscopy

Electron microscopic studies have shown that keratinocytes in the infundibulum and sebaceous duct have more desmosomes and tonofilaments than in normal skin [3, 5, 6].

In acne lesions, the stratum corneum becomes thicker and cohesive so that many laminated layers accumulate. Lipid droplets accumulate in horny cells. The keratohyalin granules are large, prominent, and abundant in size and in number [3, 5, 6]. Membrane coating granules are markedly reduced in number in the infundibulum when comedone is formed, suggesting that shedding of corneocytes becomes limited. Membrane coating granules are related to barrier permeability, but its significance is still unclear. The horny cells do not slough off and become cohesive and occlude follicular channels with dense keratinous plug. Failure of corneocytes to slough produces retention hyperkeratosis. Cell-to-cell adhesion via desmosomes in the stratum corneum and in the stratum corneum may be attributable to abnormal slough off. Infundibular cells contain lipid droplets and lamellar granules decrease due to differentiation [5].

#### 9.2.2.3 Immunohistochemical Studies

There have been numerous immunohistochemical studies to elucidate the pathogenesis of abnormal keratinization in the infundibulum and sebaceous duct.

Filaggrin, a filament aggregating protein, which is a major component of keratohyaline granules, is a marker of terminal differentiation of corneocytes [7]. Filaggrin expression is more intense in the infundibulum and sebaceous duct in acne vulgaris than in normal skin [4]. Not only superficial cells but also intermediate cells are labeled for filaggrin, suggesting that infundibular keratinocytes in acne lesions exhibit an abnormal terminal keratinization [4] (Fig. 9.1).

In regard to the pathogenesis of closed and open comedones, filaggrin expression is different in the two types of comedones in nevus comedonicus [8]. Filaggrin was involved in closed comedone, suggesting that disorder of terminal differentiation plays a role in the pathogenesis of abnormal keratinization in comedogenesis. The pathogenesis of closed and open comedones is still under investigation.

In acne vulgaris, epidermal cysts are occasionally observed. In epidermal cysts, the stage of terminal keratinization is also disturbed by the increased expression of filaggrin [9].

Ki-67, a nuclear antigen marker expressed by active cycling cells, is expressed in basal keratinocytes in the infundibulum in comedone in contrast to the normal skin [10]. In addition, expression of keratins 6 and 16, markers of phenotypic hyperproliferation with increased cell turnover, is found in ductal keratinocytes in acne lesions [11].

Concerning aberrant desquamation of cell-to-cell adhesion, desmosomes play an important role in adhesion between adjacent keratinocytes. Desmosomal antigens have been studied in healthy and acne-involved skin, but no significant differences were found [12]. There is increased expression in tenascin-C, an extracellular matrix protein glycoprotein, which migrates and increases in concentration in acne lesions [13].

## 9.3 Etiological Factors

The etiology of hyperkeratinization is still unclear. Moreover, several etiologic factors have been reported.

### 9.3.1 Cytokine

The pro-inflammatory cytokine IL-1α is associated with *P. acnes* in the role of hyperkeratinization in acne vulgaris [14]. Antimicrobials lead to a reduction in the number of comedones [13]. High levels of active IL-1α expressed by follicular keratinocytes have been reported [15]. Increased IL-1α activity in comedonal

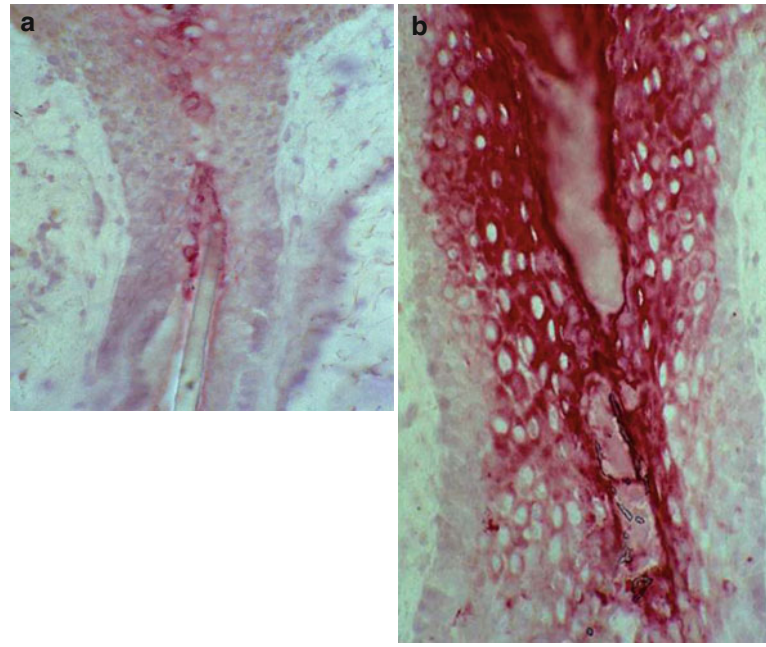


**Fig. 9.1** Alkaline phophatase and anti-alkaline phosphatase (APAAP) labeling in the infundibulum with a monoclonal antibody against filaggrin. (**a**) Normal skin: the granular layer is only positive. (**b**) Acne-involved skin: some of the intermediate cells are intensely stained and the reaction of the granular cells is the most intense

acne occurs in comedones. In acne lesions, IL-1 may contribute to keratinocyte proliferation, and IL-1α has been implicated in hyperkeratinization [15]. Human follicular keratinocytes demonstrate hyperproliferation and microcomedo formation. Comedones have been produced experimentally under the influence of IL-1α [16]: In a model of comedone formation, IL-1α activity stimulated abnormal desquamation, causing failure of integration of the follicular wall in organ culture in vitro. This process was inhibited by IL-1 receptor antagonist [16]. IL-1α may cause hyperkeratinization by a direct effect on infundibular keratinocytes involving signal transduction through IL-1 receptor [2, 17]. Changes in sebum composition may induce the release of IL-1α [2, 17]. In general aspects the pro-inflammatory cytokine IL-1α is a signal for terminal keratinocyte differentiation.

### 9.3.2 Hormonal Factors

An essential factor in acne vulgaris is androgen stimulation. Androgen plays an important role in ductal hyperkeratinization [1–3]. Dermal components of the pilosebaceous duct convert testosterone to 5α-dihydrotestosterone (DHT). DHT stimulates keratinocyte proliferation in the infrainfundibulum and the sebaceous duct [1, 18, 19]. In acne lesions, the activity of 5α-reductase, the enzyme which transforms testosterone to DHT, is higher than in normal skin [19].

### 9.3.3 Lipid Composition in Sebum

A change in sebum composition is also important for acne vulgaris. In particular, the essential fatty acid linoleic acid plays a key role. Low levels of linoleic acid alter the differentiation of sebaceous gland cells and result in hyperkeratosis of the sebaceous duct [20] with subsequent comedogenesis. The proliferation of follicular infundibular keratinocytes is also regulated by linoleic acid. Subnormal linoleic acid levels induce follicular hyperkeratinization and produce pro-inflammatory cytokines [20].

Topically applied linoleic acid is comedolytic and reduces the size of microcomedone [21]. Other lipids, such as squalene and their peroxides, and low ceramides may be involved in acne [22]. Squalene peroxides produced by *P. acnes* induce hyperkeratosis in the infundibulum [22].

Moreover, *P. acnes* produces lipases, which hydrolyze sebum triglycerides and subsequently give rise to free fatty acids. Free fatty acids may also derive from another, still unknown, comedogenetic factor [3, 23].

### 9.3.4 *P. acnes*

*P. acnes* has only recently been related to hyperkeratinization [1]. *P. acnes* extracts have been implicated in not only the development of inflammatory lesions, but also the formation of the microcomedones [24]. *P. acnes* extracts have been shown to induce filaggrin expression on the epidermis (suprabasal) in an explant skin model [24]. *P. acnes*, therefore, can modulate the terminal phase of differentiation of keratinocytes.

### 9.3.5 Integrins

Integrins play an important role in modifying the differentiation and proliferation of keratinocytes [25]. *P. acnes* extracts induced significant β1-integrin expression on both proliferating and differentiated keratinocytes [24].

### 9.3.6 Hyperproliferation

Hyperproliferating keratinocytes are observed in acne vulgaris. The $^{3}$H-thymidine uptake of comedones is increased [26].

### 9.3.7 Peroxisome Proliferator-Activated Receptors

Acne may be mediated by interaction of androgens with Peroxisome Proliferator-Activated Receptor (PPAR), which regulate sebocyte differentiation and proliferation. PPAR may induce hyperseborrhea and epithelial hyperproliferation, resulting in the hyperkaratinization observed in acne vulgaris [27].

### 9.3.8 Dedifferentiation of Sebocytes

IL-1, intercellular adhesion molecule-1 (ICAM-1), TNF-α, and IFN-γ induce dedifferentiation of human sebocytes into a keratinocyte-like phenotype, resulting in hyperkeratosis in the infundibulum in acne vulgaris [28].

### 9.3.9 Animal Models

Experimental comedones can be produced in rabbit ears by the application of comedogenic agents such as squalene and oleic acid [29].

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# The Role of the Sebaceous Gland

# 10

Christos C. Zouboulis and Evgenia Makrantonaki

## Contents



**Core Messages**

- The sebaceous gland cell is a key player in the pathogenesis of acne.
- Increased sebum excretion and alteration of lipid composition contribute to acne.
- Sex steroids and growth factors play a profound role in the regulation of sebum production.
- Emotional stress induces central and local expression of CRH and other neuropeptides, which trigger inflammation.
- The sebaceous gland cell possesses the enzyme machinery of the PG and LT pathway.
- *P. acnes* may produce proteins, which become active via binding and activation of TLR. The latter stimulate the synthesis of antimicrobial peptides and lipids.

## 10.1 Introduction

The pathogenesis of acne, the most common skin disorder, which manifests in the pilosebaceous follicle, is attributed to multiple factors such as increased sebum production, alteration of the quality of sebum lipids, inflammatory processes, dysregulation of the hormone microenvironment, interaction with neuropeptides, follicular hyperkeratinisation and the proliferation of *P. acnes*

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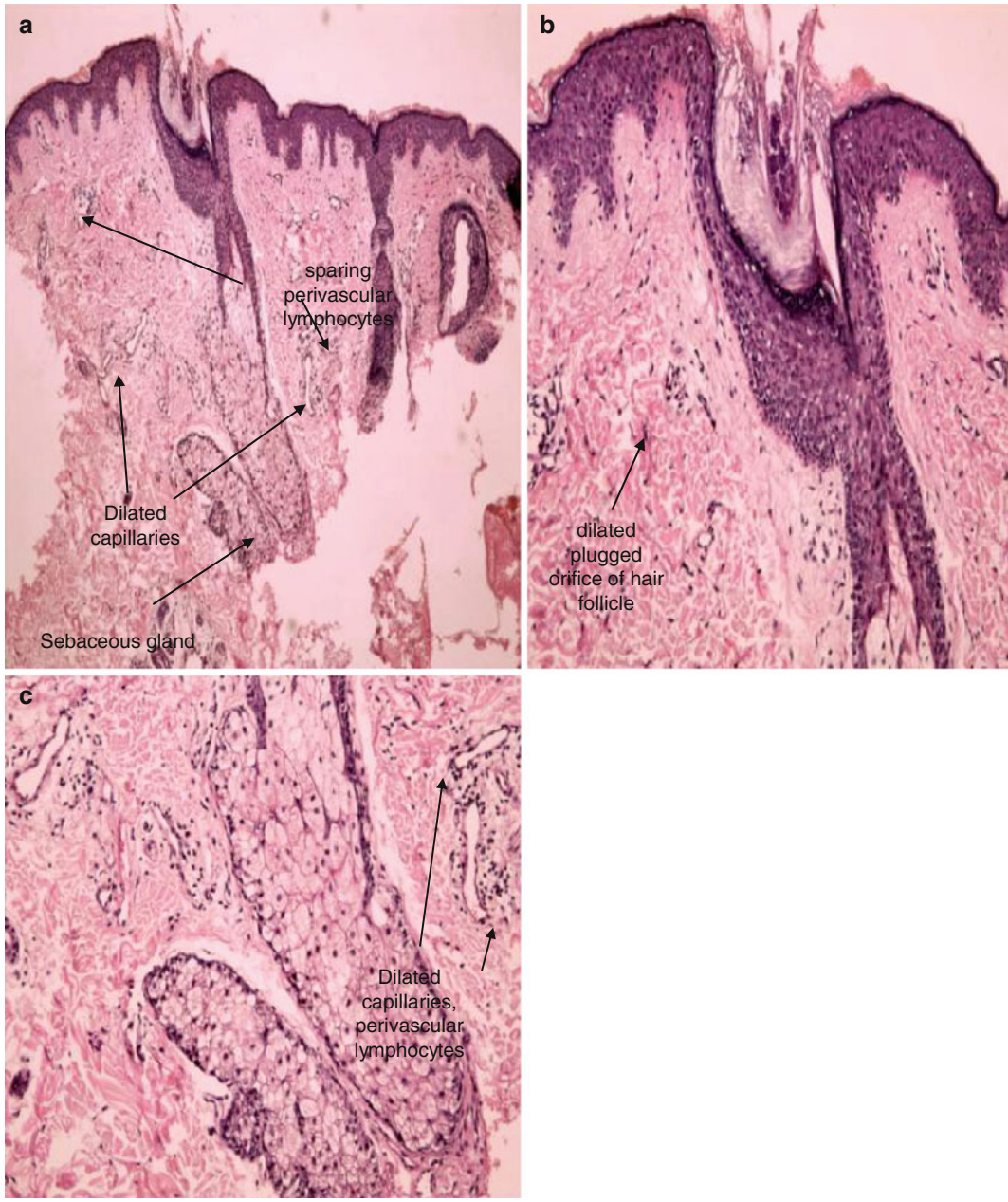


**Fig. 10.1** Pilosebaceous unit in the face skin of acne patients. Faintly hypertrophic sebaceous gland. Dilated capillaries and perivascular lymphocytes (**a**, **c**) are early sings of the inflammatory process in acne-involved skin. The dilated plugged orifice of hair follicle is a sign of acne comedone (**b**) (the photos were kindly contributed by Dr. Ruta Ganceviciene)

within the follicle (Fig. 10.1). In particular, the sebaceous gland plays an exquisite role in the initiation of the disease [1].

*Sebaceous glands* or *holocrine glands* are found over the entire surface of the body except the palms and the soles. They are largest and most concentrated in the face and scalp where they are the sites of origin of acne. The normal function of sebaceous glands is to produce and secrete sebum, a group of complex oils including triglycerides

and fatty acid breakdown products, wax esters, squalene, cholesterol esters and cholesterol [2–5]. Sebum lubricates the skin to protect against friction and makes it more impervious to moisture. Furthermore, the sebaceous gland transports antioxidants in and on the skin and exhibits a natural light protective activity. It possesses an innate antibacterial activity and has a pro- and anti-inflammatory function. It can regulate the activity of xenobiotics and is actively involved in the wound healing process [6].

In the last years, acne research has made a remarkable progress in understanding the mechanisms involved in the pathogenesis of the disease by using cell culture models and new molecular techniques. Mammal sebocytes and sebocyte-like cells (human, mouse, hamster and rat) and human sebaceous gland cell lines (SZ95, SEB-1, Seb-E6E7) [7–9] have been used in monolayer cultures as models to study specific functions involved in development, growth and differentiation of sebaceous gland cells. More complex culture systems, including three-dimensional models, are under development.

## 10.2 Sebum and Acne

Increased sebum excretion, alteration of lipid composition and the oxidant/antioxidant ratio characteristic of the skin surface lipids are major concurrent events associated with the development of acne [6]. If sebum interferes with the process of follicular keratinisation in the pilosebaceous unit, pore blockage may occur, contributing to lesion formation and acne. However, seborrhoea per se is not considered to be the only responsible factor for the development of acne, as demonstrated by the success of treatment with agents with no effect on sebum secretion rate that can inhibit the inflammatory process, such as antibiotics, topical retinoids, azelaic acid and benzoyl peroxide [10]. The composition of the produced lipids is also of great importance. Lower essential fatty acid levels were found in wax esters in twins with acne rather than in twins with no acne [11]. Moreover, low levels of linoleic acid have been observed in skin surface lipids of acne patients [12]. Evidence suggests that diet may be an important source of substrate for the synthesis of sebaceous lipids [13]. This notion is supported also by the observation that sebum contains linoleic acid, an essential fatty acid that cannot be synthesised in vivo and therefore must be obtained from the diet. It has recently been hypothesised that low glycaemic load diets may influence sebum production based on the beneficial endocrine effects of these diets [14].

On the other hand, extreme caloric restriction dramatically decreases the sebum excretion rate and these changes can be reversed when a normal diet is resumed [15, 16]. Other studies have demonstrated that increased consumption of dietary fat or carbohydrate increases sebum production and modifications to the type of carbohydrate can also alter sebum composition [17]. Typical Western diet, comprised of milk and hyperglycaemic foods, may have potentiating effects on serum insulin and insulin-like growth factor-I (IGF-I) levels, thereby promoting the development of acne [18].

Another hallmark of sebum in acne patients is the presence of lipoperoxides, mainly due to the peroxidation of squalene and a decrease in the level of vitamin E, the major sebum antioxidant [19]. Both lipoperoxides and monounsaturated fatty acid (MUFAs) are capable of inducing alteration in keratinocyte proliferation and differentiation, whereas peroxides are capable of inducing production of pro-inflammatory cytokines and activation of peroxisome proliferator-activated receptors (PPARs) [14, 19].

The biological function of sebocytes is further regulated by several factors including ligands of receptors expressed in sebocytes, such as androgens and oestrogens, PPAR ligands and neuropeptides, liver-X receptor (LXR) ligands, histamines, retinoids and vitamin D. The ligand–receptor complexes activate pathways involving cell proliferation, differentiation, lipogenesis, hormone metabolism and cytokine and chemokine release [20] (Fig. 10.2).

LXRs which are members of the nuclear receptor superfamily and play a critical role in cholesterol homeostasis and lipid metabolism

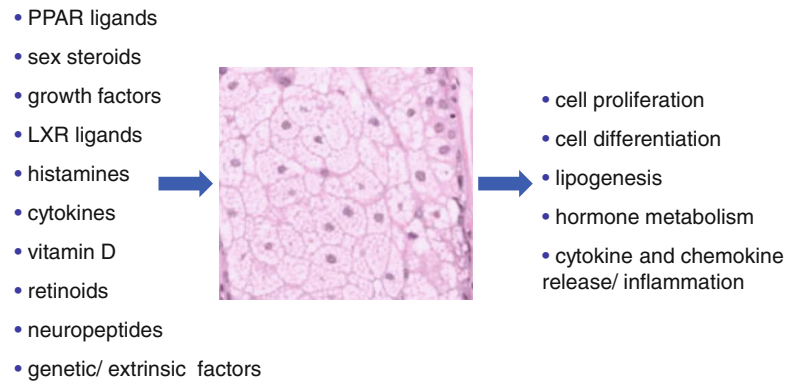


**Fig. 10.2** Regulation of the biological function of human sebaceous gland cells. Schematic overview (*PPARs* peroxisome proliferator-activated receptors, *LXR* liver X receptors)

have been documented to regulate lipid synthesis in the immortalised human sebaceous gland cell line SZ95. Treatment of SZ95 sebocytes with LXR ligands such as TO901317 or 22(R)-hydroxycholesterol enhanced accumulation of lipid droplets in the cells which could be explained through induction of the expression of the LXRalpha receptor and known LXR targets, such as fatty acid synthase and sterol regulatory binding protein-1 [21, 22].

On the other hand, sebaceous function can be also significantly modified by histamines and, conversely, antihistamines. Diphenhydramine (DPH), an H-1 receptor antagonist, significantly decreases squalene levels in human sebaceous gland cells as determined by means of high-performance liquid chromatography. These data were further verified by the identification of histamine receptors histamine-1 receptor (H-1 receptor) in human sebaceous glands [23].

Retinoids are also suggested to influence the biological function of sebocytes. Retinoic acid receptors (RAR; isotypes α and γ) and retinoid X receptors (RXR; isotypes α, β, γ) are expressed in human sebocytes [24]. The natural ligands for RAR and RXR are atRA and 9-*cis* retinoic acid. In SZ95 sebocytes 13-*cis* retinoic acid may unfold its action through a marked isomerisation to all-*trans* retinoic acid. All three compounds all-*trans* retinoic acid, 13-*cis* retinoic acid and 9-*cis* retinoic acid exhibit anti-proliferative effects [25] and inhibit sebocyte differentiation and lipid synthesis [26]. RXR agonists stimulate sebocyte differentiation and proliferation. The RXR agonist rexinoid in combination with the specific PPAR agonists, WY 14643, troglitazone and cabaprostacyclin, affects differentiation and growth in cultured primary sebocyte-like rat preputial cells [27].

The enzymatic machinery for the local synthesis and metabolism of 1, 25-dihydroxyvitamin D (3) [1,25(OH)(2)D(3), calcitriol] has been also investigated in human sebocytes. Vitamin D receptor (VDR), vitamin D-25-hydroxylase (25 OHase), 25-hydroxyvitamin D-1alpha-hydroxylase (1 alphaOHase) and 1, 25-dihydroxyvitamin D-24-hydroxylase (24 OHase) are expressed in SZ95 sebocytes in vitro. Furthermore, incubation of SZ95 sebocytes with 1,25(OH)(2)D(3) leads to a dose-dependent modulation of cell proliferation, cell cycle regulation, lipid content and interleukin-6/interleukin-8 secretion in vitro [28]. In hamster auricular sebocytes while EGF and atRA can decrease the intracellular accumulation of triglycerides and free fatty acids in the cells, 1alpha, 25-dihydroxyvitamin D3 decreases the triglyceride level but augments the accumulation of wax esters. No difference has been detected in the level of cholesterol after the above treatments [29].

## 10.3 Effects of Hormones on Sebocytes

### 10.3.1 Sex Steroids

Several studies have demonstrated that there is an association between local overproduction of

active androgens and acne. Acne patients produced higher rates of testosterone and 5α-DHT in their skin than healthy individuals [30]. High testosterone levels have been implicated with enhanced sebaceous gland activity in humans [31, 32] and consequently with diseases marked by hyperseborrhea, such as acne vulgaris. However, only a few patients with androgenic disorders exhibit hyperandrogenemia, an observation which indicates the predominance of peripheral tissue events for the occurrence of clinical signs [33].

Enhanced sebaceous gland activity is attributed to the potent androgen 5α-dihydrotestosterone (5α-DHT) [6] as sebaceous gland cells possess all necessary enzymes for conversion of testosterone to 5α-DHT [34]. The isozyme 5α-reductase type I, which catalyses the conversion from testosterone to 5α-DHT in peripheral tissues by a NADPH-dependent reaction, is expressed predominantly in skin. It is present in the cytoplasm and cell membrane compartment in skin cells [35] and particularly in facial sebocytes [34], illustrating the key role of sebaceous gland cells in androgen metabolism.

The effects of testosterone and 5α-DHT are mediated by binding to the nuclear androgen receptor (AR), also expressed in human sebaceous gland cells [36]. AR is a member of the steroid superfamily of ligand-dependent transcription factors. 5α-DHT binds to the AR with greater affinity than testosterone and the 5α-DHT/androgen receptor complex appears to be more stable [37] and, therefore, more effective.

In contrast to the in vivo observations, in vitro experiments with human sebocytes have shown that testosterone affects proliferation in a dose-dependent manner [9, 38] but not lipid synthesis [39, 40]. This contradiction has led to the assumption that cofactors may be required for the induction of the entire so-called androgenic influence of the sebaceous gland [41]. Current research has indicated that PPARs and their ligands may be the primary candidates [39, 40]. PPARs regulate multiple lipid metabolism genes in mitochondria, peroxisomes and microsomes, all prominent in sebocyte cytoplasm [39, 40].

Indeed, we have previously demonstrated the interaction of testosterone with PPAR ligands in inducing differentiation of human sebaceous gland cells and lipid synthesis [42]. PPARα is the most important PPAR that regulates lipid synthesis and inflammation [41, 43]. In addition, PPAR-α, -δ, -γ1 and -γ2 have been shown to be expressed at mRNA and protein levels in SZ95 sebocytes [39].

Dehydroepiandrosterone (DHEA) has been also shown to regulate sebum production especially in postmenopausal women [44]. Consequently, several researchers have suggested the use of DHEA as an anti-ageing agent [45, 46]. However, in in vitro experiments DHEA has been shown to have no direct effect on the biological activity of human sebocytes. Substitution with DHEA in elderly persons is accompanied by a small increase of testosterone and oestradiol, which may indeed yield an explanation of the clinical change demonstrated [44], suggesting that the action of DHEA may be implemented through indirect pathways.

### 10.3.2 Growth Factors

Growth hormone (GH) activity is considered to be mainly attributed to IGFs, but GH has also been shown to exhibit direct effects on human skin cells [47]. The increased serum GH levels in acromegaly are associated with enhanced sebum secretion [48], an observation that could be confirmed by GH treatment of human SZ95 sebocytes in vitro [49]. In acne vulgaris, increased sebum production peaks in mid-adolescence at a time that GH and IGF-I reach their highest serum levels [50]. In mini rats, suppression of GH gene expression by an antisense transgene leads to thinner skin with less collagen and increase of subcutaneous adipose tissue and also to small-sized sebaceous glands [51].

Increased serum levels of IGF-I have been observed in adult women and men with acne and the number of total acne lesions, inflammatory lesions, serum levels of dihydrotestosterone (DHT) and dehydroepiandrosterone sulphate (DHEAS), each correlated with serum IGF-I levels in women with acne [52, 53]. A correlation between the mean facial sebum excretion rate

and serum IGF-I levels has been demonstrated in postadolescent acne patients [54]. IGF-I has been localised to the peripheral cells of sebaceous glands in the rat [55], while in human skin the strongest expression of IGF-I protein has been found in maturing sebocytes and suprabasal cells of sebaceous ducts [56]. The expression of IGF-I receptor mRNA is the strongest in basal cells of sebaceous glands and immature sebocytes, whereas IGF-I receptor protein expression was uniform and intense in all regions of the gland [56]. In animal studies, IGF-I has been shown to stimulate sebocyte differentiation in vitro especially in combination with GH [50], while in human keratinocytes it acts as a mitogen [57]. On the other hand, in humans, IGF-I plays a key role in the induction of lipid synthesis in human sebocytes [49, 58]. In SEB-1 sebocytes, IGF-I increases lipogenesis by the induction of *sterol response element-binding protein-1* (SREBP-1) [58] through activation of PI3K/Akt and MAPK/ERK signal transduction pathway [59]. SREBP-1 preferentially regulates genes of fatty acid synthesis [59]. In the hamster ear sebaceous model, androgens rapidly induce the expression of SREBP-1 [60]. In addition, an interaction between the IGF-I and oestradiol signalling pathway has been described in human SZ95 sebocytes, implicating that oestrogens may have an indirect effect on the pathogenesis of acne [49].

Recent data suggest that incubation of human sebaceous gland cells with a hormone mixture consisting of growth factors and sex steroids at age-specific levels may alter the biological activity of the cells by regulating their transcriptome and thus illustrate the importance of the hormone environment for cell function [61]. Human SZ95 sebocytes treated with hormone levels that can be found in 60-year-old women produce less lipids than sebocytes treated with a hormone mixture representing that found in serum of 20-year-old women [61]. Gene expression profiling via cDNA microarray between SZ95 sebocytes under the 20- and 60-year-old hormone mixture detected differentially expressed genes, which are involved in biological processes such as DNA repair and stability, mitochondrial function, oxidative stress, cell cycle and apoptosis, ubiquitin-induced proteolysis and transcriptional regulation. The most significantly altered signalling pathway was that of transforming growth factor-β (TGF-β). A disturbed function of this cascade has been also associated with tumourigenesis, i.e. in pancreatic, prostate, intestine, breast and uterine cancer. Interestingly, genes expressed in signalling pathways operative in age-associated diseases such as Huntington's disease, dentatorubral-pallidoluysian atrophy and amyotrophic lateral sclerosis were also identified. These data demonstrate that hormones interact in a complex fashion, and sebocytes may be affected to a large extent by the changes in their circulating blood levels with age [61].

## 10.4 Effects of Neuropeptides on Sebocytes

Neuropeptides are a heterogeneous group of biologically active peptides that are present in neurons of both the central and peripheral nervous system. However, human skin and in particular the human sebaceous gland have been shown to express functional receptors for neuropeptides, such as corticotropin-releasing hormone (CRH), melanocortins, β-endorphin, vasoactive intestinal polypeptide, neuropeptide (NP) Y and calcitonin gene-related peptide. These receptors modulate the production of inflammatory cytokines, proliferation, differentiation, lipogenesis and androgen metabolism in human sebocytes [6].

CRH, the most proximal element of the HPA axis, acts as central coordinator for neuroendocrine and behavioural responses to stress. It has been shown that CRH, CRH-BP, CRH-R1 and CRH-R2 are expressed in SZ95 sebocytes at mRNA and protein level, while CRH-R1 is the predominant type (CRH-R1/CRH-R2=2). In addition, CRH significantly induces sebaceous lipids production, IL6- and −8 synthesis and may up-regulate mRNA levels of 3β-hydroxysteroid dehydrogenase/$\Delta^{5-4}$ isomerase [62, 63]. In acne-involved skin the complete CRH system is abundant especially in the sebaceous glands, possibly activating pathways which affect immune and inflammatory processes leading to the development and stress-induced exacerbation of acne [64].

Melanocortin (MC) peptides can also directly affect the function of human sebocytes via MC receptors. α-Melanocyte-stimulating hormone (α–MSH) has been demonstrated to act as a modulator of the rat preputial gland, a specialised SG-like structure of rodents [65]. The presence of both MC-1R and MC-5R which bind α–MSH was detected in primary cell cultures of facial human sebocytes. The expression of MC-5R is weaker than that of MC-1R, but it has been shown to be a marker of human sebocyte differentiation, since it is expressed in differentiated, lipid-containing sebocytes only [66, 67]. In acne-involved skin sebocytes and keratinocytes of the ductus seboglandularis showed very intense MC-1R expression in contrast to less intense scattered immunoreactivity in normal skin samples, suggesting that this receptor is involved in the initiation of acne [68]. MC-1R expression has been shown to be up-regulated by pro-inflammatory signals [69, 70]. As pro-inflammatory cytokines are up-regulated in acne lesions [71], sebocytes may respond to these signals with increased MC-1R expression, thereby generating a negative feedback mechanism for α-MSH which exerts direct anti-inflammatory actions, i.e. inhibition of IL-1-mediated IL-8 secretion [66, 68].

Cannabinoid receptors which mediate the psychopharmacological action of marijuana have been not only localised in the central and peripheral nervous system but also in human skin. Cannabinoid receptors (CR) 1 and 2 are expressed in human sebaceous glands [72], whereas the CB2 and other prototypic endocannabinoids are present in SZ95 sebocytes and may induce in a dose-dependent manner lipid production and cell death. These actions are selectively mediated by CB2-coupled signalling involving the MAPK pathway [73].

Other neuropeptides such as substance P or vasointestinal peptide may also be involved in the pathogenesis of acne vulgaris. Substance P, which can be elicited by stress, may promote the development of cytoplasmic organelles in sebaceous cells, stimulate sebaceous germinative cells and induce significant increases in the area of sebaceous glands. It also increases the size of individual sebaceous cells and the number of sebum vacuoles for each differentiated sebaceous cell, all of which suggest that substance P promotes both the proliferation and the differentiation of sebaceous glands. Substance P induces the expression of neutral endopeptidase, a potent neuropeptide-degrading enzyme, in sebaceous germinative cells and of E-selectin by perisebaceous venules. Facial skin from acne patients is characterised by rich innervation, by increased numbers of substance P-containing nerves and mast cells and by strong expression of neutral endopeptidase in sebaceous glands and E-selectin in venules around sebaceous glands, compared with normal skin [74]. Recently, ectopeptidases dipeptidyl peptidase IV (DP IV or CD 26) and aminopeptidase N (APN or CD13), which have been shown to be involved in the degradation of several NPs, especially SP, have been found to be highly expressed in human sebocytes in vivo and in vitro. Further studies have shown unexpectedly that inhibitors of DP IV and APN can suppress proliferation and slightly decrease neutral lipids, but can also enhance terminal differentiation in SZ95 sebocytes. This suggests that ectopeptidases may be new targets to modulate certain sebocyte functions and that ectopeptidase inhibitors may have potential therapeutic roles in acne pathogenesis [75].

A central integrator of nociception, the transient receptor potential vanilloid-1 (TRPV1), is expressed in human skin, in sebaceous glands in situ and in SZ95 sebocytes in vitro. It has been documented that the prototypic TRPV1 agonist, capsaicin, selectively inhibits basal and arachidonic acid-induced lipid synthesis in a dose-, time- and extracellular calcium-dependent and a TRPV1-specific manner. Low-dose capsaicin stimulates cellular proliferation via TRPV1, whereas higher concentrations inhibit sebocyte growth and induce cell death independent of TRPV1 [76]. These findings suggest the strong involvement of neurogenic factors and sebocytes in the disease process of acne.

## 10.5 Inflammation, Sebocytes and Acne

Inflammation is being regarded as a key component of the pathogenesis of acne [77]. In the last few years, there has been a debate as to whether hyperkeratinisation of the follicular duct precedes

the influx of inflammatory cells or vice versa. Recent studies support the latter hypothesis by demonstrating that an increase in IL-1 activity occurs before the hyperproliferation around uninvolved follicles and this triggers the activation of the keratinocytes [71, 78]. Expression profiling of acne-involved and uninvolved skin from acne patients and from subjects without acne via cDNA microarrays has given us a better insight into the etiological factors giving rise to acne [79]. In inflammatory acne lesions, the majority of the regulated genes, which showed to be up-regulated, are involved in inflammatory processes. These include matrix metalloproteinases, β-defensin 4, IL-8 and granulysin. No differences were noted between normal skin from acne patients and that from patients without acne in the array analysis. NF-κB, a transcription factor critical for up-regulation of many proinflammatory cytokine genes, has been shown to be activated in acne lesions [80]. NF-κB-regulated cytokine mRNA gene levels of TNF-α, IL-1β, IL-8 and IL-10 are significantly up-regulated in acne-involved skin compared to uninvolved normal adjacent skin. Elevated expression of the chemokine IL-8 is able to attract circulating cells into the tissue. Indeed, in lesional skin of acne, there is a marked increase in the presence of polymorphonuclear leucocytes (PMNs), as compared to the uninvolved skin whereas lymphocytes are prominently visible in inflammatory acne lesions as compared to normal controls [80]. Another transcription factor involved in inflammation, AP-1, has been shown to be activated in inflammatory acne lesions in vivo as well. Levels of the pro-inflammatory cytokine interleukin-1 were also up-regulated perifollicularly in uninvolved skin from acne patients. This cytokine may be responsible for the cutaneous inflammation and the resulting keratinocyte proliferation and may play a profound role in the transformation of a normal follicle into an acne lesion [71].

Inflammation is further characterised by action of active lipid mediators, such as leucotrienes (LT), prostaglandins (PG) and 15-hydroxyeicosatetraenoic acids. These molecules are synthesised from arachidonic acid (AA) or linolenic acid by the enzymes lipoxygenase (LOX) and cyclooxygenase (COX), respectively. Both COX isozymes, COX-1 and COX-2, are expressed in human sebocytes in vitro, in particular COX-2 expression is selectively up-regulated in acne-involved sebaceous glands in vivo [43]. In hamster sebocytes the expression of COX-2 has been also documented [81], while the 15-desoxy-$\Delta 12^{,14}$-$PGJ_2$ (15d-$PGJ_2$) has been shown to induce the lipid synthesis in the cells [82]. Activation of the platelet-activating factor signalling pathway (PAF, 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine) which consists of a group of phosphocholines with various biological effects, including modulation of keratinocyte function and skin inflammation, can regulate the expression of inflammatory mediators, e.g. COX-2 and $PGE_2$, as well as IL-8 in SZ95 sebocytes [83]. Transgenic keratin 5 promoter-driven overexpression of COX-2 in the basal compartment of the epidermis of the mouse and increased $PGE_2$ levels have been documented to cause sebaceous gland hyperplasia and overshooting sebum production pointing to a role of COX-2-mediated $PGE_2$ synthesis in this process [84]. Activation of PPARγ by UVB irradiation and the potent lipid-soluble oxidant tert-butylhydroperoxide (TBH) induces COX-2 expression in SZ95 sebocytes and this finding indicates a PPARγ COX-2-mediated pathway regulating sebocyte proliferation and/or lipogenesis [85].

LT are potent pro-inflammatory mediators and neutrophil attractants produced from arachidonic acid by the enzyme 5-lipoxygenase (5-LOX). Human sebocytes express all necessary enzymes for a functional LT pathway. The enzymes 5-LOX and $LTA_4$ hydrolase are expressed in SZ95 sebocytes at protein and mRNA level. These enzymes are essential for the formation of $LTB_4$. On the other hand, 15-LOX expression shows a weak expression in SZ95 sebocytes, indicating that sebocytes do not play a significant role in the biosynthesis of the anti-inflammatory 15-HETE. Treatment of SZ95 sebocytes with AA stimulates 5-LOX expression and induces $LTB_4$ synthesis [43]. In addition, AA induces the expression of the IL6 and IL8 cytokines. 5-LOX and $LTA_4$ hydrolase show a stronger expression in acne lesions than in normal skin and in uninvolved

skin of acne patients [43]. The involvement of 5-LOX in the pathogenesis of acne has led to new therapeutic strategies to deal with the disease [86].

Cytokines are present in normal sebaceous glands, and they are affected by many factors. IL-1α, tumour necrosis factor (TNF)-α, IL-6 and IL-8 are released into supernatant in unstressed sebocyte culture [43]. In a stressed environment, the amounts of released cytokines increase significantly. AA and calcium ionophore enhance the level of IL-6 and IL-8, but that of IL-1β and TNF-α is not affected [10, 43].

Psoriasin, a member of the S100 gene family, was shown to be highly expressed in the epidermis and the ductus seboglandularis of acne-involved skin in contrast to uninvolved control [87]. Psoriasin has been suggested to be involved in the pathogenesis of several inflammatory skin diseases, and its levels increase in response to inflammatory stress. Retinoic acid (RA) and inflammatory agents have been also implicated in the up-regulation of psoriasin [88, 89].

## 10.6 *Propionibacterium acnes* Effects on Sebocytes

*Propionibacterium acnes* (*P. acnes*) is a gram-positive anaerobic bacterium which among with other non-pathogenic microorganisms such as coagulase negative staphylococci and diphtheroid rods resides in pilosebaceous follicles as a member of the resident bacterial flora. The mechanism by which *P. acnes* contributes to the pathogenesis of acne is debated. While in several studies it could be shown that *P. acnes* numbers are higher in acne patients than in healthy individuals, other studies found no difference between the numbers of *P. acnes* in affected and non-affected follicles. Nevertheless, an abnormal colonisation by *P. acnes* has been implicated in the occurrence of acne via the induction of inflammatory mediators. The bacteria stimulate the production of pro-inflammatory cytokines, including interleukin-1β, -8 and −12 and tumour necrosis factor-α. It is known that *P. acnes-induced* cytokine production is mediated by Toll-like receptor 2 [90–93]. The pilosebaceous unit is an immunocompetent organ. Keratinocytes and sebocytes may act as immune cells capable of pathogen recognition and abnormal lipid presentation. Both cell types can be activated by *P. acnes* via Toll-like receptors (TLR) and CD14 and CD1 molecules [90]. The expression of TLR2, TLR4, TLR6 and CD14 has been already documented in SZ95 sebocytes [94, 95]. Recent evidence has indicated that human sebaceous glands may contribute to the skin immune defence by releasing antimicrobial peptides (AMPs). For example, human β-defensins (hBDs) are expressed in human pilosebaceous units and their expression is up-regulated in acne lesions [96]. Cathelicidin and hBD-2 are detected in cultured human sebocytes, the predominant cells residing in the sebaceous gland, and their expression levels are up-regulated in the presence of *P. acnes* [93, 97]. Each *P. acn*es strain has been shown to influence sebocyte viability and differentiation differentially which raises the possibility that certain *P. acnes* strains may be responsible for opportunistic infections worsening acne lesions [93, 97, 98]. A description of phylogenetically distinct *P. acnes* clusters has been already undertaken [99].

The MUFA, mainly palmitic acid (C16:1) and oleic acid (C18:1), both of which are bactericidal against gram-positive organisms [94], are produced by the sebaceous gland, as is sapienic acid, an important antimicrobial lipid. Stearoyl coenzyme A desaturase (SCD) 1, an enzyme responsible for the biosynthesis of MUFA, is also expressed by the sebaceous gland [100]. The TLR-2 ligand macrophage-activating lipopeptide-2 stimulates both SCD and fatty acid desaturase-2 mRNA expression in SZ95 sebocytes [94]. Lauric acid (LA) (C12:0), one of the sebum free fatty acids (FFAs), has strong antimicrobial activity in vitro against skin bacteria, including *P. acnes*. Topical application or intradermal injection of LA in vivo shows remarkable therapeutic effectiveness against *P. acnes*-induced inflammation and significant reduction in the number of bacteria [101]. Furthermore, LA, palmitic acid (PA; 16:0) and oleic acid (OA; C18:1, *cis*-9), which are the typical FFAs found in human sebum, enhanced the hBD-2 expression and

antimicrobial activity of human sebocytes against *P. acnes* [102], indicating that sebum FFAs are involved in the disinfecting activity of the human skin both through their direct antimicrobial characteristics and by inducing AMP in human sebocytes to enhance their innate immune defence ability.

The treatment of cultured sebocytes with *P. acnes* and lipopolysaccharides (LPS) significantly up-regulates the expression of proinflammatory cytokines [93]. There is a difference in the cytokine production curve over time after treatment between *P. acnes* and LPS. While LPS stimulates CXCL8, TNF-α and IL-1α, *P. acnes* stimulates CXCL8 and TNF-α only. *P. acnes* has no effect on IL-1α. Furthermore, viable *P. acnes* and not heat-killed organisms can stimulate the release of cytokines such as IL-1b, GM-CSF and IL-8 [103, 104].

### Conclusions

Together, all these current research results have allowed us to elucidate a part of the mechanisms involved in the pathogenesis of one of the most common skin disorders, acne, and critically revisit conventional concepts of its pathogenesis. In addition, it has helped us to the determination of new targets for future drug development. The sebaceous gland cell is a key player in the initiation of the disease, and sebocyte culture models have become so far very useful tools to provide new chances for further research.

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# The Role of Bacteria

# 11

Mark D. Farrar and Richard A. Bojar

## Contents



**Core Messages**

- The association of bacteria with acne goes back over 100 years.
- Members of several bacterial genera are resident on human skin including *Propionibacterium*, *Staphylococcus* and *Corynebacterium*. Of these, propionibacteria, namely *Propionibacterium acnes*, are the microorganisms most associated with acne, but evidence for their involvement remains circumstantial.
- *Propionibacterium acnes* does not cause acne but may contribute to comedogenesis through keratinocyte hyperproliferation and to inflammation through the stimulation of proinflammatory cytokine production, e.g., via Toll-like receptors (TLRs) on macrophages and T-cells.
- *Propionibacterium acnes* produces a number of extracellular molecules that may stimulate an inflammatory response and/or damage tissue. These include lipases, proteinases, hyaluronidase and CAMP factors.
- Future treatment of acne should aim to target *P. acnes* more specifically to down-regulate or prevent inflammation and reduce the reliance on antibiotics.

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## 11.1 Introduction: Historical Perspective

### 11.1.1 First Association of Bacteria with Acne

Acne is a multifactorial condition with bacterial colonisation and proliferation being a significant factor in its pathogenesis. The association of bacteria with the pathogenesis of acne goes back over 100 years. In 1896 the German dermatologist Paul Gerson Unna published histological studies on acne lesions and recorded the presence of three main organisms within the follicle that are now known to be propionibacteria (most likely *Propionibacterium acnes*), staphylococci and the yeast *Malassezia* [1]. From his observations he concluded that comedone formation was caused by propionibacteria, staphylococci were responsible for inflammation and *Malassezia* spp. played no role in acne. The following year, propionibacteria were successfully cultured from acne lesions and subsequent work demonstrated the formation of lesions following the injection of propionibacteria into the skin [2]. Therefore, *P. acnes* was believed to be the cause of acne and was termed the 'acne bacillus'.

### 11.1.2 Evidence for the Role of Bacteria

Fifty years later, the role of *P. acnes* in acne was cast into doubt with the isolation of this organism from normal human skin [3]. However, the clinical use of antibiotics to treat acne has reaffirmed the association of *P. acnes* with the disease as antibiotic treatments that reduce the number of *P. acnes* on the skin are therapeutic. Of greater significance was the observation that lack of clinical improvement in acne patients treated with erythromycin was associated with the development of erythromycin resistance in propionibacteria [4].

It is still unclear what role bacteria and in particular *P. acnes* play in the pathogenesis of acne. *Propionibacterium acnes* is still believed to be a major factor, but evidence is circumstantial. There is no simple cause-and-effect relationship, making it difficult to apply Koch's postulates to *P. acnes* and acne. Further difficulty has come from the lack of suitable in vivo models for acne and the inability to specifically target *P. acnes* with antimicrobial therapy. It is widely believed that *P. acnes* is the main microorganism resident on human skin that is involved with the development of acne lesions and this section will focus on this one bacterium. However, it is important to note that there remains the possibility that other cutaneous microorganisms, for example staphylococci and *Malassezia* spp., may play some role in acne due to their location within the pilosebaceous follicle and proximity to *P. acnes*.

## 11.2 The Microbiology of Human Skin

### 11.2.1 The Skin as a Microbial Habitat

Normal human skin is colonised by a limited number of microbial types due to the somewhat inhospitable environmental conditions. Microbial numbers are controlled by physical factors, such as pH, oxygen, nutrient availability and humidity, and through interactions with the host and with other microbial populations. Cutaneous microorganisms can produce inhibitory substances such as bacteriocins and enzymes and the human host produces a range of antimicrobial molecules such as antimicrobial peptides, e.g. defensins.

### 11.2.2 Microorganisms Colonising Human Skin

The most prevalent and numerous resident skin microorganisms belong to the genera *Propionibacterium*, *Staphylococcus*, *Corynebacterium* and *Malassezia*. Other minor residents include members of the genera *Brevibacterium*, *Micrococcus*, *Kytococcus*, *Dermacoccus* and the Gram-negative *Acinetobacter*. Less prevalent and probably considered transients rather than true

commensals are species of *Streptococcus* and *Peptostreptococcus*.

Microorganisms can colonise both the skin surface and pilosebaceous follicles. Total microbial numbers can reach $10^7$ colony-forming units (cfu) $cm^{-2}$ skin in areas rich in lipid such as the face and back and also in humid areas such as the axilla. On areas such as the volar forearm, numbers may only reach $10^2$ cfu $cm^{-2}$ skin [5].

Recently, molecular typing methods and classification of microorganisms through ribosomal RNA sequencing have been applied to human skin [6]. These studies indicate that the microbial diversity of human skin may have been underestimated and that there are more bacterial species present than previously determined through culture alone. One note of caution is that these studies used samples taken at only one single time point. Therefore it is extremely difficult to determine if those microorganisms identified are true residents or simply environmental contaminants. Nevertheless, such studies are important in our understanding of the cutaneous microflora and its role in human disease.

## 11.3 *Propionibacterium acnes* and Acne

Despite the widely held belief that *P. acnes* contributes to acne lesion formation, there is an absence of formal proof and limited evidence that colonisation by propionibacteria is required for acne lesion development [7]. What is not clear is at which stage of lesion formation *P. acnes* is involved.

### 11.3.1 Comedogenesis

Comedones arise due to an abnormal pattern of keratinisation within the sebaceous follicle and the microcomedone is believed to be the earliest type of subclinical acne lesion [8]. Two changes occur during comedogenesis: (1) keratinocytes lining the follicle wall hyperproliferate as shown by an increase in the cell proliferation marker Ki-67 and (2) cohesion between keratinocytes increases leading to a reduction in desquamation [9, 10]. The role of *P. acnes* in these processes is uncertain. It has been shown that interleukin (IL)-1α can induce the infundibulum of isolated human pilosebaceous units to undergo hyperkeratinisation [11]. Formalin-killed *P. acnes* cells do not induce the production of interleukin (IL)-1α by normal human keratinocytes in vitro [12, 13]. However, co-culture with live *P. acnes* cells induces the production of IL-1α, tumour necrosis factor (TNF)-α and granulocyte-macrophage colony-stimulating factor (GM-CSF) by keratinocytes [14]. Therefore there may be a role for *P. acnes* in comedogenesis through IL-1α-induced hyperkeratinisation. This study also provided a hypothesis for why in acne, only a proportion of follicles are affected at any one time. *Propionibacterium acnes* cells were used in different growth phases with those in stationary phase inducing the highest levels of cytokines. Differences in follicle microenvironments may result in different *P. acnes* growth phases and consequently different effects on the keratinocytes within those follicles so that only a proportion are in a state of comedogenesis.

### 11.3.2 Inflammation

The inflammatory stages of acne are of greatest significance to the patient. Inflammatory lesions can be painful and can affect the patient's self-esteem. There is increasing evidence that the initial stages of inflammation in acne involve CD4+ T-cells and infiltration of these cells into the perifollicular region occurs very early. One study used lesion mapping to accurately determine the age of inflammatory lesions. This showed the initial infiltrate in evolving acne lesions to be CD4+ T-cells and not neutrophils as previously thought [15].

Further studies have demonstrated that an inflammatory response may be the earliest event in the development of an acne lesion. An immunohistochemical comparison of biopsies of uninvolved skin from acne patients and non-acne controls showed that in acne patients normal follicles were surrounded by large numbers of

CD4+ T-cells and macrophages [16]. Reduced numbers of Langerhans cells and the absence of neutrophils compared to controls suggested the initiation of an antigen-specific immune response. These features were not associated with comedogenesis as no hyperkeratinisation was observed. Therefore inflammatory acne may be initiated by a CD4+ T-cell response to a specific antigen within the follicle, most likely bacterial in origin.

## 11.4 *Propionibacterium acnes* and Inflammation

*Propionibacterium acnes* has not been shown to be directly involved in the initiation of inflammation in acne. The number of viable propionibacteria recovered from inflammatory lesions does not correlate with the severity of disease, and in some inflamed lesions, propionibacteria cannot be recovered [7]. However, *P. acnes* produces a number of extracellular molecules that may be pro-inflammatory, and non-viable *P. acnes* cells are immunostimulatory [17].

### 11.4.1 Inflammatory Mediators of *P. acnes*

*Propionibacterium acnes* produces a number of enzymes and other biologically active molecules (Table 11.1). Some of these act as chemoattractants to cells of the immune system. These molecules can also stimulate cells involved in non-specific immune responses to produce proinflammatory cytokines such as the production of TNF-α, IL-1β and IL-8 by monocytes [18, 19]. *Propionibacterium acnes* has also been shown to possess T-cell mitogenic activity that could contribute to inflammation by activating T-cells to release pro-inflammatory cytokines [20].

One further possible pro-inflammatory activity of *P. acnes* is the activation of TLRs. The bacterium can activate TLR2 on macrophages [21]. Such activation can lead to the release of the pro-inflammatory cytokines IL-12 and IL-8 (which is a chemoattractant for neutrophils). Interaction between *P. acnes* and TLRs may also involve keratinocytes as these cells express TLR2 and produce IL-8 upon activation [22]. Therefore it is possible that *P. acnes* may contribute to inflammation in acne through activation of TLRs on keratinocytes and even sebocytes leading to release of pro-inflammatory cytokines by these cells. Following rupture of the follicle, *P. acnes* may then interact with T-cells and macrophages to exacerbate the inflammatory response.

It is important to note that interactions between *P. acnes* and keratinocytes in intact follicles are only likely to occur deep within the follicle where the cornified layer is extremely thin and fragile. Although *P. acnes* may promote inflammation through the mechanisms described above, this does not explain why inflammation only occurs in a proportion of follicles, why *P. acnes* can colonise unaffected skin/follicles and, most importantly, how acne resolves spontaneously.

## 11.5 Other *P. acnes* Products

It is important to consider other extracellular enzymes and biologically active molecules produced by *P. acnes* that may have a role in acne. The bacterium is able to produce a number of enzymes with the potential to degrade host tissue. Such enzymes include proteinases, lipases, hyaluronidase, endoglycoceramidases, sialidases, neuraminidases and CAMP factors [23]. These molecules may have a role in promoting rupture of the follicle wall and further tissue damage following rupture. The exact role, if any, of these molecules in acne is still unclear (Table 11.1).

## 11.6 Hypotheses

One of the most interesting and least understood features of acne is spontaneous resolution. Any hypothesis on the role of bacteria in acne must attempt to explain this. There is strong evidence for initial events in acne involving a specific CD4+ T-cell response to one or more antigens, possibly bacterial in origin. Changes in the

**Table 11.1** Biological activities and bioactive products of *P. acnes*

| |
|---|
| Small molecule chemoattractants |
| T-cell mitogen(s) |
| Activation of TLR2 |
| IL-1α, TNF-α and GM-CSF production by keratinocytes |
| Proteinases |
| Lipases |
| Hyaluronidase |
| Endoglycoceramidases |
| Sialidases |
| Neuraminidases |
| CAMP factors |

microenvironment of an individual follicle may lead to production of such antigens by resident bacteria. The ensuing immune response would lead to formation of a clinically inflamed acne lesion. Clearance of the stimulating antigen would then allow inflammation to be down-regulated and the lesion would resolve. Over time, tolerance to the initiating antigen may develop leading to complete resolution of the disease. The immune response to *P. acnes* varies between individuals which may explain why some people do not get acne and also why acne varies in severity between individuals.

## 11.7 Future Therapeutic Considerations

Any therapy for acne must take into account all factors contributing to the disease. With respect to *P. acnes*, current treatment involves the sometimes long-term use of broad-spectrum antibiotics. Although these can be effective at reducing *P. acnes* numbers and are therapeutic, development of antibiotic resistance in *P. acnes* and other resident microflora is a concern. A greater understanding of the interactions between *P. acnes*, human skin and the human immune system may allow for the development of a more targeted therapy that can reduce the pro-inflammatory activity of *P. acnes* and successfully treat acne without affecting other members of the normal resident microflora.

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# Inflammation in Acne

# 12

Guy F. Webster

## Contents



**Core Messages**

- *P. acnes* can induce inflammatory response by activating innate immune cells, such as monocytes/macrophages.
- *P. acnes* may simultaneously produce both high- and low-molecular-weight chemoattractants.
- TLRs are transmembrane proteins that are activated by common microbial structures such as endotoxin and peptidoglycan to trigger production of proinflammatory cytokines such as IL12 and IL18; production of antimicrobial peptides such as defensins; and matrix metalloproteinases.
- *P. acnes* contains TLR ligands that have been shown to trigger cytokine production.

## 12.1 Introduction

Acne is a complex disease with multiple pathogenic factors that act together to produce clinical disease [1]. Dystrophic keratinization is involved in the formation of the plug in the follicle (comedo or microcomedo) that is the central lesion of acne. Hormonal stimulation of the sebaceous gland occurs at puberty which causes production of sebum, a complex mixture of lipids that consists of about 50 % triglycerides. Triglycerides

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are a rich carbon source for lipase-producing bacteria and are a powerful determinant of the skin microflora through the production of inhibitory fatty acids [2]. *Propionibacterium acnes*, an anaerobic diphtheroid, dominates the follicular microflora after puberty and is the stimulus for inflammatory acne. The study of acne pathogenesis has been hampered by the lack of a suitable animal model. Although animals can be induced to have keratinous impactions in the follicles, they cannot be induced to have inflammatory lesions since animal sebum lacks triglycerides and *P. acnes* will not colonize the follicle [3].

Early attempts to explain inflammation in acne were based on study of sebum composition in acne patients. Free fatty acids were found to be elevated in skin surface lipid from patients with inflammatory acne. These were derived from lipolysis of triglycerides and were suggested to be a trigger for inflammation in acne. Therapy that reduced lesions, e.g., tetracycline, reduced the free fatty acids to normal levels, apparent confirmation that the fatty acids were central to acne inflammation. Later work showed that the lipid fraction of microcomedones was not inflammatory and that only the *P. acnes*-containing fractions induced inflammation when injected intradermally. Free fatty acids were found to be the result of *P. acnes*' metabolism and to be present in proportion to the bacterial population rather than being a facet of aberrant sebaceous gland function; and more attention began to be paid to the role of the organism itself in acne. This was not a new thought, Unna, Sabouraud, and Fleming all speculated on the possibility that the "acne bacillus" was involved in acne. Fleming went so far as to demonstrate increased agglutination of the organism by sera from acne patients, but the idea lapsed until the mid-1970s (reviewed in [4]).

## 12.2 *Propionibacterium acnes* and Acne

*Propionibacterium acnes* is the predominant organism living on sebaceous regions of the skin. A facultative anaerobe, *P. acnes* grows in the sebaceous follicle and is carried onto the skin surface by the flow of sebum. *P. acnes* derives nutrition from the triglyceride fraction of sebum and hence is absent or low in children, but rises rapidly at puberty when androgens stimulate the start of sebum secretion acne [5].

The innate immune system is composed of the various host defense systems that act in the absence of an established immune response and includes the skin barrier, phagocytes, complement, antimicrobial peptides, and pattern recognition receptors such as the Toll-like receptors (TLR). *P. acnes* interacts with the innate immune system in various ways that are involved in the production of acne lesions.

Puhvel and Sakamoto [6] studied the contents of comedones in vitro and found that comedonal material attracted human neutrophils. The attractant was water soluble and of low molecular weight. A similar factor was detected in the supernatant of *P. acnes* cultures. Lee et al. [7] found that *P. acnes* also produced higher-molecular-weight chemotactic factors, one of which was the lipase molecule itself. Subsequent studies found that *P. acnes* may simultaneously produce both high- and low-molecular-weight chemoattractants and that the majority of neutrophil chemotactic activity in *P. acnes* culture supernatant was less than 2 kDa. The amount of chemotactic material produced was proportional to the *P. acnes* population and is of a molecular weight that might conceivably diffuse from an intact follicle [8]. The comedo may also contain other inflammatory factors. Allaker et al. [9] showed that *P. acnes* produces compounds that have histamine-like activity, and Helgren et al. [10] demonstrated prostaglandin-like activity in *P. acnes* culture supernatants. Most recently, Ingham et al. [11] found significant levels of interleukin 1 (IL-1)-like activity and tumor necrosis factor (TNF)-like molecules in a majority of open comedones.

Once neutrophils arrive at the comedo, gross rupture of follicular epithelium may be caused by enzymatic digestion of the follicular wall by neutrophil lysosomal hydrolytic enzymes. In vitro studies have shown that neutrophils readily secrete their degradative enzymes extracellularly

when exposed to *P. acnes* that has been opsonized by C3b or immunoglobulin. Release of hydrolases is greatest when the anti-*P. acnes* antibody titer is elevated [12]. These degradative lysosomal enzymes are capable of digesting tissue and may promote further comedonal rupture. Finally, *P. acnes* itself also elaborates proteases and other degradative enzymes, which may also play some part in comedonal rupture.

After exposure of comedonal contents to the immune system, a clinically detectable inflammation may result. The magnitude of the response is variable. Small, superficial papulopustules or deep nodules may develop. Complement deposition has been demonstrated in both early and late acne lesions, suggesting at least one means by which inflammation may be promoted. *P. acnes* is thought to be the cause of this deposition because the organism is a potent activator of both the classic and alternative complement pathways. The alternative pathway is triggered by *P. acnes* cell wall carbohydrate and the classical pathway by *P. acnes*–antibody complexes and is activated in proportion to the antibody titer [13, 14]. Crude comedonal material also activates complement by the classical and alternative pathways and this activation is also stimulated by anti-*P. acnes* antibody [15].

*P. acnes* can also induce inflammatory response by activating innate immune cells, such as monocytes/macrophages. Vowel et al. demonstrated that *P. acnes* induces pro-inflammatory cytokine production in monocytes, although the exact mechanism by which this occurs was not known [16]. Recently, with the discovery of the Toll-like receptors, we have a better understanding of how innate immune cells respond to microbes and how this leads to immune response [17].

TLRs are transmembrane proteins that are activated by common microbial structures such as endotoxin and peptidoglycan to trigger production of pro-inflammatory cytokines such as IL12 and IL18; production of antimicrobial peptides such as defensins; and matrix metalloproteinases [18]. *P. acnes* contains TLR ligands that have been shown to trigger cytokine production [19, 20].

Finally, *P. acnes* is a persistent inflammatory stimulus, being only degraded by about 10 % per 24 h period, in contrast to other organisms, e.g., *Staphylococcus aureus* which is degraded to soluble components within hours [15]. Injected radiolabeled *P. acnes* persists in the skin for many weeks and provided explanation for the inflammation that lingers long after severely inflamed lesions are treated.

## 12.3 Explaining the Variation in Acne Severity

After puberty, most individuals have stable *P. acnes* populations, some degree of microcomedo formation and significant sebum secretion, yet only some have inflammatory acne, and only a proportion of those have severe disease. In fact, when specific factors (e.g., sebum secretion, fatty acid concentration, or *P. acnes* populations) are compared in patients with and without acne, clear differences may be difficult to detect. In each category the acne population as a group is higher than the normal group, but great overlap exists in the range of values in each disease cohort (e.g., some persons have minimal or no acne, but high sebum production and some with acne have lower values), which suggests that each of these important factors is involved in but is not the determining cause of inflammatory acne (reviewed in [21]).

A second observation to be accounted for is that in severe inflammatory acne almost all lesions arise from microcomedones, whereas larger comedones in patients with noninflammatory acne become clinically inflamed only rarely, yet show histologic evidence of previous subclinical inflammatory episodes [1]. Likewise, clinically uninflamed microcomedones from persons with no apparent acne contain neutrophil markers suggesting earlier, limited inflammatory episodes that were not sufficiently severe to produce a clinical lesion [22].

Finally, the familial association of severe acne must be explained. The observation that severe acne is familial has been made by most clinicians, but studies are few. Acne conglobata and

hidradenitis may have autosomal dominant single-gene inheritance and reports have been published of acne of similar severity in monozygotic twins [23–26]. Thus, factors favoring the development of severe acne may be genetically determined.

An explanation that accounts for all these observations centers on differing individual reactivity to *P. acnes*. There is support for this concept. In vitro studies found *P. acnes* to generate greater complement activation and lysosomal enzyme release in the presence of anti-*P. acnes* antibodies [27]. Patients with acne have elevated precipitating, agglutinating, and complement-fixing antibody titers to *P. acnes* but not to other organisms [28–31]. The antibody titers increase in proportion to the severity of acne inflammation, with little or no overlap between the normal and most severe acne groups.

Some studies have addressed the identity of the *P. acnes* antigens potentially relevant to acne. One study found that the anti-*P. acnes* antibody response in a group of patients with severe nodular acne was apparently uniform, directed against a carbohydrate structure in the cell wall [31]. Of all the potential protein and carbohydrate antigens present in the *P. acnes* to which they were exposed, these patients appeared to hyperrespond to a single antigen. This reactivity was not detected in patients with less severe acne and the mechanism by which it occurs has not been elucidated. Ingham et al. [32] have made a complementary observation.

Cell-mediated immunity to *P. acnes* is also increased in proportion to acne severity. *P. acnes-stimulated* lymphocyte transformation is elevated in mononuclear cells from inflammatory acne patients and skin test reactivity to *P. acnes* is elevated in proportion to the severity of acne inflammation [33, 34]. Wilcox et al. [35] recently studied the cellular responses in acne lesions from patients prone to scarring and those not likely to scar. They found that non-scarring patients had a greater initial influx of lymphocytes than the scarring patients, but the scarring patients had a much greater proportion of memory-effector cells, with the implication that the more severe acne patient has an immunological predisposition to severity.

Thus, there is data in support of the concept that the difference between those with inflammatory acne and those without disease is their immune reactivity to *P. acnes* and that, in at least one sense, acne may be considered a hypersensitivity disease. In past generations there were attempts to produce a vaccine against *P. acnes* with an eye to heightening immunity and preventing disease. In light of current data that would have a counterproductive and indeed disease-inducing result, but perhaps a desensitizing regimen might be possible.

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# Part IV

# Pathogenesis of Acne: Modern Aspects

# A New Concept of Acne Pathogenesis

# 13

Christos C. Zouboulis and Clio Dessinioti

## Contents



**Core Messages**

- New insights in the pathogenesis of acne include the unraveling of the role of androgens, the identification of PPARs, the new concept of inflammation as a primary event in acne pathogenesis, the role of neuropeptides in acne, and new knowledge on the mode of action of *P. acnes*.

## 13.1 Introduction

The pathogenesis of acne, the most common disease of the pilosebaceous unit, has been traditionally attributed to increased sebum production, androgen activity, follicular hyperkeratinization, and the action of *Propionibacterium acnes* (*P. acnes*) within the sebaceous follicle [1, 2].

However, our knowledge on the pathogenesis of acne has been revolutionized in the last few years by studies on the role of sebaceous glands. The development of experimental models for the in vitro study of human sebaceous gland functions overcame the lack of an ideal animal model compatible to human sebaceous glands [3–6]. These studies have fundamentally changed the view for the human sebaceous gland from "a fossil of the skin with past but no future" [7] to the "brain of the skin" [8].

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New insights in the pathogenesis of acne include the unraveling of the role of androgens, the identification of PPARs, the new concept of inflammation as a primary event in acne pathogenesis, the role of neuropeptides in acne, and new knowledge on the mode of action of *P. acnes* [9].

## 13.2 New Concepts of Acne Pathogenesis

Skin (the sebaceous gland in particular) has been shown to be a steroidogenic tissue that possesses the enzymatic machinery to synthesize androgens (testosterone) de novo from cholesterol [3]. Androgens in turn play a central role in acne, not only by increasing the size of sebaceous glands and stimulating sebum production but also by stimulating keratinocyte proliferation in the ductus seboglandularis and the acroinfundibulum, thus contributing to comedone formation [2]. Increased 5α-dihydrotestosterone may act on infundibular keratinocytes leading to abnormal keratinization [10].

Peroxisome proliferation-activated receptors (PPAR) have been identified in human sebaceous glands, whereas PPAR ligands induce sebaceous lipogenesis in cultured human sebocytes [11]. Sebaceous lipids exhibit direct pro- and anti-inflammatory properties, whereas the induction of 5-lipoxygenase and cyclooxygenase-2 pathways in sebocytes leads to the production of pro-inflammatory lipids [12].

The order of events participating in acne pathogenesis has long been debated. Although traditionally inflammation was considered to succeed ductal hypercornification, new findings changed this concept. Bioactive interleukin (IL)1α-like material was found in open acne comedones from untreated patients [13], and the addition of IL1α induced hyperproliferation of follicular keratinocytes in isolated sebaceous follicle infundibula maintained ex vivo [14]. Thus, IL1α has a central role in cutaneous inflammation and keratinocyte proliferation and may influence the evolution of acne lesions [15]. Also, inflammatory events were detected in the very earliest stages of acne lesion development. Inflammatory factors (IL1α), increased CD4+ T cells, lack of neutrophils, and reduced Langerhans cells have been found in the perifollicular epidermis from uninvolved skin from acne patients prior to hyperproliferation or abnormal differentiation of the follicular epithelium [16].

New roles in the pathogenesis of acne have been attributed to *P. acnes*. A *P. acnes* biofilm, which penetrates into the sebum-like adhesive glue has been suggested to lead to the increased cohesiveness of corneocytes seen in acne. A biofilm is a complex aggregation of microorganisms that are placed within an extracellular polysaccharide lining which are secreted after adherence to a surface. So, the microcomedones may not be the central cause of acne, as traditionally thought, but rather result from the substances secreted by *P. acnes* into the sebum in its effort to attach to the follicular lining to set up a biofilm [17]. Also, Toll-like receptors (TLR), mammalian homologues of Drosophila Toll receptors, have been implicated in acne-related inflammation. *P. acnes* may activate keratinocytes and sebocytes of the pilosebaceous unit via TLR [18] and trigger inflammatory cytokine responses by activation of TLR2 [19]. *P. acnes*-conditioned medium and formalin-killed *P. acnes* were shown to augment intracellular lipid formation in hamster sebocytes by increasing de novo synthesis of triacylglycerols [20].

An exciting role has emerged for neuropeptides in acne, with the identification of the expression of melanocortin receptors 1 (MC1R) and 5 (MC5R) in human sebocytes in vitro and in situ [21–23] and increased in situ expression of MC1R in sebaceous glands of lesional skin in acne patients [24]. α-melanocyte-stimulating hormone (α-MSH) can stimulate sebocyte differentiation and lipogenesis [10]. Importantly, KDPT, a tripeptide derivative of α-MSH, has been shown to have anti-inflammatory action in SZ95 sebocytes via suppression of IL-1β-mediated cytokine expression [25]. Moreover, corticotrophin-releasing hormone (CRH) induces the synthesis of sebaceous lipids in vitro [26], and CRH expression by keratinocytes was induced by *P. acnes* [8, 27].

We have come a long way since 1975, when Dr. Albert M. Kligman described acne as "a bewitching lady, pursued with more passion than intelligence" [28]. The multifaceted acne has been pursued with dedication and many new signaling pathways have been unraveled through robust experimental data. Nevertheless, acne never ceases to bewitch us and the search for new discoveries is yet to be over.

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# Acne and Genetics

# 14

Bodo C. Melnik

## Contents



## Abbreviations

| | |
|---|---|
| ACTH | Adrenocorticotropic hormone |
| AR | Androgen receptor |
| DHEAS | Dehydroepiandrosterone sulfate |
| DHT | Dihydrotestosterone |
| FGF | Fibroblast growth factor |
| FGFR | Fibroblast growth factor receptor |
| FoxO | Forkhead box class O transcription factor |
| GH | Growth hormone |
| GHR | Growth hormone receptor |
| IGF | Insulin-like growth factor-1 |
| IGF1R | Insulin-like growth factor-1 receptor |
| IL-1 | Interleukin 1 |
| IR | Insulin receptor |

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| | |
|---|---|
| LH | Luteinizing hormone |
| LXR | Liver X receptor |
| MAPK | Mitogen-activated protein kinase |
| MC1R | Melanocortin 1 receptor |
| MC5R | Melanocortin 5 receptor |
| MMP | Matrix metalloproteinase |
| PCOS | Polycystic ovary syndrome |
| PI3K | Phosphoinositide-3-kinase |
| PLC | Phospholipase C |
| POMC | Proopiomelanocortin |
| PPAR | Peroxisome proliferator-activated receptor |
| RAR | Retinoic acid receptor |
| RXR | Retinoid X receptor |
| SHH | Sonic hedgehog |
| SNP | Single nucleotide polymorphism |
| SREBP | Sterol regulatory element binding protein |
| 5αR-I | 5 Alpha reductase type 1 |
| TLR | Toll-like receptor |
| TNF | Tumor necrosis factor |

**Core Messages**

- The severity of acne, its extension, regional variation, clinical course, and responsiveness to treatment are influenced by genetic and environmental factors.
- Androgen receptor (AR) transcriptional activity plays a pivotal role in acne pathogenesis and is influenced by (1) genetic variants of enzymes modifying the quantity and affinity of androgens interacting with the AR complex, (2) *AR* polymorphisms, and (3) AR coregulators.
- Genetic variants of enzymes involved in androgen biosynthesis and metabolism are potential candidate genes for acne like *CYP21A2* and *SRD5A1*.
- *AR* polymorphisms with shorter CAG repeats (<20) increase AR activity and have been correlated with acne.
- Insulin-like growth factor-1 (IGF-1), insulin, as well as fibroblast growth factors (FGFs) modulate FoxO-mediated transcriptional regulation of cell proliferation, lipogenesis, inflammation, and immunity explaining the role of *FGFR2* gain-of-function mutations in acne associated with Apert syndrome and acneiform nevus.
- The absence of acne in Laron syndrome with congenital IGF-1 deficiency points to the important role of IGF-1 in the pathogenesis of acne.
- IGF-1/PI3K/Akt-mediated phosphorylation of the AR cosuppressor FoxO1 upregulates AR transcriptional activity.
- Polymorphisms of *MUC1*, *CYP1A1*, *IL1A* and *TNF* have been associated with acne, whereas studies of *TLR2* and *TLR4* polymorphisms showed no correlation with the disease.
- Future studies should focus on genetic variations of *FOXO1A*, which appears to orchestrate a plethora of gene regulatory events involved in acne pathogenesis.

## 14.1 Introduction

Hecht [1] was the first who studied the role of heredity in acne. Neonatal, nodulocystic, and conglobate acne have proven genetic influences [2]. Postadolescent acne is related with a first-degree relative with the condition in 50 % of the cases. Chromosomal abnormalities, HLA phenotypes, and polymorphisms of various genes have been associated with acne. Data from family studies confirmed familial clustering [3–5]. High heritability estimates for acne in twins were reported [6, 7]. Higher correlations of sebum excretion and the proportion of branched fatty acids in the fraction of sebaceous wax esters were found in monozygotic vs. dizygotic twins [8, 9]. A large twin study demonstrated that 81 % of the variance of the disease was attributed to additive genetic effects, whereas the remaining 19 % was attributed to unique, unshared environmental factors [10]. Apolipoprotein A1 serum levels were

significantly lower in acne twins [10]. A family history of acne is associated with earlier occurrence of the disease, increased number of retentional lesions, and therapeutic difficulties, especially a higher risk for a relapse after oral isotretinoin treatment [11]. Another twin study revealed that heritability of acne on the back was very high [12]. Remarkably, at age 14 years, facial acne in girls was less influenced by genetic factors than in boys and was significantly influenced by common environmental factors [12].

The lack of intensive research in the field of acne genetics is surprising considering its high incidence, morbidity, and immense health service costs. Polymorphism of *CYP1A1* has been reported in a subgroup of acne patients [13]. Cytochrome P-450 1A1 regulates the conversion of endogeneous retinoids, which are important sebaceous gland morphogens [13, 14]. More recently, androgen receptor gene (*AR*) polymorphisms with reduced numbers of CAG repeats have been associated with increased risk for acne [15, 16]. The fibroblast growth factor receptor-2 (FGFR2)-gain-of-function mutations of Apert syndrome and acneiform nevus of Munro helped to elucidate the role of FGFR2-signaling in acne pathogenesis [17]. A large number of tandem repeats in the polymorphic epithelial MUC1 gene has been associated with severe acne [18]. The highly conserved cytoplasmic tail of MUC1 binds β-catenin and modifies nuclear β-catenin signaling, which is known to suppress sebaceous gland development and function [19, 20]. MUC1 is overexpressed by most human carcinomas and has been associated with increased phosphoinositol-3 kinase (PI3K)/Akt signaling [21]. Increased PI3K/Akt signaling with reduced nuclear levels of FoxO transcription factors has recently been proposed to play a major role in acne pathogenesis [22]. Gene polymorphisms of peroxisome proliferator-activated receptors (PPARs), melanocortin receptors (MCRs), matrix metalloproteinases (MMPs), and pro-inflammatory cytokines like interleukin-1α (IL-1α) and tumor necrosis factor-α (TNFα) are further acne candidate genes, which may increase the disposition for the disease, modify its clinical course and responsiveness to treatment, influence the rate of sebum secretion, inflammation, and the degree of scarring [23, 24] (Table 14.1).

## 14.2 Steroid 21-Hydroxylase Gene: *CYP21A2*

Dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) are important inducers of hyperandrogenism and acne. All mutations leading to enzymatic defects with increased adrenal DHEA synthesis are candidate genes for the development of acne. Four different cytochrome P450 (CYP) enzymes are involved in the synthesis of the steroid hormone cortisol in the adrenal cortex: CYP11A1, CYP11B1, CYP17, and CYP21A2. Depending on the enzyme affected, synthesis of the other adrenal steroid hormones, mineralocorticoids, and sex steroids are deranged in different ways [25]. The vast majority of all cases of *congenital adrenal hyperplasia* (CAH) are due to steroid 21-hydroxylase deficiency. *CYP21A2* is located on chromosome 6p21.3 and mutations are associated with increased risk of hyperandrogenism and acne [26] (for details, refer to Chap. 31).

## 14.3 Steroid 5α-Reductase Type 1 Gene: *SRD5A1*

The type 1 5α-reductase (5αR-I) is encoded on *SRD5A1* located on the distal arm of chromosome 5p15 [27]. Membrane-bound 5αR-I like type 2 catalyzes the conversion of testosterone into 5α-dihydro-testosterone (DHT), the most potent naturally occurring androgen in the tissue [28]. 5αR-I is primarily expressed in the skin and has been identified in sebaceous glands, epidermis, eccrine, and apocrine sweat glands, outer root sheaths, dermal papilla and matrix of hair follicles, as well as endothelial cells of small vessels and the Schwann cells of cutaneous myelinated nerves [29–33], [34–37], [38–41]. The activity of 5αR-I is concentrated in sebaceous glands and is significantly higher in sebaceous glands from the face and scalp compared with non-acne-prone areas [42]. Full thickness acne

**Table 14.1** Observed gene variations associated with increased risk for acne

| Candidate gene (gene locus) | Protein | Mutation | Functional abnormality |
|---|---|---|---|
| CYP21A2 6p21.3 | Steroid 21-hydroxylase | Various mutations leading to deficiency | Congenital adrenal hyperplasia (CAH) with DHEA excess |
| HSD3B2 1p13.1 | 3β-Hydroxysteroid dehydrogenase II | Mutations leading to deficiency | Late-onset CAH, DHEA excess |
| CYP11B1 8q21 | Steroid 11-β-hydroxylase | Loss-of-function mutation | Late-onset CAH, DHEA excess |
| CYP1A1 15q22-24 | Cytochrome P450 | Overexpression of m1-alleles | Accelerated retinoid degradation, modification of sebocyte differentiation? |
| SRD5A1 5p15 | Steroid 5α-reductase type I | Haplotypes with PCOS and hirsutism | Increased conversion of testosterone to DHT |
| AR Xq11-q12 | Androgen receptor | CAG repeat polymorphisms (<20) GGN repeat polymorphisms | Increased androgen receptor transcriptional activity |
| FGFR2 10q26 | Fibroblast growth factor receptor 2 | Ser252Trp and Pro253Arg mutations in Apert syndrome; Ser252Trp mutation in acneiform nevus | Gain-of-function mutations with decreased FGFR2 degradation and increased PI3K/Akt activation |
| IL1A 2q14 | Interleukin-1α | Interleukin 1A +4845(G>T) polymorphism | Increased susceptibility for acne and inflammatory reactions |
| TNF 6p21.3 | Tumor necrosis factor-α | TNFα polymorphism | Increased susceptibility for acne and inflammation |
| MUC1 1q21 | Mucin 1 glycoprotein | Large number of tandem repeats | Association with severe acne, modification of β-catenin- and PI3K/Akt/FoxO signaling? |

bearing skin produced from 2 to 20 times more DHT than did normal skin [43].

Increased 5αR activity in the skin has been observed in patients with hirsutism and acne [43–46]. Predominant expression of 5αR-I was found in the skin of the pubic region in hirsute female patients [47]. Total 5αR activity was approximately four times higher in follicles of patients with polycystic ovary syndrome (PCOS) than in healthy women [48]. A significant association between a single nucleotide polymorphism (SNP) in *SRD5A1* affecting the DHT/T ratio has been found in males with type 2 diabetes [49]. In women with PCOS, haplotypes within *SRD5A1* and *SRD5A2* were associated with the risk of PCOS, whereas haplotypes only in *SRD5A1* were associated with the degree of hirsutism pointing to an important role of *SRD5A1* haplotypes in androgenic signaling within the pilosebaceous follicle [50].

Addition of IGF-1 to cultures of skin scrotal fibroblasts significantly increased 5αR activity in a dose-dependent manner [51], whereas oral isotretinoin therapy reduced skin 5αR activity [52]. Conversion of testosterone to DHT increases AR activity and signaling. Thus, IGF-1 is an important amplifier of peripheral androgen metabolism in the skin [51, 53] (Fig. 14.1).

## 14.4 Polymorphisms of Androgen Receptor Gene: *AR*

The gene encoding androgen receptor (*AR*) is located on the X-chromosome (Xq11-q12). AR belongs to a class of nuclear receptors that recognizes canonical androgen response elements.. AR is present in epidermal and follicular keratinocytes, sebocytes, sweat gland cells, dermal papilla cells, dermal fibroblasts, endothelial cells, and genital melanocytes [54, 55]. There are three major mechanisms increasing AR transcriptional activity (1) increased AR ligand binding by raised gonadal or adrenal androgen

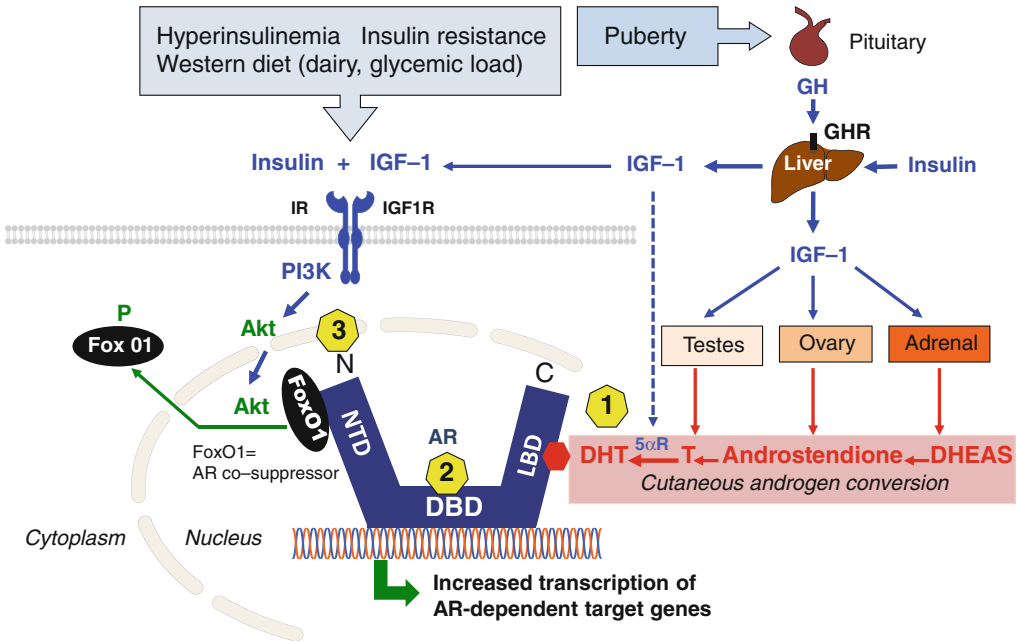


**Fig. 14.1** Regulation of androgen receptor (AR) transcriptional activity by (1) gonadal and adrenal androgens as well as intracutaneously converted androgens binding to the ligand-binding domain (LBD) of AR, (2) AR genetic variants like CAG repeat length polymorphism, (3) modification of the N-terminal activation domain (NTD) by AR coregulators like FoxO1. Increased IGF-1/insulin signaling of puberty, insulinotropic Western diet, as well as endocrine disorders with insulin resistance and hyperinsulinemia stimulate adrenal and gonadal androgen synthesis, 5α-reductase activity, and AR transcriptional activity

production as well as intracutaneous conversion of less potent to highly potent androgens like DHT, (2) elevated AR activity due to *AR* polymorphisms observed with shorter CAG and GGN repeats, and (3) increased AR activation by modifications of AR coregulators like extrusion of the AR cosuppressor FoxO1 from the AR transcriptional complex [56] (Fig. 14.1). The major AR domains include the N- and C-terminal activation domains, the ligand-binding domain (LBD), and a polyglutamine tract [57, 58]. AR is mutant in androgen insensitivity syndromes like *Kennedy spinal and bulbar muscular atrophy* and *Reifenstein syndrome*. Androgen-insensitive subjects cannot produce sebum and do not develop acne [59].

Polymorphisms that confer enhanced AR activity have been associated with androgen-dependent skin disorders. Exon 1 of *AR* encodes the N-terminal activation domain (NTD) and contains a variable length CAG repeat polymorphism that encodes a polyglutamine tract. CAG repeat numbers range between 8 and 35 and demonstrate a stable inheritance [60]. Significant amount of variation in DHT-responsiveness is related to CAG repeat [(CAG)*n*] polymorphism of *AR* [61–63]. The number of (CAG)*n* is inversely associated with the transcriptional activity of testosterone target genes [64, 65]. A length beyond 37 repeats leads to Kennedy disease (androgen deficiency syndrome) [66]. ARs with shorter polyglutamine tracts have greater ability to activate reporter genes with androgen response elements [65, 67]. Shorter CAG repeats have been associated with hirsutism [68], premature pubarche [69], ovarian hyperandrogenism [70], PCOS [71–73], androgenetic alopecia [74], hirsutism, and acne [75]. Sawaya and Shalita found a range of CAG repeats of 22 ± 4 in normal men and 21 ± 3 in healthy women. Men with acne had 21 ± 3, and women with acne had 20 ± 3, respectively [75]. Men with acne and androgenetic alopecia had 18 ± 4, and women with hirsutism had 16 ± 3 CAG repeats as well as women

with at least two androgenetic disorders [75]. Two recent genetic studies confirmed the relationship between shorter CAG and GGN repeats in *AR* with acne in Chinese acne patients [15, 16]. Moreover, prostate volume and growth in testosterone-substituted hypogonadal men is dependent on the CAG repeat polymorphism [76]. Low numbers of *AR* CAG repeats are associated with lower levels of high-density lipoprotein (HDL) cholesterol [77]. CAG repeat numbers are positively associated with serum levels of apolipoprotein A-I. Decreased apo-A-I serum levels have been observed in acne twins [10]. *AR* polymorphism with lower CAG repeats would put these acne patients to an increased risk for developing coronary heart disease and prostate cancer. In fact, an epidemiologic association between severe acne and prostate cancer has been reported [78].

Shorter GGN repeats of *AR* have been proposed to be the major determinant of common early onset androgenetic alopecia [79]. A combination of shorter CAG and GGN repeats in *AR* has been associated with increased acne risk in North East China [15].

### 14.4.1 Effect of Isotretinoin on Skin Androgen Receptor Activity

AR status was investigated in back skin of six male acne patients before and after 3 months of oral isotretinoin treatment. The treatment did not modify the binding affinity constant of the AR in the skin (0.44 vs. 0.32 nmol/l), but induced a 2.6-fold decrease in its binding capacity constant (62 vs. 24 fmol/mg cytosolic protein) [80]. This isotretinoin-induced effect on AR and the suppression of 5αR activity in the skin of acne patients treated with isotretinoin explain the potent inhibitory effects of isotretinoin on the formation of DHT and the amount of DHT bound to AR. Isotretinoin-mediated reduction of serum IGF-1 levels as well as isotretinoin-mediated upregulation of nuclear FoxO1 levels may contribute to the suppressive effects of isotretinoin on AR transcriptional activity in the skin [81, 82].

## 14.5 Genes of the Somatotropic Axis: *GH1*, *GHR*, *IGF1*, *IGFBP3*, and *IGF1R*

Increased levels of growth hormone (GH) during puberty stimulate hepatic secretion of IGF-1 after binding to the hepatic GH-receptor (GHR). IGF-1 is the main biological mediator of GH and participates in the regulation of the cell cycle, inhibiting the processes of apoptosis and stimulating cell proliferation after binding und activation of IGF1R [83, 84]. In the sebaceous gland, IGF-1 protein expression is most intensive in maturing sebocytes and suprabasal cells of the sebaceous duct [85]. IGF1R protein expression is uniform and intense in all regions of the gland [85]. In sebaceous glands IGF-1 acts as a morphogen and a mitogen [85]. Dermal cells produce IGF-1 as well, whereas epidermal basal keratinocytes are IGF-1-negative, but express IGF1R [85, 86]. Both, serum androgens and IGF-1 levels increase at puberty but the course of acne follows IGF-1 levels more closely than it does with regard to androgens [87, 88]. Increased IGF-1 levels in addition to androgens influence acne in adult men and women. While IGF-1 appears to have a stronger effect on acne in women, androgens may play a greater role in acne for men [89]. In men, serum IGF-1 levels showed a linear correlation with the rate of facial sebum excretion [90].

### 14.5.1 IGF-1, Key Regulator of Androgen Receptor Signaling

Many variables, such as age, sex, nutritional status, and GH secretion affect serum IGF-1 levels. IGF-1 stimulates adrenal, testicular, and ovarian androgen synthesis and 5αR activity converting less potent androgens to highly potent DHT. These IGF-1 effects increase AR transcriptional activity by upregulation of the quantity and affinity of androgen binding to AR [51, 53, 91–96]. Moreover, IGF-1 increases AR transcriptional activity by inhibiting FoxO1-mediated AR suppression [17, 53, 97, 98].

### 14.5.2 Environmental Versus Genetic Impacts on IGF-1 Serum Levels

In westernized societies acne has evolved into an epidemic skin disease of the adolescent population, pointing to the overwhelming role of environmental factors [99]. There is accumulating evidence for the aggravation of acne by Western diet [100]. Increased insulin/IGF-1 signaling mediated by consumption of hyperglycemic carbohydrates and insulinotropic milk and dairy products has been associated with the pathogenesis of acne and other diseases of civilization [101–105]. Milk and dairy protein consumption raises serum IGF-1 levels and elevates the somatotropic axis in children, adolescents, and adults [106–108]. Endocrine disorders like PCOS and acromegaly as well as various acne-associated syndromes featuring insulin resistance are associated with increased insulin/IGF-1 signaling [109–114]. Individuals with genetic polymorphisms related to exaggerated insulin/IGF-1 signaling may thus be more susceptible to acneigenic effects of Western diet.

### 14.5.3 IGF-1 Converges with FGFR2b-Signaling

The IGF-1 signaling pathway shares common downstream signaling cascades with other tyrosine kinase receptors like fibroblast growth factor receptors (FGFRs) (Fig. 14.2). FGFR2b-signal transduction is primarily mediated by the MAPK/ERK-, PI3K/Akt-, and phospholipase C-γ/protein kinase C pathway [115, 116]. Insulin and IGF-1 stimulate sebaceous gland lipogenesis [88]. IGF-1 via PI3K/Akt induces expression of SREBP-1, fatty acid synthase, and overall lipogenesis in SEB-1 sebocytes [117]. FGFR2b-, IGF-1-, and insulin signal transduction pathways converge downstream and increase PI3K/Akt signaling [118] (Fig. 14.2). In this regard, androgen-dependent FGFR2b signaling amplifies growth factor signaling of insulin and IGF-1. Thus, highest levels of sebum production and sebocyte differentiation are only reached when androgens cooperate with other growth factors like IGF-1, insulin, and FGFs [88, 119–121].

### 14.5.4 IGF-1 Activates Androgen Receptor Transcriptional Activity

IGF-1/insulin signaling activates androgen signaling through inhibition of the AR-cosuppressor FoxO1 [97, 98]. FoxO1 reduces androgen-induced AR target gene expression. In response to IGF-1 or insulin, FoxO1 becomes phosphorylated and inactivated. The insulin/IGF-1-mediated inactivation of FoxO1 explains the increased peripheral androgen responsiveness of insulin/IGF-1-stimulated pilosebaceous follicles.

### 14.5.5 IGF1 Polymorphism Determines IGF-1 Serum Levels

Despite its pivotal role in acne pathogenesis, there is still no information on genetic variants of *IGF1* in acne patients. It has been estimated that between 38 and 77 % of the individual variation in IGF-1 serum levels is dependent on genetic factors [122, 123]. Circulating IGF-1 levels are modified by a cytosine–adenine (CA) repeat in the proximity of the *IGF1* promoter [124, 125]. *IGF1* polymorphisms resulting in elevated circulating levels of IGF-1 may thus be important genetic factors predisposing for the development of acne.

### 14.5.6 IGF Binding Protein-3 Polymorphisms

More than 90 % of circulating IGFs are bound to insulin-like growth factor-binding protein-3 (IGFBP-3) and less than 1 % of IGFs circulate in free form [126, 127]. Thus, IGFBP-3 modulates IGF-1 signal transduction. Oral isotretinoin treatment of acne patients has been shown to reduce

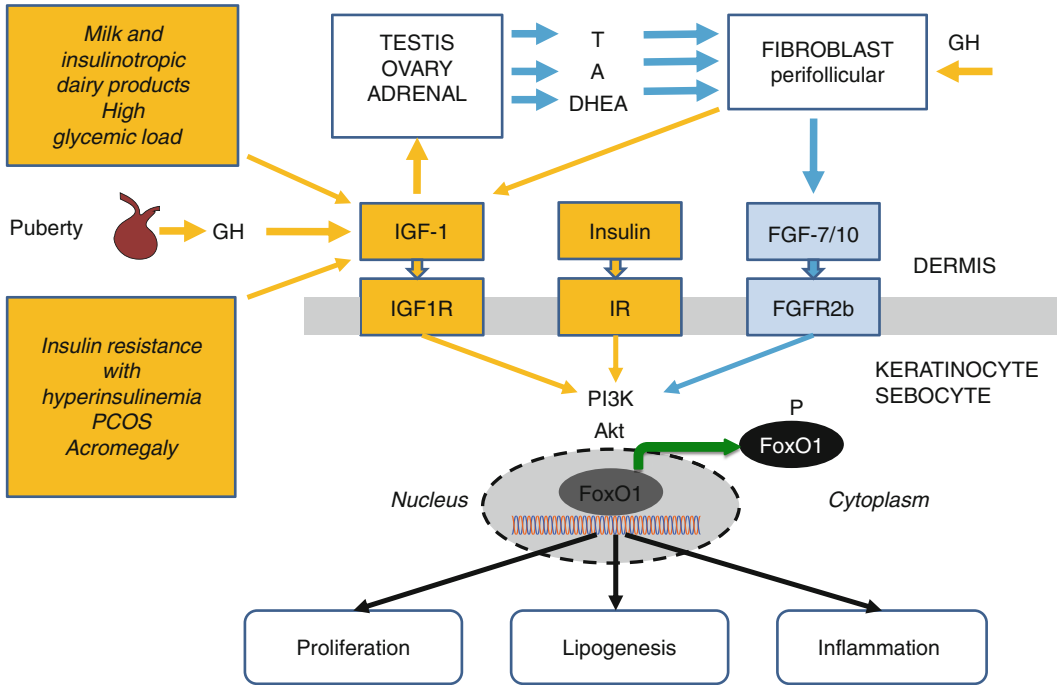


**Fig. 14.2** Converging IGF-1 receptor-, insulin receptor-, and FGFR2b signal transduction pathways in the pathogenesis of acne. Increased IGF-1 secretion of puberty stimulates adrenal and gonadal androgen synthesis. Androgens induce FGF7 and FGF10 secretion of perifollicular fibroblasts, which stimulate FGFR2b on sebocytes and follicular keratinocytes. IGF1R, IR and FGFR2b pathways activate the PI3K/Akt cascade resulting in nuclear extrusion of FoxO1

serum levels of IGF-1 and IGFBP-3 [81]. In human dermal papilla cells, *all-trans*-retinoic acid induced a fivefold increase of IGFBP-3, which inhibited IGF activity important for maintaining hair anagen growth [128]. Remarkably, a 3.43-fold increased expression of IGFBP-3 during isotretinoin treatment was exclusively observed in sebocytes but not in whole skin [129]. IGFBP-3 is not only a binding protein but also translocates into the nucleus and interferes with retinoic acid receptor (RAR)/retinoid receptor X (RXR) leading to changes of receptor transactivation [130, 131]. Nuclear IGFBP-3 is a potent inducer of apoptosis [131]. Intriguingly, IGFBP-3 is a known FoxO target gene [132]. Nuclear overexpression of IGFBP-3 might mediate isotretinoin's effect on sebocyte apoptosis. Moreover, upregulated IGFBP-3 suppressed the proliferation of transient amplifying keratinocytes and may thus contribute to isotretinoin's anti-comedogenic effect [133, 134].

*IGFBP3* is a potential candidate gene for acne like other gene polymorphisms of the somatotropic axis resulting in increased signal transduction, especially *GH1*, *GHR*, *IGF1*, *IGF1R*, insulin receptor substrate 1 (*IRS1*), phosphoinositol 3-kinase regulatory subunits (*PIK3R1*, *PIK3R2*), PI3K catalytic subunit (*PIK3CA*), as well as Akt isoforms 1–3 (*AKT1–3*), which finally control the transcriptional activities and regulatory functions of FoxO transcription factors.

## 14.6 Forkhead Box Transcription Factor Class O1A Gene: *FOXO1A*

FoxO1 is a nutrient- and growth factor-sensing forkhead box class O transcription factor, which has recently been suggested to play a key regulatory role in the pathogenesis of acne [22]. *FOXO1A* is located on chromosome 13q14.1. FoxO1 protein

has been detected in human sebaceous glands by immunohistochemistry (Liakou A et al., personal communication). FoxO1 controls major effectors involved in acne pathogenesis like AR activity, cell proliferation, apoptosis, lipogenesis, reactive oxygen species homeostasis, inflammation, innate and acquired immunity [22]. Increased insulin/IGF-1 signaling activates the PI3K/Akt cascade resulting in nuclear extrusion of FoxO proteins into the cytoplasm [135]. FoxO1 is an important AR cosuppressor and mediates nutrient and growth factor signals to the AR regulatory complex [56, 97, 98, 136]. *FOXO1A* mutants with increased transcriptional activity have been associated with longevity and reduced incidence of age-related diseases [137, 138]. Intriguingly, untreated patients with Laron syndrome and congenital IGF-1 deficiency due to loss of function mutations of *GHR* do not develop acne and have a low incidence of age-related diseases like diabetes and cancer compared to their first-degree relatives with normal insulin/IGF-1 signaling [139–141]. Cell culture studies with serum of Laron subjects with low insulin/IGF-1-signaling exhibited higher levels of nuclear FoxO1 compared to controls with normal insulin/IGF-1 signaling [140]. Thus, *FOXO1A* is a favorite candidate gene for acne as FoxO1 orchestrates key regulatory molecular players involved in the pathogenesis of acne like AR, PPARγ, LXRα, cyclins D1 and D2, p21, p27, catalase, superoxide dismutase, β-defensin-2, and TLR4 among others [22, 82]. Polymorphisms of *FOXO1A* exhibiting impaired regulatory activity might increase the risk for acne and other diseases of civilization [104].

## 14.7 Peroxisome Proliferator-Activated Receptor Genes: *PPARA, PPARB, PPARG, PPARD*

Androgens as single compounds are unable to modify sebocyte differentiation, which is stimulated by co-incubation with peroxisome proliferator-activated receptor (PPAR) ligands [142, 143]. PPARs are members of the nuclear hormone receptor subfamily of transcription factors and form heterodimers with RXRs, which regulate the transcription of various genes. Three subtypes of PPARs, PPARα, PPARδ, and PPARγ, are expressed in follicular keratinocytes and sebocytes and are involved in the regulation of lipogenesis and differentiation of keratinocytes and sebocytes [142–153]. PPARs are master regulators of lipid metabolism and cooperate with liver X receptor (LXR) [154]. An important role of LXRα in differentiation and inflammatory signaling in SZ95 sebocytes has been reported [155]. Specific agonists of each PPAR isoform stimulated sebocyte differentiation in vitro [142, 144, 145, 151, 156, 157]. Fatty acids of $n-3$ and $n-6$ origin play an important role as ligands and modulators of PPARs [158]. PPARδ ligand *linoleic acid* is the most effective agonist in stimulation of lipid formation in sebocytes and epidermal cells [142, 151, 159]. RXR agonists are known to enhance PPAR effects [147]. Testosterone metabolism to DHT and synthesis of sebaceous lipids is regulated by PPAR-ligand linoleic acid in human sebocytes [143, 151]. In cultured sebaceous cells and human sebaceous glands PPARβ/δ are expressed in greatest amounts, followed by PPARγ1 and PPARα [146, 147], whereas PPARα and PPARγ1 were found to be the main PPARs in cultured sebocytes [145]. Studies of mice chimeric for wild type and PPARγ null genotypes provide the most direct evidence that PPARγ is essential for sebaceous gland development and function [159, 160], whereas PPARβ/δ play a more general role in the regulation of lipid metabolism common to both sebocytes and keratinocytes [159]. Agonists of PPARα, PPARδ, PPARα/δ, and PPARγ increased sebaceous lipogenesis in SEB-1 sebocytes [161]. Patients treated with thiazolidinediones or fibrates had significant increases in sebum production [161]. Increased release of *substance-P* upregulated PPARγ protein expression and RNA amplification in cultured sebocytes [162]. Peroxidated squalene induced upregulation of PPARα protein and mRNA expression [163]. Endocannabinoids enhanced lipid synthesis and apoptosis of human sebocytes via cannabinoid receptor-2-mediated signaling, which upregulated PPAR transcription factors and some of their target genes [164].

There is yet no information on the role of genetic variants of PPAR and LXR genes with regard to the pathophysiology of acne. Remarkably, the Pro12Ala polymorphism of *PPARG* is associated with increased insulin sensitivity and lower hirsutism scores in PCOS [165, 166]. *PPARG* Pro12Ala appears not to be a potent modifier gene of PCOS [167]. However, a large genome-wide association study of Finnish patients identified *PPARG* as one of ten critical susceptibility genes for type 2 diabetes [168]. Recent studies on PPARα, PPARβ/δ, and PPARγ variants confirmed the importance of PPAR variants in lipid metabolism [169]. Screening of acne patients for *PPAR* and *LXR* polymorphisms might thus be a promising approach to elucidate the genetic background of acne.

Remarkably, FoxO1 is a PPARγ-interacting protein that antagonizes PPARγ activity [170–172]. FoxO1 is a cosuppressor of PPARγ and inhibits PPARγ function as well as the expression of PPARγ protein [135]. Moreover, it has been shown in skeletal muscle that FoxO1 regulates triglyceride content via interaction with the RXRα/LXRα/SREBP-1c pathway [173].

## 14.8 Fibroblast Growth Factor Receptor-2 Gene: *FGFR2*

Fibroblast growth factor (FGF) receptor-2 (FGFR2) encoded on chromosome 10q26 belongs to a family of four related but individually distinct androgen-dependent tyrosine kinase receptors. FGFRs have a similar protein structure, with three immunoglobulin-like domains (D1–D3) in the extracellular region, a single membrane-spanning segment, and a cytoplasmic tyrosine kinase domain [174]. FGFRs bind in clusters to heparan sulfate proteoglycans, enabling the ligands to cross-link the receptors. Two splice variants of FGFR2 are designated FGFR2b and FGFR2c [174]. The exclusively in epithelial cells expressed FGFR2b binds FGF7 and FGF10, but not FGF2, FGF4, FGF6, and others [175]. FGFR2b is expressed mainly in the suprabasal spinous layer of epidermis and plays a crucial role in controlling epithelial proliferation and differentiation [176]. The mesenchymally expressed isoform FGFR2c binds FGF2, FGF4, FGF6, FGF9, FGF17, and FGF18, but not FGF7 and FGF10 [175]. The lineage-specific expression of the FGFR2b and FGFR2c isoforms enables interaction between epithelial and mesenchymal layers during development and tissue homeostasis in response to different FGFs [174]. FGFR2b is expressed throughout the epidermis, hair follicles, and sebaceous glands. Deletion of FGFR2b leads to sebaceous gland atrophy [177]. The seminal vesicle shape (svs) mutation of FGFR2 in the mouse resulted in branching morphogenesis defects in the prostate and seminal vesicles [178]. FGFR2b has been shown to be important for postnatal skin development and hair follicle morphogenesis [179]. Mice expressing a membrane-bound, dominant-negative FGFR2b, lacking tyrosine kinase activity displayed epidermal atrophy, hair follicle abnormalities, dermal hyperthickening with severely delayed reepithelialization of excisional wounds [180]. Mice lacking FGFR2b survived into adulthood but displayed striking abnormalities in hair and sebaceous gland development [177]. FGFR2b plays an important role in sebaceous gland development and long-term survival of sebocytes [177].

### 14.8.1 FGFR2 Mutations in Apert Syndrome and Acneiform Nevus

Apert syndrome (MIM 101200), an acrocephalosyndactyly syndrome, is often associated with severe acne and results from specific heterozygous missense mutations at two adjacent residues of FGFR2, Ser252Trp or Pro253Arg, in the linker region between D2- and D3-immunoglobulin-like regions of the FGFR2-ligand-binding domain [181, 182]. The mutations increase FGF-ligand-binding affinity and are gain-of-function mutations [181–183]. Once activated, FGFRs signal downstream via adapter proteins and cytosolic kinases and modify responsive target genes [174]. Intriguingly, a threefold increased expression of interleukin-1α

was observed in osteoblasts expressing Ser252Trp-mutated FGFR2 [184]. Besides activating the MAPK cascade, activated FGFRs also stimulate PLC-γ/PKC and PI3K/Akt-signaling cascades [116]. Increased signaling of the Ser252Trp- and Pro253Arg-FGFR2 mutations in Apert syndrome results from maintained stay of the activated receptor complex at the cell membrane due to disturbed FGFR2 downregulation to the lysosomal compartment [185]. Increased FGFR2 signaling of mutated FGFR2 in Apert syndrome, increased androgen-stimulated FGFR2-signaling, and IGF1R-signaling of puberty may share common downstream pathways involved in the pathogenesis of acne [17, 118, 186] (Fig. 14.2). There is substantial evidence that anti-acne agents attenuate FGFR2 signal transduction in acne [187].

Munro and Wilkie described an epidermal mosaicism producing an acneiform nevus in a 14-year-old boy exhibiting a somatic Ser252Trp-mutation of FGFR2 [188]. Sharply demarcated linear acneiform lesions extending from the left shoulder to the antecubital fossa with comedones in virtually every follicle have been reported [188]. Recently, the somatic heterozygous Ser252Trp-FGFR2 mutation has been confirmed within the affected skin lesions of another male patient exhibiting a unilateral acneiform nevus [189]. Thus, the *FGFR2* mutation in acneiform nevus presenting a genetic mosaic is the same gain-of-function mutation observed in the majority of *FGFR2* germline mutations in patients with Apert syndrome frequently associated with severe acne [186, 188, 189].

## 14.9 Melanocortin Receptor Genes: *MC5R* and *MC1R*

*MC5R* is mapped on chromosome 18p11.2 and is highly expressed in multiple exocrine tissues, including Harderian, preputial, lacrimal, and sebaceous glands, and is required for production and stress-regulated synthesis of porphyrins by the Harderian gland and ACTH/MSH-regulated protein secretion by the lacrimal gland. MC5R regulates the function of multiple exocrine glands by melanocortin peptides [190, 191]. Stimulation of the sonic hedgehog (SHH) pathway in Smoothened-expressing transgenic mice resulted in increased expression of the sebocyte markers Scd3 and MC5R [192]. MC5R is an important marker of human sebocyte differentiation [193]. In human sebocytes MC5R was only detectable at the onset of differentiation and in fully differentiated cells displaying prominent lipid granules [194]. The functional link between MC5R and sebogenesis has been shown in MC5R-deficient mice exhibiting downregulated sebaceous lipogenesis [195]. Centrally produced α-MSH plays an important role in the regulation of sebaceous lipids [196, 197]. Ablation of the neurointermediate lobe of the pituitary, the source of circulating α-MSH, decreased sebaceous lipid production. In hypophysectomized and castrated rats the reduction of sebaceous lipids was fully restored by concomitant administration of α-MSH and testosterone [197]. In a primary human sebocyte culture system, α-MSH stimulated sebocyte differentiation, sebaceous lipid production, and expression of MC5R [194, 198]. α-MSH signaling via MC5R acts on a common pathway with androgen-dependent expression of MC5R by amplification of the signaling cascade androgen → FGF7/FGF10 → FGFR2b → SHH → Gli → MC5R. MC5R is a crucial target gene of SHH signaling, which plays a role in postnatal function of sebaceous glands [199, 200].. Remarkably, retinoids, which inhibit sebocyte differentiation, have been shown to reduce Gli transcriptional activity in cultured keratinocytes [201].

*MC1R* is mapped to chromosome 16q23.4. MC1R is involved in the regulation of skin pigmentation, determination of hair color, skin sensitivity to ultraviolet light, and is expressed on 95 % of melanomas [202–205]. MC1R is also expressed on human sebocytes in vitro and in situ [206]. By modulation of interleukin-8 secretion, α-MSH may act as a modulator of inflammatory responses in the pilosebaceous unit [206]. MC1R expression has been studied in 33 patients with acne and seven age-matched controls [207]. Sebocytes and keratinocytes of the *ductus seboglandularis* of acne-involved and non-involved skin showed very intense MC1R expression in

contrast to less intense immunoreactivity in normal skin [207]. Multiple variants of the MC1R gene have been reported but not yet in relation to acne genetics [208–211].

The neuroregulatory effects of the proopiomelanocortin system play an important role in sebaceous gland homeostasis [198]. Remarkably, FoxO1 suppresses the transcription of proopiomelanocortin (POMC) by antagonizing the activity of *signal transducer and activator of transcription-3* (STAT3) [212–214]. α-MSH and ACTH are the main POMC peptide cleavage products important for sebocyte biology. FoxO1 not only suppresses the expression of *POMC* but also of *CPE* encoding carboxypeptidase E that processes POMC to α-MSH [214]. Thus, FoxO1-regulated POMC gene expression and production of POMC cleavage products ACTH and α-MSH may have an important influence on downstream MC5R and MC1R signaling to the sebaceous gland. Indirect evidence from translational studies allowed the conclusion that oral isotretinoin treatment increases nuclear levels of FoxO1 [82]. Isotretinoin-mediated upregulation of hippocampal FoxO1 could thus inhibit POMC/α-MSH signaling to the sebaceous gland. In fact, it has recently been demonstrated that oral isotretinoin treatment in acne patients reduced ACTH serum levels [215]. Isotretinoin's proposed effect on the hypothalamic-pituitary axis via FoxO1-regulated POMC expression sheds a new light on MC5R- and MC1R-mediated signal transduction to the sebaceous gland. In this regard, not only *MC5R* and *MC1R* but also *FOXO1A* as an upstream regulator of MC5R- and MC1R ligand expression and processing may be important interacting candidate genes involved in the pathogenesis of acne.

## 14.10 Matrix Metalloproteinase Genes: *MMP1, MMP2, MMP3, MMP9, MMP13*

Nuclear factor κB (NF-κB) and activator protein-1 (AP-1) are activated in acne lesions with consequent elevated expression of inflammatory cytokines like TNFα and matrix degrading metalloproteinases (MMPs). These gene products have been shown to be molecular mediators of inflammation and collagen degradation in acne lesions in vivo [216]. MMPs are also downstream targets of the FGFR2b signaling pathway [217]. MMP-1 and MMP-3 are upregulated in skin lesions of acne patients [218]. *P. acnes* stimulated pro-MMP-2 expression through TNFα in human dermal fibroblasts [219]. Isotretinoin decreased the expression of MMPs in HaCaT keratinocytes (proMMP-2, proMMP-9, MMP-13) and SZ95 sebocytes (proMMP-2, proMMP-9) and reduced MMP-13 in sebum of acne patients treated with isotretinoin [220]. MMPs are important for dermal matrix remodeling and support the expansion and growth of sebaceous glands into the surrounding connective tissue. Isotretinoin inhibits scarring in acne and affects dermal tissue remodeling.

Recent evidence points to the important role of FoxO proteins in the regulation of MMP promoter activity [221–224]. In UV-irradiated dermal fibroblasts, reduced expression of FoxO1a mRNA was associated with increased MMP-1 and MMP-2 mRNA levels [225]. Contrary, addition of a FoxO1a peptide to the culture medium decreased MMP-1 and MMP-2 expression [225]. Isotretinoin-induced upregulation of nuclear FoxO levels may thus suppress MMP promoter activity as well as FGFR2-mediated MMP activity [82, 187]. It is thus conceivable that genetic variants of either individual MMP- or FoxO genes may determine the functional activity of MMPs intensifying inflammatory perifollicular reactions with dermal tissue destruction, abscess formation, and scarring as observed in conglobate acne.

## 14.11 Tumor Necrosis Factor-α Gene: *TNF*

Pro-inflammatory cytokines play an important role in acne pathogenesis [216]. TNFα is a central molecule coded by a gene that shows high level of genetic polymorphisms especially in its promoter region. *TNF* is mapped to chromosome 6p21.3. SNPs of *TNF* are associated with an

increased risk to develop chronic inflammatory diseases. Two SNPs in the regulatory region of *TNF* have recently been detected. The TNFα-857 minor T allele was found to act as a protective factor in a Hungarian study population of acne, whereas a higher occurrence of the minor-308 A allele was noted in female acne patients [24]. Intriguingly, dendritic cells from Foxo3-deficient mice exhibited enhanced production of TNFα and interleukin-6 (IL-6) implying a master role for FoxO3 in regulating pro-inflammatory cytokine production [226]. Genetic variants of the TNFα gene as well as further upstream regulators of TNFα gene expression like FoxO3a may thus affect the risk of acne vulgaris and the inflammatory hyper-reactivity of the pilosebaceous unit.

## 14.12 Interleukin-1α Gene: *IL1A*

*ILIA* mapped to chromosome 2q14 encodes interleukin-1α. IL-1α and IL-1β proteins are synthesized by a variety of cell types, including sebaceous glands, activated macrophages, keratinocytes, stimulated B-lymphocytes, and fibroblasts, and are potent mediators of inflammation and immunity. Recently, a positive association was found between the minor T allele of the *IL1A* +4845(G>T) SNP and acne, whereas no association was found with respect to any alleles of the variable number of tandem repeats (VNTR) polymorphism of the IL1RN gene. The severity of inflammatory acne symptoms correlated with the percentage of individuals carrying the homozygote T/T genotype [23].

## 14.13 Toll-Like Receptor Genes: *TLR2* and *TLR4*

Microbial ligands, including lipopolysaccharide (LPS) and bacterial lipoproteins, activate mammalian toll-like receptors (TLRs) and facilitate the transcription of genes that regulate the adaptive immune responses and induction of antimicrobial activity [227]. TLR2 is encoded on chromosome 4q32 and TLR4 on 9q32-33, respectively. TLR2- and TLR4 expression was increased in the epidermis of acne lesions in vivo [228]. TLR2 is expressed on the cell surface of macrophages surrounding pilosebaceous follicles. *P. acnes* stimulated cytokine production of monocytes through a TLR2-dependent pathway [229]. Moreover, distinct strains of *P. acnes* induced selective human β-defensin-2 and IL-8 expression in human keratinocytes through TLRs [230]. These observations point to an important contribution of TLRs in the induction of innate immunity and TLR-mediated inflammatory cytokine responses in acne [231]. Two mutations of *TLR2* causing amino acid changes Arg677Trp and Arg753Gln, as well as two polymorphisms of *TLR4* causing the amino acid changes Asp299Gly and Thr399Ile studied in 63 Caucasian acne patients and 38 healthy controls were not associated with acne [232]. Thus, TLR gene expression in acne may be upregulated as a result of other upstream regulatory events. In this regard it should be noticed that IL-1α-mediated activation of IL1R results in the activation of IL-1 receptor-associated kinases (IRAKs), which are critically involved in the IL1R/TLR-mediated signal transduction processes that regulate cellular innate and adaptive immune responses [233]. The great structural homology of IL1R and TLR and their molecular cross talk via IRAKs might be a reasonable explanation for IL-1α-induced upregulation of TLR-mediated immune responses in acne. Remarkably, *all-trans*-retinoic acid downregulated TLR2 expression and function [234].

## 14.14 Conclusion and Future Perspectives

The fact, that AR-insensitive individuals do not produce sebum and do not develop acne [59], points to a genetically determined hierarchy of AR signaling in the pathogenesis of acne. The AR is a most sophisticated transcription factor complex and convergence point integrating a diversity of upstream signals and functions [56]. Upregulated GH/IGF-1 signaling of puberty raises AR transcriptional activity by Akt-mediated removal of the AR cosuppressor FoxO1 from the N-terminal AR activation

domain [97, 98]. Genetic *AR* variants, AR upstream coregulators, and downstream effectors are most likely candidate gene-promoting acne. These are gene polymorphisms of enzymes involved in either (1) increased androgen synthesis of adrenal or gonadal origin, (2) genes involved in raised formation or conversion of cutaneous androgens increasing the affinity of androgens for AR binding and activation, like *SRD5A1*, (3) mutations of the *AR* itself leading to increased transcriptional activity like *AR* polymorphisms with reduced numbers of CAG repeats, (4) genetic variants of AR coregulators like FoxO1, and (5) mutations of downstream AR target genes [235] (Table 14.1).

Any genetic variation of components of the GH/GHR/IGF-1/IGF1R/IRS-1/PI3K/Akt/FoxO1 cascade may significantly contribute to acne pathogenesis. The pivotal role of IGF-1 becomes apparent from observations of untreated patients with Laron syndrome with congenital IGF-1 deficiency who do not develop acne despite the presence of normal ARs [139]. However, when female subjects with Laron syndrome are substituted with higher IGF-1-doses, acne and hirsutism developed [236]. Genetic variants with increased activity of FoxO1 and FoxO3 have recently been linked to longevity and lower incidence of age-related diseases [137, 138]. Potential *FOXO1A* and *FOXO3A* SNPs with reduced functional capacity may be favorite acne candidate genes, as these regulatory proteins and transcription factors orchestrate the activity of AR, cyclin D1 and D2, p21, p27, PPARγ, LXRα, SREBP-1, catalase, superoxide dismutase, β-defensin 2, TNFα, TLR4, and MMPs, thus interacting with a high number of important molecular players involved in acne pathogenesis [22, 82].

Recent evidence corroborated the important role of Wnt signaling for sebocyte differentiation and sebaceous gland morphogenesis [20, 237, 238]. Intriguingly, in mammalian cells β-catenin interacts with FoxO1 and FoxO3 [239]. Binding of β-catenin to FoxO enhances the transcriptional activity of FoxO [239]. Interestingly, high Wnt signaling with elevated levels of β-catenin is known to inhibit sebaceous gland morphogenesis and sebocyte differentiation. High nuclear levels of β-catenin bind to FoxO3 and FoxO1 and augment their transcriptional proapoptotic effects [240]. FoxOs and Tcf factors compete for the limited nuclear pool of β-catenin [241, 242]. In this regard, MUC1 polymorphisms associated with severe acne may modify the nuclear pool of available β-catenin, a mechanism which may influence the development of acne. Future studies in acne genetics should thus focus on the regulatory components of the AR transcriptional complex and gene regulatory interactions between FoxO1/AR, FoxO1/PPARγ, FoxO/β-catenin, and MUC1/β-catenin to understand genetic mechanisms of hereditary factors predisposing for acne and their relation to other endocrine and environmental factors with increased insulin/IGF-1-signaling like Western diet [104].

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# Acne and Androgens

# 15

WenChieh Chen and Christos C. Zouboulis

## Contents



**Core Messages**

- Androgens play an essential role in acne pathogenesis. Both testosterone and dihydrotestosterone can be synthesized in the skin and bind to the same androgen receptor which is strongly expressed in the sebaceous glands.
- Many clinical observations point to a close correlation between androgens and acne regarding the onset, timing, severity, iatrogenic induction, and therapeutic intervention.
- Although androgens appear to boost acne formation mainly by increasing sebum production, it is less well defined how androgens influence the proliferation and differentiation of sebocytes.
- Further study is needed to understand the effect of androgens on comedogenesis, colonization of *Propionibacterium acnes*, and inflammation.
- The local overproduction of androgens in situ can be caused by de novo androgenesis from circulating cholesterol or/and conversion of the serum dehydroepiandrosterone to dihydrotestosterone.

## 15.1 Introduction

Acne is a common skin disorder of the pilosebaceous unit affecting over 70 % of the adolescents in all ethic groups [1]. The importance of androgens

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in the pathophysiology of acne has long been recognized and corroborated by clinical observations and experimental studies. Clinical observations supporting the pathogenic role of androgens in acne include (1) close association between primary onset of acne in prepuberty and surge of the circulating dehydroepiandrosterone (DHEA) sulfate [2], (2) acne formation in young children with virilizing tumors or congenital adrenal hyperplasia [3], (3) hyperandrogenism identified in women with sudden exacerbation of acne, persistent acne beyond 30 years of age, and therapy-refractory acne, (4) absence or scarcity of sebum and acne in men with androgen insensitivity syndrome or early castration before puberty [4], (5) increased sebum production in female-to-male transsexuals given testosterone for 4–12 months [5], (6) induction of acne by systemic or topical administration of androgens or anabolic steroids [6], (7) suppression of sebum production in female acne patients treated with various antiandrogens [7, 8], (8) increased sebum production in women 60–79 years old receiving supplementary DHEA at 50 mg daily over one year [9], and (9) beneficial effect of androgen receptor blockers in the treatment of female acne [10–12].

## 15.2 Influence of Androgens on Acne Pathogenesis

The influence of androgens on acne pathogenesis is further confirmed by in vitro studies using sebaceous gland organ culture, rat prepucial glands, primary culture, or immortalized human sebocytes [13–16]. Testosterone and 5α-dihydrotestosterone (DHT) are physiologically the most potent androgens binding to the same nuclear androgen receptor, with the latter being a more active ligand [17]. Androgen receptors have been demonstrated in sebocytes in vitro and in vivo [18, 19]. Four cardinal pathophysiological factors interplay to manipulate acne development:

1. Overproduction of sebum: Sebum production is the terminal process of sebocyte proliferation and differentiation.
   (a) Sebocyte proliferation: The proliferation of sebocytes or facial sebocytes in vitro is significantly stimulated by testosterone and DHT, especially at concentrations higher than serum level [20, 21]. The influence of androgens on sebocytes appears to be dependent on the localization of the sebaceous glands [22]. DHT inhibits the death of sebocytes without involving apoptotic pathways [23]. It is unclear why MK386 (a selective type I 5α-reductase inhibitor) reduces testosterone-stimulated proliferation of sebocytes, while cyproterone acetate (an androgen receptor blocker) exhibits no effect on testosterone-induced proliferation instead inhibits the DHT-induced sebocyte proliferation [24].
   (b) Sebocyte differentiation and lipogenesis: In sebaceous gland organ culture, neither 1 nM testosterone nor 1 nM DHT has any effect on rates of cell division or lipogenesis. In the presence of phenol red with estrogenic effect, however, 1 nM testosterone or 1 nM DHT cause a significant reduction in the rate of lipogenesis [13]. The aforementioned data indicate that the effect of supplemented androgens on cell division and lipogenesis in vitro varies, depending mostly on the culture conditions [8, 25–28], which may also reflect the different situations of androgenic function in acne formation in men and in women.
2. Comedogenesis: Formation of microcomedones is caused by hyperproliferation/dyskeratinization of the infrainfundibulum of follicular canal. It remains to be determined if higher activity of the type I 5α-reductase detected in the follicular infrainfundibulum is related to the abnormal differentiation of keratinocytes [29].
3. High colonization of *Propionibacterium acnes* (*P. acnes*): Androgens do not act directly on *P. acnes*. However, in adults, *P. acnes* are found in highest numbers in sebum-rich areas of skin such as face and chest. Onset of sebum secretion and consequently expansion of the bacteria occur earlier in children who develop acne than in children of the same age and pubertal status who do not develop acne [30]. However, there is no parallel relation

between acne severity and the population density of *P. acnes*. On the other hand, the reduction of sebum with isotretinoin treatment dramatically reduces the colonization of *P. acnes* within one month of therapy and this reduction persists after discontinuation of isotretinoin therapy despite a return of sebum excretion to pretreatment levels [31].

4. Intrinsic or inductive inflammation: Although cytokines and growth factors have been shown to be able to modulate hormone secretion by directly influencing specific enzyme steps of steroidogenesis in various endocrine cell types [32], not much is known about the interaction of androgens and inflammation in the induction or exacerbation of acne. There is some laboratory evidence implying that stress and inflammation can augment the androgenesis in cultured sebocytes [33]. On the other hand, observational and interventional studies suggest that testosterone supplementation reduces inflammatory markers in both young and old hypogonadal men [34]. Testosterone can also downregulate macrophage expression of toll-like receptor 4 in the mouse [35]. In wound healing, the administration of 17β-estradiol, either systemically or topically, has been shown to reverse the fundamental repair defects in postmenopausal women, while androgens retard repair and interfere with the reconstitution of the damaged dermis [36]. This may partly explain why acne scarring is usually more common and severe in men than in women.

Some questions remain open concerning the effect of androgen in acne pathogenesis:

1. Most of the men with acne have normal circulating levels of androgens and the acne severity does not correlate with serum androgen level in women with hyperandrogenism. It is possible that androgens just play a permissive role in priming or initiating acne development especially in men, or it is the local overproduction of androgens in the skin that is crucial. Heterogeneity in the expression and responsiveness of androgen receptors or the cutaneous metabolism of androgens may also account for the different response to androgens [37].
2. The local overproduction of androgens in the skin can be caused by de novo androgenesis from circulating cholesterol or/and conversion of circulating DHEA to DHT [38]. The latter was shown to be the major pathway in a recent in vitro study [39]. Little is known about their partition in acne-prone skin as compared to normal healthy state.
3. It is unclear how androgens act on sebocyte lipogenesis. Do they act on the early differentiation of the cells or directly on the expression of lipogenic enzymes such as diacylglycerol acyltransferase, which controls the synthesis of triglycerides, the most abundant lipid in human sebum [40]?

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# Acne and Inflammation

# 16

Christos C. Zouboulis and Clio Dessinioti

## Contents



**Core Messages**

- Modern aspects of acne pathogenesis regarding inflammation in acne include new perspectives regarding the effects of *Propionibacterium acnes* (*P. acnes*), newly recognized inflammatory mediators (prostaglandins, leukotrienes), and the emerging role of neuropeptides and sebaceous lipids.
- *P. acnes* belongs to the resident microbiota and only a proportion of inflamed acne lesions are colonized by any specific microbial agent, suggesting that *P. acnes* is not a prerequisite for the initiation of inflammation in acne.
- *P. acnes* may attenuate acne inflammation by inducing Toll-like receptor-mediated proinflammatory cytokine responses in monocytes/macrophages, keratinocytes, and sebocytes.
- Certain lipids, such as arachidonic acid and linoleic acid, stimulate IL-6 and IL-8 synthesis in human sebocyte cultures in vitro.
- Lipoperoxides and monounsaturated fatty acids are capable of inducing alteration in keratinocyte proliferation and differentiation, whereas peroxides are capable of inducing production of proinflammatory cytokines and activation of peroxisome proliferator-activated receptors.

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- Leukotriene B4, a derivative of arachidonic acid, induces recruitment and activation of neutrophils, monocytes, and eosinophils and stimulates the production of pro-inflammatory cytokines in acne.

## 16.1 Introduction

Inflammation is undoubtedly one of the major factors involved in acne, and the generation of an inflammatory reaction seems to initiate the hyperkeratinization of the acroinfundibulum and the manifestation of acne lesions. However controversy exists regarding the factors leading to inflammation in acne. While acne inflammation has been suggested to be secondary to bacterial hypercolonization with *Propionibacterium acnes* (*P. acnes*), recent data support a major role of genuine inflammatory signaling in acne [1–3].

Classical aspects regarding inflammation in acne are presented in details in Chap. 12. Modern aspects of acne pathogenesis regarding inflammation in acne include newly recognized inflammatory mediators, the emerging role of neuropeptides and sebaceous lipids, and new perspectives regarding the effects of *P. acnes* (Table 16.1). Upregulated genes playing a role in acne inflammation include interleukin (IL)8, β-defensin 4, and granzyme B [11]. NF-κB and activator protein-1 are active in acne lesions with consequent increase in their target gene expression, such as inflammatory cytokines, enzymes, and matrix-degrading metalloproteinases (MMP) [12]. Besides cytokines and MMP, other pro-inflammatory mediators, such as sebaceous lipids, leukotrienes (LT), and prostaglandins (PG) have been implicated in the acne-related inflammation, and will be discussed in the following sections.

## 16.2 *P. Acnes* and Acne Inflammation

Controversy exists in regard to the role of *P. acnes* in acne and whether it initiates or aggravates inflammation, mainly due to the fact that it belongs to the resident microbiota [13]. In normal skin *P. acnes* density is higher in sebaceous-rich areas

**Table 16.1** Key players in acne inflammation

| | |
|---|---|
| *P. acnes* | *P. acnes*-conditioned medium and formalin-killed *P. acnes* induce sebaceous lipogenesis in hamster sebocytes in vitro [4]<br>*P. acnes* induces cytokine production by monocytes (IL8, IL12) via a TLR2-dependent pathway [5]<br>*P. acnes* GroEL upregulates pro-inflammatory cytokines production in keratinocytes [6]<br>Viable *P. acnes* in the stationary or exponential phase stimulate pro-inflammatory cytokine production by keratinocytes [6]<br>Nonviable *P. acnes* do not induce pro-inflammatory cytokine production by keratinocytes [6]<br>*P. acnes* induces MMP-9 expression by keratinocytes via TLR [7] |
| MMP | Mediate the rupture of the pilosebaceous follicle [8] |
| *Lipids*<br>Linoleic acid<br>Arachidonic acid<br>Squalene oxidation<br>ω3-FFA | Induce IL6 and IL8 release from sebocytes<br>Enhance LTB4 production |
| LTB4 | Mediates chemotaxis of neutrophils, monocytes, and eosinophils<br>Induces superoxide radicals<br>Activates complement<br>Induces pro-inflammatory cytokines that augment tissue inflammation<br>Stimulates IL8 production by neutrophils<br>Binds and activates PPARα |
| *Neuropeptides*<br>Substance P<br>CRH<br>α-MSH | CRH enhances the release of IL6 and IL8 from sebocytes in vitro [9]<br>Human sebocytes α-MSH peptide suppressed IL1β-induced release of IL8 [10] |

[14]. In the hope of establishing a microbial etiology for acne, various investigators have studied the microbiology of acne lesions with varying sampling techniques used. For inflamed acne lesions, *P. acnes* was found in the majority but not all of acne pustules. Most studies were limited by the fact that the duration of individual lesions was not given and an antimicrobial effect of the host immune response could be responsible for the sterility of a number of these lesions (reviewed in Shaheen and Gonzalez [14]). A study addressing inflamed lesions by time of onset, found 10 % of "1-day" pustules not to be colonized by any microorganism, while all the "3-day" pustules were found colonized, suggesting that microbial colonization is not a prerequisite for the initiation of inflammation. Furthermore, after comparison with findings on the microbial ecology of comedones, no significant difference was noted in the bacterial colonization among the comedones and the two types of papules [15]. Another study showed significantly higher density and prevalence of Propionibacteria in inflammed acne lesions, but propionibacteria were found in only 60 % of inflammed lesions [16]. So, it was suggested that microorganisms found in inflammed acne lesions are just an extension of those colonizing comedones and that their presence is not a prerequisite for the initiation of inflammation in acne [14].

It has been shown that the pilosebaceous unit (PSU) is an immunocompetent organ and that keratinocytes and sebocytes may act as immune cells and may be activated by *P. acnes* via Toll-like receptors (TLR), CD1, and CD14 molecules, leading to the production of inflammatory cytokines, thus aggravating inflammation in acne [17]. TLR are mammalian homologues of Toll receptors first defined in Drosophila. Ten TLR have been described in humans; they are transmembrane proteins with the extracellular portion composed of leucine-rich repeats, whereas the intracellular portion shares homology with the cytoplasmic domain of the IL1 receptor. TLR regulate innate immune response and are expressed on immune cells, such as monocytes, macrophages, dendritic cells, and granulocytes and TLR stimulation promotes the production of proinflammatory mediators such as cytokines, chemokines, PG, and LT [18]. When TLR are activated by a ligand, the intracellular domain leads to the nuclear translocation of the transcription factor NFκB, which then regulates the expression of many immune response genes.

*P. acnes* may mediate inflammatory cytokine responses in acne by activation of TLR on monocytes/macrophages and on keratinocytes and sebocytes of the pilosebaceous unit [17–21].

*P. acnes* induces IL8 and IL12 protein production by primary human monocytes via a TLR2-regulated pathway [18]. TLR2 is expressed on the cell surface of macrophages surrounding pilosebaceous follicles in acne lesions and *P. acnes* was shown to induce monocyte cytokine production (IL12, IL8) through a TLR2-dependent pathway [5, 22].

*P. acnes* triggers antimicrobial peptide and cytokine secretion by keratinocytes in vitro [5, 7] and the effects of *P. acnes* on TLR activation in keratinocytes have been extensively studied. TLR2 and TLR4 expressed on keratinocytes are primarily responsible for sensing peptidoglycan (PGN) and lipopolysaccharide (LPS), respectively [21]. TLR2 and TLR4 expression was increased in the epidermis of acne lesions in vivo and *P. acnes* fractions induced TLR2 and TLR4 expression as well as the expression and secretion by the keratinocytes of matrix metalloproteinase-9 in human keratinocytes in vitro [7]. Nagy et al. [5]. investigated the capability of four different strains of *P. acnes* to activate the innate immune response and the growth of keratinocytes. It was found that distinct strains of *P. acnes* significantly induced human β-defensin-2 m RNA levels and that all four strains significantly induced IL8 expression; all of these effects could be inhibited by anti-TLR2 and anti-TLR4 neutralizing antibodies. Additionally, one isolate of *P. acnes* was capable of inducing keratinocyte growth in vitro [5]. Nonviable *P. acnes* do not to induce pro-inflammatory cytokine production by keratinocytes [6]. On the other hand, viable *P. acnes* in the stationary phase of growth stimulate keratinocyte monolayers to produce significant amounts of IL1α, TNFα, or GM-CSF than unstimulated keratinocytes. Also, viable exponential-phase bacteria stimulated production of TNF-α and GM-CSF [6]. Several *P. acnes* cell envelope components such as GroEL and Dnak or lipoglycans have been identified. Moreover *P. acnes* GroEL (a heat-shock protein greatly conserved and with a significant homology to human HSP60) is able to upregulate

the pro-inflammatory cytokine production of keratinocytes. Therefore, the possibility of *P. acnes* GroEL to cross-react in the immune response to bacterial heat shock proteins with their human homologs provides a basis for autoimmunity [6]. *P. acnes*-derived GroEL, DnaK, or lipoglycans may act as ligands for the TLR [8].

*P. acnes*-conditioned medium and formalin-killed *P. acnes* derived from several *P. acnes* strains augment intracellular formation of lipid droplets in hamster sebocytes, by increasing the de novo synthesis of triacylglycerols and increasing diacylglycerol acyltransferase activity in vivo and in vitro [4]. These results indicate a direct role for *P. acnes* in the enhancement of sebaceous lipogenesis through *P. acnes*-derived soluble factor(s) [23]. Also, human SZ95 sebocytes express constitutively TLR2, TLR4, CD14, IL1α, IL1β, IL6, and IL8, and the proinflammatory cytokine production is augmented by exposure to components of Gram-negative (LPS) and Gram-positive (lipoteichoic acid) bacteria [20].

Healthy sebaceous glands also express various cytokines (IL1α, IL1β, and tumor necrosis factor-α) [1, 2, 24], while stressed sebocytes in vitro express IL-1α at the m RNA and protein levels [25].

In addition, human sebocytes produce antimicrobial lipids, antimicrobial peptides (human β-defensin-2, psoriasin, cathelicidin) which exhibit synergistic activities, and induce pro-inflammatory cytokines/chemokines via TLR-dependent mechanisms [17, 26, 27]. Certain *P. acnes* species can stimulate SZ95 sebocytes to produce the endogenous TLR4 agonist human β-defensin-2 [5] and sebaceous cathelicidin can kill *P. acnes* [28]. Human β-defensin-2 is also expressed upon exposure to lipopolysaccharides (LPS) and *P. acnes* [5]. Keratinocytes may also be an important source of antimicrobial peptides such as β-defensins and *P. acnes* trigger antimicrobial peptide and cytokine secretion by keratinocytes in vitro [5, 7]. Cultured keratinocytes may be induced in vitro to express human β-defensin-2 mRNA by distinct strains of *P. acnes* [5].

These findings indicate a direct functional induction of innate immunity in human epithelial cells, including sebocytes, without the involvement of inflammatory cells, while recruitment of the latter to the involved sites can potentiate the inflammatory events in acne [29].

## 16.3 Matrix Mettalloproteinases

Matrix Mettaloproteinases (MMPs) (collagenases, gelatinases, stromelysins, matrilysins) are a family of Zn-dependent endopeptidases produced by different types of cells including keratinocytes and sebocytes, and they are implicated in skin biology during inflammatory matrix remodeling, neovascularization, wound healing, and malignant transformation [12]. By mediating the rupture of the pilosebaceous follicle, MMPs could enhance inflammation [8].

ProMMP-9, MMP-1, and MMP-13 have been found in the sebum of facial lesions of acne vulgaris. MMP-1 and MMP-13 were secreted by HaCaT keratinocytes and proMMP-2 and pro-MMP-9 were secreted by HaCaT keratinocytes and SZ95 sebocytes [12]. An increase in TLR-2, TLR-4, and matrix metalloproteinase-9 (MMP-9) expression by human keratinocytes occurred with incubation with bacterial fractions in vitro [7].

## 16.4 Sebaceous Lipids and Acne Inflammation

Recent data indicate a close correlation between altered sebaceous lipid synthesis and inflammatory signaling, a fact that has been suggested to play a role in the initiation of lesions in acne vulgaris [3]. In acne, along with increased sebum secretion rate, qualitative and quantitative modifications of sebum occur. Keratinocytes and sebocytes may recognize altered lipid content in sebum leading to the production of inflammatory cytokines [17].

Decreased concentration of linoleic acid has been observed in skin surface lipids of acne patients. β-oxidation of linoleic acid is specific of sebocytes and it is correlated with their differentiation. Low level of linoleic acid might account for increased permeability of comedonal wall to inflammatory substances [22, 30].

The primary peroxidation product in human skin surface lipids is squalene monohydroperoxide. In vitro data showed that squalene peroxide beyond induction of HaCaT keratinocytes proliferation led

also to the upregulation and release of inflammatory mediators, which indicate a pro-inflammatory activity of by-products of squalene oxidation [31].

Stearoyl-coenzyme A desaturase (SCD) is an endoplasmic reticulum-bound key enzyme in fatty acid biosynthesis that catalyzes the Δ-9 desaturation of saturated fatty acids. The resulting monounsaturated fatty acids (MUFA) are incorporated in membrane phospholipids, triglycerides, wax esters, and cholesterol esters. Fatty acid delta-6 desaturase 2 (FADS2) converts the essential fatty acid linoleic acid (LA: C18:2, Δ9,12) to arachidonic acid (AA:20:4, ΔS, 8,11,14). AA is a long-chain, pro-inflammatory ω-6 polyunsaturated fatty acid (PUFA), which is essential in membrane phospholipids [32]. AA is the precursor of several proinflammatory lipids and of $LTB_4$ and induces a strong inflammatory signaling response in human sebocytes in vitro [32]. AA stimulates IL6 and IL8 synthesis in cultured human sebocytes [33] and enhances synthesis of sebaceous lipids [34]. When applied directly to human sebocyte cultures in vitro, fatty acids such as AA and linoleic acid, an essential dietary fatty acid, stimulate IL6 and IL8 synthesis [1, 23].

SCD and FADS2 are expressed in human sebocytes at the mRNA level in vivo and in vitro. Induction of TLR2 in SZ95 sebocytes results in upregulation of SCD and FADS2 mRNA expression and a potent inflammatory response via increased IL6 and IL8 production [32]. While linoleic acid strongly upregulated IL6 only, AA induced a mild release of both IL6 and IL8 from SZ95 sebocytes. Competitive binding of SCD selectively inhibited abnormally increased SCD mRNA levels and reduced the linoleic acid-enhanced IL8 secretion. These data may indicate that inhibition of the SCD pathway in human sebocytes results in an anti-inflammatory effect [32].

Moreover, epidemiological studies have shown that increasing the intake of ω-3 fatty acids through a diet rich in fish and seafood may result in lower rates of acne. Intake of ω-3 polyunsaturated fatty acids (PUFA) may affect the inflammatory pathways activation through their inhibitory activity on the pro-inflammatory cytokines secretion and the $LTB_4$ synthesis.

Both lipoperoxides and MUFA are capable of inducing alteration in keratinocyte proliferation and differentiation, whereas peroxides are capable of inducing production of pro-inflammatory cytokines and activation of peroxisome proliferator-activated receptors (PPARs) [31].

### 16.4.1 The Prostaglandin Pathway in Acne Inflammation

Inflammation is characterized by the action of active lipid mediators, such as LT, PG, and 15-hydroxyeicosatetraenoic acids, synthesized from AA or linoleic acid, by the enzymes cyclooxygenase (COX) and lipoxygenase (LOX). PG are lipid signaling mediators that play an important role in cutaneous physiology and pathology, including skin inflammation signaling [35].

PGE2, the major PG present in the skin, is converted from PGH2 under the catalysis of PGE synthase and functions via the PGE2 receptor isoforms EP1–EP4 [35]. Human sebocytes express PGE2 receptors EP2 and EP4 [35]. PG synthesis is differentially supported by COX, a prostaglandin endopeptidase H synthase, a rate-limiting enzyme complex, including the constitutively expressed cyclooxygenase (COX)-1 and the inducible COX-2. Both COX-1 and COX-2 were expressed in SZ95 sebocytes in vitro, and expression of COX-2 was selectively upregulated in acne-involved sebaceous glands in vivo [1]. The natural PPAR-γ1 ligand 15-deoxy-Δ [27, 36]-$PGJ_2$ augmented lipid droplet formation in hamster auricle sebaceous gland cells in vitro [37].

LTB4 plays significant roles in acne comedogenesis and inflammation (Table 16.1). It is the most potent leucocyte chemotactic mediator; it induces superoxide radicals, activates complement, and induces IL8 production by neutrophils. Also, it stimulates DNA synthesis and, therefore, proliferation of cultured human keratinocytes [1]. LTB4 is a metabolite of the LT pathway and originates from AA, via the activity of 5-LOX. Conversely, 15-LOX-1, another member of the LOX family converts AA to 15-hydroxy-eicosatetraenoic acid, which has an inhibitory effect on LTB4 generation and thus exerts an anti-inflammatory action [1].

LTB4 binds and activates PPARα, which can modulate inflammatory response in several cell types by inhibiting the expression of proinflammatory genes that regulate the production of cytokines, metalloproteinases, and acute-phase

proteins. COX-2 expression and PGE2 production are enhanced by PPARγ agonists. PPAR are expressed in human sebocytes in vivo and in vitro [1, 23]. They are regulated by fatty acid derivatives and, among other roles, negatively regulate the transcription of inflammatory response genes. This is accomplished by stimulating the catabolism of proinflammatory eicosanoids.

LTB4 inhibition in vivo reduces concomitantly pro-inflammatory sebaceous fatty acids and inflammatory acne lesions [11]. SZ95 sebocytes express LOX and LTA4 hydrolase at protein and mRNA levels. These enzymes are essential for the formation of LTB4. When SZ95 sebocytes were treated with AA, LTB4 synthesis was increased at mRNA and protein levels [1]. Immunohistochemical studies revealed weaker staining of 5-LOX and LTA4 hydrolase in healthy individuals and in uninvolved skin of acne patients than in acne lesions [1].

Human sebocytes express functional platelet-activating factor receptors, which regulate the expression of inflammatory mediators such as COX-2, PGE2, and IL8 [23].

## 16.5 Neuropeptides and Acne Inflammation

Regulatory neuropeptides with hormonal and non-hormonal activity may control the development of clinical inflammation in acne. Numerous substance P immunoreactive nerve fibers were detected near the sebaceous glands, and expression of the substance P-inactivating enzyme neutral endopeptidase was observed within sebaceous germinative cells of acne patients. Substance P promotes the development of cytoplasmic organelles in sebocytes and induces both proliferation and differentiation of sebocytes [38].

Corticotrophin-releasing hormone (CRH) induces the synthesis of sebaceous lipids in vitro [39], and adrenocorticotropic hormone evokes adrenal dehydroepiandrosterone to regulate skin inflammation [40]. CRH enhances the release of IL6 and IL8 from sebocytes in vitro by an IL1β-independent way [9]. These findings indicate that central or topical stress may influence the feedback regulation and induce clinical inflammation in early acne lesions [3].

In human sebocytes α-melanocyte-stimulating hormone (α-MSH) peptide suppressed IL1β-induced release of IL8, indicating that α-MSH may act as a modulator of inflammatory responses in the PSU [10]. The involvement of neuropeptides in acne is presented in detail in Chap. 17.

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# Acne and Neuropeptides

# 17

Ruta Ganceviciene

## Contents



**Core Messages**

- Neuropeptides (NP), together with hormones and cytokines are essential for the molecular interaction between the nervous, immune, and endocrine systems as well as for the biological homeostasis and responses to exogenous and endogenous stimuli.
- NP genes have been detected not only in the central and peripheral nervous systems but also in most peripheral tissues, including the skin.
- The PSU is both a target and a source of NPs.
- Psychological and neurogenic factors that can influence initiation and/or exacerbation of acne contribute to the multifactorial pathogenesis of acne vulgaris.
- The initiation of stress by extrinsic or intrinsic proinflammatory signals can take place in acne skin, where virtually all hormonal components of the main adaptive response to chronic systemic stress—hypothalamic-pituitary adrenal axis (HPA) axis—can be found.
- Numerous substance P (SP) immunoreactive nerve fibers were detected close to the sebaceous gland (SG), and expression of the substance P-inactivating enzyme neutral endopeptidase was observed within the sebaceous germinative cells of acne patients.

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- The so-far identified immune expression of corticotropin-releasing hormone (CRH) and of melanocortin-1 receptor (MC-1R) as a receptor for α-melanocyte-stimulating hormone (α-MSH), in acne skin introduced the suggestion that these NP are indeed involved in the pathogenesis of acne vulgaris.

## 17.1 Introduction

Although there are several well-known characteristics of acne, such as androgen induced SG hyperplasia and increased sebum production, follicular hyperkeratinization, colonization of *Propionibacterium acnes*, and perifollicular inflammation, the multifactorial nature of acne pathogenesis has not yet been completely elucidated and the mechanism of comedo formation is yet unclear. Although acne vulgaris is an inflammatory disease, it is unknown whether bacteria or their products initiate follicular inflammation [1, 2] or if free fatty acids in sebum are bacterial products [3, 4]. Increased sebum production may propagate an inflammatory tissue response of the PSU involving the release of proinflammatory cytokines including interleukin (IL)-1α, IL-1β, and tumor necrosis factor-α (TNF-α) [4, 5]. Beside cytokines, other pro-inflammatory mediators, such as leukotrienes and prostaglandins, have been implicated in the initiation of acne lesions [6]. Another long-suspected but only recently confirmed pathogenetic aspect in acne vulgaris is psychoemotional stress [7]. In recent years, a dynamic interaction between the nervous, immune, and endocrine systems has received increasing attention. There is evidence that the initiated inflammatory process in acne is in close relation not only with the altered sebum production in SG, abnormal keratinization in the ductus seboglandularis (DSG), but also with a cascade of neuroendocrine events involving regulatory NP with hormonal and nonhormonal activities [8, 9].

## 17.2 Definition and Activities of NP

NP are a heterogeneous group of molecules consisting of two or more amino acids, present in neurons of both the central and peripheral nervous system. Depending on the site of production and the target tissue, they can act not only as neurotransmitters and/or neuromodulators but also as growth factors, neurohormones, and hormones and can manifest immunomodulatory activity [10]. NP, together with hormones and cytokines, are essential for the molecular interaction between the nervous, immune, and endocrine systems, as well as for the biological homeostasis and responses to external and internal stimuli [6, 11]. Activation of the HPA axis, with the production and release of CRH, proopiomelanocortin (POMC) peptides MSH, adrenocorticotropic hormone (ACTH), β-endorphin, SP, vasoactive intestinal polypeptide (VIP), neuropeptide Y (NPY), and calcitonin gene-related peptide (CGRP), is the main adaptive response to chronic systemic stress. ACTH induces production and secretion of the potent anti-inflammatory protein cortisol, which concludes the stress response and buffers tissue damage [7, 8, 12].

## 17.3 NP and Skin Pathology

NP genes have been detected not only in the central and peripheral nervous systems but also in most peripheral tissues, including the skin [12]. The skin, being a target for neuroendocrine signals, is a source of hormones and neurotransmitters with a highly precise mechanism of interactions [13]. The responses to stress of both the skin and the central nervous system share similar but locally produced mediators [13–15]. In peripheral tissues, a particularly important response to stress is represented by inflammatory reactions. NPs are able to regulate both acute and chronic aspects

of inflammatory and proliferative activities [13] and mediate cutaneous neurogenetic inflammation. The HPA axis can also be activated by proinflammatory cytokines [16]. The functional purpose of the CRH/POMC system would be to respond to external and internal stress through local pigmentary, immune, epidermal, adnexal, and vascular structures to restrict tissue damage, stabilize skin function, and prevent disruption of internal homeostasis. Participation of NP in response to cutaneous stress and imbalances in skin stress response system or functional dysregulation of NP is associated clinically with a number of pathologic cutaneous conditions that have significant neuroimmunological components and skin diseases associated with alterations in the differentiation and/or physiology of SG, such as acne, seborrhea, androgenetic alopecia, and age-associated skin xerosis [5, 6].

## 17.4 NP and the Development of Clinical Inflammation in Acne

### 17.4.1 Immunocompetence and Neuroendocrinology of the PSU

The SG is the organ conferring on the skin an independent peripheral endocrine function and, together with sweat glands, accounts for the vast majority of androgen metabolism in the skin [17, 18]. The PSU is an immunocompetent organ [14], which also seems to be involved in responses to stress. Several lines of clinical evidence suggest that nervous system, including psychological and stress factors, can influence the course of acne [19]. Accordingly, stress hormones of the main adaptive response to chronic systemic stress—HPA—may act as players in the pathogenesis of this multifactorial skin disease. The inflammation and the altered tissue environment in the PSU are evident local stress situations and reasons for the initiation of all stress response system mechanisms in acne skin. It is generally accepted that SGs are not innervated and that the peripheral nervous system has no effect on SG biology. In contrast to rarely observed nerve fibers around SG in normal facial skin, facial skin from acne patients shows numerous fine nerve fibers, not only around but also within, sebaceous acini [20, 21]. SG expresses receptors for ß-endorphin, CRH, urocortin, POMC, VIP, neuropeptide Y, and CGRP [13, 21, 22]. After ligand binding, these receptors modulate the production of inflammatory cytokines, proliferation, differentiation, lipogenesis, and androgen metabolism in sebocytes. By means of their autocrine, paracrine, and endocrine actions, these neuroendocrine factors appear to mediate centrally and topically induced stress toward the SG, ultimately affecting the clinical course of acne [23].

### 17.4.2 SP and Acne

Facial skin from acne patients is also characterized by increased numbers of SP containing nerves and mast cells and by strong expression of neutral endopeptidase in SG compared with normal skin [20]. SP can accelerate lipid synthesis, may stimulate the proliferation as well as the differentiation of SG which may be followed by proliferation of *P. acnes*, and may influence the SG by provocation of inflammatory reactions via mast cells [20]. Immunoelectron microscopic study revealed that the numbers of interleukin-6 (IL-6)-positive mast cells and IL-6-containing mast cell granules are significantly increased in acne patients compared with controls. These findings suggest that mast cell-derived IL-6 has the potential to induce nerve growth factor in sebaceous cells, which may result in promoting innervation within and around SG in acne and has possible relationship with the inflammatory process associated with acne [21].

### 17.4.3 CRH/CRH Receptors System, SG, and Acne

The CRH, its binding protein (CRHBP), and CRH receptors (CRHR) act as a central regulatory

system of the HPA axis [22]. The biological effect of CRH and related peptides involves interactions with membrane-bound receptors CRHR type 1 (CRHR-1) and type 2 (CRHR-2) [24], and it can be modified by CRHBP on the central, local, or systemic levels [25].

CRH, CRHBP, and CRHR are widely distributed throughout the skin [22]. The presence of a complete CRH system in human sebocytes has also been confirmed [26, 27]. It is interesting and significant that increased expression of CRH is detected only in acne-involved SGs [28] (Fig. 17.1). CRH is likely to serve as an important autocrine hormone in this cell type with a homeostatic pro-differentiation activity. CRH can influence steroidogenesis independently from the HPA axis. It directly induces lipid synthesis and enhances mRNA expression of Δ5-3β-hydroxysteroid dehydrogenase [27], the enzyme that converts dehydroepiandrosterone to testosterone in human sebocytes [29]. Testosterone and growth hormone, which upregulate sebaceous differentiation [30], were found to antagonize CRH [27]. The ability of CRH to modulate inflammation when secreted in inflammatory sites has been confirmed. Its direct paracrine effects are pro-inflammatory [16], exerted via degranulation of a major immune target of CRH, the mast cells [31]. In central nervous system, cytokines regulate expression of CRH; TNF-α, IL-1, and IL-6 stimulate CRH secretion. IL-1α, IL-1β, and TNF-α are present at multiple sites in normal skin, including the SG [32]. The stronger expression of CRH in inflammatory lesions compared with normal skin, and in the epidermis of acne-involved skin, SG and other skin , compared with those of acne non-involved and normal skin [26, 28] (Fig. 17.1), also suggests that CRH may interact with inflammatory mediators and immune factors in acne. This interaction becomes especially evident after taking into account that the PSU is both an immunocompetent organ and an organ involved in responses to stress and that the free fatty acid cascade also has a special role in acne pathogenesis [33]. CRHR-1 is the major coordinator of the stress response at the central and local level [34]. Although CRHR-2 has been suggested to be the responsible CRH receptor in hair growth [34], it is also possible that it can locally regulate SG functions and have a direct influence on sebum production.

### 17.4.4 Cutaneous α-MSH, SG, and Acne

Based on the recently discovered immunosuppressive capacities of several POMC peptides including α-MSH, the potential role of α-MSH was evaluated not only as a sebotropic and pigmentation hormone but also as a modulator of inflammatory and immune tissue responses within the PSU [15, 35, 36]. α-MSH is a tridecapeptide derived from POMC by post-translational processing [22]. Melanocortin-1 receptor (MC-1R) represents the classical melanocytic α-MSH receptor. Recently, the presence of melanocortin receptors in human sebocyte cultures established from facial skin as well as in the immortalized human sebocyte cell line SZ95, was reported [35, 37]. There is increasing evidence that melanocortin peptides via melanocortin receptors can directly affect the functional state of human sebocytes and increase SG activity [38], as well as influence keratinocyte proliferation and differentiation [15, 39]. α-MSH and testosterone produce a synergistic increase in sebum production [38]. The modulatory effects of α-MSH on inflammatory and immune responses include inhibition of the effect of proinflammatory cytokines (IL-1, IL-6, and TNF-α) [40]. In SZ95 sebocytes, α-MSH partially abrogates the inductive effect of IL-1β on the secretion of IL-8 [35], an important chemokine directing neutrophils to sites of inflammation including the SG, e.g., in acne [15]. A direct stimulatory effect of the superpotent α-MSH derivative NDP-MSH on squalene expression was also demonstrated in sebocytes derived from human facial skin [38], confirming the original idea of α-MSH being a direct sebotrophin in man at least vitro.

The in situ expression of MC-1R, demonstrated by means of immunohistochemistry, in

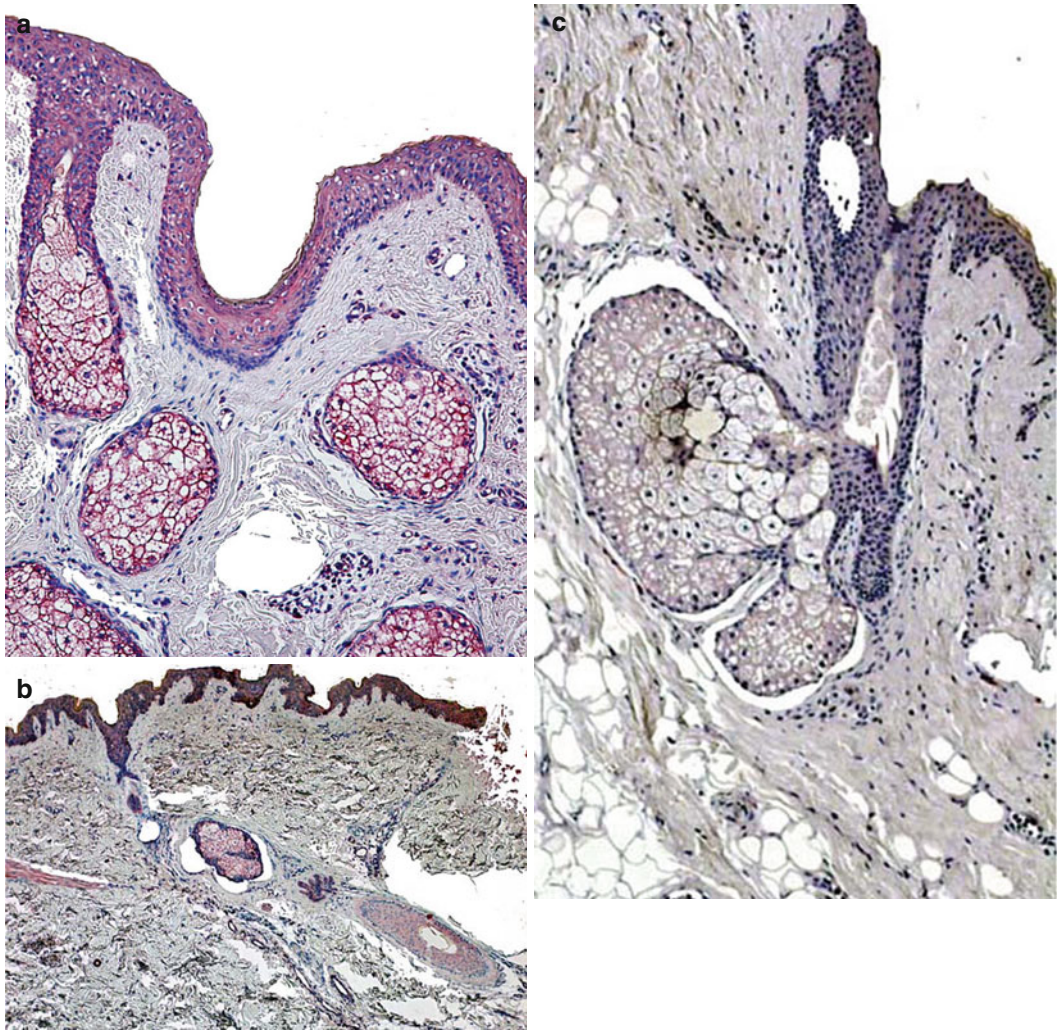


**Fig. 17.1** Localization of CRH immunostaining in SG and the DSG of involved and non-involved skin of acne patients and in healthy controls. Very strong positive reaction for CRH in all types of sebocytes—basal, differentiating and mature cells, and in nerves bundles; (**a**) significant weaker immunoreaction of SG dependent upon sebocytes differentiation stage in control acne-uninvolved skin of acne patients (**b**) and normal skin (**c**). IHC. Mayer's hematoxylin ×400

skin specimens from patients with acne vulgaris and healthy individuals showed that MC-1R is more accentuated in the SG of skin from acne patients than in SG from healthy individuals. Moreover, the reactivity of MC-1R is most prominent in basal and differentiating peripheral sebocytes, which are biologically the most active cells of the SG [41] (Fig. 17.2). As proinflammatory cytokines are upregulated in acne lesions [32, 42, 43], sebocytes may respond to these signals with increased MC-1R expression, thereby generating a negative feedback mechanism for α-MSH which exerts direct anti-inflammatory actions, i.e., inhibition of IL-1-mediated IL-8 secretion [35]. α-MSH itself is able to upregulate its own receptor [44]. Keeping in mind that acne patients are under increased systemic and cutaneous stress, aberrant α-MSH levels may induce increased MC-1R expression in SG. Possibly, upregulation of α-MSH influences the

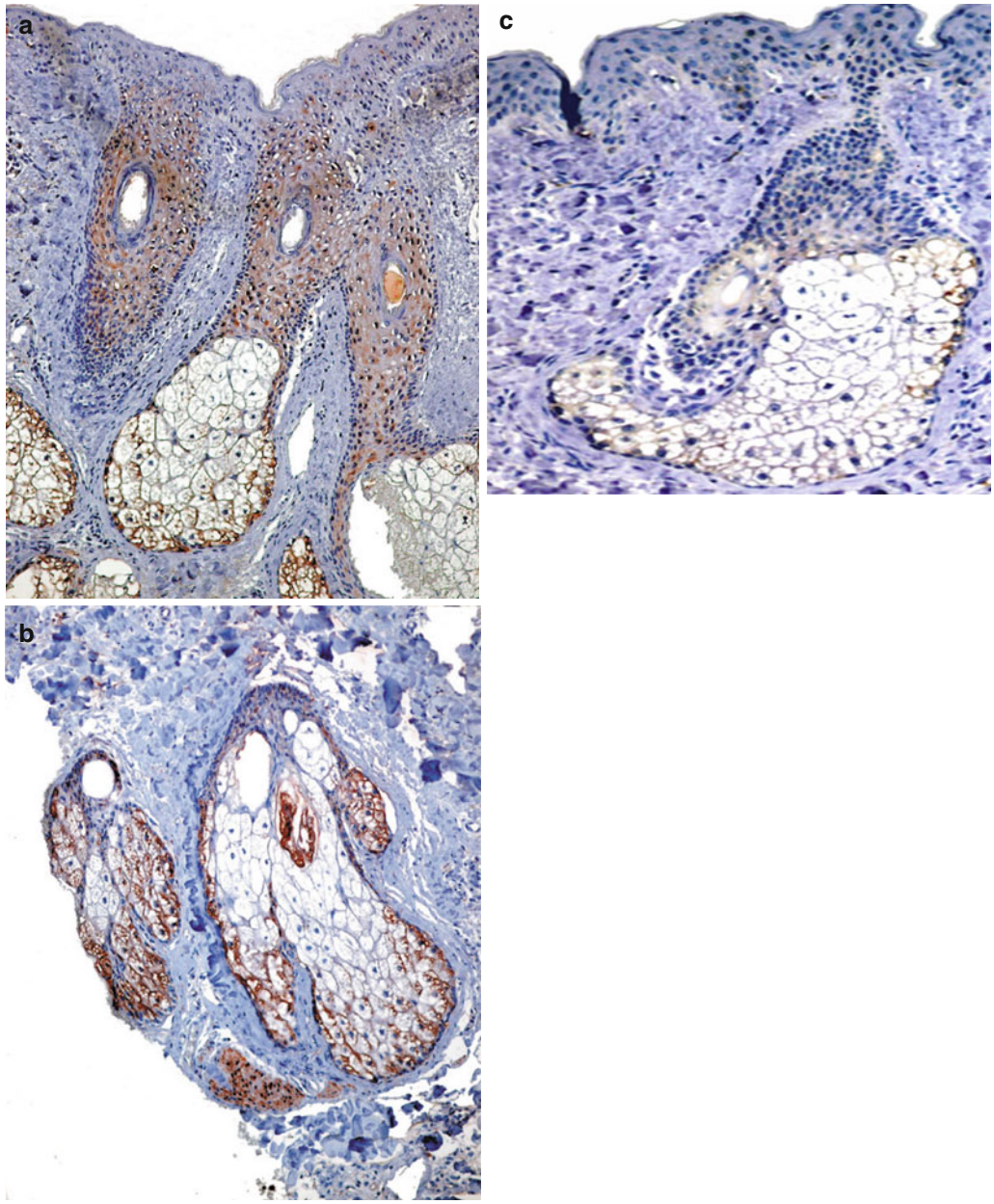


**Fig. 17.2** Localization of MC-1R immunostaining in SGs and the DSG of involved and non-involved skin of acne patients and in healthy controls. Very strong and strong immunostaining of MC-1R in almost all of the cells of involved (**a**) and uninvolved (**b**) skin is observed; reactivity is most prominent in basal and differentiating peripheral sebocytes with less intense staining of mature cells. MC-1R immunoreactivity in SGs of normal skin is less intense. (**c**) Very strong immunostaining of MC-1R in keratinocytes of the DSG of involved (**a**) and uninvolved (**b**) skin is observed in contrast to a scattered reactivity of the cells in DSG of normal skin samples (c). IHC. Mayer's hematoxylin ×200

expression of CRH, a key regulator of the pituitary and cutaneous POMC system, in acne skin [27, 28]. In addition to mediating anti-inflammatory actions, increased MC-1R expression by sebocytes in acne may confer cytoprotection from harmful cytotoxic stimuli released during inflammation (e.g., reactive oxidative species or TNF-α) [45, 46].

DSG is an anatomical structure which plays a crucial role in the pathogenesis of acne due to increased cellular turnover or keratinization [47]. α-MSH can increase the metabolic activity in HaCaT keratinocytes [48, 49]. A significant immunoreactivity of MC-1R in the DSG of acne patients' skin supports also the potential role of MC-1R as a mediator of increased cellular turnover [41].

In the light of the so-far identified direct actions of α-MSH in human sebocytes (i.e., its sebotrophic and immunomodulatory activities) and keratinocytes of DSG, it became possible for the first time to suggest that the MC-1R is indeed involved in the pathogenesis of this inflammatory skin disorder—acne vulgaris.

## 17.5 Perspectives for the Future

Further studies are needed to clarify the exact mechanisms of increased NPs expression and to define the precise role of the NPs systems in acne skin with regard to lipogenesis and inflammation in the PSU. It is very important that the peptidergic systems like SP, CRH, α-MSH, may represent targets for novel treatment of acne vulgaris in the near future.

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# Acne and Bacteria

# 18

Hirohiko Akamatsu, Setsuko Nishijima,
and Yoshiki Miyachi

## Contents



**Core Messages**

- *Propionibacterium acnes* (*P. acnes*), the predominant bacterium isolated from acne lesions, has been supposed traditionally to play an important role in the onset of acne.
- *P. acnes* belongs to the normal skin flora of the human skin and hair follicles.
- *P. acnes*, a facultative anaerobic Gram-positive bacillus, is lipophilic. This is its greatest characteristic in its growth and proliferation.
- *P. acnes* may be involved in the process of inflammation from many aspects, rather than in the induction of acne onset.

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## 18.1 Introduction

When bacteria are isolated from acne lesions, *P. acnes*, *Propionibacterium granulosum*, and *Staphylococcus epidermidis* are typically detected. In many cases, *P. acnes* alone or a mixture of *P. acnes* and *S. epidermidis* is detected. Among these bacterial species, *P. acnes* plays the most important role in the onset of acne. In this article, we focus on acne and *P. acnes*.

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## 18.2 What Is *P. acnes*?

*P. acnes*, a facultative anaerobic Gram-positive bacillus, is part of the skin flora of the human skin and hair follicles. Being lipophilic, which is its greatest characteristic, it can hardly grow without sebum. Therefore, *P. acnes* can only proliferate in lipid-rich areas of the body. In fact, McGinley et al. [1] determined the amount of sebum excreted and the number of *P. acnes* on the face, upper and lower trunk, and upper and lower limbs. They reported that the number of *P. acnes* roughly correlated with the amount of sebum excreted. The seborrheic zone, including the face, anterior thorax, and upper back, which are rich in sebum, is the common site of acne. These sites are also rich in *P. acnes*.

## 18.3 Why Does *P. acnes* Hyperproliferate in Acne Lesions?

Acne occurs as a result of increased secretion of sex hormones, a secondary sexual characteristic in the adolescence. The sebaceous gland is a target organ of sex hormones, particularly androgens, which act on the androgen receptor in the sebaceous gland and allow the sebaceous gland to mature and proliferate. This causes an increase in the excretion of sebum. At this time, hyperkeratinization occurs in hair follicles and causes narrowing and blockage of their infundibular portions. This hinders the excretion of actively secreted sebum through the skin surface, reduces the flow of oxygen into hair follicles, and produces an anaerobic condition. This condition is very favorable for *P. acnes*, which is lipophilic and anaerobic. Therefore, the proliferation of *P. acnes*, a skin flora, is increased in acne lesions.

## 18.4 What Role Does the Proliferation of *P. Acnes* Play in the Onset of Acne?

It appears that proliferated *P. acnes* plays a more important role in the onset and the progression of inflammation, from formed comedos to red papules and pustules, rather than in comedogenesis. It has been presumed that enzymes produced by *P. acnes*, particularly bacterial lipase, hydrolyze triglycerides into free fatty acids (FFA), which are considered to have comedogenic or acnegenic action. It has been reported that the number of *P. acnes* is correlated with the amount of FFA and that FFA increase slightly later than the increase in the number of *P. acnes*. On the other hand, recent research has revealed that active oxygen released from neutrophils that have reached hair follicles driven by neutrophil chemotactic factors produced by *P. acnes* plays an important role in the induction of inflammation [2]. It has been presumed that these active oxygen and FFA induce the irritation and destruction of the walls of hair follicles, causing the contents of the hair follicles to flow out into the surrounding connective tissues and thus increasing inflammation. In addition, *P. acnes* activates CD4 cells and induces the release of IL-1 alpha from keratinocytes of hair follicles. This seems to increase proliferation of keratinocytes and comedogenic potential, leading to formation of microcomedos [3, 4]. It has also been suggested that the activation of the Toll-like receptor (TLR) by the cell wall peptidoglycan of *P. acnes* may be involved in the induction of inflammation in acne. The production of IL-6, IL-8, and IL-12 in monocytes and neutrophils has been found to be dependent on TLR2. It has also been shown that TLR2-positive macrophages infiltrate the tissue surrounding the pilosebaceous units in acne lesions [5].

## 18.5 Classification of *P. Acnes*

*P. acnes* is classified into two serotypes (serotype I and II) according to the antigen structure of bacteria and also classified into five biotypes (biotype B1 to B5) according to the assimilation of ribose, erythritol, and sorbitol [6, 7]. Serotype I includes all biotypes B1 to B5, while serotype II only includes biotypes B1 and B2. Being commonly detected in acne lesions, biotype B3 seems to be greatly involved in the onset of acne [8]. We recently attempted DNA typing of *P. acnes* using randomly amplified polymorphic DNA-polymerase chain reaction (RAPD-PCR).

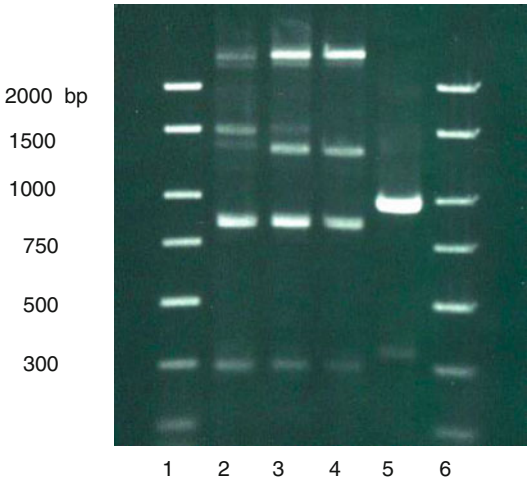


**Fig. 18.1** Classification of *P. acnes* using RAPD-PCR. 1 and 6: DNA Marker, 2: D1, 3:D1/D3, 4:D3, 5:D2

Further, we examined the detection frequency of *P. acnes* isolated from acne lesions and healthy skin by DNA type and found that most *P. acnes* bacteria could be classified into four different DNA types (D1, D2, D3, and intermediate type between D1 and D3) (Fig. 18.1). Among these four types, D3 was commonly isolated from acne lesions irrespective of age group. *P. acnes* D3 is considered to be closely involved in the onset of acne, because it was found to have a higher lipase activity and produce more coproporphyrin than *P. acnes* of the other DNA types [9].

## Conclusions

Research into *P. acnes* started when this species was isolated from acne lesions. The causal relationship with the onset of acne has been disclosed, and at present one of the mainstays of treatment for acne is antimicrobial therapy targeting *P. acnes*. On the other hand, acne is not an infection caused by bacteria, such as *P. acnes*, but is a dermatosis caused by its inflammatory effects flora. Furthermore, recent studies have been identifying genotypes of *P. acnes* that are likely to support the progression of inflammation in acne and others not. Based on these findings, it is expected that a new acne treatment that will only target types of *P. acnes* causing a clinical condition, not all types of *P. acnes*, will be treated in the future.

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# The Acne Biofilm

# 19

Kris Honraet, Bart Rossel, and Tom Coenye

## Contents



**Core Messages**

- Biofilms are the natural form of microbial growth.
- Biofilms have different properties than planktonic (free-floating) cells.
- A biofilm consists of three essential components: the microbial cells, a surface onto which these cells adhere, and an extracellular polymeric matrix, in which cells are embedded and can form larger communities.
- Biofilms are notoriously resistant to antimicrobial therapies.
- Factors considered to be responsible for this increased resistance in biofilms include restricted penetration of antimicrobials, decreased growth rate, expression of resistance genes, and the presence of resistant "persister" cells.
- *Propionibacterium acnes* can form a biofilm in acne, although it is difficult to demonstrate as it cannot be "explanted" and analyzed.

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## 19.1 *Propionibacterium acnes* and Acne

Around the beginning of the nineteenth century, Unna isolated *Corynebacterium acnes* (now known as *Propionibacterium acnes*) from acne lesions in patients, establishing the link between

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acne and local *P. acnes* infection. However, later when *P. acnes* was also isolated from normal, healthy skin [1], its concept as a pathogen greatly declined. In 1963, Kirschbaum and Kligman [2] re-confirmed *P. acnes* as a factor involved in the complex pathogenesis of acne by showing that an injection of viable *P. acnes* into sterile steatocystomas (as a model for sterile acne comedones) could convert these quiescent cysts into inflammatory lesions. Since then research has revealed that *P. acnes* influences inflammation through a wide range of pathways, ranging from neutrophil chemotaxis by *P. acnes* lipase [3] to direct induction of Toll-like receptors in keratinocytes [4]. However, the question remains whether this commensal is capable of initiating inflammation in the sebaceous gland and if so, why colonization does not always result in inflammation. In other words, what triggers *P. acnes* to play its part in acne? The answer to this question may very well be found using the concept of microbial biofilms.

## 19.2 Biofilms

Costerton and Cheng first used the term "biofilm" in the 1970s [5]. Although since then the definition of a biofilm has been changed multiple times, there are three essential components: the microbial cells, a surface onto which these cells adhere, and an extracellular polymeric matrix, in which cells are embedded and can form larger communities [6]. Over the last years, biofilm research has expanded considerably and revealed that biofilms are probably the most common form of microbial growth in nature and that the planktonic (free-floating) phenotype of microorganisms, the original subject of microbiological research over the last 100 years, could be an in vitro artifact.

Dental plaque, one of the oldest known examples of a biofilm consists of a well-defined surface (dental enamel), a matrix of polysaccharides (mainly dextran), and microbial cells (e.g., *Streptococcus mutans*) [7]. However, not all biofilms fit the biofilm definition that easily. For "mucosal" biofilms in, e.g., cystic fibrosis lungs [8] and otitis media [9], the term "surface" has a wider interpretation. In these biofilms the thick mucous layer, which is essentially abiotic (i.e., nonliving material), provides anchorage for the microbial cells and acts as a surface for biofilm formation.

One of the most important properties of the microbial cells (sessile cells) in a biofilm is that they are phenotypically different from their planktonic counterparts [10]. Depending on the microenvironment, microorganisms can regulate the expression of certain genes, allowing them to adapt to changing conditions. Although alterations in gene expression patterns can influence a large number of phenotypical properties, the increased resistance toward antimicrobial agents is one of the most remarkable. Factors considered to be responsible for this increased resistance in biofilms include restricted penetration of antimicrobials, decreased growth rate, expression of resistance genes, and the presence of resistant "persister" cells [11, 12]. This increased resistance allows biofilms to survive in various environments (including the human host) and for infection to persist after treatment. Many chronic infections are now thought to be biofilm related, which would help explain their chronic nature. Antimicrobial treatment kills off a large number of the microbial cells, thereby reducing the symptoms. However, the biofilm, in total, may persist and regrow, and cause reoccurrence of the symptoms.

Another important aspect of biofilms is the ability of sessile cells to communicate with each other using various communication systems. This process, called quorum sensing, is cell-density dependent and allows bacteria to coordinate gene expression by producing signal molecules, i.e., quorum-sensing molecules [13]. By using quorum sensing, microorganisms increase their chances of successfully infecting their host by delaying the production of virulence factors until the population has reached a certain threshold density (quorum), high enough to overwhelm the immune system [14].

## 19.3 *P. Acnes* Biofilm

*P. acnes* is an aerotolerant anaerobic, gram positive, and relatively slow growing commensal of the human skin. It produces extracellular lipases

that hydrolyze triglycerides in the sebum into glycerol and fatty acids. *P. acnes* can use this glycerol as energy source and the end product of the fermentation process is propionic acid (hence the name *Propionibacterium*). The free fatty acids are thought to play a role in the pathogenesis of acne, eliciting an inflammatory response [4].

The complete genome of *P. acnes* has been sequenced [15] and detailed analyses showed it contains several genes that may be relevant for biofilm formation. These genes include the glucosyltransferase (GTF) genes (Open reading frame (ORF) 125–134, 145–150, 1692–1700, 1185, 1791, 2181), responsible for the production of the extracellular polysaccharide matrix, genes for the production of adhesion proteins [16], and the LuxS homolog gene (ORF 405), responsible for the production of the quorum sensing molecule autoinducer-2 (AI-2) [17]. Other genes that encode enzymes for degrading skin and proteins, like hyaluronate lyase (ORF 380), endoglycoceramidases (ORF 644, ORF 2106), and sialidases (ORF 1560, ORF 1569) may contribute to the immunogenic properties of *P. acnes*.

Apart from this indirect genomic proof of *P. acnes* as a potential biofilm former, there are several reports of *P. acnes* biofilms in vivo. The first report of *P. acnes* biofilm formation was published over 20 years ago when Passerini et al. discovered this organism in biofilms from right heart flow-directed catheters [18]. Later studies have detected *P. acnes* biofilms on prosthetic hip implants [19], polymethylmetacrylate bone cement and different titanium alloys used in orthopedic materials [20], cerebrospinal shunts, surgical steel and silicone [21], prosthetic heart valves [22], and intraocular lenses [23]. Often the cells inside these biofilms produce an exopolymer similar in appearance to that of *Staphylococcus epidermidis* [21], a well-known biofilm former. Sessile *P. acnes* cells could also be implicated in endophthalmitis after cataract surgery [23] and in chronic prostatitis [24]. Qi et al. recently showed that *P. acnes* isolates causing fatal bacterial granuloma after trauma are also capable of biofilm formation [25].

## 19.4 The Acne Biofilm Fits in with the Clinical Picture of Acne

The ability of *P. acnes* isolates to form biofilms has already been extensively demonstrated. However, the question remains: does *P. acnes* form a biofilm in acne? Unfortunately, mucosal biofilms or biofilms without a clear-cut abiotic surface in general, as would be the case in acne, are difficult to demonstrate as they cannot be "explanted" and analyzed. Burkhart and Burkhart first suggested that *P. acnes* resides within the pilosebaceous unit as a biofilm [26], based on circumstantial evidence. They surmised that the failure of antibiotic treatment in acne vulgaris could well be caused by the high resistance of sessile *P. acnes* cells. This high resistance to many commercially available antibiotics (including clindamycin and penicillin) and disinfectants (including benzoylperoxide) was indeed demonstrated in several in vitro studies [17, 20, 27].

Coenye et al. also demonstrated that *P. acnes* biofilms produce significantly more lipase than their planktonic counterparts and that this was most pronounced in isolates from acne patients [17]. Lipase is a known virulence factor of *P. acnes* [3] and inhibition of lipase activity has been suggested as a possible treatment of acne [28]. Farrar et al. showed that *P. acnes* in stationary phase induces higher levels of cytokines in keratinocytes than *P. acnes* in exponential phase [29]. This is in line with the biofilm theory, as sessile cells are more comparable to stationary phase cells than exponential phase cells.

It was also shown that cells in young and mature *P. acnes* biofilms produce more of the quorum sensing molecule AI-2 than planktonic cells [17]. AI-2 is a boronated signaling molecule used by bacteria to coordinate gene expression and it is thought to be important in the regulation of virulence of biofilms [30].

The difference between the occurrence of *P. acnes* as a skin commensal in healthy hosts or as a pathogen in acne lesions could be related to phenotypical differences associated with biofilm formation (see Fig. 19.1). These phenotypical switches do not occur until a certain "quorum" of microbial cells is reached. It could be possible

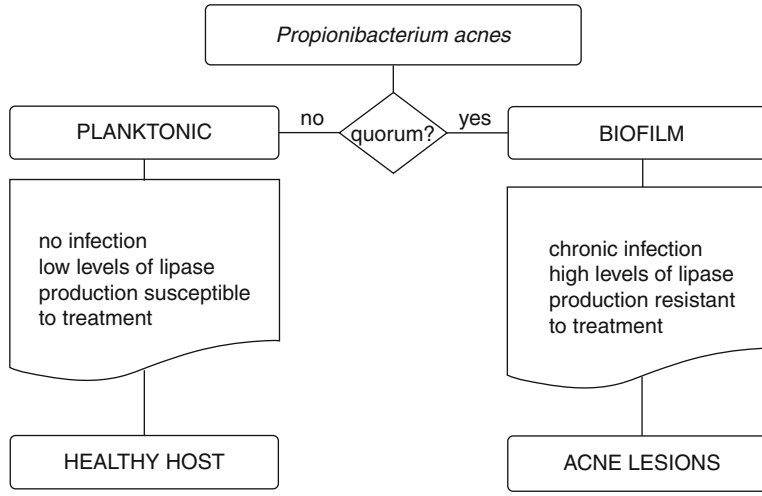


**Fig. 19.1** Hypothetical model using the biofilm concept and quorum sensing for explaining the occurrence of *P. acnes* in both healthy hosts and acne lesions

that in healthy pilosebaceous units, *P. acnes* has not reached the required "acne-quorum." As to why in certain lesions *P. acnes* reaches the "acne-quorum" is at present unclear.

**Conclusions**

- Biofilms are ubiquitous and notoriously difficult to eradicate.
- Biofilms are associated with chronic infections.
- *P. acnes* can form biofilms.
- Acne conditions may favor *P. acnes* biofilm formation.
- *P. acnes* biofilm fits in with the clinical picture of acne.
- An "acne-quorum" could explain why *P. acnes* occurs in both healthy hosts and acne lesions.

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# The Evidence Supporting a Link Between Acne and Nutrition

20

F. William Danby

## Contents



**Core Messages**

- Dietary advice that has been ignored for decades must be reconsidered.
- Dairy products contain hormones and growth factors linked to oil gland function.
- High glycemic load foods also cause elevations in hormones.
- Acne is driven by hormones acting on the oil glands and ducts.
- Controlling acne means controlling hormones.
- Controlling hormones includes controlling diet.
- *No acne regimen is complete without a dietary history and appropriate advice.*
- Dairy products contain hormones.
- High glycemic load foods cause elevations of hormones.
- Acne is driven by hormones.
- Acne can be improved by controlling hormones.
- Vitamin A may help reduce plugging of pores.

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## 20.1 The Evidence Supporting a Link Between Acne and Nutrition

Nutritional advice was a standard part of acne therapy until the 1950s when the introduction of tetracycline, promising faster therapeutic responses, began to overshadow traditional therapies. Recently the role of nutrition in acne has again attracted attention.

Food makes acne better or worse through several pathways. Dairy products come mainly from pregnant cows and contain hormones and growth factors [1]. Drinking milk can directly cause a rise in internal hormones [2]. Vitamin A levels affect keratinization. Numerous dietary components, especially fatty acids, promote or reduce the inflammatory component of the disorder [3].

### 20.1.1 Acne and Dairy

Bulkley in 1885 wrote extensively on the effect of diet in 1500 patients with acne. "Many individuals … with the idea of benefiting an eruption of acne will attempt to drink milk largely with the meals… . This is not at all desirable, and often will be found to act most prejudicially on the eruption. … it is better to entirely cut off milk as a drink at the meals, during the treatment of these cases, or, indeed, permanently." He included cheese, cake and sweets among foods thought to aggravate acne [4].

Diets to treat acne are numerous and include Barber's 1936 advice that "sweets, cakes, pastries, puddings, jam and marmalade, pig fat, chocolate, and cheese should be forbidden altogether," but the basis for such statements was generally experiential rather than evidence based.

The first well-documented study of dairy in acne was Fisher's 1965 record of over 1,000 consecutive acne patients [5]. He "observed in practice that the consumption of an abnormally large amount of cow's milk is often associated with active fluctuations of acne lesions" and stated "I believe the use of milk as a beverage in the adolescent with acne should be discouraged for benefit of improvement of the lesions." Unpublished except for a reference in Time magazine, it was presented to dermatologists but the message never reached the public consciousness [6]. Nothing of substance on the subject followed for almost 40 years.

The association of acne and dairy was solidified by Adebamowo's studies of 47,355 nurses in Harvard's Nurses Health Study (NHS), 6,094 of their daughters, and 4,273 of their sons [7–9]. A 44 % increased risk of acne was documented in the nurses who consumed more than two glasses of skim milk daily. The dose response was paralleled in their children. In the boys, the effects of increased milk intake appeared even before the arrival of synergistic endogenous pubertal Insulin-like Growth Factor-1 (IGF-1), but these three studies are epidemiological and cannot draw a causal line between milk and acne.

From the reverse point of view, the association of *no* acne with *no* milk intake was made by Cordain who described two remote populations whose members had no acne while consuming primitive diets [10]. While his research was directed at other foods and was not aimed at defining dairy exposure, Cordain has noted that drinking milk is not part of the dietary tradition of either group studied. Indeed, the concept is abhorrent to the Aché people, ruling out clinical trials. Tribal members do develop acne when exposed to a Western diet, confirming anecdotally a similar experience with the Inuit [11].

#### 20.1.1.1 Reproductive Hormones in Milk

Fisher's study of milk intake in acne raised the question of hormones in milk but he was unable to convince reviewers that these hormones could be absorbed in quantities sufficient to have physiological or pathological effects on consumers, so his paper was never published. His attempts to identify and quantitate the hormones were frustrated by cost and technical complexity. A few years later Darling's work [12], confirmed by Ginther [13] showed that milk does indeed contain reproductive hormones, including some that are 5α-reduced and so are easily turned into DHT by enzymes in the pilosebaceous units [14].

#### 20.1.1.2 Insulin-like Growth Factor-1 (IGF-1) in Milk

IGF-1 is naturally elevated during the growing years and its levels parallel the incidence and activity of teenage acne. The field is complex and evolving, but we know that ingested amino acids (milk is an excellent source) drive the production of pituitary growth hormone and that stimulates the liver to produce the IGF-1 present in increased amounts during puberty.

IGF-1 is also naturally present in cows' milk but the amount of IGF-1 in dairy product actually absorbed is challenged by the dairy industry. IGF-1 in milk is casein bound and is thought to be unavailable for absorption (this is debated) and swallowed saliva contains orders of magnitude more IGF-1, unbound to casein (and therefore possibly unprotected against digestion), that seems to have no physiological impact.

The IGF-1 debate is complicated by another controversy, the use of injectable recombinant bovine growth hormone (rBGH) to increase production of commercial milk. Concern over rBGH's effects has overflowed into discussions of the effect of IGF-1 on acne. While rBGH stimulates a 10 % increase in milk volume, there appears to be minimal effect on IGF-1 levels in that milk. More importantly, there is yet no literature bearing on the effect, if any, of rBGH on the reproductive hormone content of commercial milk [15].

Hoyt's clarification of the exaggerated hyperinsulinemic responses to the ingestion of both skim and whole milk [16] and their combined effect on IGF-1, serum testosterone, and sex hormone-binding globulin provide ever deeper insight into possible mechanisms of increased testosterone load.

In synthesis, it seems that natural endogenous IGF-1 acts synergistically to promote testosterone's effects on pilosebaceous growth. The enzymes described by Calman [17] and later by Thiboutot [14] in the infrainfundibular epithelia are not present by accident. Anything that enhances DHT production locally or assists in the delivery of its 5α-reduced precursors to the pilosebaceous intracrine system likely promotes acne. Dairy-stimulated IGF-1 supplementing the naturally elevated pubertal IGF-1 may well provide the final push to the DHT-stimulated blockade of the duct and initiation of acne (Fig. 20.1).

#### 20.1.1.3 Other Hormones and Growth Factors in Milk

Koldovsky's survey provided a list of over 60 substances present in milk that may have a synergistic effect on growth [1]. Epidermal growth factor is a tempting contender. While the dairy industry doubts whether these substances are actually absorbed, Bulkley stated "Physiologically milk is already in as perfect a condition for absorption as could be desired; its fatty particles are in the finest state of division, about the same as is observed in chyle, and its slight alkalinity favors its direct entrance into the blood" [4].

While the individual impact on acne of each of these multiple growth factors, reproductive hormones and micronutrients may never be teased out of the overall effect, there is no doubt that milk itself is designed to make newborn mammals grow, whether a tiny baby Bumblebee Bat reaching for its adult weight of 2 g or a baby Right Whale consuming its 200 L of toothpaste-consistency milk daily.

### 20.1.2 Hormones in Nondairy Foods

Studies of the effect of consuming certain foods, and the estrogen, progestogen, and androgen content of foods of both animal and vegetable origin are beginning

#### 20.1.2.1 Glycemic Load and Insulin-like Growth Factor-1

Cordain's original observations on diet and acne focused on the low glycemic load of primitive diets. Smith and Mann studied the impact of this nondairy component of diet on testosterone indicators in a clinical trial that compared a high glycemic load (and raised dairy content) diet against a higher protein/low glycemic load (and decreased dairy content) diet. Significant changes were induced in sex hormone-binding globulin, free androgen index, IGF-1, and IGF-binding protein (IGFBP) levels and were accompanied by improved acne [18].

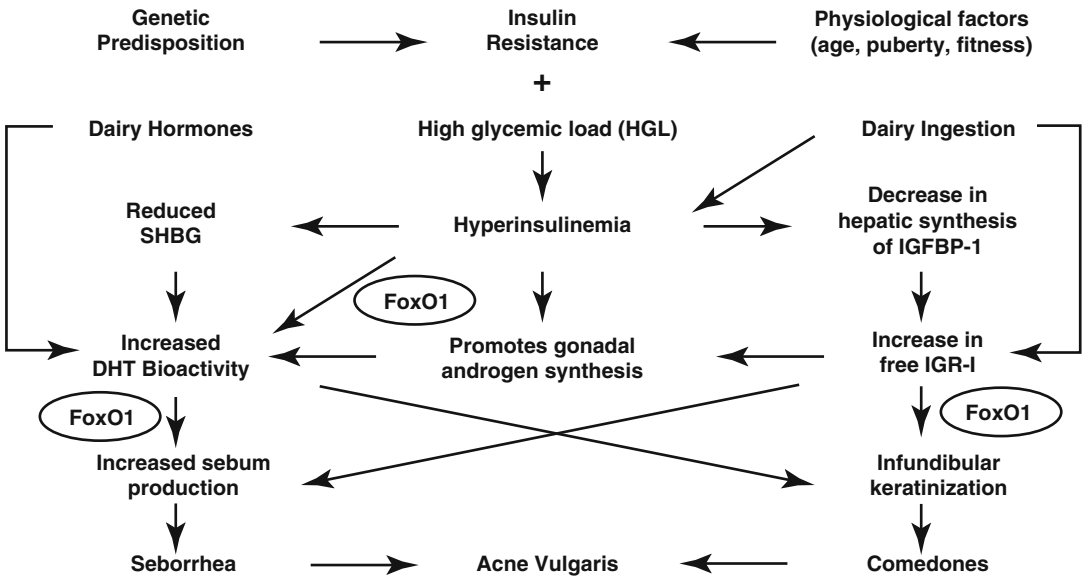


**Fig. 20.1** The influence of exogenous dietary hormones and endogenous hormones induced by dietary elements on the acnegenic hormone cascade, simplified

#### 20.1.2.2 Hormones in Meat

Recently a link between red meat and breast cancer in pre-menopausal women was demonstrated. Natural endogenous hormones in meat and exogenous anabolic molecules added to stimulate growth of animals for human consumption may be responsible, opening a whole new class of foods to question. This has not been studied in acne.

#### 20.1.2.3 Hormones in Vegetables

Although there is theoretical concern about phytoestrogens in foods, there appears to be little evidence of clinical impact, either beneficial or adverse. There is no evidence that one can improve acne with heavy intake of phytoestrogen-containing soy milk or other similar products. The benefit of switching from cows' milk to soy or other vegetable-based milk substitutes appears to be more related to avoiding the negatives of the former than to any addition of benefits from the latter.

### 20.1.3 Other Nutrients

The development of acne depends ultimately upon the creation of a keratin plug in the pilary canal and, while the chain of events that leads to failure of normal terminal differentiation of the keratinization process is not fully elucidated, there are points in the process at which nutrients may have an impact.

#### 20.1.3.1 Vitamin A

Vitamin A is essential for normal growth and differentiation of epithelia. Excess vitamin A can induce glandular or mucous metaplasia, and deprivation causes squamous metaplasia in mucous membrane and hyperkeratosis of normal stratified squamous epithelium. This continuum exists along a range of physiological vitamin A concentrations. Against this background, less than 50 % of individuals in the USA meet Dietary Reference Intakes for Vitamin A. Teens, especially females, have even less intake of vitamin A, suggesting that acne may be partly a consequence of retinol deficiency.

Prior to the availability of isotretinoin, oral vitamin A was used occasionally in acne therapy in very high doses for short periods but no trial is reported in which oral retinol supplementation towards normal serum levels was used as prophylaxis. A deficiency of Vitamin A has been proposed as a contributing factor in the development of neurological, ophthalmological, and psychological side effects of isotretinoin [19, 20].

The provision in the diet of adequate amounts of this essential substance, whose known effects include the normalization of keratinocyte differentiation, would seem a reasonable dietary target.

#### 20.1.3.2 Linoleic Acid

This essential omega-6 fatty acid is the subject of controversy because it has been associated with both comedogenicity and the inflammatory component of acne. Its low level in comedones led to the suggestion that oral supplementation might be of therapeutic value. Conversely, it has the potential to aid inflammation through prostaglandin and leukotriene pathways, and it has been suggested that the low level of comedonal linoleic acid referred to above is secondary to its consumption in this inflammatory process. Its activated form, γ-linolenic acid, has anti-inflammatory properties and is a potent inhibitor of 5α-reductase so it might be expected to mitigate acne. The net effect of dietary linoleic acid on the acne process is thus difficult to judge.

#### 20.1.3.3 Iodine and Iodides

There is no evidence that either iodine or iodides cause true comedonal acne, but flares of inflammatory acne may be enhanced and folliculitis simulating acne may occur [21].

### 20.1.4 Clinical Application of Dietary Changes

The acceptance by the public (and by the medical profession) of the unsubstantiated claim that milk is a wholesome and natural beverage for all age groups is a significant challenge to overcome in managing acne.

There really is no good evidence for the value of lifelong milk intake, indeed there are warning flags appearing, warnings of greater concerns than acne—including prostate, ovarian, and possibly breast cancer. It should not be a surprise to learn that hormonally responsive tissues respond in undesirable ways when exposed to years of unexpected hormones that our bodies have not evolved to handle.

Most dermatologists recognize the impact of hormones on acne; they see the effect of stress and the menses on their patients; but they have been tentative in considering the effect of diet and implementing new knowledge.

While we are awaiting the publication of evidence-based dietary studies, the option exists to suggest a 6-month holiday from all dairy products and high glycemic load foods to all acne patients and most especially the recalcitrant cases.

It is not necessary to ask these unfortunate and often misguided patients to wait for a double-blind study—such a study must wait for a nonhormone-containing milk substitute indistinguishable from milk and will be a long time coming. In the meantime, we know that millions of vegans, milk-allergic, and lactose-intolerant teens in developed countries and millions of individuals in non-milk-drinking societies live healthy lives with no milk. Stopping milk in the face of a well-balanced diet will cause no harm, indeed the low glycemic load and low dairy diet studied by Smith and Mann is far healthier than most diets consumed by teens in North America [18].

#### 20.1.4.1 Approach to the Patient

Patients need to know that acne is caused by hormones from three sources, that the effects are additive, and that reducing the hormone load is essential to long-term success no matter what standard acne therapy is used to clear the active lesions.

#### 20.1.4.2 Gonadal Hormones

Young men know that hormones from the testes/testicles cause beard hair growth. They must know the same stimulation process applies to the cells that line and plug the pilosebaceous ducts.

Young women generally link their menses and flares of acne. This provides a basis for discussion of using ‘hormone control’ to achieve complete acne control and also the need for a non-androgenic (non-male type) progestagen (progestin). The best is drospirenone in the form of an oral contraceptive with ethinyl estradiol. All other progestins in birth control pills, except

cyproterone acetate, are of varying androgenicity. Six months is a minimum to try oral contraceptive therapy, and some may wish this therapy indefinitely. When indicated, this is an effective treatment for a medical condition, acne, although it has the side effect of being a contraceptive. Patients must know that the acne may recur when they stop taking this medication.

#### 20.1.4.3 Adrenal Hormones

Most teens know the adrenal glands make adrenalin as part of the acute stress response, but very few know that these glands respond to the chronic stresses of daily life like homework, school, dating, money, appearance, parents, and siblings. Most readily understand and relate to this picture and to the warning that the major flare we see in the late teens during the first semester of college is the fault of the hormones from the adrenals. Unfortunately, treatment is limited.

#### 20.1.4.4 Dairy Hormones

When the subject of hormones in dairy products is eventually introduced, the hormone–acne link is usually understood. Patients and their parents are invited to review http://www.acnemilk.com, http://www.acnehelp.org.uk/dairy.htm#Dairy2, and http://www.glycemicindex.com for further details.

#### 20.1.4.5 Instructions to Patients

In the author's experience, total avoidance of all dairy products is the foundation for all acne therapy and includes cheese, butter, ice cream, cottage cheese, cream cheese, cream and all forms of fluid milk, dried milk, organic milk, Lactaid® milk, processed cheese spreads and casein, and whey-containing protein powder supplements.

Patients may be given the option of avoiding all dairy products and eating other foods, or stopping all dairy products and supplementing those they miss with nondairy substitutes. A list of 2,500 dairy-free foods is available at http://www.godairyfree.org.

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# Acne and Smoking

# 21

Dimitrios Rigopoulos and Chrysovalantis Korfitis

## Contents



**Core Messages**

- The habit of smoking is medically important.
- The influence of smoking on acne is still controversial.
- Studies have demonstrated either inverse association or no correlation or positive association between acne and smoking.
- It is not clear whether females with acne are affected differently from smoking than men.
- The underlying pathogenesis is still under research.

## 21.1 Introduction

The association between acne and smoking constitutes an ongoing subject of debate. Several studies have been conducted albeit producing inconsistent results.

Since the last century the habit of smoking has spread dramatically along with a change in lifestyle. An increased incidence of cardiovascular diseases and malignancies occurred with epidemiological studies subsequently detecting associations with aggravating factors such as smoking [1].

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## 21.2 Is There an Association Between Acne and Smoking?

In order to address this issue, several studies have been conducted; three of them supporting that there is an inverse association between acne and smoking, two more showing no association, and the remaining three exhibiting positive correlation. In 1993 Mills et al. [2] found a low prevalence of cigarette smoking among 165 patients with severe acne under isotretinoin who completed a questionnaire. Moreover Klaz et al. [3] interviewed 27,083 male patients with acne and suggested an inverse dose-dependent relationship between severe acne and cigarette consumption in men. Rombouts et al. [4] in a cross-sectional study enrolling 594 participants with 215 acne patients showed an inverse association in girls only. However the outcomes for boys were not significant.

The case–control study conducted by Firooz et al. [5] failed to demonstrate any correlation between acne and smoking. Two hundred ninety three patients with acne and 301 controls completed a questionnaire. The outcomes did not reveal any sex-related association between smokers and nonsmokers and the duration and amount of smoking were not significant parameters affecting acne patients. Similarly a study by Rigopoulos et al. [6] reported no such association. Three hundred forty seven students were enrolled and 316 questionnaires were adequately filled. Self-reported acne was present in 187 students, 84 boys and 103 girls. No correlation was found between acne and either the frequency of smoking or the numbers of cigarettes per day.

On the contrary Schäfer et al. [7] in a cross-sectional study with 896 participants and 240 acne patients concluded on a higher frequency and severity of acne among smokers in a dose-dependent manner. They also found that active smokers, men, and younger age were accompanied by a higher risk of acne. Furthermore the retrospective case–control study published by Chuh et al. [8] resulted in a positive association between acne and smoking in males but no significant correlation was found in females. They performed a database search and retrieved the social history including smoking habits of 632 acne patients and 632 controls examined in primary care practices in Hong Kong and India. The outcomes favoring the correlation of smoking with acne in male patients were consistent in both geographical areas but yet insignificant for females. Moreover in a study conducted by Capitanio et al. [9] 1,000 females aged 25–50 years were examined and acne was found in 185 of them. In 138 patients their acne consisted of non-inflammatory lesions (whiteheads, blackheads, and microcysts) only. Non-inflammatory acne was more prevalent among smokers, whereas inflammatory acne was more frequent among nonsmokers. There was no difference in cumulative smoking doses between smokers with and without acne. Also smokers who suffered from acne in puberty had a higher probability to develop adult acne than nonsmokers. In an additional group of 226 women with acne (25–50 years) the same author group assessed the age of onset of the disease, and the number, type, and distribution of acne lesions [10]. 192 of 226 patients (85.0 %) were classified as having comedonal postadolescent acne (CPAA) and 34 as having papulopustular postadolescent acne. A smoking habit was confirmed in 150 of 226 (66.3 %). Remarkably, 72.9 % of patients with CPAA were smokers as compared with only 29.4 % of those with papulopustular postadolescent acne.

The details and outcomes of these studies are concisely reviewed in Table 21.1. The discrepancy in outcomes may be explained by methodology differences, selection bias, reporting bias, genetic differences, and social background among populations, sample size, environmental factors, or even the definition of smoking.

## 21.3 Proposed Pathogenetic Mechanisms

The effect of smoking on acne is still debatable and the mechanism of action is still unknown. It is proposed that acne may be exacerbated by stress [11]. Also a higher risk for smoking or

**Table 21.1** Studies examining the association between smoking and acne

| References | Study design | Outcome |
|---|---|---|
| Mills et al. [2] | Questionnaire based, 165 patients | Inverse association |
| Klaz et al. [3] | Interview, 27,083 male patients, 237 with severe acne | Inverse dose-dependent association in severe acne group (males only) |
| Rombouts et al. [4] | Cross-sectional, 594 participants, 215 patients | Inverse association in girls, no association in boys |
| Firooz et al. [5] | Case–control, 293 patients, 301 controls | No association |
| Rigopoulos et al. [6] | Questionnaire based, 316 participants, 187 patients (self-reported) | No association |
| Schäfer et al. [7] | Cross-sectional, 896 participants, 240 patients | Positive dose-dependent association |
| Chuh et al. [8] | Retrospective case–control, 632 patients, 632 controls | Positive association in males, no significant association in females |
| Capitanio et al. [9, 10] | Interview, 1,000 female participants, 185 patients/226 female patients clinically examined | Positive association in non-inflammatory acne (females only)—Comedonal postadolescent acne (CPAA) in 85 % of the patients—72.9 % CPAA patients and 29.4 % with papulopustular postadolescent acne were smokers |

substance abuse appears to be prevalent among adolescents experiencing anxiety [12]. In such case, anxiety could be a confounding factor in the association of smoking with acne. Furthermore, nicotine induces hyperkeratinization when applied to skin at high concentrations by binding to nicotine acetylcholine receptors expressed by keratinocytes [9].

The inverse association between smoking and acne reported by some authors can be attributed to the inhibition of the inflammatory component of acne through vasoconstriction or immunosuppression induced by smoking [4, 13]. Additionally the numerous effects of smoking on the skin, such as impaired vasoreactivity, increased lipid peroxidation [9], problematic wound-healing, and collagen synthesis [7] have been implicated in the pathogenesis of acne lesions.

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# Antimicrobial Peptides in Acne

# 22

István Nagy and Lajos Kemény

## Contents



**Core Messages**

- The epidermis has a powerful innate immune system that protects the host from bacterial and fungal infections.
- Keratinocytes and sebocytes are immunologically active cells capable to identify and kill invading microbes.
- Keratinocytes and sebocytes recognize highly conserved structures of the pathogens termed Pathogen-Associated Molecular Patterns (PAMPs) by different Pattern Recognition Receptors (PRRs).
- Activation of PRRs results in the production of effector molecules, such as antimicrobial peptides and pro-inflammatory cytokines/chemokines. These mediators have direct microbicidal effects and attract professional immune cells into the skin.
- Antimicrobial peptides are effector molecules of innate immunity as well as regulators of acquired immune responses, inflammation, and wound repair.
- In addition to genetic, hormonal, and environmental factors, inflammatory mediators, such as antimicrobial peptides, have been implicated in the occurrence of acne via the recruitment of an inflammatory infiltrate.
- Several antimicrobial peptides are highly expressed in acne, with corresponding receptors found on professional immune cells involved in skin inflammation.

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## 22.1 Introduction

Normal human skin supports the growth of commensal microflora and it is colonized with a wide variety of microorganisms such as *Propionibacterium acnes* (*P. acnes*), *Staphylococcus epidermidis*, and *Malassezia furfur*. In addition to normal flora, the skin is constantly challenged by a large number of external pathogens, most of which do not cause clinical symptoms. Importantly, in healthy individuals, the deeper layers of the skin remain free of infections suggesting that skin has the ability to fight against invading microbes [1]. Indeed, skin has a powerful innate immune system that protects the host from bacterial and fungal infections. Within the epidermis, keratinocytes and sebocytes represent two, immunologically active cell types, which are able to identify and kill invading microbes. Keratinocytes and sebocytes recognize highly conserved structures of the pathogens, termed Pathogen-Associated Molecular Patterns (PAMPs), by Pattern Recognition Receptors (PRRs), such as Toll-like Receptors (TLRs). Signaling through PRRs activates a chemical cutaneous defense system which results in the production of pro-inflammatory cytokines/chemokines and antimicrobial peptides. Within the skin, these mediators possess dual function: they not only display direct microbicidal activity but also attract professional immune cells. Therefore, pro-inflammatory mediators play crucial role in a number of skin infections, forming complicated networks between keratinocytes, sebocytes, and infiltrates of immune cells. This crosstalk occurs, partly, via antimicrobial peptides and their receptors.

## 22.2 Ancient and Modern: Innate and Acquired Immunity

Innate immunity is the most ancient and well-known system for defense against microbial infections. It has evolved a detection system, a limited set of receptors (e.g., Toll-like receptors, TLRs) against microbial signatures that remain invariant inside a class of microbes [2]. Given that epithelial cells lie at the interface between the host and the environment, the expression of TLRs on these cells provides the first line of defense against invading pathogens through the recognition of microbial motifs. Although termed PAMPs, these motifs are not restricted to distinct pathogens since they include structural molecules such as lipopolysaccharide (LPS), lipoteichoic acid (LTA), peptidoglycan (PGN), lipoarabidomannan (LAM), flagellin, zymosan, or double-stranded (ds) RNA, which are common to multiple species of bacteria, yeast, or viruses, respectively. In addition, a number of endogenous ligands, such as heat-shock proteins or β-defensins, are also TLR ligands. These endogenous molecules are also called "danger signals" released from dying or dead cells in order to trigger an inflammatory response [2].

The innate immune network of the skin consists of a range of pre-existing, rapidly mobilized host defense components including keratinocytes, neutrophils, mast cells, eosinophils, macrophages, and sebocytes. The key cellular components of the pathophysiologic processes of the skin are the keratinocytes, cells that are in a unique position between the interface of the environment and the host organism [3]. The findings that keratinocytes, which form 95 % of all epidermal cells, express PRRs and are potent source of antimicrobial peptides and pro-inflammatory chemokines/cytokines emphasize their key role in the innate immune responses of the skin [4, 5]. Epidermal keratinocytes express, in a constitutive or inducible manner, at least 7 out of 11 known TLRs (TLR1-TLR6 and TLR9) [6–11] as well as nucleotide-binding oligomerization domain protein 2 (NOD2) [12]. Recognition of PAMPs by PRRs initiates quick innate immune responses such as phagocytosis and the production of antimicrobial compounds and inflammatory mediators resulting in the killing and elimination of microorganisms. In addition, these mediators link innate and acquired immunity, as they also function as chemoattractants for the effector cells of the acquired immune response [3].

A rapid innate immune response mediated by keratinocytes subsequently promotes acquired immunity [13]. Importantly, upon cutaneous inflammation, innate and acquired immunity operate simultaneously, leading to extravasation

and homing of cutaneous lymphocyte-associated, antigen-expressing (Cutaneous lymphocyte antigen [$CLA^+$]) memory T cells to the skin, permitting them to encounter and respond to appropriately presented antigen. The ability of T, but also B, cells to recombine antigen receptor genes during development provides an efficient and powerful acquired immune system with nearly unlimited specificity for antigen. Nevertheless, a fundamental aspect of mammalian biology, immunologic memory, is a relatively recent evolutionary event.

## 22.3 Antimicrobial Peptides in Acne

Activation of PRRs, expressed by epidermal keratinocytes and sebocytes, is directly involved in the induction of antimicrobial peptides [12, 14, 15]. This diverse family of small, mostly cationic polypeptides exerts a broad spectrum of cytotoxic activity against bacteria, fungi, parasites, and enveloped viruses. In addition, these peptides modify the local inflammatory response and activate mechanisms of innate and acquired immunity. During the inflammatory processes of the skin, keratinocytes are the main cellular sources of antimicrobial peptides and their expression levels correlates with the susceptibility of the skin to infections. The local accumulation of antimicrobial proteins offers a fast and very efficient way to prevent microbes from establishing an infection. Expression of antimicrobial peptides is induced upon encounter with pathogens as well as during wound healing [16–18]. PAMP-mediated activation of antimicrobial genes can be further increased by pro-inflammatory cytokines produced at sites of inflammation [16–21].

Most keratinocyte-derived antimicrobial peptides belong to defensin and cathelicidin gene families, although other cutaneous peptides, such as chemokines or Peptidoglycan Recognition Proteins (PGRPs) also demonstrate antimicrobial activity. These multifunctional antimicrobial peptides—that are able to kill or inactivate a wide spectrum of microorganisms—play an important role in skin defense and disease pathogenesis.

An increase in the level of antimicrobial peptides has been associated with the initiation and development of both acne and rosacea, suggesting that antimicrobial peptides and their receptors may be important mediators of inflammation in acne [22–24]. Structural cells of the skin, such as keratinocytes and sebocytes, express several antimicrobial peptides in response to *P. acnes* or its structural proteins. As a result—and due to the potential of these molecules to attract various classes of inflammatory cells—T cells, monocytes/macrophages, and dendritic cells are recruited to the sites of infection, where they increase antimicrobial peptide levels by secreting these proteins on their own. The combinatorial diversity in responsiveness to antimicrobial peptides ensures the proper tissue distribution of inflammatory infiltrate under normal as well as pathological conditions. Importantly, antimicrobial peptides are readily detected in acne lesions with local cellular infiltrates carrying the corresponding receptors.

### 22.3.1 β-Defensins

Mammalian β-defensins are small (4–5 kDa) cationic peptides, 28–42 amino acids long, and contain six cysteine residues forming three disulfide bridges. Members of this family have broad spectrum antimicrobial activity; in addition, some also possess immune modulatory effect by recruiting macrophages and dendritic cells to the place of infection [25]. Several β-defensins have been recently identified being expressed by keratinocytes; two of these proteins, hBD-1 and -2, have been implicated in acne pathogenesis.

The expression of hBD-1 is constitutive in epidermal keratinocytes and shows antimicrobial activity against predominantly Gram-negative bacteria such as *Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) [26, 27]. The constitutive expression of hBD-1 in the suprabasal layers of the epidermis suggests that it contributes to the innate resistance of the skin. hBD-1 is expressed in the pilosebaceous unit and its expression is upregulated in acne lesions (Table 22.1). Although its expression is

**Table 22.1** Antimicrobial peptides in acne

| Name acne | Antimicrobial activity | | | Chemotactic for | Induced in acne |
|---|---|---|---|---|---|
| | Gram+ | Gram– | Fungi | | |
| hBD-1 | (+) | + | ? | T cells<br>Dendritic cells | +? |
| hBD-2 | + | + | + | T cells<br>Dendritic cells<br>Mast cells<br>Neutrophils | + |
| LL-37 | + | + | + | T cells<br>Mast cells<br>Monocytes<br>Neutrophils | + |
| Granulysin | + | + | + | Monocytes<br>T cells<br>Dendritic cells<br>NK cells | + |

constitutive, moderate upregulation was observed in most acne vulgaris lesions [28]. Even though the significance of this finding is still not clear, it is reasonable to propose that the increase in hBD-1 expression is a secondary effect and is due to the perilesional infiltrate.

hBD-2 was originally isolated from the desquamated scales of psoriatic skin [17]. Several data suggest a complex role for hBD2 in cutaneous host defense. It not only has microbicidal effect against various microorganisms, such as *E. coli*, *P. aeruginosa*, *Staphylococcus aureus* (*S. aureus*), or *Streptococcus pyogenes* (*S. pyogenes*) [20] but also acts as a chemoattractant for immature dendritic cells, neutrophils and mast cells, and induces the migration of memory T cells. In vivo expression of hBD-2 is localized to the upper layer of the epidermis and the stratum corneum. hBD-2 was also found in the intercellular space indicating that the lipid "permeability" barrier of the skin contains antimicrobial substances [29]. In correlation with the localization of hBD-2 in the more differentiated suprabasal layers of epidermis, the expression of hBD-2 is differentiation regulated [18, 26]. Furthermore, the abundant expression of hBD-2 in inflamed and in infected skin, parallels with the finding that its expression is induced by Gram-positive (*E. coli*, *P. aeruginosa* and *P. acnes*) and Gram-negative (*S. aureus* or *S. pyogenes*) bacteria and also by fungi *Candida albicans* in cultured keratinocytes and in reconstructed human epidermis [17, 21, 23, 30–32]. In vivo, hDB-2 binds to chemokine (C-C motif) receptor 6 (CCR6): the secretion of hBD-2 by epidermal cells activates professional immune cells, inducing their migration from the skin into local lymphoid organs, leading to the generation of cellular immune response through the activation of antigen-specific T cells [33]. Thus, hBD-2 plays multiple roles in cutaneous host defense (a) it provides the first line of defense against infection by acting as a "natural antibiotic" against sensitive pathogens; (b) it plays a key role in the initiation of acquired immune responses against infections by directing the migration of dendritic- and/or T cells and inducing the maturation of dendritic cells. These findings implicate hBD-2 as a link between the innate and acquired immune responses during skin infections.

Similarly to hBD-1, hBD-2 is expressed in the pilosebaceous unit and it is upregulated in acne lesions (Table 22.1) [24, 28]. Keratinocytes and sebocytes are an important source of hBD-2 in acne and, importantly, the inducibility of hBD-2 is (a) *P. acnes* strain specific and (b) TLR dependent [22, 23]. Interestingly, hBD-2 does not have any bacteriostatic or bactericidal effect against *P. acnes*; thus it is likely that the contribution of hBD-2 to acne pathogenesis is the regulation of adaptive immunity by recruitment of T cells and neutrophils to the place of abnormal *P. acnes* colonization [22, 23].

### 22.3.2 Cathelicidin

Cathelicidins are bipartite molecules with an N-terminal cathelin domain and an antimicrobial C-terminal domain [34]. Humans have only one cathelicidin gene (*Camp*) that is expressed as an inactive precursor protein (hCAP-18) in neutrophils, mast cells, eccrine glands, and keratinocytes [16]. Because it is stored as a precursor, it requires additional processing, accomplished by proteinase 3, to yield its C-terminal antimicrobial peptide LL37. In vivo, LL-37 provides with protection against necrotic skin infection caused by Group A Streptococci and it also exerts antimicrobial activity against wide variety of Gram-positive and Gram-negative bacteria [35]. Similarly to β-defensins, LL-37 play multiple roles in the fight against pathogens: in addition to its antibiotic effect, it has potential to recruit mast cells, neutrophils, monocytes, and T cells to inflammation foci, is involved in the re-epithelization of skin wounds, and induces angiogenesis [19, 36–38]. Importantly, cathelicidin has synergistic activity with (a) β-defensins against *S. aureus* and (b) psoriasin against *S. aureus* and *P. acnes* [39, 40]. Importantly, LL-37, β-defensins and psoriasin are all expressed in sebocytes suggesting that sebocytes actively contribute to the immune defenses of the skin. Yet, the total antimicrobial activity in sebocytes is likely due to several antimicrobial peptides acting together [39].

On the skin surface, LL-37 is normally processed to smaller peptides with enhanced antimicrobial functions but lesser inflammatory effects. Rosacea is defined by abnormal inflammation and vascular reactivity in facial skin and patients with rosacea express abnormally high levels of cathelicidin in the LL-37 peptide form [41]. Strikingly, proteolytically processed forms of cathelicidin found in patients with rosacea were found to be dramatically different from those in healthy individuals, where LL-37 is rare and shorter forms predominate. The cathelicidin peptides are a result of a posttranslational processing abnormality associated with an increase in protease activity in the epidermis [41]. Furthermore, the injection of cathelicidin peptides derived from rosacea patient resulted in inflammation in recipient mice [41]. Thus, in patients with rosacea, exacerbated innate immune response, such as the increased expression of antimicrobial peptides and their abnormal processing leads to disease.

### 22.3.3 Granulysin

Granulysin is localized to cytolytic granules and is lytic against both microbes and tumors [42]. It functions both as a cytotoxic agent against pathogenic bacteria and as a chemoattractant that activates monocytes to produce cytokines [43]. Granulysin directly kills *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, and *Plasmodium falciparum* [44].

Granulysin is an antimicrobial peptide whose expression is significantly increased in inflammatory acne lesions (Table 22.1) [24]. Granulysin and synthetic granulysin-derived peptides kill *P. acnes* in vitro and have potential anti-inflammatory effects, such as the suppression of *P. acnes*-induced cytokine release [45]. The key feature of effective anti-acne agents is their ability to maintain antimicrobial activity within the lipid-rich cutaneous environment. Granulysin-derived peptides maintain antimicrobial activity within sebaceous environment and have minimal effect on host cell viability, suggesting that they may not only be efficient antimicrobials but also safe topical agents [45]. These properties make granulysin-derived peptides ideal candidates for the treatment of acne.

## 22.4 Perspectives

Differential expression of antimicrobial peptides appears to play a major role in the susceptibility of patients with chronic inflammatory skin disorders, reacting to infectious complications. Increased expression of antimicrobial peptides in psoriasis correlates with low rate of secondary infection; in contrast, low expression level of antimicrobial peptides characterizes individuals with atopic dermatitis, who are highly susceptible to bacterial and viral infections. Interestingly, antimicrobial

peptides all seem to be inducible in acne, suggesting that they actively contribute to the pathogenesis or to the resolution of the disease. Even though the actual concentrations of antimicrobial peptides in the skin and in the sebaceous gland remains unknown, it is reasonable to propose that the primary role of antimicrobial peptides in acne is the recruitment of professional immune cells to the sites of abnormal *P. acnes* colonization, hence initializing inflammatory events.

Antibiotics have been the most powerful weapons against microbial invaders for more than six decades. The development of multidrug-resistant bacterial strains has, however, severely limited the effectiveness of traditional antibiotics. It has been recently proposed that future compounds developed to treat acne should be able to reduce pro-inflammatory lipids in sebum, downregulate pro-inflammatory signals in the pilosebaceous unit, and reduce sebum production [46, 47]. Moreover, increase in frequency of resistant *P. acnes* strains is becoming a major clinical issue and underscores the need to identify new therapeutic agents.

Various antimicrobial peptides are expressed in healthy skin without any visible signs of inflammation, suggesting that (a) antimicrobial peptides may be induced in the absence of pro-inflammatory cytokines/chemokines and (b) resident skin microbiota may facilitate antimicrobial peptide induction without inflammation. This leads to the challenging hypothesis that the beneficial effects of resident microbiota may come from their ability to induce antimicrobial peptide expression [48]. The identification of microbial components, inducing solely antimicrobial peptides and not pro-inflammatory cytokines/chemokines, would promote artificial stimulation of antimicrobial peptide synthesis. Consequently, increased protection toward infection could be offered.

### Conclusions

Keratinocyte- and sebocyte-derived antimicrobial peptides induced by various pathogens, for example, *P. acnes*, possess dual function: they not only display direct microbicidal activity against bacteria and fungi but also regulate the recruitment of various classes of phagocytic cells, T cells, and monocytes into the sites of infection. Therefore, structural cells of the skin can be regarded as potent immune cells as they fulfill the requirements for the induction of both innate and adaptive immune response. Accumulating evidence supports the role of antimicrobial peptides and their receptors in the development of acne, thus modifying current concepts regarding comedogenesis and inflammation resulting in clinical acne lesions. Still, much remains to be learned about the pathogenesis of acne regarding the role of *P. acnes* and antimicrobial peptides. Consequently, understanding the induction and mechanisms of action of these proteins represents an emerging area of investigation that may facilitate the design of novel therapeutical approaches.

These exciting discoveries extend our current understanding of skin innate immune functions and may give rise to future perspectives in the treatment of inflammatory skin disorders, such as acne.

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# Acne and Antimicrobial Lipids

# 23

Christos C. Zouboulis

## Contents



**Core Messages**

- Currently reported data strongly indicate a central role of sebaceous lipid quality and not quantity on the development of acne and other inflammatory skin diseases.
- Several lipid fractions, especially sebaceous lipid fractions, also express antibacterial activity, possibly protecting the sebaceous gland from major infections.

## 23.1 Introduction

The most obvious function of the sebaceous gland is to excrete sebum [1, 2]. For a long time hyperseborrhea has been considered as a major etiopathogenetic factor for the development of acne. However, current research provides evidence that sebum quantity per se cannot be the only responsible factor, as demonstrated by the success of treatment with agents with no primary effect on sebum excretion rate [3]. Indeed, additional functions of the gland are associated with the development of acne (Table 23.1), with prominent among them alterations in sebaceous lipid fractions.

## 23.2 Sebaceous Glands and Innate Immunity

Keratinocytes and sebocytes, as major components of the pilosebaceous unit, may act as immune-active cells capable of microbial

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**Table 23.1** Sebaceous gland functions, which are possibly involved in the development of acne

- Production of sebum [4]
- Regulation of cutaneous steroidogenesis [5–9]
- Regulation of local androgen synthesis [6]
- Interaction with neuropeptides [10, 11]
- Synthesis of specific lipids with antimicrobial activity [12]
- Exhibition of pro- and anti-inflammatory properties [9, 13–15]

recognition and abnormal lipid presentation (see Chap. 16). Acting that way, keratinocytes and sebocytes may be activated by *P. acnes* and recognize altered lipid content in sebum, followed by the production of proinflammatory cytokines. In addition, antimicrobial peptides, such as defensin-1, defensin-2, and cathelicidin, are expressed and are immune reactive in the sebaceous gland [16–19]. Human β-defensin-2 (hBD-2) is expressed upon exposure to lipopolysaccharides and *P. acnes* [18] and upregulated by sebum free fatty acids [19]. Stearoyl coenzyme A desaturase (SCD), an enzyme responsible for the biosynthesis of monounsaturated fatty acids, is also expressed by the sebaceous gland [20, 21]. The TLR-2 ligand macrophage-activating lipopeptide-2 stimulates both SCD and its downstream enzyme fatty acid desaturase-2 in SZ95 sebocytes.

## 23.3 Sebum

Sebum is the first demonstrable glandular product of the human body [22]. It is a mixture of relatively nonpolar lipids [22, 23], most of which are synthesized de novo by the sebaceous gland of the mammals to coat the fur as a hydrophobic protection against overwetting and for heat insulation [22, 24]. The composition of sebum is remarkably species specific [4, 22, 25].

## 23.4 Sebaceous Lipids

Human sebaceous glands secrete a lipid mixture containing squalene and wax esters, as well as cholesterol esters, triglycerides, and possibly some free cholesterol [22, 23, 26–28]. Bacterial hydrolases convert some of the triglycerides to free fatty acids on the skin surface [29, 30], however, there is also evidence indicating that sebaceous glands can also synthesize considerable amounts of free fatty acids [15].

## 23.5 Alterations in Acne

It is not long ago that the oxidant/antioxidant ratio of the skin surface lipids [31] and currently alterations of fatty acid composition [32, 33] have been taken into consideration in the etiopathogenesis of acne and other skin diseases (Fig. 23.1). Lower essential fatty acid levels were found in wax esters in twins with acne rather than in twins without acne [34]. The sebaceous ω9-fatty acids sapienate C16:1δ6, palmitate C16:0, and oleate (C18:1) are very effective against Staphylococcus aureus [12, 16, 20, 35]. Lipids at the skin surface, mostly secreted from the sebaceous glands (90 %) and transported through the follicular canal, are part of the innate immunity of the skin and contribute to the antimicrobial skin barrier. On the other hand, dysfunction of the upstream lipidogenic enzymes stearoyl-CoA desaturase and fatty acid desaturase 2 is associated with skin infection and inflammation [20, 21]. However, neither all ω6-fatty acids are comedogenic nor all ω9-fatty acids (Fig. 23.2) inhibit comedogenesis. For example, oleate alters the calcium dynamics in epidermal keratinocytes and induces abnormal follicular keratinization leading to comedogenesis in rabbit skin but to minor irritation in human skin [36]. Overall, free fatty acids were detected to express proinflammatory and anti-inflammatory properties [13, 19, 37, 38].

Altered ratio between saturated and unsaturated fatty acids has been indicated as an important feature to be considered in addition to the altered amount of specific fatty acids such as linoleate (LA; C18:2), an essential ω6-fatty acid that cannot be synthesized in vivo, and therefore must be obtained from the diet [33]. High levels of sebum LA may protect from the development of comedonal acne [39]. On the other hand, low LA levels have been observed in skin surface

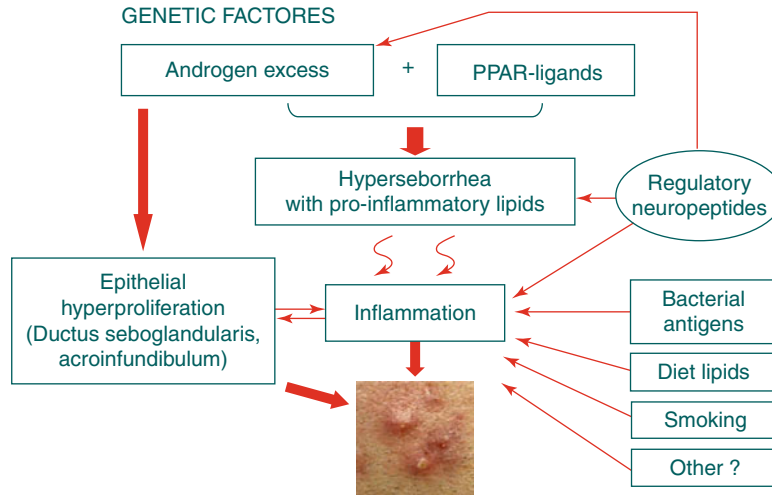


**Fig. 23.1** Modern aspects of acne pathogenesis. Androgens, PPAR ligands, regulating neuropeptides, and environmental factors lead to hyperseborrhea, to epithelial hyperproliferation into the ductus seboglandularis and the acroinfundibulum, and to expression of proinflammatory chemokines/cytokines, which promote the development of comedones and inflammatory acne lesions (by Zouboulis et al. [2])

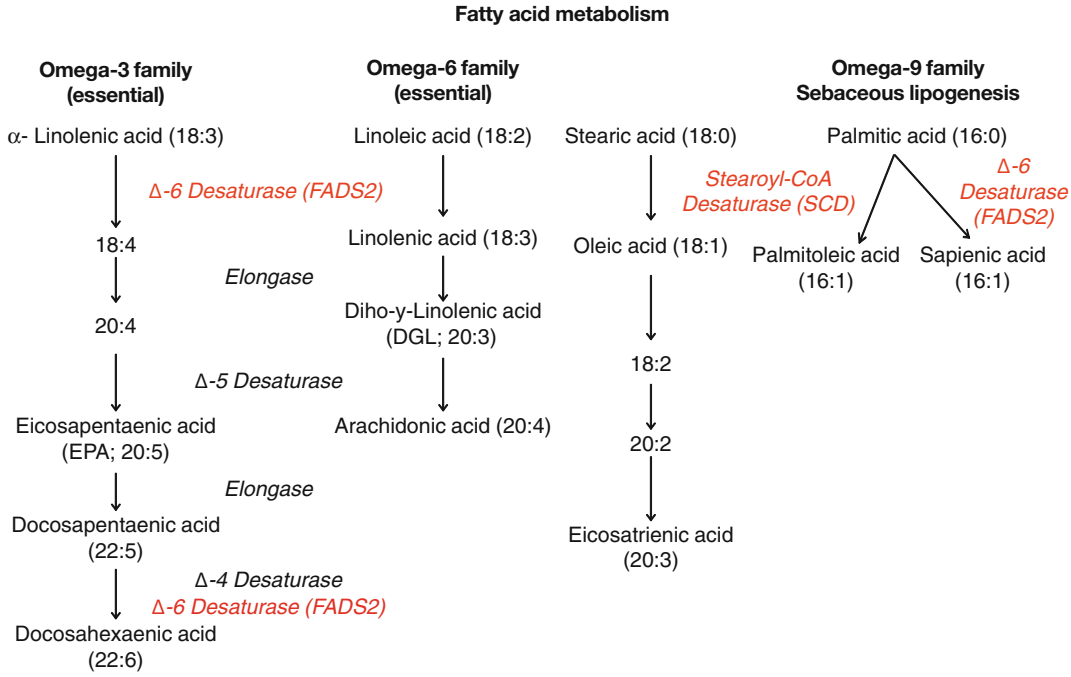


**Fig. 23.2** Fatty acid metabolism and sebaceous lipogenesis

lipids of acne patients [40]. Its topical application reduces microcomedones and inhibits steroid 5α-reductase activity [41, 42].

Particular attention has been focused on peroxidation of squalene, another sebaceous gland-specific lipid, e.g., by UV radiation, which led to comedogenesis on the rabbit ear skin [43]. Moreover, squalene peroxide seems able to induce an inflammatory response beyond cytotoxicity and comedone formation [33]. Oxygen and microorganisms transform "native" sebum with lysis of triglycerides to fatty acids being the most pronounced activity [7, 44]. Certain components of this complex mixture of molecules present in the sebum are clearly cytotoxic or irritant, provoking reactive follicular hyperkeratosis and comedone

formation—the first step to acne. As discussed above, IL-1α levels are a hallmark of comedogenesis [45, 46] and, while *P. acnes* is unable to induce IL-1α expression in the pilosebaceous unit [47, 48], oleate—through keratinocyte toxicity—causes increased IL-1α mRNA levels. The quantities of lipid peroxide, IL-1α, and NF-κB were found significantly higher in the content of comedones than those in the stratum corneum, indicating that the accumulation of a certain amount of lipid peroxide in the content of comedones may play an important role in the progression of comedogenesis [25] and the inflammatory changes detected in these apparently non-inflammatory lesions [2, 15]. In any case, scarce inflammatory infiltrates around the ductus seboglandularis and later on perifollicular infiltration are closely associated with comedone formation [2, 15, 49] and does not develop in a later stage leading to "inflammatory comedones," as previously reported [43].

## Conclusions

Increased sebum excretion, alteration of lipid composition and the oxidant/antioxidant ratio of the skin surface lipids are major concurrent events associated with the development of acne [1]. Interestingly, currently reported data strongly indicate a central role of sebaceous lipid quality and not quantity on the development of acne and other inflammatory skin diseases. Moreover, several lipid fractions, especially sebaceous lipid fractions, also express antibacterial activity, possibly protecting the sebaceous gland from major infections.

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# Natural and Artificial Suntanning

# 24

Anja Thielitz and Harald P.M. Gollnick

## Contents



**Core Messages**

- There are no controlled clinical studies to support the therapeutic effect of UV radiation or suntanning in acne.
- Few observational studies show minor efficacy of UVB or UVB/UVA radiation which is inferior to established topical treatments.
- The effect of UV radiation on acne is mainly related to camouflage of inflammatory lesions resulting from UV-induced erythema.
- UV radiation, particularly UVA, enhances comedogenic properties of sebum by squalene peroxidation.
- UV radiation interacts with concomitant acne treatments by decreasing stability of topical retinoids and aggravation of phototoxic effects of tetracyclines.
- The short-term camouflage effect of suntanning is counteracted by long-term aggravation of skin aging and carcinogenicity.

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## 24.1 Introduction

Acne is a frequent reason to use sunbeds and has been identified as an "appearance motive" for tanning [1]. Patients with skin diseases such as

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psoriasis, eczema, and acne use sunbeds more often than unaffected individuals [2]. Despite the frequent use of natural or artificial UV radiation in the past, the available evidence to support the UV treatment of acne is very low. Only few observational studies dating from 1978 to 1987 and no controlled clinical studies exist.

### 24.1.1 Mechanism of Action

UV radiation has pleiotropic effects on skin cells depending on dosage and skin condition. Studies investigating directly UV-induced effects in acne patients on a molecular level are lacking. However, from in vitro and in vivo models and observations in other skin diseases, conclusions about possible effects of UV light on acne skin can be hypothesized. In hair follicle keratinocytes, UVB suppresses proliferation and induces apoptosis [3]. In psoriatic skin, keratinocyte proliferation markers and the dermal and epidermal T cell infiltrate were reduced after narrow-band UVB [4], which might have a similar impact on pathogenetic factors of acne. On the other hand, in hairless mice, UVB induced sebaceous hyperplasia [5]. UV-induced $H_2O_2$ regulates acetylcholinesterase activity, which is itself highly present in the adnexal structures and regulates keratinocyte and sebocyte differentiation [6]. Furthermore, narrow-band UVB suppresses *P. acnes* growth [7]. These possible anti-inflammatory effects in acne are counteracted by pro-comedogenic effects which result from UVA-induced squalene peroxidation and have been demonstrated in the rabbit ear model [8].

## 24.2 Clinical Evidence

No controlled clinical studies are available supporting the use of artificial or natural UV exposition in the treatment of acne. Some observational and explorative studies exist [9–13], which have been performed more than 20 years ago.

Although the initially reported results were quite promising, UV therapy has not been further followed up in the therapy of acne, probably because the results were inferior to other available therapies or the cost/side effect–benefit ratio was inadequate to pursuit this treatment further. All performed studies consistently report that UV therapy is not suitable for severe acne forms. One major methodological drawback of the available studies is that no lesion counts were performed, but severity scores mixing up mixing-up different lesion forms and erythema. Corresponding to in vitro observations, UVB, and a combination of UVB and UVA were more efficient than UVA alone [9]. No effects on comedone counts were found with either therapy.

One study investigating the effect of selective ultraviolet phototherapy (SUP), a mixture of borderline UVA and UVB wavelengths, reported 75 % good or excellent results after a mean number of 31.2 treatments in mild to moderate acne forms [10]. Similar results were found in another study investigating 20 patients radiated three times a week with UVA/B over 7 weeks [11]. Another SUP therapy study performed in 67 acne patients reported excellent results in 42/44 acne patients with mild forms, whereas severe acne showed only a minimal or no response [12]. Another small study with 18 patients reported a reduction of acne severity grade from 1.4 to 0.9 after 20 UVA radiations three times a week [13]. Interestingly, both studies [11, 13] reported also a suppression of seborrhea, which might result from UV erythema-related skin dryness, because animal models suggest rather a sebaceous hyperplasia resulting from UV radiation [5].

Based on the available evidence, the use of UV radiation cannot be recommended in acne therapy. The short-term camouflage and possible anti-inflammatory effects induced UV erythema and tanning are counteracted by negative effects in the acceleration of skin aging and the cumulative carcinogenicity risk.

## 24.3 Interaction with Concomitant Acne Therapy

Although the therapeutic use of UV radiation is obsolete in modern acne therapy, the patient-related use of natural and artificial suntanning

**Table 24.1** Interactions of acne drugs with UV light

| Drug | Interaction |
|---|---|
| Topical tretinoin | Degradation (81–90 %), photosensitivity |
| Topical tretinoin microsphere gel | Few degradation (6–16 %), photosensitivity |
| Adapalene | Mild photosensitivity |
| Tazarotene | Mild photosensitivity |
| Azelaic acid | Oxyradical-scavenging activity (protective) |
| Benzoyl peroxide | Mild photosensitivity |
| Clindamycin | None |
| Nadifloxacin | None observed as yet (but known phototoxicity of fluoroquinolones) |
| Doxycycline ≫ tetracycline, lymecycline > minocycline | Phototoxicity |
| Isotretinoin | Photosensitivity |
| Clindamycin-BPO | Mild photosensitivity |

must be taken into account especially when topical or systemic anti acne drugs are prescribed.

Problems can occur both on the patient side, like increased sun sensitivity due to reduced stratum corneum thickness (topical and systemic retinoids) or general skin irritation (retinoids and BPO) or phototoxic reactions (tetracyclines), as well as on the product-related side, which might lose its chemical stability during sun or light exposure. Although a recent study excluded photocarcinogenic effects in solar-irradiated hairless mice treated with BPO or BPO/Clindamycin [14], it should be taken into account that BPO is a free radical generating compound that enhanced UV-induced carcinogenesis in other murine models [15]. Table 24.1 summarizes the interactions of topical and systemic acne drugs with sun/light exposure [16–21].

## 24.4 Clinical Guidelines for the Use of Suntanning in Acne

- Direct and prolonged sun (or artificial UV) exposure should be avoided especially during therapy with retinoids, BPO, and systemic tetracyclines, and sunscreens are recommended during the sunny season.
- Topical retinoids should be applied preferably in the evening to avoid stability problems, especially when tretinoin is used.
- During the sunny seasons and in UV-sensitive individuals, doxycycline treatment should be avoided or minimized (dose-dependent phototoxicity) or highly effective sunscreens permanently used.
- No "therapeutic suntanning" should be recommended.
- If individuals report improvement of their acne after sun exposure and refuse to avoid suntanning, drugs with no or protective interactions with UV light (e.g., azelaic acid) should be preferred.

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# Acne and Environmental Pollution (Chloracne)

# 25

Qiang Ju and Lonqing Xia

## Contents



**Core Messages**

- Environmental pollutants can result in a variant of acne, which was first described in 1887 by Von Bettman and later by Herxheimer in 1889, who suggested that it was caused by chlorine exposure and hence called "chloracne" based on the similarity of its clinical features with acne vulgaris.
- Chloracne is caused by systemic exposure to certain halogenated aromatic hydrocarbons "chloracnegens" and is considered to be one of the most sensitive indicators of systemic poisoning by these compounds. Dioxin, a large family of halogenated aromatic hydrocarbons, is the most potent environmental chloracnegen.
- Most cases of chloracne have resulted from occupational and non-occupational exposures, non-occupational chloracne mainly resulted from contaminated industrial wastes and contaminated food products.
- Non-inflammatory comedones and straw-colored cysts are the primary clinical manifestation of chloracne. Cysts increasing in number is a sign of aggravation of chloracne. Generalized lesions can appear on the face, neck, trunk, extremities, genitalia, axillary, and other areas. Other skin lesions always are

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accompanied such as decreased sebum secretion with skin xerosis, pigmentation, porphyrinopathy, hirsutism, skin thickening, palmoplantar hidrosis, and palmoplantar hyperkeratosis.

- Chloracne has a chronic course, as chloracnegens are highly lipophilic and can remain in body fat for long periods of time. The severity of chloracne is related to the level of exposure to chloracnegens, the chloracnegenic potency, and individual susceptibility.
- Histopathology of chloracne is characterized mainly by hyperplasia of epidermal cells, while follicular and sebaceous glands are replaced by keratinized epidermal cell. The pathogenesis of chloracne may be related to the imbalance of epidermal stem cell.
- Chloracne has acneiform skin lesions, which differ from acne vulgaris lesions, in their etiology, pathogenesis, clinical features, histopathology, and treatment.
- Chloracne appears to be resistant to all tested forms of treatment. The only way to control chloracne is to avoid exposure to chloracnegens.

## 25.1 Introduction

Although technological progress has created great benefits, at the same time a lot of industrial by-products and chemical wastes have been produced. Human health has been greatly affected by these environmental pollutants [1]. The skin is the largest organ in the human body and one of its main functions is to protect the body from noxious substances. Environmental pollutants are related to skin diseases such as contact dermatitis, chemical depigmentation, and chloracne [2]. Acne vulgaris is generally considered to be a disorder of adolescence, but environmental pollutants can result in an acneiform eruption called chloracne, a typical environmental skin disease, which is characterized by acne-like lesions, such as comedones (blackheads and whiteheads), cysts, and pustules, that occur following systemic absorption of chemical "chloracnegens."

## 25.2 Etiology: Chloracnegens

Chloracne results from environmental exposure to certain halogenated aromatic hydrocarbons and is considered to be one of the most sensitive indicators of systemic poisoning by these compounds. Chloracne was first described in 1887 by Von Bettman [3] and by Herxheimer in 1889 [4], who suggested that it was caused by chlorine exposure and hence called "chloracne" based on the similarity of its clinical features with acne vulgaris. From then on, a number of chloracnegenic chemicals have been identified, such as chlorinated phenols, chloronaphthalenes, polychlorinated biphenyls (PCBs), and other polychlorinated compounds, which include polyhalogenated dibenzofurans, polychlorinated dibenzo-*p*-dioxins, and chlorinated azo- and azoxybenzenes [5]. All chloracnegenic compounds are known to share certain structural features including molecular planarity and two benzene rings with halogen atoms occupying at least three of the lateral ring positions. The position of the halogen substitutions appears to be critical, as it is known that substitutions leading to molecular non-planarity dramatically diminish chloracnegenic activity [2].

Dioxins belong to a great family of halogenated aromatic hydrocarbons, which consists of tricyclic aromatic compounds, and hydrogen atoms can be substituted by up to eight chlorines, thus permitting about 75 isomers. Dioxins are regarded to be class 1 carcinogens and endocrine disruptors, and are also the most potent environmental chloracnegens. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) with four chlorine atoms in lateral positions is the most biologically active isomer, and is one of the most toxic substances known [6] (Fig. 25.1). Chloracne is the most consistent manifestation of dioxin intoxication and considered to be its reliable "hallmarker" [7].

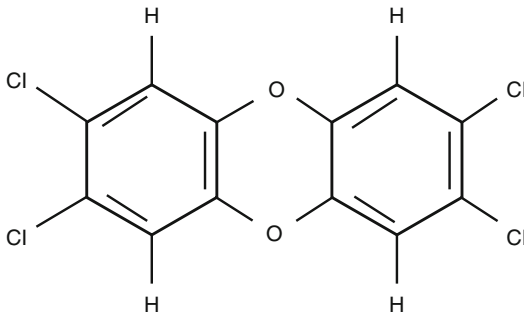


**Fig. 25.1** Chemical structure of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)

Dioxins or other chloracnegens are absorbed into the human body by direct contact, inhalation or ingestion. Generally the average TCDD concentration in healthy individuals is less than 10 ppt (part per trillion) [8], while it is over several hundreds of ppt in a patient with chloracne [9]. Dioxin is stable and highly lipophilic, and its half-life is about 7–11 years [10].

### 25.2.1 Epidemiology

Most cases of chloracne have resulted from occupational and non-occupational exposures (environmental exposures). Non-occupational chloracne mainly resulted from contaminated industrial wastes and contaminated food products.

In a study of 109 workers who had been engaged in the production of pentachlorophenol, chloracne had been noted since 1974. The prevalence of chloracne was 73.4 % (80/109) in total and 95.2 % (20/21) in a trichlorobenzene (TCB) tank area where dioxin and dibenzofurans levels were thousands of parts per million. [11]. Another survey in 3,538 workers of a factory exposure to TCDD showed that 11 % had chloracne [12].

In addition, a widely publicized example was the accident occurred at a chemical plant near Seveso of Italy in 1976. 2 kg of TCDD were discharged into the atmosphere during an explosion and 135 cases of chloracne were diagnosed among polluted 2,000 inhabitants (6.7 %); most of them (88 %) were children under 14 years old, while 0.1 % patients with chloracne was found among "healthy" controls [9]. Another accident was the widespread ingestion of tainted rice cooking oil contaminated with polychlorinated biphenyls in Yucheng in Taiwan, when 17.5 % have chloracne [13]. Examination of the skin in a group of 288 Vietnamese veterans with a past (17–22 years ago) history of exposure to the herbicide known as Agent Orange revealed persistent chloracne lesions in 11.5 % of these subjects [14].

### 25.2.2 Clinical Manifestations

Usually after exposure to chloracnegens, the first onset of chloracne is erythema or edema on the face. Then, non-inflammatory comedones and straw-colored cysts develop in a few days, occasionally pustules, noninfectious abscesses, and scars can be seen [15].

The distribution of the lesions of chloracne is characteristic. In the beginning, skin lesions appear on the face and neck, and later extend to the trunk, extremities, genitalia, or other areas. Generally, comedones appear more often on the face and neck, especially on the area below and to the outer side of the eye (the so-called malar crescent) and in the postauricular triangles. The ear lobes, suboccipital hairline, and groin are often involved. The cysts often appear on the neck, shoulders, trunk, penis, scrotum, and axillae. The nose, perioral skin, and supraorbital regions are usually spared. An increasing number of cysts is a sign of aggravation of chloracne. Other skin lesions include decreased sebum secretion with skin xerosis, pigmentation, hirsutism, skin thickening, palmoplantar hidrosis, and palmoplantar hyperkeratosis [15–17].

Since chloracne is not only a skin disease but a systemic toxic disease, it is sometimes accompanied by other systemic symptoms such as fatigue, anorexia, neuropathy, impotence, dysfunction of liver function, hyperlipidemia, anemia, arthritis, thyromegaly, and ophthalmitis [1].

Chloracne is characterized by chronicity, due to the fact that chloracnegens are highly

lipophilic and can remain in the body fat for long periods for time. Normally, it takes about 2–4 weeks from exposure to chloracnegens to the onset of clinical symptoms, but after the cessation of exposure it needs at least 2–3 years to recover, or sometimes over 15–30 years [13, 18]. The severity of chloracne is related to three major factors, including (1) intensity and duration of exposure ("dosage"), (2) relative "chloracnegenic potency" of the specific compound, and (3) "individual susceptibility" [7]. A study showed that young people and people with light hair color maybe more susceptible to chloracnegens [8].

### 25.2.3 Histopathology

Hambrick [19] studied the histopathologic features of lesions of chloracne in different stages of evolution in human volunteers and described that in early lesions of chloracne the epithelial cells of the outer root sheath forming the wall of the proximal portion of the infundibulum and the sebaceous duct appeared increased in number, resulting in dilatation of the proximal infundibulum.

The walls of the sebaceous glands were thickened and merged with the infundibular wall. Hyperplasia of the epidermal cells, with incomplete keratinization, was manifested by a thick parakeratotic cell layer surrounding a mass of keratinized epidermal cells, which began the proximal filling of the infundibulum.

In later stage lesions, almost all pilosebaceous units were involved. There was a definite decreased size of the sebaceous glands, with reduced numbers of cells and reduced size of sebaceous lobules, which otherwise had a normal appearance. Still later stage lesions consisted of small comedones, with almost all vellus hair follicles showing thickening of the outer root sheath, dilated infundibula filled with sebum, and absence of sebaceous lobules. The maximum infundibular dilatation occurred proximally, resulting in either bottle-shaped formations, with the neck near the surface, or columnar funnels along the entire length of the infundibular structure [19–21].

### 25.2.4 Diagnosis and Differential Diagnosis

Chloracne is easy to be diagnosed by a history of exposure to chloracnegens, the characteristic clinical manifestations and histopathology, and a high serum concentration of chloracnegens. Chloracne presents with acneiform comedos and cysts that differ from acne vulgaris in etiology, pathogenesis, clinical features, histopathology, and treatment (Table 25.1).

### 25.2.5 Possible Pathogenesis

The exact cellular and molecular pathogenesis of chloracne is still unclear. The major effect induced by chloracnegens in different skin structures is alteration of cellularity that results in prominent hyperplastic or hypoplastic responses. This indicates different epithelial structures in the skin respond to chloracnegens in a different way: epidermis and infundibulum, which is characterized by epidermal-like type of differentiation undergo prominent hyperplasia, while sebaceous and sweat glands lose their secretory activity and are replaced by keratinizing cells [22].

Earlier views thought that SGs are replaced by keratinized epithelial cells because SGs undergo squamous metaplasia and keratinization in patients with chloracne [23]. Recently Panteleyev and Bickers [22] produced a hypothesis to explain the pathogenesis of chloracne based on epidermal stem cell theory that chloracnegen-induced transformation of the pilosebaceous unit is driven by activation and accelerated exit of cells from the stem cell compartment coupled with a shift from a pilosebaceous differentiation pattern to an epidermal one. This may result in imbalance in early multipotent cells commitment and their preferential differentiation along an epidermal lineage with consequent diminution of SG and lower HF portion along with prominent epidermal/infundibular hyperplasia and hyperkeratinization. This process maybe controlled by a signal pathway of aryl hydrocarbon receptor(AhR), $\beta$-catenin, c-Myc, and Indian Hedgehog (IHH) expressed in the cells [24, 25].

**Table 25.1** Differential features of acne vulgaris and chloracne [22]

| | Acne vulgaris | Chloracne |
|---|---|---|
| **Clinical features** | | |
| Age group affected | Adolescence and early adulthood | Any age group |
| Anatomic localization | Face including the nose, upper back, and chest areas | Retroauricular and malar, axillae, groin, extremities; nose is spared |
| Inflammation | Inflammatory lesions are common | Inflammation is very rare (only as a secondary effect after cyst rupture) |
| Sebum production | Increased | Decreased; xerosis as a common associated condition |
| **Histopathology** | | |
| Initial lesion | Limited comedones, papules, pustules, cysts | Myriad comedones |
| Sebaceous gland | Hypertrophic | Atrophic gradual replacement with keratinocytes |
| Sweat gland | Uninvolved | Palmoplantar hyperkeratotic lesions;acrosyringial plugging |
| Hair follicle | Thinning of the infundibular epithelial wall | General hyperplasia of the infundibulum, sebaceous gland duct and significant thickening of the upper follicle |
| **Biochemistry and microbiology** | | |
| Biochemistry of comedone | More free fatty acids, triglycerides, and total Triglyceride pool | More squalene, wax ester, and cholesterol |
| Hormones | Androgen dependent; testosterone and dihydrotestosterone stimulate sebum production | The role of androgens in chloracne is unknown |
| Microflora | *Propionibacterium acnes* and *Propionibacterium granulosum* in sebaceous gland duct and hair canal | No bacteria |
| **Therapy** | | |
| | Effective under treatment of antibiotics, retinoids, and other methods | Resistant to therapy |

### 25.2.6 Treatment

Although some individual reports showed that retinoids, corticosteroid, dermabrasion, and light electrodesiccation maybe useful in the treatment of chloracne, chloracne appears to be resistant to all tested forms of treatment. So the only way to manage chloracne is to prevent exposure to chloracnegens [26]. Once exposure happens, affected individuals should be removed from exposure sites and try to eliminate accumulated chloracnegens from the body. Recently a study found that a synthetic dietary fat substitute known as olestra can combine with chloracnegens and accelerate their fecal excretion [27]. Another study showed that combined dietary olestra and caloric restriction causes a 30-fold increase in the rate of excretion of labeled compound [28], which maybe a possible treatment in the future.

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# Myths and Beliefs of Acne Pathogenesis: Diet, Smoking, Hygiene

# 26

Batya B. Davidovici and Ronni Wolf

## Contents



**Core Messages**

- Acne is the most prevalent skin condition. It has a substantial impact on the quality of life of teenagers worldwide.
- It is interesting that the myths, misconceptions, and commonly held beliefs surrounding acne are similar among acne patients from different societies and cultures.
- In this chapter we present the conflicting arguments and the evidence base for some of the most popular myths and beliefs regarding acne pathogenesis.
- We reviewed acne and dairy products, acne, chocolate, and fatty foods, acne, poor skin hygiene, and soaps, acne and smoking, as well as other miscellaneous subjects.
- Unfortunately, after reviewing the existing data, there is no clear proof to determine whether most of these issues are facts or misconceptions.

## 26.1 Introduction

Acne is the most prevalent skin condition, affecting to some degree 85 % of the population aged 11–30 years [1]. It is not a life-threatening condition; however, it lasts for years; it can cause scars and furthermore as Koo wrote: "It is important to look beyond the physical scarring, for there is no

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disease that has caused more insecurity and feelings of inferiority than acne" [2]. Despite the high prevalence of acne vulgaris in adolescents the overall knowledge pertaining to the causes, natural course, and therapy was found in several studies to be very low not only among patients but also among final year medical students [3] and even among family physicians and nurses [4, 5]. On the other hand myths, misconceptions and commonly held beliefs surrounding acne still exist among patients as well as among well-meaning friends and relatives [6, 7].

Ironically, there is some difficulty with totally debunking these perceptions, as there has been little research to elucidate the mechanisms behind these perceived myths [8].

In recent years many studies evaluating the knowledge, beliefs, and perceptions regarding acne causation among acne patients and their families have been carried out. In a study from Greece, high-school students implicated diet (62.3 %), hormones (55.1 %), poor hygiene (42.4 %), stress (31.9 %), infection (14.9 %), and genetics (5.7 %) as causes for their acne [9]. Another study among acne patients visiting a community-based hospital in Saudi Arabia found that most patients believed that hormonal imbalance and dirt were the major causes of acne [10]. In Canada, patients referred to a community-based dermatologist for management of acne vulgaris completed a self-administered questionnaire. Acne was most often believed to be caused by hormonal and genetic factors, although diet, poor skin hygiene, and infection were also implicated [7]. In another study that analyzed the knowledge of acne causation among English teenagers, 11 % of the responders blamed greasy food as the main cause of the disease [11].

It is interesting that no major differences were noted in the beliefs and perceptions of the pathogenesis of acne among acne patients from different societies and cultures.

Since most of the topics are profoundly reviewed in other chapters (i.e. acne and nutrition, acne and androgens, acne and bacteria, etc.) and given our current level of knowledge, the best we can do is present the conflicting arguments and the evidence base for some of the most popular myths and beliefs regarding acne pathogenesis. Unfortunately, after reviewing the existing data, there is no clear proof to determine whether most of these issues are facts or misconceptions. We can just promise that the jury is still out [12].

## 26.2 Acne and Diet

Hippocrates wrote: "Let food be your medicine, and let medicine be your food." The last decade has witnessed an enormous increase in public awareness of the cause-and-effect relationship between diet and health. This trend, actively popularized by agents with purely commercial interests and by the media, has drastically changed the perceptions and attitudes of consumers towards the image and importance of the daily diet. As mentioned before, the public perceives the role of food in acne causation as pivotal. Therefore today, 2000 years following Hippocrates, one of the most common questions concerning acne is "doctor, is it something I ate?" And we as their trusted dermatologist should provide unbiased truths on the effects of various diets on their acne condition. In an attempt to advise them knowledgeably on the subject of nutrition one is inundated with and confused by the mountains of epidemiologic studies that appear in the scientific, pseudoscientific, and nonscientific literature. Unfortunately though, convincing trials are lacking as it turns out that there are no meta-analyses, or well-designed scientific trials that follow evidence-based guidelines for providing solid proof in dealing with this issue [13] [14]. The present section tries to review the up-to-date information, without pretension to provide a clear-cut message on this controversial issue.

### 26.2.1 Ecologic Studies

A difference in the prevalence of acne between non-Westernized and fully modernized societies has been noted and diet has been suspected to be the reason. Schaefer [15], a general practitioner who spent almost 30 years treating Inuit (Eskimo)

people as they made the transition to modern life, and later Bendiner [16] reported that acne was absent in the Inuit population when they were still living and eating in their traditional manner. However, the prevalence of acne became similar to that in Western societies after their acculturation. Surveys of disease in some rural African villages in Kenya [17], Zambia [18], and the Bantu in South Africa [19] report far less acne than is found in the descendants of these areas who now live in the UK or the USA. More convincing is the study conducted on schoolchildren from Purus Valley, a rural region in Brazil [20]. Out of a total of 9,955 children (age 6–16 years), only 2.7 % had acne vulgaris. A more recent observation reports the prevalence of acne in two non-Westernized isolated populations: the Kitavan Islanders of Papua New Guinea and Ache hunter-gatherers of Paraguay [21]. The diet of the Kitavan people as well as the Ache community includes mainly "traditional foods" composed of mainly locally cultivated foods. An analysis of 1,200 Kitavan subjects (including 300 aged 15–25 years) and 115 Ache subjects (including 15 aged 15–25) found not a single case of acne of any grade. The authors suggested that the absence of acne in non-Westernized societies is attributable to environmental factors, mainly local diets, which have a substantially lower glycemic index than a Western diet. However even they admit that an alternative explanation of the low prevalence of acne in these non-Westernized populations is that of genetic susceptibility to acne, especially in view of the fact that the people in these isolated regions live in close-knit and closed communities. In epidemiology it is called the "ecological fallacy," meaning that even if such a link is supported by biologically plausible hypotheses of mechanism of causation, it does not provide proof of a causal relationship, as the individual diet of the subjects who develop acne is not known and confounders cannot be assessed [22]. It can even be postulated for the purpose of discussion that the dietary restrictions which Western adolescents with acne employ in managing their condition are trivial compared to the differences between their diets and those of hunter-gatherers. Or as Sherlock Holmes noted that: "Circumstantial evidence is a very tricky thing. It may seem to point very straight to one thing, but if you shift your own point of view a little, you may find it pointing in an equally uncompromising manner to something entirely different." (Sherlock Holmes, in Arthur Conan Doyle's "The Boscombe Valley Mystery," 1981)

### 26.2.2 Acne and Dairy Products

Could milk cause acne? In 1949, Robinson reported 1,925 patients who kept food diaries and found that milk was the most common food implicated in acne flares [23]. A more recent paper also supporting an association between milk consumption and acne was based upon the Nurses' Health Study II cohort [24]. The study revealed that intake of milk during adolescence was associated with history of teenage acne. This association was more marked for skimmed milk than for other forms of milk, suggesting that the finding is unlikely to be caused by the fat content of milk. The authors hypothesize that this association may be caused by the presence of hormones and bioactive molecules in milk. It was shown that acne in teenagers correlates with hormonal activity [25]. Milk contains placenta-derived progesterone and other dihydrotestosterone (DHT) precursors, including 5a-pregnanedione and 5a-androstanedione. These compounds are only a few enzymatic steps away from DHT, the main acne stimulator, and the enzymes required to mediate the change are present in the human pilobaceous unit [26]. In addition milk contains a multitude of growth-stimulating hormones [27]. The most likely of all candidates for co-stimulation with the steroid hormones of pilosebaceous function and dysfunction is insulin-like growth factor-1 (IGF-1), which is present in ordinary milk. IGF-1 stimulates the synthesis of androgens in the ovary, adrenals, and testicles. Insulin itself and, even more so, IGF-1 have been demonstrated to stimulate hair follicle growth and sebocyte growth [28, 29]. Accordingly, it was shown that the blood level of IGF-1 in prepubertal, pubertal, adolescent, and early adult humans resembles accurately the prevalence curve of acne in this population. Human and bovine IGF-1 share the same amino acid sequences and several milk

proteins protect IGF-1 from digestion in the gut [30]. Therefore, it is likely that IGF-1 may mediate some of the effects of comedogenic factors, like androgens, growth hormone, and glucocorticoids [31]. Although the biologic explanation seems plausible, the study is not innocent from methodological pitfalls. First, the validity of data collected by distantly recalled eating habits and vaguely defined disease is questionable. Moreover, since the analysis of this study was cross sectional a causal relationship cannot be determined. In a cross-sectional study a temporal correlation cannot be established; thus, the direction of the association between the alleged cause and the effect cannot be defined. As a consequence a reverse causation cannot be ruled out. Therefore, the association between acne and milk found in this study should be treated with caution.

An alternative hypothesis explaining the association between milk and acne suggested that the iodine content of milk might also be playing a role in the development of the acne [32]. It was claimed that iodine intake could exacerbate acne [33]. The concentration of iodine in milk has been shown to vary according to the season and geographic location, but significant levels of iodine were found in milk in different countries [34–36]. Thus, it was concluded that the observed association of dairy products with acne might be secondary to the iodine content of the dairy products ingested. However, whether iodine in any concentration causes true acne is debatable. Acneiform eruption can be triggered by halides [37] and iodine was also recognized as causing an acneiform eruption. However, the comedo, the initial lesion in acne, is not part of this eruption.

So, can milk cause acne? On the basis of the existing evidence, it could be concluded that the association between dietary dairy intake and the pathogenesis of acne is slim.

### 26.2.3 Acne, Chocolate, and Fatty Foods

Dietary factors especially chocolate, oily, or fatty foods and high sugar content foods were repeatedly nominated as causing or exacerbating acne. But is there convincing evidence for such a link? The effect of dietary fat content on insulin resistance has been a subject of controversy. On the one hand animal studies almost uniformly show increases in insulin resistance accompanying high-fat diets, particularly saturated fats [38–43]. However, the results of clinical investigations in humans are much less conclusive. Whereas some studies indicate a link between dietary fat intake and insulin resistance [44–47], most studies show no such relationship [48–53], and the general consensus among the experts today is that the available valid scientific data are insufficient to prove such a correlation. A very similar situation exists with the influence of carbohydrate contained in foods ("glycemic index") and insulin sensitivity. It is proposed that high glycemic indexes lead to hyperinsulinemia and a resulting cascade of endocrine consequences (increased androgens, increased insulin-like growth factor 1, altered retinoid signaling pathways), which mediate acne [21, 54].

Whereas several animal studies demonstrated an inverse correlation between a high glycemic index, hyperinsulinemia, and insulin resistance [55–58], the few studies on humans have yielded inconsistent results or failed to show such an effect [59–61], and most of the experts have taken the position that not enough valid scientific data are available to support such a link [62]. Moreover, it is generally accepted that the severity of acne is correlated with facial sebum secretion. It has been hypothesized that high-fat or high-carbohydrate foods may exacerbate acne by production of more comedogenic sebum—by increasing blood lipid levels or by producing "less fluid sebum" [63] and thence greater obstruction of pilosebaceous follicles, setting the stage for follicle rupture and secondary inflammatory changes. Several experimental studies on animals (most of them dated) have demonstrated that feeding high-fat or high-carbohydrate diets increased sebaceous output [64–66]. These studies have been criticized by many experts for using faulty techniques [65]. Similarly, several human studies have also demonstrated that diet may change the amount and composition of excreted sebum, i.e., an increase in lipid secretion when

either excess carbohydrates or fats were given [67–70]. An important study by Pappas et al. [71] showed that sebaceous glands can and do use fatty acids from the bloodstream for the synthesis of sebum.

So far for the pathogenesis but can chocolate or oily foods cause or exacerbate acne? There are surprisingly few studies that have examined the role of these dietary elements in acne. The studies of acne and chocolate of Grant and Anderson [72] and Anderson [73] have considerable methodological shortcomings. They performed trials of chocolate, milk, and roasted nuts in university students and found no effect on acne, but the trials were small and uncontrolled and had very short follow-up periods and inadequate statistical analysis. The subjective self-assessed measure of global dietary quality in Chiu et al.'s study [74] renders these findings of limited credibility. The trial of Fulton et al. [75] was methodologically stronger. This trial, a single-blind placebo-controlled crossover study performed in American hospital acne clinic attendees and male prisoners, found no effect of chocolate on acne or on sebum production or composition. The placebo bar was of a similar fat and sugar composition to the study chocolate bar. Therefore, while this study might suggest no role for the cocoa content of chocolate bars in acne genesis, the role of the complete product remains open to question. Furthermore the treatment period for both chocolate and placebo bars was just 4 weeks. Given the 4-week treatment periods and 3-week washout period in the crossover design, it may be that there was insufficient study duration to observe the relevant changes.

A small study, 16 subjects and 13 matched controls [76], of patients with acne found no difference in sugar consumption between the two groups—though patients with seborrheic dermatitis had higher levels of sugar consumption.

In another study by Fulton et al. no effect has been established between chocolate, dairy products, shellfish, or fatty foods [75]. Although the study by Adebamawo et al. suffered from several methodological limitations as explained before, high-fat or high-carbohydrate foods such as sweets, pizza, and French fries were not found to cause acne [24].

In conclusion, mostly unjustified perceptions about the importance of diet in acne pathogenesis are widely held [77], although the evidence for its role is not strong. In the few studies that have been undertaken, no specific foods (including fatty foods and chocolate) have been identified as causative factors [12, 78]. Thus, we are bereft of scientific evidence-based answers to the question regarding the nutrition in relation to acne etiology.

## 26.3 Acne, Poor Skin Hygiene, and Soaps

Poor skin hygiene is one of the most ancient beliefs concerning acne pathogenesis, and therefore the need for skin cleanliness is widely held among acne patients [4, 7, 79]. They perceive that open comedones or blackheads are full of dirt. But the black color of open comedones is probably not composed of any extraneous dirt. It was initially thought to be result of oxidation of fats; however, melanin staining has been incriminated by some [80] but refuted by others [81]. Additionally, excessive sebum production does occur in most acne patients [82–84]. This surface oil is also perceived as dirty, and washing away these oils from the skin will stop pores blocking and decrease acne. But in fact these surface lipids have little to do with acne production, and while it is true that pores do get functionally blocked, this blockade occurs at a depth beyond washing techniques, and attempts at scrubbing and obsessive washing will add nothing to management.

For generations, patients and physicians believed that successful treatment of acne depended on the degreasing of the skin to an extent, which produces noticeable peeling [85]. In fact, soap has been advocated in the treatment of acne since the nineteenth century [86].

Reviewing published studies on acne and skin cleansing revealed that they are mostly too small or with other methodological faults and therefore do not permit the achievement of convincing conclusions in the era of evidence-based medicine. For example, in a review by Solomon and Shalita they make detailed suggestions regarding

skin cleansing in acne, although they cite little evidence to support their recommendations [87]. Improvements in acne have been noted in a ten-subject uncontrolled study of a medicated face wash [88]. Beneficial effects were also noted in another uncontrolled and incompletely reported study of face washing [89], a study in which an abrasive was used in addition to a medicated wash in some subjects but had no non-wash controls [90]. Similarly, improvement was noted in an open uncontrolled and incompletely reported study of a cleansing bar and the "Buf-puf" abrasive device [91] and in studies in which medicated soap or acidic syndet bar was compared with unmedicated soap, but in which, again, no non-wash comparison was studied [92, 93]. Reported randomized controlled studies of a 4 % chlorhexidine gluconate skin cleanser preparation with controls using in one study 5 % benzoyl peroxide and, in another two studies, the vehicle employed in the chlorhexidine preparation. There was no significant difference in acne lesion counts at 8 and 12 weeks in the chlorhexidine/benzoyl peroxide study. The combined data of the two chlorhexidine/vehicle studies showed significantly less acne lesions at 8 and 12 weeks in the chlorhexidine-using subjects than in the unmedicated vehicle-using controls.

A povidone-iodine cleanser was reported to improve acne in randomized controlled trials [94], but statistical reporting was deficient. Swinyer et al. studied the effect on acne of three treatment regimens. Each treatment regimen included a different cleansing/washing modality. However each regimen also included a different systemic or topical antibiotic combination, so the role of cleansing or washing cannot be adequately assessed in this study [95].

On the other hand, face washing has been proposed as being traumatizing, and so exacerbating acne [96, 97] and as increasing the skin irritation adverse effects of topical tretinoin and isotretinoin (though not other topical therapies) in acne treatment [95, 98, 99]. As a consequence, in the 1980s, pharmaceutical companies began suggesting that irritation of the skin was not necessary for acne control. Mildness has become the major benefit claimed for soaps and testing for mildness now ranks among the first concerns of the manufacturing industry [100].

Additionally, in the past commonly used soaps and shampoos have been found to be comedogenic when applied to the rabbit ear [101].

Since evidence for the role of a lack of facial hygiene in acne pathogenesis and for face cleansing in its management is mostly of poor quality we can conclude, as one of the above-cited authors admitted that, at best, face washing for acne "continues to be empirical therapy" [89]. However, one cannot ignore that washing meets various people's needs of hygiene, social, and cultural functions. It contributes to a feeling of well-being as well as improving the appearance and smell of the skin. Rather than promoting health, its importance is in the feeling; therefore there is no surprise that most patients will resort to cleansing products long before consulting a dermatologist [7].

## 26.4 Acne and Smoking

Numerous clinical studies have documented smoking-induced inhibition of immune and inflammatory functions [102–104]. Nicotine enhanced keratinocyte adhesion, differentiation, and apoptosis and inhibited keratinocyte migration [105]. Nicotine also inhibited inflammation through effects on the central and peripheral nervous systems [106]. Nicotine altered immune responses by directly interacting with T cells. Nicotine administration via a transdermal delivery system was shown to suppress the cutaneous inflammatory response to sodium lauryl sulfate and UVB radiation [107]. This would suggest a negative association between smoking and acne, which is an inflammatory skin disease. However, reviewing the available studies, which show varying results, it seems that the relationship between tobacco smoking and acne remains unclear.

Mills et al. were the first to study the association between acne and smoking and demonstrated a low prevalence of smokers among 165 patients with severe acne treated with isotretinoin [108]. Of 96 men, almost 20 % were smokers compared with an expected 35 % from national statistics.

Of 69 women, the prevalence was 12 % compared with an expected 33 %. Therefore they hypothesized an anti-inflammatory action of nicotine. However, the study had several methodological limitations. Only hospital patients with severe acne who had been receiving isotretinoin were included. Due to the cross-sectional design it was not known if these patients had already changed their smoking status because of the disease and whether the results are applicable to the situation in the general population where mild and moderate acne predominates. The data of these acne patients were not compared with a control group derived from the study base, but with expected prevalence derived from national statistics, which also include a considerable percentage of subjects with acne. That could lead to misclassification and underestimation of the effect. Information on possible confounders or quantity of smoking was also not available.

In another large-scale cohort of young men with severe acne, active smokers showed a significantly lower prevalence of severe acne than nonsmokers; in addition an inverse dose-dependent relationship between smoking and severe acne prevalence was found [109]. However, this study had also methodological limitations: the inclusion of only males and only severe acne and the exclusion from the study protocol of acne therapy. Also, owing to the cross-sectional nature of the study, it was not possible to delineate the time sequence of severe acne development and smoking. Some subjects may have started smoking after the onset, or even as a consequence, of acne, or vice versa. Furthermore information on possible confounders was lacking

On the other hand, Jemec et al. [110] found that smoking was not significantly associated with acne in a random sample of 186 subjects. Similarly, Firooz et al. [111] compared smoking status of 293 acne patients to 301 patients suffering from other dermatological conditions in a case–control study. After accounting for acne's higher prevalence and greater severity in men, no significant correlation was found between acme and smoking.

To complete the "spectrum of results" in a cross-sectional study of 896 citizens of the City of Hamburg [112] acne prevalence was significantly higher in active smokers as compared with nonsmokers. Moreover, a significant dose-dependent relationship between acne severity and daily cigarette consumption was shown. These findings show that acne is more frequent and severe among smokers and follows a dose-dependent association. From these findings it seems justified to consider smoking a risk factor for acne. However, due to the cross-sectional nature of the study it was not possible to characterize the time sequence of acne and smoking.

In view of the controversial association between acne and smoking, some studies have shown that cigarette smoking aggravates acne; others did not confirm this association, or even showed a protective effect; we can conclude that available data do not support any association between acne vulgaris and smoking. Thus the silver lining of this dark and smoky cloud is still not clear.

## 26.5 Miscellaneous

### 26.5.1 Acne and Infection

Patients believe that acne is an infection and that they are infectious to others. The fact is that *Propionibacterium acnes* has a role in the involution of the disease from simple comedones to inflammatory lesions. However, it is a secondary phenomenon once the disease has been initiated. *Propionibacterium acnes* is an obligate anaerobe living in the oxygen-free environment of the pilosebaceous apparatus and beyond any influence of surface washing, and as such it is not infectious.

### 26.5.2 Acne and Sexual Activity

There are misconceptions regarding the association of sexual activity and acne. For example that too much sex or masturbation may worsen acne. Or that once females begin having a regular sex life their acne will improve. Although acne is associated with androgen metabolism at the level of the sebaceous glands, there is no basis to either of these

rather strange extrapolations. The only correlation between sex and acne that appears supported in the literature is that of a decreased quality of life and sexual satisfaction among women who suffer from polycystic ovary syndrome and acne [113].

### Conclusions

Despite the inundation of epidemiologic studies mostly of unsatisfactory quality and the abundance of beliefs and perceptions among acne patients regarding the pathogenesis of acne, there is a paucity of reliable information. Yet, the question of whether common perceptions and beliefs prove to be fact or misconception is more than an academic issue. It is of importance due to the practical implications of these beliefs for acne management, adverse effects, expense, and potential psychological sequelae. Alas, after reviewing the relevant published data we can conclude that insufficient serious effort has been invested in investigating these questions, which are prevalent and consistent across different cultures. At present, we are bereft of scientific evidence-based reliable answers. We hope that the day when we would be able to knowledgeably advise our acne patients on trivial subjects is not too far.

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# Part V

# Acne: Clinical Aspects

# Understanding Acne as a Chronic Disease

# 27

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## Contents



**Core Messages**

- In most cases acne is not an acute disease but rather a condition that continuously changes in its distribution and severity.
- Acne can be a physically (scar development) and psychologically damaging condition that lasts for years.
- Acne has clinical characteristics to be defined as chronic disease according to the World Health Organization criteria.

## 27.1 Introduction

Acne is widely considered to be a simple, self-limited disorder of adolescents. The majority of lay people, but also many physicians, believe that acne is a self-limiting disorder so that treatment is only required in extreme cases. However, not only successful acne treatment can become difficult, but acne, itself, can be a devastating disease for the patient, both because it manifests on visible body parts and in children near puberty, who are vulnerable both socially and psychologically, and because it can heal with considerable scar sequelae [1].

## 27.2 Acne Is a Chronic Disease

In most cases acne is not an acute disease but rather a condition that continuously changes in its distribution and severity [1]. Usually, acne

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| | Acne | Atopic dermatitis |
|---|---|---|
| Basic character | Inflammatory | Inflammatory |
| Duration | >3 months – >10–30 yr | >3 months – >5–40 yr |
| Genetic background | Yes, long-term courses, polygenic | Yes, polygenic |
| Age of onset | ~10 | ~ 1 |
| Self-limited | >80 % (3rd decade) | >80 % (2nd-3rd decade) |
| Relapses | Frequently | Frequently |
| Counselling | Intervals/years | Intervals/years |
| Medication | Continuously/intervals | Continuously/intervals |
| Social impact | Yes | Yes |
| Psychologic impact | Yes | Yes |
| *Post disease sequelae* | | |
| Physical | Yes | Yes |
| Psychologic | Yes | Yes |

**Fig. 27.1** WHO criteria for classifying acne as a chronic disease (after Gollnick et al. [1])

treatment is necessary for many months and sometimes years. And mostly, despite treatment, acne may cause scarring and associated negative psychological effects.

Therefore, it is important for dermatologists to educate other clinicians and patients that acne is often a chronic disease and not just a self-limiting disorder of teenagers. For many patients, acne has characteristics that the World Health Organization (WHO) has used to define chronicity of diseases [2, 3] a prolonged course, a pattern of recurrence or relapse, manifestation as acute outbreaks or slow onset, and a psychologic and social impact that affects the individual's quality of life.

In the evaluation of acne as a chronic disease, it may be important to use the WHO criteria to compare it with atopic dermatitis, a widely accepted chronic disease (Fig. 27.1) [1, 2]. The similarities between the two diseases are striking. Moreover, there is wide evidence that acne can be a physically (scar development) and psychologically damaging condition that lasts for years [4–10], even if they do not always correlate with the clinician's assessment of severity at one point in time [1, 11]. In addition, there is evidence that acne can persist into adult years in as many as 50 % of individuals [5, 12–15].

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# Clinical Aspects of Acne Vulgaris

# 28

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## Contents



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## 28.1 Introduction

Acne vulgaris, the most common disease of the skin, may present itself in a plethora of clinical forms, depending on the distribution, type of lesions, tendency to and manifestation of scarring, age at disease onset, and persistence of acne after the time of physiological regression [1]. The beginning of acne frequently occurs during the prepubertal period when adrenal androgens stimulate the pilosebaceous unit. Ovarian and testicular androgens play a key role in the development of acne in puberty. Consequently, acne vulgaris can begin in children as young as 6 or 7 years depending on the onset of adrenarche. Gradually, acne progresses in a cephalocaudal way resulting in the predominance of acne lesions on the chin, mandible, and neck just inferior to the mandible in adults and particularly adult women [2].

In this chapter we will present a classification of the different clinical presentations of acne. Acne vulgaris may be classified according to severity as mild, moderate, or severe acne and according to the lesions that predominate in a given

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patient in comedonal, papulopustular, nodular, nodulocystic, or conglobate acne (Table 28.1) [3, 4] (see relevant Chaps. 43 and 44).

## 28.2 Mild Acne Vulgaris: Acne Comedonica

**Core Messages**

- Comedogenesis is due to the accumulation of corneocytes in the pilosebaceous unit.
- Different types of comedones have been described which include microcomedones, ordinary open or closed comedones, macrocomedones, sandpaper comedones, and missed comedones.
- Comedonal acne should be differentiated from drug-induced comedones, pomade acne, and chloracne.

### 28.2.1 Etiology

Comedogenesis is one of the four major etiological factors of acne. In the normal follicle, the keratinocytes are shed as single cells to the lumen and then excreted [5, 6]. In acne, keratinocytes hyperproliferate and are not shed as in the normal follicle. Also, they become densely packed along with monofilaments and lipid droplets [7–10].

The mechanisms that control this process have not yet been fully elucidated. Different factors seem to play a role. It has been suggested that *P. acnes* biofilm and biological glues that assist adherence of *P. acnes* to the follicular wall find their way into the sebum and might be the cause of increased cohesiveness of keratinocytes, leading to comedones [11]. A relative decrease in sebaceous linoleic acid may account for the increase in the proliferation rate of the basal keratinocytes and the abnormal differentiation of the follicular keratinocytes in the follicle wall of microcomedones and comedones [12–14]. Also, local cytokines (IL-1α), lipid composition, and androgens are thought to have an important role [8, 15–18] (see relevant Chap. 9).

Nevertheless, comedones can resolve naturally, and study of this phenomenon may contribute to increased understanding of the pathogenesis and natural history of acne.

### 28.2.2 Clinical Presentation of Acne Comedonica

Different types of comedones have been described. It is important for the physician to recognize these different types as treatment may differ accordingly [7]. In most patients, several types of comedones coexist (Fig. 28.1).

#### 28.2.2.1 Microcomedones

Microcomedones are not visible by the naked eye and represent a histological entity. Biopsy sections of normal-looking skin in patients with comedonal acne may show histological features of microcomedones in 28 % of cases [15]. The fact that the microcomedone is the initial acne lesion highlights the need of applying topical acne therapies not only on clinically apparent lesions but on the whole face.

**Table 28.1** Classification of forms of acne vulgaris

| Acne forms | Acne forms (morphology) | Comedones | Papules/pustules | Nodules | Nodes, cysts, sinus tracts |
|---|---|---|---|---|---|
| Mild | Comedonica<br>Papulopustulosa | Comedones are the main lesions<br><20 | Small and few in number<br><10 | – | – |
| Moderate | Papulopustulosa<br>Nodosa | 10–40 | 10–40 | ± | – |
| Severe | Nodulocystica<br>Conglobata | 40–100/fused | >40 | >10 | Many |

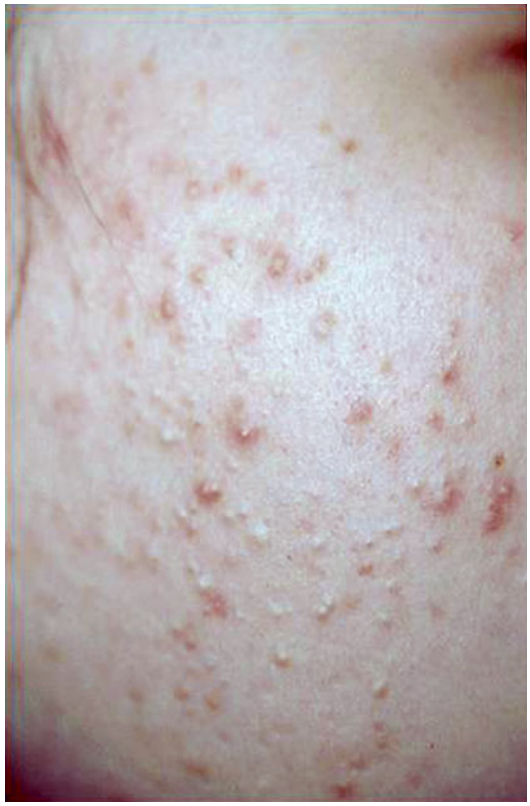

**Fig. 28.1** Comedonal acne

#### 28.2.2.2 Open and Closed Comedones (Ordinary Comedones)

Open and closed comedones are easily recognizable as they appear as blackheads or whiteheads, respectively.

#### 28.2.2.3 Sandpaper Comedones

Sandpaper comedones present as very small, almost confluent closed comedones resembling sandpaper and affect mainly the forehead. They are a therapeutic challenge as they are difficult to treat, may become inflamed, and show little or variable response to oral antibiotics and topical retinoids. Best results are obtained with treatment with oral isotretinoin at a dose of 0.5 mg/kg/day [5].

#### 28.2.2.4 Macrocomedones

Macrocomedones are defined as blackheads or more commonly whiteheads, larger than 1 mm in size. They may be a cause of a slow and poor response to oral isotretinoin or a cause of acne flare-up during isotretinoin therapy [19] (see relevant Chap. 52).

#### 28.2.2.5 Missed Comedones

Stretching the skin, and using a good light, at a shallow angle, will allow visualization of comedones in about 20 % of patients, which would have been otherwise missed and therefore not treated.

### 28.2.3 Differential Diagnosis

Comedonal acne should be differentiated from drug-induced comedones and pomade acne [20]. Drug-induced comedones may result from treatment with oral, topical, intranasal, or intrathecal corticosteroids or oral steroids [15, 18].

Pomade acne is characterized by numerous comedones on the forehead, occurs mainly in Afro-Caribbeans, and is due to the application of defrizzing agents to their hair [15].

Moreover, comedonal acne is a hallmark of chloracne. While inflammatory lesions may be present, they are less frequent. Chloracne comedones are resistant to topical or oral retinoid treatment, but may respond to gentle cautery. Antibiotics with or without benzoyl peroxide can be used for inflammatory lesions [21]. Non-inflammatory lesion may result in scarring. Some patients may demonstrate systemic problems that persist despite the withdrawal of the chloracne agent [22].

## 28.3 Mild and Moderate Inflammatory Acne Vulgaris: Acne Papulopustulosa and Acne Nodosa

**Core Messages**

- Inflammatory acne lesions may be macules, papules, pustules, or nodules.
- Acne can be primarily papular or pustular according to the predominant lesions, but there may be an equal number of comedones and papules (comedopapular acne) or papules and pustules (papulopustular acne).

- Acne papulopustulosa should be differentiated from other acneiform dermatoses, including drug-induced acne, gram-negative folliculitis, acne aestivalis (Mallorca acne), and papulopustular rosacea.
- Scarring may occur even in moderate cases.
- Patients often seek treatment for acne once inflammatory lesions occur.

### 28.3.1 Etiology

After the formation of microcomedone which is the initial acne lesion, clinically apparent lesions may occur, which may be either non-inflammatory lesions (comedones) or, if *P. acnes* proliferates and generates inflammatory mediators, inflammatory lesions (macules, papules, pustules, or nodules) (see relevant Chaps. 16 and 18).

### 28.3.2 Clinical Presentation and Differential Diagnosis

Inflammatory acne lesions may be macules, papules, pustules, or nodules. Acne can be primarily popular, pustular, or nodular (acne nodosa) according to the predominant lesions, but there may be an equal number of comedones and papules (comedopapular acne) or papules and pustules (papulopustular acne, Figs. 28.2 and 28.3) [23].

Acne papulopustulosa should be differentiated from other acneiform dermatoses, including drug-induced acne (see relevant Chap. 33), gram-negative folliculitis, acne aestivalis (Mallorca acne), and papulopustular rosacea. Acneiform dermatoses are follicular reactions and not variants of acne vulgaris. They present clinically with monomorphous inflammatory lesions, usually papules or pustules. Comedones are uncommon (Table 28.2) [24]. Drug-induced acne may be caused by corticosteroids, anabolic steroids, corticotropin, vitamins $B_1$, $B_6$, $B_{12}$, $D_2$, anticonvulsants, lithium, isoniazid, quinidine, cyclosporine, iodides, and bromides [24]. The patient's history of drug intake, the sudden onset and the monomorphous nature of the lesions, the absence

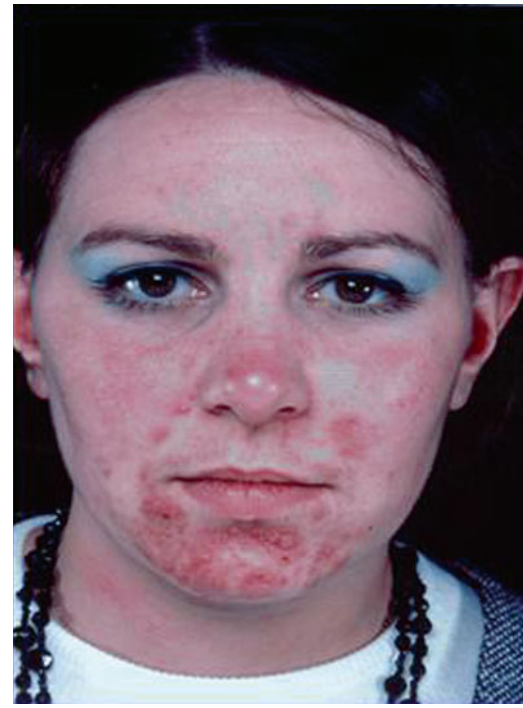

**Fig. 28.2** Mild papulopustular acne

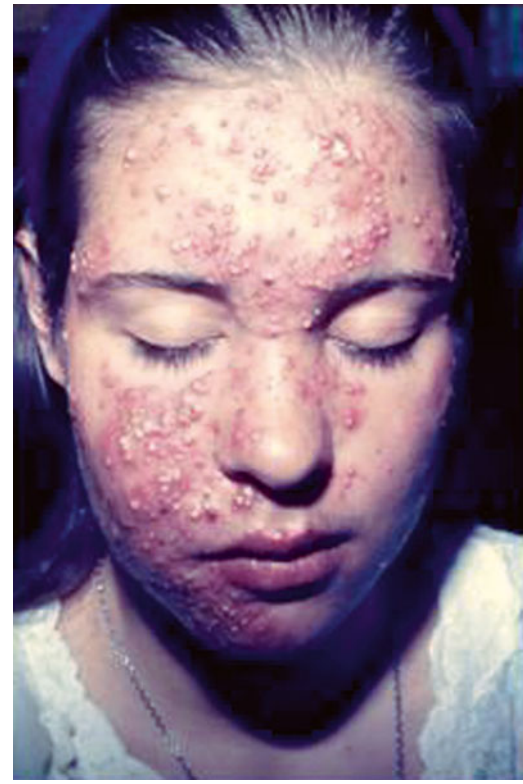

**Fig. 28.3** Moderate papulopustular acne

**Table 28.2** Differential diagnosis of papulopustular acne

| Eruption | Clinical presentation | Histologic findings | Patient history |
|---|---|---|---|
| Drug-induced acne | Monomorphous papules or pustules<br>Comedones uncommon<br>Sudden onset<br>Localization on the trunk and upper extremities | Degeneration of the follicular epithelium, with a localized intrafollicular and perifollicular neutrophilic inflammatory reaction | History of drug intake |
| Gram-negative folliculitis | Papules, pustules | | Long-term oral antibiotic acne treatment |
| Acne aestivalis | Monomorphic follicular papules containing a small central core of horn<br>Localization on the sides of the neck, chest, shoulders, upper arms, cheeks | | Sun exposure |
| Papulopustular Rosacea | No comedones<br>±Transient or permanent erythema at the convexities of the face | Not diagnostic | Females<br>30–40 years<br>Chronic course |

of comedones, and the localization on the trunk and the upper extremities should lead to correct diagnosis. Gram-negative folliculitis is caused by overgrowth of gram-negative species due to long-term oral antibiotic intake and may be considered in the case of treatment failure or acne flare-up during antibiotic therapy. Acne aestivalis presents after sun exposure and consists of multiple papular lesions, on the sides of the neck, the chest, shoulders, upper arms, and occasionally cheeks [24].

## 28.4 Severe Acne Vulgaris: Acne Nodulocystica

**Core Messages**

- Severe acne nodulocystica is characterized by the presence of numerous nodules and cysts, while more than 40 comedones, papules, and pustules are also present.
- Since severe nodulocystic acne may lead to scarring, the acne patient may experience low self-esteem, lack of self-confidence, perceived social rejection, anxiety, and depression.

### 28.4.1 Introduction

Since severe nodulocystic acne may lead to scarring, it may have profound psychological and social influence on the patient's life. As a result, acne patients may experience low self-esteem, lack of self-confidence, perceived social rejection, anxiety, and depression [25–27].

### 28.4.2 Clinical Presentation

Severe acne nodulocystica is characterized by the presence of numerous nodules and cysts, while more than 40 comedones, papules, and pustules are also present (Fig. 28.4).

## 28.5 Severe Acne Vulgaris: Acne Conglobata

**Core Messages**

- Acne conglobata is an uncommon form of acne vulgaris that presents with numerous comedones, papules, pustules, nodules, abscesses, and draining sinus tracts involving mainly the chest, back, and buttocks.
- It usually affects males and starts in adulthood.

- It is considered a maximum form of acne vulgaris because of its chronic, persistent course and severity.
- The association between acne conglobata, palmoplantar pustulosis, and arthropathies is well established.
- Differential diagnosis includes acne fulminans, chloracne, tropical acne, and nodulocystic acne vulgaris.
- Acne conglobata is often resistant to therapy, running a chronic course and causing significant scarring and psychological impairment to the patient.

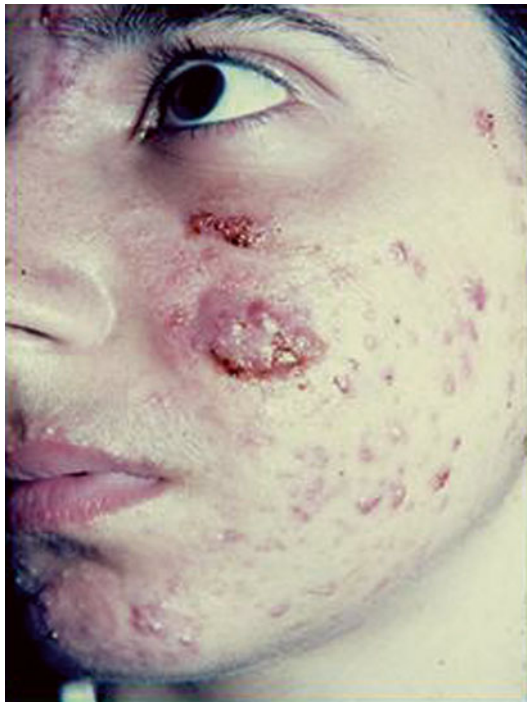

**Fig. 28.4** Severe nodulocystic acne

### 28.5.1 Introduction

Acne conglobata is a highly inflammatory form of acne which presents with comedones, nodules, abscesses, and draining sinus tracts. It is a rare condition which mainly affects males and usually starts in adulthood [28]. There is a well-established association between acne conglobata, palmoplantar pustulosis, and arthropathies, and the term synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome has been proposed in order to include these diseases in a unique syndrome (see relevant Chap. 77) [29, 30].

Acne conglobata is considered a maximum form of acne vulgaris because of its chronic, persistent course and its severity [28].

### 28.5.2 Etiology

Acne conglobata has been associated with hidradenitis suppurativa and dissecting cellulitis of the scalp, which are considered inflammatory diseases of adnexal structures. The primary event seems to be the follicular occlusion, which results in rupture and a consequent inflammatory reaction to keratin and bacteria [31]. This association is probably wrong, because current evidence indicates that the etiology of these diseases is distinct.

The pathogenesis of acne conglobata is unknown. The frequent recovery of coagulase-positive staphylococci and occasionally β-hemolytic streptococci suggests that it may represent a pyoderma, although in some cases bacterial cultures from pustules do not reveal any pathogenic bacteria [28, 32].

Severe acne conglobata may be associated with an XYY syndrome. Such patients have male external genitalia and normal testes and are fertile. They are unusually tall, may be mentally retarded, and present aggressive behavior [33]. Normal HLA-A and HLA-B antigen frequencies have been found in a series of 65 patients [34].

Hormone substitution therapy with testosterone in Klinefelter's syndrome or for growth retardation in excessively tall boys may aggravate preexisting acne [35]. Also, androgen-producing tumors or intake of anabolic steroids for muscle enhancement (see relevant Chap. 34) are additional well-known provocation factors [36]. Exposure to halogenated aromatic hydrocarbons, e.g., dioxins, or ingestion of halogens, e.g., thyroid medication or hypnotics, sedatives, or lithium treatment may induce acne conglobata [37].

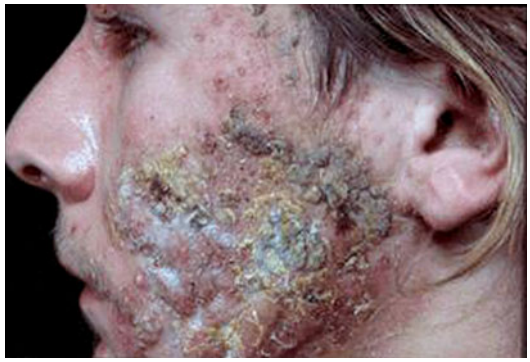

**Fig. 28.5** Severe conglobate acne

### 28.5.3 Clinical Presentation

Patients with acne conglobata are predominantly males with extensive acne characterized by severe nodular inflammation and scarring. A hallmark of this disease is the presence of grouped comedones, mainly on the posterior neck and upper trunk. Comedones may consist of whiteheads and/or blackheads (Fig. 28.5) [15].

Draining sinus is a variant of a nodule and is seen in severe forms of acne such as acne conglobata and acne fulminans as well as in hidradenitis suppurativa [38]. It presents in the form of a persistent lesion of linear or angular shape with a discharge of pus or blood. It persists for years, with no tendency to spontaneous resolution [39].

Conglobate acne is often more pronounced on the back rather than on the face, but there are reports of facial localization [40].

Acute anterior uveitis has been reported in an HLA B27-positive patient with acne conglobata and sacroiliitis, but whether this represents a true association or a coincidental finding remains to be seen [41].

Acne conglobata may occur in association with hidradenitis suppurativa as part of the follicular occlusion triad (acne conglobata, hidradenitis suppurativa, and dissecting cellulitis of the scalp) [20].

### 28.5.4 Histology

Histopathological examination of a typical skin lesion usually reveals ducts and cystic lesions in the middle and lower dermis lined by keratinizing epithelium, and an inflammatory infiltrate consisting of neutrophils, lymphocytes, and histiocytes, around follicles, which can often disrupt the normal dermal architecture [23, 32]. The draining sinus histopathologically is characterized by dissecting tracts of follicular epithelium which burrow through the necrotic tissue to the skin surface [39].

### 28.5.5 Differential Diagnosis

Acne conglobata should be differentiated from acne fulminans, tropical acne, chloracne, and cystic acne vulgaris (Table 28.1). The more advanced age of onset, the highly inflammatory nature of lesions, and the localization on the back aid to correct diagnosis.

Since lesions of acne conglobata can affect inguinal and axillary regions, it may be confused with hidradenitis suppurativa [28].

Rosacea fulminans (also called pyoderma faciale) is rare dermatosis which affects predominantly women well past adolescence. It localizes exclusively o the face, presenting with numerous fluctuant inflammatory nodules and papules which may fuse. Its etiology is unknown, and it represents neither an infectious condition nor a variant of acne conglobata. Treatment with isotretinoin in combination with topical and systemic corticosteroids is successful. Clearance of the lesions may result in minimal scarring with no recurrence [42].

A Mycobacterium chelonae I infection mimicking acne conglobata has been reported in an immunocompetent host, highlighting the importance of excluding infectious causes when facing an inflammatory facial exanthem. The patient presented with tender, multiple nodules on the chin and the mucosa of the inferior lip [43]. Mycobacterium chelonae belongs to the nontuberculous mycobacteria that are facultative pathogens in humans. It usually causes systemic infection with cutaneous involvement in immunosuppressed patients and skin infection in immunocompetent patients [44, 45]. Differential diagnosis from acne

conglobata was based on the absence of comedones, involvement of labial mucosa, and a lack of response to antibiotic therapy (minocycline, lymecycline, benzoyl peroxide). Also, histological examination and culture of the biopsy specimen contributed to diagnosis [43].

### 28.5.6 Prognosis

Acne conglobata has a recalcitrant, chronic course, thus leading to significant psychological distress. Extensive scarring is a common complication which often produces pronounced disfigurment [28]. Furthermore, there has been a report of fatal squamous cell carcinomas complicating long-standing acne conglobata in a father and daughter [46].

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# Clinical Aspects of Acne Fulminans

# 29

Andreas D. Katsambas, Clio Dessinioti,
and William J. Cunliffe

## Contents



**Core Messages**

- Acne fulminans is characterized by the sudden onset of painful, ulcerative crusting acne in association with systemic signs and symptoms including fever, weight loss, arthralgia, and myalgia.
- It is a rare condition and it affects almost exclusively adolescent boys.
- It should be differentiated from acne conglobata based on the presence of ulcerative lesions and systemic features, its sudden onset, and its resistance to systemic antibiotics.
- Unlike acne vulgaris, open and closed comedones are uncommon and polyporous comedones and non-inflammatory cysts are absent.
- It does not usually recur but leaves extensive scarring.

## 29.1 Introduction

Acne fulminans (also referred as acute febrile ulcerating acne conglobata with polyarthralgia and leukemoid reaction, or acne maligna) is a serious disease of sudden onset, associated with systemic symptoms and abnormal laboratory findings [1]. The term acne fulminans was coined by Plewig and Kligman in 1975 in order to describe acute febrile ulcerative acne conglobata with polyarthralgia and is considered a very uncommon complication of acne [2, 3].

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## 29.2 Etiology

The cause of acne fulminans is uncertain, but immunological, bacterial, and hereditary causes have been proposed.

A hypersensitivity response to either sebum or bacterial antigens has been suggested [4]. Specific cell-mediated immunity to *Propionibacterium acnes* was shown to increase during the course of acne fulminans [5].

An inflammatory or immunological mechanism could account for the presence of erythema nodosum, an increased response to *P. acnes* antigen in skin tests, and an increased cellular immunity using the leucocyte migration inhibition test [6–8].

Systemic isotretinoin has been suspected as one of the triggering factors of acne fulminans. Isotretinoin may induce increased fragility of the pilosebaceous duct, leading to a massive contact with *P. acnes* antigens and/or *P. acnes* chemoattractants [9]. This hypothesis supports the introduction of isotretinoin after systemic steroid treatment has been established [10].

Alternatively, a relation to circulating androgens or a familial association has been postulated [9, 11, 12]. Reports of the possible association of acne fulminans with specific HLA phenotypes are inconclusive. Acne fulminans has been reported in two siblings with identical HLA phenotypes (A2, 3; B7, 44; DR4, 11; DQw7, w8) [12]. Interestingly, an allelic polymorphism within the human tumor necrosis factor alpha and beta promoter region has been shown associated with the HLA A1, B8, and DR3 alleles, which were also present in a patient with acne fulminans [9, 13, 14].

## 29.3 Clinical Presentation

Acne fulminans typically presents in young adults, mainly adolescent boys between the ages of 13 to 16, although females can also be affected [9, 12, 15–17].

The patients usually have mild to moderate acne until the sudden rupture of microcomedones results in an extensive, liquefying necrosis, involving neighboring follicles. Hemorrhagic nodules and plaques are formed which evolve in ragged ulcerations whose base is filled with gelatinous, necrotic material. Lesions are extremely painful and may affect the face, neck, chest, and back (Fig. 29.1) [1]. This sudden onset of ulcerative crusting acne is associated with systemic signs and symptoms including fever, weight loss, arthralgia, and myalgia [18]. Poor appetite, hepatosplenomegaly, erythema nodosum, leukocytosis, and elevated erythrocyte sedimentation rate may also be noted [3]. Nevertheless, patients with acne fulminans and minimal or absent systemic findings have been described [17].

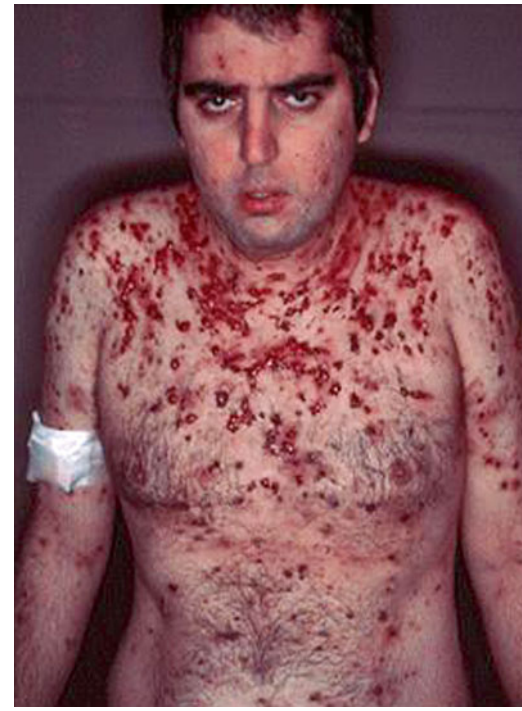

**Fig. 29.1** Acne fulminans

Acne fulminans may affect the iliosacral, iliac, and knee joints, causing the patient to walk in a characteristic, painful, bent forward way. Erythema nodosum on the shins occasionally occurs [1]. Aseptic, osteomyelitis-like, osteolytic bone lesions of the sternum, the clavicles, the hips, ankles, humerus, and the sacroiliac joints have been reported [1, 11].

In acne fulminans, unlike acne vulgaris, open and closed comedones are uncommon, and polyporous comedones and non-inflammatory cysts are absent [1].

**Table 29.1** Differential diagnosis between acne fulminans and acne conglobata

| | Acne fulminans | Acne conglobata |
|---|---|---|
| Sex | Almost exclusively adolescent boys | Usually men |
| Age | 13–16 years old | Adulthood |
| Onset | Sudden | Slow |
| Localization | Face, neck, chest, back | Face, neck, chest, back |
| Clinical features | Hemorrhagic ulcerations | Nodules, cysts, polyporous comedones |
| Systemic features | Very common: fever, leukocytosis, arthralgia, myalgia, osteolytic bone changes, erythema nodosum, hepatosplenomegaly | Uncommon |
| Successful treatment with systemic antibiotics | No | Yes |

## 29.4 Histology

Early lesions demonstrate an intense dermal abscess composed of granulocytes. Follicles and sebaceous glands are destroyed. The epidermis becomes necrotic secondary to hyalinized thrombotic vessels and profuse bleeding into the skin. The hemorrhagic skin necrosis is then surrounded by a mixed granulocytic and lymphocytic infiltrate [1].

## 29.5 Laboratory Findings

There are no characteristic laboratory findings in acne fulminans. Bacterial cultures from blood, joint fluid, and bone lesions are negative. *Staphylococcus aureus* can occasionally be isolated from skin lesions [11]. Antistaphylococcal, antistreptococcal, and antivirus antibody levels are negative. Other laboratory findings may include increased erythrocyte sedimentation rate and C-reactive protein, leukocytosis (sometimes with a leukemoid reaction), elevated levels of liver enzymes, thrombocytosis, microscopic hematuria, proteinuria, and normochromic, normocytic anemia [1].

Since androgen excess has been mentioned as a cause of acne fulminans, a genitourinary ultrasound in females and evaluation of serum levels of testosterone, follicle-stimulating hormone, luteinizing hormone, estradiol, progesterone, dehydroepiandrosterone sulfate, 17-hydroxyporgesterone, cortisol, and prolactin may be of value [1, 9, 19].

## 29.6 Differential Diagnosis

Acne fulminans should be differentiated from acne conglobata, as it is more severe and resistant to systemic antibiotics. It is associated with systemic features including fatigue, arthralgias, myalgias, fever, and hepatosplenomegaly. On the other hand, acne conglobata is characterized by a less sudden onset and by the presence of more nodules, cysts, and polyporous comedones (Table 29.1) [1].

## 29.7 Prognosis

Although there are few data, even in the larger series, regarding the number of patients who relapse after treatment, recurrent acne fulminans is considered extremely rare [3].

Despite its dramatic onset, the long-term prognosis appears to be good and chronic sequelae other than scarring are very rare. Occasional mild musculoskeletal pain in previously affected areas has been reported in some patients [1].

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# Childhood Acne

# 30

Maria Isabel Herane

## Contents



**Core Messages**

- Acne is a disease that can be seen in the newborn, first year of age, early childhood, prepubertal age, and puberty.
- High sebum rate, high androgens levels, tumors, and endocrinopathies are among the causes.
- Severe and persistent infantile acne and mid-childhood acne should be evaluated for hyperandrogenemia
- An early recognition of the disease in these age groups and prompt initiation of therapy prevent the sequelae of emotional distress and scarring.
- Hereditary factors play an important role in infantile acne.

## 30.1 Introduction

Acne is a disease that can be seen in infants from neonatal age, early childhood, prepubertal age, and puberty. It is characterized by a facial eruption of non-inflammatory and inflammatory lesions. In the neonate it is usually mild and transient due mainly to considerable sebum excretion rate; infantile acne can be more severe. High androgen levels of adrenal origin in girls and of adrenal and testes in boys have been implicated as the underlying pathogenic mechanisms [1, 2]. In prepubertal acne important factors like high serum levels of dehydroepiandrosterone

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sulfate and early appearence of comedones are predictors of severe or long-standing acne in this age. The differential diagnosis includes different diseases depending on the stage of infantile acne. The management of infantile acne is mainly with topical treatments. Reassurance of the benign character of the disease is necessary. Very exceptionally the use of combination treatments and the addition of systemic therapies like antibiotics are prescribed in infants and young children with inflammatory lesions. The use of isotretinoin is considered in persistent nodulocystic acne susceptible to scarring or to prevent psychological sequelae. Any abnormal age of onset should be considered as a cutaneous marker of hyperandrogenism and a further evaluation is mandatory [3].

## 30.2 Neonatal Acne

### 30.2.1 Clinical Features

Neonatal acne is present at birth or appears shortly after in the first weeks of life. It is more common than fully appreciated, and if the diagnosis is based on a few comedones, more than 20 % of newborns are affected [4, 5]. The most common lesions are papules and pustules and a subset of patients with a certain amount of comedones plus inflammatory lesions are considered of having an early-onset androgen-driven neonatal acne. Lesions in general are few in number and usually localized on the face, more often cheeks and forehead. Most cases are mild and transient. Lesions appear at 2–4 weeks healing spontaneously, without scarring, in 4 weeks to 3 months. The condition may persist, however, until the age of 6–12 months. Neonatal acne has been suggested to be more frequent in males [1, 2] (Fig. 30.1).

Neonatal cephalic pustulosis (NCP) has been referred by some authors as being neonatal acne. Lesions of NCP are papules and pustules localized to the face, most often cheeks, chin, eyelids, and forehead, and less commonly with extension to upper chest, scalp, and neck. No comedones are present. NCP develops in association with skin colonization of the *Malassezia* species

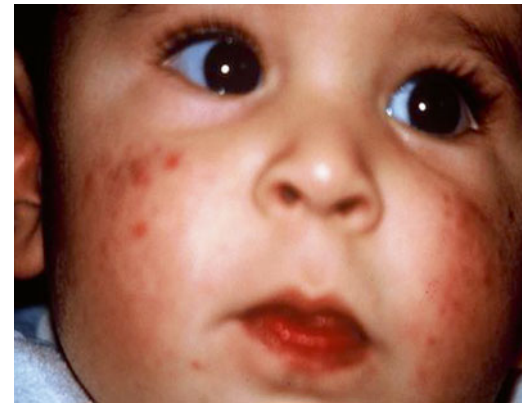

**Fig. 30.1** Neonatal acne: papules on the cheeks

(mainly *Malassezia sympodialis* and *Malassezia globosa*) during the first weeks of life [6]. The exact role of *Malassezia* in NCP remains unclear as the yeast is part of the normal flora of infant face skin. Malassezia has been demonstrated in smears of pustules of affected children, but in up to 38 % there is lack of correlation of negative smears and presence of NCP [7]. One possible explanation is that NCP can develop as a consequence of an overgrowth of lipohilic yeasts at birth that leads to an inflammatory reaction in a certain group of neonates with intense sebum production. The cutaneous inflammation initiates a poral and follicular occlusion [8].

### 30.2.2 Pathogenesis

The pathogenic mechanisms of neonatal acne remain unclear. A positive family history of acne supports the importance of genetic factors. Familial hyperandrogenism with acne and hirsutism gives the evidence that maternal androgens may play a role through transplacental stimulation of sebaceous glands and there is a direct correlation between high maternal and neonatal sebum excretion [9, 10].

### 30.2.3 Differential Diagnosis

The differential diagnosis of neonatal acne/NCP should consider pustular disorders in the neonate

such as erythema toxicum neonatorum, infantile acropustulosis, and transient neonatal pustular melanosis; infectious diseases of bacterial, viral, or fungal origin; bilateral nevus comedonicus; acneiform eruptions due to the use of topicals oils and ointments; or as a consequence of a virilizing luteoma in pregnancy [4, 9, 11–13]. Acneiform eruptions due to maternal medications should be ruled out with a thorough family history. Fetal hydantoin syndrome in mothers receiving phenytoin during pregnancy can present as an acneiform eruption plus various skeletal and craniofacial dysmorphic features. Lithium in pregnant women and high doses of corticosteroids during the last term of pregnancy may induce acneiform eruptions in the neonates and sometimes in the mother as well [2, 5, 9].

Rarely neonatal acne/NCP is related with an underlying endocrinopathy. In order to rule out classic congenital adrenal hyperplasia (CAH) or other endocrinopathy a careful history and physical examination should be done including height, weight, growth rate, signs of virilization, and blood pressure. If hyperandrogenism is suspected the screening tests required are dedydroepiandrosterone-sulfate (DHEAS) to evaluate adrenal function and free testosterone to detect increase of biologically active testosterone [5].

## 30.3 Infantile Acne

### 30.3.1 Clinical Features

Infantile acne (IA) usually starts later than neonatal acne, generally between 3 and 6 months but also as late as 16 months. It is less common than neonatal acne and boys are more frequently affected [14, 15]. A family history of severe acne in one or both parents might be present [9, 16]. The pattern is more inflamed and widespread than neonatal acne. Lesions are localized on the face with the cheeks being the most affected area. Clinically open and closed comedones combined with papules and pustules in a moderate involvement are common and present in 62 % of cases [14] (Fig. 30.3). Occasionally cystic lesions can be seen. The course is variable. Some

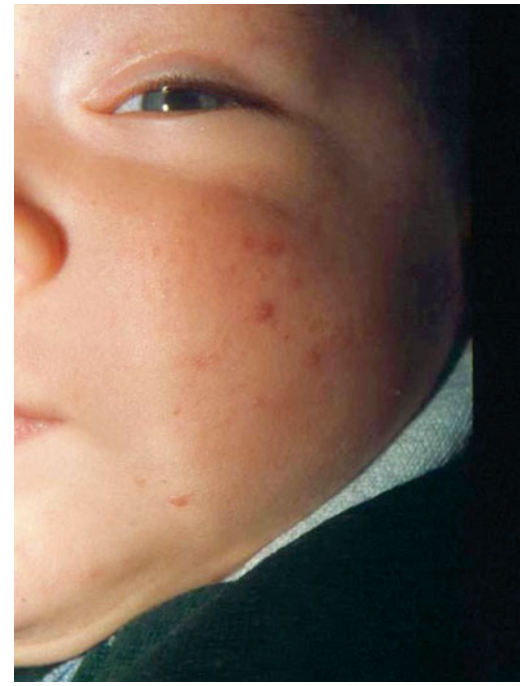

**Fig. 30.2** Infantile acne

cases disappear in 1 or 2 years, but others are persistent and resolve by the age of 4 or persist until puberty [2]. Very rarely forms of facial conglobate acne including extensive nodules, draining sinuses, and severe inflammation leading to marked scarring can be seen. Infantile acne, especially conglobate infantile acne, may be related with severe forms of the disease in adolescence [9, 17]. Overlaps with neonatal acne are not rare (Fig. 30.2).

### 30.3.2 Pathogenesis

The exact cause of IA is not clear. Genetic factors including inheritance of size and activity of sebaceous glands, seborrhoea, large-pore skin, and inflammation play a role. Evidence of the importance of maternal androgens is established through familial hyperandrogenism of acne and hirsutism [18]. Mainly the infant's hormonal milieu plays an important role. During the neonatal period there is an increased sebum excretion rate that decreases at 6 to 12 months to almost no detectable levels, in relation with a

reduction in sebaceous gland volume. During the first 6–12 months of life in boys there is an increase in luteinizing hormone (LH) and testosterone as a consequence; there is virtually no androgen production of testicular origin from the age of 1 year up to adrenarche. In contrast, in girls, testosterone levels drop rapidly from birth up to 2 weeks [19–22].

In both sexes the adrenal neonatal gland is a "fetal gland" with an enlarged zona reticularis where androgens are produced; high levels of DHEA stimulate sebaceous glands. This zone disappears at the age of 1 year and reappears in adrenarche.

In summary, IA could be due to the "fetal adrenal gland" plus testicular androgens, explaining the predominance of IA in boys. The persistent androgen production of the fetal adrenal gland could explain the observations of a number of infants with acne vulgaris in the first 6–9 months of age. Most patients do not have any abnormality [23].

### 30.3.3 Differential Diagnosis

Infantile acne must be differentiated from acneiform eruptions due to topical skin products such as ointments, creams, pomades, and oils applied by the parents in a process well known as acne venenata infantum. The lesions take 6–8 weeks to resolve once the products are discontinued. Acne pomade frequently seen in African-American populations is due to the use of products containing comedogenic substances in order to tight curly hair. It is mainly a monomorphic comedonal eruption, sometimes with inflammatory papules [2, 5]. Systemic, topical, and inhaled corticosteroids can cause an acneiform eruption or a periorificial eruption involving mainly the perioral, perinasal, and periocular area and may be associated with ocular involvement and genital vulvar lesions in girls. A family history is present in 20 % of the cases [9, 24].

Skin contact, ingestion, or inhalation of aromatic hydrocarbons with chlorine groups (chloracne) may occur because of accidental exposure. The clinical findings are greatly depending on the nature and intensity of the exposure and in skin level from acute chemical burns to comedones that represent the hallmark of chloracne. Lesions are located nearly in every follicle contaminated, especially in the sebaceous and vellus follicles of the face. The favorite locations in the face are cheeks, forehead, and notably behind the ears. The comedones develop after 1–2 months and later they might get inflamed; the condition continues for months or even years. Milder cases disappear spontaneously. Widespread atrophic and hypertrofic scars mark the end stage of the disease [25, 26].

In cases of severe inflammatory acne or in acne conglobata the differential diagnosis should consider pyodermas and panniculitis of various origins.

In severe and persistent IA hyperandrogenism should be excluded. A good physical examination could exclude precocious puberty. Other exams such as bone age measurements and levels of follicle-stimulating hormone (FSH), LH, testosterone, and DHEAS are the basic encdocrinological approach. Children should be referred to an endocrinologic evaluation in case of any abnormality [3].

## 30.4 Mid-Childhood Acne

This type of acne occurs between 1 and 7 years of age. Acne is very rare in this group and when it occurs patients should be evaluated for hyperandrogenemia.

### 30.4.1 Pathogenesis

During the neonatal period and for approximately one year the adrenal secretes androgens; then they disappear until mid-childhood around 7 years of age when the zona reticularis is physiologically producing androgens again. Acute onset of the disease in between the age of 1 up to 7 years, persistent or severe acne in this age, or virilization should rule out a group of disorders such as premature adrenarche, CAH classical and not classical, gonadal and adrenal tumors, and

**Table 30.1** Mid-childhood/prepubertal acne: investigations for endocrine disorders

| |
|---|
| Bone age |
| Growth chart |
| Tanner stage |
| Testosterone total and free |
| DHEAS |
| Androstenedione |
| LH |
| FSH |
| Prolactin |
| 17 OH-progesterone |

precocious puberty. The evaluation necessary for an initial approach is listed in Table 30.1.

If testosterone is over 100–200 ng/dL CAH (DHEAS, androstenedione, 17-OH), Cushing syndrome (DHEAS, androstenediones, cortisol), and polycystic ovarian syndrome (free testosterone, prolactin, LH/FSH >3) should be excluded.

If total testosterone is greater than 200 ng/dL it is necessary to rule out adrenal tumors (DHEAS) and ovarian tumors.

### 30.4.2 Differential Diagnosis

Acne at this age can be confused with keratosis pilaris of the cheeks and with keratin cysts particularly when they are inflamed. Both lesions are common in atopics. Occasional reports of mid-childhood acne due to D-actinomycin are available in the literature [27]. Periorificial dermatitis can be seen in this age due to the use of corticosteroids or cosmetics such as sun blockers [28] (Fig. 30.3). Cases of eccrine hydrocystomas with multiple vesicular lesions at the nose can also be confused with IA (Fig. 30.4).

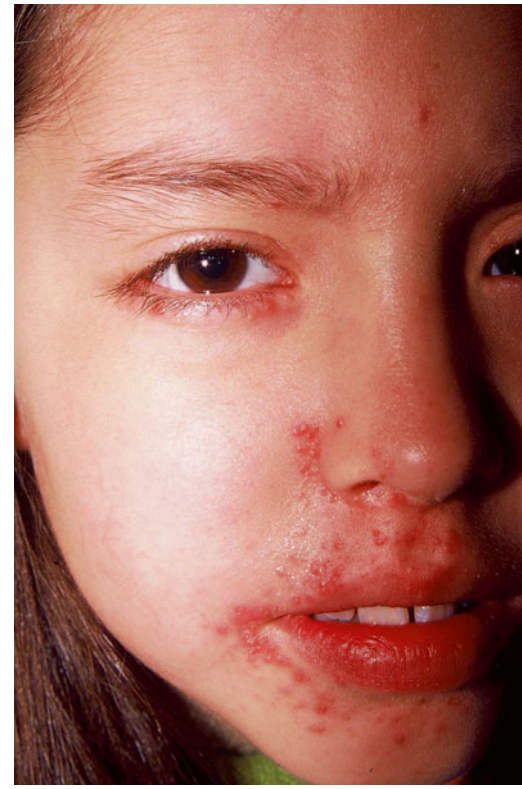

**Fig. 30.3** Periorificial dermatitis. Multiple papules in perinasal, periocular and perioral areas

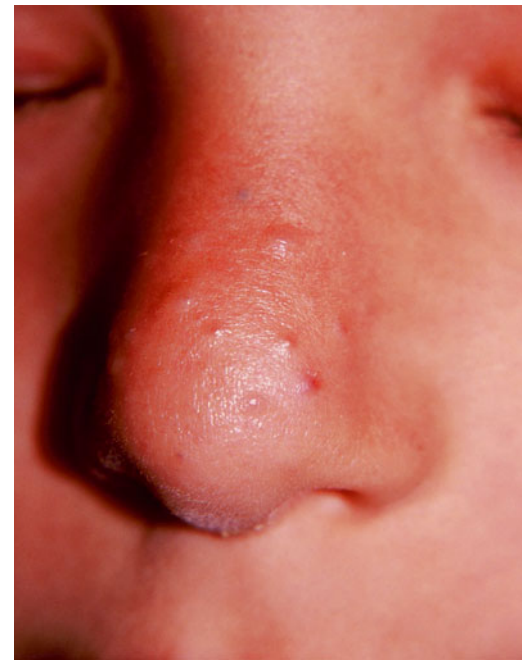

**Fig. 30.4** Multiple eccrine hydrocystomas

## 30.5 Prepubertal Acne

### 30.5.1 Clinical Features

Early onset of acne before obvious signs of puberty is a recognized phenomenon associated more with pubertal development than with age. There is apparently a genetic predisposition.

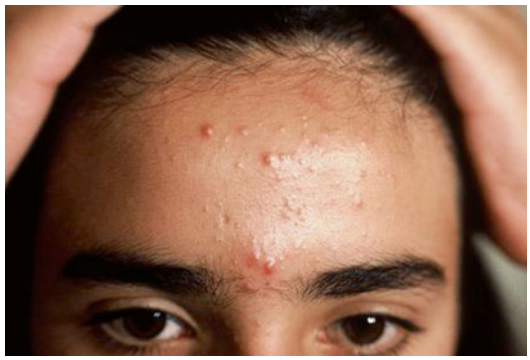

**Fig. 30.5** Prepubertal acne: seborrhea, comedones and inflammatory lesions in mid-forehead

Acne can be present in girls as young as 8 years old, may be the first sign of pubertal maturation, and is associated with excretion of androgenic steroids and increase in sebum rate. The most common locations of acne in this group are mid-forehead, nose, and chin. Comedones may appear before other signs like pubic hair and areolar development in girls and before testicular enlargement in boys [29] (Fig. 30.5).

There is also a correlation between earlier menarche in girls with severe acne (12.2 years) compared to those with moderate and mild disease (12.4 and 12.7 years) [30]. The number of comedones is also predictive of the severity of acne in the future. Mid-pubertal girls with severe comedonal acne showed more comedones 3 years before menarche and this finding is related to higher levels of DHEAS and total and free testosterone as compared to girls with mild acne, the hormone levels being usually within the normal range [30]. Pubertal maturation and acne tend to occur earlier in African-American girls not being a racial difference in acne or differences in hormone levels adjusted to pubertal development. As a conclusion, early development of comedonal acne, DHEAS, and free and total testosterone at normal-high levels are good predictors for severe disease or long-term acne [31].

### 30.5.2 Pathogenesis

In pubertal development there are two components to be considered. Normal adrenarche related to maturation of adrenal glands and true puberty as a result of maturation of ovaries in girls and testis in boys and mediated by hypothalamic–pituitary axis. Adrenarche starts at the age of 6–7 years in girls and 7–8 years in boys and is due to high levels of DHEA and DHEAS, expressed clinically by seborrhea, odor, appearance of terminal and sexual hair, and the presence of acne. The process is a continuum during mid-puberty [32, 33].

Cases of early pubertal development, hirsutism, and recalcitrant acne to conventional therapies should alert for evaluation of hormonal abnormalities. Excess of androgens in girls may be from adrenal gland or ovary origin. The cause might be adrenal hyperandrogenism, exaggerated menarche, exuberant production of adrenal androgens, Cushing disease, classical and non-classical CAH, adenomas, or carcinomas. The ovarian contribution in girls more commonly is the result of polycystic ovarian syndrome associated with obesity and insulin resistance. Very rarely androgen excess can be a manifestation of benign or malignant tumors. In boys acne may be the only sign of androgen excess and a study in cases of resistant acne to treatment should exclude nonclassical CAH. A thorough endocrine evaluation should be performed in suspicious cases (Table 30.1).

### 30.5.3 Differential Diagnosis

The differential diagnosis is essentially similar to mid-chilhood acne. Adverse effects of certain drugs such as corticosteroids, anticonvulsants, lithium, and isoniazid can develop acneiform eruptions. Occasional cases of childhood rosacea, granulomatous periorificial dermatitis, and other granulomatous face papules in infancy can be included in the differential diagnosis [34, 35]. Sporadic cases of hydradenitis suppurativa associated with acne must be considered at this age [36].

The importance of genetics factors in acne should be considered. At this age there is a strong correlation with family history, and if the patient has an identical twin, there is a 98 % of probability

that the other twin can develop the disease. The age of onset, sebum excretion rate, and number of comedones can be very similar in both twins, but the inflammatory severity of acne may not be identical. Knowing the existence of some genetic disorders such as some chromosomal abnormalities (46 XYY, 46 XY+, partial trisomy 13) and rare syndromes such as Apert's syndrome (acrophalangosyndactyly), pediatricians should be aware that they might develop severe acne or acne in unusual areas [9, 37, 38]. The presence of atopy in children is correlated with a lower incidence of acne due to a lower sebum excretion and different sebum pattern.

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# Congenital Adrenal Hyperplasia and Acne in the Male Patients

31

Clio Dessinioti and Andreas D. Katsambas

## Contents



**Core Messages**

- Congenital adrenal hyperplasia describes a group of autosomal recessive disorders characterized by enzyme defects in the biosynthetic pathway of cortisol, aldosterone, and androgens.
- The clinical phenotype is typically classified as classic (C-CAH, the severe form) or nonclassic (NCAH, the mild or late-onset form). Classic congenital adrenal hyperplasia is subclassified as salt-wasting or simple-virilizing forms, depending on the degree of aldosterone deficiency.
- 21-hydroxylase deficiency results in the majority of NCAH and is associated with symptoms starting in childhood (precocious puberty, acne) or only later in adult life (in male patients: acne, infertility).
- Biochemical diagnosis consists of the determination of 17-hydroxyprogesterone levels, the immediate substrate for 21-hydroxylase, before and after ACTH stimulation, and may be confirmed by genetic testing.
- Further studies are needed to better understand the association between congenital adrenal hyperplasia and acne in male patients as well as to determine optimal treatment regimens for these patients.

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## 31.1 Introduction

Androgen excess may have a profound effect on the skin, soma, and psyche of our patients [1]. The role of adrenal androgens in the development of acne is well known and the severity of early acne has been shown to correlate well with pubertal maturation (adrenarche and testis maturation) in young adolescent boys [2]. Although in women acne may present with other signs of hyperandrogenism, such as hirsutism or menstrual irregularities, in men acne may be the only sign of androgen excess. Congenital adrenal hyperplasia (CAH, MIM 201910) represents one of the causes of androgen excess, which, in turn, may cause or exacerbate acne via increased seborrhea [3].

Congenital adrenal hyperplasia is one of the most common inborn metabolic disorders [4]. It describes a group of inherited autosomal recessive disorders characterized by enzyme defects in the biosynthetic pathway of cortisol, aldosterone, and androgens. In these disorders, loss of negative feedback inhibition due to cortisol deficiency leads to increased secretion of ACTH from the pituitary gland, subsequent hyperplasia of the adrenals, and stimulation of adrenal steroidogenesis [5] (see Chap. 46).

The clinical spectrum of CAH ranges from classical congenital adrenal hyperplasia (C-CAH) associated with complete loss of enzyme function with presentation in the neonatal period to milder or nonclassical (NCAH) forms presenting in adolescence or adulthood. NCAH patients produce normal amounts of cortisol and aldosterone at the expense of mild-to-moderate overproduction of sex hormone precursors.

## 31.2 Pathophysiology and Genetics of CAH

Each form of congenital adrenal hyperplasia has its own unique hormonal profile, which depends on the type of the underlying enzyme defect. Deficiency of the 21-hydroxylase (21-OH) enzyme, due to deletions or deleterious mutations in the 21-hydroxylase gene (*CYP21A2*), is responsible for more than 95 % of cases of congenital adrenal hyperplasia and it represents one of the most common autosomal recessive disorders [5]. Eleven mutations, deletion, translocation, or genetic changes, in general, were composed of over 90 % of all changes recognized so far [6].

Duplicated 21-OH genes, an active gene CYP21, and a pseudogene (CYP21P) are located on chromosome 6p21.3, within the HLA class III gene region, about 30 kb apart. Different mutations of the CYP21 gene are responsible for varying degrees of impairment of 21-OH activity that cause a spectrum of disease expression [7, 8]. Most patients are compound heterozygotes and the clinical phenotype is generally related to the less severely mutated allele and consequently to the residual 21-OH activity [9]. 21-OH is a cytochrome P450 that catalyzes the conversion of 17-hydroxyprogesterone (17-OH PG) to 11-deoxycortisol. 21-OH is also required for mineralocorticoid production, and its deficiency leads to impaired synthesis of aldosterone, in case of classic CAH (C-CAH) [5]. As a result of this blocked enzymatic step in cortisol biosynthesis, substrate precursors, such as 17-OHP and progesterone, accumulate in excess and are then converted to androgens, mainly androstenedione, resulting in signs and symptoms of hyperandrogenism (Fig. 31.1) [9].

It has been suggested that the most common form of NCAH is due to 21-OH deficiency [10, 11]. Three missense mutations have previously been shown to be associated with the NCHA form: Val282Leu in exon 7 (the most frequent), Pro 454Ser in exon 10, and Pro31Leu in exon 1 [12, 13]. These mutations affect the secondary structure of the 21-OH enzyme, resulting in residual activity of 20–60 % in vitro [14, 15].

## 31.3 Epidemiology of CAH Due to 21-OH Deficiency

Classical congenital adrenal hyperplasia occurs in approximately 1/15,000 births, while NCAH is much more frequent with an incidence of 1:500 to 1:1,000 in various Caucasian populations [13]. NCAH forms are far more common than the classic forms and affect 1 % of the general population, many of them being undiagnosed [16]. The

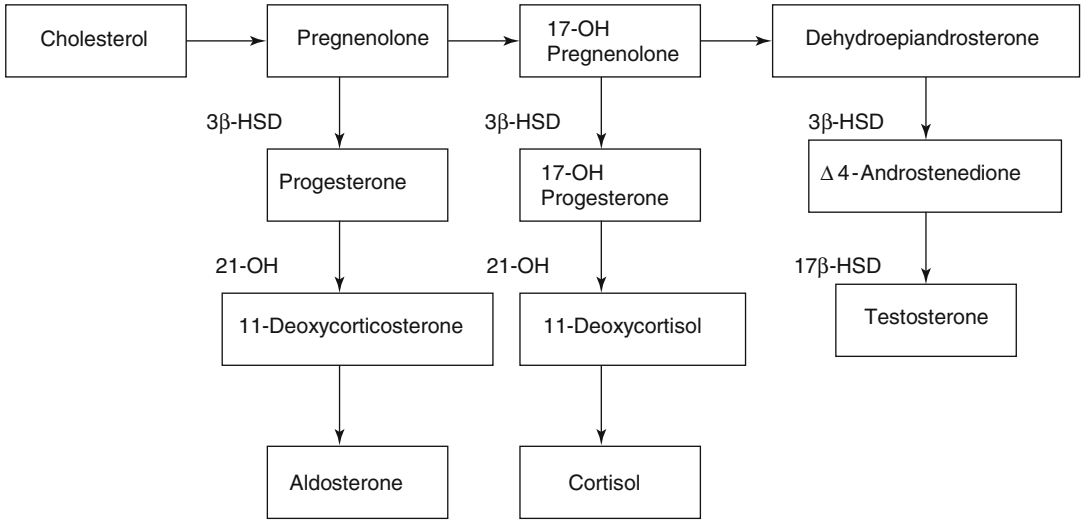


**Fig. 31.1** Simplified scheme of the role of 21-hydroxylase in the adrenal steroidogenesis pathway. *3β-HSD* 3**β**-hydroxysteroid dehydrogenase; *21-OH* 21-hydroxylase; *17β-HSD* 17**β**-hydroxysteroid dehydrogenase

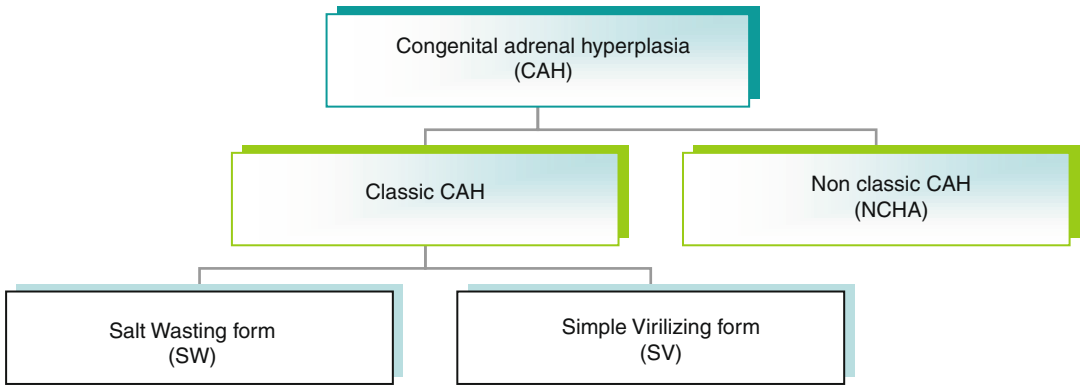


**Fig. 31.2** Clinical forms of congenital adrenal hyperplasia

frequency of NCAH due to 21-OH deficiency is estimated to be 0.1–0.2 % of the general population, 1–2 % of Hispanics and Yugoslavs, and 1–4 % of Ashkenazi (Eastern European) Jews [12, 17].

## 31.4 Clinical Manifestations

Congenital adrenal hyperplasia can be classified according to symptoms and signs and according to age at presentation. The clinical phenotype is typically classified as classic, the severe form, or nonclassic (NCAH), the mild or late-onset form. Sometimes congenital adrenal hyperplasia may remain asymptomatic (cryptic form). Classic congenital adrenal hyperplasia is subclassified as salt-wasting (SW) or simple-virilizing (SV) forms, depending on the degree of aldosterone deficiency (Fig. 31.2) [9, 18].

Correlations between the CYP21 genotype and phenotype have been studied in various ethnic and racial groups. Mutations producing enzymes that retain 20–60 % of normal activity are associated with NCAH, while more serious mutations resulting in totally ablate enzyme activity or 1–2 % of normal activity are associated with classic CAH [8].

While the severe forms of the disease responsible for salt-wasting or simple virilization have been extensively studied, the NCAH 21-OH deficiency is less well characterized, especially in adults [11]. Most studies of CAH involve female patients [11, 19–22]. However, only few of them have specifically addressed acne in these patients [21]. Insulin insensitivity in females with NCAH has been described, but it has not been established whether an association with acne exists in these patients [23]. On the other hand, male patients with CAH and acne have not been sufficiently studied.

### 31.4.1 Classic Congenital Adrenal Hyperplasia

Both the SV and the SW forms of 21-OH deficiency are characterized by increased adrenal androgen secretion, which results in prenatal virilization of the female genitalia and postnatal virilization of both boys and girls [24]. In addition, lethal—if left untreated—electrolyte disturbances (low serum sodium, high serum potassium, vascular collapse) are a characteristic of the SW form of the disease [11].

Postnatally, in untreated boys and girls, androgen excess results in rapid growth, advanced epiphyseal maturation, and ultimately, early epiphyseal closure and short stature. Also, untreated patients present progressive penile or clitoral enlargement, early appearance of facial, axillary, and pubic hair, and acne. In puberty, suppression of gonadotropins by adrenal testosterone and adrenal "rests" stimulated by ACTH lead to infertility in male patients, as a result of poor compliance with glucocorticoid treatment. Some men with CAH have hypogonadotropic hypogonadism and small testes, potentially reversible with increased glucocorticoid suppression [9, 25].

### 31.4.2 Nonclassic Congenital Adrenal Hyperplasia

A few NCAH cases are detected by newborn-screening programs, but most are missed because of the relatively low baseline levels of 17 OH PG [26]. NCAH is a heterogenous disorder, associated with symptoms of androgen excess presenting either in childhood (precocious puberty) or sometimes later in adulthood (acne, infertility) [11, 20]. Precocious puberty may present in childhood, with advanced bone age, accelerated growth, and premature development of pubic or axillary hair. Nevertheless, growth is eventually arrested because of early epiphyseal fusion which compromises final height (Tall children, short adults) [22].

Female patients with NCAH can be asymptomatic or present with hirsutism, which is the most common symptom. Moreover, studies in female patients show that NCAH may present with menstrual irregularities, obesity, short stature, infertility or subfertility, and skin disorders, including hirsutism, seborrhea, and/or acne in peripubertal period. These clinical characteristics of NCAH do not differ from those in female patients with polycystic ovary syndrome (PCOS) or hyperinsulinemia [19, 22, 27]. Male patients with NCAH may be asymptomatic or present with acne or infertility [28]. Severe cystic acne refractory to oral antibiotics and isotretinoin has been associated with NCAH due to 21-OH deficiency [29–31]. Most of the men with NCAH are fertile and the prevalence of NCAH due to 21-OH is not greater among infertility clinics. Oligospermia or unilateral testicular enlargement is rare (Table 31.1). Cortisol synthesis during stress is not impaired or severe enough to cause death from adrenal insufficiency [32].

## 31.5 Laboratory Investigations for CAH in Male Patients

Adrenal androgens have rarely been investigated in men with acne. Elevated DHEA-S and 17-OH PG have been reported in men with severe cystic acne compared with controls, while other studies failed to support these findings [3, 30, 33–35]. Also, elevated serum androgen levels have been found in cases of acne associated with congenital adrenal hyperplasia (11β- and 21β-hydroxylase deficiencies) [36].

**Table 31.1** Clinical features of 21-OH congenital adrenal hyperplasia

| Classic adrenal hyperplasia | | Non-classic adrenal hyperplasia | |
|---|---|---|---|
| Females | Males | Childhood | Adulthood |
| Reduced fertility | Reduced fertility | Premature pubarche | Menstrual irregularities[a] |
| Salt wasting[b] | Salt wasting[b] | Pseudoprecocious puberty | Infertility |
| Hirsutism, acne | Acne | Tall stature | Short stature |
| Virilization of the external female genitalia | Hypogonadotrophic hypogonadism Small testes | Cystic acne | Acne |
| Rare ovarian adrenal rest tumors | Testicular adrenal rest tumors | | Oligospermia[c] |
| Menstrual irregularities | | | Testicular enlargement[b] Hirsutism[a] |

[a]Women
[b]Salt-wasting form only
[c]Men

**Table 31.2** Investigations for congenital adrenal hyperplasia in male patients with acne

- Thorough medical history: infertility, acne
- Physical examination: testicular examination
- Basal plasma17-hydroxygesterone
- ACTH-stimulated plasma 17-hydroxyprogesterone
- Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH)
- Testosterone, DHEA-S, androstenedione
- 21-desoxycocrtisol
- Testicular ultrasound
- Semen analysis

Biochemical diagnosis of CAH relies on the determination of 17-OH PG, the immediate substrate for 21-OH. A basal 17-hydroxyprogesterone level >6.1 nmol/L (>2 ng/mL or 200 ng/dL) can serve for screening for NCAH [21]. Further endocrinological investigations are summarized in Table 31.2.

The ACTH stimulation test is the best screening test for evaluating adrenal gland function, and it is valuable in cases of mild forms of congenital adrenal hyperplasia with normal basal adrenal steroids [18]. It is the principal challenge test for estimating the relative activity of adrenocortical enzymes and it has been used for the biochemical diagnosis of NCAH due to various enzyme deficiencies [10]. Blood samples are obtained before (0 min) and 60 min following Tetracosactide, 25 IU (hormonally active ACTH fragment, Synacthen, Novartis, Nürnerg, Germany) intravenous injection. Basal and stimulated 17-OH PG levels are determined. The possibility of CAH is considered if basal 17-OH PG levels are elevated and/or ACTH-stimulated 17-OH PG is more than 260 ng/dL (7.87 nmol/L) above the basal level [3, 18]. Furthermore, the diagnosis of 21-OH-deficient NCAH is established by the response of 17-OH progesterone to adrenocortical stimulation with levels >30.3 nmol/L (>10 ng/mL) [21]. On the other hand, borderline biochemical data are difficult to interpret [11].

### 31.5.1 Molecular Diagnosis

The utility of genotype analysis of the 21-OH gene has been proposed in hyperandrogenic women presenting symptoms ranging from hirsutism, acne, and amenorrhea to decreased fertility, in order to distinguish heterozygous from wild-type individuals and to characterize biochemically borderline individuals [11]. There are no relevant studies in men. Nevertheless, in clinical practice, molecular biology is not routinely available.

## 31.6 Treatment of Acne in Male Patients with NCAH

Treatment of NCAH is a controversial issue and depends on the main problem of the patient.

For the treatment of acne associated with NCAH in male patients, oral glucocorticoids are administered in order to counteract adrenal

androgen production [18]. Low-dose prednisone (2.5–5 mg/day) or low-dose dexamethasone (0.25–0.75 mg) can be given orally at bedtime, although the latter incurs a higher risk of adrenal suppression [18, 37]. Oral methylprednisolone (initial dose of 1 mg/kg/day) in combination with oral isotretinoin was a successful treatment for acne fulminans in a boy with NCAH [33]. In order to ensure that glucocorticoids are efficacious, the serum DHEAS level can be monitored for a decrease or normalization. To check for adrenal suppression, an ACTH stimulation test should be performed 2–3 months after initiation of therapy. This involves assessing the plasma cortisol level 30 min following an injection of 250 μg/m [10] ACTH. A raise in plasma cortisol by appropriate amounts (>16 μg/dL) indicates that the adrenal gland is not suppressed [38].

Long-term administration of glucocorticoids, even at low doses, is associated with the risk of osteoporosis, especially in teenagers whose bone development is still ongoing. Therefore, low-dose glucocorticoids should not be taken for a time period longer than 6 months [18].

**Conclusions**

The frequency of congenital adrenal hyperplasia in cases of refractory acne or in acne that persists beyond the usual age has not been systemically studied [3]. However, the knowledge that acne may be the only presenting sign of hyperandrogenism in male patients highlights the need of correcting irregularities of adrenal androgen metabolism, such as CAH, in some patients with difficult-to-treat acne.

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# Adult Acne

# 32

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and Andreas D. Katsambas

## Contents



**Core Messages**

- Adult acne may be persistent from adolescence or late onset, arising for the first time after age 25 years; it may last into the sixth decade.
- Women are affected more often than men.
- There appears to be a familial predilection.
- Although the pathogenesis of adult acne is similar to that seen at other ages, hormonal influences appear to be more important in adult women.
- Common underlying hormonal causes include polycystic ovary syndrome (PCOS) with or without the metabolic syndrome and, less frequently, late-onset congenital adrenal hyperplasia (CAH).
- Premenstrual flares of acne are common in adult women.
- Adult acne affects the lower third of the face, especially the chin and perioral area. Deep inflammatory papules and nodules are more prevalent than comedones.
- Proper diagnosis is dependent on a thorough medical and family history, a physical examination, and a laboratory investigation to look for signs of hyperandrogenemia and features of the metabolic syndrome.
- Adult acne tends to be more refractory to treatment and can cause physical and emotional discomfort deserving of special consideration.

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## 32.1 Introduction

Acne vulgaris is a disorder that usually appears at puberty and resolves in late adolescence or early adult life. However, there are a significant number of adults who also suffer from acne. This chapter will review the epidemiology of adult acne, its etiology, pathogenesis, and clinical presentation, a suggested clinical and laboratory evaluation, and an approach to therapy. Adult acne can be divided into persistent acne which continues into adult life from the teen years and adult-onset acne which first appears after age 25 years. Much of the pathogenesis, clinical presentation, and therapy are comparable in both types and they will be discussed together.

## 32.2 Epidemiology of Adult Acne

Data assessing the prevalence of adult acne in the general population are scarce. In a group of 200 patients over age 25 referred for acne in the UK, 18.4 % of women and 8.3 % of men had true late-onset disease appearing first after age 25 years [1]. Of 749 patients over age 25 who were examined, 12 % of women and 3 % of men were found to have significant acne [2]. Similarly, in 787 women over age 20 in Australia, 13.6 % were found to have acne [3]. In a review of office utilization between 1990 and 1994 by patients of mean age 24 ±11.5 years in the USA, 10 % of acne visits occurred between 35 and 44 years of age [4]. In another USA survey of almost 100 patients aged 18–54 years, the mean duration of acne was 20.4 years [5]. In France, in a study of over 3,000 women, 17 % had clinical and 24 % physiologic acne. Of these women, 41 % had late-onset acne [6]. Another estimate in the UK found that 14 % of women between the ages of 26 and 44 had acne [7]. In a 2008 USA study of 1,013 randomly accessed subjects between the third and sixth decades of life who answered a questionnaire, there were 50.9 % of women and 42.5 % of men aged 20–29 who responded positively to having acne; this declined gradually to 15.3 % and 7.3 % respectively at ages 50 years and older [8]. Thus, depending on the type of study and criteria used, the prevalence of adult acne ranges in women from 12 to 51 % and in men from 3 to 42 %.

The exact prevalence of adult acne and the proportion of persistent vs. late-onset disease are difficult to assess: prevalences tend to be higher in studies with self-reported data compared to examined patients. There are regional differences in genetic and environmental factors, and the impact of therapy may not be comparable. However, it is safe to conclude that adults with acne are not rare and that women tend to have a higher prevalence than men.

## 32.3 Etiology and Pathogenesis of Adult Acne

Similar to acne at every age, adult acne is a multifactorial disorder. Endogenous factors include genetic predisposition, abnormal keratinization, colonization with *Propionibacterium acnes* and other bacteria, heightened inflammatory response, and hormonal stimulation of sebum production, especially in women. Exogenous factors include drugs, trauma from manipulation (acne excoriée), stress, and cosmetic usage (Table 32.1).

A. Endogenous Factors

1. Genetic Predisposition to Acne
   Genetic predisposition is one of the primary endogenous factors influencing adult acne. In a survey of 236 patients with persistent acne in the UK, 50 % of patients with adult acne were reported to have at least one first-degree relative with mature acne [1]. The same investigators reported that in 204 referred acne patients over the age of 25, the relative risk of acne occurring in a first-degree relative was 3.93 [2]. It has

**Table 32.1** Factors influencing adult acne

| Endogenous | Exogenous |
|---|---|
| Genetic predisposition | Drugs |
| Abnormal keratinization | Trauma (acne excoriée) |
| Colonization by *P. acnes* and others | Stress |
| Inflammation | Cosmetics |
| Hormonal stimulation of sebum | |

been suggested, primarily by twin studies, that heredity plays an important role in the pathogenesis of acne [9]. Genetic factors may determine the failure of acne-prone follicles to normally evolve into acne-resistant follicles in early adult life [2].

2. Abnormal Keratinization, Bacterial Colonization, and Inflammation
   The four factors which are considered to be important to the pathogenesis of all types of acne are also influential in adult acne. Abnormal keratinization, bacterial colonization, and inflammation are discussed in detail elsewhere in this book. It had been postulated that the increase in adult acne may be related to an increased carriage of antibacteria-resistant bacteria [1]. However, analysis of the cutaneous microflora in adolescent, persistent, and late-onset acne patients and controls presented no differences and therefore does not explain the pathogenesis of the different disease subsets. This is perhaps not surprising as acne is known to have a multifactorial etiology [10]. Similarly, changes in the inflammatory response to *P. acnes* cannot explain adult acne; in fact, immune responses wane with age.
3. Hormonal Influences on Adult Acne
   During puberty, under the influence of rising serum androgens there is sebaceous gland hyperplasia and an increase in the sebum excretion rate. Comedogenesis and an increase in the cutaneous microflora also occur during this period. In most cases, the onset of acne will occur at puberty and generally persist into early adulthood. In a minority of individuals, the disease will persist longer. It is possible that the mechanisms involved in the pathogenesis of adolescent, persistent, and late-onset acne may be different [10].

   Special mention should be made of the role of hormones in adults with acne.[33] There is some evidence that men with mild forms of congenital adrenal hyperplasia (CAH) and elevated androgens are acne prone [11, 12]. In 16 Japanese men, no increases in serum androgen were found [13]. However, there is much more evidence for the role of hormones in adult women with acne. There are numerous series documenting elevated free testosterone (T), dihydrotestostrone (DHT), and/or dehydroepiandrosterone sulfate (DHEAS), as well as low sex hormone binding globulin (SHBG) in both persistent and late-onset adult acne. In many studies, the individual serum levels of androgens have been found to be abnormal; in other studies, individual serum levels of hormones are normal, but mean androgen levels are higher in the patients with acne [14–16].

   Another piece of evidence that acne is hormonally controlled is the observation of a clinical flare of acne in the premenstrual phase of the menstrual cycle. This was confirmed in a study of women 18–44 years of age with acne which showed that 63 % had documented premenstrual inflammatory acne flares [17]. Although possibly caused by elevated androgens, another hypothesis for the etiology of the premenstrual flare is a relatively lower mid-cycle peak of estrogen in women with acne.

   Correlation of adult acne to signs and symptoms of polycystic ovary syndrome (PCOS), as well as other hyperandrogenic disorders such as congenital adrenal hyperplasia (CAH) and Cushing disease, is also well documented and supports the role of hormone abnormalities in adults with these conditions [18]. These disorders are discussed fully elsewhere in this book. Postmenopausal acne has been postulated to occur because of the influence of residual adrenal and ovarian androgens acting unopposed by estrogen [19].

   An end-organ cutaneous abnormality of androgen metabolism, in particular the conversion of T to DHT by type 1 5α-reductase in acne-prone follicles, is also likely to be important [20]. Genetic factors may determine abnormal follicular keratinization or sebaceous gland

**Table 32.2** Common drugs known to cause or exacerbate acne in adults

| |
|---|
| Progestins without estrogen |
| Anabolic steroids |
| Lithium |
| Epidermal growth factor receptor-targeted chemotherapy |
| Glucocorticosteroids (topical, inhaled, systemic) |
| Isoniazid |
| Iodides, bromides |
| Antiepileptic drugs |

androgen response in individuals with persistent acne [10]. Moreover, insulin-like growth factor-1 (IGF-1) levels may influence sebum production and acne in adult men and women [21].

B. Exogenous Factors

1. Drugs
   A variety of medications used by adults can cause acneiform reactions or precipitate true acne. Some of these are listed in Table 32.2. Mechanisms may differ for each drug. Of special note are the progestin-only contraceptives, given orally, injected, implanted, or in an intrauterine device. These forms of contraception have become more widespread and are often a hidden cause of adult acne [22]. In men, body builders and those seeking better athletic performance may be taking anabolic steroids [23]. Oral or topical testosterone may be prescribed for perimenopausal women to increase libido. Lithium is used for bipolar disorder and well known to exacerbate or initiate severe, refractory inflammatory acne. Epidermal growth factor receptor (EGFRI) targeted chemotherapy drugs such as erlotinib and gefitinib can cause severe pustular acne which may be treated with concomitant acne therapy with oral antibiotics [24]. A full discussion of drugs and acne can be found elsewhere in this book.
2. Trauma.
   Although the original term for traumatically exacerbated acne is acne excoriée de jeunes filles (excoriated acne of young girls), it is evident that facial manipulation is a common occurrence in adults with acne, especially women [6]. Although 97 % of a large survey said they manipulated their acne lesions, some patients do this to an extreme. This compulsive manipulation of the skin can lead to unsightly pigmentation and true scarring out of proportion to the degree of acne. This behavior may vary from a simple habit to a manifestation of serious obsessive–compulsive disorder (OCD) [25]. Over-vigorous facial treatments may also exacerbate acne.
3. Stress.
   It has been suggested that acne in adult women is related to chronic stress which leads to enhanced secretion of adrenal androgens, resulting in sebaceous hyperplasia and the subsequent induction of comedones [19, 26]. Elevated serum cortisol levels in acne patients have been correlated with levels of emotional stress [27].
4. Cosmetics
   Cosmetics have not been found to be an important etiological factor in adult acne [23]. Currently since most cosmetics designed for the face have non-comedogenic formulations, they are less likely to cause acne. However, use of greasy moisturizers and sunscreens not intended for facial use can still be a factor.

## 32.4 Clinical Manifestations of Adult Acne

Adult acne may be either persistent or late onset: persistent acne (Fig. 32.1a, b) represents a continuum from adolescence into adult life whereas late-onset acne (Fig. 32.2) has been defined as occurring for the first time after age 25 years. While early pubertal acne initially occurs on the forehead and proceeds down the central part of the face [28], adult women tend to have acne on the lower third of the face, especially on the chin and in the perioral region (Fig. 32.3) [27]. In young patients, comedones appear first and predominate [28]. In adult women, deep-seated

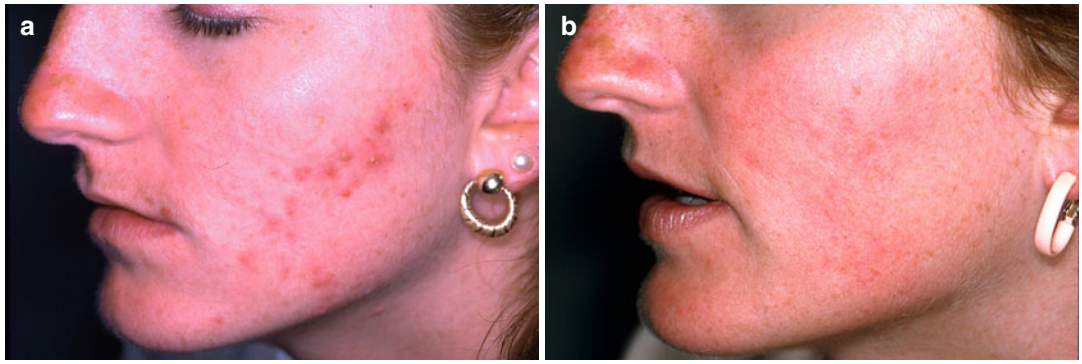


**Fig. 32.1** (**a**) Persistent acne in 21-year-old woman. (**b**) The same patient one year later on treatment with an estrogen-containing oral contraceptive

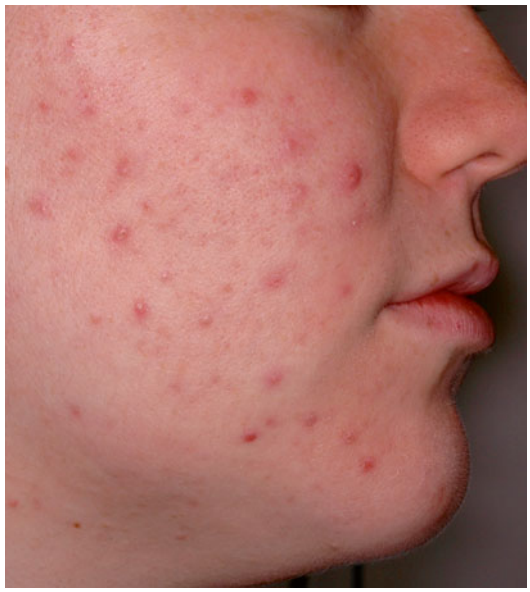

**Fig. 32.2** Late-onset acne in a 27-year-old attorney. She also has female pattern hair loss and a normal hormonal profile

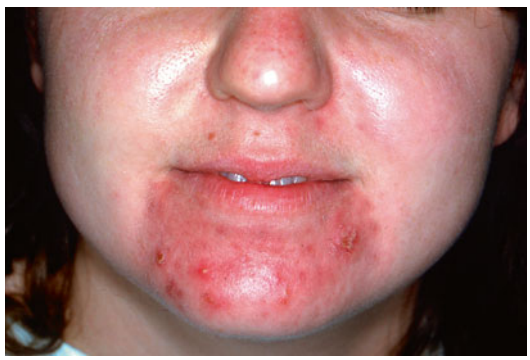

**Fig. 32.3** A 27-year-old woman with deep inflammatory acne limited to her chin

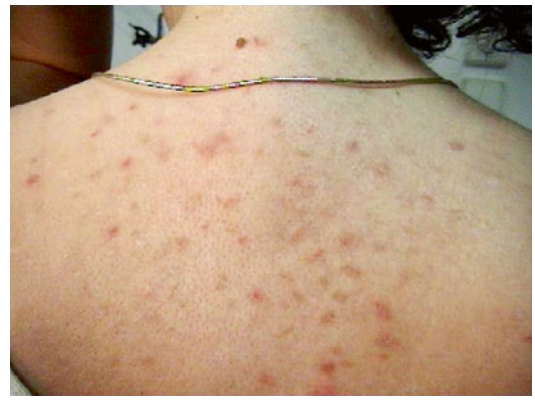

**Fig. 32.4** Adult acne on the back

inflammatory papules and nodules are most common [6]. Comedones are rare and may be especially large ("macrocomedones") and resistant to therapy [7]. A premenstrual flare of deep papules or nodules in the late luteal phase of the menstrual cycle is a common complaint in many adult women [6, 17]. In some women, acne may persist throughout the menstrual cycle. Acne can also occur sporadically and affect the trunk, especially in postmenopausal women (Fig. 32.4). Acne excoriée is very common. [6]

## 32.5 Evaluation of the Adult Patient with Acne

(A) History (Table 32.3)
Persistent and late-onset acne is distinguished by whether acne was continuous since adolescence or first appeared after age 25 years.

**Table 32.3** Evaluation of the adult woman with acne

| |
|---|
| History |
| Age of onset |
| Family history |
| Menstrual history |
| Use of comedogenic topical preparations |
| Use of medications including progestin-only contraceptives |
| Physical findings |
| Hirsutism |
| Female pattern hair loss |
| Virilization (clitoromegaly, deepening voice, increased muscle mass) |
| Acanthosis nigricans |
| Obesity with high waist/hip ratio |
| Laboratory testing |
| Leutinizing hormone/follicle-stimulating hormone ratio (LH/FSH) >3 |
| Free testosterone (free T)* |
| Dehydroepiandrosterone sulfate (DHEAS)* |
| Sex hormone binding globulin (SHBG) |
| 17 α OH progesterone |
| Delta 4 androstenedione |
| Fasting glucose and insulin |
| Fasting lipid profile (triglycerides, HDL, LDL, VLDL cholesterol) |
| Imaging studies (pelvic ultrasound, CT, or MRI of adrenals and ovaries) |

Family history often reveals a familial predilection to acne with first-degree relatives affected. Many women will complain of menstrual irregularities, usually oligomenorrhea. It is imperative to inquire about use of topical preparations such as moisturizers, sunscreens, and vigorous cosmetic facial treatments. Inquiry about oral medications, especially those started within a few months of the onset of acne, is needed. Patients should be asked about use of progestin-only contraceptives.

(B) Physical Examination

Concomitant findings of hirsutism and female pattern hair loss strongly suggest hyperandrogenemia. True virilization with clitoromegaly, deepening voice, or increased muscle mass is rarer and suggestive of an androgen-secreting tumor. Acanthosis nigricans and obesity with an increased waist–hip ratio are often signs of the metabolic syndrome.

(C) Laboratory Evaluation

The essential screen for hyperandrogenemia is free T, DHEAS, and LH / FSH ratio: elevated free T and DHEAS and an LH/FSH ratio of >3 are suggestive of PCOS. Sex hormone binding globulin (SHBG) is often depressed. If the metabolic syndrome is suspected, fasting levels of glucose, insulin, and lipids (triglycerides and HDL, LDL, and VLDL cholesterol) are useful screens for Type 2 diabetes mellitus and lipid abnormalities predisposing to heart disease. To diagnose CAH, it is necessary to measure 17 α OH progesterone, 3 β OH steroid dehydrogenase, and delta 4 androstenedione at baseline or after stimulation with ACTH. Dexamethasone suppression tests can detect adrenal tumors or Cushing disease. Not all patients with hormonally dependent acne will have abnormal blood tests, probably because some have increased end-organ cutaneous sensitivity to androgens.

In terms of imaging studies, pelvic ultrasound will easily identify ovarian cysts, but PCOS can occur without ovarian cysts and not all patients with PCOS have them; thus pelvic ultrasound is not a definitive test. Computerized tomography (CT) scans or magnetic resonance imaging (MRI) of the adrenals and ovaries are important if androgen-secreting tumors are suspected.

## Conclusions

In summary, although adult acne shares many features of other types of acne, it has some unique characteristics: it occurs more often in women than in men, may be familial, and is highly influenced by hormones. Adult acne affects the lower third of the face with primarily deep inflammatory papules and is more difficult to treat. Hormonal therapy and isotretinoin are mainstays of treatment. The surprisingly high prevalence of adult acne and its effect on quality of life make it an important entity to recognize and address properly.

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# Drug-Induced Acne

# 33

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## Contents



**Core Messages**

- Drug-induced acne (DIA) is an acne-like eruption caused or aggravated by certain medication.
- DIA is characterized by an acute onset, occurrence often away from acne age, widespread involvement, and monomorphous papulopustular eruption with follicular localization.
- Pathogenesis of DIA varies depending on the culprit drug.
- DIA is diagnosed in the course of the medical history with special attention paid to the drugs most often related to it—corticosteroids, androgens (testosterone, other anabolic steroids), isoniazid, lithium, epidermal growth factor receptor inhibitors (EGFRI), etc.
- The risk of DIA is associated with the dose, the treatment duration, and the past history of acne
- DIA resolves usually with the discontinuation of the offending drug.

## 33.1 Introduction: Definitions

Drug-induced acne (DIA) is an acne-like eruption precipitated or aggravated by certain medication. The culprit drug can be one orally administered, topically applied, or inhaled.

The earliest report of DIA dates from 1928, when acne-like lesions were described with the

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**Table 33.1** Drugs with acne-inducing capability

| Drugs with undoubted causal relationship to acne | Drugs with considerable but insufficient data | Drugs occasionally associated with acne |
|---|---|---|
| Corticosteroids | Cyclosporine A | Tetracyclines? |
| Androgens (anabolic steroids, testosterone) | Vitamin B6 | Vitamin B1 |
| Lithium | Vitamin B12 | PUVA |
| Isoniazid | Vitamin D2 | Propylthiouracil |
| Halogens (iodides, bromides) | Phenobarbiturates | Sirolimus |
| Antimalarials (chloroquine, chinin) | Disulfiram | Voriconazole |
| Antiepileptica (phenytoin) | Azathioprine | Dactinomycin |
| Corticotropin | Quinidine | Rifampicin |
| EGFR inhibitors (acneiform eruption) | Amoxapine | Etanbutol |
| | TNF-alpha inhibitors | |
| | Tetraethynilthiuram | |
| | Tricyclic antidepressants (Amineptine) | |
| | Thireostatica (Thiouracil) | |

use of iodides and chlorinated hydrocarbons [1]. Nowadays the number of patients with DIA is rising. On the one hand, there are many new drugs–epidermal growth factor inhibitors and TNF alpha inhibitors, which have acne in the list of their side effects. On the other hand, organ transplant surgery and oncology use many treatment regimens with a high dose of hormones and immunosuppressors, which can also cause acne as a side effect.

## 33.2 Epidemiology

Considering their acne-inducing capacity, drugs related to acne fall into the following categories:

– Drugs **with undoubted causal relationship to acne.**
– Drugs about which we have **considerable**, **though insufficient**, **data.**
– Drugs **occasionally reported to be associated with acne** (Table 33.1).

## 33.3 Clinical Manifestations

### 33.3.1 Main Characteristics of the Drug-Induced Acne

Drug-induced acne (DIA) is very similar to common acne, yet there are a number of differences to distinguish its clinical picture. DIA is characterized by:

- **Rapid onset**
- **Occurrence** often **away from acne age**
- **Medical history of** diseases and/or **pharmacological therapy:**
  – Also complete history of all over-the-counter medications, supplements, and herbal medicine can point to the responsible agent.
- Widespread involvement:
  – Appearance on the face and neck is typical, but acne lesions can spread over other parts of the body (forearm, buttocks).
- Monomorphous eruption:
  – Eruption consists of inflammatory papules or papulopustules, in contrast with the polymorphic picture seen in acne vulgaris.
  – Comedones, if present, are later secondary lesions, a sequel to encapsulation and healing of the primary abscess [2].
- **Follicular localization** of the lesions (which explains the use of the term "acne folliculitis").
- Acute or subacute course of the disease
- Resolve of the main part of the lesions with the discontinuation of the inducing drug.

## 33.4 Corticosteroids

Since the 1950s topical and systemic corticosteroids have been used in medical therapy. One of their well-described side effects is the steroid acne [1]. Steroid acne has become more common since the advent of organ transplant surgery and oncological treatment regimens [3].

Steroid acne is a result of high-dose systemic corticosteroids; inhaled steroid therapy, or inappropriate use of huge amounts of topical corticosteroids on the face. The severity of the eruption seems to be related to the dose, the treatment duration, and the past history of acne [3].

The exact pathogenesis is still uncertain. The accelerated chronological progression of infundibular spongiosis, hyperkeratosis, microcomedo formation, and hair follicular rupture is significant for the development of the papules and papulopustules in steroid acne [3].

The eruption usually starts following several weeks of treatment. Steroid acne is observed as a monomorphous papulopustular eruption. Nodules and cyst formation are rare. It is located predominantly on the trunk and extremities, with less involvement of the face. Steroid acne has been described with a similar clinical picture to Pityrosporum folliculitis [4]. Sometimes the acneiform eruption develops on the background of erythema, which favors the distribution of topical corticosteroid application.

Steroid acne usually resolves after discontinuation of the drug. The conventional treatment for acne vulgaris is recommended if the steroid drug should be continued. Tretinoin treatment is often preferable [5].

## 33.5 Anabolic-Androgenic Steroids

Anabolic steroids, anabolic-androgenic steroids (AAS), are a class of synthetic steroid hormones related to the testosterone. Abuse of AAS by athletes and nonprofessional bodybuilders has reached alarming extent. DIA occurs in about 50 % of AAS abusers and is an important clinical indicator (see also Chap. 34) [6]. Androgens are also used as anabolic reagent to treat muscle wasting. Attenuated androgens (stanozolol—0.5–2.0 mg daily) are helpful in the treatment of hereditary angioedema.

Androgens are essential for the acne etiopathogenesis. Their role is to stimulate the development and secretory activity of the sebaceous gland. Examination of skin biopsy specimens from persons using AAS demonstrates dramatic hypertrophy of the sebaceous glands [7]. High dosages of testosterone and anabolic-androgenic steroids increase skin surface lipids, the cutaneous population of *Propionibacterium acne*, and the cholesterol and free fatty acids of the skin surface lipids. The mechanism of action of AAS may differ between compounds due to variations in the steroid molecule and affinity to androgen receptors.

AAS usually cause aggravation of preexisting acne vulgaris especially in females. In both males and females acne as a side effect is frequently reported, as well as hypertrophy of sebaceous glands, increased sebum excretion, and alopecia. Both severe forms—acne fulminans and acne conglobata—were described as induced by anabolic steroids.

## 33.6 Testosterone

Testosterone-induced acne is very common and could be observed in both sexes. In males testosterone is used to treat hypogonadism and excessively tall stature. High-dose testosterone treatment seems to trigger acne fulminans. It can be presumed that testosterone leads to longer lasting induction of androgen receptors resulting in acne fulminans [8]. Patients asking for hormonal height reduction should be aware of this rare but serious side effect. Acne fulminans is observed in 1–2 % of adolescent boys treated for excessively tall stature with testosterone [9]. Hormone replacement therapy in aging males has also been reported to improve body composition, bone and cartilage metabolism, certain domains of brain function, and even decrease cardiovascular risk.

In females late-onset acneiform eruptions are observed after testosterone replacement therapy following ovariectomy. Testosterone administration to postmenopausal women is controversial, but still practiced. Some studies indicate acne and/or hirsutism after use of methyltestosterone replacement therapy in up to 38 % and 36 %, respectively; other studies suggest a much lower incidence of approximately 5 % [10]. Postmenopausal women have been treated with testosterone patches, because of a newly described "hypoactive sexual desire disorder." According to the first investigations acne, hirsutism, hair loss, and deepening of the voice

occurred more frequently in women using testosterone patches than in women on placebo. In about 30 % to 60 % of the affected women, these adverse effects failed to resolve on treatment cessation [11].

In both sexes testosterone is used for the treatment of protein wasting diseases associated with cancer, burns, traumas, or AIDS, anemia secondary to chronic renal failure, aplastic anemia, and hereditary angioedema. In all the above-mentioned cases testosterone-induced acne is noted as a side effect.

For most clinical applications, testosterone is administered as longer acting esters through intramuscular injections, surgical implantation for implants and pellets, or transdermal delivery, such as patches and gels. In general, these administration routes are not very convenient and are sometimes associated with fluctuation in serum testosterone level followed by testosterone-induced acne and hirsutism [12].

Generally, retinoids are the treatment of choice, when the therapy with testosterone should continue.

## 33.7 Lithium

Lithium is used in psychiatry in the form of lithium citrate and lithium carbonate mainly for the treatment and prophylaxis of affective psychic disorders. Long-term lithium therapy causes a variety of dermatological problems such as DIA and psoriasis [13]. Just as in psoriasis lithium can worsen acne vulgaris or can cause acne in a person who has never experienced acne before. Male patients taking lithium are more susceptible to developing cutaneous reactions than their female counterparts [14].

The therapeutic effect of lithium is slowly achieved because the cells are slowly saturated with lithium ions. It is possible that acne, just like psoriasis, occurs at the moment of cells saturation, when the patient begins to improve his or her mental condition. Lithium works not through an androgen receptor mechanism, but through direct, sometimes toxic effects on the follicular epithelium [15]. It is questionable whether, as in other dermatoses, the serum level of lithium

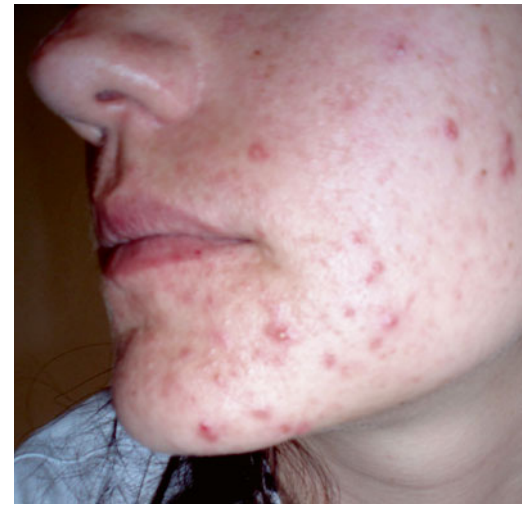

**Fig. 33.1** DIA due to antidepressants

plays a role in the provocation of DIA. Lithium-induced acne is probably caused by the neutrophilic chemotaxis and their degranulation inducing the inflammatory cascade (as in psoriasis). Follicular plugging due to direct influence of lithium on the follicular keratinocytes adds to the mechanism of action [7].

Acne lesions due to lithium appear 2–3 months after the start of the therapy [1]. The clinical pictures consist of inflammatory papules, pustules, cysts, and nodules (Fig. 33.1). Severe forms, such as acne conglobata and hidradenitis suppurativa, have been described [16]. Usually post-inflammatory scarring is present.

Therapy is extremely difficult. Oral retinoid is not the right treatment for this type of acne, as depression is a registered side effect in about 1 % of patients who take it. Also the interaction between lithium and tetracycline must be borne in mind: co-administration results in elevated lithium levels. Experts suggest discontinuation of lithium and switching to alternative drugs.

## 33.8 Isoniazid

Out of various types of skin eruptions induced by antituberculous drugs, acneiform eruptions are mild and less common [17]. First Bereston [18] in 1959 described acneiform eruptions due

to isoniazid. Since then many authors have reported isoniazid as a cause for such eruptions—alone or in combination with rifampicin and ethambutol [19, 20].

The frequency of isoniazid-induced acneiform eruption is estimated at 1.42–2.5 % [7, 21] according to two big studies. It is suggested that isoniazid can induce acne and pellagra in slow inactivators of the drug [22].

The skin lesions develop after long treatment with isoniazid. The clinical picture consists predominantly of inflammatory follicular papules. Comedones in isoniazid-induced acne are a debatable topic, but consensus prevails regarding the monomorphic state of the papules. Usually the eruption is mild, but there are some reports describing more severe forms of acne including SAPHO syndrome [23].

Isoniazid-induced acne resolves after the discontinuation of the drug.

## 33.9 Halogens (Iodines, Chlorides, Bromides)

Iodines and bromides frequently cause acne-like eruptions or exacerbate preexisting acne. There are numerous inhaled or orally taken pharmaceutical products containing the latter. Iodines are found in many asthma preparations, expectorants, kelp containing supplements and teas, combined mineral and vitamin supplements, and contrast dyes. There is a debate linking milk and acne [24]. It raises three questions: whether levels of iodine in milk are too high and therefore contribute to acne; what is the source of the iodine; and whether there is a valid link between iodine and acne vulgaris per se.

Sedatives, analgesics, and cold remedies often contain bromides and in rare cases long time therapy can cause acne-like eruption.

Chloracne is a condition due to systemic poisoning most often in occupational settings (*see also Chap.[25]*).

Chemicals that contain iodines, bromides, and other halogens can also induce an acneiform eruption similar to that of steroid acne; however, the iodide-induced eruption may be more extreme. Internal changes involving the ophthalmic, nervous, and hepatic systems may also occur.

Treatment consists of discontinuation of the culprit drug or food additive.

## 33.10 EGFRI

Inhibitors of EGFR (cetuximab and erlotinib) are commonly used as therapeutic agents in oncology. In contrast to currently used oncological treatments, these inhibitors almost always cause skin and skin adnex toxicity. About 85 % of treated patients develop to more or lesser extent an acneiform eruption [25]. Some authors [26] believe that terms as acne, acne-like, or acneiform should be avoided and suggest papulopustular rash as a correct diagnosis for this skin changes.

The pathomechanism of EGFRI-induced rash is unclear and distinct from acne vulgaris. EGFRI can block the normal development, differentiation, and functioning of the keratinocytes and thus cause occlusion of the hair follicles. Also EGFRI can lead the sebaceous glands to increase production of inflammatory mediators.

DIA occurs in more than 50 % of the patients one week after the initiation of the treatment. Usually skin eruption is mild to moderate in severity. It consists of follicular papules and sterile pustules, which affect the face and upper trunk (Fig. 33.2) [27]. Distribution of the rash is similar to that of acne vulgaris, but, unlike acne, might

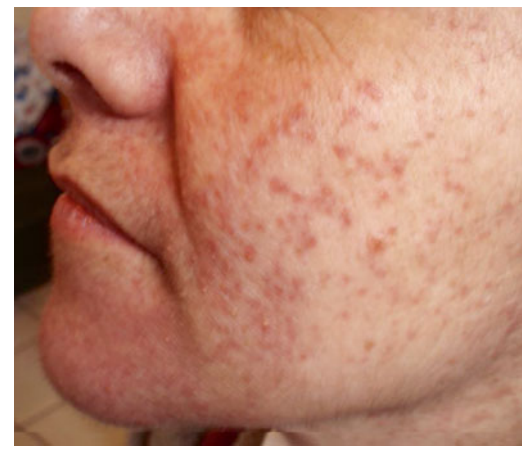

**Fig. 33.2** Acneiform eruption due to EGFR inhibitors

affect areas such as the lower legs and dorsal arms. Comedones are never found [28].

The histological finding reveals increased numbers of inflammatory cells and debris in the superficial dermis, varying degrees of edema and vasodilation, keratin plugs in dilated follicular infundibula, and ruptured follicles [15].

Most reports [29] indicate that topical anti-acne products, oral tetracyclines, and oral corticosteroids constitute an effective therapy. The promising approach of circumventing EGFR inhibition in skin through the use of topical agents has led to the identification of vitamin K3 (menadione) as a potential therapy for the rash. Successful treatment with oral isotretinoin has also been reported [30].

According to some authors EGFRI-induced acne may have a positive relation to survival [31].

## 33.11 Vitamin B

There are only a few studies discussing the role of vitamins B6 and B12 in the induction or aggravation of acne. Exacerbation or onset of DIA has been seen with high doses of B12 (5–10 mg/week). There isn't an established dose concerning vitamin B6.

The exact mechanism is not certain yet. Jansen et al. [32] suggest that prolonged excretion of the causative substances might cause an irritation of the follicular epithelium and subsequently produce an inflammatory reaction. Also sorbitol or iodine present in some ampoules of B12 might be the causative agent.

The incubation period varies from immediate appearance of skin lesions after the first injections to 13 days following it. Women seem to be almost exclusively affected.

The eruption is monomorphic and of a particular type [33]. The clinical picture consists of disseminated small follicular papules or papulopustules on the face (especially on the forehead and chin), on the upper parts of the back and chest, and on the upper arm [34]. A single case of severe acne rosacea, temporally associated with a daily ingestion of 100 mcg of B12 (with 100 mg of B6), has been reported. The rash resolved upon discontinuation of both drugs and recurred upon readministering half the doses [35].

The acneiform rash fails to respond to the usual treatment but generally fades within a short time after vitamin B6 or vitamin B12 treatment has been stopped. Typically the skin lesions disappear within 8–10 days after stopping vitamin B therapy.

## 33.12 Diagnosis

### 33.12.1 Four Points of Making Diagnosis

1. Detailed history with a record of:
   (a) When drug treatment started
   (b) Dosage regimen
   (c) Therapy duration
2. Absence of additional triggering factors (hormonal levels, occupation).
3. Clinical relationship between the introduction of the drug and the onset of an acne-like eruption.
4. Withdrawal of the drug followed by improvement of the dermatological status.

## 33.13 Differential Diagnosis of DIA

Some conditions mimic DIA. The most common differential diagnosis is Pityrosporum folliculitis produced by an overgrowth of the Malassezia species, often secondary to oral or systemic corticosteroids or secondary to broad-spectrum antibiotics such as the tetracycline family used in acne. This is often misinterpreted as "tetracycline-resistant acne."

Other folliculitis from bacterial origin, eosinophilic pustulosis, and some clinical forms of Rosacea should be taken into consideration.

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# Body-Builder Acne

# 34

Christiane Bayerl

## Contents



**Core Messages**

- Androgenic anabolic steroids (AAS) are synthetic derivatives of the male hormone testosterone. "Androgenic" comes from the Greek "andros" and "genein," which mean "man" and "to produce." AAS increase protein synthesis in the cell and are therefore called "anabol," deriving from the Greek and meaning "to build up."
- Any steroid that is anabolic is also androgenic.
- Two-thirds of body-builders use supra-physiologic doses of testosterone as eugonadal men accessible through illicit channels in many health and athletic clubs or via Internet.
- AAS increase sebum secretion, *Propionibacterium acnes* population, and the cholesterol and free fatty acids in skin surface lipids.
- Acne occurs in 50 % of AAS abusers. The clinical manifestation of body-builder acne is acne conglobata or acne fulminans.
- The recognition of AAS abuse is crucial to alert the user to the broad spectrum of hazards and dangers. Dermatologists are in the favorable position of being able to detect the abuse by the clinical signs.
- A high glycemic load diet—also frequently used by body-builders—might be an additional factor in acne development.

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Definition

Body-builder acne is induced by the intake of AAS with the intention to build up cellular tissue, especially muscles. AAS are a class of steroid hormones related to the hormone testosterone. They have androgenic and virilizing properties, with acne as one of the most frequent side effects.

## 34.1 Introduction/Epidemiology of AAS Abuse

Since the third century a.d. during the Olympic Games, athletes took bull testicles to increase endurance. Nowadays, AAS are used to boost the athletic performance or to improve the body shape. AAS are derivatized androgens. Properly combined with diet and intensive training, they are capable of increasing strength and muscle bulk. Use of AAS in sports is a controversial issue and also a reason for medical concern. The International Olympic Committee bans doping. Unfortunately, AAS abuse is not limited to competitive athletes, where it is officially prohibited. AAS are also commonly used for body shaping due to aesthetic reasons or regularly taken by body-builders. There are estimations that as many as one million Americans abuse these drugs. Cardiotoxic side effects and disturbances in neuroendocrine and immune functions such as sterility, gynecomastia in males, and psychological changes like increased aggression, higher risks of liver neoplasia and heart disease, balding, and acne are some of the main manifestations of AAS abuse [1]. Myocardial injury in athletes with AAS abuse is published in a number of case reports of sudden cardiac deaths in young athletes. In the USA, over 500,000 individuals currently taking AAS for nonmedical purposes are high school children [2]. In Germany 48.1 % of AAS users acquire the drug illegally [3]. An anonymous anti-doping hotline in Sweden revealed that 30 % of AAS abusers regularly attended a gym (Table 34.1). The most commonly abused AAS were testosterone, nandrolone-decanoate, methandienone, and stanozolol. The ten most frequently reported side effects of AAS in men were aggressiveness, depression, acne, gynecomastia, anxiety, potency problems, testicular atrophy, sleeping disorders, fluid retention, and mood swings. In women with AAS abuse, menstruation disturbances, hair growth in the face, deeper voice, and enlarged clitoris were reported [4]. Another study on AAS abuse showed changes in libido and mood wings as the most frequent side effects, followed by acne in 43 % of abusers and the others mentioned before [5].

**Table 34.1** Epidemiology of AAS abuse, modified according to Melnik [3]

| Groups of AAS abusers | Percentages of persons taking AAS (%) |
|---|---|
| School boys in the USA | 11 |
| School girls in the USA | 2.5 |
| School boys/girls in Australia | 3.2 |
| College athletes in the USA or Great Britain | 17–20 |
| Body-builders and weight lifters in Belgium | 38–58 |
| Male Amateur body-builders in the USA | 80 |
| Female amateur body-builders in the USA | 40 |
| Male gym attendants in Germany | 13.5–24 |
| Female gym attendants in Germany | 8 |
| Male gym attendants in Great Britain | 9 |

AAS are not only taken orally. Other possible sources of AAS might be topical application of AAS in anticellulite creams leading to deepening of the voice in women. Moreover, testosterone replacement therapy after ovariectomy has been shown to lead to circumscribed hypertrichosis and late-onset acneiform eruptions, and finally, a man using injectable AAS reported homolateral gynecomastia, infertility, acne, and striae distensae [6].

## 34.2 Pharmacology

Routes of administration of AAS are primarily oral or parenteral. Some anabolic steroids are also administered topically, transdermally, or intramuscularly [7].

The natural occurring AAS is testosterone (17beta-hydroxy-4-androsten-3-one).

Stanazol as well as Danazol are well-known drugs in dermatology as they are used in the treatment of hereditary angioedema over 20–40 years in many patients. In about 50 %, side effects are reported such as hirsutism, weight gain, menstrual irregularities, postmenopausal bleeding, acne, and mood swings [8].

Oxandrolone (17beta-hydroxy-17alpha-methyl-2-oxa-5alpha-androstan-3-one) is a synthetic product, often taken orally by body-builders. It does not aromatize and consequently does not convert to estrogen, which might cause gynecomastia. Oxandrolone provides elevated androgen levels for about 8 h and is typically combined with testosterone to further enhance body mass gain [9].

Nandrolone (17beta-hydroxyestra-4-en-3-one) is a naturally occurring AAS, but present in small quantities. It is sold as decanoate ester ("Deca") or as a phenylpropionate ester. Nandrolone decanoate is approved for the treatment of osteoporosis in postmenopausal women or aplastic anemia. The administration route is intramuscular with a half-life of 15 days. It is not metabolized in DHT and consequently does not affect scalp, skin, or prostate in low doses. Nevertheless, side effects are erectile dysfunction and cardiovascular damage.

Others are methandrostenolon, methenolon, and more. Mostly combinations thereof are used such as Sustanon ("Sus"), a combination of four esters of testosterone [3, 9].

## 34.3 Clinical Manifestations

Acne in general is an indicator of AAS abuse occurring in 50 % of all abusers [3]. Body-builder acne is especially frequent in young men between 18 and 26 years of age. Body-builder acne appears under the clinical manifestation of both acne conglobata and acne fulminans, induced by AAS abuse (Fig. 34.1).

## 34.4 Etiology and Pathogenesis

Acne is among the most frequent self-reported untoward responses to AAS, whose administration disturbs the regular endogenous production

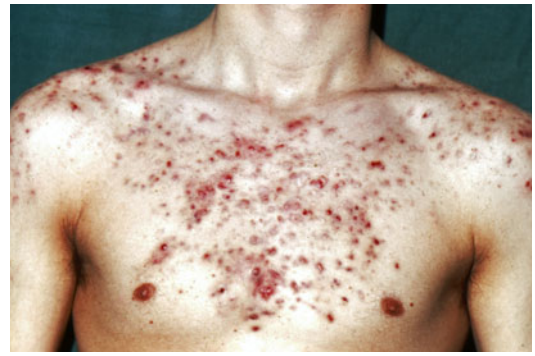

**Fig. 34.1** Acne conglobata after puberty in a young body-builder with AAS abuse that occurred after a preexisting mild facial acne in puberty

of testosterone and gonadotropins persisting months after drug withdrawal.

The mechanism of action differs among AAS compounds because of the variations in the steroid molecules and their affinity to androgen receptors, their interaction with steroid-metabolizing enzymes, and the individual level of sexual hormone binding globulin (SHBG). The mechanisms identified up to now for skin focus on 5-alpha reductase that converts AAS into dihydrotestosterone (androstanolone) which acts on different target organs such as the male accessory glands, skin, and prostate. Moreover, AAS are antagonistic to estrogens and competitive antagonists to the glucocorticoid receptors [3, 10].

In skin biopsy specimens of AAS abusers, giant hypertrophy of the sebaceous gland was shown. Moreover, an increase in skin surface lipids, the cutaneous population of propionibacteria acnes, and the cholesterol and free fatty acids in the skin surface lipids was observed [11, 12].

Recently, it was shown that in the prostaglandin metabolism of lipogenesis, AAS contribute indirectly by increased expression of the nuclear receptor PPAR-γ1. Nuclear receptors in general induce lipogenesis and differentiation of sebocytes [13].

Effects of AAS on immune responses have also been studied in vitro in cell cultures and in mouse models. 17-beta esterified AAS (nandrolone decanoate) and 17-alpha esterified AAS (oxymethenelone) inhibit antibody production and induce IL-1 beta and TNF-alpha. 17-beta

esterified AAS (nandrolone decanoate) inhibits INF production and corticotropin production after viral infection [1].

## 34.5 Differential Diagnosis to Body-Builder Acne

Concomitant factors for people in the body-builder scene might be drugs or food supplements that cause no typical acne, but acneiform eruptions. Culprits are vitamins such as B2, B6, B12, and D2 or iodides. These are contained in some of the fitness drinks in the gym. The membership fee for the gym usually includes free fitness drinks which are generally abundantly consumed. Additionally, fruit drinks are consumed that are often supplemented with B vitamins. Moreover, health pills or nutritional supplementation pills are other sources of widely used vitamins. Quinine induces acne eruptions as well and is found in some nonalcoholic drinks (e.g., bitter lemon) popular among young people attending a gym [14–16].

The first typical clinical sign of acneiform eruptions is follicular inflammation. As the large sebaceous follicles are primarily affected, eruptions occur mainly on the face, V-shaped on the chest, on the back, the shoulder, and the upper arm. Usually, and in contrast to acne vulgaris, the lesions show a monomorphic picture as in steroid acne.

Since acneiform eruptions are not related to acne vulgaris, the condition clears up after withdrawal of the drugs.

## 34.6 Laboratory Monitoring

The natural occurrence of hormones in the human body makes abuse difficult to detect. That has been a problem in anti-doping programs. The detection of synthetic drugs in urine is not easy either and depends on the half-life of the AAS. Nandrolone, for instance, is indirectly detectable in urine tests by the presence of its metabolite, 19-norandrosterone. Moreover, it was shown that analysis of ASS abuse can be done in the hair by gas chromatography–mass spectroscopy [17].

Topical low-dose application of testosterone in postmenopausal women complaining about reduced libido was studied in clinical trials and showed the desired effects such as increased sexual interest. In this indication and all other legally approved indications (e.g., wasting syndrome, weight loss), application is safe under regular control of the testosterone and/or other hormone levels [6].

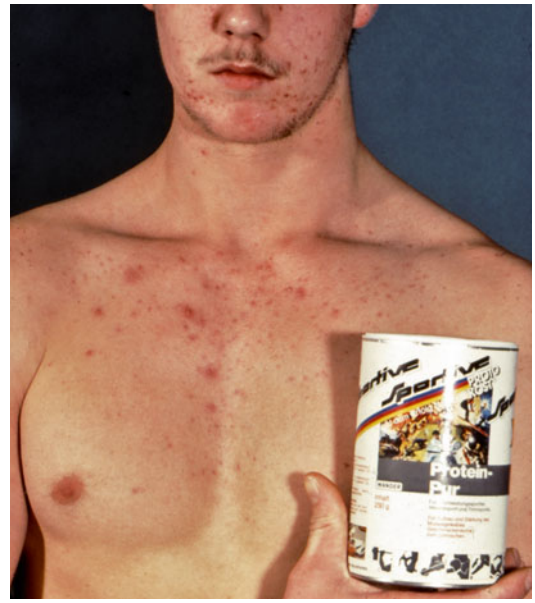

**Fig. 34.2** Young man frequently attending a gym who takes protein nutrients and multivitamin mixtures (including B6, B12 vitamins) to gain muscle mass

## 34.7 New Concomitant Factors for Acne Development in Body-Builders

Body-builders and especially young gym users tend to ingest additionally high protein foods, such as protein supplementation (Fig. 34.2), amino acid preparations, creatine, dehydroepiandrosterone, or growth hormones.

It was recently suggested that dietary glycemic load may be one environmental factor contributing to the variation in acne prevalence

worldwide. A non-randomized, parallel, controlled feeding trial showed that increases in dietary glycemic load augmented biological activity of sex hormones and insulin-like growth factor (IGF-1). This suggests that these types of nutrition may aggravate potential factors involved in acne development [18].

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# Acne Cosmetica

# 35

Zoe Diana Draelos

## Contents



**Core Messages**

- Acne cosmetica refers to the onset of acne following the use of skin care, cosmetic, or hair care products.
- Lists of comedogenic ingredients exist, but are not helpful when evaluating the effect of a final formulation on comedone formation.
- Comedogenicity, which is the onset on comedones, must be distinguished from acnegenicity, which is the onset of inflammatory papules.
- The most common ingredients associated with acne cosmetic are vegetable oils used in ethnic hair care preparations and lip gloss products.
- Most currently marketed products are tested for comedogenicity using the human back model and acnegenicity employing in-use testing.
- Some "acne" may actually represent an acneiform eruption, which is a follicular irritant contact dermatitis.

## 35.1 Introduction

Dermatologists frequently encounter patients who are concerned about the effects of cosmetics and skin care products on their complexion. Since the course of acne waxes and wanes with hormonal influences, stress, and treatment

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interventions, it may be difficult to establish a cause and effect relationship. Patients may wonder whether the use of a certain moisturizer or cosmetic might result in worsening acne. This chapter deals with the issue of acne induction by skin care products and cosmetics, a condition termed acne cosmetica.

## 35.2 Definition

The concept of acne cosmetica was introduced by Kligman and Mills in a 1972 paper describing a low-grade acne characterized by closed comedones on the cheeks of women aged 20–25 [1]. Many of these women had not experienced adolescent acne and the authors proposed that substances present in cosmetic products induced the formation of closed comedones and, in some cases, a papulopustular eruption [2]. This paper introduced the cosmetics industry to the need to test skin care products and cosmetics for the production of comedones [3]. Methodologies for product testing were developed to meet this newly identified phenomenon.

## 35.3 Comedogenicity Testing

Comedogenicity testing required the development of a human-relevant model where observable comedone formation from topical product application was possible. Research led to development of the rabbit ear comedogenicity model, which was the first testing standard. The model involved applying the cosmetic or skin care product to the ears of New Zealand white albino rabbits. One ear served as a control, while the other ear received 0.5 mL of the test material 5 days per week for 2 consecutive weeks. The ear was visually evaluated for the presence or absence of enlarged pores and hyperkeratosis daily. At the completion of the 14-day study, the animal was biopsied to look for hyperkeratosis of the sebaceous follicles [4]. If hyperkeratosis was present on both the control and test ear, then the tested material might be comedogenic.

A variation on the traditional rabbit ear assay was proposed by Tucker et al. [5]. They noted that a linear increase in the degree of follicle enlargement in the rabbit ear was noted after 4 weeks of application of a comedogenic substance. This enlargement could be captured noninvasively by making a Silastic elastomer mold of the follicular ostia and measuring the change in size over time.

There were several problems associated with the rabbit ear model [6]. First, some assessments were made without a biopsy, instead relying solely on visual inspection of the rabbit ear, which is less sensitive than a microscope examination. While visual assessment may be used to evaluate comedones, microcomedones cannot be detected. Microcomedones, now known to be important acne precursor lesions, can only be identified through microscopic examination. Second, some studies have confused follicular dilation with comedone formation. Follicular dilation is a side effect of cutaneous irritation and not necessarily the same as comedone formation. Third, the use of immature or aged rabbits may not yield accurate data since sebum production is reduced in mature rabbits. Fourth, the rabbit ear may not accurately simulate the human face: many substances that produce comedones in the rabbit ear model produce pustules and inflammatory papules, not comedones, on the human face.

With the upcoming ban on animal testing and the shortcomings of the rabbit ear model, human testing is becoming the standard methodology for comedogenicity assessment. Most testing laboratories are now using the upper back of human volunteers as a test site [7]. Volunteers must have the ability to develop upper back comedones. This ability is assessed by applying cyanoacrylate glue to a microscope slide and allowing the glue to polymerize in contact with the upper back skin. Once the glue has set, the slide is pulled from the back taking with it any comedonal plugs that might be present. If sufficient comedonal plugs are present, the subject may be appropriate for inclusion in a test panel. Subjects with around 10 comedonal plugs in a one by one centimeter area are optimal.

Once the panel has been assembled, the test product is applied under an occlusive patch to the upper back for 28 days. The patch is typically reapplied Monday through Friday for the four weeks. A negative control patch is applied with no product and a positive control patch with a comedogenic substance, such as coal tar, is placed. Cyanoacrylate follicular biopsies of each patched site are made at the end of the test to evaluate keratin plugging. If the keratin plugging has increased at the site of the test product and the positive control, then the product may be comedogenic. If there is no increase or a decrease in follicular plugging at the test site, then the product may be noncomedogenic. Small increases in follicular plugging would be considered indeterminate.

While this human test has the potential for greater accuracy than the animal model, it has some inherent problems also. Since most of the tested products are for female facial application, testing a product on the upper back may be problematic, since the pores and sebum secretion patterns of the face are different than the back. One variation of this study uses young individuals with acne who apply a product for 4–8 weeks. Lesion counts are made before and after the test period; however, the upper back method is more commonly employed [4]. Pre- and post-marketing surveillance have also assumed importance for product comedogenicity evaluation, since an in-use test may be optimal.

## 35.4 Comedogenic Substances

One of the early concepts of comedogenicity testing was to evaluate the formulation for the absence of ingredients with known comedogenic potential. Shortly after the introduction of the concept of acne cosmetica, lists of comedogenic substances appeared in the literature. Table 35.1 lists the ingredients typically associated with comedone formation [8, 9].

It may not be scientifically accurate to assume formulations with no known comedogenic substances are noncomedogenic. These lists were generated by applying pure raw materials to the rabbit ear in the manner previously described. In most formulations, many ingredients are present in lesser concentrations and combined chemically to create the final product. Thus, comedogenic ingredients may not produce comedones in the final formulation [10]. For this reason, it is not sufficient to hand patients a list of comedogenic substances and assume that no problems will be encountered.

Closer inspection of the list of ingredients in Table 35.1 reveals substances that are commonly used in cosmetics and skin care products. The list contains some of the most effective emollients (octyl stearate, isocetyl stearate), detergents (sodium lauryl sulfate), occlusive moisturizers (mineral oil, petrolatum, sesame oil, cocoa butter), and emulsifiers [11]. Yet, most products that contain these ingredients are noncomedogenic when tested on the upper back of human volunteers. Comedogenicity can only be evaluated in light of the patient's susceptibility to the formation of comedonal plugs. Some individuals can use cocoa butter daily as a facial moisturizer without difficulty, while others experience comedone formation. It is not yet fully understood, why certain individuals are more prone to comedone formation than others [12].

Due to the controversy regarding comedogenicity, the American Academy of Dermatology held a consensus conference designed to address the issue in a medically meaningful manner. The goal of the Invitational Symposium on Comedogenicity [13] was to standardize the methodology for comedogenicity testing. The American Academy of Dermatology determined that *"If the animal model does not show evidence of comedogenesis, the test material under consideration is unlikely to be comedogenic in human skin. One-plus reactions are also unlikely to cause reactions in humans. Two-plus or three-plus responses require sound scientific judgment. Reformulation should be considered or the product should be adequately tested in humans before general use."* It should be noted that the comedogenic grades used in this statement are based on a 0, meaning no comedogenicity potential, to 3,

**Table 35.1** Standard list of possible comedogenic substances

| |
|---|
| Butyl stearate |
| Cocoa butter |
| Corn oil |
| D&C red dyes |
| Decyl oleate |
| Isopropyl isostearate |
| Isopropyl myristate |
| Isostearyl neopentanate |
| Isopropyl palmitate |
| Isocetyl stearate |
| Lanolin, acetylated |
| Linseed oil |
| Laureth-4 |
| Mineral oil |
| Myristyl ether propionate |
| Myristyl lactate |
| Myristyl myristate |
| Oleic acid |
| Oleyl alcohol |
| Olive oil |
| Octyl palmitate |
| Octyl stearate |
| Paraffin |
| Peanut oil |
| Petrolatum |
| Propylene glycol stearate |
| Methyl oleate |
| Petrolatum |
| Safflower oil |
| Sesame oil |
| Sodium lauryl sulfate |
| Stearic acid |
| Stearyl alcohol |

indicating severe comedogenic potential. These guidelines were followed for developing the list in Table 35.1.

## 35.5 Acnegenicity

Acnegenicity is completely separate issue from comedogenicity. Substances that are comedogenic cause comedones, or blackheads, whereas substances that are acnegenic cause papules and pustules. Comedogenicity is due to follicular plugging, whereas acnegenicity is due to follicular irritation [14]. Thus, substances that are comedogenic are not necessarily acnegenic and vice-a-versa.

At first glance, acnegenicity also may seem rather simple. A list of substances that irritates the follicular ostia could be generated and then used to pick skin care products and cosmetics for patient use. Unfortunately, lists of acnegenic substances are useless since the interaction of ingredients, as well as their concentration, is important. But of more importance, is the individual patient susceptibility to acne formation [15]. Cosmetics that are acnegenic in one patient are not necessarily acnegenic in another patient.

It is interesting to note that, in a general dermatologist's practice, the phenomenon of acnegenicity due to cosmetics is a more common occurrence than comedogenicity due to cosmetics. This makes acnegenicity a more important issue than comedogenicity. However, the incidence of comedone and acne formation due to cosmetics is rare, considering the number of persons who use such products on a daily basis.

## 35.6 Acneiform Eruptions

It is difficult for the dermatologist to distinguish between acne and acneiform eruptions by definition. Many of the "breakout" reactions patients report to cosmetics are probably acneiform eruptions rather than true acne. This can be determined by history. The most common time for a "breakout" to present is 48 h after initiation of a new cosmetic product. This is insufficient time for follicular rupture to occur with the presentation of an inflammatory papule or pustule. True acneiform eruptions occur between 2 and 4 weeks after continuous topical application of an acnegenic formulation.

What then is the true cause of patient reported "breakouts" due to cosmetic application? I believe that follicular irritant contact dermatitis causes the majority of the adverse reactions to cosmetic products. The irritant reaction presents as perifollicular papules and pustules, which are

indistinguishable from acne. It is the time course that allows the correct diagnosis. Irritant contact dermatitis can occur 48 h after new product application and will rapidly disappear when the application has been discontinued. This is much different than the 2–4 weeks required for the development of acne.

The most common irritant ingredient ubiquitous to all oil in water emulsions is the emulsifier. This is typically a detergent designed to solubilize the oil in the water maintaining product stability as a single phase. I believe this is the most common cause of acneiform eruptions due to cosmetic products accounting for the large number of products reported to cause "breakouts" by some patients. Solutions to the problem of acneiform eruptions include the use of powder products, such as facial foundations, blush, and eye shadow, which do not contain emulsifiers.

## 35.7 Product Testing and Development

Noncomedogenic and nonacnegenic products can be developed through careful testing practices. The most reliable evaluation method is an in use test in a human panel of sufficient size to obtain statistical significance. This requires 40–60 subjects who are prone to comedonal and inflammatory acne or have a prior history of acneiform eruptions to cosmetics. It is important to select subjects who might likely manifest acne cosmetica. Subjects who have never experienced acne will make poor panelist as the study results will not be relevant to the at risk population.

Once the panel is carefully constructed, subjects should apply a single product to the face for 3 months with monthly evaluations by a dermatologist to properly diagnose acne cosmetica. In addition, early study evaluations should occur at 48 h, to rule out irritant and allergic contact dermatitis, and at 2 weeks to assess overall tolerability. Products tested in this manner have the highest probability of success. There is no in vitro substitute or animal model that can match the testing accuracy of a well supervised clinical test.

## 35.8 Treatment and Determination of Cause

Once acne cosmetica has been diagnosed, it is imperative that the offending skin care product or cosmetic is removed. Other formulations can be substituted. The remaining comedones can be treated topically with comedolytics, such as benzoyl peroxide and salicylic acid or retinoids [16]. The most difficult determination is whether the worsening comedones are product related or due to a hormonal cause or from an acne treatment failure [17]. Acne cosmetica is easiest to diagnose in women who have never experienced acne until after use of a particular cosmetic or skin care product.

### Conclusions

In summary, acne cosmetica should always be kept in mind when assessing an acne patient for the first time. Refractory acne cases should also be reviewed in light of the possibility of acne cosmetica. In addition, cosmetic manufacturers should test products prior to marketing to ensure that the formulations are noncomedogenic and nonacnegenic in relevant models.

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# Acne in Persons with Dark Skin

# 36

Shyam Verma

## Contents



**Core Messages**

- It is important to discuss acne in dark skin specifically as most of the textbooks on the subject have a paucity of literature in this regard. There are notable clinical and cultural differences in acne and its treatment in dark skinned people.
- It is possible that early lesions of acne in people with dark skin have a more pronounced inflammatory element and that may lead to post-inflammatory hyperpigmentation or what is also called "acne pigmented macule" (APM).
- Early treatment of acne lesions is considered a wise therapeutic decision which would hopefully tackle the inflammation mentioned above. More studies are warranted in the phenomenon of acne in dark skin. There may be interesting findings when histological findings are compared in people with varying pigmentation from Caucasians at one pole and Africans on the other with all the intermediate races in whom acne is not studied enough.
- Post-inflammatory hyperpigmentation is a significant problem in persons with dark skin and that prompts these patients to seek vigorous and often injudicious treatment with high expectations, as any phenomenon adding a dark blemish on

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their already dark skin is considered culturally unacceptable.
- Many persons with dark skin color tend to use hair oil and pomades as seen in Africa and South Asia. These hair oils can cause acne and acneiform lesions. Also, many of these patients apply skin lightening creams that can also cause acne and acneiform lesions. Therefore eliciting a history of application of cosmetics and personal care products is of paramount importance.

## 36.1 Introduction

Acne in people with dark skin is an enigmatic entity. The dark skin in this context comprises skin of persons of African origin, those from the Indian subcontinent, other countries of Asia, and of Hispanic populations. It is also one of the commonest conditions for which people with dark skin seek dermatologic consultation in many countries. Acne in these people is a double insult due to the frequently accompanying hyperpigmentation. Though the disease by and large remains the same in terms of its etiopathogenesis, clinical presentation, and treatment, there are certain subtle differences which warrant a short but separate chapter on this entity. This chapter aims at highlighting the differences in acne in dark skinned people compared to acne occurring in lightly pigmented Caucasian skin. The basics of epidemiology, pathogenesis, clinical features, and treatment of acne are not discussed in this chapter for the sake of brevity and to avoid repetition.

## 36.2 Epidemiology

If one looks at the global population distribution it is clear that the number of persons with dark skin far outnumber those with white skin. The population of persons with dark skin is increasing year after year even in hitherto white dominated countries. An indicator of this is a reliable US statistical report where it is projected that if the current trend of growth of populations continues, about 48 % of US population will be Non Caucasian by the year 2050 [1]. Also, certain continents and subcontinents have predominantly dark skinned population (Fitzpatrick types IV–VI) like Africa and the Indian subcontinent where acne is a commonly encountered condition but there is a paucity of statistics from these areas. There are many prevalence studies done on acne in pigmented skin which indicate that the prevalence of acne is slightly less in this population compared to that in people with white skin. The other possibility is that people with white skin seek dermatologic consultation a bit more frequently than do people with dark skin [2]. However, in India, with its second largest population in the world if one bars eczemas as a group of disorders, acne would rank first or second commonest reason for a dermatologic consultation. However with the current trend of population growth Western dermatologists in countries like the USA will see many more persons with dark skin coming for treatment of acne and its sequelae [3]. Many of the studies done so far have compared acne in white skin with acne in black skin. More studies from countries with dark skinned populations like the Indian subcontinent are warranted and would throw more light on the subject.

## 36.3 Pathogenesis

There is not much supporting evidence to conclude that pathogenesis of acne in persons with dark skin is different from those with white skin. Details of such studies are beyond the scope of this chapter but individual comparative studies have been done on acne in people with dark skin and those with white skin. They include studies on *Propionibacterium acnes* density, sebaceous glands, and sebum production in these populations [4–6]. However there is no comparative study of these populations in the pilosebaceous follicular ductal hyperkeratosis. Comparative studies of sebaceous glands and their activity in

black skin versus white skin are few. Most of them have very small number of subjects and are quite contradictory. Kligman and Shelley have found larger sebaceous glands and higher surface sebum levels in richly pigmented people of African origin. Nicolaides and Rothman have found 60–70 % more lipid levels in the hair of people with African origin compared to that of people with white skin. However this study has been questioned because they have not taken into account physical qualities of the hair like weight, size, and diameter. On the other hand Aberdeen et al. have measured the sebum production rate using sebumeter and sebutape and have found that people with white skin, those of African descent and people from the Asian continent show no difference in sebum excretion rate [7]. In short the jury is still out as to whether there are truly any differences in sebaceous gland size and sebum secretion in these populations. More studies need to be done especially on dark skinned people from countries of Asia and on Hispanic populations.

Interesting histological differences have been documented in lesions of acne in Caucasian skin versus skin of African Americans [8]. Halder et al. biopsied comedones, papules, and pustules from female subjects and documented a profound infiltration of neutrophils in comedones of these subjects which are otherwise supposed to be noninflammatory. Papules and pustules showed similar findings and the inflammation were found to be extending the affected lesions. Taylor et al. suggest that if additional studies indicate evidence of inflammation in comedonal acne, a separate entity like "inflammatory comedonal acne" should be coined [2]. The presence of inflammatory comedonal acne, the inflammation of seemingly noninflammatory acne, and the obviously inflammatory lesions may account for the tendency of people with dark skin to develop post-inflammatory hyperpigmentation.

## 36.4 Clinical Features

It appears that persons with white skin have a higher incidence of severe nodulocystic acne when compared to their counterparts with dark skin. However patients with dark skin do very often tend to seek treatment for their acne. It is important to note that many large dark skinned populations live in economically backward countries where treatment is sought from specialists and charlatans alike [9]. Sociocultural factors also affect acne and its treatment in dark skinned people.

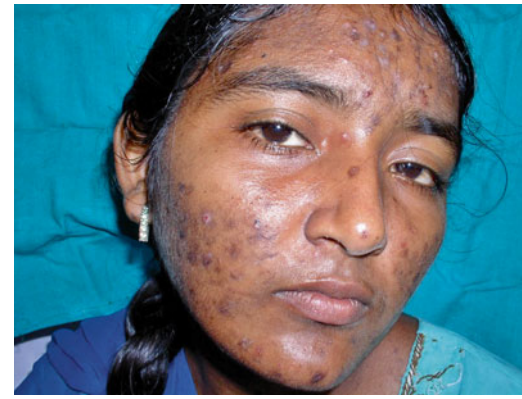

**Fig. 36.1** Active acne lesions with pigmentation as well as post-inflammatory hyperpigmentation

One of the characteristic findings in people with dark skin and acne is the presence of pigmented active lesions and post-inflammatory hyperpigmentation (PIH), also known as acne hyperpigmented macule (AHM) [2]. This problem is more pronounced in young patients who frequently pick and excoriate their acne which almost invariably results in some degree of hyperpigmentation (Fig. 36.1). Prolonged exposure to sunlight, inadequate use of sunscreens, and exposure to high levels of dust, especially in young patients who frequently ride scooters and motorcycles, are factors for post-inflammatory hyperpigmentation too. In fact many patients from this population are more concerned with the sequelae of hyperpigmentation rather than lesions of acne. This is also the reason why patients in many countries in the Indian Subcontinent and Africa use topical steroids and depigmenting creams, many of them prescribed by unauthorized medical practitioners, bought without prescription, and dispensed by pharmacists. A very important underlying cultural phenomenon in these populations is the overwhelming desire to

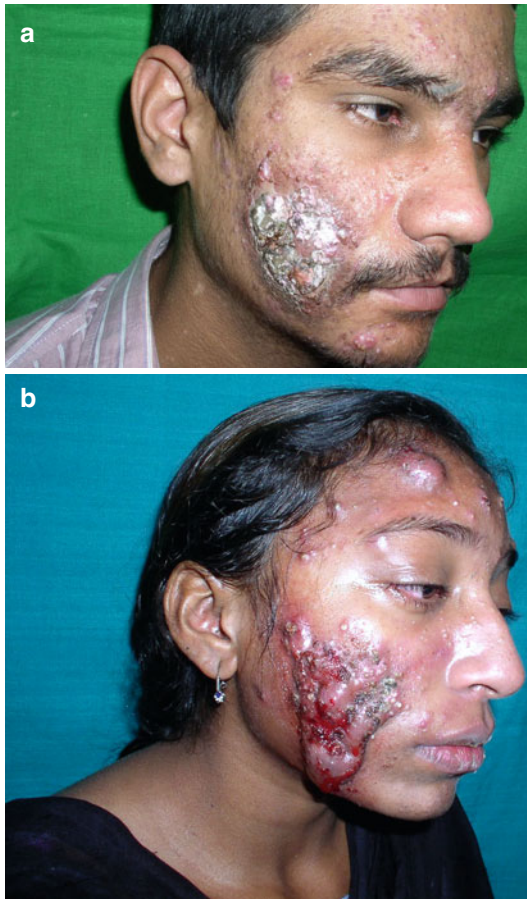


**Fig. 36.2** Papulopustular nodular acne in a male (**a**) and conglobate acne in a female (**b**) of Indian descent leading to keloid formation

be light skinned or "fair" [10]. Darkly pigmented persons, especially people of African descent, also have a higher incidence of keloids resulting from nodulocystic acne (Fig. 36.2).

One of the most commonly used products responsible for acne on the forehead and face is hair oils and pomades in people with dark skin from the Indian subcontinent and Africa respectively. It is common to see lesions of acne on the forehead and temple of users of these products as they tend to gravitate downwards after application (Fig. 36.3). Use of scented oils is also responsible for contact dermatitis and secondary post-inflammatory hyperpigmentation on the forehead

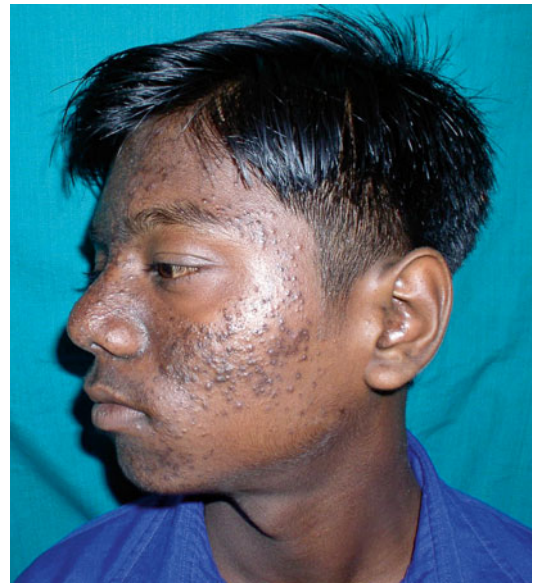

**Fig. 36.3** Hyperpigmented acne lesions mainly distributed on forehead due to application of indigenous hair oils

in addition to acne. There is also the possibility of a pigmented contact dermatitis due to these oils. Pigmentation along with acne or its resultant scarring is unseemly, cosmetically disfiguring and is a major social embarrassment seriously hampering quality of life in people with dark skin. Topical steroid-related acneiform eruptions are also well known among dark skinned people living in the Indian subcontinent and Africa where prescription drugs are available across the counter due to non-implementation of rules governing such drugs.

The overall manifestations of acne do not significantly differ in dark individuals from those with light skin. The treatment also remains the same in this population but all the topicals, especially the gel-based ones, that are irritant can result in varying degrees of post-inflammatory hyperpigmentation. It is therefore prudent to advise dark skinned patient of acne to start topical treatment gradually and increase the duration weekly. There is no scientific documentation but benzoyl peroxide in dark skinned people tends to cause a pigmentation with a very subtle xerosis without scaling which is different from irritant dermatitis caused by

topical retinoids. Further studies are warranted for this phenomenon. One of the reasons why post-inflammatory hyperpigmentation is encountered in dark skinned patients after application of topical retinoids and benzoyl peroxide is that erythema is not a feature that is readily appreciated on dark skin. The patient therefore continues to apply the topical until symptoms occur or post-inflammatory hyperpigmentation occurs. It is therefore wise to look for other clinical parameters of inflammation while treating acne with topical agents that may irritate the dark skin.

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# Part VI

# Prognostic Factors of Acne

# Acne and Heredity

# 37

Brigitte Dréno

## Contents



**Core Messages**

- Heredity may influence the clinical severity of acne.
- The influence of genetic factors and heredity in acne has been shown in studies in monozygotic twins.
- A family history of acne is associated with persistence of acne in adult life, with resistance to treatment, higher risk of recurrence, more widespread lesions, and an earlier onset of acne.
- Oral treatments were more often used and relapse after isotretinoin was more frequent in acne patients with a history of family acne.
- Several candidate genes possibly involved in inflammatory acne have been proposed: epithelial genes, cytochrome genes, genes regulating androgen receptors and cutaneous androgen metabolism found in sebaceous glands, and inflammation and remodeling genes involved in the expression of the NFkB transcription factor.

## 37.1 Introduction

The role of heredity and its impact on the clinical severity of acne has been suggested by several studies. In 1960, Hecht [1] was the first to assess the role of heredity for acne. He

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demonstrated that if one of the parents had presented with acne in his/her youth, the child who resembled him/her most had 80 % probability of developing acne himself/herself. It was later resumed in several clinical studies [2–4] of which some had been performed in twins [5–7]. One study of 95 pairs of twins presenting with acne showed that 98 % of monozygotic twins were affected versus 46 % of dizygotic twins [6]. The two other ones [5, 7] confirmed this high concordance in monozygotic compared to dizygotic twins. In one of them [5] the influence of genetic factors and family history on the occurrence of acne was estimated to be 81 %. A link was shown between family factors and the susceptibility to persistence of acne into adulthood [8–10]. Finally, a recent study performed in 2006 showed that the concept of family acne is associated with an early onset of lesions characterized by greater risk of scarring and more widespread lesions [11]. When a family history can be shown to exist [9] acne is more difficult to treat, with longer treatment periods and greater risk of recurrence.

## 37.2 A Prognostic Factor of Response to Treatment

The role of heredity on therapeutic response remains unclear. In this context, a prospective epidemiologic study [11] compared clinical and evolutive features of acne and response to treatment in 151 acneic patients with or without family history of acne. The clinical profile was similar in the two groups, but acne appears to occur earlier and more often before puberty in acne patients with a family history of acne. The number of comedones differed significantly according to the origin of the family history of acne: it is higher if both parents presented with acne. On the other hand, no relationship was shown between superficial or deep inflammatory lesions and family history of acne. This raises the hypothesis of the possible influence of a genetic factor on the microcomedone, which is the most primary lesion of acne. The extension of acne beyond the face (on the arms and chest) was notably more frequent for patients whose mother (mother alone or mother + father) had presented with acne. These results regarding retentional lesions and acne extension, which are more frequent when the mother presents with acne, raise the question of the importance of maternal heredity for acne severity. At the therapeutic level, oral treatments were more often used and relapse after isotretinoin more frequent in the group with history of family acne.

Another study [12] identifying risk factors of relapse after stopping isotretinoin confirmed the value of heredity as prognostic factor. This prospective open study concerned 52 patients with moderate to severe acne and in a multivariate analysis show that severe seborrhea and high score of inflammatory lesions at the end of the treatment, an early age, prepubertal acne, acne extended to the trunk, notion of previous treatment by topical retinoids, and family history of acne were factors increasing significantly the risk of relapse.

## 37.3 Genetic Studies

Genetic studies offer a structured means of understanding the causes of acne and the identification of novel therapeutic targets. The nature of protective effects is still unknown, but genetic studies also have the potential to identify mechanisms for this protective effect and to find novel strategies to prevent the severe form of the disease.

To this day, several candidate genes possibly involved in inflammatory acne have been proposed:

- Epithelial genes: the glycoproteins PEM and MUC1 [13].
- Cytochrome genes: P-450 1A1 able to induce a deficit of natural retinoids leading to abnormal differentiation of sebocytes and keratinocytes [14, 15].
- Genes regulating androgen receptors and cutaneous androgen metabolism found in sebaceous glands [16–20].
- Inflammation and remodeling genes involved in the expression of the NF kappa B transcription factor [21–28].

Further factors related to family history have been reported [24]. However, probably the previously identified candidate genes may have only a minor overall impact on disease susceptibility, compared to those that remain to be discovered. Being able to identify genes involved in the development of acne would enable to make significant progress in four areas of acne: early therapeutic treatment, development of new therapeutic molecules especially targeted in innate immunity, prognosis and hence improvement in the social dimension of treating patients, and the possible transfer of results to other diseases belonging to the spectrum of auto-inflammatory diseases.

**Conclusions**

On the whole these results tend to support a role of genetics for acne: a teenager whose parents presented with acne has a higher risk of developing acneic lesions compared to a subject with no family history of acne. In addition, regarding therapeutic features, the family history of acne was associated with the need for a higher number of systemic treatments and with a higher risk of failure after isotretinoin treatment. Finally, the « motherly » factor seems to play a predominant role compared to the « fatherly » factor, with a higher frequency of comedones and a more marked extension of acne on the chest and arms. This evidence of a genetic influence on acne has to stimulate research for responsible genes.

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# Acne Neonatorum

# 38

Andreas D. Katsambas and Clio Dessinioti

## Contents



**Core Messages**

- Acne neonatorum is manifested mainly by closed comedones and also by open comedones and inflammatory lesions.
- Hyperactivity of sebaceous glands, stimulated by neonatal androgens, has been implicated in its pathogenesis.
- The role of *Malassezia* species in its pathogenesis remains controversial.
- The association between neonatal acne and neonatal cephalic pustulosis remains unclear.
- Differential diagnosis should include other pustular dermatoses of the neonate, including infectious diseases of bacterial, viral, or fungal etiology, transient neonatal pustular melanosis, neonatal sebaceous gland hyperplasia, infantile acne, acne venenata infantum, and acneiform eruptions due to lithium or phenytoin during pregnancy.
- In recalcitrant or severe acne neonatorum, hyperandrogenemia should be excluded.
- Acne neonatorum is usually mild and transient, and parents are to be reassured of its self-limited course.

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## 38.1 Introduction

Acne is generally considered to be a disease of adolescence, although it can also affect neonates, infants, children, and adults [1]. A neonate is

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defined as a newborn less than 28 days of age. A plethora of dermatoses such as infectious and noninfectious disorders, including allergic conditions, genodermatoses, and acne neonatorum (neonatal acne) may present as pustular eruptions during this period [2].

The clinical importance of neonatal acne lies mostly in the differentiation from infectious diseases, the exclusion of an underlying cause of virilization, and the suggested association with severe acne in adolescents [1, 3, 4].

Whether neonatal acne represents a distinct condition, or if the term neonatal cephalic pustulosis corresponds to the same entity, remains controversial.

## 38.2 Pathogenesis

The pathogenesis of neonatal acne remains unclear (Table 38.1). Several mechanisms have been proposed.

### 38.2.1 Role of Increased Seborrhea

During the neonatal period, there is a considerable sebum excretion rate [6, 11]. The adrenal glands are relatively large and produce significant quantities of beta-hydroxysteroids, which stimulate the sebaceous glands to enlarge [12]. After the age of 6 months, sebum excretion rate decreases to almost undetectable levels, due to a significant reduction of sebaceous gland size [6, 11]. High maternal sebum excretion has been correlated to neonatal sebum excretion, suggesting that maternal factors influence infant sebaceous glands [13].

**Table 38.1** Factors that may be involved in the pathogenesis of acne neonatorum

- Genetic factors: positive family history of acne [1]
- Stimulation of neonatal sebaceous glands by maternal androgens [5]
- Stimulation of neonatal sebaceous glands by infant adrenal (for both male and female infants) or testicular (for male infants) androgens [1, 4]
- Increased sebum secretion during the first months of life [6]
- Controversial role of *Malassezia* species [3, 7–10]

### 38.2.2 Role of Androgens

Neonatal acne has been attributed both to maternal androgens and fetal androgens produced by gonads and adrenal glands [14]. On the one hand, the transplacental transfer of maternal androgens, rather than their transfer via breast milk, has been incriminated for the stimulation of neonatal sebaceous glands [5].

On the other hand, hyperactivity of sebaceous glands, stimulated by neonatal androgens from the adrenal glands in girls and the adrenal glands and testes in boys, has been implicated in neonatal acne pathogenesis [5].

In both male and female infants, the neonatal adrenal gland is primarily a "fetal" adrenal gland consisting of an enlarged zona reticularis, the androgen-producing zone, and producing high levels of DHEA. Increased DHEA levels, in turn, stimulate sebaceous glands, until around 1 year of age when DHEA levels disappear following the decrease of the fetal adrenal gland [1, 4].

At birth, and persisting for the first 6–12 months of life, boys have early pubertal levels of luteinizing hormone (LH) and consequently of testosterone. Thus, although both male and female infants have an adrenal contribution to their elevated androgens, boys in addition have testicular androgen, which could account for the higher prevalence of neonatal acne in male infants [1].

Acne of pregnancy has not been associated with acne neonatorum. A positive family history of acne or the presence of familial hyperandrogenism may play a role, supporting the importance of heredity in acne [1, 14].

### 38.2.3 Role of *Malassezia* Species

Newborn skin is sterile at birth [15], but resident flora may be detected within the first hours of life. By the age of 6 weeks, the total number of organisms is comparable to that found in adults.

*Staphylococcus epidermidis* is the most common bacterium, and yeast flora is represented by non-lipophilic yeasts (*Candida* species) and lipophilic yeasts (*Malassezia* species) [15]. Malassezia species are saprophytic of normal human adult and child skin [16, 17]. Both the age at which neonates become infected and the route by which healthy neonate skin is colonized with *Malassezia* are unclear [7].

In neonates, a role for Malassezia species (*Malassezia furfur*, *Malassezia globosa*, or *Malassezia sympodialis*) in the cause of facial acne-like pustulosis (neonatal cephalic pustulosis) was first suggested by Aractingi et al. [18] and subsequently by other authors [10, 19]. The severity of pustulosis has been correlated with the isolation of *M. sympodialis* [8, 19].

Environmental factors, maternal contact and neonatal skin characteristics, including sebum secretion rate and quality, probably affect neonatal skin colonization with *Malassezia* [19]. The mother seems to be the first reservoir for the child's colonization, as in one study 60 % of *M. sympodialis*-positive neonates shared, at birth, the same yeast species with their mother [19]. The absence of complete correlation might be explained by a better adaptation of *M. sympodialis* compared to *M. globosa* for the neonatal skin or by other sources of colonization such as the nursery personnel or other family members [19].

Further factors that influence neonate skin colonization with Malassezia include the length of stay in an intensive care unit, gestational age, birth weight, use of parenteral nutrition, use of antimicrobial medication, presence of a central venous catheter, surgery, and the use of a nasogastric tube [16, 17, 20].

However, cases of neonatal cephalic pustulosis (NCP) with negative mycological data suggest multifactorial causes for this dermatosis [7, 21]. An alternative explanation is that NCP is a consequence of an overgrowth of lipophilic yeasts at birth that results in an inflammatory reaction consisting of inflammatory pustules. This cutaneous inflammatory reaction may occur in predisposed neonates with increased sebum production, which may lead to follicular or poral occlusion [19, 22].

A recent study showed that Malassezia is neither a direct causative factor of neonatal cephalic pustulosis, nor is Malassezia colonization related to the development or clinical stage of the disease [7].

Moreover, since Malassezia has not been isolated in a series of cases with acne neonatorum, it has been proposed that neonatal acne may be an early presentation of comedonal acne and not a response to *Malassezia* [3, 22].

## 38.3 Clinical Manifestations

Neonatal acne (acne neonatorum, AN) may be present at birth or appear during the first 4 weeks of life. If the diagnosis of AN is based on the presence of even a small number of comedones, it may affect up to 20 % of newborns [1]. It is more commonly seen in boys (5:1) [23].

AN is characterized predominantly by closed comedones, but open comedones and erythematous papules and pustules may also be present. Cysts and nodules are very rare, but may lead to scarring [5]. The lesions affect predominantly the face, especially the cheeks, chin, eyelids, and forehead, and may also involve the scalp, neck, and upper chest [24].

Confusion exists as to whether neonatal acne truly exists or if the term neonatal cephalic pustulosis (NCP) is a more accurate description [25].

A type of neonatal cephalic pustulosis that is clinically similar to classic neonatal acne has been linked to skin colonization of the *Malassezia* species [8, 19, 22]. Further studies are warranted in order to discern the clinical characteristics of neonatal acne and neonatal cephalic pustulosis [25].

## 38.4 Differential Diagnosis

Pustular eruptions in neonates present a diagnostic challenge to the dermatologist. During the neonatal period (defined as the first 4 weeks of life), the infant is extremely vulnerable to bacterial, viral, and fungal infections. In addition, differential diagnosis includes neonatal

**Table 38.2** Differential diagnosis of neonatal pustular eruptions

| Infectious | Non-infectious |
|---|---|
| Bacterial<br>*Staphylococcus aureus* (bullous impetigo)<br>*Listeria monocytogenes*<br>*Streptococcus* (β-hemolytic group B)<br>*Pseudomonas aeruginosa*<br>*Hemophilus influenzae* | Erythema toxicum neonatorum<br>Infantile acropustulosis<br>Transient neonatal pustular melanosis<br>Pustular miliaria<br>Eosinophilic pustular folliculitis of infancy<br>Milia<br>Sebaceous gland hyperplasia |
| Viral<br>Herpes virus infections | Acneiform eruptions<br>Acne venenata infantum<br>Acneiform drug reactions<br>Chloracne |
| Fungal<br>Candidiasis<br>Pityrosporum folliculitis | Genodermatoses<br>Congenital self-healing Langerhans cell histiocytosis<br>Epidermolysis bullosa<br>Incontinentia pigment |
| Parasitic<br>Scabies | |

cephalic pustulosis, milia, miliaria, sebaceous gland hyperplasia, infantile acne, acne induced by topical oils and ointments (acne venenata infantum), adrenal hyperplasia, and acneiform reactions following use of medication such as lithium, steroids, or hydantoin during pregnancy [1, 5, 24]. Moreover, chloracne, an acneiform eruption sparing the centrofacial region, may occur due to accidental topical, inhalation, or oral exposure to chlorinated aromatic hydrocarbons [1]. Genodermatoses such as incontinentia pigmenti, self-healing Langerhans cell histiocytosis, and epidermolysis bullosa may also present as pustular eruptions during the neonatal period (Table 38.2) [2].

Transient benign pustular eruptions such as neonatal acne should be differentiated from serious and life-threatening conditions that require immediate therapy and prolonged hospitalization, such as viral and fungal infections [26].

*Neonatal cephalic pustulosis* (NCP) has been recently described. There are no consistent data about the prevalence of neonatal cephalic pustulosis; it has been reported as 10 %, 12 %, and 66 % by different authors [8, 10, 19]. Aractingi et al. first described neonatal cephalic pustulosis in 1991 [18]. It is a neonatal pustular eruption that presents in similar fashion to neonatal acne. NCP appears during the first weeks of life and the most common lesion is an erythematous papulopustule. Comedones are typically absent [8], although a subset of patients may present with comedones and inflammatory lesions, and may have early-onset androgen-driven neonatal acne.

Diagnostic criteria of neonatal cephalic pustulosis were defined by Rapelanoro et al. [10] as the presence of pustules on the face and neck, age at onset younger than 1 month, isolation of Malassezia by direct microscopy in pustular material, elimination of other causes of neonatal pustulosis, and response to topical ketoconazole therapy. Nevertheless, the causative role of Malassezia has been questioned [7].

The association between neonatal acne and neonatal cephalic pustulosis remains unclear.

*Erythema toxicum neonatorum* (ETN) is an inflammatory skin reaction of the neonate [27]. Its incidence has been reported to be approximately 40 %, with predominance in males [27]. Although ETN is a common dermatosis, its etiology and pathogenesis remain unknown. A significantly increased incidence of ETN has been observed in neonates born of a first pregnancy, at term and by vaginal delivery, fed with milk powder substitute or a mixed diet, and born in summer or autumn [27].

ETN usually appears after 24–72 h of life, although it has also been reported at birth [28, 29]. The lesions appear as erythematous macules and evolve to red, white, or yellow papules, to a vesicular and pustular eruption on an erythematous base. They are asymptomatic and evanescent and affect mainly the face, chest, trunk, and extremities, while sparing the palms and soles. Diagnosis may be confirmed by the presence of eosinophilia (which may be present in 15 % of the cases) and eosinophils by a Tzanck smear or a Gram's stain of the pustular content of the lesions [26].

**Table 38.3** Laboratory investigations in neonatal pustular eruptions

| | |
|---|---|
| Erythema toxicum neonatorum | Smears of the pustules: eosinophils<br>Eosinophilia |
| Infantile acropustulosis | Tzanck smear: neutrophils<br>Gram stain: neutrophils |
| Pustular miliaria | Bacterial culture: *S. aureus* |
| Impetigo | Gram staining<br>Bacterial culture: *S. aureus* |
| Fungal infections | 10 % KOH microscopic examination |
| Viral infections | Cytologic smears: multinucleated giant cells<br>Negative bacterial culture<br>Negative fungal culture |
| Persistent neonatal acne | FSH, LH<br>Total, free testosterone<br>DHEA, DHEAS |

ETN is self-limited and the lesions disappear spontaneously after lasting 1–3 days [30]. Thus, no treatment is required and parents are to be reassured of the benign nature of this condition [26].

*Infantile acropustulosis* is an uncommon, self-limited dermatosis of unknown etiology, affecting mainly black neonates. It may begin during the neonatal period and persist in infancy and early childhood [31]. It presents with pruritic red papules, which evolve within 24 h into vesicles and pustules. They are located on the hands and feet, and less often on the scalp, face, and trunk. Diagnosis is based on the distribution of lesions, their recurrence in crops every 2–3 weeks and stains of the pustules (Table 38.3).

*Transient neonatal pustular melanosis* is a rare dermatosis of unknown etiology. It presents at birth or during the first day of life with asymptomatic vesiculopustules without surrounding erythema. These lesions then rupture and evolve into hyperpigmented macules with a surrounding scale [26]. The chin, neck, upper chest, thighs, buttocks, abdomen, palms, and soles are commonly affected [32].

*Infantile acne* by definition starts later than acne neonatorum, usually after 3 months of life. It has a more persistent course and is characterized by lesions that are more inflamed than those of acne neonatorum. In addition to closed and open comedones, papules, pustules, nodules, and cystic lesions with a scarring potential, may develop [1, 5] (see Childhood Acne, Chap. 31).

*Pustular miliaria* is rare in neonates. Miliaria results from sweat retention due to occlusion of the immature sweat duct, rupture of the ducts, and consequent sweat escape into the surrounding epidermis [26]. It affects mainly the flexures and the clothed areas of the body. It resolves after 3–4 days with the use of light cotton clothing in cool environment [33].

*Neonatal sebaceous gland hyperplasia* should not be confused with acne neonatorum, as it is characterized by many, small yellow–white follicular papules, mostly on the nose and cheeks, without comedones or inflammation [1].

## 38.5 Diagnosis

In neonatal acne, a careful history of the disease and a physical examination of skin lesions are typically sufficient for the correct diagnosis. However, when in doubt, a history of maternal infections during pregnancy and simple laboratory investigations may facilitate diagnosis (Table 38.3) [2].

Tzanck smear is useful to exclude herpes simplex, varicella-zoster virus, or cytomegalovirus. Gram's stain is useful to rule out bacterial infections such as impetigo, and routine potassium hydroxide (KOH) preparation is used to rule out candidiasis [26]. Invasive investigations are usually not needed [2].

In persistent cases of neonatal acne, infantile hyperandrogenemia should be excluded, and detailed evaluations for congenital adrenal hyperplasia, a virilizing tumor, or underlying endocrinopathy are warranted. In these cases, physical examination for precocious puberty, bone age measurements, and laboratory evaluations, including FSH, LH, testosterone, dehydroepiandrosterone (DHEA), DHEA sulfate, are warranted [6]. Any abnormality needs referral to a pediatric endocrinologist [24].

## 38.6 Prognosis and Treatment

Parents should be reassured that acne neonatorum is usually mild and transient [1]. The majority of cases are mild and transient, showing spontaneous resolution with no scarring in 4 weeks to 3 months, although there are cases that may persist until 6–12 months of age [3, 5]. Neonatal acne may evolve into infantile acne, and it has been associated with severe acne in adolescence [3, 5].

In most cases, daily cleansing with soap and water is sufficient and no treatment is required [3, 5]. If necessary, treatment of neonatal acne is similar to therapy of acne in older age groups. Comedones may be treated with 20 % azelaic acid cream or 0.025–0.05 % tretinoin cream. For inflammatory lesions, topical erythromycin or benzoyl peroxide or a benzoyl peroxide/topical clindamycin combination may be used. Alternatively, salicylic acid 1 % and resorcin 1 % cream may be used [1, 3].

If systemic antibiotics are required, erythromycin is the treatment of choice [4].

Of note, tetracyclines are contraindicated in children younger than 8 years old as they cause damage to developing bones and teeth [24, 34].

Neonatal cephalic pustulosis is a benign, self-limited disorder and the majority of cases do not require treatment [5]. However, treatment with 2 % ketoconazole cream twice per day for 1 week, may lead to more rapid clearance of the lesions [10, 19].

Whether neonatal acne represents a distinct condition, or if the term neonatal cephalic pustulosis corresponds to the same entity, has yet to be clearly defined. Further studies are warranted in order to clearly define the characteristics of both these dermatoses that may present during the neonatal period [8, 9].

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# Serum Androgens

# 39

WenChieh Chen and Christos C. Zouboulis

## Contents



**Core Messages**

- Refractory or severe infantile acne may indicate congenital adrenal hyperplasia due to 11β-hydroxylase deficiency or the presence of an adrenocortical tumor.
- Patients with a history of infantile or childhood acne are predisposed to a higher incidence and greater severity of acne vulgaris at puberty.
- Elevation of dehydroepiandrosterone or dehydroepiandrosterone sulfate may be associated with development of neonatal, infantile, childhood acne, and the initiation of pubertal acne.
- Adult acne in women includes persistent postadolescent acne, and late-onset acne when the acne formation is seen after 25 years of age. It is characterized by lower face accentuation and is frequently associated with adrenal or ovarian hyperandrogenism.
- Both adrenal and ovarian tumors should be explored if acne is associated with hirsutism, male-pattern hair loss, or other virilizing signs, especially when a high level of serum total testosterone over 200 ng/dL is present.

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## 39.1 Introduction

The number of sebaceous glands remains approximately the same throughout life, whereas their size tends to increase with age. The development and function of the sebaceous gland in the fetal and neonatal periods appear to be mainly regulated by maternal androgens and by endogenous steroid synthesis. A strong increase in sebum excretion occurs a few hours after birth, reaching its peak during the first week and slowly subsides thereafter. A new rise takes place at about age 9 years with adrenarche and continues up to age 17 years, when the adult level is reached [1].

Although androgens play an essential role in acne pathogenesis, most patients with acne, especially men, have normal circulating androgen levels. The absence of correlation between acne severity and other clinical markers of androgenicity in women suggests that in most cases, factors other than hyperandrogenemia are necessary for development of acne [2].

The definition of hyperandrogenism and measurement of hyperandrogenemia remain controversial. Hyperandrogenism may be further divided into "central circulating hyperandrogenism" with androgens originating from ovaries or adrenals and "peripheral local hyperandrogenism" in which androgen excess happens in situ in the skin. Measurement of one or more of the following parameters are used to monitor hyperandrogenism: serum levels of total testosterone (T), free testosterone, delta-4-androstenedione, 5α-dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), or DHEA sulfate (DHEAS), sex hormone binding globulin (SHBG), and serum free androgen index as well as urinary 5α-androstane 3α-17β-diol (3α-Adiol glucuronide), and 17-ketosteroids. It remains uncertain, whether DHT, 3α-Adiol glucuronide, or androsterone glucuronide/sulfate can better reflect the peripheral hyperandrogenism and the peripheral 5α-reductase activity [3].

## 39.2 Neonatal and Infantile Acne

Infantile acne is a rare condition with male predominance which begins at a mean age of three weeks and last mostly 4–6 months [4, 5]. Neonatal and infantile acne may reflect the relatively high androgens from the adrenal in girls and the adrenal and testes in boys characteristic of this age [6], although most infants seem to show no pathologic endocrinopathy [5]. Infants with refractory acne or severe nodulocystic acne should be evaluated for signs of virilization and accelerated growth. Hormone disturbance such as congenital adrenal hyperplasia due to 11β-hydroxylase deficiency or the presence an adrenocortical tumor should be ruled out, especially with an elevated level of DHEA and DHEAS [7, 8]. Patients with a history of infantile acne appear to show the trend toward higher incidence and greater severity of acne vulgaris in their teenage years [9].

## 39.3 Childhood or Prepubertal Acne

Acne in childhood has been suggested to be strongly associated with the development of severe acne during adolescence [1]. Its beginnings are heralded by increased activity of the sebaceous glands and faulty follicular keratinization, which are already evident in mid to late childhood [10]. If other virilizing signs are recognized or the acne is seen in the preschool age, then further examination is warranted to exclude underlying functioning androgenic tumors.

## 39.4 Pubertal Acne

Acne, especially the comedonal type, can be the first sign of pubertal maturation in girls, even preceding pubic hair and areolar development. Concentration of DHEAS is significantly and specifically associated with the initiation of acne

in young girls, while estradiol, total and free T, progesterone, T to estradiol ratio, and SHBG levels show no difference in subjects with or without acne [11].

## 39.5 Adult Acne in Women

Adult acne usually refers to acne formation after 25 years of age and can be further divided into (1) persistent postadolescent acne as defined by acne of adolescent onset persisting into adulthood and (2) late-onset acne (acne tarda) when the first episode of acne is seen in the adulthood. The prevalence of facial acne in adult women ranges from 14 to 40 % [12–14]. In our own study, around 38 % of the women had adult acne, of them 87 % had persistent postadolescent acne, while 13 % had acne tarda [14]. Clinically these acne forms tend to predominate in the lower face with perioral involvement running a more indolent course [15].

In a case–control study of white women with acne tarda, women with both acne and hirsutism showed significant difference in the mean SHBG, free androgen index, and DHEAS, while women with acne but without hirsutism showed significant difference only in DHEAS as compared to controls [16]. In addition to androgens, increased IGF-1 levels may also influence adult acne, especially in women [17].

As for the origin of androgens, more than 50 % of women with adult acne had some sort of ovulation disorders or polycystic ovaries, of them higher values of androstenedione, DHEA, DHEAS, and luteinizing hormone (LH), and a higher LH/follicle-stimulating hormone (FSH) ratio could be detected [18, 19]. Dexamethasone suppression test may be useful to detect the adrenal androgen excess in women with adult acne. Following the test, the DHT and T of adrenal origin were significantly higher in the acne patients than in the control subjects [20].

The serum total testosterone is most commonly measured in routine practice to detect hyperandrogenemia. Polycystic ovary disease is suspected if its level is between 150 and 200 ng/dL, while an ovarian tumor usually induces a higher level (>200 ng/dL) [2]. A serum DHEAS level greater than 700 μg/dL may reflect adrenal tumors, while a value in the range of 400–700 μg/dL may be associated with congenital adrenal hyperplasia. Adrenocortical tumors can also cause a high level of serum total testosterone without deviation of serum DHEAS level [21].

## 39.6 Postmenopausal Acne

Postmenopausal acne originates at or after menopause more commonly in darker skinned, formerly oily-skinned, large-pored women who usually did not experience adolescent acne [22]. Unopposed adrenal androgens present after ovarian failure was supposed to be the chief causes of this condition [23]; however, recent studies stress again the significant contribution of postmenopausal ovary to the circulating pool of T [24]. Postmenopausal acne in concurrence with other virilization signs such as hirsutism or male-pattern hair loss should be a warning sign for an underlying functional disturbance or tumors in ovary or adrenals [25].

## 39.7 Acne in Adult Men

There are few studies addressing the hormone levels in adult men with acne. In an age-matched control study, no significant difference existed in the LH, FSH, 17 alpha-hydroxyprogesterone, DHEAS, estradiol, and SHBG levels, while the strongest correlation appeared to exist with androstenedione and 11-deoxycortisol [26].

**Conclusions**

A plentiful of evidence confirms the initiative and permissive role of androgens in acne development, however, the circulating androgen levels does not correlate with acne severity. Serum total testosterone and

dehydroepiandrosterone (sulfate) remain the most commonly used clinical markers to detect hyperandrogenemia, while inconclusive data exist concerning the detection of cutaneous androgen overproduction and metabolism. An exaggerated hyperandrogenemia in women warrants a thorough exclusion of an underlying adrenal or ovarian tumor.

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# Body Mass Index

# 40

Clio Dessinioti and Christos C. Zouboulis

## Contents



**Core Messages**

- The possible mechanisms to link increased body mass index (BMI) with acne include the higher presence of polycystic ovary syndrome (PCOS) in overweight females, the higher serum androgen levels found in obese subjects, and the possible role of an imbalanced diet on acne.
- On the other hand, insulin resistance is found both in obese and non-obese patients with PCOS.
- Only a limited number of well-designed studies have explored the association of a high BMI with acne.
- Existing data is controversial, with some studies reporting an association of higher BMI with acne, while others report an association of higher BMI with a lower risk of acne.
- Further studies are needed specifically addressing this intriguing association.

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## 40.1 Introduction

Body mass index (BMI) is one of the most accurate ways to measure obesity in practice. BMI is calculated by dividing the body weight with the square of height (kg/m$^2$). According to the World Health Organization, the normal range of BMI is

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between 18.5 and 24.9, and individuals with a BMI of 25–30 are considered to be overweight, while those with a BMI over 30 are classified as obese [1].

The possible mechanisms to link increased BMI with acne include the increased rate of polycystic ovary syndrome (PCOS) in overweight females, the higher serum androgen levels found in obese subjects, and the possible role of an imbalanced diet in acne.

Excessive weight and obesity are common in PCOS (30–75 %) [2]. Taking into account the link between acne and PCOS, a potential association of weight and BMI with acne could be hypothesized. High serum insulin-like growth factor (IGF)-1 and high androgen levels, found in PCOS, have been associated with acne [3] and sebum production increases in response to both androgens and IGF-1 [4]. Obese women have higher serum total testosterone and lower sexual hormone-binding protein levels than non-obese women. Insulin resistance is one of the pathogenetic factors of PCOS [5], although it has been observed in both obese and non-obese women with PCOS [6].

Also, overweight individuals tend to have less balanced diets characterized by a large intake of carbohydrates (bread, pasta, potatoes, sweets) and fat. In view of reported associations of a diet rich in carbohydrates and fat with acne (see Chaps. 20 and 26), the question arises whether increased BMI, as an indirect effect of diet, could influence acne.

In this chapter we will discuss the evidence concerning the role of BMI in acne vulgaris.

## 40.2 Body Mass Index in Acne: What Is the Evidence?

Few studies have explored the association of a high BMI with acne. A large twin study in adult women based on 458 pairs of monozygotic and 1,099 pairs of dizygotic twins, showed no significant differences between acne twins and non-acne twins for weight and BMI [7]. Also, in adult women with PCOS, no association was found between acne and increased BMI (>25 vs. <30) [8]. Another study in women with acne showed no association with BMI [9]. Interestingly, obese women were less likely to have acne than non-obese women ($p < 0.004$) in a Taiwanese study, although higher serum testosterone levels and an association with PCOS were found in obese patients [10]. Peripheral hyperandrogenism does not correlate with acne. Similarly, lower risk of acne with increased BMI was reported in a Mediterranean study of PCOS women [11].

Some mechanisms have been proposed to explain the reported association of a higher BMI with a lower risk of acne. The increase in adipose tissue, found in overweight patients, is associated with an increase in the enzyme aromatase [12, 13]. Aromatase, an enzyme that converts testosterone to estradiol, can be found in the sebaceous glands [14] and may play a role in removing excess androgens.

On the other hand, a study in 3,274 prepubertal children (aged 6–11 years) in Taiwan, showed an association of increased BMI (overweight or obese) with acne development. However acne was not a frequent finding in this age group (7.3 %), as acne mainly affects adolescents [1]. A high BMI was found to be independent risk factor for inflammatory acne in Ghana (OR: 2.0, 95 % CI: 0.93–4.3). Interestingly, a striking difference was found between the prevalence of acne in rural (0.2 %) and urban schools (12.9 %), which could be explained by differences in diet or other environmental factors [15]. A study of 62 women with PCOS showed a higher risk of acne in obese women. However, the majority of women (88.7 %) included in this study were obese, which makes these results difficult to interpret [16].

**Conclusions**

A limited number of well-designed studies have examined the role of BMI in acne development. Existing data are controversial, with some studies reporting an association of higher BMI with acne, while others report an association of higher BMI with a lower risk of acne.

The measurement of waist-to-hip ratio might be more accurate in assessing the risk of increased BMI with acne. Increased waist-to-hip ratio (android appearance) has been associated with increased testosterone, hirsutism, and infertility [17]. Further studies are needed specifically addressing the intriguing association of BMI with acne development.

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# Sebum Secretion, Skin Type, and pH

# 41

Sang-Woong Youn

## Contents



**Core Messages**

- Increased facial sebum secretion is a common finding in patients with acne.
- Increased sebum secretion does not always match the sites with increased acne lesions.
- Increased sebum secretion is not synonymous with the severity of acne.
- Facial skin type does not predict the risk for acne.
- Skin surface pH (SSPH) is related to sebum secretion and *Propionibacterium acnes*, but the correlation is not significant.
- Using the Sebumeter® is a rapid, convenient method for quantitative sebum measurement.
- Sebum secretion affects the determination of skin type and SSPH but the correlation is weak.
- As prognostic factors of acne, the amount of sebum secretion, facial skin type, and SSPH are not definitive.

## 41.1 Introduction

Increased facial sebum secretion is a common finding during the period when acne commonly develops. Patients with acne frequently think that facial sebum is the cause of their disease and want to lower or remove it completely. Sebum

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is always listed as one of the important factors involved in the pathogenesis of acne. Quantitative measurement of sebum has only recently become possible; currently, we have limited information on the secretion of sebum itself. The cosmetic skin type is another common method of assessing facial sebum secretion and the skin surface pH (SSPH) is partially affected by facial sebum secretion. In this chapter, sebum secretion, facial skin type, and SSPH will be reviewed with regard to their prognostic significance for acne.

## 41.2 Sebum Secretion and Acne

Concerns about sebum secretion are focused primarily on the face; the relationship of sebum secretion and acne at other sites is unclear. For example, the scalp is an area of high sebum secretion; however, comedogenesis of the scalp is rare even in patients with severe acne [1]. The production of increased sebum production in patients with acne is stimulated by androgen release after the development of secondary sex characteristics [2] and coincides with a surge in the onset of acne. In addition, patients with acne frequently have oilier skin than patients without acne [3]. Thus, the increase in sebum secretion, in patients with acne, has been thought to be associated with the development of acne.

### 41.2.1 Sebum Measurement Methods

#### 41.2.1.1 Gravimetric Methods

Gravimetric measurement of sebum directly measures sebum collected from the skin surface using a variety of solvents or sebum-absorbing materials [4]. This is a labor-intensive method and time consuming; therefore, it is not commonly used for measuring sebum in the clinical setting. Solvents such as ether and acetone and absorbent paper such as cigarette paper, bentonite gel, or frosted glass have been used for collecting sebum [4, 5].

#### 41.2.1.2 Photometric Methods

These are indirect sebum measuring methods. Using absorbent plastic tape (Sebumeter®) or microporous hydrophobic polymer film (Sebutape® or Sebufix®), the examiner puts these products in contact with the skin surface. The absorbed sebum changes the transparency of the tape or film; the photometric differences are then measured using special devices. The Sebumeter® displays the amount of sebum as μg/cm$^2$ in a second but does not reflect the distribution of actively secreting follicles. The Sebutape® measures the active follicle distribution, but it cannot measure the amount of sebum directly. The Sebufix® shows the distribution of sebum with the aid of a UV-light camera and calculates the sebum secreting area from the area evaluated [4].

### 41.2.2 Past Trials to Elucidate Sebum Secretion as a Prognostic Factor for Acne

Pochi and Strauss were the first to report on excessive amounts of sebum secretion in patients with acne [6]. They used gravimetric methods with cigarette paper. They applied absorbent cigarette paper to the forehead of patients, waited three hours, and then measured the weight of the collected sebum using certain elusive chemicals. A global three-grade acne grading system was used to evaluate severity. This study demonstrated a relationship between acne and sebum secretion. However, they neglected to evaluate regional variations of facial sebum secretion and focused only on the area of the face with the highest sebum secretion, the forehead. The main limitation of the study was the investigators attempt to match the objective sebum amount with a subjective crude global grading. Harris et al. also used global acne grading based on visual assessment and the use of a 15 % bentonite clay for collecting sebum [7]. However, neither study attempted to match acne lesion distributions and the sites at which the sebum was measured.

### 41.2.3 Sebum Secretion: A Prognostic Factor for Acne Patients?

An increase in sebum secretion is not the sole cause of the development of acne. Temporal

interaction between sebum secretion and *P. acnes* colonization in the pilosebaceous unit is another important aspect of sebum activity in acne pathogenesis. The initiation of sebum secretion and the expansion of *P. acnes* have been observed prior to the development of acne in children. Acne-prone children showed higher sebum output and *P. acnes* density than did children not prone to developing acne. Therefore, delaying the onset of sebum secretion might prevent the development of severe acne [2].

Prior studies on facial sebum secretion in acne patients have demonstrated a definite elevation of sebum secretion measurements on the face [7, 8]. However, the increase in sebum measurements does not directly relate with acne severity. A recent study showed only minimal correlation between the topographical development of acne lesions and the amount of sebum secreted. [3].

Stress is a trigger for aggravating acne. A study on the relationship of psychological stress, sebum, and acne in adolescents [9], showed that the amount of sebum produced was not affected by stress. Therefore, the acne aggravated by stress may not be caused by sebum secretion.

Androgen, stress, or other aggravating factors that can trigger the development of acne are likely not the sole causes of sebum secretion. An individual's basal level of sebum secretion and the changes that occur with sebum secreting conditions differs from person to person. The factors involved in interindividual variations may affect the sebum secretion levels and acne-prone status as well as interfere with the correlation of sebum secretion and acne severity.

## 41.2.4 Reduction of Sebum Production: A New Target for Acne Management

### 41.2.4.1 Cosmetic Ingredients

Skincare products might play a role in controlling sebum production. However, no commercially available cosmetic ingredients have been developed to reduce sebum production. Recently, a 2 % niacinamide preparation was suggested for lowering sebum production [10].

### 41.2.4.2 Superficial Chemical Peeling

Glycolic acid or Jessner's solution peeling are popular superficial peeling methods for acne. Especially for comedonal acne, these methods have been recommended for the exfoliation of occluded pores and the elimination of comedones. Salicylic acid, an ingredient of Jessner's solution, is known to cause comedolysis. Jessner's peeling has been said to lessen facial sebum secretion for days to weeks [11]. However, a recent study on the sebosuppressive effects, one month after peeling, showed that neither of these methods affected sebum secretion [12]. Therefore, the sebosuppressive effects after peeling only lasts for a short time.

### 41.2.4.3 Laser Therapy

Far-infrared laser devices such as the Smoothbeam® (1,450 nm) [13] or the Aramis® (1,540 nm) [14] are directed at the sebaceous glands in the dermis. These devices heat the dermis and damage sebaceous glands; subsequently there is reduction in sebum production and improvement of the acne lesions. However, the effect is temporary and repeated therapy is needed to prolong the acne-free period.

### 41.2.4.4 Photodynamic Therapy (PDT) for Acne

δ-aminolevulinic acid (ALA) PDT is another new therapeutic measure targeted to the pilosebaceous unit and *P. acnes*. A pilot study of 15 patients showed that sebum secretion did not decrease at 1, 2, 3, or 10 weeks after 1 PDT [15].

## 41.2.5 Future of Sebum Secretion Control

Isotretinoin and some anti-androgen preparations inhibit sebum production. However, they may have many side effects. New medications for sebum control are needed. Peroxisome proliferators-activated receptors (PPARs) is a transcriptional factor involved in adipogenesis [16] and in sebocyte differentiation [5]. Sebocyte differentiation and lipid metabolism are critical to sebum production. Therefore, controlling PPAR activity could provide a novel therapeutic approach to the control of acne.

## 41.3 Skin Type

### 41.3.1 Facial Cosmetic Skin Type

Conventional classification of facial skin type is based on personal experience with cosmetics use. This classification approach was used before the development of facial sebum measuring methods. Oily, normal, dry, and combination skin types are the generally accepted categories of facial skin type. The characteristics of each skin type are listed in Table 41.1.

### 41.3.2 Classifying Facial Skin Type

Some trials attempted to develop guidelines for skin type classification using bioengineering devices [17–19]. The trials are not yet definitive due to confounding factors. There are discrepancies between subjective descriptions and objective measurements [18]. Seasonal variation in sebum secretion can alter the skin type in some individuals; [19] for example, the Combination type, which is characterized by a mixed oily T-zone with dry U-zone, is sometimes confused with a simple oily skin type.

**Table 41.1** Characteristics of cosmetic facial skin type

| Cosmetic skin type | Characteristics |
|---|---|
| Oily | Enlarged pores<br>Shiny skin<br>Thick, dull colored<br>Frequent pimples<br>Easily peel-off after make-up |
| Normal | No visible pores<br>Normal tone<br>Smooth texture<br>No pimples |
| Dry | Invisible pores<br>Feels tightness after washing<br>Bright tone<br>Focal scales<br>Fine wrinkles around eyelid, lip and cheeks |
| Combination[a] | Greasy T-zone (Forehead, nose, chin)<br>Dry U-zone (cheeks, eyelids) |

[a]Combination skin type has the mixed characteristics of oily T-zone and dry U-zone

### 41.3.3 Facial Skin Type and Acne

Although the facial skin type definitely depends on facial sebum secretion, the objective skin types in individuals with acne and without acne are not significantly different [20]. A crude four-point scale for skin type classification is usually applied. To explain the prognostic effects of skin type on acne, the concept of facial skin type should be well structured and well designed to detail regional phenomenon on the face.

## 41.4 Skin Surface pH

### 41.4.1 Factors Influencing Skin Surface pH

SSPH reflects the condition of the stratum corneum, sebum, or sweat secretion, living microorganism, and exogenous materials applied onto the face. Factors influencing the SSPH are classified as endogenous and exogenous factors. Endogenous factors include age, anatomic sites, ethnic or gender differences, sebum, sweat, and skin diseases. Exogenous factors include skincare products, topical medications, occlusive dressings, and skin irritants [21].

### 41.4.2 Skin Surface pH and Acne

With respect to acne, differences in the amount of sebum secretion and *P. acnes* colonization likely affect the SSPH. The excreted sebum on the skin surface has a moderate effect on the SSPH [21]. Sebum secretion in T-zone is greater than in U-zone, and SSPH levels are higher in U-zone than in T-zone. An inverse correlation has been reported between sebum levels and SSPH especially in high sebum-secreting areas such as the forehead and chin in women [22].

*P. acnes* produces propionic acid, acetic acid, and free fatty acids; these acids might alter the SSPH. At the same time, especially in inflammatory acne, damaged hair follicles cause the loss of buffers in the tissue that change SSPH. Therefore, the overall effect of *P. acnes* on the SSPH cannot

be measured [15]. Kim et al. studied the sebum secretion and pH in subjects with and without acne. The SSPH in acne patients was slightly higher than in the subjects without acne; however, these differences were not statistically significant. The SSPH was found on all sites of the face, in high and low sebum-excreting zones.

Currently, a correlation between SSPH and acne severity has not been confirmed. SSPH is more important to the cosmetics industry than it is to dermatology practice. However, management of acne with cosmeceuticals is increasing in dermatology practice.

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# Lipids in Serum and Sebum

# 42

Emanuela Camera and Mauro Picardo

## Contents



**Core Messages**

- Even if the sebaceous gland has autonomous lipid synthetic capacity and the expression of lipogenetic enzymes has been demonstrated in the sebaceous gland or in sebocyte cell lines, several data indicate a possible correlation between serum and sebum lipids.
- The sebaceous gland can sequester circulating lipids and remodel the sebaceous type. Extent of lipid biotrasformation in sebocytes has not been completely clarified yet.
- Modulation of HMG-CoA reductase activity, the rate-limiting enzyme in the cholesterol biosynthetic pathway, is modulated in sebocytes in vitro by exogenous supply of cholesterol.
- Pharmacological treatments of hyperlipidemia and diabetes with the PPARs ligands enhance the sebum secretion, indicating that the systemic lipid metabolism has a similar impact to the mechanism of control of the sebaceous gland activity.
- Retinoids inhibit the sebaceous secretion by affecting the peripheral distribution and sequestration of triglycerides and cholesterol.
- Conditions of altered proportion of serum lipoproteins are associated with acne incidence or modification of sebum

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composition, i.e., lower apolipoprotein A1 serum levels correlate with a higher risk to develop acne, whereas in the hyperlipoproteinemia (type IV) proportion of wax and cholesterol esters in sebum is significantly higher than the normality.
- Dietary deficiency of essential fatty acids can have an impact on acne incidence.

## 42.1 Introduction

The influence of the general lipid metabolism on the sebum synthesis in the sebaceous gland is still an underinvestigated area of the pathogenetic mechanisms of acne development. The evidence that acne is prevalently observed in the western world populations implies a role of dietary habits, energy supply, and food complexity as co-causative factors of the disease [1]. Moreover, lipid metabolism is not a mere processing of the food introduced with the diet, but it is the result of the complex interaction between dietary habits and genetic background. This complex interaction affects the lipid uptake from the gastrointestinal tract, as well as the biosynthesis of lipoproteins in the liver and their sequestration in the peripheral tissues, which likely include skin.

Lipid metabolism in the skin has recently gained attention due to the consideration of skin as a metabolic organ and thus as a relevant player in the maintenance of the body homeostasis. Furthermore, unlike the adipose tissue that stores lipids for energetic purposes, skin rather remodels lipid substrates to build up specific functional structures like the impermeable barrier and the sebaceous film. The question arising is whether the bloodstream feeds the biosynthetic pathways of sebaceous lipids and whether the interplay between serum and sebaceous lipids can be specified.

## 42.2 Sebaceous Gland Function and Sebum Composition

Analyses of sebum have shown how complex is its composition and how many differences exist with the lipid classes present in the blood. In sebum, triglycerides and fatty acids account for the predominant proportion together (57.5 %) followed by wax esters (26 %) and squalene (12 %). The least abundant lipid in sebum is cholesterol, with which its esters, accounts for the 4.5 % of total lipids [2].

Squalene and wax esters are the most characteristic products of the sebaceous lipid secretion and coincidentally they correspond to the major components supplying skin with protection. Squalene is an intermediate product in the biosynthetic pathway leading to cholesterol and can also be found in the blood as a result of a lipid leakage from the cholesterol biosynthetic process. However, levels reached in sebum are far more abundant than those in serum or plasma [3]. Likely, sebocytes have evolved a mechanism that halts the cholesterol biosynthesis and favors the accumulation of squalene. Additionally, sebaceous secretion displays other specific lipids, such as fatty acids presenting unshared unsaturation positions and side-chain branches.

There is evidence that sebocytes possess a full competence for lipid synthesis, and studies performed on the incorporation of radiolabeled acetate have demonstrated a de novo lipid synthetic capacity of the sebaceous gland [4]. However, there is no conclusive research clarifying to which extent the sebaceous gland synthesizes sebum lipids *de novo*, uptakes preformed lipids form the bloodstream, or remodels lipid precursors.

## 42.3 Uptake of Circulating Lipids

Lipids circulate in the blood embedded in specialized supramolecular structures mostly synthesized in the liver, known under the name of lipoproteins, formed by assembling various lipids with apolipoproteins. Their purpose is

distributing lipids of different classes among the receiving peripheral tissues, which express the lipoprotein receptors. The sebaceous gland and the human sebocyte cell line SEB-1 have proven to express the LDL receptors at mRNA levels [5].

Cutaneous alterations deriving from the sebaceous gland atrophy, as well as hyperlipidemia, are phenomena associated with the overexpression of human apolipoprotein C1 in mice, indicating that the uptake of circulating lipids plays a role in the sebogenesis [6]. Release of exogenous fatty acids from lipoproteins in the recipient cells is partly undertaken by lipoprotein lipase, which has been shown to be expressed in the human sebaceous gland at the mRNA level [5]. Thus, cells uptake fatty acids mostly deriving from the extracellular milieu, whereas de novo synthesis occurs at lesser extent.

To be metabolized, fatty acids have to cross the plasma membrane and to be activated to their CoA thioesters. Although free diffusion through the membrane cannot be excluded, free fatty acids are mostly translocated to the cytoplasm through an active mechanism involving a six-member Fatty Acids Transport Protein (FATP) family. FATP4 is found highly expressed in the human sebaceous gland and colocalizes with Nile Red-stained lipid droplets [7]. Multiple functions of FATP have been recognized. In particular, FATP4 is a fatty acid transporter and a very long-chain acyl-CoA synthetase [8]. These findings imply that sebaceous glands have the capacity to sequester dietary cholesterol and fatty acids from their environment, namely endogenously derived lipid sources, and that plasma lipid and lipoprotein concentration may have a role in determining sebum lipid composition.

## 42.4 Plasma Lipids, Lipoproteins, and Apolipoproteins in Acne

Studies comparing the composition of circulating lipids with that of sebum, are only a few and not conclusive. Some indirect evidence of the influence exerted by the systemic lipid metabolism on sebogenesis is provided. Studies on adult males with hyperlipoproteinemia (type IV) have shown that the excretion rate of the skin surface lipids is similar to those observed in normolipemic individuals; however, the proportion of wax and cholesterol esters is significantly higher [9].

Lower serum level of apolipoprotein A1 represents a risk factor for the development of acne, as it was found to be significantly lower in female acne twins. By contrast, HDL, cholesterol, and triglycerides were not modified [10]. In the dislipidemic disease, decreased apolipoprotein A1 levels associate with low plasma HDL in the hypoalphalipoproteinemia. Proteomics of plasma in subjects consuming supplements of α-tocopherol (134 or 268 mg/day) has revealed that proapolipoprotein A1 and apolipoprotein A1 is time and dose-dependently upregulated [11]. Besides, α-tocopherol is delivered to the skin surface through the sebaceous secretion [12, 13]. Decreased vitamin E level has been described in sebum of acne patients and unpublished observations gathered in our clinical practice seem to be in favor of the effectiveness of α-tocopherol in ameliorating symptoms in mild to moderate acne.

In patients with severe nodular cystic acne HDL-cholesterol, apolipoprotein A and the hepatic lipoprotein lipase were significantly lower than unaffected controls or subjects with acne vulgaris. The effectiveness of isotretinoin in improving cystic acne lesions is paralleled by the elevation of HDL-cholesterol and hepatic lipoprotein lipase at levels comparable to the normality [14]. However the chronic rise of cholesterol, triglycerides, very low density (VLDL), and low density lipoprotein (LDL) cholesterol following oral retinoids may predispose to atherosclerosis [15]. Studies on the kinetic of radiolabeled triglyceride-rich emulsion containing radioactive cholesteroyl-oleate and triolein injected intravenously showed that patients using isotretinoin had a decreased peripheral distribution of triglycerides and cholesterol demonstrated by their prolonged permanence in the plasma and suggesting that the decreased sebum secretion observed in patients under retinoid therapy can be partly ascribed to the inhibition of cholesterol and triglycerides sequestration by peripheral tissues, including the sebaceous gland [16].

## 42.5 Pathways of the Biosynthesis of Sebum Components

Enzymes presiding the pathway that leads to cholesterol synthesis and those involved in the sequestration and processing of lipids to form long-chain fatty acids and their ester derivatives like glycerides, cholesterol esters, and wax esters have been found and characterized in the human sebaceous gland and sebocytes. Moreover, regulation of the lipogenetic enzymes by the supply of exogenous lipids has been demonstrated.

### 42.5.1 Cholesterol and Squalene Metabolism

Cholesterol and squalene share the first steps of their biosynthesis in the sebaceous gland. 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is the rate-limiting enzyme for the *de novo* cholesterol synthesis, is fairly active in the human sebaceous gland [5]. Expression and modulation of HMG-CoA synthase, which is upstream the HMG-CoA reductase, has been investigated in the sebaceous gland [17]. Nevertheless, cholesterol itself does not take part in sebogenesis, as its synthesis is interrupted at the level of squalene, which instead accumulates in the lipid droplets. Squalene synthase catalyzes head-to-head condensation of two molecules of farnesyl pyrophosphate, with reduction by NADPH, to yield squalene. Expression of squalene synthase at mRNA levels and activity can be detected in sebocytes in culture [18]. Cholesterol enters the cells by the LDL receptor-mediated endocytosis causing inhibition of HMG-CoA reductase transcription and translation and stimulation of the enzyme degradation [19]. As HMG-CoA reductase is regulated by the cholesterol levels in the sebaceous gland environment, cholesterolemia could have some impact on the squalene levels in the sebum.

In humans 26–46 % of skin surface cholesterol is derived from the bloodstream [20]. However, the amount of skin cholesterol has no apparent relationship with hypercholesterolemic or normocholesterolemic conditions of subjects [21]. Nevertheless, sebaceous glands respond to higher levels of lipoproteins by lowering the lipidogenic capacity through inhibition of the HMG-CoA reductase activity, indicating intracellular delivery of exogenous cholesterol through interaction with the LDL receptor [5]. Interestingly, the enzymatic activity of HMG-CoA reductase varies considerably in the apparently healthy skin of acne-unaffected individuals (CV = 30–46 %). Moreover, the declined sebum production with age can be at least in part ascribable to a lower activity of HMG-CoA reductase in older subjects.

### 42.5.2 Enzymes Involved in the Metabolism of Fatty Acids

In sebum, fatty acids are characterized by a large diversity, since linear or branched side chains, long side chains with odd or even carbon number, and unusual position of unsaturations are represented. In humans, fatty acids synthase (FAS) is highly expressed in tissues specialized in the lipid metabolism, including the sebaceous gland [22]. Indeed, sterol regulatory element-binding proteins (SREBPs) affect the expression of genes for both fatty acid and cholesterol synthesis. In particular, SREB1 is increased in SEB-1 human sebocyte in culture following stimulation with insulin-like growth factor (IGF-1) [23]. FAS gene is a target of Liver X Receptor (LXR), which is a member of the nuclear receptors superfamily [24]. The sebaceous gland uses acetate, proprionate, isobutyrate, isovalerate, and 2-methyl-butyrate as starters to produce straight-even, straight-odd, iso-even, iso-odd, and anteiso-odd chained fatty acids by extension with the addition of 2-carbon moieties derived from the malonyl-CoA, whose synthesis is catalyzed by acetyl-CoA carboxylase (ACAC) [17]. Branched fatty acids are found collectively as a specific marker of the sebaceous lipid production, being absent in plasma and other tissues, although little is known on the enzymes involved in their biosynthetic pathways. They account for a low percentage of the total fatty acids in the sebum. Fatty acid desaturase 2 (FADS2) or Δ6-desaturase is the major desaturase found

**Table 42.1** Enzymatic activities involved in sebum production

| Enzyme | Substrates | Product |
|---|---|---|
| 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthase | Acetyl-CoA + Acetoacetyl-CoA | HMG-CoA |
| HMG-CoA reductase | HMG-CoA | Mevalonic acid |
| Acetyl-CoA carboxylase (ACAC) | Acetyl-CoA + $CO_2$ | Malonyl-CoA |
| Δ6-desaturase or fatty acids desaturase-2 (FADS2) | linoleate, αlinolenate, palmitate | Δ6-monounsaturated fatty acids |
| Δ9-desaturase or stearoyl-CoA desaturase (SCD) | Long-chain fatty acids | Δ9-monounsaturated fatty acids |
| Acyl: CoA:diacylglycerol acyltransferase (DGAT) 1 and 2 | Diacylglycerol and acyl-CoA-derived fatty acids | Glycerol esters |
| Acyl-CoA wax alcohol acyltransferase (AWAT) 1 and 2 | Long-chain alcohol and acyl-CoA-derived fatty acids | Wax esters |
| Acyl-CoA cholesterol acyltransferase (ACAT) 1 and 2 | Cholesterol and acyl-CoA-derived fatty acids | Cholesterol esters |

in the sebaceous gland, wherein it preferentially converts palmitic acid (16:0) to sapienic acid (16:1, Δ6), which is unique to the human sebum and represents ca. 25 % of the total fatty acids. Elongation of sapienic acid by 2-carbon unit and further unsaturation leads to the formation of sebaleic acid (18:2, Δ5,8), which is also specific for human sebum. In other tissues, the Δ6-desaturase enzyme preferentially converts the essential fatty acids linoleate (18:2, Δ9,12) and α-linolenate (18:3, Δ9,12,15) into γ-linolenate (18:3, Δ6,9,12) and stearidonic acid (18:4, Δ6,9,12,15), respectively. Δ6-desaturase is detected in differentiated sebocytes with a full lipid synthetic capacity occupying the suprabasal layers of the sebaceous gland, providing a functional marker of activity and differentiation of sebocytes [25] (Table 42.1).

High sebum secretion rate is associated with increased percentage of monounsaturated fatty acids observed in acne patients and during puberty, indicating a sebocyte-specific metabolism [26, 27]. Accumulation of some Δ9 isoforms of monounsaturated fatty acids may occur in undifferentiated cells in the basal layer of the sebaceous gland. During the process of differentiation, sebocytes translate toward the core of the sebaceous gland, and Δ6 unsaturated fatty acids progressively accumulate and dilute the Δ9 lipids content to less than 0.5 %. Immunoreactivity of Δ9-desaturase or stearoyl-CoA desaturase (SCD) has been demonstrated in the human sebaceous gland and immortalized sebocytes, where it is localized in the cytoplasm [28–30].

SCD-1 is the rate-limiting enzyme involved in the synthesis of monounsaturated fatty acids, and in mice SCD-1 activity is associated with plasma triglyceride levels. It preferably oxidizes palmitoyl-CoA and stearoyl CoA at the carbons 9–10 forming palmitoleyl-CoA and oleoyl-CoA, respectively. This gives the enzyme Δ9-desaturase its name [31]. The fatty acid desaturation index (the plasma ratio of 18:1/18:0) has been used as a marker of SCD-1 activity to investigate the relationship of SCD-1 to familial combined hyperlipidemia (FCHL). However, the human sebaceous gland lacks SCD-1 activity together with Δ9-desaturase activity according to unpublished data from Ge et al. [25].

Linoleic acid is considered to be directly involved in the sebaceous lipid synthesis with its levels in wax esters being significantly reduced in acne patients [32]. Moreover, experimental data suggest that it is incorporated in the epidermal lipids of the infundibulum. In experimental models, linoleic acid is preferentially transformed into two carbons precursors in the sebaceous gland, through the activation of β-oxidation, which yields acetyl-CoA. The latter product feeds the biosynthetic pathway, which leads to squalene and wax esters formation [33]. Since linoleic acid is an essential fatty acid, its plasma levels likely regulate its concentration in the sebocytes.

For the synthesis of very long-chain fatty acids present in a concentration higher than those observed in plasma, skin is equipped with three elongases subtypes, of which one allows elongation of 16–18 carbon long fatty acids, whereas the other two lead to the synthesis of very long fatty acids [34].

### 42.5.3 Glycerol, Wax, and Sterol Esters Synthesis

Acyl CoA:diacylglycerol acyltransferases (DGAT) 1 and 2 are the key enzymes that catalyze the final step in the major pathway of triglyceride synthesis by using diacylglycerol and fatty acyl CoA as substrates [35]. Triglyceride are considered to be a nutritional supply for *Propionobacterium acnes*. DGAT-dependent triglyceride synthesis can be targeted to pharmacologically reduce the sebum production. The flavoinoid nobiletin decreases the amount of triglycerides in the sebaceous lipids produced by insulin-differentiated hamster sebocytes, in a fashion comparable to 13-cisRA and *all-trans* (at)RA [36].

Wax monoesters account for the major component of sebum synthesized by wax synthase enzymes, which conjugate a long-chain fatty alcohol to a fatty acyl-CoA by forming an ester bond. Thus, it is likely that wax esters are produced in a two-step biosynthetic pathway involving a fatty-acyl-CoA reductase and wax synthase enzymes.

Wax synthase exhibits selectivity toward fatty acids for their incorporation in wax esters. Palmitic acid is preferentially included in wax esters over its monounsaturated congener palmitoleic acid (16:1, Δ9) and the elongated product stearic acid (18:0), which in turn is preferred over oleic acid (18:1, Δ9) for wax esters synthesis. Among members of the diacylglycerol acyltransferase 2 (DGAT2) gene superfamily, two human acyl-CoA wax alcohol acyltransferase (AWAT 1 and 2) have been identified, which are expressed in the human skin. The confinement to the sebaceous gland has been proven by in situ hybridization with probes for AWAT 1 and 2, with the latter one primarily expressed in the cytoplasm of undifferentiated peripheral sebocytes [37].

Esterification of cholesterol seems to be an evolutionary mechanism favoring the storage of sterols in the cytoplasm. The enzymes that catalyze sterol esters formation are acyl-CoA cholesterol acyltransferase (ACAT) 1 and 2. ACAT1 is highly expressed in the sebaceous gland, where it allows for the incorporation of cholesteryl esters into cytoplasmic lipid droplets. On the other hand, ACAT2 is mainly involved in the lipoprotein assembly in the enterohepatic system [38].

## 42.6 Nuclear Hormone Receptors in the Regulation of Lipid Metabolism

The identification of the role played by peroxisome proliferator-activated receptors (PPARs) in the cell growth differentiation and lipid metabolism of sebocytes has indicated a correlation between sebum and peripheral lipid metabolism [39].

Among the different subclasses of PPARs tagged with α, δ, and γ [39–41], PPARα plays a role in the cell uptake and β-oxidation of fatty acids, whereas PPARγ has a more pronounced effect on the control of lipidogenesis in different cell types, including sebocytes. Some data have been obtained by evaluating in vivo the sebum secretion rate of patients treated with PPARs ligands. Fibrates, which are PPARα ligands, are used in the treatment of hyperlipidemic disorders as they lead to the reduction of plasma triglycerides by increasing their peripheral sequestration, whereas thiazolidinediones, which are PPARγ ligands are administered to control diabetes. In adult patients undergoing hypoglycemic and hypolipidemic therapies, enhancement of the sebum secretion has been observed without clinical acne. Although similar intracellular pathways control both systemic and sebocyte lipid metabolism, the increased sebum secretion per se does not prompt acne appearance, further supporting the multifactorial feature of this disease. However, further investigations are required to

define the effects of pharmacologically induced sebum production in young subjects, where other factors can potentially interact with the increased seborrhea. In contrast, PPARα and PPARγ ligands inhibited the sebaceous lipogenesis of freshly isolated or cultured sebaceous gland [41].

## 42.7 Dietary Fatty Acids and Acne

In acne patients, the skin surface lipids, a mixture of epidermal and sebaceous ones, present a diminished level of linoleic acid, which is uptaken from the diet [42]. This deficiency of essential fatty acids is believed to play a role in the control of keratinization of the follicular epithelium and the inflammatory response. Intake of ω-6 and ω-3 polyunsaturated fatty acids (PUFAs) may affect the inflammatory pathways activation.

The western diet typically provides a higher supply of ω-6 over ω-3 PUFAs, with a ratio between 10:1 and 20:1 [43, 44], which is higher than the 2:1 ratio found in the non-westernized diet [1]. Epidemiological studies have shown that increasing the intake of ω-3 fatty acid through a diet rich in fish and seafood results in lower rates of acne [43]. Ω-3 fatty acids exert important anti-inflammatory effects through their inhibitory activity on the pro-inflammatory cytokines secretion and the leukotriene $B_4$ ($LTB_4$) synthesis, mechanisms demonstrated to be beneficial for acne [45–47].

Arachidonic acid, the major dietary ω-6 PUFA, is the precursor of $LTB_4$ in the lipoxygenase (LOX) pathway. Studies designing diets lower in saturated fatty acids and higher in polyunsaturated fatty acids and daily fibers for investigating their effects on acne symptoms have focused on the consequent glycemic load and protein levels, whereas changes in the blood lipoproteins and saturated vs. unsaturated lipids in serum and sebum following the above interventions have been mostly overlooked [48]. Effects of dietary fats were indirectly investigated in study pointing out a role played by chocolate in triggering acne lesions. As a pseudo-chocolate bars with 28 % partially hydrogenated vegetable oil were used as controls, no differences with chocolate bar were found. Fats in the pseudo-chocolate bars likely masked effects of chocolate due to competition with the prostaglandin production and altered contribution to inflammation [49].

From a limited study conducted in ten subjects, it was unlikely that the fluctuations observed in the sebum fatty acid composition, including branched ones, occurred as changes in the diet or the metabolism as the monitoring time was over 2 months. Instead variability was observed between the different subjects suggesting a interindividual difference in the processing of this particular class of sebaceous lipids [50]. A larger twin study investigating the sebum secretion in 40 pairs of adolescent acne twins found higher correlation in monozygotic twins vs. dizygotic twins [51]. Differences in the iso-even fatty acids proportion were very small in identical twins, whereas inter-pairs differences were comparable to the non-twin population, suggesting that the synthesis of branched fatty acids is under genetic control [52].

**Conclusions**

There is a dated controversy whether lipids, especially in the form of fatty acids and triglycerides, can be sequestered unchanged by sebocytes from the bloodstream and used as starting substrates for the sebum component synthesis.

The interplay between plasma/serum levels of cholesterol, triglycerides, fatty acids, phospholipids, and the sebum composition and secretion rate has been little investigated. Little evidence demonstrates a role of the systemic pathways of lipid synthesis, distribution, and sequestration, in the sebum secretion levels and acne development. A number of sebogenic enzymes have been shown to be expressed in the sebaceous gland or sebocytes; however, the comprehensive elucidation of the sebum biosynthetic pathways awaits further investigations. Especially the pathways leading to the formation of lipids, which are typically sebaceous, such as branched fatty acids and fatty acids with unshared unsaturation positions, remain to be elucidated. The evidence recently accumulated on the lipid synthesis capacity of sebocytes in culture indicates pathways of lipid synthesis as suitable targets in the pharmacological treatment of acne.

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# Part VII

# Clinical Evaluation of Acne

# The Leeds Acne Grading Technique

# 43

Alison M. Layton

## Contents



**Core Messages**

- The aim of evaluative research is to determine whether one treatment is superior to another and ultimately to guide clinicians towards the therapy most likely to benefit the patient.
- Reproducible methods of assessment are essential in evaluating treatments and in turn disseminating accurate trial results to Healthcare Professionals.
- There is a large array of evaluation tools currently in use for acne. Many of these are not validated and this in turn prohibits good secondary analysis of trial data and also complicates the interpretation of individual study results.
- There are difficulties in developing a single gold standard outcome measure for the use in acne vulgaris and the relative merits of lesion counting versus severity grading remain open to debate.
- The development of the more valid and reliable outcome measures for acne should be seen as a priority supported by the development of more innovative methods of assessing acne.
- Lesion counting is theoretically the most accurate and sensitive method of evaluating acne to date, but it is extremely time consuming. There is a degree of variability between different

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assessors and the same assessor at different time points.
- The Leeds technique is to date the most widely used Global acne grading system and represents a photo-numeric grading scale.

## 43.1 Introduction/Definitions

The ultimate goal of a medical intervention is to induce a positive change in the patient's health status. Outcome measures are defined as a change in the patient's current and/or future health status. There is a significant lack of standardisation of methods used to assess acne vulgaris. Reviews have highlighted inconsistencies in evaluation methods used in acne trials [1, 2].

To date there is no firm consensus in terms of what is the most accepted assessment regime for acne and with the frequent introduction of novel scales the problem is compounded.

The lack of methodological consistency influences the interpretation of studies examining relative efficacy of various treatments.

The Leeds technique is currently the most widely used grading system for acne and is based on comparisons with photographic standards rather than qualitative descriptions.

The original set of photographs was published in 1984 [3] with a second set appearing in 1989, and the scale was completely revised in 1998 [4].

## 43.2 Methods

In the original assessment, the scale assigned grades from 0 representing no acne to 10 representing the most severe Leeds grade of acne, with 7 sub-groups at 0.25 intervals between grades 0 and 2, whilst the revised version uses only whole number grades from 0 to 12. The authors also used lesion counts which defined active lesions from less active lesions when conducting clinical trials.

The back and chest are evaluated separately in these grading systems and a set of standards is supplied with the 1998 version [4]. In this latter version, grading system for non inflammatory lesions is also included based on photographic reference points (figures of acne grading).

The Revised Leeds technique embraces experience over 15 years whereby the team photographed many patients with acne affecting the face and trunk. Approximately, 1,000 photographs were categorised into a rank order of severity.

The photographs were ranked by a panel consisting of the authors and a team of four acne assessors.

The shortlist of photographs was then subsequently ranked on four further occasions by the authors. The criteria for the severity of the acne included extent of inflammation, range of size and inflamed lesions and associated erythema.

## 43.3 The Photo-Numeric Scale

Photography captured predominately inflammatory lesions. Thus, the overall assessment of acne was based on the number of inflamed lesions and known inflammatory intensity.

Figures 43.1a–m demonstrate an extensive range of facial acne grades of increasing severity numbered 1–12 with a grade 1 (Fig. 43.1a) being the least severe grade and 12 (Fig. 43.1m) being the most severe.

Figure 43.2a–h demonstrates patients with acne on the back arranged in order of increasing severity to produce a grading system (1–8) for acne on the back.

Figure 43.3a–h demonstrates acne on the chest showing increasing intensity in acne, grades from 1 to 8 for acne on the chest.

This grading scale does not take into account the patients who have a high density of acne in a disproportionate geographical area, e.g., acne localised to the chin or the nose or patients who have acne in a nevoid distribution.

In addition, those patients who have large, asymmetrical lesions will not necessarily be captured within this grading system. However, the authors suggested that patients with severe nodular acne should be considered in the higher grading ranges.

It is recognised that many patients with acne have a mixture of non-inflammatory and inflammatory lesions. However, a small proportion of patients will have predominately non-inflamed lesions.

The revised Leeds acne grading scale does not take non-inflamed lesions into account as such. However, a separate scoring system (Fig. 43.4a–c) shows three patients with predominately non-inflamed lesions of increasing severity that could be used as the basis for the grading system (grade 1–3) for non inflamed acne.

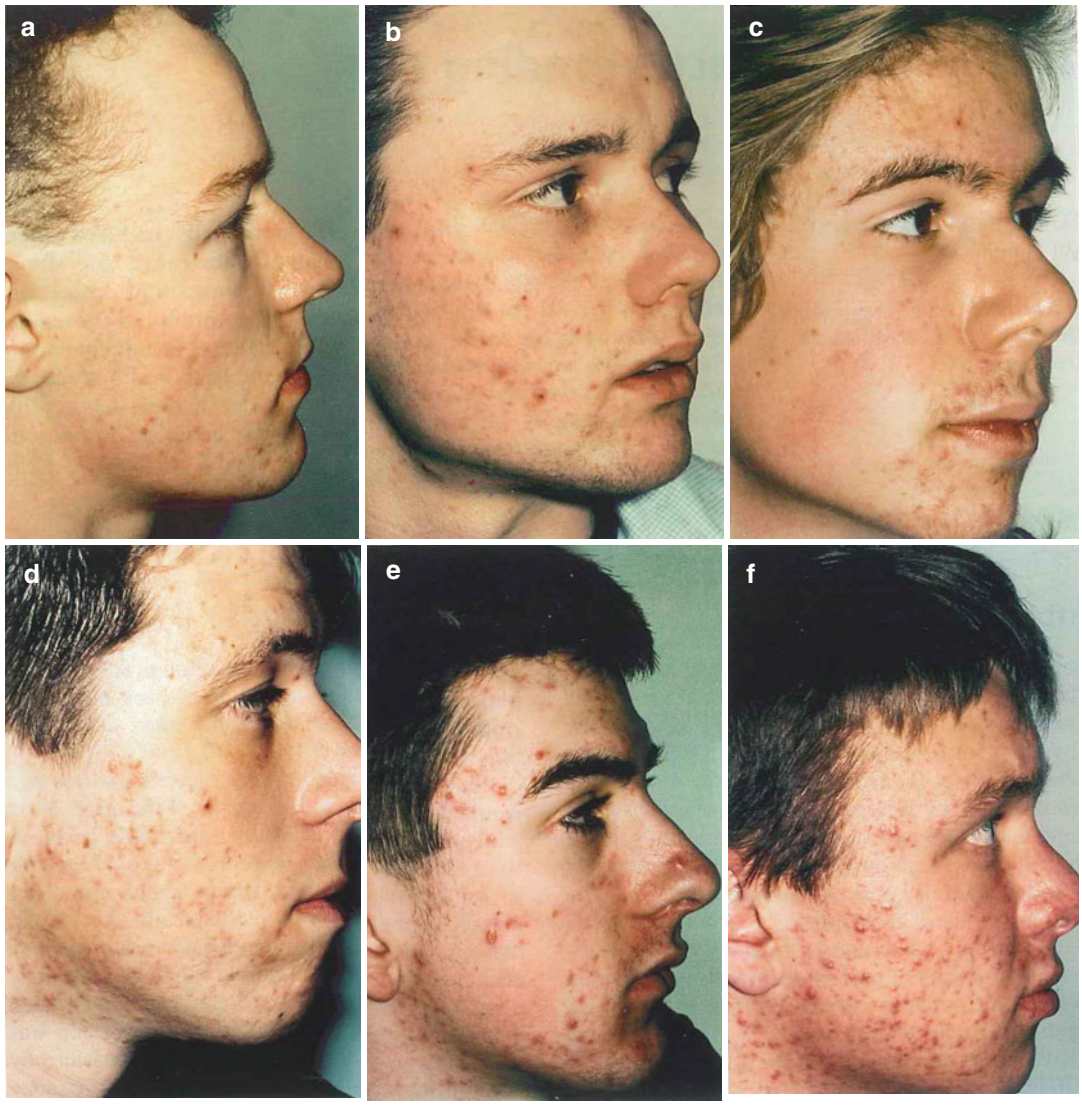



**Fig. 43.1** Grades of facial acne: (**a**) grade 1; (**b**) grade 2; (**c**) grade 3; (**d**) grade 4; (**e**) grade 5; (**f**) grade 6; (**g**) grade 7; (**h**) grade 8; (**i**) grade 9; (**j**) grade 10; (**k**) grade 11; (**l**) grade 12; (**m**) nodulocystic acne

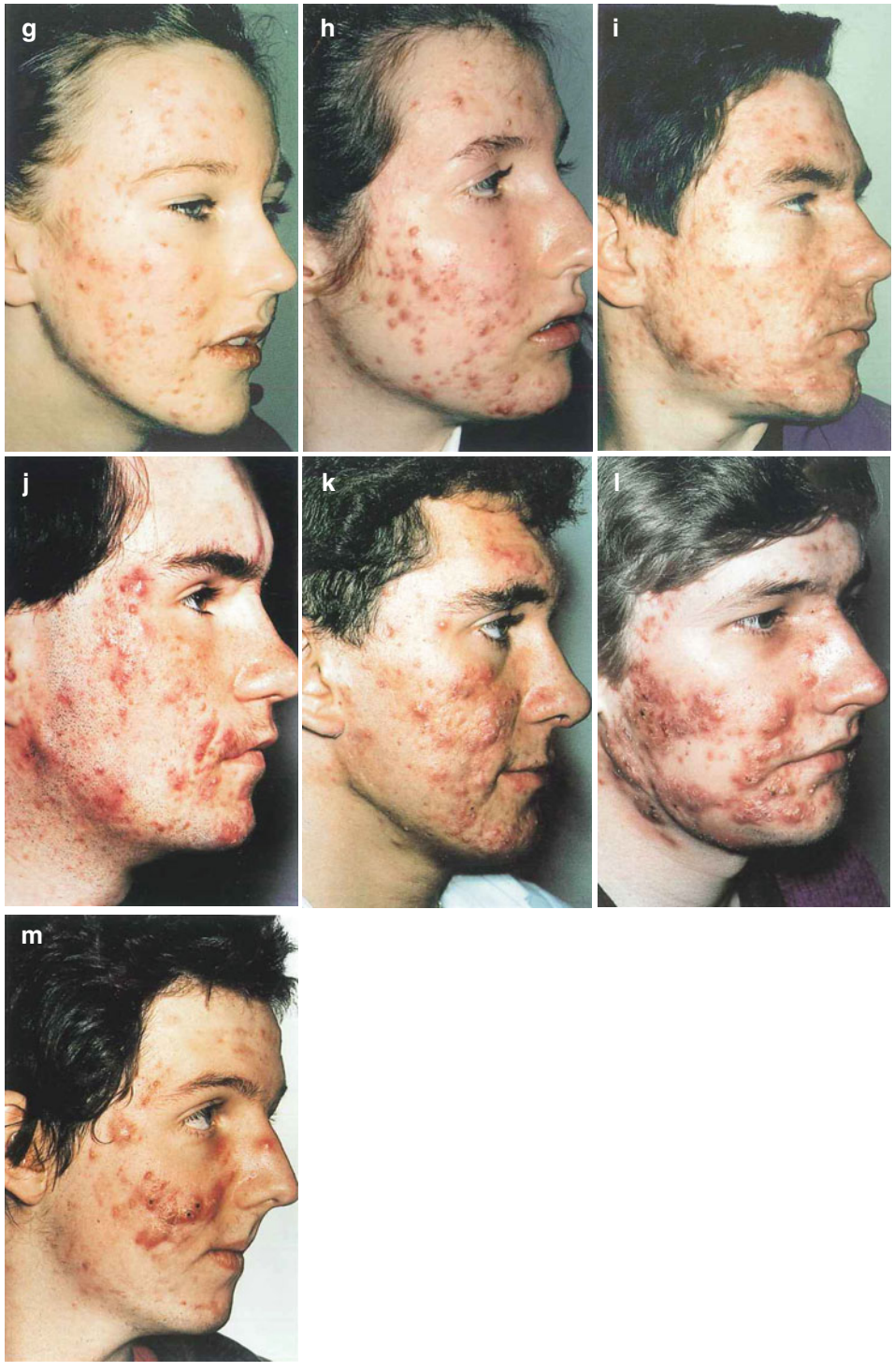



**Fig. 43.1** (continued)

## 43.4 Quantitative Evaluation of Lesions and Reliability

The Original Leeds system sub-divides lesions into non-inflammatory lesions (open and closed comedones), superficial inflammatory lesions (papules and pustules), and deep inflammatory lesions (nodules and macules). The degree of erythema is also used to sub-divide the lesions into active and less active. Lesion counting is used in the context of clinical trials but is time consuming and can lead to significant variability between different assessors and the same assessor at different times.

The Original published paper contained some preliminary reliability testing using two assessors and 432 patients.

The intra-assessor variation showed that whilst exact agreements only occurred in 22–48

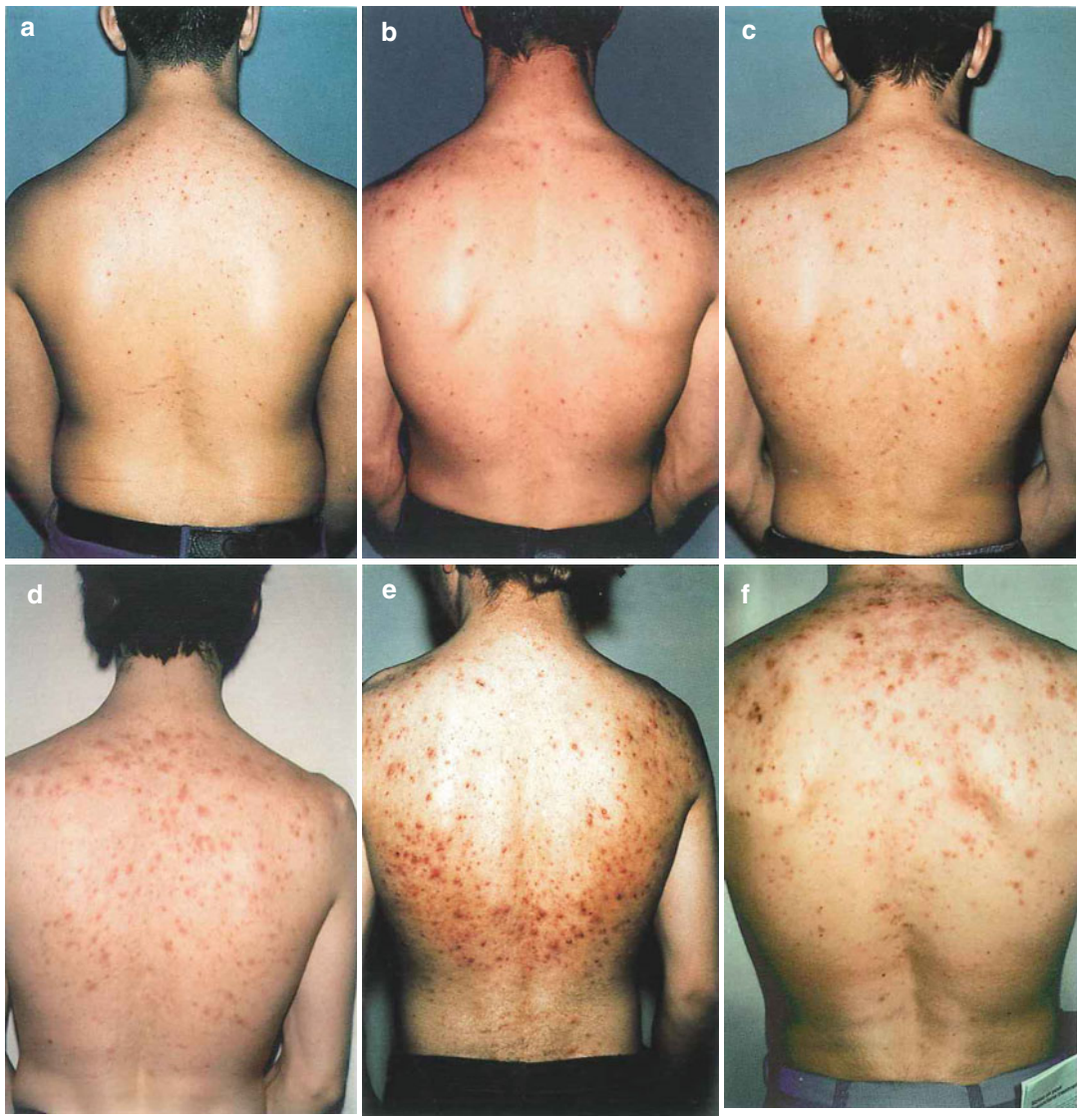
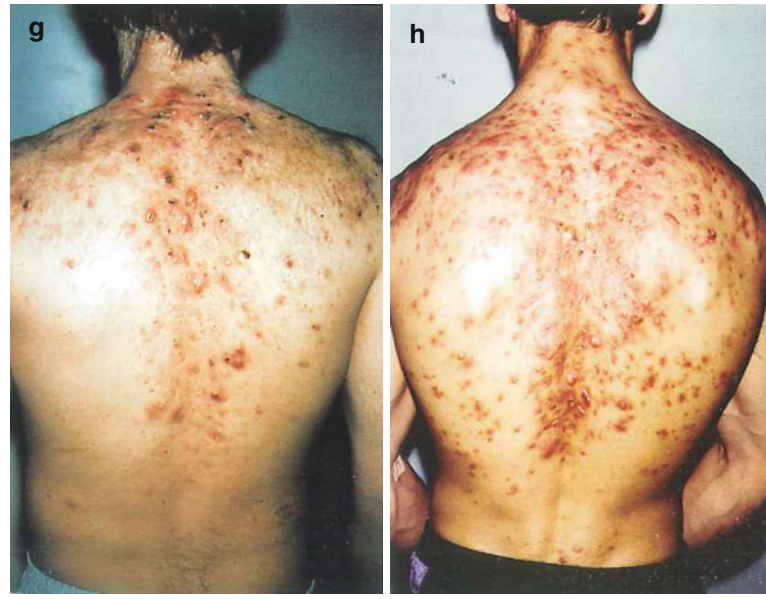



**Fig. 43.2** Grades of acne on the back: (**a**) grade 1; (**b**) grade 2; (**c**) grade 3; (**d**) grade 4; (**e**) grade 5; (**f**) grade 6; (**g**) grade 7; (**h**) grade 8

**Fig. 43.2** (continued)



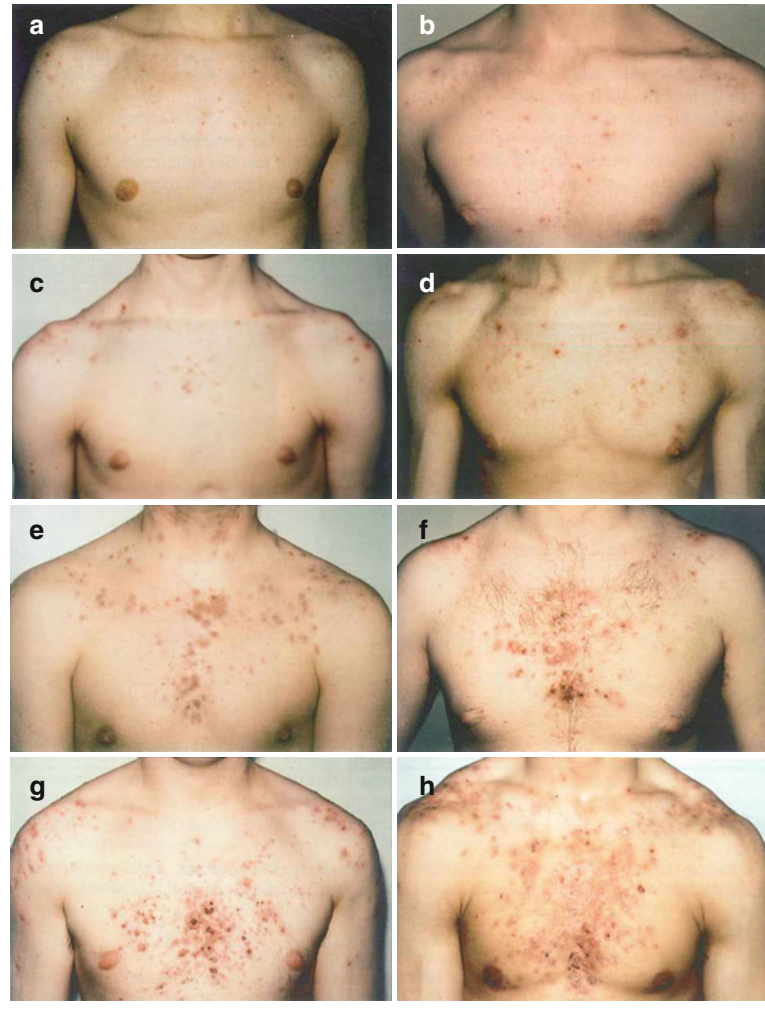




**Fig. 43.3** Grades of acne on the chest: (**a**) grade 1; (**b**) grade 2; (**c**) grade 3; (**d**) grade 4; (**e**) grade 5; (**f**) grade 6; (**g**) grade 7; (**h**) grade 8

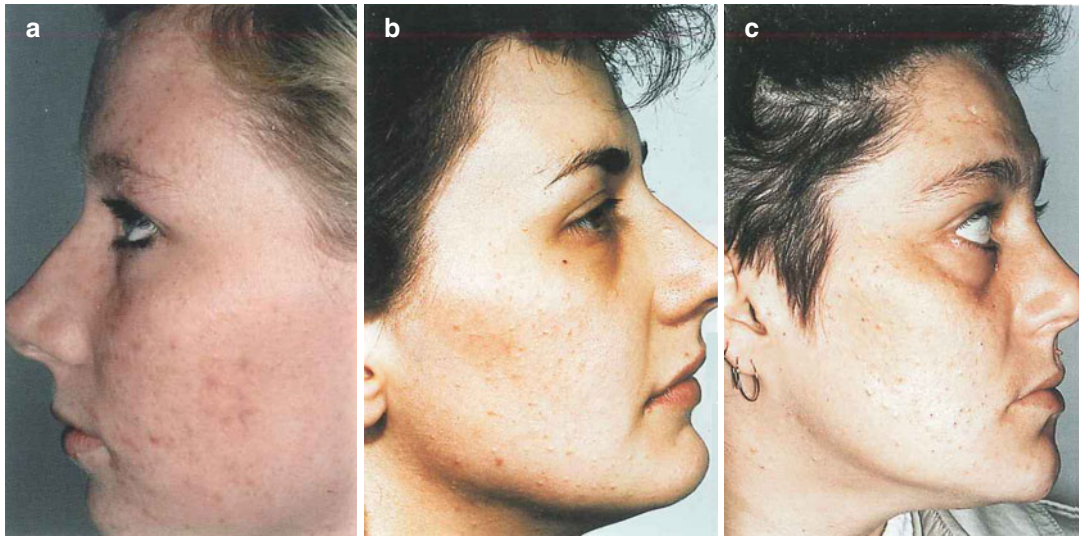



**Fig. 43.4** Grades of noninflamed acne: (**a**) grade 1; (**b**) grade 2; (**c**) grade 3

patients (5–11 %) depending on the lesion type examined, a greater than 10 % difference in lesion counts between two sessions occurred in 43–108 (10–25 %).

Similarly, the two doctors lesion counts agreed exactly in 17–39 cases (4–99 %) and different in their assessments by more than 10 % in 52–130 patients (12–30 %).

In all cases there was greater variation in the assessments of non-inflammatory lesions than inflammatory lesions. Training improves agreement both within and between raters [5].

In a separate study involving 45 patients, lesion counts were found to correlate significantly at 1 % level with Leeds acne grades and simple global mild to moderate assessments assigned from photographs.

## 43.5 Reliability

The reliability of the original scale was tested and without correcting for chance, the grades assigned by two assessors remained constant between sessions in 69 % of cases (210/306) and 65 % (230/356) of cases, and they were in agreement in 48 % of cases (49/102).

It has been shown that the correlation between lesion count and the grade of acne is significant at the 1 % level. The revised version in 1998 is not validated.

## 43.6 Discussion

The choice of assessment when evaluating outcome measures in clinical trials should be based on evidence of its reliability and validity in response to change as well as the acceptability, ease of use and clinical utility.

Acne is particularly difficult to asses as it manifests spontaneous exacerbations and resolutions.

Severity of acne should not just be based on the inflammatory appearance but should take into account non-inflammatory lesions and scarring as well as psychosocial and social effects of the disease.

When assessing acne it is vital to examine the lesions in the right environmental circumstances with appropriate lighting. Factors that could complicate the pictorial grade of acne include irritant dermatitis associated with topical therapy.

The importance of palpation to assess the depth of lesions should not be discounted.

### Conclusions

There are many methodologies used to assess acne vulgaris. The literature contains

numerous variations many of which have been used once in clinical trials without validation.

The 1985 Leeds technique represents one of the more complex grading scales and has found the most widespread use in clinical studies facilitating comparison of results. However, the later modification of this system has not been fully validated so is not directly comparable with the original version meaning that meaningful interpretations of clinical studies using the original and later Leeds technique may cause some confusion.

The most exact method of clinical evaluation is lesion counting, and this is therefore the most suitable currently for use in clinical trials but is not always practical in everyday clinical practice.

We continue to have problems adopting a universally accepted assessment tool for acne. Novel methods continue to be introduced each year, many of which are not validated.

A uniform, international method of classifying acne to allow meaningful comparison from one to study to the next is required.

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# Evaluation of Clinical Severity by Acne Grading and Lesion Counting

# 44

Jerry K. Tan

## Contents



**Core Messages**

- Acne severity is a multifaceted concept comprised of the type and extent of primary acne lesions, secondary lesions including scarring, psychosocial impact, and recalcitrance to prior therapy.
- Global grading is a holistic approach combining multiple elements of acne into an overall severity system while lesion counting is reductionistic, focusing solely on numbers of primary lesions.
- Lesion counting can detect changes in lesion type and/or number and is especially pertinent for clinical drug trials.
- While lesion counting is more reliable than global grading, procedural standardization is essential for consistency in evaluations.
- Global grading is based on photographic templates, descriptive text, or dominant primary lesions.
- Global grading is practical and clinically relevant but less reliable than lesion counting.
- Current global grading systems inclusive of truncal and facial acne include the Leeds system, Global Acne Grading System (GAGS), and the Comprehensive Acne Severity System (CASS).

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## 44.1 Introduction

An essential foundation for scientific inquiry in medicine is the quantification of disease severity. Such measures are an imperative in patient care, clinical trials, and epidemiologic research. For clinicians, severity measures serve to establish treatment options, guide the need for ongoing therapy, and to evaluate treatment effectiveness. For clinical drug trials and regulatory authorities, these are critical outcome measures upon which to establish evidence of treatment efficacy. For epidemiologists, they facilitate the study of disease within and between populations. However, for these measures to be useful and effective, they must be accurate, reliable, and capable of reflecting change. Furthermore, their uptake and utilization requires that they also be practical and relevant to their intended application.

The cutaneous examination is the primary basis for clinical severity evaluation in dermatology. In acne, the severity of active disease is dependent on lesion type, size, density, distribution of involvement at affected sites, and progression in complications including scarring [1]. This clinical array justifiably lends complexity to the development of an acne severity classification system. Consequently, lesion counting and global grading are two disparate methods of measuring acne severity based on differing philosophical approaches, reductionistic, and holistic, respectively. The purpose of this chapter is to review the development, relevance, and application of these methods as measures of clinical severity determination in acne.

## 44.2 Lesion Counting

The cutaneous morphology of acne vulgaris may be divided into primary and secondary lesions. The former denote lesions characteristic of active acne while the latter represent their sequelae. Primary lesions of acne are subdivided into noninflammatory (comedones) and inflammatory (papules, pustules, nodules, cysts). Noninflammatory lesions are comprised of open and closed comedones (blackheads and whiteheads, respectively). These are solid minute papules on a non-erythematous base typically measuring no more than 1–3 mm diameter and from which inspissated sebum and keratotic debris may be expressed. Those in which the sebum is partially oxidized by exposure to air and thus discolored grey-black are termed open comedones (blackheads), while those that are completely intraepidermal are termed closed comedones (whiteheads). Inflammatory lesions range from erythematous papules and pustules to larger nodules and fluctuant cysts. Nodules are defined as inflamed indurated lesions measuring ≥5 mm diameter. Some may become fluctuant and are termed cysts. With rupture, these may eventuate into draining sinus tracts. Examples of secondary lesions include post-inflammatory erythema, dyspigmentation, and scarring.

Acne lesion counting is based on the concept that reducing multiple elements to focus only on primary lesions provides a simpler and more objective surrogate measure of overall severity. Proponents of this method posit that lesion counting is more useful than global grading as it distinguishes small differences in treatment responses and permits evaluation of the effect of treatment on specific lesion types [2]. This method was first published as a measure of acne severity in 1966 in the conduct of a clinical drug trial [3]. Since then, lesion counting has become a standard measure of acne in clinical research studies. It is particularly suited to this application as counts present an array of continuous variables amenable to statistical testing.

In lesion counting, primary lesion types are counted independently: comedones, papules/pustules, and nodules/cysts. Facial demarcation zones are defined by: superiorly at the border of the anterior hairline or approximation thereof in the presence of alopecia; laterally at the temporal fringe and extending inferiorly along the preauricular margin; and inferiorly at the margin of the jawline and chin.

Procedural standardization is essential for consistency in evaluations to optimize reliability. In addition to training of raters, one of the most important aspects of lesion counting is proper preparation of the subject and the setting.

Subjects should be advised to avoid tanning and the sites of examination should be free of foundation, coloring agents, moisturizers, and makeup. Men should not have beards or moustaches and be advised to shave gently on the morning of their assessment. The use of a head or hair band maintains hair off the forehead during the procedure and assists in visualization of the forehead. The counting procedure is conducted without magnification or stretching of affected skin, using natural sunlight spectrum or white light illumination. Palpation is allowed to assist in discriminating macular erythema from inflammatory papules. Comfortable seating should be provided for both subject and rater to reduce fatigue. Excessive heat generation from high intensity light sources should be avoided as this may lead to subject perspiration and obscuration of lesions. Adequate time is required and is particularly important with higher absolute counts, therefore, allocating 10 min per subject should be considered a minimum duration [4]. Nevertheless, less experienced raters may require more time. A mechanical counting device may be useful as is the use of a facial template dividing the face into five regions: forehead, each cheek, nose, and perioral region [5]. A consistent grid pattern of counting within regions may be also useful.

Two previous studies have evaluated the reliability of lesion counting. In the first of these, the raters were comprised of three physicians and nine nurses. Intra-class correlation coefficients (ICC), defined as the ratio of subject to total variance, were used as a measure of rater reliability. ICC values approaching 1.0 indicate excellent reliability, while values less than 0.75 are considered less acceptable [6]. Reliability estimates between raters were 0.52 for non-inflammatory lesion counts, 0.76 for inflammatory counts, and 0.56 for a 6-point global evaluation scale. Little information was available regarding the reliability estimates for individual raters on global grading [5]. However, a more recent study of 11 dermatologists provided more details on reliability of lesion counts and global grading between and within raters. In this study the raters were separated into two groups—receiving a training session either prior to or after two subject evaluation sessions [4]. The training session was comprised of a review of primary lesion morphology, the use of a facial template, a review of morphological confounders, and specific training on a 6-category global assessment scale. The group trained initially demonstrated inter-rater reliability estimates of 0.68, 0.72, and 0.65 for noninflammatory lesions, inflammatory lesions, and global grading, respectively. Corresponding mean intra-rater reliability estimates were 0.83, 0.79, and 0.69, respectively. Together, these findings imply that lesion counting, particularly of inflammatory lesions, was more reliable than global grading. The training session did improve group reliability in non-inflammatory lesion counting and increased the proportion of raters with good reliability in all three outcome assessments. Practice improved reliability in measuring all three outcome variables and enhanced group reliability. The lowest regional reliability estimates for lesion counts were observed at the nose and supports excluding this region from lesion counting of facial acne.

Despite the apparent simplicity and objectivity of lesion counting, this procedure does have limitations. The clinical relevance of varying lesion types and counts are inadequately defined: such an analysis would require determining the effect of simultaneous changes in both type and number of lesions. The process of lesion counting is not simple or completely objective as clinical judgment and subjectivity frequently are necessary [7]. Some examples include deciding between post-inflammatory erythema with residual induration from inflammatory papules; prominent pilosebaceous orifices from comedones; and dermal inflammation of inflammatory nodules encompassing regressed lesions, papular scars, or comedones thereby artefactually making them appear inflamed. Additionally, the impracticality due to time requirements makes this procedure unlikely to be incorporated into regular clinical use. If largely restricted to clinical trialists and acne researchers, findings obtained with this method would not be readily translatable to clinical practice. Furthermore, beyond the face, there is scant prior use of this method for truncal sites of involvement.

## 44.3 Global Acne Grading

The multiplicity of features contributing to overall clinical acne severity led an expert consensus panel convened by the American Academy of Dermatology in 1990 to acknowledge that a global system would be the best method of acne grading. Furthermore, they declared that while classification based on morphological features was feasible, a strictly quantitative definition of severity was not [1]. An overall or global system of severity determination allows for assimilation of multiple elements comprising acne. Global grading systems of acne can combine these elements into a scale of severity based on the totality of the clinical presentation or gestalt. The categories are then established upon an experiential prior repertoire of the spectrum of severity.

Global acne assessments are of particular value in clinical practice, where lesion counts are impractical due to time constraints; and in clinical investigations, where a global qualitative evaluation is considered to be a pivotal outcome measure and of greater clinical relevance than lesion counts alone [8]. Attributes of an ideal global acne scale have been described and include: restricted number of categories to enhance practicality, adequate description of categories to reduce observer variability (increase reliability), clinical relevance in defining severity levels for treatment allocation, static measurements not anchored to a previous observation, universality for application in clinical practice and research, high degree of correlation with lesion counts [9], responsivity to reflect change, and comprehensiveness for common areas of involvement such as the face, chest, and back [10]. Inability of previous systems to fulfill these attributes may explain the lack of a singular gold standard consistently used in practice or research despite the existence of more than 25 global acne grading systems for acne [11]. Initial attempts at acne grading were based on simple four category grading scales in which acne was conceptualized as primarily centered on the face. Indicators of increasing severity included progression from non-inflammatory to inflammatory lesions and subjective increase in lesion quantity [12, 13]. Only in the most severe categories of these grading systems was truncal involvement included. These scales, however, inadequately accounted for patients with clinically significant truncal but minimal facial involvement. Recognition of the need for greater detail in defining categories led to development of a 9 grade facial acne severity system, which was also demonstrated to be clinically relevant [7]. This scale, subsequently adapted by including extent of involvement, had been shown to correlate with papule and pustule counts [14]. Subsequently condensed to six categories, this system has served as an investigator global assessment of facial acne in clinical drug trials and has been shown to be the most reliable of five global systems evaluated [5]. In a recent study of reliability in lesion counting and global grading using this 6-category scale, however, the latter has been found to be somewhat less reliable than lesion counts [4].

Acne grading limited to the face is inadequate in practice, however, as other anatomical regions are commonly affected. Indeed, just over half of patients affected by acne have truncal involvement [15]. Global acne systems were subsequently developed to include severity evaluation of the chest and back. In these, severity at each region was based either on the dominant lesional type [16] lesion counts [15, 17], photographic standards [18, 19], or on previously developed facial global grading scales adapted to include the trunk [10].

The Leeds system is based on a series of photographs of facial and truncal acne selected to best represent increasing severity by an expert panel of three dermatologists [18]. These were ranked by the panel on four further occasions as a means of content validation. The resulting series of photographs for inflammatory acne comprised 12 facial grades and 8 each for the chest and back. Furthermore, there are three additional grades for non-inflammatory facial acne [19]. The varying representations of severity and the large number of categories within each region, however, make this system cumbersome to apply in clinical practice. Furthermore, this system does not adequately differentiate those with the lowest acne grades [10]. The

**Table 44.1** Patient grading with the Comprehensive Acne Severity Scale (CASS)

| Grade | Description | Face | Chest | Back |
|---|---|---|---|---|
| Clear | No lesions to barely noticeable ones. Very few scattered comedones and papules | | | |
| Almost clear | Hardly visible from 2.5 m away. A few scattered comedones, and few small papules and very few pustules | | | |
| Mild | Easily recognizable, less than ½ affected area involved. Many comedones, papules, and pustules | | | |
| Moderate | More than ½ affected area involved. Numerous comedones, papules, and pustules | | | |
| Severe | Entire area involved. Covered with comedones, numerous papules, and pustules and few nodules and cysts | | | |
| Very severe | Highly inflammatory acne covering the affected area, with nodules and cysts present | | | |

Global Acne Grading System (GAGS), a quasi-quantitative system in which the total severity score is derived from a summation involving lesion type and anatomical regions of involvement (five facial regions and chest/upper back) [20], has not been validated nor evaluated for reliability. The Comprehensive Acne Severity System (CASS) was developed by application of a preexisting 6-category facial investigator global assessment scale to include the chest and back. This scale has been used as one of the pivotal outcome measures for regulatory drug approval in the USA [21]. Demarcation zones for truncal evaluation with this system were: chest defined as the anterior torso superiorly from the suprasternal notch extending laterally to shoulders, inferiorly by a horizontal line at the xiphoid process; and back as posterior torso with superior demarcation from shoulders extending to base of the neck and inferiorly by the level of the costal margin. Each of these regions was then individually graded for acne with the severity template (Table 44.1). This system has been validated against the Leeds system where it demonstrated both a high level of correlation and responsivity to treatment. Comparing both systems at all three sites, acne graded by CASS more closely approximated a normal distribution and more clearly distinguished the clear/almost clear from mild severity categories, a critical issue in defining treatment success in clinical trials and practice [10]. The reliability of this system as applied to facial acne has been previously demonstrated [4]. This validated static system fulfills many of the attributes recommended for an ideal global system including a restricted number of categories to facilitate practicality, comprehensiveness to enhance content validity, reliability, practicality, and universality with prior inclusion as an outcome measure in clinical drug trials.

## Conclusions

Lesion counting and global grading are manifestations of opposing philosophical approaches to acne severity determination, reductionistic, and holistic, respectively. As lesion counting does not incorporate the complete spectrum of features comprising acne, it serves as a surrogate marker at best. However, it offers a measure of reliability lacking in current global systems. In contrast, while current global systems are not entirely holistic as they do not incorporate scarring or psychosocial impact, they do attempt to assess a more complete and encompassing presentation of active acne.

In clinical practice, lesion counting is likely to be impractical due to time limitations. In that context, global grading measures may be more consonant with the needs of clinicians and relevant to patients in their quest for disease resolution, aptly denoted by *clear/almost clear* acne grading. In clinical trials for new acne therapies, the research paradigm requires measures that are clinically relevant, highly reliable, amenable to statistical testing, and lesion specific. The use of both global grading (ordinal scales) and lesion counts (continuous

scales) provides complementary outcome measures that fulfill these requirements. Thus, the value of these divergent measures depends on the setting in which they are used and on the issues inherent to the measures themselves.

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# Modern Technology for Imaging and Evaluation of Acne Lesions

# 45

Georgios N. Stamatas and Nikiforos Kollias

## Contents



**Core Messages**

- Acne is a pleomorphic skin condition involving several stages and clinical manifestations such as excessive sebum production, hyperkeratinization of follicles, bacterial presence in follicles, inflammation (erythema), edema (raised lesions), and often leftover marks including hyperpigmentation and scarring. Each of these parameters can be documented and quantified by appropriate imaging methods.
- Film photography has evolved to high quality digital imaging and is useful for keeping a permanent record of the progression of the condition during treatment allowing for retrospective analysis.
- Polarization imaging allows for the preferential enhancement of either superficial (surface topography) or subsurface (erythema, pigmentation) aspects of the skin condition.
- Fluorescence imaging can be used to document the presence of clogged pores (open comedones fluoresce white) and the existence of *Propionibacterium acnes* (porphyrin by-products fluoresce orange-red) in the infundibula.
- Spectral imaging provides the investigator with quantitative intensity maps of erythema, edema, and pigmentation that are sensitive enough to be able to document preclinical inflammatory lesions.

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- In vivo video and confocal microscopy are used in acne research to document manifestations of the disease at the microscopic level.
- Future advances in imaging technologies will give new tools to the acne researcher to generate novel insights of the acne pathophysiology, as well as create and test better treatments.

## 45.1 Introduction

Acne is a pleomorphic skin disease. The evolution of an acne lesion involves several stages (a) preclinical manifestations (noninflammatory lesions), (b) emergence of inflammatory lesions, (c) clearance, and (d) leftover marks such as post-inflammatory hyperpigmentation (PIH) and scars (affected dermal structures).

An important etiological feature of acne is the presence of microcomedones. They are the result of pilosebaceous ductal hypercornification and sebaceous hyperactivity. Enlargement of a microcomedone may lead to an open comedone (blackhead) or a closed comedone (whitehead). Another etiological feature is the presence of *Propionibacterium acnes* (*P. acnes*) in an anaerobic environment such as that of a hyperactive sebaceous gland. The overgrown sebaceous glands are prone to rupturing inside the dermis. Such cases are followed by a foreign body inflammatory reaction.

The emergence of an inflammatory lesion is accompanied by local capillary vasodilation and increased vascular perfusion manifested clinically as erythema. Vasodilation often leads to local increases in extracellular fluid in the dermal tissue (edema) manifested as a raised lesion (papule). Sebaceous exudate mixed with dead neutrophils (pus) constitutes the contents of a pustule.

The resolution of a lesion most of the times does not leave any mark, but in certain cases inflammatory pathways stimulate the increase of melanin production by melanocytes leading to PIH. In some other severe cases the inflammatory processes destroy the natural structures of the dermal extracellular matrix resulting in the formation of a scar.

**Table 45.1** Imaging technologies that aid in the evaluation of clinical aspects of the acne

| | |
|---|---|
| Increased sebum production (skin oiliness) | Parallel polarization imaging |
| Pore size | 3D and parallel polarization imaging |
| Hypercornification | Fluorescence imaging |
| *P. acnes* presence | Fluorescence imaging |
| Erythema | Spectral and orthogonal polarization imaging |
| Edema | Spectral imaging in near infrared |
| Topography of raised lesions | 3D and parallel polarization imaging |
| Post-inflammatory hyperpigmentation | Spectral, orthogonal polarization, and fluorescence imaging |
| Dermal matrix structure | Optical coherence tomography |
| Acne scars | 3D and parallel polarization imaging |

In the following paragraphs, we present various imaging modalities that can help us to document noninvasively all of the clinical aspects of the acne evolution mentioned above (Table 45.1). Moreover, beyond allowing us to assess the severity of acne-related parameters, imaging methods can be used to generate a permanent record of the disease, where global evaluations, comedo counts, and inflammatory lesion counts can be performed retrospectively by investigators or automatically by image analysis programs. In this chapter, by the term "imaging" we will cover a variety of optical noncontact methods (except when otherwise stated) that are used to document different aspects of the acne pathophysiology.

## 45.2 From Film Photography to High-Resolution Digital Imaging

Photography is a helpful tool that allows the physician or the investigator to follow the development of acne or the effectiveness of a treatment. Photographs taken from a patient at each visit create a permanent documentation record that

can be evaluated retrospectively by the same physician or by a panel.

Early reports on the use of standardized photography for documenting acne and following the effects of treatments appeared in the scientific literature in the 60s [1–3]. In the 70s Cook et al. proposed a grading scale of acne severity based on photographic standards [4]. Soon after photographic methods and retrospective grading were compared with clinical visual grading and "reasonable agreement" was reported [5, 6].

Acquisition of photographs during clinical trials allows having a permanent record that can be examined retrospectively. The value of such a permanent record is exemplified by Leyden et al., who report a retrospective grading from 5 investigators of photographs of 577 patients participating in 7 multicenter trials comparing topical retinoids for the treatment of acne [7]. The photographs were acquired using the same standardized protocol in all trials. Each patient was photographed at baseline and at the end of treatment (week 12 or 15). At each time clinical photographs were taken of the face at three angles: right, front, and left. The photographs were presented to the graders in slide form in a blinded fashion at 3 sessions over 3 consecutive days. Intra- and inter-investigator consistency was also tested and good correlations were demonstrated.

Advances in electronics made digital photography (or imaging) accessible to clinicians and to patients. Digital imaging allows for (a) automatic color calibration, (b) supervised or automatic image analysis to extract relevant features, (c) ease of storage of large numbers of photos, (d) communication of photos via electronic means (digital presentations, e-mail, website postings, etc.), (e) presentation of photos at desired magnifications (limited only by the camera optics and image resolution), (f) automatic registering of photo-evaluations via specialized software, etc. Such advantages have been exploited by investigators in the following examples.

Youn et al. used supervised digital imaging analysis to record the number of noninflammatory (comedonal papules) and inflammatory lesions (inflammatory papules, pustules, nodules, and cysts) [8]. The surface of the face in each image was divided into five regions: forehead, right cheek, left cheek, nose, and chin. Three graders marked digitally each noninflammatory lesion with a gold circle and each inflammatory one with an orange circle. The software automatically counted the number of each type of lesions marked at each of the five facial regions.

Another clinical application of digital imaging interesting for acne is in teledermatology. The rapid pace of improvement in the technology and reduction in price of consumer cameras allows consumers to capture digital images at home and communicate them to their physician. A study by Qureshi et al. showed that an online tutorial is enough for training consumers to acquire high quality images of their skin [9]. There was however only moderate agreement on diagnosis-related indicators, such as the presence or absence of pustules or papules and acne versus rosacea. These results indicate that other modalities, such as polarization or fluorescence imaging (see below), should be included in telemedicine to give the physician a better picture. This would however demand specialized cameras or fixtures for cameras.

Digital imaging and image analysis have been also helpful in the study of early stages of an acne lesion involving comedone formation [10]. In this case images are acquired not directly of skin in vivo but of cyanoacrylate biopsies extracted from comedone-involved areas.

The investigator attempts with imaging to document what the physician perceives during the examination of a lesion. The binocular aspect of human vision and the fact that the physician can use different angles of view during the examination allows for a three-dimensional (3D) perception of a lesion. Limited to two dimensions a single image can only partially capture the totality of a physician's perception. To overcome this limitation a variety of imaging modalities that provide further information have been developed [11].

## 45.3 Polarization Imaging

The use of polarizers in imaging gives the benefit of selectively enhancing surface or subsurface features of the imaged area of skin (Fig. 45.1).

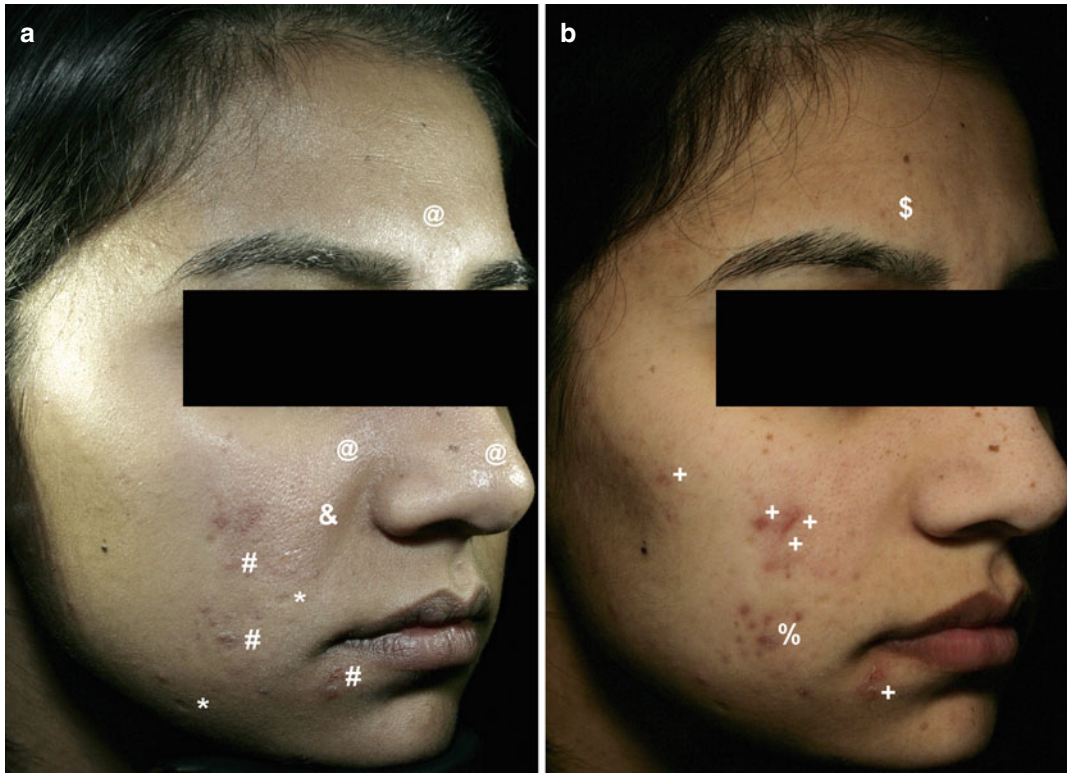


**Fig. 45.1** Example of polarization imaging for documenting acne. (**a**) A typical parallel-polarized image of an acne patient. The acne-related skin issues that can be documented include: excessive sebum production (*commercial at*), enlarged pores (*ampersand*), raised lesions (*number sign*), and scars from previous lesions (*asterisk*). (**b**) The same patient viewed using orthogonal polarization. The skin conditions that can be documented include: erythematous lesions (*plus sign*), erythema mixed with pigmentation (*percent sign*), and post-inflammatory hyperpigmentation marks from previous lesions (*dollar sign*)

One polarizing filter is required to be placed in front of the light source and a second one in front of the camera lens. The filter on the light source is often termed "polarizer" and the one on the camera lens is termed "analyzer."

When the polarization axes of the two filters are parallel to each other (parallel polarization imaging), the skin surface features are enhanced on the acquired image. Such modality can be applied to acne research for the study of papule size, the involvement of skin pore size, the involvement of skin "oiliness" (the more oily the skin the more shine can be captured in the image), and the three-dimensional surface structure of acne scars (Fig. 45.1a).

On the other hand, when the analyzer axis of polarization is perpendicular to that of the polarizer (orthogonal or cross polarization imaging), subsurface features are enhanced in the acquired image. In this case we are enhancing the presence of color in the image by blocking the specularly reflected light (glare) and collecting preferentially the photons that have crossed the skin surface, entered and diffused through the tissue, and reemerged on the surface. Due to the optical properties of the tissue that include wavelength-dependent absorption and scattering, not all photos that enter the skin reemerge out of the tissue. For example, blue and green light is strongly absorbed preferentially by hemoglobin moieties, but red light is only minimally absorbed; therefore, in areas of high local concentration of hemoglobin (such as in an inflamed acne lesion) only red light

can diffuse back out of the skin surface and the skin "looks red" (erythema).[1] Applications in acne research include digital documentation of erythema in the case of inflammatory lesions and pigmentation in the case of acne-related post-inflammatory hyperpigmentation (Fig. 45.1b).

Phillips et al. using orthogonal polarization imaging reported that visualization of inflammatory acne lesions was enhanced with clear delineation of erythematous borders [12]. Retrospective evaluation of standard and orthogonal polarization imaging of patients with acne lesions by a panel using the Cunliffe scale [13] resulted in significantly higher values for the polarized images. To overcome shortcomings of conventional photographs, such as the difficulty to differentiate papules from small nodules, Rizova and Kligman used polarized photography to record the evolution of acne lesions of five volunteers over a period of 16 weeks including 8 weeks of adapalene treatment [14]. They reported that while parallel polarized images were important for visualizing the degree of lesion elevation and the level of skin surface greasiness, the cross polarized images depicted accurately the extend of subsurface erythema and inflammation.

The polarization principle has been applied beyond imaging to clinical visual evaluation. Devices are now commercially available that combine a polarized light source with goggles with polarizing filters in a head fixture resembling a miner's hat. The polarizer of the light source is allowed to rotate so that the user can switch from parallel to orthogonal polarization. Also commercially available are dermoscopy instruments equipped with polarizer filters. To our knowledge there are no reports in the literature to date about the use of such instruments specifically on following acne patients.

[1] Large deep vessels appear to be blue due to light scattering by dermal collagen fibers on top of a highly concentrated strong absorber (hemoglobin), rather than due to hemoglobin absorption alone.

## 45.4 Fluorescence Imaging

In fluorescence imaging the illumination source (often a flash unit) is filtered to emit in short wavelengths (long UVA or blue range), and a second filter is placed in front of the camera lens to receive light in longer wavelength range blocking the excitation. Fluorescence photographs of the face of most adolescents and adults present bright foci that relate to hyper-keratinization in open comedones (white) and production of protoporphyrin IX by *P. acnes* (orange-red) [15]. Figure 45.2 exemplifies these patterns of fluorescence. The later allows for detection of bacterial presence on the skin. Only open comedones fluoresce. Furthermore, as melanin attenuates both incident and emitted radiation, this method is enhancing the contrast of skin pigmentation [16], making it a suitable technique for the study of acne-related PIH.

Although the presence of punctuate orange-red fluorescence on the face visualized by a UV lamp was reported as early as 1927 [17], the use of a camera (light amplifying video camera) to record the image and subsequent image analysis to count the foci was first reported in 1989 [18] and the first mention of using fluorescence photography was published in 1996 [19]. In this report fluorescence photography was used to study the effects of clindamycin treatment compared to vehicle in 40 patients with mild to moderate acne vulgaris. The change in the number of open comedones of the treated group occurred concurrently with a decrease in the number of fluorescent foci. Pagnoni et al. demonstrated the depopulation of *P. acnes* in sebaceous follicles following 7 days treatment with 10 % benzoyl peroxide [20]. They demonstrated that the decrease in porphyrin fluorescence during and after treatment correlated with the reduction in *P. acnes* density from scrub cultures. In a different study the same group demonstrated using polymeric pore strips that *P. acnes*-related fluorescence is located deep in sebaceous follicles [21]. Recent developments in the technology of light emitting diodes (LEDs) allowed for the development of a simple narrow-band illumination

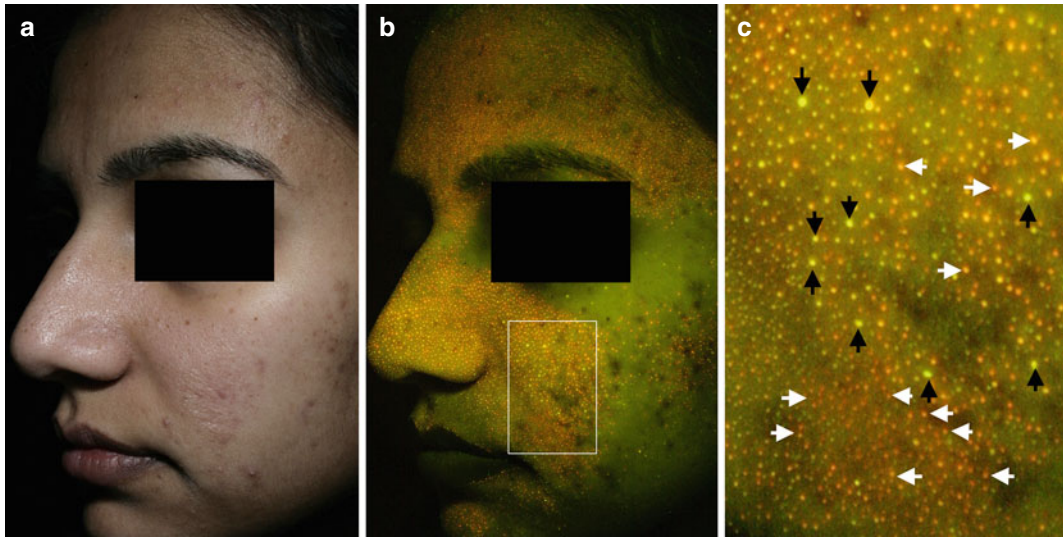


**Fig. 45.2** Example of fluorescence imaging for documenting acne. (**a**) A typical traditional digital image of an acne patient. (**b**) The corresponding fluorescence image (using blue excitation). Note the *green background* of collagen and elastin fluorescence, the *dark red areas* of erythematous lesions, and the punctuated fluorescence of open comedones. (**c**) Digital magnification of the *square* shown in (**b**). *Black arrows* point to examples of the "white" fluorescence of the "horn" material in open comedones and *white arrows* point to orange-red fluorescence of porphyrin by-products of *P. acnes*

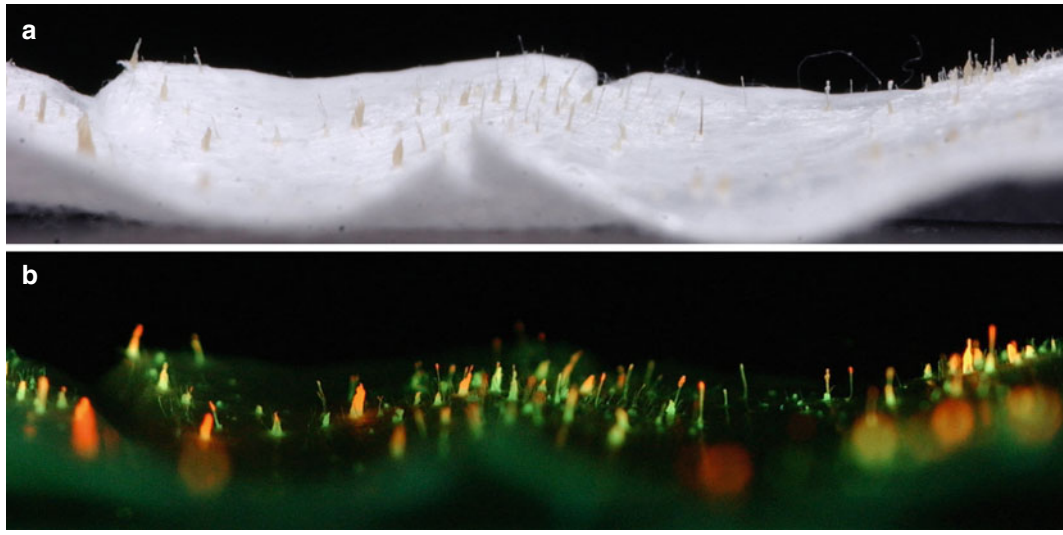


**Fig. 45.3** Illustration that *P. acnes* resides within the sebaceous follicle. A pore strip was applied on the nose of a volunteer and after removal was imaged under (**a**) visible and (**b**) fluorescence (under blue excitation) modes. In the visible image the extracted sebaceous follicles are shown in the background of the *white strip*. In the fluorescence image the orange-red fluorescence at the tips of the follicles indicates the presence of porphyrins and therefore of *P. acnes*

system specifically tuned at the excitation wavelength (405 nm) of *P. acnes*-related fluorescence [22]. The finding that porphyrin fluorescence originates from inside the skin rather than the skin surface is illustrated in Fig. 45.3, where a pore strip has been imaged at an oblique angle and under narrow depth of field conditions using visible and blue-excitation fluorescence modes.

Since the strip is a negative replica of the skin, the orange-red fluorescence on the tips of the extracted follicles indicates that *P. acnes* being an anaerobe resides with the follicles.

Beyond imaging, fluorescence spectroscopy has also been shown to be useful as a noninvasive tool in the assessment of noninflammatory acne. Gonzalez et al. used the rhino mouse model to demonstrate that there is a strong correlation between skin fluorescence spectral features and the size of utriculi (pseudocomedones) measured by histology. They showed that the progression of comedolysis during retinoid treatment can be monitored noninvasively using fluorescence spectroscopy [23].

## 45.5 Spectral Imaging

Inspired by the accuracy and specificity of diffuse reflectance spectroscopy, narrow-band cross-polarized spectral imaging has been developed for the evaluation and mapping of erythema and pigmentation. In this method apart from the polarizers on the light source and the camera lens (that are placed orthogonally to enhance the skin color information), narrow-band interference filters centered at characteristic wavelengths are placed in sequence in front of the detector. The object of interest is imaged sequentially at different wavelengths. The resulting stack of images of the same object (image cube) is a 3D structure with two spatial and one spectral dimension. This is equivalent with the notion of having a reflectance spectrum at each picture element (pixel) of the image. Using spectral analysis we can calculate the apparent concentration value of a skin chromophore (oxy-hemoglobin, deoxy-hemoglobin, and melanin) at each pixel. If we continue to capture spectral images in the near infrared region of the spectrum, we can add water in the list of chromophores. The value of evaluating the concentrations of these molecules is that they relate directly to erythema (oxy-hemoglobin) [24], blood stasis (deoxy-hemoglobin) [25], pigmentation (melanin) [25, 26], and edema (water) [27]. We can therefore assess the severity of cutaneous inflammation.

We have recently reported on the use of spectral imaging in the assessment of the intensity and extent of erythema and edema in acne lesions monitored over a period of 1 week [28]. Based on spectral imaging of the whole face, erythema and edema maps were created. The erythema maps were found to have improved contrast compared to traditional color images and therefore easier to perform lesion counts. Choosing an appropriate intensity threshold the erythema maps software can be designed to perform automatic lesion counting, an important parameter in the assessment of acne severity [3, 5, 29] (See also Chap. 44. In parallel to the erythema map where all the inflammatory lesions could be clearly seen, the edema map demonstrated only the ones that are at the stage of papules. Erythema intensity and area of involvement were also measured locally for target lesions, and the evolution of these parameters could be plotted over time. Such graphs can be used for example in comparative analysis of treatments. The sensitivity of the erythema maps exceeds that of clinical grading and consequently the contrast in these images is enough to identify lesions even before visible erythema can be detected. These lesions, termed emerging or preclinical, can be documented even 3 days before the inflammation can be detected in regular visible images. It has been demonstrated that treatments can be designed to target these emerging lesions [30].

Although the chromophore maps calculated from spectral images is an accurate and sensitive method (directly derived from spectral analysis), it is based on specialized equipment that are not currently widely available to dermatology practice, such as spectral imaging cameras. There have been several attempts to develop algorithms towards the aim of calculating erythema maps from images captured by common digital color cameras [31–35]. There are however several limitations to this approach. First of all the intensity and color of the captured color image is a function of (a) illumination and collection geometry, (b) geometry of the imaged subject (e.g., curved surfaces will result in shadows and uneven illumination), (c) specular reflections, (d) skin optics involving at least four independent parameters

(concentrations of oxy-hemoglobin, deoxy-hemoglobin, and melanin and a light scattering parameter), etc. Therefore, it is impossible to take into account all these independent variables by recording only three: the red, green, and blue (RGB) channels of the captured image. Therefore, at best such algorithms result in approximations of true erythema maps, and they should be always compared to the "gold standard" of spectral imaging. Still, having recognized their limitations, such algorithms (due to their relative ease of use) can be useful in cases of a well-designed imaging setup and experimental conditions.

## 45.6 In Vivo Video and Confocal Microscopy

In vivo microscopy is another example of the application of imaging in the study of acne. In this case the probe comes in contact with the skin area of interest (usually an individual lesion). Techniques such as polarization for the enhancement of surface or subsurface features can be easily adapted on an in vivo microscope.

Rizova and Kligman report the use of video microscopy to follow the progression of adapalene treatment at specific comedones [14]. After 1 week of treatment the infundibulum was extruded and by day 17 the comedones were completely resolved.

Recently, comedolysis has been studied by in vivo confocal microscopy in the rhino mouse model [36]. The transformation of utriculi towards normal follicular structure was followed during retinoid treatment and the confocal images correlated well with analysis of routine histological sections.

## 45.7 Other Types of Imaging Methods

The raised 3D structure of papules and pustules [37], as well as the surface structure of acne scars [38, 39] can be analyzed by 3D imaging methods. Such methods include (a) image capturing by two or more cameras viewing the object from different angles (resembling the human binocular vision) and using specialized algorithms for reconstructing the 3D information, (b) laser profilometry, in which a laser line is projected and photographed, then deviations from linearity are translated to height information, and (c) projecting computer-generated patterns of light and dark fringes onto the sample surface using a spatial light modulator.

Optical coherence tomography (OCT) is an interferometric imaging method in which the contrast is given by changes in the index of refraction of microstructures. OCT was used to demonstrate production of new collagen bundles following the treatment of acne scars using Erbium:YAG laser in a thermal mode [40]. The new collagen formation was confirmed with histology and immunohistochemistry.

Magnetic resonance imaging (MRI) equipment has been adapted to achieve high spatial resolution so that structures within and below the skin can be visualized. Such instruments have been used to demonstrate noninvasively 3D structures in the skin including acne lesions [41].

Finally, acne lesions have been analyzed by a method that relates to mapping of skin capacitance values in two dimensions that can be analyzed as a digital image [42]. In this case a two-dimensional array of capacitance sensors comes in contact with the skin site of interest. The capacitance value measured and the position of each sensor are recorded and presented as an image. In contrast to the methodologies presented so far, this is a contact method and is affected by the applied pressure and contact time. Comedones are characterized by low capacitance due to the hydrophobic nature of sebaceous lipids. A rim of high capacitance that was reported around inflammatory papules and pustules can be explained by the local increase of pressure during probe contact with the skin due to the raised structure of the lesion.

## 45.8 Conclusions and Future Trends

It is safe to speculate that advancements in imaging technologies will continue to trigger interest in the research community of biophysical

applications. The major advantage of such methods being noninvasive and most times even noncontact will continue to establish them as methods of preference for researchers and physicians. In the near future auto-classification of acne lesions using multimodal imaging [43] will substitute the existing subjective evaluation systems of acne lesions.

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# Part VIII

# Hormones and Acne

# Acne and Congenital Adrenal Hyperplasia

# 46

Catherine Dacou-Voutetakis

## Contents



**Core Messages**

- Acne related to increased androgen production, as a result of defective steroidogenesis in the adrenal cortex, does not present distinct characteristics that could lead to a search for congenital adrenal hyperplasia (CAH). Hence, knowledge and a high index of suspicion will uncover a relevant pathogenetic mechanism.
- Acne in the prepubertal stage is more likely to result from increased androgen production by the adrenals (premature adrenarche or congenital adrenal hyperplasia) than in other age groups.
- The most frequent form of CAH associated with acne is a deficiency of 21-hydroxylase, an enzymatic defect of steroidogenesis caused by mutations in the CYP21A2 gene.
- The diagnosis of 21-hydroxylase deficiency is based on raised values of 17-hydroxyprogesterone in a 0800 blood sampling (>5 ng/ml) and/or an increased value after synthetic ACTH stimulation (>10 ng/ml at 60 min).
- The contribution of heterozygous CYP21A2 mutations to the clinical expression of acne is not clear. It must be mentioned however, that in two studies, an increased frequency of carriers of CYP21A2 gene mutations was found in individuals with acne.

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- It is anticipated that the recognition of the underlying pathology is important not only for optimum therapeutic approach but also for genetic counseling, since CAH, especially the nonclassical form, constitutes one of the most frequent endocrinometabolic disorders and is transmitted by a recessive mode of inheritance.

## 46.1 Introduction: Definitions

Acne constitutes a multifactorial skin disorder which has a very adverse psychological impact in all individuals but more so in adolescents [1, 2]. From many natural paradigms and from systematic studies, the role of hormones in the appearance of acne has been substantiated [1–4]. Specifically, androgens affect the pilosebaseous unit by inducing sebum production [5].

All disorders associated with acne as well as acne appearing with normal puberty have androgen production (or overproduction) as a common denominator. Such disorders include CAH, Polycystic Ovarian Syndrome (PCOS), hyperinsulinism, or androgen producing tumors [3, 5–7]. In the present writing an account of data related to the role of CAH in acne appearance will be outlined.

Congenital Adrenal Hyperplasia is a term applied to describe a complex of disorders related to deficiency of enzymes involved in the synthesis of cortisol from cholesterol in the adrenals [7] (Fig. 46.1).

The clinical manifestations of CAH are variable and depend on the location and the degree of

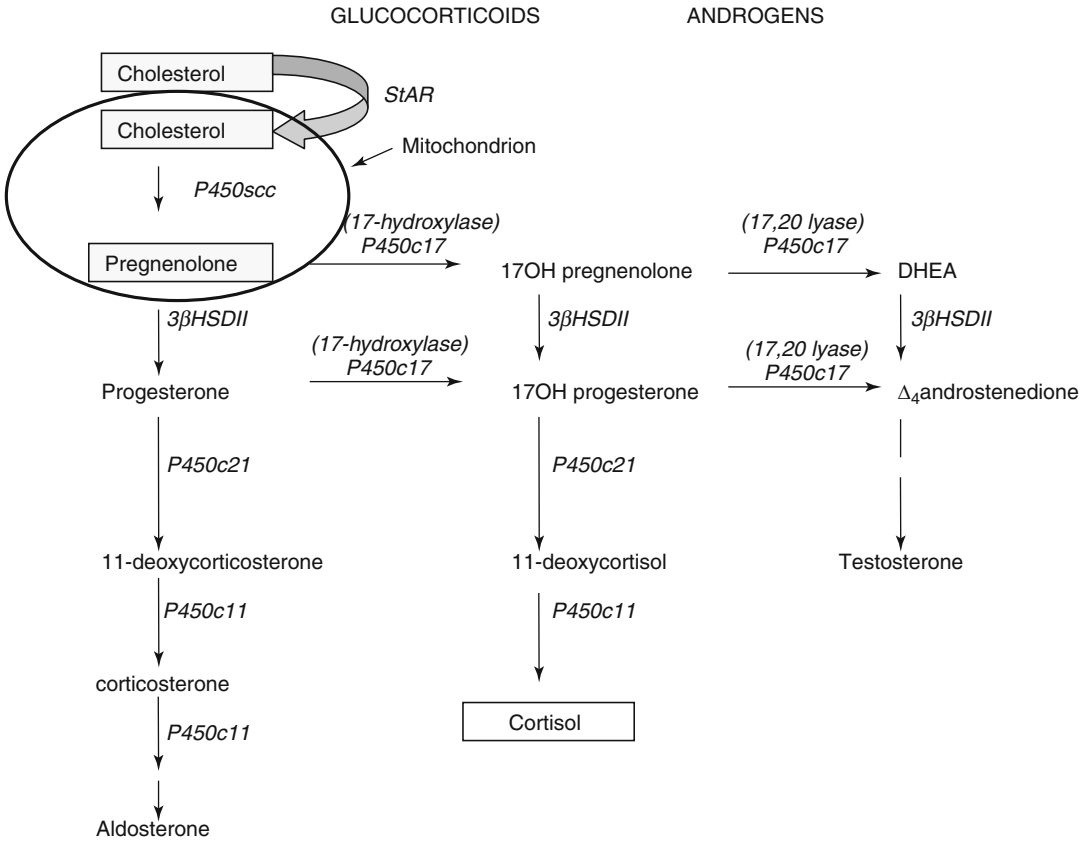


**Fig. 46.1** Adrenal Steroidogenesis

the enzymatic defect but, in general, are related to both insufficient synthesis of the end product, namely cortisol, and the accumulation of steroids prior to the enzymatic block, as well as to raised levels of adrenocorticotropic hormone (ACTH). Thus, the skin manifestations are hyperpigmentation from the elevated ACTH and those caused by excess androgen production, namely acne and hirsutism.

It must be emphasized that not all enzymatic defects in adrenal steroidogenesis are associated with hyperandrogenism. In enzymatic defects involving early steps of steroidogenesis, like StaR (steroidogenic acute regulation protein) or side chain cleavage enzyme (SCC), not only cortisol but also androgen synthesis is also inhibited and, therefore, symptoms of excess androgens are lacking [7].

It is of interest to mention that in the severe forms of the disease the defect in cortisol synthesis (Addisonian symptoms) leads to early initiation of glucocortisoids and consequent suppression of androgens so that skin manifestations (acne or hirsutism) are mild or absent.

Despite the many forms of defective adrenal steroidogenesis, the one related to insufficiency of 21-hydroxylase is the most frequent, covering more than 90 % of all cases of CAH. The gene encoding the 21-hydroxylase enzyme (CYP21A2) is located on the short arm of chromosome 6 (6p 21) within the HLA complex. The molecular defects of the CYP21A2 gene include deletions, conversions, and more than 100 missense, nonsense, and frame shift disease—causing mutations. Despite the large number of mutations, ten molecular defects account for approximately 95 % of the derangements causing 21-hydroxylase deficiency worldwide [7–9].

The clinical manifestations are mainly determined by the type of molecular defect. In other words there is a high degree of concordance between clinical expression and the type of molecular derangement [10].

Based on the severity of the clinical manifestations, we distinguish two main forms of CAH caused by 21-hydroxylase deficiency: the classical form which is subdivided into the salt wasting (most severe one) and the simple virilizing, and the nonclassical (NC). The NC form may go undiagnosed for many years, and it is not unusual to recognize this form in asymptomatic adults during family studies, initiated because of an affected relative (propositus).

The skin manifestations in CAH are primarily encountered in the nonclassical form of the disease and especially in mild cases which have gone unrecognized, since the patients with the severe forms are diagnosed and treated promptly.

## 46.2 Acne at the Various Developmental Stages

### 46.2.1 Acne in Infancy or Acne Infantum

It is a rare form of acne, primarily affecting males. It is manifested in the first 6–9 months of life or even earlier with a predilection for the cheeks, and usually disappears after a period of 18 months. Despite this knowledge about the evolution of this process, a search for androgen overproduction is recommended. As a matter of fact, a recent report described a 23-month-old boy with "newborn acne," refractory to various treatments, who, upon appropriate testing, was found to have a defect in 11-beta-hydroxylase, verified by molecular studies, which revealed compound heterozygote mutations of the CYP11B1 gene [11].

### 46.2.2 Childhood Onset

The most frequent clinical condition in childhood related to increased androgen production is Premature Pubarche (PP). Premature pubarche is diagnosed if pubic hair develop prior to 8 years in girls and 9 years in boys [12].

Most cases of PP are designated as "idiopathic." The underlying pathogenetic mechanism of PP seems to be an earlier maturation of the adrenal zona reticularis which is hormonally expressed as a rise of plasma dehydroepiandrosterone sulfate (DHEAS).

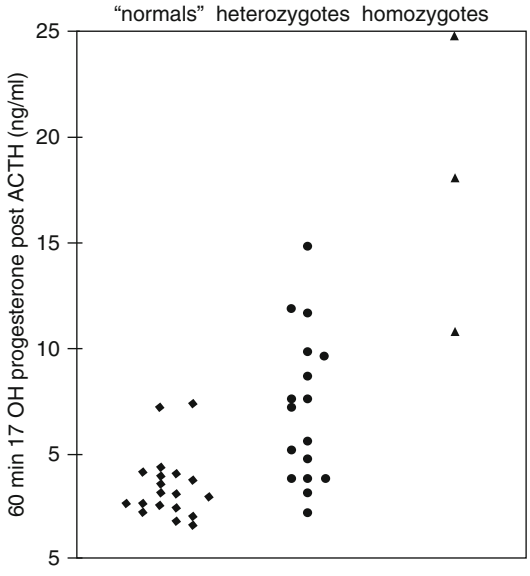


**Fig. 46.2** 17OHP values 60 min post-ACTH administration in normals, heterozygotes, and homozygotes

In a study of 48 children with premature pubarche, we found molecular defects in the CYP21A2 gene in 45.8 % of the cases. In most cases (37.5 %) heterozygocity was detected, whereas in 8.3 % homozygocity was present. There were no clinical criteria to distisguish the CYP21A2 mutations carriers from those without mutations. The Synachten test was diagnostic in all homozygous cases, the basal values being 3.5 ± 1.7 ng/ml and the peak 17.9 ± 7.1 ng/ml. In heterozygotes, the corresponding values were 1 ± 0.5 ng/ml and 7.1 ± 3.6 ng/ml. It must be underlined that in a number of cases overlapping values are detected and hence, the ACTH stimulation test is not always diagnostic [8, 13, 14] (Fig. 46.2).

We must mention, however, that by using the sum of basal plus 60 min values of 17OHP during the Synachten test and a cut-off point of this value of 4.9 ng/ml, there is a 76.5 % certainty of recognizing heterozygocity for CYP21A2 gene mutation.

With regard to acne, some lesions were present in almost all cases of PP but differences between carriers and noncarriers of CY21A2 mutations were equivocal (unpublished observations).

The role of heterozygous mutations remains a mute question.

In many genetic disorders transmitted by autosomal recessive mode of inheritance, heterozygotes may present mild relevant symptomatology. The same possibly holds true for carriers of CAH. Ostleve et al. [15] studied the carrier status of patients with acne with a mean age of 27.1 years. Approximately, 30 % of the 31 subjects who had CYP21A2 gene analysis were found to be carriers. It must be emphasized that the molecular analysis included a search for deletions and three point mutations. Only 6 of the affected individuals had abnormal 17-hydroxyprogesterone response to ACTH stimulation, a finding also emphasizing the uncertainty of results based on the ACTH stimulation test. The contribution of the molecular defect detected to the acne problems in these patients cannot be foreseen, neither the therapeutic implication can be elaborated upon. Nevertheless, the findings must not be considered irrelevant.

### 46.2.3 Acne at Puberty

In cases of CAH prior to therapy initiation, acne presents in almost all cases and reappears during periods of poor androgen suppression, as a result of noncompliance or lack of dosage adjustment to changes in body surface area.

It is of interest that with good control, girls or boys with CAH infrequently have problems with acne requiring specific care. These data are derived from personal observations since there is no systematic study for this aspect in subjects with CAH.

At puberty, girls with a history of premature pubarche, irrespective of defects in the CYP21A2 gene, develop ovarian hyperandrogenism more frequently than girls with chronologically appropriate pubarche. Moreover, such girls frequently suffer from polycystic ovarian disease [16]. With such an evolution, the additional pool of androgens (from the ovaries) is expected to aggravate preexisting acne in individuals with PP. As it was mentioned earlier, individuals with the severe form of CAH (classical forms) are not given enough time to develop a disturbing picture of

acne. Especially, girls are diagnosed quite early, in the newborn period, because of ambiguous external genitalia and symptoms of adrenal insufficiency (vomiting, failure to thrive, hyponatremia, hyperkalemia). Girls with mild virilization or boys with the simple virilizing form of CAH may escape detection and are diagnosed later, at age 3–8years, either because of acne, advanced growth, and/or development of pubic hair.

Adolescents with the NC form, especially males are more likely to go undiagnosed by their caring physician and visit the dermatologist for acne [17].

## 46.3 Diagnostic Steps

In all cases of acne presented in infancy or at the prepubertal stage, even if not accompanied by other signs of hyperandreogenism, a basal value of 17-hydroxyprogesterone must be determined early in the morning (about 0800). If the results are equivocal, a synthetic ACTH test (Synachten test) should be carried out. This is performed by the administration of Synachten (0.25 mg IV). Blood samples for 17-hydroxyprogesterone are obtained prior to (basal value) and 60 min post-Synachten (peak value).

Results interpretation: A basal value of 17-hydroxyprogesterone > 5 ng/ml and/or a peak value > 10 ng/ml strongly indicate NC CAH (homozygous mutation of the CYP21A2 gene).

A sum value >4.9 ng/ml (basal plus 60 min of the Synachten test) may indicate presence of heterozygocity [8].

In general, in patients with acne a specific diagnosis is very important not only for therapeutic options but also for genetic counseling. It must be underlined that in males with late onset CAH, the association of acne with an underlying enzymatic defect of adrenal steroidogenesis has higher possibility to escape recognition than in females [18]. Although a number of males with NC CAH appear asymptomatic, they may be found to present oligospermia or reduced fertility or harbor adrenal or testicular adenoma.

So the dermatologist should keep in mind that males presenting with severe acne must be screened for NC CAH.

## 46.4 Therapy

In the classical form, glucocorticoids will be initiated and tailored to body size and serum androgen levels at the follow-up visits. In the form with salt loss (salt wasting classical CAH) a mineralocordicoid will be added to the therapeutic regimen [7].

In the NC form there is some skepticism for initiating glucocorticoids if the patients are almost asymptomatic [9]. There is no doubt that in women with acne, hirsutism, and/or menstrual irregularities, therapy will be initiated but in asymptomatic individuals and, especially, males the need for glucocorticoids therapy has been questioned.

The approach certainly needs individualization. However, it must be kept in mind that in males, adrenal or testicular adenomas may develop so that if one chooses not to treat with glucocorticoids the patient has to be followed up closely [9].

If severe acne is present in either gender and is refractory to the usual treatment and the androgens profile is diagnostic of CAH, specific therapy with glucocorticoids should be given systematically.

In cases of heterozygocity, as it is expected, no glucocorticoid therapy is required. In such cases, as in homozygotes, genetic counseling must be offered to the individual and his/her family.

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# The Acne Genes

# 47

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and Christos C. Zouboulis

## Contents



**Core Messages**

- As one of the most common and complex skin diseases, the inheritance of acne is unlikely to follow simple Mendelian models but rather the polygenic inheritance with phenotypes complicated by a great deal of interaction between genes and the environment especially the sex hormones.
- So far, no commanding genes have been identified in acne development. Candidate genes may include those molecules regulating keratinocyte differentiation in the hair infundibulum (retinoid metabolism and epidermal growth factor), sebocyte proliferation and differentiation (steroidogenesis, insulin signaling, peroxisome proliferator-activated receptor), and inflammation induced by *Propionibacterium acnes* (Toll-like receptors).
- Syndromes accompanied by acne may also point the way to the future research, such as polycystic ovarian syndrome, PAPA syndrome, and Apert syndrome.

## 47.1 Introduction

Acne is one of the most common skin diseases. Many epidemiologic studies and twin studies have provided substantial evidence about the

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genetic influence in the development of acne [1–5], at least in certain stages of acne such as neonatal acne, teenage acne [6], adult persistent acne, or in special forms of acne such as acne comedonica, acne inversa [7, 8], acne fulminans [9], or in acne severity [10] and therapeutic resistance [11]. Acne is very likely mediated by polygenic inheritance or multifactorial inheritance attributed to the interplay between multiple genes and the environment, especially the sex hormones. It is unknown if each candidate "acne gene" contributes equally or additively to the disease phenotype, or whether there exists a master gene that presides or leads the disease development. All the candidate genes may influence each other and perpetuate the disease process. The problem in many of the existing epidemiologic studies may include (1) a small sample size with single or few families examined without matched control; (2) lack of standardization in the disease definition or severity classification; (3) variability of age onset, duration, course, and psychosocial influence.

### 47.1.1 Acne Genes, Acne Pathogenesis and Acne-Associated Syndromes

Another approach to identify the "acne genes" is to look into the pathogenic factors contributing to acne development, including (1) hyperkeratosis of hair follicles, (2) sebum overproduction, (3) inflammation, and (4) *Propionibacterium acnes*.

Studies on "complex syndromes" manifesting with acne may also shed light on the genetic influences of acne formation. However, not much has been performed in screening the potential genes. There is so far no gene being identified to cause or contribute substantially to acne development. The following discussion proceeds on a logical way, based mostly on experimental research and clinical observation.

1. Hyperkeratosis of the hair infra-infundibulum:
   One of the earliest lesions in acne development is the microcomedone, the histology of which shows proliferation/retention hyperkeratosis in the infra-infundibulum part and sebaceous duct of sebaceous hair follicles [12]. It is conceivable that the molecules influencing epidermal proliferation and differentiation will play a role in acne formation, such as retinoic acid and epidermal growth factors. Polymorphism in the human cytochrome P-450 1A1 gene (CYP1A1), one of the most active isozymes involved in interconversion of endogenous retinoids and their natural metabolites, has been demonstrated to be associated with acne development [13]. On the other hand, CYP26A1, one of the key enzymes in inactivation of all-trans-retinoic acid, was also found to have a strong constitutive expression restricted to basal epidermal keratinocytes, eccrine sweat glands, and sebaceous glands [14], which merits further examination on its function in comedogenesis. In vitro studies and newly clinical experience in oncology lend support to the role of epidermal growth factors and their receptors in acne pathogenesis [15, 16]. Controversial results exist in terms of the effect of insulin-like growth factor [17, 18]. Apert syndrome or acrocephalosyndactyly is characterized by early development of severe inflammatory acne on the face and trunk, with extension to the upper arms and forearms [19]. Mutation in fibroblast growth factor receptor (FGFR)-2 was found to be a significant causal factor [20], and mice lacking epidermal Fgfr2b displayed striking abnormalities in hair and sebaceous gland development [21]. It would be interesting to see whether gene polymorphisms of these molecules also occur in acne patients.
2. Sebum overproduction:
   Twin studies have shown that sebum excretion rate measures alike in identical twins but significantly different in nonidentical twins [22, 23]. As sebum production is strongly influenced by androgens, potential genes regulating androgenesis and androgen action have been focus of interest. The sex-determining genes SRY, SOX-9, WT-1, SF-1, and DAX-1 were found to play a pivotal role in regulation of steroidogenesis, where SRY and SOX-9 seem to potentiate steroidogenesis, but DAX-1 antagonizes the androgen function [24]. Our previous work proved the cutaneous expression of these genes except SF-1 while the protein levels of

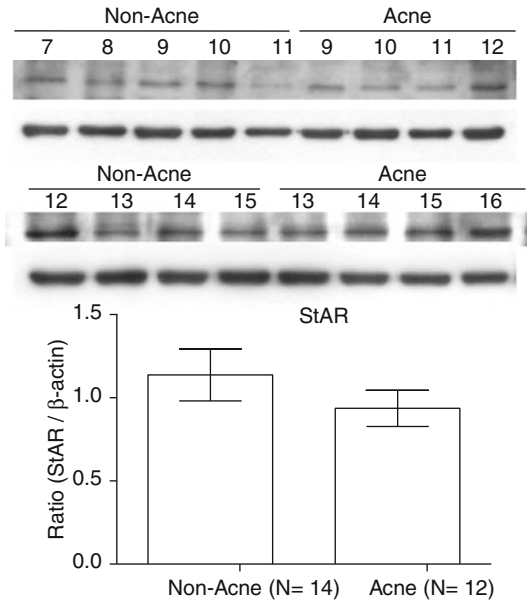


**Fig. 47.1** Western blot study of the cutaneous expression of DAX-1 protein. Significantly higher expression could be seen in the facial skin from 15 non-acne (mean age 45 years, range 19–58) as compared to 16 acne-prone (mean age 37 years, range 14–58) male patients ($p<0.005$, Wilcoxon rank-sum test). Primary antibody used was rabbit antihuman DAX-1 polyclonal IgG (Santa Cruz, CA, USA) at a concentration of 1:250 [24]

DAX-1, SRY, and WT-1 were significantly higher in the bald scalp of men with androgenetic alopecia [25]. As compared to 16 acne-prone patients, the facial skin from 15 patients without acne had a higher expression of DAX-1 protein (Fig. 47.1). On the other hand, there was no difference in the protein expression of steroidogenic acute regulatory protein (StAR) and type I 3β-hydroxysteroid dehydrogenase in patients with or without acne (Fig. 47.2), although their mRNA amount was found to be higher in the bald scalp of men with androgenetic alopecia [26]. The available data failed to establish the association between androgenetic alopecia and the genes encoding steroid sulfatase (STS) and the two 5α-reductase isoenzymes (SRD5A1 versus SRD5A2) [27–29], meanwhile little is known about their relation to acne occurrence. On the other hand, people with a shorter CAG repeats in the androgen receptor gene were found to have an increased androgen sensitivity and thus higher risk for development of precocious pubarche and ovarian hyperandrogenism [30].

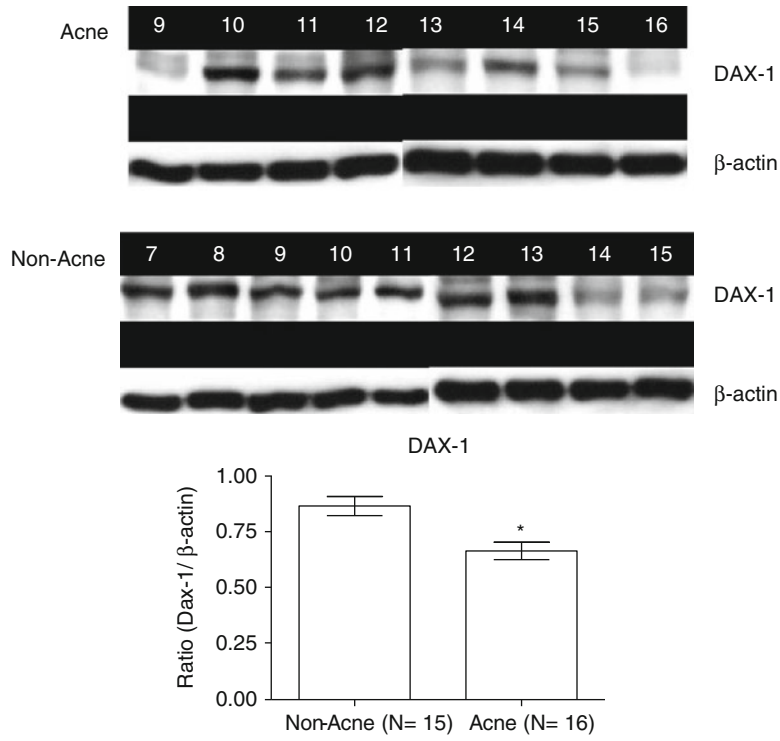


**Fig. 47.2** Western blot study of the cutaneous expression of steroidogenic acuter regulatory protein (StAR). No difference of protein expression could be detected in the facial skin from 14 non-acne (mean age 36years, average 17–55) as compared to 12 acne-prone (mean age 29 years, average 18–55) male patients ($p=0.320$, Wilcoxon rank-sum test). Primary antibody used was rabbit anti-human StAR polyclonal IgG (Santa Cruz, CA, USA) at a concentration of 1:100

Some syndromes and their candidate genes may also pose a research target:

(a) Polycystic ovarian syndrome: under investigation are genes related to steroidogenesis (e.g., CYP11A), insulin resistance (e.g., insulin gene VNTR; variable number of tandem repeats), gonadotropin function, obesity, sex hormone binding genes, fetal programming, and X-chromosome inactivation [31, 32];

(b) Nonclassical congenital adrenal hyperplasia and steroid 21-hydroxylase deficiency: The functional significance of the mutations of CYP21A2 in acne pathogenesis is ambiguous [33–35];

(c) HAIR-AN syndrome (hyperandrogenism, insulin resistance, acanthosis nigricans): The possible genes remain elusive and mutations in the tyrosine kinase domain of the insulin receptor gene was found to be rather irrelevant [36]. In addition, although the involvement of cortcotropin releasing hormone/alpha-melanocyte-stimulating hormone/melanocortin receptor system in sebocyte biology was implied by many in vitro and in vivo studies, more concrete evidence is needed to confirm its clinical significance [37, 38].

3. Inflammation:
PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum, and cystic acne), a multisystemic autoinflammatory syndrome, has been described in a three-generation kindred with autosomal-dominant transmission. The culprit gene was mapped to chromosome 15q [39], where mutations in proline serine threonine phosphatase-interacting protein (PSTPIP), or CD2-binding protein 1 (CD2BP1), a tyrosine-phosphorylated protein involved in cytoskeletal organization, were suspected to be a causative element [40]. Familial cases of SAPHO syndrome with synovitis, acne, pustulosis, hyperostosis, and osteitis have been published [41], but the corresponding gene is not yet identified.

4. *Propionibacterium acnes*:
Toll-like receptors (TLR) have been recognized to be fundamental molecules in mediating innate immunity [42]. In vivo expression of TLR-2 and TLR-4 was enhanced in the epidermis of acne lesions; moreover, in vitro incubation of the human keratinocytes with bacterial fractions induced a rapid increased expression of TLR-2 and TLR-4 as well as matrix metallo-proteinase 9 (MMP-9) [43], indicating that *Propionibacterium acnes* can trigger inflammatory cytokine responses in acne by activation of TLR2 [44]. However, gene polymorphisms in TLR2 and TLR4 were not associated with acne vulgaris [45].

Many molecules affect not only one pathogenic pathway; androgens and cytokines may also act upon the infundibular hyper-/dyskeratosis [15, 46]. The peroxisome proliferator-activated receptor (PPAR) family can regulate the sebocyte differentiation [47, 48] as well as keratinocyte proliferation/differentiation [49] and even inflammation [50].

In the future, strict and uniform diagnostic criteria, improved application of the candidate gene approach using haplotype-based analyses, replication of positive results in large cohorts, more family-based studies, gene selection from expression studies, and whole-genome approaches will enhance identification and determination of acne genes [51].

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# Vitamins and the Skin

# 48

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## Contents



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## 48.1 Introduction

**Core Messages**

- Vitamin A (vit. A) is essential for normal differentiation and maintenance of epithelial tissues in skin and mucous membranes, vision (retinaldehyde), reproduction (retinol), and embryonic morphogenesis.
- A range of vitamin A derivatives (retinoids) have been approved for the topical or systemic treatment of mild to severe, recalcitrant acne, photoaging, psoriasis, and hand eczema.
- Retinoids interact with two types of nuclear receptors which act as ligand-dependent transcription factors: Retinoid acid receptors (RARs) and Retinoid X receptors (RXRs).
- Vitamin D can be absorbed from the diet or synthesized in the skin. Keratinocytes are able to synthesize the biologically active vitamin D metabolite $1,25(OH)_2D_3$ from 7-dehydrocholesterol and under the influence of ultraviolet B radiation.
- Vitamins C and E are powerful antioxidants that have been proven to protect the skin against photodamage.
- Dietary carotenoids, although exhibiting reduced bioavailability, are absorbed and distributed to tissues including skin and protect humans against solar UV damage.

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## 48.2 Vitamin A

Vitamin A (retinol) and its two main metabolites, retinaldehyde and retinoic acid, are critical for the development, maintenance, and differentiation of skin and other epithelial tissues. The normal plasma concentration of vitamin A is 0.35–0.75 μg/ml. Retinoids, vitamin A derivatives, are natural or synthetic molecules which have immunomodulatory and anti-inflammatory effects, influence the epidermal cell growth and differentiation, and have effects on sebaceous gland activity and epidermal lipids. A range of vitamin A derivatives have been approved for the topical or systemic treatment of mild to severe, recalcitrant acne, photoaging, psoriasis, and hand eczema [1, 2].

Retinoic acid is a major oxidative metabolite of vitamin A and has two isoforms: the all-*trans* retinoic acid and the 13-*cis* retinoic acid, with normal plasma concentrations of 0.55–1.20 and 0.80–2.40 ng/ml, respectively [3]. *All-trans retinoic acid* (tretinoin) was the first topical retinoid to be synthesized and *13-cis-retinoic acid* (isotretinoin) is a worldwide leading systemic agent used in the treatment of severe acne [4, 5]. It is efficacious against all major pathogenetic factors implicated in acne pathogenesis, namely seborrhoea, follicular hyperkeratinization, *Propionibacterium acnes* hypercolonization, and inflammation. Retinaldehyde, a metabolite of vitamin A, is produced by the in vivo oxidation of retinol and is essential for vision. Retinaldehyde is a natural metabolite of retinol that does not bind to RARs; its biologic activity results from conversion of tretinoin by epidermal keratinocytes, similarly to retinol and retinyl esters, which are used in cosmetic preparations. *Polyaromatic retinoids*, also called *arotinoids*, indicate the third synthetic retinoid generation, including adapalene used for the topical treatment of acne [6] and tazarotene that is FDA approved for the treatment of psoriasis, acne, and photoaging [7].

*Etretinate* was the first monoaromatic synthetic retinoid, and together with its free acid metabolite *acitretin*, they are used as systemic therapeutic agents for the treatment of psoriasis. Also, oral Alitretinoin (9-*cis*-Retinoic Acid) is a new therapeutic agent used in the treatment of hand eczema.

The activity of retinoids is suggested to be mediated at the molecular level through a non-receptor-mediated endocytosis. Retinoids interact with two types of nuclear receptors which act as ligand-dependent transcription factors: Retinoid acid receptors (RARs) and Retinoid X receptors (RXRs). Retinoid acid receptors (RARs) bind all-trans retinoic acid and 9-*cis* retinoic acid with high affinity, while RXRs selectively interact with 9-*cis* retinoic acid [8].

Retinoid receptors target and regulate the genes that have retinoid-responsive elements (RARE and RXRE) in their promoter regions. Retinoids have been shown to have effects on epidermal growth and differentiation and on sebaceous gland activity. They promote cell proliferation in normal epithelia, whereas they normalize it in hyperproliferative conditions. They also induce and modulate the expression of growth factors and their receptors; they inhibit angiogenesis and they have immunomodulatory and anti-inflammatory properties.

## 48.3 Vitamin D

Vitamin D is the precursor of the biologically active vitamin D metabolite 1,25-dihydroxyvitamin D. Vitamin D can be absorbed from the diet or synthesized in the skin under the influence of ultraviolet B (UVB) radiation from 7-dehydrocholesterol (7-DHC) [9].

The biologically active vitamin D metabolite 1,25-dihydroxyvitamin D ($1,25(OH)_2D$, calcitriol), which circulates in the blood, is synthesized from vitamin D which is hydroxylated in the liver in C-25 position by a cytochrome P450 enzyme, the vitamin D-25-hydroxylase (CYP27A1), before it gets hydroxylated a second time in the kidney in C-1 position by another cytochrome P450 enzyme, the 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1).

Recent in vitro studies on anephric humans demonstrated that cultured human keratinocytes, and other cells as monocytes, macrophages,

osteoblasts, prostate and colon cells, all express the enzymatic machinery for the synthesis of $1,25(OH)_2D_3$ [10, 11]. In keratinocytes, studies could even prove the presence of 1α-hydroxylase (CYP27A1) and 25-hydroxylase (CYP27B1) [12, 13] which makes keratinocytes the only cell type known until today, that is able to synthesize $1,25(OH)_2D_3$ from 7-dehydrocholesterol.

Expression of VDR, CYP27A1, CYP27B1, CYP24A1 mRNA was detected in human sebocytes, showing their ability to both synthesize and metabolize the biologically active vitamin D metabolite $1,25(OH)_2D_3$. Incubation of SZ95 sebocytes with $1,25(OH)_2D_3$ resulted in a dose-dependent suppression of cell proliferation, modulation of cell cycle regulation, and of apoptosis. Expression of VDR and CYP24A1 was upregulated in SZ95 sebocytes along with vitamin D analogue treatment. It is likely therefore that vitamin D endocrine system is of high importance for regulation of sebocyte function and physiology, including sebum production. SZ95 sebocytes express vitamin D receptors and the enzymatic machinery to synthesize and metabolize biologically active vitamin D analogues [14].

Vitamin D and/or its receptor (vitamin D receptor, VDR) regulate several cutaneous functions including inhibition of proliferation, stimulation of differentiation, promotion of innate immunity, regulation of the hair follicle cycle, and suppression of tumor [15, 16]. Most of these functions of vitamin D, particularly its effect on epidermal keratinocyte differentiation, are mediated by $Ca^{2+}$. Vitamin $D_3$ has been shown to suppress lipogenesis in hamster sebaceous glands in vitro [17]. It has been found that human SZ95 sebaceous cells strongly express key components of the vitamin D system (VDR, 25OHase, 1αOHase, 24OHse) [14, 18]. Local synthesis or metabolism of vitamin D metabolites may be of importance for various cellular functions of sebaceous gland cells including growth regulation. Vitamin $D_3$ significantly increases SZ95 sebocyte amount, in a dose- and time-dependent manner. Also, incubation of SZ95 sebocytes with vitamin $D_3$ resulted in a dose-dependent suppression of sebaceous cell lipogenesis [14].

## 48.4 Vitamin C

Vitamin C (L-ascorbic acid) is the body's major aqueous-phase antioxidant. Since our skin protects us from environmental free-radical stress as well, the presence of vitamin C is extremely important. Exposure to sunlight and environmental pollution depletes vitamin C from the skin [19, 20].

Vitamin C has been proven to be photoprotective; however, since it does not absorb light in the UV spectrum, it does not itself act as a sunscreen. As an antioxidant vitamin C deactivates UV-induced free radicals and decreases UVB-related erythema by 52 % [21].

Topical vitamin C can also exhibit anti-inflammatory activity. Post-laser resurfacing (with the "older" $CO_2$-lasers) redness persists for at least 3–4 months after treatment. With vitamin C applied before and after laser surgery, this redness of inflammation was markedly decreased after and healing took only 2 months [22].

The mechanism of this anti-inflammatory action in vitro is attributed to decreased activation of the transcription factor NF-κβ (nuclear factor kappa beta), the factor responsible for many pre-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukins Il-1, Il-6, and Il-8 [23].

Perhaps the most important action of vitamin C on the skin is the stimulation of collagen synthesis, since it is an essential cofactor for the two enzymes responsible for collagen synthesis: prolyl hydroxylase and lysyl hydroxylase. The first makes the collagen molecule stable while the later crosslinks the collagen to give structural strength [24].

Furthermore it has been demonstrated that vitamin C acts directly on DNA to increase the transcription rate and to stabilize the procollagen messenger RNA [25]. By enhancing collagen synthesis, vitamin C can directly correct the collagen loss that causes wrinkles. Exciting studies in vitro compared newborn with elderly (80- to 95-year-old) fibroblasts. In vitro addition of vitamin C to the culture medium drove the elderly cells to higher proliferation rates than normal the newborn fibroblasts. Even the newborn fibroblasts

proliferated almost four times better when exposed to vitamin C. Fibroblasts in the presence of vitamin C also synthesized more collagen. Newborn fibroblasts synthesize a larger percentage of collagen than elderly cells, but again, when elderly cells were exposed to vitamin C in vitro, they produced more collagen than the normal, newborn fibroblasts [26].

In contrast to the increased synthesis of collagen, other in vitro studies suggested a possible inhibition of vitamin C on elastin biosynthesis by fibroblasts. This might be advantageous in reducing the solar elastosis due to photodamage [27].

## 48.5 Vitamin E

Vitamin E is an important lipid-soluble and membrane-bound antioxidant. It constitutes a potent free-radical quencher that deactivates aggressive radicals and terminates damaging chain reactions protecting primarily the lipids of cell membranes. Although Vitamin E is stored primarily in the adipose tissue, it is also delivered to the skin by sebum [28, 29].

Although several forms of vitamin E exist in natural dietary sources, humans use predominantly a-tocopherol because a specific a-tocopherol transfer protein selectively transfers a-tocopherol into lipoproteins [30].

Many studies have demonstrated protection from UV-induced damage to the skin by topical vitamin E formulations [31–34] as well as UV-induced damage of inflammation (erythema, sunburn) and hyperpigmentation (tanning) as well as protection from the chronic UV-induced damage of actinic keratosis and skin cancer [31, 33, 35–37].

Moreover, the occurrence of seborrheic dermatitis is associated with a change in the quality of sebum lipids and vitamin E [38].

Also, peroxidation of squalene (a lipid unique to sebum) results in HaCaT keratinocytes proliferation and to a stimulation of inflammatory mediators in vitro. Skin surface and comedonal lipids from acne patients are rich with polar lipids mainly derived from squalene oxidation. Vitamin E is found in the skin surface lipids as a significant constituent of human sebum. In sebaceous-rich sites there is a continuous secretion of vitamin E, which is directly correlated with squalene levels [39, 40].

## 48.6 Dietary Carotenoids

Carotenoids are highly lipophilic pigments that are synthesized by all photosynthetic organisms and some non-photosynthetic microorganisms but not animals. The most common dietary carotenes are the acyclic lycopene and its biosynthetic downstream cyclic products: β-carotene and α-carotene (most common provitamin A carotenoids). Humans only consume approximately 50 different carotenoids from various sources in their diet and approximately half of them are found in human plasma [41].

Only recently dietary bioactives as carotenoids have started to gain appreciation as photoprotective agents based on scientific investigation and evidence from nutritional research. These nutrients accumulate in the skin to possibly exhibit endogenous protection to the skin. They pass the intestinal epithelial barrier and reach the systemic circulation via lymphatics, to be deposited in tissues including skin [42–44].

Carotenoids exhibit a concentration gradient in the layers of skin with a higher amount in the dermis and lower levels in the stratum corneum. It is unclear whether stratum corneum has higher utilization or lower deposition when compared to the deeper layers, and certain regional variations may also be observed in carotenoid level, with higher concentrations of total carotenoids measured in the forehead, palm of hand, and dorsal skin whereas lower levels are present in the arm and the back of hand [45, 46].

Diets or supplements containing more than 30 mg of carotenoids per day and for 4 weeks may result in carotenodermia, a condition characterized by yellowish discoloration which is reversible upon cessation of responsible supplementation or carotenoid-enriched diet [47–49].

Ultraviolet radiation (UV) represents one of the most important environmental hazardous physical agents that the skin encounters on a daily basis and

throughout a person's lifetime. UV irradiation may cause tissue injury and cutaneous inflammation signifying sunburn [50, 51], immunosuppression [52, 53], premature aging of the skin called photoaging [54], and skin cancer [55, 56].

Nutritional bioactives like carotenoids could provide important protection of the skin against the damaging effects of UV irradiation. The efficacy of β-carotene [57–63] and lycopene in systemic photoprotection has been extensively investigated in the last few years [64–66]. Carotenoids have gained considerable attention as agents that neutralize Reactive Oxygen Species (ROS) [67] and are among the most effective naturally occurring scavengers of single oxygen and peroxyl radicals [68–70].

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# Urinary Hormone Analysis in Acne

# 49

Markus G. Mohaupt and Bernhard Dick

## Contents



**Core Messages**

- Analysis of urinary steroid hormone metabolites is available as "steroid profiling."
- Steroid profiling has been useful in acne research and clinical diagnosing.
- Steroid profiling does reveal inborn and acquired errors of metabolism based upon apparent enzyme activities and/or upon pattern analysis.
- Inborn enzymatic defects are detectable by applying substrate/product ratios including those which lead to an adrenogenital syndrome such as 3β-hydroxysteroid dehydrogenase, 21-, and 11β-hydroxylase deficiencies. Minor diseases might require "steroid profiling" during ACTH stimulation.
- Urinary "steroid profiling" should be applied, if rare diseases are suspected such as an 11β-hydroxysteroid dehydrogenase type 1 deficiency.
- Pattern analysis can help to identify patients with endocrine active adrenal tumors.
- Androgen production can be assessed.
- A definite diagnosis of diseases such as a polycystic ovary syndrome is not to be based on urinary "steroid profiling."

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## 49.1 Introduction-Definitions

The analysis of urinary steroid hormone metabolites allows to detect multiple endocrinopathies involved in the evolution of acne. The word "profile," introduced in the mid-1960s represents a multicomponent chromatographic analysis permitting to identify individual traits [1]. The ultimate goal of a single profile determining all components of interest with sufficient quantitative and qualitative discrimination has not yet been achieved. Pattern analysis is clearly an advantage of steroid hormone metabolite profiling in order to detect inborn or acquired errors of metabolism [2, 3].

## 49.2 Overview

Relevant diseases associated with errors of steroid hormone metabolism and acne detectable by the analysis of steroid hormone metabolites, include enzymatic defects associated with an adrenogenital syndrome, such as deficient 3β-hydroxysteroid dehydrogenase [4], 21-hydroxylase, and 11β-hydroxylase activities, or reduced 5α-reductase and increased 17-hydroxylase activities.

Furthermore, cortisol excess of any reason is easily detectable by the 24-h urinary free cortisol excretion with a high sensitivity and specificity [1, 5, 6]. Pattern recognition will allow to suspect a pituitary or adrenal hormone-producing tumor [1]. Some authors detected changes in the urinary excretion of steroid hormone metabolites in patients with polycystic ovary syndrome; however, the usefulness for a clinical diagnosis of the disease remains a matter of debate [7–9]. Yet, an increased availability of androgen metabolites will be detectable [7].

## 49.3 Profiling Urinary Steroid Hormone Metabolites

Several techniques have been applied to profile urinary steroid hormone metabolites. These include column liquid chromatography, paper chromatography, thin-layer chromatography, high-performance liquid chromatography, or high-performance liquid chromatography-mass spectrometry. With the availability of inexpensive capillary dedicated automated mass spectrometers, gas chromatography-mass spectrometry has been routinely introduced [1].

## 49.4 Steroid Hormones of Interest and Calculating Apparent Enzyme Activities

To allow differential diagnosis between an adrenogenital syndrome, pituitary or adrenal tumors, and an overproduction of androgens, steroids of interest and typical urinary metabolites can be defined [2]. These include primary steroid hormones with assigned hormonal functions, such as cortisol, and secondary steroid hormones, such as dehydroepiandrosterone, proximate to the primary hormones, which allow to assess errors in the biosynthetic pathway [1]. The most relevant primary steroid hormones and their metabolites are listed (Table 49.1) and depicted in Fig. 49.1.

In many diseases relevant to the etiology of acne, hormones with a circadian rhythm are involved. Thus, every 24-h urine collection has to be verified for adequate sampling by measuring 24-h urinary creatinine excretion. As is frequently the case, daily excretion of urinary steroid hormone metabolites require careful adaptation to appropriate measurement techniques by the patients. An important tool to control for sampling errors by the patients, though only infrequently used in reports of urinary steroid hormone excretion, is the relation to creatinine in the sample thus easily adjusting for over- or undersampling errors [11].

Most of the ratios should be applied beyond the neonatal period. Since the severity of a given disorder may cover a whole clinical range, mild forms might differ only slightly from normal [13]. Steroid hormone excretion rates are also subject to incorrect sampling compromising circadian information [12]. In patients with compromised renal failure, there may be a change of hormone excretion or a change in enzyme

**Table 49.1** (modified according to [1])

| Primary steroid hormones | Typical urinary steroid hormone metabolites |
|---|---|
| Cortisol (F) | Cortisol (F) |
| | Tetrahydrocortisol (THF) |
| | Tetrahydrocortisone (THE) |
| | 5α-Tetrahydrocortisol (5αTHF) |
| Aldosterone | Tetrahydroaldosterone [10] (TH-Aldosterone) |
| Progesterone | Pregnanediol (PD) |
| Testosterone | Androsterone (AN) |
| | Etiocholanolone (ETIO) |
| Dihydrotesterosterone | 5α-Dihydrotestosterone |
| Estradiol | Estriol |
| **Secondary steroid hormones** | **Typical urinary steroid hormone metabolites** |
| 17α-Hydroxyprogesterone | 17α-Hydroxypregnanolone (17-HP) |
| | Pregnanetriol (PT) |
| | 11-Oxo-pregnanetriol (11-Oxo-PT) |
| 11-Deoxycortisol (substance S) | Tetrahydro-11-deoxycortisol (THS) |
| Deoxycorticosterone (DOC) | Tetrahydro-deoxycorticosterone (THDOC) |
| Corticosterone (B) | Tetrahydro-11-dehydro-corticosterone (THA) |
| | Tetrahydro-corticosterone (THB) |
| | 5α-Tetrahydro-corticosterone (5αTHB) |
| Androstenedione | Androsterone (AN) |
| | Etiocholanolone (ETIO) |
| Dehydroepiandrosterone (DHEA) | 16α-Dehydroepiandrosterone (16αDHEA) |
| | Dehydroepiandrosterone (DHEA) |

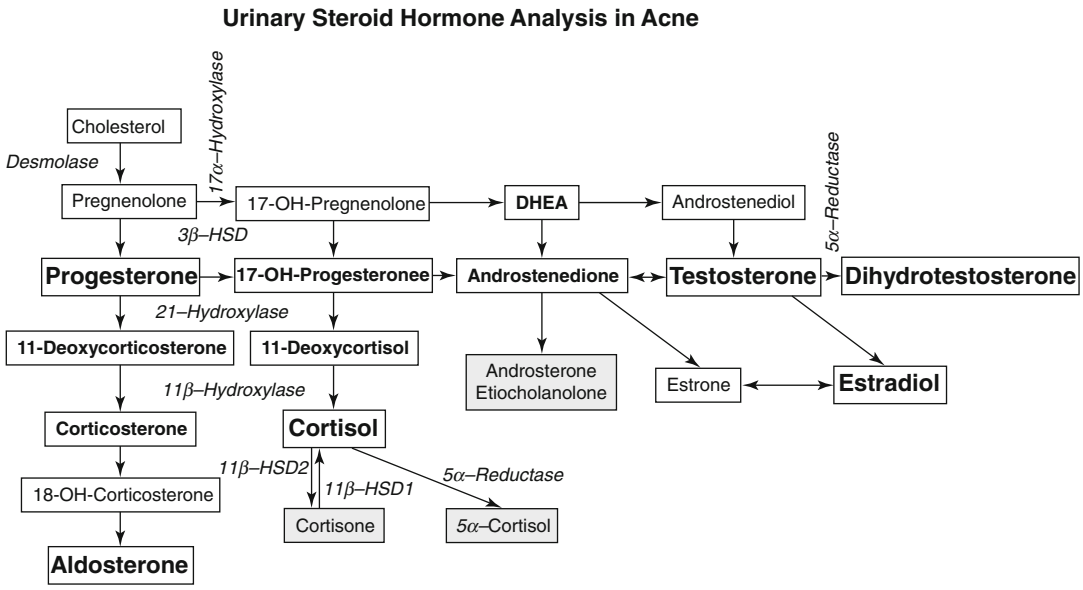


**Fig. 49.1** Primary (*large bold*), secondary (*bold*), and steroid hormone intermediates (*light*). *Gray background* indicates inactive steroid hormone metabolites. *3β-HSD* 3β-hydroxysteroid dehydrogenase and *11β-HSD1/2* 11β-hydroxysteroid dehydrogenase type 1/2 (modified according to [12])

**Table 49.2** Ratios of substrate to product used to calculate apparent enzyme activities

| Enzyme of interest | Ratios indicating apparent enzyme activity |
|---|---|
| 3β-Hydroxysteroid dehydrogenase [13] | DHEA/(THE+THF+5αTHF)<br>PT/(THE+THF+5αTHF) |
| 21-Hydroxylase [15] | 17HP/(THE+THF+5αTHF)<br>PT/(THE+THF+5αTHF) |
| 17α-Hydroxylase [16] | (5αTHB+THB+THA)/(THE+THF+5αTHF)<br>(5αTHB+THB+THA)/(AN+ETIO)<br>THDOC/(THE+THF+5αTHF) |
| 11β-Hydroxylase [17, 18] | THS/(THE+THF+5αTHF)<br>THDOC/(THE+THF+5αTHF) |
| 5α-Reductase [19] | THB/5αTHB<br>THF/5αTHF |
| 11β-Hydroxysteroid dehydrogenase type 1 | THE/(THF+5αTHF) [20]<br>(THF+5αTHF)/THE [21] |

activities [14]. Using these metabolites, next to a pattern analysis, apparent enzyme activities may be calculated by using the ratios of substrate to product of a given enzyme to discriminate inborn errors of metabolism leading to clinical diseases such as an adrenogenital syndrome (Table 49.2).

## 49.5 Applications in Acne Research and Clinical Decision Making

Early reports could not find differences in urinary fractional 17-ketosteroid excretion using paper chromatography in males with acne or in young children from families with a high incidence of acne [22, 23]. Other authors detected an increased urinary excretion of 17-ketosteroids in patients with acne who followed therapeutic interventions [24–26].

Changes in the ratios of 5α/5β metabolites, as assessed by urinary steroid profile analysis using capillary column chromatography, have been detected following isotretinoin treatment, which suggested sensitivity of 5α-reductase activity [27]. Gas-liquid and high performance liquid chromatography have been repetitively used to estimate the extent of 5α-reduction by measuring the urinary excretion of androstanediol and testosterone, and to evaluate human androgenicity [28, 29].

Pattern analysis by using steroid hormone metabolite profiling allows to identify changes in enzyme activities such as those involved in the adrenogenital syndrome. Urinary 17-ketosteroids were measured before (basal) and after ACTH testing in women suspected to have a defect in 11β-hydroxylase activity leading to an a postmenarchial onset of virilization [30]. Oligomenorrhea directed the identification of symptoms of an androgen excess. Analysis of urinary 17-ketosteroid excretion led to classify these women into groups with either polycystic ovary syndrome, adrenal block, or combined adrenal and ovarian hyperandrogenism, subsequent to pattern analysis [31]. Interpreting urinary steroid hormone metabolites, a rare combination of 21- and 11β-hydroxylase deficiency, has been diagnosed in familial congenital adrenal hyperplasia which is associated with acne [32]. In addition to reduced 11β-hydroxylation, cases of apparent cortisone reductase deficiency (11β-hydroxysteroid dehydrogenase type 1) result in an ACTH-driven androgen production [21]. Urinary "steroid profiling" has been also successfully used to identify 3β-hydroxysteroid dehydrogenase deficiency [33].

Urinary free cortisol and cortisol metabolites were measured to diagnose and to follow children with hypercortisolism due to Cushing's disease as etiology of steroid-induced acne [34].

**Conclusions**

Urinary steroid hormone metabolite profiling can be used to identify inborn and acquired metabolic disorders [35]. Since quality and comparability are major issues, external quality assessment is mandatory in networks such as the "European Research Network for the Evaluation and Improvement of Screening, Diagnosis and Treatment of Inherited Disorders of Metabolism" (ERNDIM) [36]. The study by Phillips and coworkers revealed that in addition to biochemical accuracy, the comments accompanying the results varied considerably in length, clearness of the clinical diagnosis, and the advisories on further

recommended tests [36]. In the author's experience it is important to identify an institution with an external quality assessment scheme to verify reliable test results and sufficient interpretations based upon formal qualifiers and personal clinical experience.

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# Laboratory Evaluations in Acne

# 50

Clio Dessinioti and Christos C. Zouboulis

## Contents



**Core Messages**

- When evaluating the acne patient, the questions arise of whether laboratory evaluations are justified for acne vulgaris either in terms of diagnosis, monitoring during acne treatment, or for a hormonal work-up.
- Acne diagnosis is usually easily made based on clinical grounds and no laboratory evaluations are required.
- Laboratory hormonal evaluations may be indicated when hyperandrogenemia is suspected, that is, in acne resistant to therapies, in adult acne patients, and when clinical signs of hyperandrogenism are present. Hormonal work-up screens for endocrinologic abnormalities most commonly associated with acne include the polycystic ovary syndrome (for women) and nonclassical congenital hyperplasia (for men and women).
- Larger, prospective studies will address the need of laboratory monitoring during long-term minocycline therapy, especially in patients with underlying systemic diseases.
- The frequency of blood monitoring tests during oral isotretinoin therapy varies from country to country. Laboratory evaluations should be carried out at baseline and at weeks 4 and 8. If test

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results are normal and isotretinoin dose is not increased, no further testing may be needed unless the patient has known risk factors.
- In clinical practice, laboratory evaluations should be considered in the context of the individual acne patient.

## 50.1 Introduction

Acne vulgaris is a chronic inflammatory skin disease mainly affecting adolescents and young adults. When evaluating the acne patient, the questions arise of whether laboratory evaluations are justified for acne vulgaris either in terms of diagnosis, monitoring during treatment, or for a hormonal work-up. This chapter addresses these questions aiming to provide available scientific data regarding laboratory evaluations for acne.

## 50.2 Laboratory Evaluations for the Diagnosis of Acne

Acne vulgaris presents with characteristic lesions including comedones, papules, pustules, and nodules (see Chap. 28) and is localized on the face, trunk, and/or upper arms. Acne diagnosis is usually easily made based on a clinical basis and no laboratory evaluation is required. In case of an indefinite diagnosis, culture of pustular material for bacteria may be carried out to exclude a cutaneous infection (pyoderma).

Invasive diagnostic procedures, such as a cutaneous biopsy, are not required for acne diagnosis.

## 50.3 Hormonal Evaluations in Acne

Acne is a chronic disease, affecting individuals of all ages [1]. When an underlying hormonal disorder is suspected, depending on the acne form, the age of acne onset, and accompanying clinical symptoms and signs, hormonal evaluations for hyperandrogenemia are indicated.

In particular, routine testing is not recommended for childhood acne unless androgen excess is a concern. Ascertaining levels of total and free testosterone, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH) may be helpful to screen patients for whom an endocrinologic abnormality, e.g., polycystic ovary syndrome (PCO), is suspected [2].

There are studies showing elevation of free testosterone, DHEA, and androstenedione levels in patients with acne vulgaris, usually associated with other clinical signs of hyperandrogenism such as hirsutism, alopecia, or menstrual disturbances [3–9]. However, most acne patients do not have endocrinologic abnormalities and persistent or severe acne can be the only clinical sign of androgen excess in women. This could be explained by an end-organ sensitivity of the pilosebaceous unit to androgens [10].

Hormonal evaluations may be indicated when hyperandrogenemia is suspected, that is, in acne resistant to therapies, in adult acne patients, and when clinical signs of hyperandrogenism are present. Clinical signs of hyperandrogenism include androgenic alopecia, seborrhea/acne/hirsutism/alopecia (SAHA) syndrome (see Chap. 75), cushingoid features, increased libido, clitoromegaly, deepening of the voice, and acanthosis nigricans. In female patients with severe acne, acne of sudden onset, or acne associated with hirsutism or irregular menstrual periods, it is recommended to screen patients for an underlying endocrine disorder [10]. In those cases, the disorders most commonly sought for endocrinologic abnormalities include PCO or nonclassical congenital hyperplasia (NCAH) (see Chaps. 31, 46, 76).

Severe cystic acne refractory to oral antibiotics and isotretinoin has been associated with NCAH [11]. Moreover, acne may be the sole presenting sign of NCAH in females and males [12, 13]. NCAH is associated with other hyperandrogenic symptoms such as hirsutism, androgenic alopecia, or increased seborrhea. CAH consists

of a heterogenous group of autosomal inherited disorders due to enzymatic defects in the biosynthetic pathway of cortisol and/or aldosterone, resulting in glucocorticoid deficiency, mineralocorticoid deficiency, and androgen excess. Androgen excess affects the pilosebaceous unit resulting in cutaneous manifestations such as acne [13, 14].

The determination of 17-hydroxyprogesterone (17-OH PG), the immediate substrate for 21-hydroxylase (–OH), is used for biochemical diagnosis. A case-controlled study of 82 acne male patients showed that 17-OH PG levels were significantly higher in acne patients compared to controls [12].

For mild NCAH with normal basal adrenal steroids, the adrenocorticotropin (ACTH) stimulation test is recommended. This test should be performed in the morning, during the early follicular phase (days 3–7 of the menstrual cycle). CAH is considered if basal 17-OH PG levels are elevated (above 200 ng/dL or 6.0 nmol/L) and/or ACTH-stimulated 17-OH PG exceeds 1,000 ng/dL (30 nmol/L) [13, 14].

PCO may present with acne as a marker of hyperandrogenism. Also, although uncommon, acne may be the sole clinical cutaneous manifestation of PCO [10, 15]. The establishment of diagnostic criteria for PCO has been a matter of debate. Diagnosis is currently based upon an international agreement (The Rotterdam Consensus Group in 2003) and is defined by the presence of at least two out of three of the following: (1) oligomenorrhea or amenorrhea, (2) clinical hyperandrogenism or serum androgen excess, and (3) polycystic ovaries by a pelvic ultrasound [16]. Several other diagnoses should be excluded, e.g., CAH, Cushing's disease, hyperprolactinemia, and hypothyroidism. To evaluate the metabolic risk of women with PCO syndrome, an oral glucose tolerance test, including insulin and c-peptide determinations, LH releasing hormone tests, and determination of serum lipids are indicated [14].

Screening tests for hyperandrogenism include DHEAS, total/free testosterone, LH, FSH, prolactin, and 17-OH PG. These tests should be done in the luteal phase of the menstrual cycle [17].

**Table 50.1** Hormonal evaluations in acne

| Hormonal evaluations | Clinical association |
|---|---|
| LH, FSH | PCO |
| Total, free testosterone | PCO<br>Ovarian tumor |
| DHEAS | CAH<br>Adrenal tumor |
| 17-OH PG | CAH |
| ACTH stimulation test | CAH |
| TSH | NCAH |
| Prolactin | PCO |

Laboratory hormonal evaluations for acne are summarized in Table 50.1.

Urinary hormone analysis in acne is discussed in the relevant chapter (see Chap. 49).

## 50.4 Laboratory Monitoring Evaluations During Acne Treatment

Acne treatments include topical and oral agents. No laboratory evaluations are needed during topical acne treatment. Laboratory evaluations in the context of monitoring during acne treatment may be necessary with oral treatments, including antibiotics and isotretinoin.

### 50.4.1 Oral Antibiotics

Antibiotics such as tetracyclines (first generation: oxytetracycline, tetracycline chloride; second generation: doxycycline, minocycline, and lymecycline) and macrolide antibiotics (erythromycin, azithromycin) are a mainstay of treatment for moderate and severe acne and treatment resistant forms of inflammatory acne. Lymecycline is a second-generation, semisynthetic tetracycline, and azithromycin is a methyl derivative of erythromycin that has been found to be effective in treating non-inflammatory and inflammatory acne lesions [18].

All tetracyclines are generally well tolerated. Minocycline has been reported to cause a number of rare but severe side effects, including hypersensitivity reactions and autoimmune disorders

(lupus-like syndrome, autoimmune hepatitis, arthritis, thyroiditis, polyarteritis nodosa) [19, 20]. A retrospective study of 97,694 individuals aged 15–35 years with acne in the UK, followed for 520,000 person-years, investigated physicians' reports of lupus erythematosus (LE). Among these patients, minocycline was used in 24.8 %, doxycycline in 15.6 %, other tetracyclines in 42.3 %, and no tetracycline antibiotic in 17.3 %. The overall hazard ratio for the association of minocycline to LE was 2.64 (95 % CI: 1.51–4.66). LE often required systemic therapy. There was a strong association between the duration of exposure to minocycline (length of treatment or total dose) and LE. No association was noted for doxycycline or the other tetracyclines in this study [20]. p-ANCAs are antibodies directed against anti-myeloperoxidase-3 of the neutrophils. Three young women treated with minocycline for more than 2 years for acne developed P-ANCA-positive cutaneous polyarteritis nodosa [21, 22]. p-ANCA have been detected in other cases of minocycline-related lupus and/or hepatitis [23–25].

Larger, prospective studies will address the need of laboratory monitoring during long-term minocycline therapy, especially in patients with underlying systemic LE or first-degree relatives with systemic LE or patients with known liver disease [26]. Laboratory monitoring evaluations are generally not indicated during treatment with oral macrolides or oral tetracycline or doxycycline.

### 50.4.2 Oral Isotretinoin

Systemic isotretinoin was introduced as a treatment for acne in 1982 (see Chaps. 62 and 63). Oral isotretinoin has been associated with elevations of serum triglyceride levels in approximately 25 % of patients and mild-to-moderate elevations of liver enzymes in 15 % of patients [27]. Case reports of drug-induced hepatotoxicity, leukopenia [28], and thrombocytopenia [29] have prompted the widespread practice of frequent laboratory monitoring of patients undergoing isotretinoin therapy.

Retrospective studies found little evidence for the use of routine laboratory testing [30, 31]. A retrospective study of 141 patients treated with isotretinoin (at a dose of 0.5–1.0 mg/kg) for acne showed that very few statistically significant elevations in liver enzymes or lipid profiles occurred. In only one case treatment discontinuation has been necessary [32]. There were statistically significant elevations in triglycerides, cholesterol, and aspartate aminotransferase (AST or SGOT), with triglyceride levels showing the largest average change (60 % increase). All abnormalities were apparent within the first 2 months of therapy. One patient developed very large increases in both AST and alanine aminotransferase (ALT or SGPT) levels and had to discontinue therapy, and he was not included in the statistical analysis [32]. Previous studies have shown rare laboratory abnormalities that seldom led to withdrawal of therapy [31, 33–38].

A review of 1,000 acne patients treated with isotretinoin showed that none had laboratory changes to result in cessation of therapy [39]. Another retrospective study of 1,292 acne patients treated with isotretinoin in private practice was evaluated for laboratory abnormalities. Between 1992 and 1994 laboratory tests were performed before treatment and every 4 weeks during treatment. From 1994 to 1999 only a single laboratory evaluation was performed after the initial 4 weeks of treatment as routine. Laboratory evaluations were carried out in 876 patients, including complete blood count, liver function tests, blood lipids, and pregnancy test. Serum creatine kinase (CK) levels were measured in patients undergoing strenuous physical activity during treatment. Cholesterol elevations were noted in 6.1 % and triglyceride elevations in 5.1 %. Liver enzymes were moderately elevated in a minority of patients (percentage not reported). CK increased levels were noted in 3.4 %. All abnormal values returned to normal despite continuation of isotretinoin. The authors concluded that there is no need to perform routine laboratory tests in young and healthy acne patients treated with isotretinoin, but underline the need for adherence to guidelines of preventing pregnancy [30].

In another study, 91 patients treated with oral isotretinoin (0.5 mg/kg/day) were monitored monthly for alterations in the results of blood tests, including glucose, liver and kidney tests, hemogram, cholesterol, triglyceride, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, and urine analysis. Statistically significant changes were observed in cholesterol ($p<0.001$), triglyceride ($p<0.001$), and LDL-cholesterol ($p=0.001$), while no significant changes were noted in liver enzymes, creatinine, glucose, or hemogram. The increase in cholesterol, triglyceride, and LDL-cholesterol levels was below twofold of the upper limit and thus there was no need to stop treatment. Only one patient had to discontinue treatment due to increased liver function tests. There was no correlation between pre- and posttreatment blood levels and the total dose of isotretinoin [40]. Similarly, laboratory findings did not necessitate isotretinoin discontinuation in other studies [30, 41].

While there have been published case reports of dramatic reductions in hematological parameters with oral isotretinoin [28, 29, 42, 43], i.e., thrombocytopenia or neutropenia, a population-based study in a large number of patients showed very few abnormalities during isotretinoin treatment. A retrospective population-based analysis of laboratory abnormalities during isotretinoin therapy for acne included 13,772 acne patients. Substantial increases in the cumulative incidence of abnormalities were seen in serum lipid and transaminase levels, but not in hematologic parameters during isotretinoin treatment, compared with the baseline period. The cumulative incidence of new abnormalities, in patients with normal values at baseline, was 44 % for triglyceride levels and 31 % for total cholesterol level. The cumulative incidence for new abnormalities in transaminase levels was low (11 %) and most elevations were mild (91 %). Moderate-to-severe abnormalities in triglyceride, total cholesterol, and transaminase levels were generally transient and reversible. Normal baseline values for serum lipid or transaminase levels did not preclude the development of an abnormality during treatment. The authors concluded that except for patients in whom a hematologic abnormality is suspected prior to or during treatment, the diagnostic yield of routine monitoring of white blood cell count, hemoglobin level, and platelet count during isotretinoin therapy is too low to be clinically useful [44].

There are several limitations in published studies that make the interpretation of data difficult. The reported abnormalities in transaminase level might be related to comorbid hepatic conditions, concomitant medical therapy, or alcohol consumption, which have not measured. Limited sample sizes diminish the precision of these studies' estimates, and methodological differences including the lack of standard criteria for defining abnormal values and different arbitrary cut points make these studies difficult to compare.

Acne is a skin disease; blood testing during oral isotretinoin treatment should aim to detect laboratory abnormalities while being cost-effective. Recommendations on laboratory monitoring during oral isotretinoin therapy propose baseline and monthly pregnancy tests for females, a baseline fasting cholesterol level, triglyceride level, and standard liver function tests. The frequency of blood monitoring tests during oral isotretinoin therapy varies from country to country. Laboratory evaluations should be carried out at baseline and at weeks 4 and 8. If test results are normal and isotretinoin dose is not increased, no further testing may be needed unless the patient has known risk factors [17]. There is no uniform good evidence-based data directing physicians how exactly to interpret abnormal laboratory results, when to either decrease or discontinue the therapy [32].

In clinical practice, laboratory evaluations should be considered in the context of the individual acne patient. The presence of a laboratory abnormality is not necessarily clinically significant, while the absence of a laboratory abnormality does not preclude an adverse clinical outcome [44].

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# Part IX

# Treatment of Acne

# Evidenced-Based Treatment of Acne

# 51

Christos C. Zouboulis and Aikaterini I. Liakou

## Contents



**Core Messages**

- Acne is a dermatological disease with multifactorial pathogenesis and diverse treatment options that should be used by dermatologists on an evidence-based mode.
- A topical antimicrobial monotherapy is not recommended; combinations with topical retinoids, benzoyl peroxide, or azelaic acid and in women with systemic hormonal antiandrogens are advisable.
- Topical retinoids should be applied as monotherapy in comedonal and papulopustular acne and in combination with BPO, recommended antibiotics, azelaic acid, and/or systemic antibiotics in moderate and severe acne.
- Benzoyl peroxide is recommended in mild papulopustular acne as basis therapy, whereas in moderate and severe acne in combination with retinoids, antibiotics, azelaic acid, and/or systemic or topical antibiotics.
- Systemic therapy with antibiotics is recommended for the treatment of moderate-to-severe inflammatory acne and as a basis therapy for any form of inflammatory acne that does not respond adequately to topical therapy.
- Systemic isotretinoin therapy (cave: pregnancy) is recommended as a basis

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therapy for severe acne that is unresponsive to topical and systemic antibiotic therapy.
- The antiandrogenic hormonal therapy is not recommended as a primary monotherapy for noncomplicated acne.

## 51.1 Introduction

Acne is the most common dermatologic disease and manifests with different clinical presentations and in varying ages, but mostly at about 70–95 % of all young people aged 15–18 years [1]. Acne lesions occur especially on the face and upper trunk. In the majority of patients acne regresses spontaneously after puberty. In 10 % of cases, however, the disease persists over the 25th year of age. Acne can be classified according to the clinical picture, the age of onset, and its severity (Table 51.1).

In this chapter, the various therapeutic possibilities according to the current German S2k guidelines [2] (Fig. 51.1) and the European S3 guidelines [3] for treatment are summarized.

**Table 51.1** Classification of acne

| |
|---|
| According to the clinical picture |
| • Acne comedonica |
| • Acne papulopustulosa |
| • Acne papulopustulosa/nodosa |
| • Acne conglobata |
| • Acne fulminans |
| According to the age of onset |
| • Acne neonatorum |
| • Acne infantum |
| • Acne praecox |
| • Acne vulgaris |
| • Acne tarda |
| According to the severity |
| • Mild acne |
| • Moderate acne |
| • Severe acne |

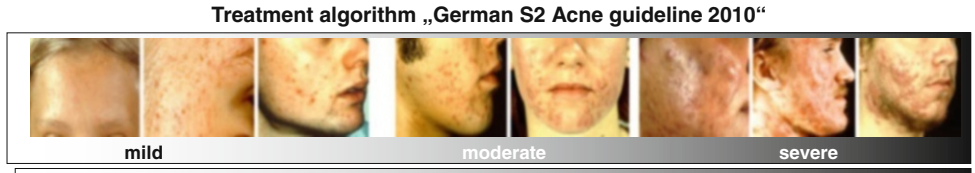


**Fig. 51.1** Acne treatment after the German S2k guidelines (Nast et al. [2])

## 51.2 Topical Treatment

A topical antimicrobial monotherapy is not recommended. It is only advisable for mild-to-moderate acne in combination or fixed preparations with topical retinoids, benzoyl peroxide, or azelaic acid. In women with moderate acne topical antimicrobial therapy is also recommended in combination with systemic hormonal antiandrogens. Contraindication of erythromycin is preexisting liver disease, of clindamycin pregnancy and lactation, and of tetracyclines pregnancy, lactation, severe hepatic dysfunction, and renal failure. The topical antimicrobial therapy is applied 1–2×/day and the treatment should last from 2 to 12 weeks. A prolongation of treatment is not recommended because no significant improvement of the achieved therapeutic outcome is expected; in contrast increased prevalence of antibiotic resistance against *Propionibacterium acnes* can occur.

Topical therapy with benzoyl peroxide (BPO) is recommended in mild papulopustular acne as basis therapy, whereas in moderate and severe acne in combination or in fixed preparations with retinoids, antibiotics, azelaic acid, and/or systemic antibiotics or in combination or in fixed preparations with topical antibiotics. A known sensitization to BPO is the only restriction of application. BPO is applied 1–2×/day and the treatment should be performed over 8–12 weeks.

Topical therapy with retinoids is basis monotherapy in comedonal and papulopustular acne (adapalene > isotretinoin, tretinoin), whereas in moderate and severe acne in topical combination or fixed preparations with BPO, recommended antibiotics, azelaic acid, and/or systemic antibiotics. The major contraindication is pregnancy and lactation, because of the dose-independent teratogenicity. Topical retinoids should be applied 1–2×/day; the treatment duration is 8–12 weeks.

Topical therapy with azelaic acid is recommended for comedonal and papulopustular acne as well as for moderate and severe acne in combination with BPO, antibiotics, retinoids, and/or systemic antibiotics. Azelaic acid is applied 2×/day and should last longer than 12 weeks.

## 51.3 Systemic Treatment

Systemic therapy with antibiotics (doxycycline > minocycline, tetracycline) is recommended for the treatment of moderate-to-severe inflammatory acne and as a basis therapy for any form of inflammatory acne that does not respond adequately to topical therapy. Systemic antibiotics are not recommended as monotherapy, but in combination with topical retinoids, BPO, or azelaic acid and in women with hormonal oral antiandrogens. The recommended daily dose of doxycycline is from 50 mg/day to 2 × 100 mg/day, for minocycline 2 × 50 mg/day, for tetracycline HCl 2 × 500 mg/day, and for erythromycin 2 × 500 mg/day. The treatment should last between 1 and 3 months. If there is no preexisting liver disease, laboratory controls during this brief antibiotic therapy is not required. Depending on seasonal and individual UV exposure light protection against UVA is required under doxycycline, minocycline, and tetracycline.

Systemic isotretinoin therapy is recommended as a basis therapy for severe acne (papulopustular acne/nodosa or conglobata) that is unresponsive to topical and systemic antibiotic therapy. The recommended daily dose is in papulopustular acne/nodosa at least 0.3 mg/kg/day as a loading dose and in acne conglobata at least 0.5 mg/kg/day in 2 daily doses. The duration of treatment at the above-mentioned daily dose is at least 6 months. At the beginning of therapy, one month after the start of treatment and every 3 months during treatment serum liver enzymes and lipids (cholesterol, triglycerides) should be controlled. Women of childbearing age must sign a consent form before isotretinoin therapy. A pregnancy test should be negative twice before, monthly during treatment, and 5 weeks after the end of therapy.

The antiandrogenic hormonal therapy (ethinylestradiol combined with cyproterone acetate, chlormadinone acetate, dienogest, desogestrel, or drospirenone) is not recommended as a primary monotherapy for noncomplicated acne. It is recommended for female patients with moderate papulopustular acne to acne conglobata,

in young women of reproductive age with signs of peripheral hyperandrogenism with/without hyperandrogenemia, in adult women with acne tarda as a sign of peripheral hyperandrogenism, in adult women with persistent acne despite the administration of classical therapy, and also in patients with SAHA (seborrhea, acne, hirsutism, androgenetic alopecia) syndrome. An increased thromboembolic risk is to be considered when initiating therapy with hormonal antiandrogens; the therapy should last at least 12 months.

Systemic corticosteroids are not recommended for standard use in acne, but only in special cases such as in systemic inflammatory complications (e.g., acne fulminans) or exacerbation under systemic isotretinoin therapy.

**Conclusions**

Acne is a dermatological disease with multifactorial pathogenesis and diverse treatment options that should be used by dermatologists on an evidence-based mode.

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# The Difficult Acne Patient

# 52

Andreas D. Katsambas and Clio Dessinioti

## Contents



**Core Messages**

- The acne patient may prove difficult to treat, as acne may relapse after initial clearing, persist in spite of treatment, worsen during therapy, or result in scarring.
- Treatment failures or flare-ups during oral antibiotic treatment may be associated with poor compliance, inadequate duration of treatment, a high sebum excretion rate, gram-negative folliculitis, or resistance of *Propionibacterium acnes*.
- After completion of oral isotretinoin therapy, the risk of relapse may be reduced by maintenance therapy with a topical retinoid.
- Combination therapy of a topical retinoid or benzoyl peroxide with oral or topical antibiotics is recommended in order to maximize clinical efficacy and minimize *P. acnes* resistance.
- Endocrine evaluation may be useful for women whose acne relapses shortly after isotretinoin therapy or is refractory to conventional acne treatments.
- Acne during pregnancy should be minimally treated. If systemic treatment is necessary, erythromycin is the treatment of choice.

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- There is a plethora of different approaches for the treatment of acne scarring, including a combined 0.1 % retinaldehyde/6 % glycolic acid cream, chemical peelings, laser resurfacing, dermabrasion, fillers, and skin surgery.

## 52.1 Introduction

Acne is the most common skin disease, and it may affect almost 80 % of adolescents and young adults 11–30 years of age [1].

Acne treatment may occasionally fail, and the acne patient may prove difficult to treat; acne may relapse after initial clearing, it may persist in spite of treatment, or it may worsen during therapy. Also, women with acne during pregnancy may represent a difficult-to-treat group of patients and merit special consideration.

## 52.2 Recalcitrant Acne and Acne Flare-Ups During Treatment

### 52.2.1 Treatment Failure and Acne Flare-Ups During Antibiotic Treatment

Treatment failures or flare-ups during oral antibiotic treatment may be associated with poor compliance, inadequate duration of treatment, a high sebum excretion rate, gram-negative folliculitis, or resistance of *Propionibacterium acnes* [2, 3] (Table 52.1).

In order to maximize compliance, a thorough discussion with the patient before treatment initiation is essential. The patient should be given clear instructions, and he or she should be informed about potential side effects and that clinical improvement typically requires 4–8 weeks of therapy [3] (see Chap. 53).

Gram-negative folliculitis is caused by gram-negative species, such as *Klebsiella*, *Pseudomonas*, *Proteus*, and *Enterobacter* and should be treated with systemic antibiotics (usually ampicillin) and/or isotretinoin [3].

**Table 52.1** Management of treatment failures and acne flare-ups

| | |
|---|---|
| Poor compliance | Discuss with the patient, improve compliance |
| Inadequate duration of isotretinoin treatment | • Cumulative isotretinoin dose 120–150 mg/kg<br>• Maintenance treatment with topical retinoid or benzoyl peroxide |
| Development of gram-negative folliculitis | Systemic antibiotics and/or isotretinoin |
| Resistance of *P. acnes* | • Avoid antibiotic monotherapy<br>• Discontinue antibiotic use after clinical improvement<br>• Avoid use of chemically dissimilar oral and topical antibiotics<br>• Use combination therapy of a topical retinoid or benzoyl peroxide with oral or topical antibiotics |
| High sebum excretion rate | • Oral isotretinoin<br>• Hormonal treatments |
| Macrocomedones | • Gentle cautery |
| Moderate recalcitrant acne | • Oral isotretinoin<br>• Rule out androgen excess<br>• Rule out late-onset congenital adrenal hyperplasia |
| Initial worsening with isotretinoin treatment | • Low-dose isotretinoin<br>• Initial concomitant use of low-medium dose of oral corticosteroids and tapering in order to avoid or treat initial flare-up |

*P. acnes* is among the major factors contributing to acne pathogenesis [4]. Resistance of *P. acnes* to antibiotics is an emerging problem, and it has been linked to reduced clinical efficacy of antibiotic treatments [5]. Resistance is more common with erythromycin, less common with tetracycline, doxycycline, and trimethoprim, and rare with minocycline [6]. A strategy that has been proposed to minimize microbial resistance is to discontinue oral antibiotics when acne control is achieved and to avoid antibiotic monotherapy. Instead, using combination therapy of a topical retinoid or benzoyl peroxide with oral or topical antibiotics is recommended [7]. Also,

topical antibiotics should not be used as monotherapy due to their relatively slow onset of action and risk of bacterial resistance. Concomitant use of chemically dissimilar oral and topical antibiotics should be avoided [7].

Moreover, in moderate cases of acne unresponsive to conventional therapy, systemic isotretinoin may be used, although it is not currently approved for this indication [8].

### 52.2.2 Association of Recalcitrant Acne with Hyperandrogenism

Hyperandrogenism, including polycystic ovary syndrome, is to be ruled out in women whose acne is severe, is of sudden or late onset, is refractory to therapy, and/or is associated with other signs of hyperandrogenism. These include menstrual irregularities, infertility, acanthosis nigricans, and the seborrhea/androgenic alopecia, hirsutism/acne (SAHA) syndrome [9, 10] (Table 52.2). These patients often have insulin resistance and are at increased risk of developing diabetes mellitus and cardiovascular disease. Consequently, appropriate therapy is crucial for these patients in order to avoid these long-term complications.

Women with acne associated with proven ovarian or adrenal hyperandrogenism, hirsutism, androgenetic alopecia, severe sebum secretion, or premenstrual flares may benefit from hormonal therapy [10]. Also, hormonal therapy with or without the concomitant use of oral antibiotics is indicated in women with recalcitrant acne who desire contraception and have no contraindications regarding the use of oral contraceptives [10] (see Chap. 64).

In male patients, acne may be the only clinical sign of androgen excess. In case of severe acne, unresponsive to oral retinoids or resistant to conventional treatment, endocrinology tests may be performed. These include LH (luteinizing hormone), FSH (follicle-stimulating hormone), testosterone, dehydroepiandrosterone sulfate, androstenedione, and 17-hydroxyprogesterone. In addition, an adrenocorticotropic hormone (ACTH) stimulation test is warranted to detect patients with mild forms of congenital adrenal hyperplasia that present with normal basal adrenal steroids. The ACTH stimulation test is performed by injecting the hormonally active ACTH fragment (25 IU) (Tetracosactide, Synacthen®, Novartis, Nurnberg, Germany) after the collection of blood for the determination of basal 17-hydroxyprogesterone serum levels. After 60 min another blood sample is collected for the determination of stimulated 17-hydroxyprogesterone serum levels. Late-onset congenital adrenal hyperplasia is considered if basal 17-hydroxyprogesterone is increased and/or ACTH-stimulated 17-hydroxyprogesterone lies between 1,000 and 10,000 ng/dL [11] (see Chap. 31).

**Table 52.2** Laboratory evaluations to rule out androgen excess in the difficult acne patient

| |
|---|
| LH |
| FSH |
| Testosterone |
| DHEAS |
| Androstenedione |
| 17-hydroxyprogesterone |
| ACTH stimulation test |
| Insulin |

Late-onset congenital adrenal hyperplasia, also referred as nonclassical steroid 21-hydroxylase deficiency, is an autosomal recessive disorder due to mutations of the 21-hydroxylase gene. When recalcitrant acne is attributed to late-onset congenital adrenal hyperplasia, low-dose methylprednisolone is recommended in order to counteract adrenal androgen production. Of note, systemic glucocorticoids should not be taken for a period longer than 6 months, due to a risk of osteoporosis. Concomitant treatment with oral isotretinoin may be initiated [11].

### 52.2.3 Acne Flare-Ups During Isotretinoin Treatment

An acne flare-up may occur during the first 2 months of oral isotretinoin treatment in 6 % of patients. In severe cases, oral prednisone 0.5–1.0 mg/kg daily for 2–3 weeks may be needed, with gradual tapering. If this is not sufficient, isotretinoin should be reduced or even

discontinued. If isotretinoin is discontinued, it should be reinitiated at a lower dose of 0.1 mg/kg daily and slowly increased to 0.5 mg/kg daily [2, 3].

Oral corticosteroids at a low-medium dose over a period of 4–6 weeks with gradual tapering may be administered at the beginning of isotretinoin treatment in order to avoid initial flare-up from developing [2, 3].

In order to avoid initial worsening and adverse events, treatment can begin with a low or very low dose of 0.2–0.3 mg/kg/day for 1 month and then slowly increase to 0.5–0.7 mg/kg/day for the remaining of treatment (accumulative dose of 120–150 mg/kg) [2, 3].

Gentle cautery of macrocomedones is crucial before oral isotretinoin initiation in order to avoid acne flaring or even acne fulminans. During this procedure, a local anesthetic cream is applied for an hour, and then macrocomedones are treated with cautery for less than 1 s and with a temperature sufficient enough to just char paper toweling [12].

## 52.3 Relapsing Acne

Oral isotretinoin has revolutionized acne treatment. It is approved for the treatment of severe, recalcitrant nodular acne, but it may also be useful for less severe forms of acne that are recalcitrant to conventional treatments or for acne that may cause physical or psychological scarring [13].

Nevertheless, recurrence of acne after a course of oral isotretinoin has been reported in approximately 30–50 % of patients, and a second course of isotretinoin is often needed (Fig. 52.1). Risk factors for acne relapse include low-dose regimens, severe acne, prepubertal acne, a family history of acne, and acne involving the trunk [14, 15] (see Chap. 66).

Intermittent moderate-dose isotretinoin has been proposed for adult patients with mild acne unresponsive or rapidly relapsing after treatment with oral antibiotics [1].

Furthermore, acne may relapse after a successful treatment with oral antibiotics, in which case the same antibiotic should be prescribed [7].

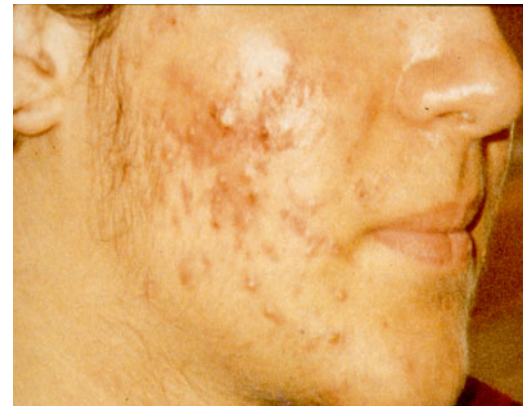

**Fig. 52.1** Difficult acne patient: relapsing acne in an adult female patient associated with signs of hyperandrogenism (hirsutism)

Maintenance therapy with a topical retinoid may reduce the relapse rate and sustain acne remission, by controlling microcomedo formation which is the primary acne lesion [7]. In addition, an endocrine evaluation may be useful for women whose acne relapses shortly after isotretinoin therapy [10].

## 52.4 Management of Side Effects During Isotretinoin Treatment

Treatment of acne with systemic isotretinoin is associated with certain reversible, dose-related side effects. Mucocutaneous side effects develop in 80–90 % of patients, and headaches, musculoskeletal side effects, elevations in serum lipids, and liver enzymes may be observed in up to 20 % of patients [2].

Low-dose isotretinoin regimens have been proposed as an alternative for moderate cases of acne unresponsive to conventional treatments. Amichai et al, showed that patients treated with low-dose isotretinoin for 6 months (20 mg/day, approximately 0.3–0.4 mg/kg daily) showed less severe mucocutaneous effects and laboratory abnormalities than patients treated with higher doses. During the 4-year follow-up period, acne relapses occurred in 3.9–5.9 % of the patients according to their age [8].

Treatment with vitamin E (α-tocopherol) has been proposed in order to prevent many of the toxic reactions associated with high-dose retinoid therapy; however, a large-scale, double-blind, randomized study in patients with acne vulgaris showed that concomitant administration of vitamin E (800 IU daily) does not change typical side effects of isotretinoin given at a dose of 1 mg/kg daily [16].

Hypertriglyceremia and hypercholesterolemia occur in 25 % of patients, but they are reversible after treatment withdrawal. An increase of liver enzymes may occur in 15 % of patients, but is generally mild and transient despite continued treatment. Rarely is treatment discontinuation warranted due to laboratory abnormalities [1, 2].

Oral isotretinoin use has been associated with a plethora of psychiatric adverse events, including depression, psychosis, mood swings, violent behavior, suicide, and suicide ideation. These psychiatric symptoms were initially thought to be idiosyncratic reactions to the drug. While some studies and case reports have reported mood disorders, depression, suicidal ideation, and suicides in patients taking isotretinoin [17], other studies have failed to show such an association [18], thus not allowing for a definite conclusion to be drawn.

## 52.5 Severe Acne During Pregnancy

Generally, acne in pregnancy should be minimally treated when the dermatologist deems it to be necessary and the patient agrees with this decision [7].

However, some female patients with severe acne and risk of scarring will need treatment. Recommendations concerning the use of topical treatments during pregnancy differ depending on the country. In some countries, use of topical azelaic acid or topical erythromycin is permitted. Systemic treatments that are contraindicated during pregnancy include oral isotretinoin, oral tetracyclines, and hormonal therapies. If needed, systemic erythromycin is the treatment of choice. For severe inflammatory acne, short courses of oral corticosteroids may be useful after the first trimester. Cooperation of the treating dermatologist with a gynecologist is advised in order to determine optimal treatment for the patient [7].

## 52.6 Scarring

Although acne is not a life-threatening disease, it may cause scarring and significant psychological distress which may range from mild anxiety, embarrassment, low self-esteem, and perceived social rejection to depression and suicide [7].

Pathogenesis of acne scars is complex and may involve severe inflammatory response to *P. acnes*, proliferation, and remodeling (see relevant Chap. 71). Acne scars may be divided into three types: icepick, rolling, and boxcar. Currently available treatments for acne scars include chemical peeling, laser resurfacing (see Chap. 70), dermabrasion, fillers, and skin surgery [19].

**Conclusions**

Although acne is a benign skin disease, it may represent a therapeutic challenge. Relapse of acne after initial improvement, flare-up during therapy, treatment failure, scarring, or the development of severe acne during pregnancy may place the acne patient in a difficult-to-treat situation.

In this review, we have analyzed different approaches to these therapeutic dilemmas in order to enhance treatment outcomes and achieve *restitutio ad integrum*.

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# Improving Compliance with Acne Therapy

# 53

Andreas D. Katsambas

## Contents



**Core Messages**

- Poor compliance has been reported to be the most common cause of nonresponse to acne medication.
- Few studies assessing patient compliance exist in acne.
- A range of disease-related (past history of acne medications, Dermatology Life Quality Index score) and social factors (sex, age, employment status, smoking, alcohol intake) may influence compliance with acne treatments.
- Compliance, efficacy, and simplicity of dosage regimen are closely related. Efficacy relies on good dosing compliance, and good compliance results from convenience in use and treatment tolerability.
- Patient compliance is greatly influenced by the dermatologist, and strategies to improve compliance include considering patient's preferences for treatment, educating the acne patient, designing new formulations, and keeping side effects to a minimal.
- Patient education involves a thorough discussion before treatment initiation, giving clear instructions, explaining the potential role of diet, sunlight, stress, and cosmetics in acne, and informing the patient on expected side effects.

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- The patient should be informed about the most frequently expected side effects, and he/she should be provided with simple what-to-do advice.

## 53.1 Introduction

Although acne is thought to be the most common dermatosis with a good response to treatment, there are cases when treatment fails (see Chap. 52). Poor patient compliance is thought to be a major reason for acne treatment failure, and medication adherence is critical to efficacy [1, 2]. This chapter will review strategies to improve patient compliance including patient education, the advent of new formulations, and the avoidance of side effects.

## 53.2 Assessment of Patient Compliance

Although there has been increasing interest in the assessment of patient compliance, only a limited number of studies exist in acne. In order to improve compliance, we should first be able to recognize the responsible factors that influence it. It has been shown that a range of disease-related and social factors may influence compliance with treatment in acne (Table 53.1).

Possible factors that may affect compliance were investigated in an open prospective study of 403 acne patients who were treated either with isotretinoin or with conventional therapies. Being female, married, employed, and not paying for prescription were characteristics associated with increased medication adherence [3]. Also, patients receiving oral isotretinoin for the first time were most compliant (increased medication adherence) compared with patients who had received isotretinoin more than once (87.5 % vs. 60.5 %, respectively). This finding was attributed to the loss of faith in the effectiveness of isotretinoin after the failure of a first course [3]. Other studies have also suggested that first-time use encourages compliance [4]. Moreover, the correlation between either age or the Dermatology Life Quality Index (DLQI) score and medication adherence was significantly negative in this study, indicating that younger patients and those more psychologically affected by acne are less likely to comply with proposed treatments [3]. A large-scale worldwide observational study of adherence with acne therapy showed an overall poor adherence rate of 50 %. Poor adherence was significantly associated with the occurrence of side effects, lack of improvement, previous systemic therapy, lack of knowledge about acne treatment, consultation with a primary care physician, and lack of patient satisfaction with treatment. Factors that had a positive effect on adherence included more severe acne, use of cosmetics, and knowledge of acne therapy [5].

**Table 53.1** Characteristics associated with increased patient compliance

| | |
|---|---|
| Social characteristics | Females |
| | Older age |
| | Married |
| | Employed |
| | Nonsmokers |
| | Nondrinkers |
| | Not paying for prescription (no cost) |
| Disease-related factors | First-time users of oral isotretinoin |
| | Higher DLQI score |
| Iatrogenic factors | The role of the dermatologist |

Patient compliance is greatly influenced by the dermatologist, and strategies about educating the acne patient, choosing the most appropriate treatment regimen for the individual patient, and keeping side effects to a minimal will be discussed in the following section.

## 53.3 Strategies for Improving Patient Compliance: The Role of the Dermatologist

### 53.3.1 Considering Patient's Preferences

Treatment has to be tailored according to the individual patient. If the recommended treatment interferes significantly with the patient's lifestyle,

patient compliance will be minimal and the result of treatment poor [2].

Moreover, patient compliance might be enhanced by taking into account patient preferences for acne medications [6]. Adolescents often abandon acne treatments prematurely because of a slow onset of action, irritation, or inconvenience in use. Male patients generally do not like using many different products, so a simple regimen consisting of a cleansing soap and one topical combination treatment should suffice for cases of mild acne.

Strategies to improve adherence and the resulting outcomes of topical therapies include simplifying the treatment regimen and identifying cues that remind patients to use the medication. Also, it should be taken into account that the compliance reported by patients often greatly exceeds reality, and it has been proposed to question patients on the quantity of oral medication they have used, in order to maximize compliance [2].

As far as topical acne treatments are concerned, fixed-dose combination formulations and once-daily treatments may enhance compliance [1, 4, 7].

**Table 53.2** Strategies to improve compliance in acne therapy

| Improving patient compliance | What to do |
|---|---|
| General approach | Tailor treatment to the individual patient |
| | Select a treatment that will not interfere with the patient's lifestyle |
| | Take into account patient's preferences |
| Educating the patient | Discussion before treatment |
| | Provide clear instructions |
| | Explain the rhythm of improvement |
| | Explain the role of cosmetics |
| | Explain the role of sunlight, diet, stress |
| | Explain potential side effects |
| | Use of maintenance therapy |
| New formulations | Micronized isotretinoin |
| | Extended-release minocycline |
| | New topical combination formulations |
| Minimizing side effects | Short-contact topical retinoids |
| | Low-dose oral isotretinoin when indicated |
| | Avoid monotherapy with antibiotics |

## 53.3.2 Educating the Patient

Patient education is outlined in Table 53.2 and should include the following steps.

### 53.3.2.1 Discussion Before Treatment

A discussion before any treatment proposal is mandatory. The dermatologist should spend at least 20 min with an acne patient in the first counseling visit.

The natural course of acne has to be explained in simple, understandable phrases and terms. Scientific terminology should be avoided. We suggest the use of a simple figure (Fig. 53.1) showing the expected severity and duration of acne. The patient should understand that acne usually presents at the age of 12–14 years old, gradually progresses during adolescence, and finally resolves by the age of 23–27 years old in the majority of patients [2].

On the other hand, there are cases when acne persists beyond the expected age, and thus, no patient is "too old to have acne." Adult acne frequently causes discomfort and cosmetic disability with inflammation, pigmentary changes, and scarring. Physicians should be sensitive to all these issues and should consider the implications of psychosocial disability caused by acne when managing these patients [8] (see Chap. 32).

Patients often have questions concerning the potential role of diet, sunlight, or stress on their acne, which should be adequately answered (see Chaps. 24, Natural and artificial sun tanning). A review of the literature reveals that there is not sufficient scientific data to provide consistent and good-quality patient-oriented evidence on this controversial issue [7, 9]. It remains to be seen whether certain foods (especially saturated fats or foods with a high glycemic index) may cause hyperinsulinemia in humans. We feel that more systematic controlled studies are warranted so that a final conclusion on the diet–acne hypothesis may be drawn. Until then, if the patient reports

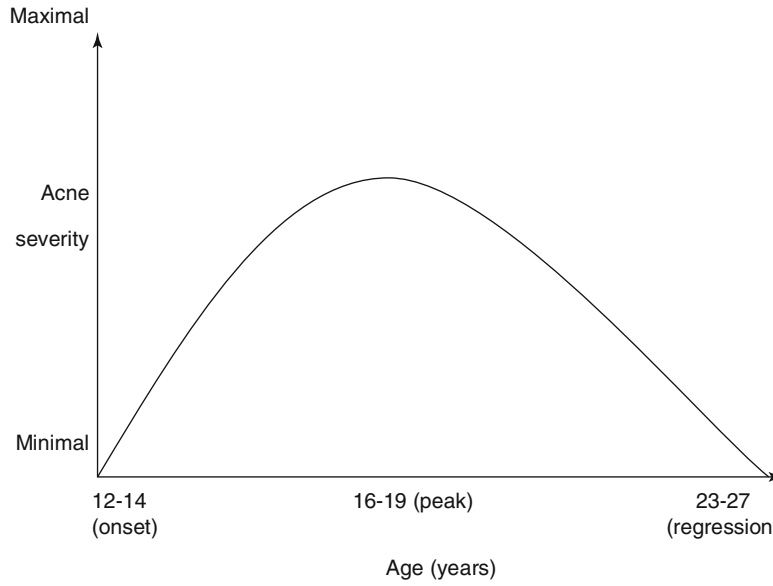


**Fig. 53.1** Expected natural course of acne

that certain foods, such as chocolate, pizza, or "junk" foods, result in an acne flare-up, we suggest to advise him or her to avoid them.

Exposure to sunlight has a beneficial effect on acne in the majority of cases, especially when acne is localized on the back and chest, but deterioration may be noted in 20 % of patients. If acne patients insist that sunlight has a negative effect on their acne, then they should be advised to avoid sun exposure [2].

Stress has traditionally been the main culprit in aggravating acne according to our patients. It has been reported that 74 % of acne patients and their parents think anxiety exacerbates acne [10]. Nevertheless, little research has been undertaken to investigate if this perception can be substantiated. A significant association between acne severity and increased stress levels during examination periods has been reported in a prospective study of 22 patients, even after controlling for changes in diet and sleep habits. However, the authors pointed out that the association observed could in part be due to worsened acne itself causing increased stress, instead of the reverse [11]. Various mechanisms have been proposed to explain how stress may aggravate acne vulgaris. Glucocorticoids and adrenal androgens, which increase with stress, are hormones known to influence acne and corticotropin-releasing hormone increases sebaceous lipogenesis and upregulates cutaneous conversion of androgen precursors to testosterone [12]. Also, neuroactive substances within the epidermis, such as substance P, have been incriminated to upregulate lipid synthesis in sebaceous cells and to stimulate the proliferation of sebaceous glands [13].

#### 53.3.2.2 Give Clear Instructions

Before starting any therapy for acne, it is necessary to advise the patient to apply topical therapeutics (e.g., topical retinoids), not only to the lesions themselves but also to the surrounding uninvolved skin, in order to target the microcomedone, the primary lesion of acne that is not visible by the naked eye [1].

In order to minimize irritation associated with the use of topical retinoids, short durations of application should be adopted at first, with gradual increments in application time as tolerated [8]. Also, patients should be advised to use a gentle cleanser and a moisturizer [1].

Oral isotretinoin should be instructed to be taken in two divided doses, with food, in order to increase its bioavailability. Also, treatment should be started at lower doses and increased according to tolerability [7, 14].

In order to sustain acne remission, patients should be informed about the need of maintenance

therapy with a topical retinoid, as it results in a reduction of comedones and micorcomedones [1].

#### 53.3.2.3 Explain the Rhythm of Improvement

It is recommended to inform the patient about the possible length of time required for clinical improvement to begin. Sometimes an aggravation may be experienced during the first few weeks of therapy, but in most patients acne will improve by 60 % in 4 months and by at least 80 % in 6 months [15]. Furthermore, the patient should be aware that systemic treatment should be continued for a sufficient period of time in order to achieve optimal results: 6–8 months for isotretinoin, 6 months to 1 year for hormonal treatments, and up to 6 months for oral antibiotics [2].

#### 53.3.2.4 Explain the Role of Cosmetics

Skin care products are a necessary complement to acne medications [16]. They are also suggested in order to counteract the drying effect of topical retinoids, benzoyl peroxide, azelaic acid, and oral isotretinoin. Noncomedogenic and nonacnegenic cosmetics and makeup should be recommended for acne patients [2, 17].

#### 53.3.2.5 Explain Expected Side Effects

An explanation of the most frequent side effects to expect with a proposed acne treatment should be provided to the patient, together with simple advice on how to handle them. If the patient is informed in advance on what to expect and what to do, and has already agreed to that, there is little chance of decreased compliance. The more common side effects associated with acne treatments and simple what-to-do points are presented in Table 53.3.

The benefits and risks of oral isotretinoin treatment should be explained to patients or parents of minors. Some patients are reassured to learn that isotretinoin is a naturally occurring endogenous compound [1, 18]. Given the fact that isotretinoin results in dryness of the lips (100 %), skin (50 %), nasal passages (30–50 %), and eyes (20 %), it may cause dermatitis, cheilitis, epistaxis, and conjunctivitis. The frequent application of moisturizers is usually sufficient and only rarely are topical steroids or antibiotics required. Patients who wear contact lenses may need to switch to eyeglasses because of the conjunctival dryness [19].

### 53.3.3 Designing New Formulations

The desire for acne treatments associated with a decreased risk of adverse events, and hence, better compliance, has led to the emergence of new formulations.

New and emerging systemic antibiotics include lymecycline, azithromycin, anti-inflammatory dose doxycycline, and a new extended-release (ER) minocycline formulation. These agents may

**Table 53.3** Expected side effects with acne treatments and what-to-do suggestions for the patient

| Acne treatment | | Side effect | What to do |
|---|---|---|---|
| Topical treatment | Retinoids | Irritant dermatitis | Apply gradually to the face<br>Noncomedogenic moisturizers |
| | Benzoyl peroxide | Bleaches clothes | White shirt |
| | Azelaic acid | Irritant dermatitis | Noncomedogenic moisturizers |
| Systemic treatment | Minocycline | Headaches<br>Dizziness<br>Drowsiness | Discontinue |
| | Doxycycline | Photosensitivity | Avoid sun exposure |
| | Azithromycin | Gastrointestinal upset | Take with food |
| | Isotretinoin | Cheilitis/Dermatitis<br>Rhinitis<br>Myalgia<br>Arthralgia<br>Teratogenicity | Moisturizers<br>Nasal ointment bacitracin<br>Avoid rigorous exercise<br>Paracetamol, nonsteroidal anti-inflammatory drugs<br>Contraception during and for 1 month after isotretinoin discontinuation |

potentially improve compliance through enhanced efficacy (lymecycline), a favorable safety profile (azithromycin, ER minocycline), or reduced bacterial resistance (anti-inflammatory dose doxycycline) [7]. Indeed, compliance, efficacy, and simplicity of dosage regimen are closely related. Efficacy relies on good dosing compliance and good compliance results from convenience in use and treatment tolerability [1, 5].

Once-daily use of a micronized and more bioavailable formulation of oral isotretinoin has been proposed for severe recalcitrant nodular acne. This new formulation can be taken with food at a single daily dose of 0.4 mg/kg, with the same clinical efficacy to the standard twice-daily formulation [20].

### 53.3.4 Minimizing Side Effects

The development of side effects during treatment and hence diminished patient tolerability can lead to decreased compliance.

There is evidence that clinical side effects and laboratory abnormalities associated with oral isotretinoin use are dose dependent. The use of oral isotretinoin by 638 patients with moderate papulopustular acne, at a dose of 0.3–0.4 mg/kg/day for 6 months (mean cumulative dose: 66.8–70.2 mg/kg) in a prospective open-label study, was shown to be effective and linked with a low incidence of severe mucocutaneous side effects and laboratory abnormalities. In particular, hyperlipidemia was noted in only 4.2 % of patients treated with low-dose isotretinoin compared with 35 % in patients receiving the classic regimen. Elevation of liver enzymes was found in 4.8 % of patients compared with 10 % in patients treated with the classic dose. A 4-year follow-up of these patients revealed that acne relapse occurred in 3.9 % of the patients aged 12–20 years and in 5.9 % of the patients aged 21–35 years [21].

An acne flaring may occur during the first 2 months of isotretinoin treatment (at a dose of 0.5–1.0 mg/kg/day) in 6 % of patients. Depending on severity, it may require the administration of 0.5–1.0 mg/kg/day of prednisone for 2–3 weeks with gradual taper thereafter, with or without the need for isotretinoin reduction or discontinuation. A lower starting dose of isotretinoin has been recommended in order to avoid this adverse event [14].

**Conclusions**

Since acne is a chronic disease, it may necessitate treatment for months or years. Improving patient compliance is a prerequisite for optimal treatment results. The role of dermatologists is central in considering patients' preferences for treatment, educating the acne patient, using new formulations, and keeping side effects to a minimal.

When the relationship between doctor and patient has been built on trust and confidence, all acne may be optimally managed.

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# Keratolytic Treatment

# 54

Ali Alikhan and Howard I. Maibach

## Contents



**Core Messages**

- This chapter examines keratolytic agents utilized in acne treatment. Despite varying mechanisms of action, these agents target aberrant desquamation and proliferation of keratinocytes.
- Keratolytic agents have long been the cornerstone of acne therapy, coming in a variety of formulations and potencies. Though novel retinoid agents have expanded our therapeutic arsenal, established treatments like benzoyl peroxide still play a prominent role in acne therapy.
- Controlled trials have established effective keratolytic regimens and dosages for various acne presentations.
- Laboratory research has more precisely defined how keratolytic agents function. A colorimetric protein assay utilizing the tape strip method will be of invaluable use in measuring keratolytic efficacy and extending their value.

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## 54.1 Introduction

Topical keratolytic agents have long been employed for acne treatment. Shalita et al. state that "the first histologically visible change in acne is a disruption in the normal pattern of keratinization, resulting in dense, coherent squamae of

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keratinous material that accumulate to form a plug in the orifice of the follicle, leading to formation of the microcomedo" (precursor acne lesion). Furthermore, these aberrancies in proliferation, adhesion, and differentiation of the keratinocytes obstruct the infundibulum and the sebaceous duct, paving the way for excessive sebum secretion, bacterial overgrowth, and inflammatory response due to release of bacterial and cellular products.

Under light microscopy, microcomedones are visualized as layers of horny cells surrounding a sebum and bacteria core [1]. Keratolytic agents are thought to function by relaxing the cohesiveness of the stratum corneum layer, which serves as a crucial, life-sustaining barrier, keeping hydration "in" and harmful foreign agents "out." The mechanism of action does not involve keratin lysis as the name implies, but rather disintegration of desmosomes and hemidesmosomes, which link keratinocytes and bind them to the extracellular matrix respectively [2]. In this manner, these agents modulate and correct abnormal follicular keratinization.

Currently many classes of keratolytics exist (Table 54.1). Available in varying concentrations and vehicles, they may be specifically indicated depending on the type, duration, and severity of acne. The proceeding text covers widely available topical and oral keratolytics, controlled trials comparing keratolytic agents, and in vivo keratolytic protein assays. Uncontrolled trials and older acne treatments are discussed briefly.

**Table 54.1** Keratolytics currently used in the USA

| Name | Class | First introduced | Concentration(s), % | Vehicle(s) |
|---|---|---|---|---|
| Salicylic acid | β-hydroxy acid | – | 2.0 | Bar, foam |
| Glycolic acid | α-hydroxy acid | – | – | – |
| Benzoyl peroxide | Organic peroxide | 1920s | 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 8.5, 9, 10 | Gel, liquid, bar |
| Tretinoin | Retinoid | 1962 | 0.025, 0.05, 0.1, 0.01, 0.025, 0.05, 0.04 | Cream, gel, liquid |
| Isotretinoin | Retinoid | 1979 | 10 mg, 20 mg, 30 mg, 40 mg | Oral |
| Tazarotene | Retinoid | 1997 | 0.1, 0.05, 0.5 | Gel, cream |
| Adapalene | Retinoid-like | 1996 | 0.1 | Gel, cream, pledgets, solution |
| Azelaic acid | Dicarboxylic acid | – | 15.0, 20.0 | Cream, gel |
| Sulfur | Sulfur | – | 10.0 | Bar |
| Urea | Urea | – | – | – |
| Resorcinol | Phenol | – | – | – |
| Clindamycin/benzoyl peroxide | Antibiotic combination | – | 1.0/5.0 | Gel |
| Erythromycin/benzoyl peroxide | Antibiotic combination | – | 3.0/5.0 | Gel |
| Sulfur/sodium salfacetamide | Antibiotic combination | – | 5.0/10.0 | Tube, gel, cream, lotion |
| Benzoyl peroxide/urea | Keratolytic combination | – | 4.5/10.0, 8.5/10.0 | Liquid, gel |
| Sulfur/benzoyl peroxide | Keratolytic combination | – | 2.0/5.0, 5.0/10.0 | Lotion |

Table derived from: TP Habif, 2006. Skin Disease: Diagnosis and Treatment, 2nd edition. Elsevier Mosby, Philadelphia

## 54.2 Benzoyl Peroxide

Benzoyl peroxide (BPO), a mainstay treatment of mild-to-moderate acne for decades, has antimicrobial, anti-inflammatory, and anti-comedogenic effects. Acting through oxidation and formation of free radicals, its bacteriostatic activity is superior even to that of topical antibiotics [3]. It decreases inflammation by killing PMNs, preventing the release of reactive oxygen species [4] and was recently shown to be a keratolytic in vivo. Unfortunately, oxidative destruction of the stratum corneum may deplete cutaneous vitamin E, resulting in oxidation of surface lipids and proteins; this may predispose to skin dryness and desquamation [5].

BPO is absorbed effectively into the epidermis and converted to benzoic acid, with approximately 2 % entering the systemic circulation [6–8]. Its lipophilicity allows it to enter and accumulate in the lipid-rich pilosebaceous units and subcutaneous fat [4]. It is an FDA Pregnancy Category C agent, with little known about potential fetal harm or breast milk excretion, and positive in the rodent photocarcinogenicity assay.

It is widely available, both over the counter and by prescription, and comes in different concentrations, ranging from 2.5 to 10 %. Adverse effects include dryness, peeling, burning, and redness of skin, with contact allergy in 1–2 % of patients [3]. Additionally, the water-based formulations may exert less drying, scaling, burning, and erythema than the alcohol-based formulations [3, 9]. Of note, an oxidizing agent, BPO can bleach hair, clothes, and colored fabrics. It may also inactivate tretinoin if both are applied concurrently [10]; in contrast, adapalene and tazarotene remain stable in the presence of BPO [6].

The 2.5 % formulation may be as effective as the 5 % and 10 % formulations in reducing inflammatory lesions and producing positive global ratings, while causing fewer adverse reactions than the 10 % solution [11]. Compared to vehicle, 2.5 % BPO significantly decreased inflammatory lesions and improved global ratings; by the end of the 8-week study, the only significant adverse effect was peeling [11]. In a split-face, double-blind trial, a combination of BPO 5 %/urea 8 % lotion was not more efficacious in diminishing acne than BPO 5 % lotion alone; the combination took longer to dry and was stickier according to subjects [12].

Despite disappointing results with urea, combination therapy with topical antibiotics and BPO may be more effective than BPO alone. Both the clindamycin/BPO and the erythromycin/BPO formulations have shown superior efficacy when compared to either the antibiotic or BPO alone [13]. Three well-designed, randomized, double-blind, vehicle-controlled, multicenter clinical trials comparing the clindamycin/BPO gel with each individual agent and vehicle demonstrated significantly superior efficacy in inflammatory lesion reduction after 10–16 weeks [4]. In two of the trials, global improvement assessments demonstrated significantly greater improvement in the combination group. Furthermore, the side-effect profile (dry skin, peeling, and erythema) of combination therapy is comparable to that of BPO alone [4] (Table 54.2).

Leyden et al. compared clindamycin/BPO and erythromycin/BPO demonstrating statistically equivalent lesion reduction and global improvement, with similar tolerability [14] (Table 54.3). Additionally, a vehicle-controlled, randomized trial examining a 5 % BPO/1 % clindamycin combination gel in acne rosacea demonstrated significant improvement in papules/pustules and flushing/blushing after just a few weeks [15]. These results suggest a viable alternative to traditional rosacea treatments, which can produce systemic side effects.

In vivo data suggest that the increased efficacy of a BPO/antibiotic combination may have an immunologic basis, as demonstrated by decreased antioxidant enzyme activities in leukocytes after month-long combination treatment [16]. Additionally, this combinatory approach may prevent the evolution of resistant *P. acnes* strains [17].

## 54.3 Retinoids: Tretinoin, Tazarotene, Adapalene

Topical retinoids encompass a group of powerful, comedolytic, anti-comedogenic, and anti-inflammatory agents. They are powerful keratolytics, targeting both primary and secondary prevention of comedones [6].

Retinoids exert their effects through nuclear receptor families RAR (retinoic acid receptors) and RXR (retinoic X receptors), subsequently inducing retinoic acid-responsive target gene expression [18–20]. Both receptor families are ligand-dependent transcription factors and consist of three receptor subtypes (α, β, and γ), encoded by three separate genes [21].

Although RARα is ubiquitous in embryonic skin, RARγ is the most abundant RAR in human epidermis, cultured keratinocytes, and dermal fibroblasts [21, 22]. Retinoids also inhibit expression of certain genes by downregulating other transcription factors, notably AP-1 and NF-IL6 [19]. This inhibitory action may be partly responsible for the anti-proliferative and anti-inflammatory actions of retinoids [21].

Prior to binding with nuclear RARs, retinoids must first bind to intracellular proteins. Cellular retinoic acid proteins (CRABP I and II) are present in the skin. Intracellular retinoid concentrations are dependent upon CRABP, primarily type II [19]. However, CRABP II is not essential for biologic retinoid activity as adapalene does not bind to it; interestingly, it may play a role in retinoid-induced epidermal irritation [21].

Through this genetic regulation, retinoids are thought to affect cellular differentiation and proliferation [20]. Experimental studies, some using primary neonatal mouse epidermal keratinocyte cultures, have confirmed this concordant decrease in keratinocyte differentiation and proliferation [23]. Retinoids also regulate activity of keratinocyte adhesion and cohesion molecules, resulting in breakdown and obliteration of the horny plug [22].

Mechanisms of action are numerous and include normalization of epidermal proliferation and differentiation, inhibition of neutrophil chemotaxis, expression of TLRs involved in immunomodulation, and anti-inflammatory effects via inhibition of prostaglandins, leukotrienes, and IFN-gamma release. Retinoids may exert an anti-inflammatory response by inhibiting the release of proinflammatory cytokines (interleukins 12 and 8 and tumor necrosis factor) via downregulation of monocyte Toll-like receptors (TLR) [24, 25]. Interestingly, *P. acnes* acts through TLR-2 to stimulate proinflammatory cytokine production [21, 26].

Combination therapy involving topical retinoids and antimicrobials allows targeting of different pathophysiologic factors in acne vulgaris [19]. This combination approach is optimal in patients with both inflammatory and comedonal lesions given the different but complementary mechanisms of action present in both agents [19]. Additionally, topical retinoid therapy, by weakening the horny layer barrier, may increase skin permeability, enhancing penetration of antimicrobial agents. Increased cell turnover of follicular epithelium enables greater access of antibiotic into the canal which houses *P. acnes*.

A large retrospective, vehicle-controlled study of inflammatory acne (mild/moderate to severe) demonstrated clinically significant improvements with tazarotene 0.1 % gel and 0.1 % cream, adapalene 0.1 % gel, and tretinoin 0.1 % microsponge treatment [25]. These treatments along with tretinoin 0.025 % gel produced significant improvement in global acne response [25]. Among these, tazarotene 0.1 % cream and 0.1 % gel showed a greater frequency of clinically significant improvement when compared to adapalene or tretinoin gel [25]. Between-retinoid comparisons demonstrated tazarotene to have the greatest efficacy on the overall inflammatory acne severity and global response scales [25] (Table 54.2).

The major drawback of topical retinoids is local skin irritation and acne exacerbation, also termed "retinoid flare," which may occur during the first month of treatment and last several weeks [6]. This flare-up may be secondary to release of follicular inflammatory factors after topical retinoid treatment [27].

Another limiting factor of retinoids, particularly oral agents, is their teratogenicity, resulting in severe fetal malformations if exposure occurs

during the first trimester. Malformations include microtia/anotia, conotruncal heart defects and aortic-arch abnormalities, thymic defects, and central nervous system malformations [28]. Several case reports suggest these effects may not be limited to oral retinoid therapy, with limb reduction defects and ear malformations reported with maternal use of topical retinoids [29, 30]. However, Jick et al., in a retrospective study, did not substantiate this suggestion, and the clinical issue remains sub judice [31].

## 54.4 Tretinoin

The first topical retinoid to be studied, tretinoin binds with high activity to all three RAR subtypes and to CRABP, and with low activity to RXRs. It is an effective comedolytic agent, which increases epithelial cell turnover and modulates abnormal keratinization (that leads to microcomedone formation). It also acts in an anti-comedogenic manner, preventing formation of microcomedones [21]. Mills and Kligman, using a cyanoacrylate follicular biopsy technique, demonstrated a profound microcomedone reduction in 8 and 12 weeks [32]. From an immunological perspective, in vitro studies have demonstrated that tretinoin downregulates and decreases surface expression of TLR-2 and CD14 mRNA, preventing secretion of interleukins (perhaps IL-1α, 12, and 8), tumor necrosis factor, and interferon-γ, as well as production of free radicals [22, 24].

In a large multicenter trial, 0.025 % tretinoin cream significantly reduced inflammatory and non-inflammatory acne lesions compared with vehicle by week 12; side effects included eruption, dry skin, and exfoliation [33]. Polyolprepolymer-2, which localizes drug molecules in upper skin layers, preventing deep penetration, may diminish adverse cutaneous reactions [33]. A large study demonstrated earlier favorable global assessments with 0.025 % tretinoin with PP-2 cream vs. a 0.025 % tretinoin cream, but no significant difference in side effects [33]. PP-2 forms a liquid reservoir of polymer and solubilized drug on the skin surface, slowing percutaneous absorption and transcellular cutaneous diffusion, potentially targeting folliculo-infundibular delivery in the process [34]. Some clinical trials have demonstrated reduced irritation as less drug penetrates the skin [34] (Table 54.2).

The Microsponge Delivery System found in 0.1 % microsphere gel also helps reduce drug release rate and increase drug retention in the SC, inhibiting deeper penetration [6]. Tretinoin is trapped within porous copolymer microspheres, which selectively localize to the follicle, releasing tretinoin over time and producing less irritation (than the standard 0.025 % cream) due to reduced concentration on the skin [22]. A study examining tretinoin gel microsphere 0.04 % compared to vehicle demonstrated significant reduction in total, inflammatory, and non-inflammatory acne by week 12 [24]. About 90 % of subjects reported none or only mild adverse events; there were no significant differences in tolerability between the treatment and control groups at week 12 [24]. Moreover, tretinoin 0.1 % microsphere gel significantly reduces facial shine at 3 and 6 h posttreatment when compared with tretinoin 0.025 % cream [35].

Numerous trials have demonstrated the efficacy of tretinoin in various forms of acne. Patience is advised as full effect may take 2–4 months; adherence is essential as tretinoin serves to control rather than cure acne. Recently, a hydrogel containing 1 % clindamycin and 0.025 % tretinoin was found to be more efficacious in treating inflammatory and non-inflammatory acne lesions than either agent alone or vehicle [36]. These results were confirmed by two large studies; adverse effects were similar in frequency and severity to tretinoin alone [36]. Furthermore, a BPO 6 % cleanser–tretinoin 0.1 % microsphere gel demonstrated significantly greater inflammatory lesion reduction than tretinoin alone [37].

In a split-face ultrastructural study comparing 0.1 % tretinoin to emollient cream, an 80 % decrease in microcomedones was demonstrated on the tretinoin side at 12 weeks [1]. Employing the technique of skin surface biopsy, microscopic examination of comedones showed progressive loss of the cohesiveness and significant alterations in epithelial structure; thick keratinous

**Table 54.2** Controlled clinical trials comparing keratolytic agents in acne vulgaris treatment

| Authors | Comparison | Lesions | Placebo | Results: brief |
|---|---|---|---|---|
| Lucky et al. (1998) | 0.025 % tretinoin gel vs. 0.025 % tretinoin gel containing polyolprepolymer-2 vs. vehicle over 12 weeks | All types | Vehicle | Both treatments significantly more effective than vehicle. Polyolprepolymer-2 treatment has significantly less peeling and drying. |
| Cunliffe et al. (1998) | Meta-analysis of five 12-week-long randomized trials comparing 0.1 % adapalene gel vs. 0.025 % tretinoin gel | All types | Vehicle only in one study | Both treatments had equivalent efficacy in reducing lesion count; adapalene works more rapidly with greater tolerability. |
| Bershad et al. (2002) | 12-week trial comparing 0.1 % tazarotene gel once daily vs. 0.1 % tazarotene gel twice daily in short-contact (<5 min) application vs. vehicle twice daily | All types | Vehicle | Both groups were comparable and significantly more efficacious than vehicle |
| Lookingbill et al. (1997) | Combined results of two double-blind, 11-week-long, randomized trials comparing 1 % clindamycin/5%benzoyl peroxide gel, 1 % clindamycin gel, 5 % benzoyl peroxide gel, and vehicle | All types | Vehicle | All three treatments were significantly better than vehicle. Combination gel was significantly superior to two individual agents in global improvement and reduction of inflammatory lesions; it was also better than clindamycin in treating non-inflammatory lesions. |
| Shalita et al. (1999) | Multicenter, controlled, 12-week-long trial comparing 0.05 % tazarotene gel vs. 0.1 % tazarotene gel vs. vehicle | All types | Vehicle | At 12 weeks, both tazarotene gels produced significant success rates and decreased total and non-inflammatory lesions. Only 0.1 % gel significantly reduced inflammatory lesions; it was also significantly more efficacious than 0.05 % gel, with decrease of total and non-inflammatory lesions and success rates |
| Leyden et al. (2005) | Retrospective, vehicle-controlled, photographic assessment comparing tazarotene 0.1 % gel, adapalene 0.1 % gel, tretinoin 0.1 % microsponge, tretinoin 0.025 % gel, and tazarotene 0.1 % cream | Inflammatory | Vehicle | All treatments had significant improvement in global response compared to vehicle. All except tretinoin gel had clinically significant improvement in inflammatory acne. Between-retinoid comparisons demonstrated tazarotene to have significantly greater incidences of clinically significant improvement compared to adapalene or tretinoin gel. |
| Leyden et al. (2005) | Combined results of two double-blind, randomized, 12- or 15-week-long trials comparing 0.025 % tretinoin/1 % clindamycin hydrogel with each agent alone and vehicle | All types | Vehicle | All treatments were more efficacious than vehicle. Combination treatment was more efficacious in treating inflammatory and non-inflammatory lesions compared to either agent alone, and its side-effect profile was similar to tretinoin. |
| Galvin et al. (1998) | Two controlled, randomized studies comparing 0.1 % adapalene gel with a total of six different tretinoin formulations and petrolatum in terms of tolerability after 3 weeks | – | Petrolatum | Adapalene had a better tolerability profile than tretinoin 0.1 % cream, tretinoin 0.05 % cream, tretinoin 0.025 % cream, tretinoin 0.01 % gel, tretinoin 0.025 % gel, and tretinoin 0.1 % gel microsphere, and an equivalent tolerability to petrolatum. |

| | | | | |
|---|---|---|---|---|
| Chalker et al. (1987) | Multicenter, controlled study comparing Iso 0.05 % gel twice daily for up to 14 weeks with its vehicle | Mild to moderate acne | Vehicle | Iso gel was significantly more effective in reducing inflammatory lesions after 5 weeks, and non-inflammatory lesions and acne severity grade after 8 weeks. Two Iso patients dropped out due to skin irritation. |
| Mills et al. | Three double-blind, 8-week-long studies comparing 2.5 % benzoyl peroxide, 5 % benzoyl peroxide, 10 % benzoyl peroxide, and vehicle | Mild to moderately severe inflammatory acne | Vehicle | 2.5 % BPO formulation was more effective than vehicle and equivalent to 5 % and 10 % concentrations in reducing the number of inflammatory lesions; 2.5 % formulation had less desquamation, erythema, and burning than the 10 % preparation, but tolerability was equivalent to the 5 % gel. |
| Katsambas et al. (1989) | 3 month double-blind study comparing 20 % azelaic acid cream to its vehicle | Moderate inflammatory acne | Vehicle | At 2 and 3 months, azelaic acid showed significant improvement in reducing inflammatory lesions compared to its vehicle. Azelaic acid showed significant comedone reduction compared to its vehicle in all visits. There was also a significant difference in overall evaluation. The only significant side-effect difference was burning sensation. |
| Shalita (1981) | 12-week trial comparing 0.5 % salicylic acid in an alcoholic detergent solution (Stri-Dex medicated pads) vs. placebo (pads soaked in buffered water) | Mild to moderate acne | Vehicle | The treatment group experienced significant reductions in inflammatory lesions and open comedones compared to the placebo group. The treatment group also had significantly more “good” or “excellent” responses than the placebo group. |
| Spellman et al. (1998) | 12-week double-blind, randomized trial comparing azelaic acid 20 % cream glycolic acid solution with tretinoin 0.025 % cream and vehicle lotion | Mild to moderate acne | Vehicle | Both groups experienced significant lesion reduction and global improvement compared to vehicle. The combination treatment was significantly better in decreasing inflammatory lesions than tretinoin, while producing significantly fewer adverse effects. Both treatments had equivalent non-inflammatory lesion reduction. |
| Thiboutot et al. (2007) | 12-week randomized, double-blind trial comparing combination adapalene 0.1 % gel BPO 2.5 % gel vs. adapalene 0.1 % gel vs. BPO 2.5 % gel vs. vehicle | Inflammatory and non-inflammatory | Vehicle | The combination was significantly more effective than the monotherapies in investigator’s global assessment and reduction of inflammatory, non-inflammatory, and total lesions. Tolerabililty of combination treatment was similar to adapalene monotherapy. |
| Thiboutot et al. (2006) | 12-week randomized vehicle-controlled study comparing 0.3 % adapalene gel to 0.1 % adapalene gel | Inflammatory and non-inflammatory | Vehicle | Adapalene 0.3 % gel was significantly superior to 0.1 % gel in various efficacy assessments, total lesion reduction, and inflammatory lesion reduction. Tolerability profile was similar in both concentrations. |

plugs infested with bacteria were transformed into a few wispy layers of keratin with few bacteria [1]. Using transmission electron microscopy, it was possible to track microcomedones with compact, adherent stratum corneum morphing into spongy, loosely adherent layers of corneocytes [1]. From a combination therapeutic standpoint, the alteration in SC integrity incurred during tretinoin treatment may enhance penetration of other agents such as BPO and topical antibiotics (see paragraph above) [1].

Surprisingly, topical tretinoin has poor percutaneous absorption and does not alter systemic retinoid levels, which stay constant despite application [6]. Side effects include peeling, erythema, dryness, burning, and itching [6, 22]. Pustular eruptions may occur initially, but are alleviated with concomitant erythromycin [22]. Additionally, tretinoin may bring out the postinflammatory darkening which occurs in healing acne of darker-skinned patients [27]. Tretinoin-induced skin irritation may be explained by a flexible chemical structure, resulting in nonselective action and the ability to activate numerous pathways, resulting in various biological effects [21]. Applying a moisturizing cream along with topical tretinoin or oral tretinoin significantly improves skin dryness, roughness, and desquamation, increasing subjective skin comfort [38].

Adverse effects are exacerbated by sunlight, extremes in weather, oxygen, and "comedogenic" skincare products. They can be reduced by spacing out applications and/or diminishing frequency and concentration of the product [22]. Additionally, tretinoin should not be used with BPO (an oxidizing agent), which can result in degradation and deactivation. Despite some evidence to the contrary, topical tretinoin is not advised during pregnancy and lactation. Potential for systemic exposure and excretion in breast milk has not been adequately studied.

## 54.5 Isotretinoin

Introduced in the late 1970s, oral isotretinoin (Iso) remains a mainstay for severe, recalcitrant nodulocystic acne unresponsive to topical therapy and systemic antibiotics [19] (see relevant Chap. 63). Its efficacy extends beyond correction of hyperkeratinization to include actions on the sebaceous gland (decreases size and secretion), anti-comedogenic properties, and reduction of *P. acnes* via creation of an unfavorable follicular environment [39].

## 54.6 Tazarotene

Tazarotene, a topical acetylenic retinoid indicated in both psoriasis and acne vulgaris, is hydrolyzed by keratinocyte esterases to tazarotenic acid, its active metabolite [19]. It binds all three RARs but activates gene expression only in RAR β and γ; downregulation of AP-1 and lack of RXR binding are observed [19, 21, 40]. In doing so, it normalizes the keratinization pattern and decreases coherence of follicular keratinocytes, manifesting both comedolytic and anti-comedogenic properties [20]. Tazarotene also has anti-inflammatory properties [20]. In the systemic circulation, tazarotenic acid is rapidly converted to inactive sulfur-oxidized forms, resulting in limited exposure [40].

A randomized, double-blind, vehicle-controlled study demonstrated that 0.05 % and 0.1 % tazarotene gels significantly decrease total lesions, decrease non-inflammatory lesions, and produce a higher success rate than vehicle at 12 weeks [20]. Moreover, 0.1 % gel was significantly more efficacious than 0.05 % gel and demonstrated a significant decrease in inflammatory acne at 12 weeks [20]. A more recent randomized trial comparing tazarotene 0.1 % cream to adapalene 0.1 % cream demonstrated tazarotene to be significantly and rapidly more effective in reducing comedone count and producing global improvement, with no significant difference in side effects at 12 weeks [20]. Although only non-inflammatory lesions could be compared in this study, other studies have demonstrated efficacy in inflammatory lesions as well [41]. Furthermore, a large clinical trial suggests that even short-contact application (>5 min) once daily for 12 weeks produces significant reduction in both inflammatory and non-inflammatory acne lesions [42].

With our armament of acne medications, standard acne treatment now involves using multiple

agents, each with its own mechanism of action. To that end, a multicenter, double-blind, randomized trial found a daily BPO 5 %/clindamycin 1 % gel–tazarotene 0.1 % cream regimen to be more effective than daily tazarotene monotherapy in reducing comedo count and inflammatory lesion count (in those with ≥25 baseline inflammatory lesions), with a similar, if not slightly improved, tolerability profile [43].

Currently, only the 0.1 % formulation of tazarotene is approved by the FDA for acne; it is primarily used in cases of acne refractory to tretinoin and adapalene treatment [6]. Nonetheless, animal studies have demonstrated that tazarotene has low systemic absorption with no toxic effects even at high topical doses [40]. Additionally, after 12 weeks of normal tazarotene application, serum samples from 22 subjects demonstrated limited systemic exposure with most below the quantifiable limit (<0.05 ng/ml) [20].

Local side effects typically occur; these include itching, burning, irritation, and erythema [6, 20]. In fact, tazarotene is thought to be the most irritating of the topical retinoids. In the Bershad study cited above, half of patients applying tazarotene for only 2–10 min daily reported local skin irritation. These side effects are most common during the first 2 weeks of therapy; cream formulations, alternate-day application, and short-contact therapy can curtail side effects [22].

Despite little evidence of fetal malformations or spontaneous abortions, topical tazarotene is an FDA Pregnancy Category X drug; little is known about its excretion in breast milk. Of all topical retinoids in acne treatment, it is the only one requiring sufficient contraception in women of childbearing age [22].

## 54.7 Adapalene

Adapalene, a derivative of retinoic acid, binds selectively to RAR β and γ in vitro but can activate gene expression through all three RARs; it does not bind CRABP II, but increases CRABP II mRNA [19, 21]. It has comedolytic, anti-proliferative, and anti-inflammatory properties [21]. Its anti-inflammatory action stems from inhibitory effects on PMN chemotactic response, free radical production, and Toll-like R2 receptors expressed by perifollicular monocytes [22]. It also inhibits production of leukotrienes by 5- and 15-lipoxygenase pathways [21, 22]. Furthermore, adapalene may have a dose-dependent response, with 0.3 % statistically superior to 0.1 % in several different measures, while demonstrating equivalent tolerability [44].

A meta-analysis of five large randomized trials (composed of 900 patients) demonstrated equivalent acne reduction, quicker onset of action (significant at 1 week), and fewer side effects in 0.1 % adapalene gel compared to 0.025 % tretinoin gel [45]. Side-effect profile was significantly better in regard to scaling, erythema, dryness, immediate and persistent burning, and immediate pruritus [45]. With its three aromatic rings, adapalene demonstrates higher stability than tretinoin in the presence of light, dark, and BPO [10]. In a study comparing the chemical stability of 0.1 % adapalene gel/10 % BPO and 0.025 % tretinoin gel/10 % BPO after 24 h of actinic light exposure, approximately 100 % of adapalene remained intact versus only 20 % of tretinoin [46].

In a study examining two 21-day-long trials, adapalene 0.1 % gel demonstrated greater tolerability and significantly less irritation than tretinoin 0.1 % cream, tretinoin 0.05 % cream, tretinoin 0.025 % cream, tretinoin 0.01 % gel, tretinoin 0.025 % gel, and tretinoin 0.1 % gel microsphere [47]. Furthermore, in both studies, adapalene 0.1 % gel was no more irritating than the petrolatum control [47]. Favorable tolerability to adapalene may be explained by its receptor specificity, neutral molecular structure, and lack of breakdown products.

A study comparing 0.1 % adapalene gel, 5 % BPO, and a 0.1 % adapalene/5 % BPO combination demonstrated no significant difference between the groups in efficacy or side effects (erythema, dryness, or burning) [48]. Additionally, all three treatments were significantly effective in reducing inflammatory and non-inflammatory acne lesions [48]. Adapalene reduced non-inflammatory lesion counts by 68.75 %, inflammatory lesion counts by 55.45 %, and total lesion counts by 65.48 % [48]. A more recent study testing a

0.1 % adapalene/2.5 % BPO combination gel against vehicle and individual monotherapies demonstrated combination therapy to have faster onset of action, significantly greater reductions in all lesion types, and no increase in adverse effects compared to monotherapy [26].

Adapalene's particle size (diameter between 3 and 10 microns), along with its lipophilic properties, results in optimal follicular duct penetration [21]; furthermore, after 5 min of exposure, 14-C-labeled adapalene applied to human skin in vitro demonstrates radiosensitivity in the pilosebaceous units, with sparse activity in the SC and epidermis [10].

Adverse effects, including erythema, scaling, dryness, pruritus, and burning, occur mainly during the first month and decrease thereafter [10]. Nevertheless, in comparative trials, adapalene demonstrates a more favorable side-effect profile than its relative, tretinoin. Cyanoacrylate strip data suggest that application of adapalene 0.1 % gel every other day may be effective maintenance therapy in microcomedone reduction, resulting in decreased exposure [49].

## 54.8 Azelaic Acid

Azelaic acid, a naturally occurring, saturated C9-dicarboxylic acid, modifies epidermal keratinization (cytostatic), combats both aerobic and anaerobic bacteria (reducing *P. acnes* proliferation), and exhibits anti-inflammatory activity [19, 50]. This anti-inflammatory activity may potentially be mediated through inhibition of hydroxyl- and superoxide radical production by neutrophils [51]. Contributing to its anti-inflammatory properties, in vitro, azelaic acid is an oxygen-free radical scavenger, inhibiting hydroxylation of aromatic compounds and arachidonic acid peroxidation [50, 52]. To date no published reports of azelaic acid bacterial resistance have surfaced.

In their review article, Fitton and Goa describe that azelaic acid, in vivo, affects differentiation of human keratinocytes by decreasing synthesis of filaggrin (keratin filament aggregating protein) [52]. This results in alterations of epidermal keratinization, including reductions in the number and size of keratohyaline granules and tonofilament bundles in the SC, abnormal tonofilament arrangements, intercellular edema, swollen mitochondria, enlargement of RER, and reductions in the thickness of the horny layer in infundibular areas [52, 53]. Azelaic acid functions in a cytostatic, anti-proliferative manner on keratinocytes, affecting both early and terminal phases of keratinocyte differentiation, with primary effects on mitochondria and RER [53].

In only 2 weeks of topical treatment, 200 µl of 20 % azelaic acid attenuated tetradecane-induced comedo formation in the rabbit ear, a model of follicular epithelial hyperplasia [52, 54]. These microscopic and experimental findings indicate keratolytic and anti-comedogenic properties for azelaic acid via normalization of disordered keratinization of the follicular infundibulum. This is further evidenced by reduction in non-inflammatory acne lesions after topical treatment (see studies below).

Cyanoacrylate skin surface biopsies have demonstrated significant reductions (>50 %) in comedo count after 4 months of twice-daily 20 % azelaic acid treatment when compared to vehicle [55]. Additionally, comedone reduction was similar in magnitude to that of 0.05 % retinoic acid cream [55].

Azelaic acid has demonstrated significant inflammatory and non-inflammatory acne reduction in numerous studies, even when compared to tretinoin, BPO, erythromycin, and tetracycline [50, 51]. Comparing 20 % azelaic acid to 0.05 % tretinoin over 6 months, one group found statistically equivalent comedone and total lesion reduction and similar overall improvement [56]. However, tretinoin use led to increased erythema, scaling, and irritation-induced discontinuation than did azelaic acid [56]. Another trial comparing 20 % azelaic acid with 5.0 % BPO demonstrated a more rapid initial effect with BPO but similar results for global response and inflammatory lesion reduction by 4 months [57]. Keeping with the theme, azelaic acid demonstrated milder, more transient adverse events than BPO [57]. Pooling together results of four trials, Mackrides et al. determined that after 6 months of treatment, 65–85% of patients experienced a ≥50% decrease in number of lesions (good-to-excellent clinical response) (Table 54.3).

**Table 54.3** Uncontrolled clinical trials comparing keratolytic agents in acne vulgaris treatment

| Authors | Comparison | Lesions | Placebo | Results |
|---|---|---|---|---|
| Akman et al. (2007) | Isotretinoin for first 10 days of each month for 6 months vs. each day in first month and first 10 days of each month for 5 months vs. daily for 6 months | Moderate and severe | None | Acne scores were significantly lower for all groups posttreatment. No difference in groups for total lesions but daily was more effective than intermittent for severe acne. Daily treatment also demonstrated significantly greater SE profile. |
| Leyden et al. (2001) | 10-week trial comparing 5 % benzoyl peroxide/1 % clindamycin, 5 % benzoyl peroxide, and 5 % benzoyl peroxide/3 % erythromycin | Moderate to moderately severe | None | All treatments had significantly reduced non-inflammatory acne reduction. BPO/clindamycin had significantly greater reduction in inflammatory lesions and greater overall improvement rated by physicians and patients compared to BPO. Efficacy was statistically similar to BPO/erythromycin. SE of BPO/clindamycin similar to BPO alone. |
| Katsambas et al. (1989) | 6-month trial comparing 20 % azelaic acid cream and 0.05 % tretinoin cream | Comedonal but patients had both | None | Similar decreases in comedone and total lesion count as well as overall response rate. AA had significantly fewer side effects. |
| Cavicchini et al. (1989) | 6-month single-blind trial comparing 20 % AA cream vs. 5 % BPO gel | Papulopustular acne | None | BPO more rapid initially but by 4 months equal inflammatory lesion reduction and overall response; additionally, BPO had more intense and longer-lasting side effects |
| Korkut et al. (2005) | Open-labeled, prospective study comparing 0.1 % adapalene gel, 5 % BPO lotion, or combination of 0.1 % adapalene gel +5 % BPO treatment | Non-inflammatory and inflammatory | None | All three treatments were effective in treating non-inflammatory and inflammatory lesions, but there was no significant difference between them in efficacy or side effects. |
| Tanghetti et al. (2006) | Multicenter, randomized, 12-week-long trial comparing tazarotene 0.1 % cream once daily vs. tazarotene 0.1 % cream once daily + clindamycin 1 %/BPO 5 % gel once daily | Moderate-to-severe inflammatory acne | None | Combination therapy resulted in significantly greater comedone reduction than tazarotene alone. In patients with >25 inflammatory lesions, combination therapy also resulted in a significant inflammatory lesion reduction. Both were equally well tolerated. |

A 12-week controlled study of azelaic acid 20 % vs. vehicle demonstrated significant improvement in mild-to-moderate acne [56]. During the 3 months, inflammatory lesions decreased by 72 %, comedones by 55.6 %, and 64 % of treated patients had good-to-excellent improvement [56]. Symptomatic improvement is typically observed within 4 weeks of commencing therapy [6].

Transient side effects lasting 2–4 weeks have been described [50]. These include burning, erythema, dryness, scaling, pruritus, and hypopigmentation. Nonetheless, there is some evidence that azelaic acid may improve the overall wearability (feel, smoothness, evenness, and ease of application) of a facial foundation [51].

After application of azelaic acid, 3–5 % remains on the SC, up to 10 % penetrates into the epidermis and dermis, and 4 % is absorbed systemically (although this can double with gel formulations) [6]. Nevertheless, baseline serum and urine levels are not altered by topical usage and are primarily dependent on dietary intake of whole grain cereals and animal products [6]. It is

an FDA Pregnancy Category B drug as animal studies have shown favorable results; meaningful human studies are lacking.

Despite efficacy as a monotherapy, a large randomized trial demonstrated that azelaic acid functions better in combination [51].

## 54.9 Salicylic Acid

A core component in many OTC acne treatments, salicylic acid (SA) is a widely available topical keratolytic agent. It may have a profound structural effect on the SC, resulting in disruption of intercorneocyte cohesion and subsequent desquamation [58]. Dissolution of intercellular cement is further supported by scanning electron microscopy, which has demonstrated marked squamous cell separation in salicylic acid-treated human skin [59]. Bashir et al. demonstrated the keratolytic properties of salicylic acid using a novel tape stripping/protein assay method described later (see Table 54.4). Mills and Kligman using cyanoacrylate follicular biopsy demonstrated significant decreases in microcomedone count. Although various concentrations exist (0.5–10 %), 2 % is the maximum strength allowed by the FDA in OTC products.

In five human subjects, microcomedo formation was induced via 10 % coal tar distillate ointment at four sites on the back; formation was confirmed by cryanoacrylate biopsy [60]. At each site, subjects were treated with one of three different concentrations of SA (0.5 %, 1 %, and 2 %) twice daily for 2 weeks and one site was left untreated [60]. Ultimately, lesions were rebiopsied and examined microscopically; all three concentrations displayed tremendous comedolytic activity, with the 2 % preparation superior to the lower concentrations [60]. Microcomedo quantitative reduction reached nearly 50 % in the 2 % SA group [60].

Two 12-week studies comparing 0.5 % and 2 % SA pads to placebo pads demonstrated significant efficacy in reducing inflammatory acne, non-inflammatory acne, and total lesions, while producing significantly higher proportions of good-to-excellent overall treatment assessments [60]. In one study, 60 % of patients using 2 % and 0.5 % SA pads experienced a 75–100 % decrease in total lesion count, compared to 2 % of patients receiving placebo [60]. In both studies side effects were minimal and well tolerated [60]. In a study comparing medicated pads with 0.5 % salicylic acid in an alcoholic detergent (Stridex™) to placebo (pads soaked in buffered water), the treatment group experienced a 54 % reduction in inflammatory acne compared to 29 % in the placebo group [61]. Reductions of open comedones and total lesions were also significant compared to placebo [61].

A 12-week study found 2 % SA cream superior to 5 % BPO cream in reducing closed comedones, open comedones, inflammatory lesions, and total lesions [60]. A 4-week crossover study comparing a 2 % SA acne cleanser to a 10 % BPO wash demonstrated that only patients treated with the SA cleanser had a significant decrease in comedonal lesions [62]. Stated differently, both groups demonstrated significant improvement in comedonal count when treated with SA, whereas

**Table 54.4** Studies using colorimetric protein assay to measure keratolytic potential

| Authors | Drug | Result |
|---|---|---|
| Bashir et al. (2004) | Aqueous solution 2 % salicylic acid 3 formulations | Statistically significant mass of SC removed after 6 h and 20 tape strips in all three experimental groups (salicylic acid pH 3.3, salicylic acid pH 3.3 w/menthol, salicylic acid pH 6.95) compared to vehicle, untreated, and untreated but occluded groups. |
| Waller et al. (2005) | Aqueous solutions of 0.05 % all-trans RA, 2 % BPO, and 2 % SA | Statistically significant mass of SC removed after 6 h and 25 tape strips in all three experimental groups compare to vehicle, untreated, and occluded groups. The first ten tape strips from SA group removed more protein than the other groups; at 10–15 strips, treatments were comparable; at 16–25 strips, protein removed from BP sites was greatest. |

BPO treatment either worsened or insignificantly improved comedonal quantity [62]. Recently, a small study comparing a 2 % SA/1 % clindamycin combination with placebo demonstrated a significant reduction in inflammatory and non-inflammatory lesions, with 71 % of subjects reporting improvement after 8 weeks (compared to 11 % of placebo group) [63].

Salicylic acid is well absorbed as evidenced by numerous studies; its bioavailability in topical application varies according to duration of contact [8, 64]. One study estimated bioavailabilities for topically applied SA at 57.6 and 44.0 % for hydroalcoholic and cream delivery vehicles, respectively [65]. The same study also demonstrated the hydroalcoholic vehicle to have superior peak plasma SA concentrations and earlier time to peak when compared with a cream vehicle [65].

In a related study, absorption was enhanced significantly in a mineral oil/petrolatum ointment compared to an ointment containing polyethylene glycol, glycerol, petrolatum, and 10 % urea (Kerasal) [66]. New chemical peels using 30 % salicylic acid in polyethylene glycol vehicle have demonstrated efficacy and safety, with marked reductions in comedones and papules [67]. Polyethylene glycol may be a more tolerable vehicle than the commonly used ethyl alcohol in salicylic acid chemical peels [67].

Although local skin irritation (e.g., peeling) at concentrations >2 % is common, systemic toxicity is rare [6]. However, if applied to large areas of the body for prolonged periods of time, salicylate toxicity, toxic inner ear damage, and hypersensitivity reactions are plausible [6]. To that end, these manifestations are uncommon in appropriate acne therapy. Like several other keratolytic agents, salicylic acid is an FDA Pregnancy Category C agent, with unknown effects on breastfeeding.

## 54.10 Sulfur

Sulfur, a yellow nonmetallic element, has many dermatological indications, including but not limited to acne vulgaris, rosacea, seborrheic dermatitis, and dandruff [68]. Once a very common ingredient in acne treatments, sulfur has recently fallen out of favor, partly due to its pungent odor [69]. In the acne arena, sulfur is thought to be keratolytic and bacteriostatic. After application to skin, sulfur reacts with cysteine in the SC, resulting in reduction to hydrogen sulfide [68]. Hydrogen sulfide is thought to break down keratin and inhibit growth of *P. acnes* [68].

Appearing in a variety of vehicles (lotions, creams, soaps, ointments), it appears to be more efficacious when used in combination with other drugs, namely, BPO and sodium sulfacetamide [6]. Clinical trials have demonstrated that lotions containing sulfur 5 % with sodium sulfacetamide 10 % have resulted in reduction of inflammatory lesions, comedones, and seborrhea [68]. Interestingly, this combination is also effective in acne rosacea, an inflammatory skin disorder involving the cheeks, nose, and forehead [68]. In clinical trials, sulfur and sulfur/sodium sulfacetamide have demonstrated superiority in reducing overall severity and inflammatory lesion count when compared to Metronidazole gel and oral Tetracycline [68].

Sulfur penetrates skin; it is detectable in the epidermis at 2 h, throughout the skin in 8 h, and completely undetectable by 24 h [68]. Additionally, there is no evidence of systemic absorption in intact skin [68]. Early studies, using human and animal subjects, demonstrated that elemental sulfur, while having a positive role in diminishing papules and pustules, may possibly induce comedone formation [68, 70]. Later studies did not confirm these results despite identical treatment conditions [68, 71]. Rare, transient side effects include dryness, itching, and malodorous skin. Nonetheless, given a lack of knowledge, it is an FDA Pregnancy Class C drug with nothing known regarding breast milk excretion.

## 54.11 Glycolic Acid

Glycolic acid, a naturally occurring organic acid (α-hydroxy acid), is a component in many cosmetic formulations. In the context of acne, research has been conducted examining glycolic acid chemical peels. Superficial chemical peels may serve as valuable adjuvant therapy in acne.

Various chemical preparations have been employed, all of which result in a partial-thickness skin injury, or peel [72]. Comedones are removed after only two or three peels, and the procedure may be repeated every 2 or 3 weeks [73]. Between peels, low concentrations of glycolic acid may be used as a daily cleanser to prevent re-occlusion of follicles [73].

Glycolic acid, a hydrophilic compound with keratolytic properties, is present in many peel formulations due to its desquamating efficacy. According to Kessler et al., "this desquamation reduces corneocyte cohesion, keratinocyte plugging, and enables the extrusion of inflammatory contents."

Glycolic acid mainly effects deeper, newly forming levels of SC, leading to a sheet-like separation [74]. The exact mechanism of action may be due to inhibition of ionic bond forming enzymes involved in creating sulfated and phosphorylated mucopolysaccharides, glycoproteins, sterols, and lipid phosphatides [74]. This results in fewer electronegative groups on the outer walls of keratinocytes and corneocytes, effectively diminishing cohesion forces [74]. This diminished cohesion loosens keratinocytes in the follicular epithelium, resulting in breakdown of comedones, inhibition of comedone formation, and unroofing of pustules [73].

A randomized split-face prospective clinical trial comparing glycolic acid to Jessner's solution (salicylic acid, lactic acid, and resorcinol) demonstrated significant acne improvement in both after three treatment sessions. Furthermore, glycolic acid was associated with significantly less exfoliation than Jessner's solution, resulting in more facile makeup application and suggesting a more favorable side-effect profile [75]. In a similar study comparing glycolic acid and salicylic acid peels, both were equally effective by the second treatment; however, salicylic acid demonstrated greater sustained effectiveness and a more favorable side-effect profile [72]. A study examining 35 % and 50 % glycolic acid peels on Asian patients found significant resolution of comedones, papules, and pustules, decreased follicular pore size, acne scar improvement, and few side effects [76].

A combination of azelaic acid 20 % cream–glycolic acid lotion was compared with tretinoin 0.025 % in a 12-week, vehicle-controlled study [27]. The azelaic acid–glycolic acid treatment produced significantly greater inflammatory lesion reduction and equivalent non-inflammatory lesion reduction, while causing less dryness, scaling, and erythema than tretinoin [27].

## 54.12 Resorcinol

Due to limited information about resorcinol, all of the following information was extracted from a review article by Karam in 1993 [77]. No longer significantly used in the USA, resorcinol, an isomer of hydroquinone and a relative of phenol, is soluble in water, ether, and alcohol. It is a reducing agent with antibacterial and keratolytic properties. Even at low concentrations, it can disrupt hydrogen bonds of keratin. A 50 % resorcinol paste is used in other countries for chemical peels. It is used to treat the postinflammatory hyperpigmentation, erythema, and shallow scars resulting from facial, chest, upper back, and buttocks acne. Contraindications include pregnancy and skin type VI, due to inadequate data regarding complications. Side effects include burning sensation and paresthesia, which can be felt anywhere from 2 to 30 min after application. Burning intensity increases initially, stopping after 1 h; despite discomfort, pain is usually tolerable. Additionally, subsequent resorcinol applications cause more intense burning sensation, prompting shorter exposure. Corticoid creams and cold compresses may provide some relief. Dizziness immediately after the peel may last 10–15 min and is probably secondary to flushing related to resorcinol application.

## 54.13 In vivo Keratolytic Potential of Benzoyl Peroxide, Retinoic Acid, and Salicylic Acid

The SC desquamating effect of three keratolytics will be presented in table format (see Table 54.4) using data obtained from colorimetric protein assays described by Dreher et al. in 1998 [78].

The process begins with cutaneous application of the agent; the agent is placed on a patch and taped onto the subject's skin for a predetermined number of hours. After this period, placement and removal of tape strips (number varies by study) onto the site of topical treatment is performed. The assay involves immersion and shaking of SC adhering tapes in sodium hydroxide solution resulting in extraction of the soluble SC protein fraction. The solution, now containing SC protein, is neutralized with HCl, as the assay is not effective under strongly alkaline conditions. The protein assay is performed using the Bio-Rad Detergent Compatible Protein Assay Kit and following the prescribed microassay procedure. This assay is similar to the Lowry assay and is based on reaction of protein with an alkaline copper tartrate solution and Folin reagent. Finally, absorbance at a wavelength of 750 nm is measured using a Hitachi U-2001 UV–vis Spectrophotometer. This method allows for quantification of microgram amounts of SC and diminishes confounding factors, namely, vehicle and water uptake by the SC.

The protein measured using the assay described can be compared amongst groups, with statistical analysis allowing determination of strong and weak keratolytics. Nonetheless, SC removal via tape stripping in treatment and control groups is attributable to keratolytic mechanisms, which loosen SC cohesion. The disintegrated SC is subsequently pulled up on the adhesive.

In the first keratolytic bioassay using this technique, salicylic acid was examined [58]. Keratolytic efficacy of salicylic acid was determined as a function of pH. The test preparations were aqueous vehicle control of pH 7.4, 2 % SA aqueous solution of pH 3.3, 2 % SA aqueous solution of pH 3.3 with menthol, and 2 % SA aqueous solution of pH 6.95. A statistically significant mass of SC was removed after 6 h and 20 tape strips in all three experimental groups compared to vehicle, untreated, and untreated but occluded groups. However, after ten strips the SA pH 3.3 solution with menthol and the SA pH 6.95 solution removed significantly more SC than any other group, including the SA pH 3.3 solution. These data suggest that a neutral preparation of SC results in adequate SC uptake and a pronounced keratolytic effect. Moreover, the salicylic acid pH 6.95 solution was associated with the least skin irritation among treatment groups. This finding differs from the results of a previous study, which demonstrated that SA penetrated the skin better in its neutral form (acidic pH) compared to ionized form (neutral pH) [79].

In the second keratolytic bioassay using the aforementioned technique, salicylic acid, BPO, and retinoic acid were examined [80]. The test preparations were 0.05 % all-trans retinoic acid, 2 % salicylic acid at pH 6.95, 2 % BPO, vehicle, untreated skin, and occluded but untreated skin. After 3 h of treatment, only BPO treatment removed significantly more SC on 25 strips than untreated skin, while the other treatments did not achieve statistical significance. At 3 h, SA had greater SC amounts removed in the first ten superficial strips, while deeper strips 11–25 demonstrated BPO to have the greatest SC removal.

Statistically significant masses of SC were removed after 6 h and 25 tape strips in all three experimental groups when compared to vehicle, untreated, and occluded groups. At 6 h, the first ten tape strips from SA group removed more protein than the other groups; at 10–15 strips, treatments were comparable; at 16–25 strips, protein removed from BP sites was greatest.

These in vivo human results indicate that all three treatments tested are effective keratolytics, which may account, to some degree, for their effectiveness against acne vulgaris. Furthermore, based on the stratified analysis of tape stripping, it appears that salicylic acid may be more optimal in treating mild, superficial acne as while BPO may be better suited for deeper, inflammatory acne conditions. BPO's ability to loosen SC at deeper levels complements its antimicrobial properties, resulting in an effective anti-inflammatory agent for papulopustular acne. Additionally, it appears that BPO appears to be effective even with short-term administration. RA had inferior SC disruption at 3 h but significant disruption at 6 h, indicating time-dependent keratolytic effects, consistent with its well-studied interaction with nuclear receptors and alteration of gene transcription.

**Conclusions**

Taken together, a century of clinical trials and clinical use support the efficacy of keratolytics in acne. We suspect that the near future will provide more rapid advances—based upon the power and ease of interpretation of the newly devised in vivo human keratolytic assay.

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# Topical Antibiotics

# 55

Brigitte Dréno

## Contents



**Core Messages**

- Topical antibiotics used in acne include cyclines, clindamycin, and erythromycin.
- The main target is the inflammatory acne lesion, but topical antibiotic show some efficacy in comedones as well.
- Topical antibiotics are well tolerated and effective for mild to moderate inflammatory acne vulgaris.
- The main problem remains the risk of development of bacterial resistance, which is still under-investigated in acne patients. Thus, the recommendations are to avoid using topical antibiotics alone and for a long duration and to preferentially combine them with benzoyl peroxide or topical retinoids.

## 55.1 Different Types of Topical Antibiotics

Three main types of topical antibiotics are used in acne: Clindamycin, erythromycin in concentrations of 1–4 % with or without the addition of zinc and cyclines. Clindamycin and erythromycin are the most popular [1]. Topical tetracycline is less often used and rarely meclocycline is used. A liposome-encapsulated 1 % clindamycin preparation has been proposed and on the basis of a clinical trial appears therapeutically superior over conventional 1 % clindamycin solution in

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the treatment of acne vulgaris. A new water-based gel once-a-day formulation of clindamycin 1 % would be an effective alternative to the twice-a-day topical solution formulation in the treatment of acne vulgaris [2].

## 55.2 Mechanisms of Action

Topical antibiotics have both antibacterial and anti-inflammatory mechanisms. The main anti-inflammatory properties are suppression of leukocyte chemotaxis and decrease in the percentage of pro-inflammatory free fatty acids in skin surface lipids. Moreover, erythromycin and tetracycline can inhibit lipase production by *Propionibacterium acnes* in vitro at a concentration lower than the minimal inhibitory concentrations.

Concerning the bactericidal effect of the three main types of antibiotics on *P. acnes*, the published papers suggest that topical erythromycin has a moderate direct effect on *P. acnes* reducing not significantly the number of surface and follicular bacteria. The antibacterial effect of clindamycin on *Propionibacterium acne* would be a little more important.

This means that topical antibiotics could act on inflammatory lesions more by an antiinflammatory activity and in particular by inhibiting inflammatory substances produced by *P. acnes* (lipase, metalloproteases, chemotactic factors, etc.).

## 55.3 Level of Efficacy According to the Literature

### 55.3.1 Topical Antibiotics Alone

A bibliographic Medline (PubMed) search, covering the years 1969–2010, reveals 190 clinical trials on topical antibiotics, the majority between 1980 and 1989. In addition, in 1990, Eady et al. [3] and in 1998 Toyoda and Morohashi [4] reported a strict and critical evaluation of topical antibiotics in acne. Based on these reviews, it appears that erythromycin is the most effective topical antibiotic on inflammatory acne lesions (94 % of improvement with erythromycin, 82 % for clindamycin, and 70 % for tetracycline). However, it was shown that the efficacy of erythromycin has decreased significantly over the years 1980–2000. [5] No significant difference may be noted between 1 and 4 % erythromycin. Concerning the noninflammatory lesions (comedones), no matter what the type of topical antibiotic used (tetracycline, clindamycin, or erythromycin), the percentage of reduction of comedones remains low, inferior to 30 %.

### 55.3.2 Topical Antibiotics Compared to Systemic Antibiotics

Several studies have been performed comparing 500 mg daily of tetracycline with topical antibiotics for 12 weeks [6]. No significant different were noted between topical and oral antibiotics on the reduction of inflammatory lesions during 12 weeks. However, these results have to be interpreted with caution, as the dosage of tetracycline used was lower than the one used in clinical practice.

### 55.3.3 Combination Topical Therapies Including a Topical Antibiotic

#### 55.3.3.1 Zinc Salts

Holland et al. [7] showed that the growth of erythromycin-resistant strains of *Propionibacterium acnes* is inhibited by the addition of 300 µg/ml of zinc to 1000 µg/ml of erythromycin. In vivo, the results are varying according the studies permitting no conclusion.

#### 55.3.3.2 Retinoids

Two main interests: topical retinoids increase the spectrum of activity of topical antibiotics to retentional lesions (comedones) and increase the penetration of topical antibiotics in the pilosebaceous follicle [8]. Clindamycin or erythromycin combined with a topical retinoid (tretinoin 0.025 % or isotretinoin) is more efficient than when used alone [9].

#### 55.3.3.3 Topical Antibiotics and Benzoyl Peroxide

This association could induce an earlier onset of action on inflammatory lesions, with a good tolerability profile [10].

### 55.3.4 Side Effects

#### 55.3.4.1 Cutaneous Side Effects

The tolerability of topical antibiotics is generally excellent. The main side effect is a mild irritation with erythema and itching. Pseudomembranous colitis has been observed only after topical treatment with clindamycin HCl and clindamycin phosphate. This good tolerability explains that topical antibiotics are often prescribed even in the summer.

#### 55.3.4.2 Bacterial Resistance

A survey, conducted throughout Europe, showed that at least 50 % of acne patients are colonized by erythromycin- and clindamycin-resistant strains of *P. acnes* [11]. Resistance appears to emerge through either selection of pre-existing resistant bacterial strains or through *de novo* acquisition of a resistant phenotype. There is a cross resistance between erythromycin and clindamycin. Two types of mutations (rRNA 16S and 23S) have been found [12], conferring to the strains a cross resistance to MLS antibiotics macrolides, lincosamides, and type B streptogramins. The resistant strains would appear about 2 weeks after starting topical antibiotics.

Bacterial resistance raises two questions: Which are the potential risks at the clinical level for the patients? Does the presence of these resistant strains decrease the effectiveness of antibiotics largely used today to treat the acne? At the clinical level, there are three studies suggesting a correlation between the presence of antibiotic-resistant *P. acnes* and decreased clinical response to treatment. Concerning the potential risk of resistance to topical erythromycin and clindamycin for acne patients, it is essentially related to the transfer of resistance to other bacteria specifically *Streptococcus* and *Staphylococcus aureus*. Thus, Otto' study demonstrates that topical erythromycin increases the frequency of *S. aureus* at the nostril orifice [13]. In conclusion, until today, no formal conclusion has been given to these two questions. This is in particular related to the fact that the antibiotics can act on acne lesions by two different mechanisms: anti-infectious and anti-inflammatory [5].

## 55.4 Other Less Frequent Topical Antibiotics

### 55.4.1 Meclocycline

Meclocycline is an oxytetracycline derivative available as 1 % cream. One study has shown a significant efficiency on inflammatory lesions compared to vehicle [14].

### 55.4.2 Nadifloxacin

Nadifloxacin is a synthetic fluoroquinolone derivative (nadifloxacin).

Nadifloxacin is a potent, broad-spectrum, quinolone agent approved for topical use in acne vulgaris and skin infections in Japan. Nadifloxacin 1 % cream was as efficacious and safe as erythromycin 2 % and extremely low numbers of nadifloxacin-resistant microorganisms were detected in the treatment period. However, as exposure of pathogenic and colonising bacteria to antibiotics results in drug resistance, it is not desirable to use an important, broad-spectrum antibiotic, which belongs to a class of agents widely used systemically to treat a wide variety of infections, as a topically applied preparation [15].

**Conclusions**

Two main antibiotics (erythromycin and clindamycin) are used worldwide. Topical antibiotics have been used for many years in acne. They have proved their efficacy in inflammatory lesions. However, today, from all the data of the literature about the efficacy of topical antibiotics, recommendations about the use of topical antibiotics can be summarized in Table 55.1 [16]. These

**Table 55.1** The main rules for using topical antibiotics in acne patients

| |
|---|
| 1. Target: superficial inflammatory lesions |
| 2. Avoid topical antibiotics where other topical acne treatments (retinoids, benzoyl peroxide) can be expected to bring the same benefit |
| 3. Use topical antibiotic in a combined therapy with retinoids or benzoyl peroxide. |
| 4. Change topical antibiotic used alone for another topical treatment when no or slight improvement is obtained after 2 weeks |
| 5. Try to avoid continuing topical antibiotics on a long period (6–8 weeks) |
| 6. Check the compliance of the patient |

recommendations could help to avoid the development of bacterial resistance and prevent any related risks for our patients.

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# Benzoyl Peroxide

# 56

Joachim W. Fluhr

## Contents



**Core Messages**

- The main indication of BPO is mild inflammatory (papulopustular) acne as monotherapy, as well as moderate inflammatory acne in combination with other acne treatments.
- BPO is regarded as standard therapy for mild to moderate papulopustular acne.
- BPO has good antibacterial and mild keratolytic activities.
- BPO reduces antibiotic-resistant *Propionibacteria* strains, e.g., induced by topical treatment with antibiotics.
- BPO is available in 2.5 %, 5 %, 10 %, and 20 % strengths with efficacy increasing with higher concentrations.
- The irritating effects such as burning, redness, and desquamation are dose and application frequency dependent.
- Combination therapies with topical antibiotics, azelaic acid or retinoids are increasingly being recommended, especially in fixed drug formulations.
- BPO, based on its high oxidative capacity, is a potent bleaching agent. Patients should be warned that acne therapy with BPO can lead to bleaching of colored or dark clothing, bedding, and even dark hair.

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## 56.1 Introduction

Benzoyl peroxide (BPO) was introduced in the treatment of acne in 1930s. The present review on BPO is partially based on a recent evidence-based medicine EBM analysis [1, 2]. BPO with sum formula C14H104 (Fig. 56.1) is poorly soluble in water and ethanol, soluble in ether, acetone, and chloroform. BPO is considered the gold standard in topical acne treatment. Anaerobic bacteria are reduced by oxidative mechanisms and the induction of resistant strains, e.g., in topically applied antibiotics is reduced. Topical formulations are available at concentrations of 2.5 %, 5 %, 10 %, and 20 %. The effect is dose dependent, but the irritation increases with higher concentrations.

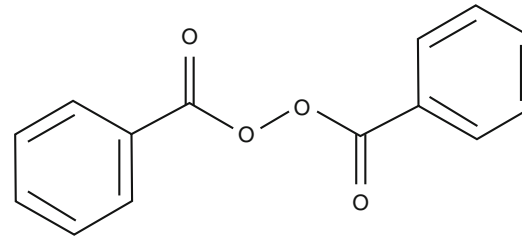


**Fig. 56.1** Formula of benzoyl peroxide

## 56.2 Indications

The main indication of BPO is mild inflammatory (papulopustular) acne as monotherapy, as well as moderate inflammatory acne in combination with other acne treatments. In the last years it has become part of a combination therapy with topical retinoids and antibiotics or in combination with systemic antibiotics. Initially the combination was introduced as erythromycin–BPO formulations due to the dramatic increase of antibiotic resistant *Propionibacterium acnes* (*P. acnes*) strains especially against erythromycin [3].

## 56.3 Mechanism of Action

BPO acts through oxidation and the formation of free radicals causing a reduction of propionibacteria. This mechanism helps prevent in the induction of resistance in *Propionibacterium acnes* often observed during long-term acne treatment with antibiotics. Micromolar BPO concentrations inhibit the release of reactive oxygen species from human neutrophils—an important step in the inflammatory response in acne. Noticeable drug-induced cytotoxicity has been observed in neutrophils [4]. In cell-free experiments BPO exhibited a mild inhibition of protein kinase C and no inhibition of calmodulin (known as regulator of reactive oxygen species release). Thus the clinical antiinflammatory action of BPO is probably not mediated by protein kinase C or calmodulin. As BPO launches a potent oxidative attack on the stratum corneum (SC), it might reduce the antioxidative defenses of this layer. A recent study concluded that during BPO therapy α-tocopherol (vitamin E) is lost from the epidermal barrier [5]. This loss and the resulting oxidation of lipids and proteins might explain the common side effects of skin dryness and desquamation. Corneocyte plugs in the follicular ostia are loosened in a dose-dependent fashion but to a lesser extent than with retinoids. A recent publication could demonstrate keratolytic activity for BPO [6]. There is no reduction in sebum secretion.

## 56.4 Adverse Effects

### 56.4.1 Typical Adverse Effects

Redness, desquamation, and a burning sensation of treated skin are dose-dependent major symptoms of therapy. The most frequent side effect of BPO is skin irritation which is linked to concentration and formulation. High BPO concentrations can exhibit significant irritative effects, especially in alcohol-containing gels. These can be prevented by choosing low BPO concentrations (3–5 %) or lower application frequency (e.g., every other day. Using a 2.5 % BPO gel, redness, desquamation, and burning, will occur more rarely than with 10 % BPO formulations but at a similar rate compared to a 5 % gel [7]. BPO, based on its high oxidative capacity, is

a potent bleaching agent. Patients should be warned that acne therapy with BPO can lead to bleaching of colored or dark clothing, bedding, and even dark hair.

### 56.4.2 Rare Side Effects

BPO can sensitize and cause allergic contact dermatitis. Incidence has been estimated at 1:500 [8]. Most of the sensitizations are based on topical use of BPO in the treatment of leg ulcers in previous decades. However a sensitization is rarely seen in acne patients. Recently a case of contact angioedema was reported [9]. Since BPO is now only rarely used in the antibacterial therapy of leg ulcers, these numbers are declining. Phototoxicity toward UVB occurred in 8–24 tested volunteers but not for UVA [10].

## 56.5 Duration and Concentration of Therapy

Various BPO formulations are available (gel, rinse-off products, shampoo, cream, emulsion, and lotion). Strengths ranging from 2.5 % to 10 % are offered (2.5 %, 3 %, 4 %, 5 %, and 10 %). Effects are quickly visible (1–2 weeks) and a 4–8-week course is generally adequate in mild acne. The entire involved area should be treated with a thin film of BPO gel one to three times daily. Long-term treatment or short contact therapy with a BPO rinse-off product can follow to prevent relapse. A controlled study shows that 2.5 % and 5 % are equally effective as 10 %, the side effects being less [11]. Papulopustular acne grades I–II can usually be controlled by 5 % BPO.

## 56.6 Evidence-Based Data

Despite the existence of only very few randomized, double-blind studies, BPO is viewed as the "standard" in acne trials for topical treatment. Even though the first therapy report in 1934 only achieved EBM level 5 (based on expert opinion), in later studies in which BPO was compared to clindamycin or erythromycin or azelaic acid and even with placebo, an EBM level of 2b (Based on cohort study or randomized, double-blind placebo-controlled study without follow-up and with larger confidence intervals) was reached [12–15]. Only one study exists in which BPO (20 %) was directly compared to placebo [16]. Recently combination therapies with topical antibiotics or retinoids have been conducted reaching a maximum EBM level of 2b [17–28]. In a comparative study BPO was the most cost-effective treatment. Topical BPO and BPO/erythromycin combinations are similar in efficacy to oral oxytetracycline and minocycline and are not affected by propionibacterial antibiotic resistance [29] (EBM level 2b; $n = 649$).

## 56.7 Combination Therapy

### 56.7.1 Benzoyl Peroxide and Topical Antibiotics

Combination therapies with topical antibiotics (erythromycin, clindamycin) have been well studied and show an increase in efficacy (EBM level 2a). Studies of the combination of BPO and tretinoin as well as BPO and topical isotretinoin exist. These combinations are superior to monotherapy, but with the combination of BPO and tretinoin as well as adapalene, side effects such as burning, redness, and desquamation may increase [30]. The induction antibiotic-resistant strains in Acne patients can be reduced by combining topical antibiotics with BPO.

### 56.7.2 Benzoyl Peroxide and Topical Retinoids

The improved efficacy of tretinoin 0.05 % in combination with benzoyl peroxide (BPO) compared to each of the active ingredient alone has been shown [31] (EBM-level 3b, $n = 150$). Both substances must be applied alternately to avoid oxidative degradation of tretinoin. Tretinoin

microsphere gel showed improved stability toward UV-and oxidative-induced degradation [32]. Its combination with a BPO 6 % cleanser resulted in a greater reduction of inflammatory acne lesions than monotherapy with 0.1 % tretinoin microsphere [33] (EBM level 2c, $n=87$). The combination of clindamycin and benzoyl peroxide with tretinoin was well tolerated and showed improved efficacy as compared to tretinoin combined with clindamycin; however, the addition of tretinoin to the combination of clindamycin and BPO induced no additional efficacy [24] (EBM level 2c, $n=132$). The efficacy of adapalene gel 0.1 % reduce and prevent the development of microcomedones as recently shown in a 12-week maintenance treatment study after previous combination therapy with BPO 2.5 % and adapalene 0.1 % in patients with mild to moderate acne [34] (EBM level 2b, $n=49$). Recent studies with BPO either alone or as combination therapy including fixed combinations have focused on irritation (EBM-level maximum 2c) [35–38].

### Conclusions

BPO is regarded as standard therapy for mild to moderate papulopustular acne. BPO has good antibacterial and mild keratolytic activities. The main indication of BPO is papulopustular acne and acne in adolescents. Furthermore it can be used in pregnant and lactating females and in adults as a monotherapy. Recently combination therapies with topical antibiotics, azelaic acid, or retinoids are becoming more and more popular initially due to the reduction of antibiotic-resistant *propionibacteria* strains. BPO is available in 2.5 %, 5 %, 10 %, and 20 % strengths with efficacy increasing with higher concentrations as do the irritative effects such as burning, redness, and desquamation. BPO, based on its high oxidative capacity, is a potent bleaching agent. Patients should be warned that acne therapy with BPO can lead to bleaching of colored or dark clothing, bedding, and even dark hair.

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# Topical Retinoids

# 57

Anja Thielitz and Harald P.M. Gollnick

## Contents



**Core Messages**

- Topical retinoids play a crucial role in the treatment of acne because they suppress microcomedone formation and reduce both noninflammatory and inflammatory lesions.
- A retinoid is defined as a molecule that binds to and activates nuclear hormone receptors (retinoic acid receptors, RARs and retinoid X receptors, RXRs) either directly or by metabolic conversion and thereby elicits transcription of retinoic acid-responsive genes.
- Several types of topical retinoids are used to treat acne. Those used in a topical form for the treatment of acne include tretinoin (all *trans-retinoid* acid), isotretinoin (13-*cis* retinoid acid), adapalene, and tazarotene, whereas retinaldehyde, retinol, and retinyl esters are used in cosmetic preparations.
- Topical retinoids exert comedolytic and anticomedogenic effects because they influence proliferation and differentiation of keratinocytes and reverse the abnormal desquamation by increasing the follicular epithelial turnover and accelerating the shedding of corneocytes.
- Topical retinoids and retinoid analogues exhibit anti-inflammatory and immunomodulatory effects that may help to

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explain their efficacy in the resolution of inflammatory lesions.
- The combination of topical retinoids with topical or systemic antimicrobials enhances treatment efficacy and is useful in almost all types of inflammatory acne.
- Monotherapy with topical retinoids is efficient in acne comedonica, mild inflammatory acne, and during maintenance treatment after initial combination therapy.
- Local adverse effects, including erythema, dryness, itching, and stinging, occur frequently during the early treatment phase with topical retinoids. Their impact varies with the vehicle formation, skin type, frequency and mode of application, use of moisturizers, and environmental factors such as sun exposure or temperature.

## 57.1 Introduction

Topical retinoids represent a mainstay of acne treatment because they expulse mature comedones, reduce microcomedone formation and exert immunomodulatory effects [1]. The first-generation retinoid tretinoin (*all-trans*-retinoic acid) as well as the synthetic third-generation polyaromatics adapalene and tazarotene are approved for acne treatment by the US Food and Drug Administration (FDA), whereas topical isotretinoin (13-*cis* retinoic acid) is accredited in Canada and Europe. Retinaldehyde and retinyl esters are used in cosmetic preparations.

### 57.1.1 Mechanism of Action

The biological effects of topical retinoids are mediated and regulated by nuclear hormone receptors (retinoic acid receptors, RAR, and retinoic X receptors, RXR) and cytosolic-binding proteins. Retinoids influence proliferation and differentiation of cells [1] and reverse the abnormal desquamation by increasing the follicular epithelial turnover and accelerating the shedding of corneocytes, which leads to an expulsion of mature comedones and suppression of microcomedone formation [1–3]. Tretinoin was shown to inhibit the synthesis of tonofilaments and promote the detachment of desmosomes, thus lessening the attachment between keratinized cells. The change of the "follicular milieu" of the sebaceous gland apparatus by prevention of hypercornification promotes an inhospitable aerobic environment for *Propionibacterium acnes* and is likely to enhance the penetration of other topical drugs. A direct antibacterial effect against *P. acnes* has been shown for retinaldehyde only [4]. Various in vitro and in vivo studies demonstrated also direct immunomodulatory activity of topical retinoids [5, 6] (Table 57.1).

**Table 57.1** Anti-inflammatory and immunomodulatory effects of topical retinoids

| Assay/model | Effects |
|---|---|
| IL-6 release in A431 cells | Inhibition by tretinoin |
| IFN-γ production | Inhibition by tretinoin, tazarotene |
| Nitric oxide release in fibroblasts | Inhibition by tretinoin |
| Expression of collagenase via AP-1 modulation | Inhibition by tazarotene |
| Human PMN 5- and 15-lipoxygenase activity | Inhibition by adapalene > isotretinoin > tretinoin |
| Burst of oxygen free radicals of rabbit PMN | Inhibition by adapalene = tretinoin > isotretinoin |
| Human PMN chemotaxis | Inhibition by tretinoin > isotretinoin > adapalene |
| TLR2-expression on monocytes, keratinocytes | Inhibition by adapalene, tretinoin |
| UV erythema (guinea pig) | Inhibition by adapalene, tretinoin, isotretinoin |
| Croton-oil induced edema (rat) | Inhibition by adapalene |
| Arachidonic acid induced ear edema (mouse) | Inhibition by adapalene, isotretinoin |
| Carrageenan-induced paw edema (rat) | Inhibition by adapalene |

### 57.1.2 Indications

Topical retinoids are efficient in comedonal and inflammatory acne and all types of contact acne due to external agents. In combination with other topical or systemic agents, they are suitable for the first-line treatment of almost all severity grades of acne.

They are ideal for maintenance treatment due to their multifactorial anti-acne efficacy without inducing bacterial resistance and their ability to prevent microcomedone formation.

## 57.2 Tretinoin

Tretinoin (all-trans-retinoic acid) was first used in the early 1960s by Stüttgen and Beer. It binds to all retinoic acid receptors and upregulates and binds to the cellular retinoic acid-binding protein II (CRABP II), the predominant intracellular-binding protein in skin. Tretinoin is effective as a single-agent therapy in patients with mild-to-moderate either comedonal or inflammatory acne [7, 8]. Furthermore, tretinoin is effective against microcomedones with a significant reduction of 50 % after 6 weeks and 80 % after 12 weeks of treatment with 0.1 % tretinoin cream [2]. Tretinoin is available as gel (0.01 % and 0.025 %), cream (0.025 %, 0.05 %, 0.1 % and 0.4 %), liquid (0.025 %, 0.5 % and 0.1 %), lotion (0.1 %), ointment (0.05 %), compresses (0.05 %), gel microsphere (0.04 % and 0.1 %), and polymer cream (0.025 %). The latter, tretinoin trapped with copolymer microspheres (Retin-A Micro® gel, Ortho-Neutrogena, USA) or prepolyolprepolymer-2 gel or cream (Avita®, Bertek pharmaceuticals, USA) gradually release the active ingredient over time and were developed to achieve improved cutaneous tolerability [9, 10]. Tretinoin 0.025 % gel containing polyolprepolymer-2 demonstrated comparable efficacy to a conventional gel but significantly less peeling and dryness and was comparable to a commercially available tretinoin 0.025 % cream in terms of efficacy and safety [11, 12]. Another advantage of tretinoin microsphere gel compared to its conventional preparation is its increased improved stability towards UV- and oxidative-induced degradation.

**Table 57.2** Evidence for the use of tretinoin in combination therapies

| |
|---|
| Tretinoin + Topical erythromycin |
| Tretinoin + Topical clindamycin |
| Tretinoin + BPO (alternate application) |
| Tretinoin microsphere + Clindamycin/BPO |
| Tretinoin + Oral tetracycline |

### 57.2.1 Tretinoin-Combination Therapy

The treatment efficacy of tretinoin can be enhanced by combination with topical antimicrobials. A superiority toward monotherapy has been shown in clinical studies for the combination of tretinoin and erythromycin and, with highest evidence levels, for the combination of clindamycin and tretinoin [13–15]. For both combinations, fixed preparations are available. The combination with benzoyl peroxide is possible when both substances are applied alternately, e.g., tretinoin in the morning and benzoyl peroxide (BPO) in the evening, to avoid oxidative degradation of tretinoin. The combination of tretinoin microsphere gel combination with a benzoyl peroxide 6 % cleanser resulted in a greater reduction of inflammatory acne lesions than the monotherapy with 0.1 % tretinoin microsphere, without increased skin irritation [16]. The efficacy and safety of combination with a fixed clindamycin/BPO preparations has been demonstrated for tretinoin microsphere gel 0.04 and 0.1 %. The triple combination showed improved efficacy compared to a combination of tretinoin microsphere and clindamycin, but was comparable to a fixed clindamycin/BPO combination [17].

Topical tretinoin in combination with oral tetracycline was more effective than either drug given alone and resulted in a faster therapeutic response [18] (Table 57.2).

### 57.2.2 Tretinoin-Safety

The major adverse effect of tretinoin and other topical retinoids is local skin irritation, including erythema, peeling, dryness, burning, itching, and pustular flaring occurring in some subjects

shortly after initiation of therapy. The irritative potential depends on the concentration and formulation of the product [19]: Tretinoin 0.1 % cream and tretinoin 0.05 % cream were more irritating than tretinoin 0.025 % gel, tretinoin 0.01 % gel, and tretinoin 0.025 % cream. The irritative potential of tretinoin microsphere gel 0.1 % and tretinoin 0.05 % emollient cream was in the range of tretinoin 0.025 % cream. Tretinoin 0.025 % gel-containing polyolprepolymer-2 was significantly better tolerated than a conventional gel [11]. Retinoid-induced skin irritation can be relieved by the regular use of a gentle moisturizing cream as an adjunctive treatment [20].

Topical administration of all-trans-retinoic acid did not significantly increase systemic retinoid plasma levels, which remained in the range of natural endogenous levels and were more influenced by nutritional and diurnal factors [19].

Several case reports exist that report fetal congenital abnormalities that can also be seen in retinoid embryopathy after topical application of tretinoin in the first trimester [21]. However, two cohort studies including 645 and 495 women supported that topical tretinoin is not associated with an increased risk for minor malformations that are consistent with the retinoic acid embryopathy [22, 23].

Topical tretinoin is FDA pregnancy Category C, which means that a risk cannot be ruled out because data in humans are lacking and animal studies are either positive or data are also lacking. Prescription is possible when benefits outweigh the risks, however, administration during pregnancy is hard to justify because safer treatments are available. During lactation, avoidance of topical tretinoin is advised, because excretion via breast milk has not been studied and adverse reactions in nursing infants have not been ruled out. Safety and efficacy in children below the age of 12 have not been established.

## 57.3 Topical Isotretinoin

Isotretinoin is the 13-*cis* isomer of tretinoin and is available in topical formulations (0.05 % gel or cream, 0.1 % cream) in countries outside the USA. The binding activity to RAR is low and it does not bind to RXRs or CRABP.

Isotretinoin gel 0.05 % is comparably effective to tretinoin cream 0.05 % [24] and adapalene gel 0.1 % [25]. A fixed combination of isotretinoin 0.05 % and erythromycin 2 % was superior to isotretinoin alone in the reduction of inflammatory lesions [26].

### 57.3.1 Topical Isotretinoin-Safety

Isotretinoin 0.05 % produces symptoms of irritative dermatitis including erythema, scaling, burning, and dryness in a range comparable to benzoyl peroxide gel 5 % [19]. Isotretinoin was slightly better tolerated than tretinoin 0.05 % cream, but significantly worse than adapalene gel 0.1 % [24, 25].

Several reports indicated that percutaneous systemic absorption is negligible after topical application of isotretinoin 0.05 % gel, even after multiple applications [27]. The results suggested systemic absorption to a lesser extent than with the USA recommended daily allowance of vitamin A supplementation.

Because oral isotretinoin is a potent teratogen and designated pregnancy category X, the use of topical isotretinoin, which is not FDA designated, is contraindicated during pregnancy and lactation and should be used with caution in women of childbearing potential. Safety and efficacy in children below the age of 12 have not been established.

## 57.4 Adapalene

Adapalene is a synthetic third-generation topical retinoid derived from naphthoic acid, which is available as 0.1 % gel, 0.1 % cream and solution, and as 0.3 % gel. Its methoxyphenyl adamantyl side chain renders the substance stable to oxygen and light [28] even after mixture with benzoyl peroxide lotion and 24 h of light exposure. A meta-analysis of five well-controlled trials [29] involving more than 900 patients demonstrated equivalent efficacy of adapalene 0.1 % and tretinoin 0.025 % with a mean reduction of total acne

lesions of 57 % in patients receiving adapalene for 12 weeks and 53 % in those receiving tretinoin, however, with a more rapid onset of action and a considerably greater local tolerability during adapalene treatment. Adapalene gel 0.3 % demonstrated superiority to adapalene gel 0.1 % and vehicle and was well tolerated [19].

### 57.4.1 Adapalene-Combination Therapy

Numerous studies have been performed to assess the clinical efficacy of adapalene, used either as monotherapy [30] or as part of combination therapies [31]. The combination of adapalene 0.1 % with clindamycin 1 % phosphate lotion or clindamycin 1 % solution demonstrated superiority over the monotherapy in the reduction of inflammatory lesions counts after 12 weeks of treatment in patients with mild to moderate acne. The combination therapy was well tolerated; few observed adverse events were mild in nature.

Furthermore, adapalene is the first topical retinoid whose chemicophysical properties allow a fixed combination with benzoyl peroxide in a stable galenic formulation, which was demonstrated in a multicenter 12-week parallel group study involving 517 subjects with moderate to moderately severe acne. The fixed combination of adapalene 0.1 % and benzoyl peroxide 2.5 % gel provided significantly greater efficacy for the treatment of acne vulgaris relative to the monotherapies as early as week 1, with a comparable safety profile to adapalene [32]. These results have been further confirmed in two large clinical trials comprising 1,668 [33] and 1,670 [34] patients with similar results. Adverse events were more frequent with the combination therapy (mainly due to an increase in mild-to-moderate dry skin), occurred early in the study, and were transient. The safety of the fixed adapalene/BPO combination was assessed in a 12-month long-term safety study including 452 subjects and showed constant good tolerability [35].

The efficacy of adapalene has also been investigated in combination with a fixed combination of benzoyl peroxide 5 % and clindamycin 1 % (BP/C) gel [36]. The continuous combination of adapalene and BP/C produced significantly greater reductions in noninflammatory and total lesions after 12 weeks as compared to adapalene as monotherapy and was better tolerated, which might be explained by the excipient moisturizing components of the BP/C gel, glycerine, and dimethicone.

**Table 57.3** Evidence for the use of adapalene in combination therapies

| |
|---|
| Adapalene 0.1 % + Topical clindamycin |
| Adapalene 0.1 % + BPO 2.5 % or in fixed combination |
| Adapalene 0.1 % + Clindamycin/BPO |
| Adapalene 0.1 % + Doxycycline 100 mg/day |
| Adapalene 0.1 % + Lymecycline 300 mg/day |

The efficacy of adapalene gel 0.1 % in combination with oral antibiotics was studied in two 12-week, multicenter, randomized, and investigator-blind studies involving 242 patients with moderate to moderately severe acne (adapalene 0.1 % gel plus lymecycline 300 mg/day) and 467 patients with severe acne (adapalene 0.1 % gel plus doxycycline 100 mg/day) [31]. Both studies demonstrated a significantly greater reduction of inflammatory lesion counts of the combination therapy compared to the antibiotic alone at week 8 and 12 (Table 57.3).

### 57.4.2 Adapalene-Safety

Local adverse effects associated with adapalene use include erythema, scaling, dryness, pruritus, and burning, but usually of mild intensity. In comparative trials, adapalene was shown to be significantly less irritating than tretinoin 0.025 % or other concentrations of tretinoin gel or cream, tretinoin microsphere gels 0.04 % and 0.1 %, or tazarotene cream 0.05 % and 0.1 %, even when applied in combination regimens with clindamycin 1 % lotion, erythromycin 2 % gel, benzoyl peroxide 5 % gel, erythromycin–benzoyl peroxide gel, or with fixed benzoyl peroxide/clindamycin gels [19].

Absorption of adapalene 0.1 %/0.3 % gel or 0.1 % cream through human skin is low, which makes interaction with systemic drugs unlikely.

Adapalene is labeled FDA pregnancy category C. Animal studies showed teratogenic

effects at high doses only after oral application, but data in human pregnant women are lacking to rule out a risk. One case report exists of a women treated with adapalene gel during the first 13 weeks of pregnancy, who delivered a therapeutically aborted fetus at 22 weeks with anopthalmia and optic chiasma [37].Although the legal situation allows to prescribe adapalene if the potential benefit outweighs the risks, avoidance of adapalene during early pregnancy is recommended. Excretion via breast milk has not been studied and safety and efficacy in children below the age of 12 have not been established.

## 57.5 Tazarotene

Topical tazarotene, approved for acne treatment only in the USA, has shown therapeutic efficacy compared to its vehicle as 0.1 % gel [38] or 0.1 % cream [39] , the latter demonstrating absolute mean percent reduction of 43 % for all lesions after 12 weeks of treatment. Comparative trials showed superior efficacy of tazarotene gel 0.1 % compared to tretinoin 0.025 % gel and tretinoin 0.1 % microsponge gel in the reduction of noninflammatory lesions and overall disease severity [19]. Furthermore, tazarotene 0.1 % gel or cream were superior to the corresponding adapalene formulations, providing significantly greater reductions in overall disease severity, noninflammatory lesion count, and inflammatory lesion count, with similar tolerability slightly in favor of adapalene [19]. The use of tazarotene 0.1 % gel every other day to reduce irritation was equally effective to adapalene 0.1 % applied daily [40]. Furthermore, the efficacy and safety of a short-contact regimen of tazarotene gel 0.1 % applied once or twice daily compared to its vehicle has been demonstrated [41].

### 57.5.1 Tazarotene-Combination Therapy

The efficacy and tolerability of tazarotene 0.1 % gel were investigated in combination with benzoyl peroxide 4 % gel, erythromycin 3 %/benzoyl peroxide 5 % gel, and clindamycin phosphate lotion. None of the combinations was better than monotherapy in reducing noninflammatory lesions, but the triple combination with erythromycin/benzoyl peroxide significantly increased reduction of inflammatory lesions, whereas greater global improvement was achieved in combination with clindamycin phosphate lotion only [42].

Another triple combination of tazarotene 0.1 % gel with a fixed clindamycin 1 %/benzoyl peroxide 5 % gel significantly enhances efficacy versus monotherapy and potentially tolerability, which might be due to the emollients in the fixed combination [43].

Tazarotene 0.1 % gel was also tested in combination with oral minocycline 100 mg/day during a 12-week open-label study and subsequent 12-week maintenance phase, in which the subjects were randomized into three groups receiving either the combination or the antibiotic or the topical retinoid alone. Thirty-one of 189 initial recruited subjects completed a 6-month combination therapy without significant adverse events, of which 70 % maintained a >75 % improvement from baseline. However, as the focus of this study was the maintenance evaluation, no conclusions can be drawn in terms of efficacy compared to monotherapy during the initial active treatment phase [44] (Table 57.4).

**Table 57.4** Evidence for the use of tazarotene in combination therapies

| |
|---|
| Tazarotene + Erythromycin/BPO |
| Tazarotenene + Clindamycin |
| Tazarotene + Clindamycin/BPO |

### 57.5.2 Tazarotene-Safety

Local adverse effects are similar to those observed with other topical retinoids and include erythema, burning/stinging, itching, and dryness. Tazarotene was shown to be the most irritative retinoid in comparative trials [19]. In a

study comparing the cumulative irritation scores of tazarotene 0.1 % compared to different concentrations of tretinoin cream (0.02–0.1 %), tazarotene gel demonstrated the highest irritation score of all tested products followed by tazarotene cream. Furthermore, irritation potential of tazarotene cream 0.05 % and 0.1 % is significantly higher than that of adapalene 0.1 % cream, whereas tazarotene cream 0.05 % (not approved for acne) and adapalene gel 0.3 % showed equal tolerability slightly in favor of adapalene. The irritative potential of tazarotene can be reduced by short-contact application once or twice daily [39] or by an every other day regimen [40]. The cream is generally better tolerated than the gel.

Percutaneous penetration of tazarotene is limited, and the systemic bioavailability of tazarotene (measured as tazarotenic acid) is low, approximately 1 % after single and multiple topical applications to healthy skin.

Tazarotene is designated pregnancy category X, prohibiting its use during pregnancy and breastfeeding. Women of childbearing potential should use adequate birth-control measures when topical tazarotene is used. Tazarotene was teratogenic in animals after oral administration of high doses, but not after topical exposure. As yet, reports of pregnancies in tazarotene-treated patients did not report any abnormalities.

## 57.6 Retinaldehyde

Retinaldehyde, a key intermediate molecule in the metabolism of natural vitamin A by keratinocytes, has both mild comedolytic effects and antibacterial activity against gram-positive bacteria including *P. acnes* [4], which is likely due to the aldehyde group. A cosmetic preparation of 0.1 % retinaldehyde/6 % glycolic acid has shown superiority over its vehicle patients with mild to moderate acne and was well tolerated [44]. The preparation was also effective in the prevention and treatment of acne scarring and reduction of postinflammatory hyperpigmentation [19].

## 57.7 Clinical Guidelines for the Use of Topical Retinoids in Acne

The clinical use of topical retinoids has been facilitated by development of the third-generation retinoid adapalene as well as new galenic formulations of tretinoin, both showing better tolerability than the first-generation retinoids. Furthermore, variations in the application mode and frequency have been established and help to minimize side effects of more irritating substances, such as tazarotene.

Despite this progress, tolerance varies and individual adjustment and patient instruction are still necessary to ensure compliance as a prerequisite for long-term success. It is essential to explain the patients the time and duration of expected side effects, such as mild irritative dermatitis, and to advise them how to prevent and treat possible adverse reactions.

When prescribing a topical retinoid, the following points should be considered for patient counseling:

- Excessive washing with soaps should be avoided, and washing should be performed with warm water and a gentle cleanser.
- The retinoid should not be applied directly after shaving, and aggressive adstringents or ethanol-containing aftershaves or toners should be avoided.
- The patient should stop all other OTC acne treatments, such as abrasive peelings, except those recommended by the physician.
- Direct and prolonged sun (or artificial UV) exposure should be avoided, and sunscreens are recommended during the sunny season.
- Weather extremes such as cold or heat/humidity can worsen the symptoms of retinoid dermatitis.
- When applying the retinoid to the face, the corners of the eyes and mouth should be avoided, because they are easily irritated.
- The use of a moisturizer for the skin and lipsticks or petrolatum can prevent and alleviate symptoms of retinoid-dermatitis [20].
- The patient should know that irritation generally occurs in the early treatment phase and

reactions often completely disappear upon treatment continuation.

- The time course of the expected improvement should be discussed. The value of treatment should not be judged before 8–12 weeks. However, with the new fixed combination therapies, often a rapid improvement can be seen already after 1–2 weeks.

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# Azelaic Acid

# 58

Mauro Picardo and Monica Ottaviani

## Contents



**Core Messages**

- Azelaic acid is a C-9 dicarboxylic acid presenting several biological activities related to the principal factors involved in acne pathogenesis. The diacid reduces *Propionibacterium acnes* proliferation, induces the normalization of keratinisation process, interferes with sebogenesis, and possesses anti-inflammatory activity.
- Clinical studies have shown efficacy in treating both inflammatory and noninflammatory acne lesions with good compliance and patient satisfaction.
- No induced bacterial resistance has been reported, even after a long time treatment.
- No phototoxicity or sensitization, have been described and no interactions with other drugs have been recognized.
- Adverse effects are usually limited to transient erythema and local mild cutaneous irritation, making it safe for acne treatment during pregnancy.
- Azelaic acid can be useful both as monotherapy or in combination with other antiacne agents leading, in most cases, to an overall improving efficacy.

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## 58.1 Azelaic Acid

Azelaic acid is a naturally occurring aliphatic C-9 dicarboxylic acid with several biological properties. The interest in the possible therapeutic applications came out in the 1980s when studies on the pathogenesis of Pityriasis versicolor, showed that in vitro dicarboxylic acids are competitive inhibitors of tyrosinase, a key enzyme for melanogenesis, leading to the use of dicarboxylic acids, and in particular azelaic acid, in the treatment of hyperpigmentary disorders . The beneficial effects of the topical application of a 20 % azelaic acid cream was proven in benign hyperpigmented disorders such as melasma and postinflammatory melanosis and effectiveness was also reported in some cases of lentigo maligna and melanoma [1, 2]. The coincidental findings of improvement in acne lesions in subjects with melasma led to new investigations on azelaic acid's properties and possible applications in acne [3].

## 58.2 Azelaic Acid in the Treatment of Acne

Even if the therapeutic mechanism in acne is not completely understood and still under investigation, several biological properties of azelaic acid, demonstrated both in vitro and in vivo, could account for this activity. Properties of azelaic acid directed against the etiopathogenesis of acne include (a) the antimicrobial effect on several aerobic and anaerobic microorganism, including *Propionibacterium acnes*; (b) the cytostatic action observed on proliferative keratinocytes which can inhibit follicular hyperkeratosis; (c) the inhibition of the 5-alpha-reductase activity, possibly responsible for reduction in sebum secretion; and (d) the interference with the inflammatory process. In the last few years, an innovative formulation in 15 % gel formulation has contributed to the enhancement of clinical efficacy, leading to further consider azelaic acid as a valid therapeutic option for the treatment of mild to moderate acne vulgaris and rosacea [4] (Fig. 58.1).

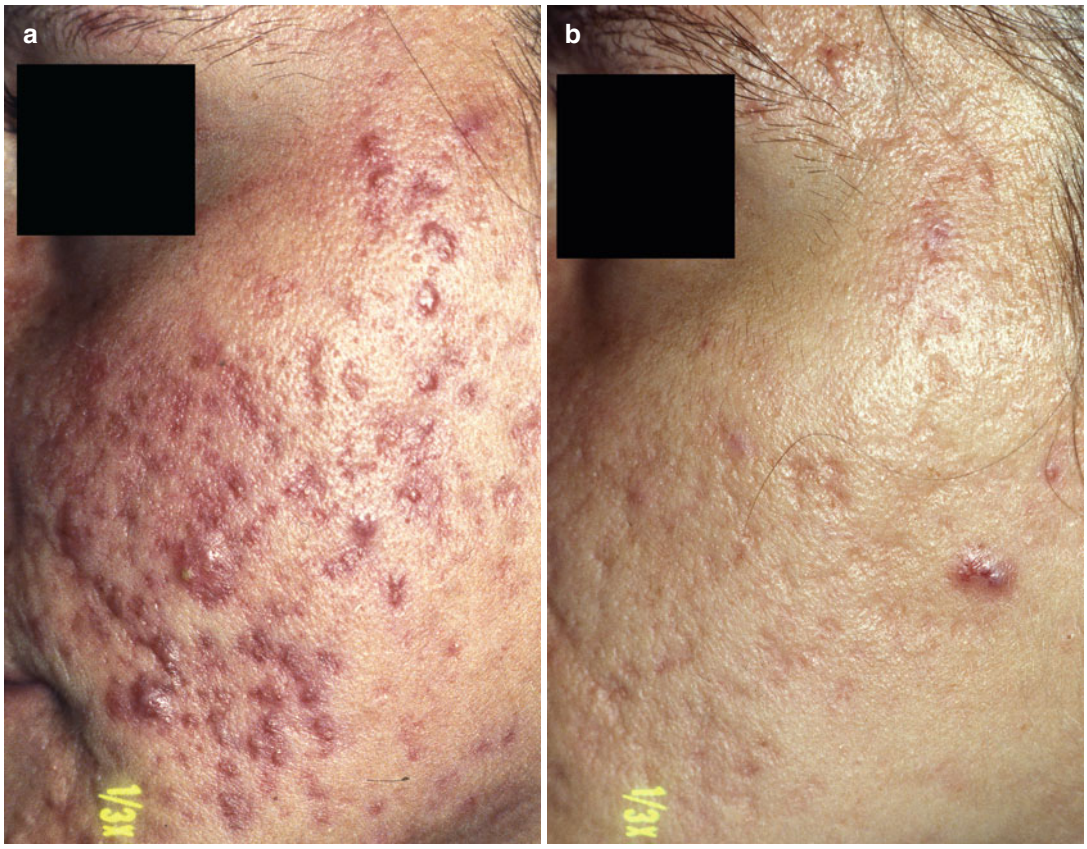
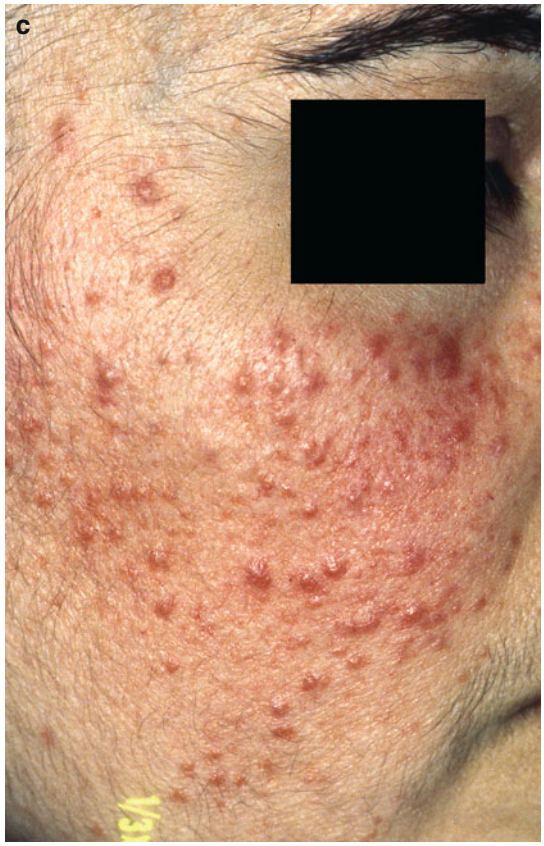



**Fig. 58.1** Acne before (**a**, **c**) and clinical results obtained after the treatment with azelaic acid (twice a day for 1 year) (**b**, **d**, respectively)



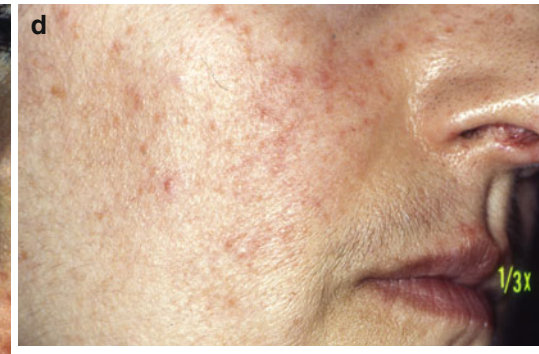




**Fig. 58.1** (continued)

## 58.3 Antibacterial Properties

Azelaic acid has a predominant antibacterial action, inhibiting the growth of *Propionibacterium acnes* and *Staphylococcus aureus*, although it is not an antibiotic [3]. The antimicrobial activity is correlated to the inhibition of protein synthesis and seems to be dose- and pH dependent and associated with the ability of azelaic acid to interfere with transmembrane pH gradient [5]. The reduction of intrafollicular *P. acnes* density in the treated areas produces a reduction of free fatty acids arising from triglycerides from the action of bacterial lipases [6].

## 58.4 Antikeratinizing and Comedolytic Activity

In vivo and in vitro studies showed that azelaic acid is able to induce remarkable alteration in the proliferation and differentiation of epidermal keratinocytes. The ability of counteracting the hyperkeratosis of the follicular duct could be due to the interference with mitochondrial oxidoreductases [7, 8] and to the dose- and time-dependent inhibition of DNA synthesis. Moreover, azelaic acid specifically inhibits, in vitro, the synthesis of cytoplasmic proteins correlated to the terminal steps of keratinization and, in vivo, results in a decrease in the number and size of keratohyalin granules and a normalization in filaggrin expression after the treatment of acne and seborrheic skin [9, 10]. The reduction in the epithelial hyperplasia has been observed at both the histological and clinical level, with a significant decrease in the volume and numbers of comedones [11–13].

## 58.5 Sebostatic Activity

The sebosuppressive action of azelaic acid is still controversial because according to some authors the

effect is not relevant [6, 10, 14], whereas in recent studies an average reduction in the sebum production of about 14–15 % on the forehead, chin and cheek after 3 months of treatment has been reported [15]. The sebostatic effect could be due to the capability of the diacid to act as a competitive inhibitor of 5-alpha-reductase [7, 8], the enzyme that converts testosterone in 5-dihydrotestosterone, responsible for sebaceous gland stimulation. However, the effectiveness of azelaic acid in controlling sebogenesis needs further investigations to be proven.

## 58.6 Anti-inflammatory Properties

The anti-inflammatory activity of azelaic acid has been demonstrated in several clinical studies, with the same reduction of inflammatory acne lesions compared to topical benzoyl peroxide or clindamycin [4, 16], and an approximately similar efficacy with oral tetracycline [14]. Considering that reactive oxygen species (ROS) may initiate or participate in the inflammatory process, some papers have evaluated their involvement in the pathogenesis of acne. It has been reported that patients with inflammatory acne generate higher levels of hydrogen peroxide generation by neutrophils, as compared to comedonal acne patients and healthy subjects, suggesting a role in the induction of manifestations and in the damage of the follicular epithelium. Therefore their inhibition could improve the evolution of the lesions [17]. Azelaic acid, in vitro, is a scavenger of hydroxyradicals generated by different mechanisms and is capable of inhibiting ROS generation by neutrophils [17, 18]. Moreover, recent studies investigating the mechanisms in reducing inflammation processes indicate that azelaic acid could counteract the inflammatory cascade through the inhibition of the generation of ROS and of pro-inflammatory cytokines [19].

## 58.7 Clinical Trials

Clinical efficacy of azelaic acid has been demonstrated by several studies. Vehicle controlled trials showed the ability of the 20 % cream to efficiently act against both inflammatory and noninflammatory lesions, with a reduction in papules and comedones of about 70 % and 56 %, respectively, after 3 months of treatment [20]. A significant reduction of inflamed lesions has been reported in another controlled trial after 1 month, whereas 2 months were necessary for comedones, associated with a significant decrease in follicular *P. acnes* [6]. Similar results have been obtained with the 15 % gel formulation, confirming the effectiveness of this treatment in mild to moderate acne [21]. After 6 months of treatment, the efficacy of 20 % azelaic acid cream was comparable to other topical antiacne agents such as 5 % benzoyl peroxide gel and 0.05 % tretinoin cream [22, 23]. Similarly, patients treated for 4 or 5 months achieved good to excellent results as well as those treated with topical antibiotics such as 2 % erythromycin [24]. Moreover, azelaic acid produced clinical results comparable to those of oral tetracycline, with a slower time-response in case of deep inflamed lesions; however, at the end of 4 months treatment, the overall results were comparable to those achieved with tetracycline [25]. No bacterial resistance has been associated with azelaic acid treatment.

Azelaic acid has no recognized interaction with other drugs; therefore, the combination with other antiacne treatments can lead to a better efficacy. In particular, for severe acne, the association with an oral antibiotic, such as minocycline, resulted in a highly effective treatment, comparable to oral isotretinoin [26]. Maintenance therapy with azelaic acid prolongs the recurrence-free interval [26]. An overall improvement similar to that obtained with 0.025 % tretinoin cream has been noticed when azelaic acid is combined with 15 % and 20 % glycolic acid lotion.[27].

In all clinical trials, the most frequent adverse effects experienced were a mild transient erythema and cutaneous irritation [28] and, for this reason, azelaic acid usually obtains high patient compliance and satisfaction. Moreover the diacid is neither toxic nor phototoxic, it is not teratogenic, and no contact sensitization has been reported.

Recently, in order to introduce some amelioration in the delivery of the compound, a new gel formulation with a lower nominal concentration of azelaic acid has been developed. The single-phase

water-based gel contains 15 % micronized particles of azelaic acid (1–10 μm in diameter) enhancing drug release and skin bioavailability. The low lipid content (3 %) results in a lower stickiness of the formulation, and the high water percentage (70 %) is associated with a less irritant and soothing effect of the treatment resulting in an overall greater effectiveness [29]. The hydrogel formulation was approved by the FDA for the treatment of rosacea and, in many European countries, also for the treatment of acne. Two randomized, multicentric, controlled trials proved that the efficacy of the gel was comparable to that achieved with 5 % benzoyl peroxide and 1 % clindamycin, with a similar reduction of inflamed lesions and a local irritation lower than with benzoyl peroxide [15, 16] and a European study assessed the safety and efficacy of this formulation encountering both physicians and patients satisfaction for the clinical results [4].

In conclusion, based on the experimental data and the results of clinical experience, azelaic acid can be considered among the therapeutic repertoire in the treatment of patients with mild to moderate acne, even for a long period, in combination with other treatments, according to the clinical course of the disease of acne.

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# Emerging Acne Treatments

# 59

Anthony V. Rawlings

## Contents



**Core Messages**

- Effective acne treatments have several targets such as reducing sebogenesis, correcting the follicular epithelial dysfunction, reducing *Propionibacterium acnes* colonization, and mitigating skin inflammation. Emerging technologies to influence these targets are being researched.
- Retinoic acid metabolism blocking agents (RAMBAs) are being investigated for facial acne vulgaris. Manipulation of other retinoid metabolism enzymes and chromatin remodeling agents may also offer benefit.
- Two recently identified peroxisomal proliferator activated receptor (PPAR) agonists, octadecendioic acid and phytosphingosine, are reported to reduce acne lesions. Phytosphingosine also potentiates the activity of conventional treatments such as benzoyl peroxide. However, these new agents also possess antimicrobial activities.
- Inhibition of dipeptidyl peptidase IV and aminopeptidase N have been shown to reduce sebaceous hyperplasia, follicular hyperproliferation, and inflammation and is a promising technology route.
- Further combinatorial approaches are anticipated to improve the effectiveness of acne treatments.

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## 59.1 New Retinoid-Like Approaches to Acne Treatment

Clearly retinoids are effective acne treatments whether they are first-generation retinoids such as retinoic acid, second generation such as etretinate, or third generation such as adapalene and tazarotene. Nevertheless, these molecules exert their effects through nuclear receptors. Nuclear hormone receptors, e.g., the alpha, beta, and gamma isoforms of the retinoid X (RXR) and retinoic acid receptors (RAR) or the peroxisomal proliferator-activated receptors (PPAR) exert their effects directly on genes by binding to DNA [1, 2]. The pleiotropic effects of retinoids in particular are due to the existence of multiple RA receptor isoforms and as a result of the different combinations of RAR–RXR heterodimers [3]. RARs and RXRs mainly act as heterodimers on binding to the retinoic acid response element (RARE). The RAR's can be activated by binding all-trans retinoic acid (atRA) or 9cisRA, however, RXRs can only be activated by 9-cis retinoic acid (9cisRA).

Considering atRA, retinol, and further opportunities for improving their efficacy, the metabolic fate of retinoids generally in skin is controlled by two classes of intracellular-binding proteins: the cellular retinol-binding protein type I (CRBP I) and the cellular retinoic acid-binding protein type II (CRBP II) [4–6]. These sequester a retinoid so that it is only available for reaction with specific enzymes. The holo-CRBP retinol complex can serve as a substrate for lecithin: retinol acyl transferase (LRAT) [6] in the basal keratinocytes when the retinoid status is high. Conversely when low it serves as a substrate for retinol dehydrogenase synthesizing retinal which ultimately gets converted to atRA . The transport into the nucleus and further metabolism of atRA is controlled by CRBP I & II. It is suggested that CRBP I transport atRA into the nucleus, while CRABP II sequesters excess atRA in the cytoplasm facilitating its degradation. Metabolic inactivation of atRA to 4-hydroxyretinoic acid and 18-hydroxyretinoic acid occurs via a cytochrome P450 enzyme (CYP26A1) [7, 8]. This hydroxylase activity is actually induced in vivo by atRA in human epidermis but can be inhibited by azoles. In the presence of low dose atRA or retinol (ROH), azoles amplify the human skin responses to retinoids in a manner characteristic of the retinoids at a higher dose [9]. These agents have been called retinoic acid metabolism breakdown agents (RAMBA's) or retinomimetics [10]. Examples include ketoconazole, liarozole, and talarozole. Oral talarozole (1 mg, daily) in an open-label single arm study on 17 subjects with moderate to severe facial acne reduced total lesions by 76 %, inflammatory lesions by 77.4 % and noninflammatory lesions by 58.3 % ($p < 0.001$). Improvement was still pronounced 4 weeks after the last drug intake.

In human keratinocytes atRA regulates its own biosynthesis from ROH through the regulation of retinol esterification and as such RAMBA type agents may not optimal [11]. Treatment with atRA induces LRAT activity in proliferating keratinocytes and reduces the conversion of ROH to RA resulting in sequestration of ROH in retinylesters. Acyl retinol acyl transferase activity is also present in the suprabasal layers (ARAT [6]). Several other enzymatic steps have been identified that if manipulated can deliver improved retinoid responses, particularly by inhibiting retinol esterification [2, 11, 12] (Fig. 59.1). The retinol boosting effects were assessed in vivo by measuring the CRABP II response and for their effects on skin photodamage [11, 12]. These approaches were the first generation of cosmetic retinomimetics. These approaches may prove to be useful for the treatment of acne (Fig. 59.1).

Nuclear hormone receptors are also regulated epigenetically [13]. Chromatin is tightly packed inside the nucleus and is a complex consisting of DNA, histones and nonhistone proteins. A nucleosome is the basic building block of chromatin which contains 147 base pairs of DNA wrapped around a core of four histone partners—an H3–H4 tetramer and 2 H2A–H2B dimers. When condensed this structure represses gene transcription. In the absence of ligand the nuclear

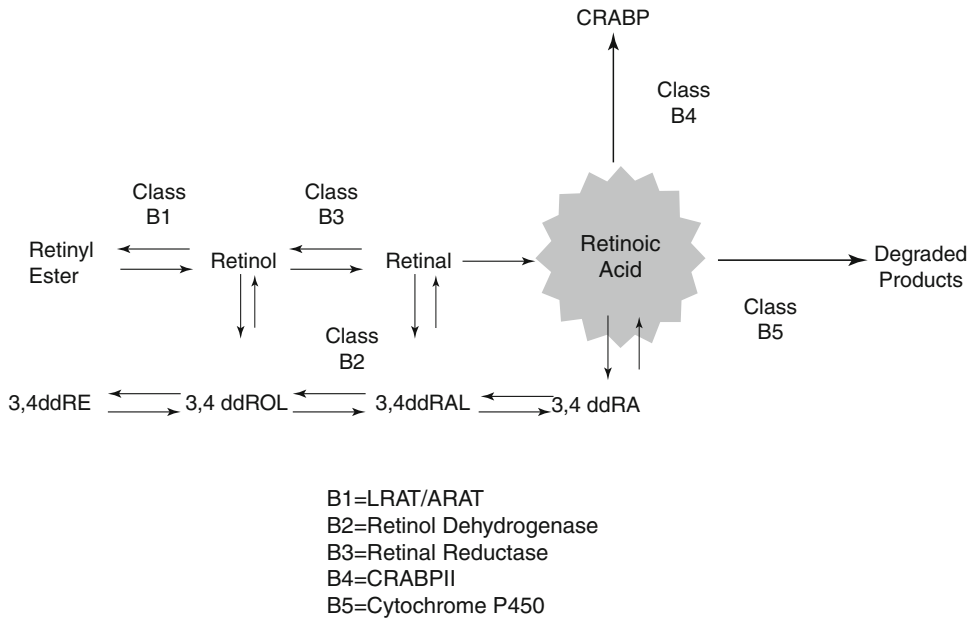


**Fig. 59.1** Schematic of retinoid metabolism and potential enzymatic steps to influence

receptors recruit nuclear corepressor proteins such as nuclear receptor corepressor (NcoR) or the silencing mediator for retinoid and thyroid hormone (SMRT) and Sin 3 which in turn forms a complex with histone deacetylase enzymes (HDAC) resulting in transcriptional silencing of genes. This suppression occurs because deacylation of the histone proteins creates conformational changes in the chromatin structure limiting the access and binding of the nuclear receptors and RNA polymerase to the related genes. Ligand binding causes the receptors to undergo a conformational change releasing the corepressors and recruiting histone acetylases (CBP/p300 or the steroid receptor coactivator; SRC-1) that open up the chromatin and thus function as transcriptional coactivators. Acetylation of lysine residues in the N-terminal of histones opens up the chromatin structure and allows gene transcription [14]. Enhancement of retinoid activity, or any nuclear hormone receptor, is anticipated by combining HDAC inhibitors with retinoids. The synergistic effects on keratinocytes have already been proven [15]. Research on their effectiveness on acne is continuing.

## 59.2 Octadecenedioic Acid: A Novel Dicarboxylic Acid for the Treatment of Acne

Azelaic acid is a $C_{9:0}$ dicarboxylic acid which improves follicular keratinization, possesses antimicrobial activity against *P. acne*s, and has some anti-inflammatory efficacy via effects on neutrophilic granulocytes. It is used at very high concentrations (20 %), although somewhat lower concentrations (15 %) have recently also been shown to be effective [16]. The $C_{18:1}$ dicarboxylic acid, octadecenedioic acid, was recently developed [17] and tested for its antimicrobial activity against *P. acnes* because of its structural similarity to azelaic acid.

To test for antimicrobial activity azelaic acid or octadecenedioic acid-containing agar plates were inoculated with *P. acnes*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*. End-point MIC-values were determined by observing the plate of lowest concentration of agent that inhibited visible microorganism growth. Octadecenedioic acid was found to be very effective against *P. acnes* as well as *S. aureus* and *S. epidermidis* (0.04 %, 0.07 %, and 0.31 %, respectively).

Against *P. acnes* and *S. aureus*, octadecenedioic acid was over 50-fold more active than azelaic acid when compared on a molecular basis [17].

Octadecenedioic acid was tested clinically at 10 % in an o/w-emulsion on 20 volunteers comparing a commercial benzoyl peroxide benchmark control for 12 weeks. The study population consisted of mild to moderate acne sufferers between the ages of 13 and 35. Antiacne clinical efficacy was determined using the "Leeds Scale" and by counting acne lesions. Reductions in the levels of all types of lesions were associated with both treatments. These changes were statistically significant to baseline ($p < 0.05$). 73 % of patients treated with 5 % benzoyl peroxide and 53 % of patients treated with 10 % octadecenedioic acid had a decrease in overall acne grade at week 12. Although the treatment effect of benzoyl peroxide was numerically superior to octadecenedioic acid, it was not statistically superior but this was at the expense of adverse facial irritation such as scaling, burning, and erythema. In contrast, much reduced negative reactions were perceived from the octadecenedioic acid treatment. As a first study this new acid is a promising treatment for acne. Clearly it is an antimicrobial but does it possess any other activities?

Very recently, advances in fundamental sebaceous gland research have suggested that PPARs might also be implicated in sebogenesis [18]. As mentioned previously, PPARs are members of the nuclear hormone receptor superfamily and have been shown to be important in the regulation and catabolism of dietary fats [19], the stimulation of epidermal differentiation [20, 21], the reduction of inflammation [22, 23], and the reduction of melanocyte proliferation [24, 25]. These activities are regulated through one or more of the three isoforms of PPARs: PPARα, PPARδ, and PPARγ. In human skin, epidermal differentiation is predominantly regulated by PPARα and to a lesser extent by PPARδ, inflammation through PPARα and some PPARγ, and melanocyte proliferation mainly via PPARγ. Using human chest sebaceous glands as 7-day cultured whole organs, Downie et al [18]. were able to demonstrate that activators of PPARα and PPARγ inhibited the rate of sebaceous lipogenesis and reduced the synthesis of the sebum-specific lipids squalene and triacylglycerol in human sebaceous glands. They conclude, "As suppression of sebum secretion is associated with reduced acne activity, the nuclear hormone receptors involved may open new avenues in the development of novel acne treatments." This, however, is still unconclusive as others have found increased sebogenesis in cell culture. The group of Zouboulis [26, 27], for instance, describe the stimulatory effects of linoleic acid on sebogenesis and its interactions between androgens on neutral and polar lipid synthesis. Nevertheless, linoleic acid when applied topically to acne patients produced an almost 25 % reduction in the size of follicular casts and microcomedones [28] and most recently Ottaviani et al [29]. reported that the increased expression of PPARs induced by squalene peroxides in HaCat keratinocytes leads to the downregulation of inflammatory mediators. So is octadecenedioic acid a PPAR agonist and is this how it has some of its activity in acne patients?

To determine this a reporter gene assay using HeLa cells transfected with chimeric receptor genes fused to a PPAR ligand-binding domain and a reporter gene with the luciferase/luciferine system was performed. The results demonstrated that octadecenedioic acid is a pan-PPAR agonist with a greater specificity for PPARγ ($EC_{50}$ being approximately $10^{-6}$ M, whereas the affinity constants for α and δ were tenfold lower) [30].

Octadecenedioic acid has the potential to interact on all targets in acne: enhanced differentiation to prevent the increased cornification of the sebaceous duct, reduction of sebum production to counteract hyperseborrhea, and reduction of inflammation. These PPAR-related effects combined with its demonstrated antimicrobial properties to overcome the hypercolonization with microbes such as *P. acnes* make octadecenedioic acid a viable nonantibiotic alternative for the treatment of acne.

## 59.3 Phytosphingosine: A Novel Sphingoid-Base for the Treatment of Acne

Ceramides are present in skin and consist of N-acylated sphingoid bases [31]. However, some of these sphingoid bases occur freely in

the non-amidated form. The most common member of this group found in nature is (2*S*, 3*R*)-D-ERYTHRO-2-amino-1,3-octadec-4*E*-enediol, namely sphingosine. Another member is phytosphingosine (PS), typically consisting of an 18-carbon chain that incorporates a 2-amino-1,3,4-triol for its lipid head grouping.

How is this molecule useful for the treatment of acne, however? Firstly, PS possesses antimicrobial activity [32, 33]. Minimal inhibitory concentration of PS for *P. acnes* was 0.2 g/L. Secondly, PS mitigates inflammation and improves keratinocyte differentiation. In keratinocyte cell culture, PS reduced the expression of pro-inflammatory chemokines like interleukin-8 (IL-8), CXCL2, and Endothelin-1 and increased the expression of differentiation markers like loricrin, involucrin, transglutaminase1, and filaggrin. Additional benefits may be derived from the effect of topical PS as it is known to act as a precursor to ceramides, and ceramides are known to be reduced in the skin of acne subjects. It has been demonstrated by electrospray-ionization-mass spectroscopy (ESI-MS) on extracts of the lipid phase of cultured keratinocytes that PS can be taken up efficiently by the cells and PS can further be metabolized and converted to glucosylceramides, which are the precursors of the different barrier-ceramides.

Equally Kim et al. [34] have demonstrated that phytosphingosine stimulates the differentiation of human keratinocytes and inhibits TPA-induced inflammatory epidermal hyperplasia in hairless mouse skin. In this respect sphingoid bases have also been identified as PPAR ligands [35] and PS was identified as a pan PPAR ligand in the order PPARγ, PPARα, and PPARδ with 57 %, 36 %, and 17 % activity [36].

Nevertheless, the only proof of the effect of PS on the alleviation of acne is through a clinical study [37, 38]. Volunteers with moderate inflamed acne on the face participated in a half-face study and had evaluations at baseline and days 30 and 60. PS was compared with benzoyl peroxide and the combination was also evaluated. Since the combination of BPO and PS in a formulation has been shown to be unstable (chemical interaction between the active ingredients), the two compounds were separated from each other in a two-chamber dispenser. On its own, PS diminished the number of papules and pustules (89 %) but not comedones. Equally, benzoyl peroxide decreased papules and pustules by 32 % and comedones by 22 %. However, the combination of 0.2 % PS with 4 % benzoyl peroxide resulted in a synergistic effect with a 72 % reduction in comedones and 88 % reduction in pustules and papules. Nevertheless a much faster response was observed. After 30 days of treatment the number of papules and pustules, and comedones were diminished to 60 % and 43 %, respectively, compared to 25 % and −6 % with PS only, or to 10 %, and 15 % with benzoyl peroxide only. Although PS was not able to prevent the formation of comedones, it was able to at least control the number of comedones that were induced by the particular placebo formulation alone. Taken together PS, like octadecenedioic acid also has multiple activities and exerts its effects as a bacteriostatic agent as well as being an anti-inflammatory and keratinocyte differentiating agent possibly by being a PPAR ligand.

## Conclusions

Novel approaches are being sought for the treatment of acne including inhibitors of dipeptidyl peptidase IV and aminopeptidase N which so far in vitro has been shown to be a potentially useful antiacne route [36]. Current technologies are particularly focusing on the manipulation of retinoid metabolism and enzymes involved in chromatin remodeling. Although ligands for PPARs appear to be promising for the treatment of acne, their effects on sebogenesis is still controversial. Zieuton, an oral 5-Lipoxygenase inhibitor is useful and reduces potential PPAR agonists [37, 38]. However, PPARγ agonists but not antagonists have been reported to decrease sebaceous gland size and the dihydrotestosterone effects on the glands in the Fuzzy rat [39, 40]. Nevertheless two agents, octadecenedioic acid and phytosphingosine, appear to be useful for the treatment of acne and may be acting as PPAR ligands and antimicrobial agents.

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# Oral Antibiotics

# 60

Falk R. Ochsendorf

## Contents



**Core Messages**

- Acne is a multifactorial disease in which *Propionibacterium acnes* modulates and triggers inflammatory events.
- Indications for oral antibiotics include moderate and severe acne, acne resistant to topical treatment, and acne extending over large parts of the body surface.
- Oral antibiotics used include first- (tetracycline HCL, oxytetracycline) and second-generation cyclines (doxycyline, lymecycline, minocycline) and erythromycin. Other macrolides (roxithromyin, azithromycin) were used successfully, but have no advantage and should be reserved for systemic diseases. Trimethoprim is a third-line antibiotic.
- Oral antibiotics act both by reducing *P. acnes* and thus decreasing its pro-inflammatory properties as well as directly inhibiting inflammation by several mechanisms.
- Oral antibiotics reduce inflammatory lesions by about 50 % after 3 months.
- There are no differences in terms of effectivity between the different substances. So the choice has to consider resistance (rates and induction, advantage of cyclines), pharmacokinetics (advantage of second-generation cyclines), side effect profile (advantage of doxycyline and lymecycline), and costs.

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- There is no clear dose–response relation. Low dose antibiotic therapy favors the development of resistance with the exception of using sub-inhibitory concentrations.
- Combination therapies (retinoids, benzoyl-peroxide, azelaic acid, oral contraceptives) increase effectivity of oral antibiotics.
- Cyclines are contraindicated during pregnancy, lactation, and in children < 8 years. Erythromycin is contraindicated in cardial arrhythmias. Side effects include mild gastrointestinal disturbances (~4 % cyclines, 4–7 % erythromycin). Minocycline has rare but potentially severe side effects. Erythromycin shows many drug interactions. The effectivity of oral contraceptives is not impaired by cyclines and erythromycin.
- Therapies longer than 3 months are rarely beneficial. Oral antibiotics should not be used as maintenance therapy.

## 60.1 Introduction

*Propionibacterium acnes* (*P. acnes*) plays a role in acne pathogenesis. In 1954 oral tetracyclines were first evaluated in acne, others followed. The compounds used have both antibacterial and anti-inflammatory properties. Oral antibiotics were and are still widely used for the treatment of moderate to severe inflammatory acne. Five million prescriptions were written for this purpose in the USA between 1996 and 1998 (1.4 million for isotretinoin; [1]). Although the efficacy of antibiotics is well known to the clinician the study data supporting this impression are not as well founded as with other acne therapeutics. This is due to a variety of methodological problems, such as inconsistent information on baseline characteristics, heterogeneity of assessment schemes and outcome criteria, differing dosages, and treatment duration [2–5].

## 60.2 Antibiotics Used in Acne Therapy

Several antibiotics are active against *P. acnes* in vitro, such as penicillin and can be used to treat sepsis due to this agent [6]. However, they have limited to no effect in acne (penicillin, cephalosporins, aminoglycosides, chloramphenicol) [2, 7, 8]. Antibiotics which can be used in acne have to reach the follicular canal of the sebaceous follicle. So cyclines, macrolides, clindamyin, cotrimoxazole, trimethoprim, and quinolones are effective acne therapeutics.

### 60.2.1 Cyclines

Cyclines comprise a class of antibiotics with the members tetracycline HCl, oxytetracycline, lymecycline, doxycycline, and minocycline. They are the mainstay in acne therapy due to their very good efficacy and their good safety profile. Side effects include gastrointestinal disturbance and some drug-specific effects (see below). The cylines show cross resistance within the class, but no cross resistance to other antibiotics.

### 60.2.2 Macrolides

Oral macrolides, mainly erythromycin, but also roxithromycin and azithromycin, are effective in acne. However the insolicitous use of antibiotics in acne led to a large percentage of erythromycin-resistant *P. acnes* [9]. This limits its use as a clear correlation between carriage of erythromycin-resistant *P. acnes* and poor clinical efficacy was demonstrated [10]. Macrolides are well known to induce resistance very fast. Macrolides should therefore be only given in certain situations such as intolerance or contraindications to cyclines (e.g., pregnancy and breastfeeding). Erythromycin and clindamycin are frequently cross resistant.

### 60.2.3 Clindamycin

Oral clindamycin is rarely used in acne. It is needed for severe systemic infections, so it should be deliberately used in acne because of

potential development of resistance. Furthermore it has potentially serious adverse effects (pseudomembranous colitis [11]).

### 60.2.4 Cotrimoxazole and Trimethoprim

These antibiotics are not licensed for acne therapy. They appear to have an effect in acne. Trimethoprim was advocated as third-line treatment in certain situations (no effect of cyclines/macrolides, contraindications to isotretinoin). It is cheap and has a low resistance profile. However, in a patient series 29 % of patients stopped therapy due to inefficacy [12].

### 60.2.5 Quinolones

One Japanese study showed levofloxacin to be effective in acne [13]. However oral quinolones should not be used in acne because of the small amount of compelling efficacy data, the potential for antibiotic resistance (particularly the development of quinolone resistance in commensal bacteria [14, 15]), the price, and side effect profile (potentially on cartilage in adolescents, agitation, headache, hallucination, gastrointestinal disturbance, arthralgia, tendinitis, and photosensitivity [16]).

## 60.3 Mechanism of Action

### 60.3.1 Antibacterial Activity

There is no correlation between the density of *P. acnes* on the skin and either the severity of acne or the degree of inflammation. Furthermore the percentage of reduction of *P. acnes* after antibiotics does not correlate with the clinical effect [17]. However living *P. acnes* is associated with generation of pro-inflammatory cytokines, stimulation of the Toll-like receptor 2, induction of a specific T-helper cell immune-response, and thus the formation of inflammatory lesions in acne [18]. These pro-inflammatory properties of *P. acnes*, the fact that a successful antibiotic treatment of acne is associated with a reduction in the *P. acnes* population and the therapeutic failure of antibiotic therapy in patients harboring erythromycin- or tetracycline-resistant *P. acnes* favors the relevance of a real antibacterial activity of antibiotics in acne [19].

Cyclines, macrolides, and clindamycin inhibit bacterial protein synthesis at the ribosomal level by different mechanisms. Trimethoprim and sulfamethoxazole interfere with bacterial folate metabolism and quinolones inhibit bacterial DNA gyrase.

### 60.3.2 Anti-inflammatory Activity

The antibiotics used in acne showed several anti-inflammatory properties in vitro. These include lipase inhibition, inhibition of phagocytosis, leukotaxis, and ROS generation, decreased secretion of TNF-a, IL-1, and IL6, increased secretion of IL-10, decreased activation of C3 (cyclines), dose-dependent inhibition of lymphocyte mitosis, and matrixmetalloproteinases [20–23]. The efficacy of subinhibitory doses of doxycyline suggests that these non-antibacterial effects play an important role [24].

## 60.4 Antibiotic Usage

### 60.4.1 Indication

Antibiotics are indicated for the management of moderate and severe acne, acne resistant to topical treatment ,and acne extending over large parts of the body surface [25].

### 60.4.2 Effectiveness

Antibiotics are definitely more effective than placebo, but no significant differences between the different classes or substances within a class could be demonstrated (Table 60.1, Fig. 60.1) [2, 5, 26, 27]. After 12–24 weeks, a 19–91 % decrease of inflammatory lesions (mean 54 + 20 %) and a 6–80 % decrease (mean 44 + 13 %) in non-inflammatory lesions can be expected (Fig. 60.1). The effectiveness of tetracyclines was impaired if resistant strain were present in one study [28] but not in another [29]. There was no decrease in effectiveness of cyclines since 1962 [26].

**Table 60.1** Comparison of different antibiotics in acne (after [5])

| Substance | | Comparator | Level of evidence* |
|---|---|---|---|
| *Antibiotic* | | *Placebo* | |
| Tetracycline | > | Placebo | A |
| Doxycycline<br>Minocycline<br>Lymecycline | > | Placebo | B |
| Cotrimoxazole | > | Placebo | B |
| Clindamycin | > | Placebo | C |
| *Antibiotic* | | *Antibiotic* | |
| Oxytetracycline | = | Minocycline | A |
| Tetracycline | = | Minocycline | B |
| Lymecycline | = | Minocycline | B |
| Tetracycline | = | Erythromycin | B |
| Doxycycline | = | Azithromycin | B |
| Doxycycline | = | Erythromycin | C |
| Doxycycline | = | Minocycline | C |

*Evidence level (according to [4] A: Moderate to strong evidence (at least two studies of acceptable quality with a moderate to strong statistical evidence for a clinically relevant endpoint or effect). B: Evidence is of medium strength (only one comparative study exists; different studies reached different qualitative conclusions; large differences are not statistically significant; the study quality is obviously so poor to prevent acceptance of statistical significance). C: The evidence does not allow for a final scientific conclusion (lack of sound data, contradictory data, qualitatively poor data)

### 60.4.3 Pharmacology

The pharmacologic data are summarized in Table 60.2. They may influence the choice of the compound. Although not less effective, first-generation tetracyclines (tetracycline HCL, oxytetracycline) and erythromycin need to be taken at least twice daily. In contrast to second-generation cyclines (doxycycline, lymecycline, minocycline), the absorption of first-generation cyclines is impaired by food and milk. This may impair compliance, effectiveness, and increase the development of resistance.

### 60.4.4 Dosage

A wide variety of different daily antibiotic dosages were used (375 mg–1,000 mg/day first-tetracyclines, 50–100 mg/day for minocycline, 40–200 mg/day for doxycyline, and 150–300 mg/day for lymecycline, 1,000 mg/day erythromycin, 300 mg/day roxithromycin, 500 mg azithromycin 4days/month or 1–3 days/week, trimethoprim 300 mg/day). The standard dosages are 1,000 mg/day for tetracyclines, 100 mg/day for doxycyline, 300 mg/day for lymecycline.

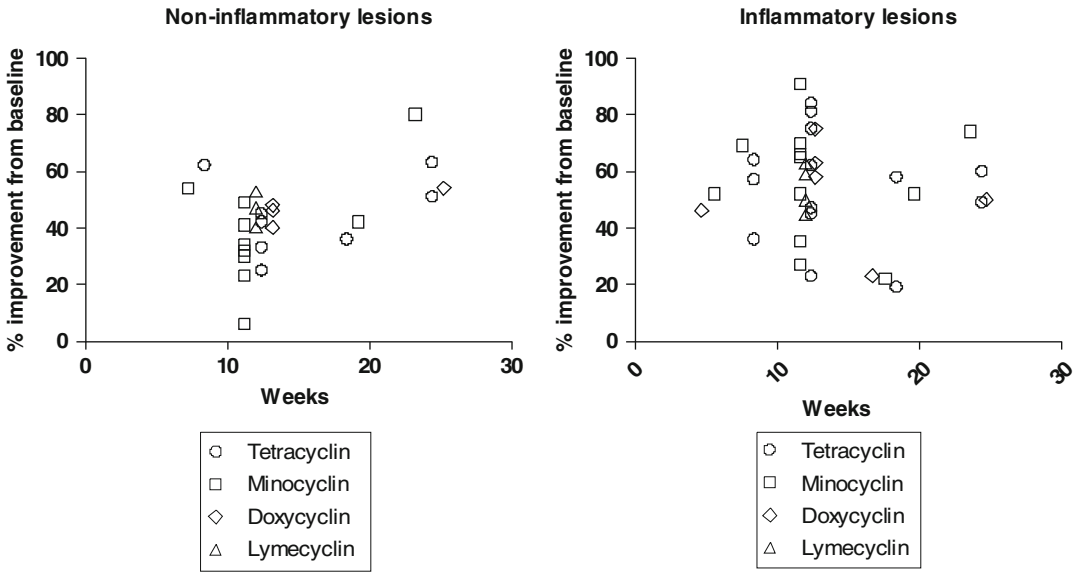



**Fig. 60.1** Effects of oral tetracyclines on noninflammatory and inflammatory lesion (percentage of improvement in comparison to baseline; data taken from [27]). Each point depicts the result of one study)

**Table 60.2** Pharmacokinetics of oral antibiotics (first-generation cyclines = tetracycline, second-generation cyclines = doxycycline, lymecycline, minocycline)

| | Tetracycline | Doxycycline | Lymecycline | Minocycline | Erythromycin |
|---|---|---|---|---|---|
| Absorption (%) | 75 | 90 | 80 | 90 | 35 |
| Interaction with food | + | – | – | – | – |
| Interaction with milk | + | (+)[a] | – | – | – |
| $T_{1/2}$ (h) | 7–8 | 16–22 | 10 | 17–18 | 2 |
| $T_{max}$ (h) | 3–4 | 2–3 | 3 | 2–3 | 0.5–2 |
| Serum protein binding (%) | 55–70 | 90 | 50 | 80 | 70–80 |
| Metabolism/clearance | Renal | Biliary | Renal | Renal | Biliary |

[a]30% less than first-generation cyclines

### 60.4.5 Dose–Response

A clear dose–response relation could not be shown in a pooled data analysis of published studies [26]. A double-blind study found that an initially higher dose of minocycline (100 mg 4 weeks, later 50 mg) was superior to 50 mg throughout the 12 weeks [30]. In the study with subantimicrobial doses of doxycycline (2 × 10 mg/day), it took 6 months to reach the same percentage of improvement as in the 12 weeks studies with a standard dose of 100 mg/day [24]. Layton reported a relationship between the response to erythromycin or minocycline therapy and the sebum secretion rate (r -0.53). A possible explanation may be the dilution of the drug in the sebaceous follicle [31]. So higher dosages of antibiotics (doxycycline and minocycline up to 200 mg daily, lymecycline up to 600 mg) may be useful in patients with increased seborrhea, but may be associated with more side effects [27].

### 60.4.6 Length of Therapy

Antibiotic therapy longer than one month appears to improve therapeutic effects. Therapies longer than 3 months offer little advantage [32, 33]. The continuation of a combination of systemic minocycline plus topical tazarotene (3 months) for another 3 months showed no statistical difference to a tazarotene monotherapy at study end. As the risk of developing antibiotic resistance is known to increase when antibiotic treatment is continued beyond 3 months, longer therapies should be restricted to individual cases [34].

### 60.4.7 Combination Therapy

It was shown that the combination of topical tretinoin/oral tetracycline [35], adapalene/doxycycline [36], as well as adapalene/lymecycline [37] lead to a more rapid reduction of bacteria, greater efficacy, and more prompt response than monotherapy. The combination of minocycline with azelaic acid was effective even in severe acne [38]. Also the combination of oral antibiotic with 5 % BPO was more effective than antibiotic monotherapy [39]. In a double-blind study the combination of tetracyclines with 2 mg cyproterone acetate/50 µg ethinyl–estradiol was superior to antibiotic monotherapy after 6 months [40].

### 60.4.8 Resistance to Antibiotics

Several reports demonstrate an association between the presence of resistant *P. acnes* and therapeutic failure. While this is clearly demonstrated for erythromycin, the association of tetracycline resistance and therapeutic failure is less well established [19]. Recently no association between resistant *P. acnes* and therapeutic success was found [29]. These apparent discrepancies can be explained by the complex relation of inhibitory concentrations, resistance mechanisms, drug dosage, and concentration in the sebaceous follicle [19]. However due to the

possible transmission of resistance genes to other bacteria, antibiotics should be used more prudently [17, 41].

The following strategies to prevent the emergence of resistant strains were recommended [27]:

1. Do not use antibiotics when other acne treatments can be expected to bring about the same degree of benefit.
2. Use antibiotics according to clinical need.
3. Do not use antibiotics as a monotherapy.
4. Stop antibiotic therapy when you and the patient agree there is no further improvement or the improvement is only slight (assessment after 6–8 weeks [28]).
5. Try to avoid continuing antibiotics beyond 3 (–6 months). Antibiotics are not suited for maintenance therapy.
6. Use benzoyl peroxide either concomitantly or pulsed as an antiresistance agent.
7. Do not switch antibiotics without adequate justification (i.e., reuse the same antibiotic for subsequent courses if patients relapse).

## 60.5 Adverse Events

### 60.5.1 Contraindications

Cyclines are contraindicated in children under 8–12 years (varying according to national licenses) and in pregnancy due to their effect on growing bone tissue (causing inhibition of skeletal growth in the fetus and discoloration of growing teeth). Erythromycin is contraindicated in cases of prolonged QT-intervals, drugs prolonging QT-intervals, relevant bradycardia, cardiac arrhythmias, disturbance of electrolytes (hypokalemia, hypomagnesemia), and use of terfenadine, astemizole, cisapride, pimozide due to the risk of ventricular arrhythmia [42].

### 60.5.2 Adverse Events

Table 60.3 summarizes the adverse effects of the oral antibiotics used. Cyclines are usually well tolerated. They can produce gastrointestinal

**Table 60.3** Side effects of oral antibiotics used in acne

| | Tetracycline | Doxycycline | Lymecycline | Minocycline | Erythromycin |
|---|---|---|---|---|---|
| Gastrointestinal symptoms[a] | + | + | + | + | + |
| Vaginal candidiasis | + | + | + | + | + |
| Esophagitis | (+)[b] | (+)[b] | | | |
| Phototoxicity | + | (+)[c] | | | |
| Hyperpigmentation | | | | + | |
| Drug-induced lupus erythematosus | | | | +[d,e] | |
| Cholestatic hepatitis, pancreatitis, pseudomembranous colitits | | | | | ((+))[f] |
| Exanthema | (+) | (+) | (+) | (+) | (+) |
| Headache | ((+))[g] | ((+))[g] | ((+))[g] | ((+))[g] | ((+)) |

+ ca. 4 % (–13 %)
(+) Rare
((+)) Single cases
[a]Gastrointestinal symptoms: nausea, diarrhea, flatulence, candidiasis
[b]If taken at bedtime without enough fluid intake
[c]Dependent on UV-A dose
[d]8,8 cases/100,000 person-years, plus autoimmune-hepatitis or hypersensititvity syndrome
[e]Mainly women after a mean of 19 months, RR 2.64 (95 % KI 1.51–4.66)
[f]During long-term therapy control of ANA and liver enzymes
[e]In therapies longer than 3 weeks control of blood-count, liver-, and kidney function
[f]Cranial hypertension

disturbances (nausea, gastrointestinal irritation, diarrhea, bloating, candidiasis) (~ 4,5 %, placebo 0,9 %; [2]). In a case–control study tetracyclines had an increased risk for hepatotoxicity (actual use: odd's ratio (OR) 3.7 (95 % confidence interval (CI) 1.19–11.45), past use: OR 2.72 (1.26–5.85), while such risk was much lower or lacking for doxycycline (actual intake: OR 1.49 (0.61–3.62), past use: 1.74 (0.99–3.06; [43]).

Of all cyclines, minocycline is most likely to cause side effects. Minocycline was furthermore associated with rare but potentially severe side effects. There are reports of autoimmune disorders such as lupus erythematosus-like syndrome, autoimmune hepatitis, thyroiditis, polyarteritis nodosa and hypersensitivity reactions (pneumonia, eosinophilia, serum-sickness-like syndrome: DRESS drug reactions with eosinophilia and systemic symptoms), arthritis, vasculitis, and hepatitis [3]. Hepatitis occurs in the first treatment weeks or after 12 months of treatment, as autoimmune hepatitis preferentially in females. In a retrospective cohort study (97,694 patients) minocycline was associated with the development of lupus erythematosus (OR adjusted for age, sex: 3,11 (CI 1.77–5.48)). This association was not found for tetracyclines and doxycyline [44]. A large proportion of minocycline-treated patients showed an elevated ANA-titer and ANCA-antibodies with clinical symptoms ([45]. Therefore the use of minocycline is not advocated as first-line therapy [3], [46].

Erythromycin (1 g daily) caused diarrhea (7 %), colics (7 %), nausea (2 %), vaginal discharge (2 %) and single cases of headache and dizziness (literature in [5]). Table 60.3 summarizes the side effects.

### 60.5.3 Drug-Interactions

The resorption of tetracyclines can be decreased by anti-acids, milk, iron salts, charcoal (least for minocycline). Tetracyclines increase the effects of oral antidiabetics, oral anticoagulants, cyclosporine A, digoxin (not doxycycline), and methotrexate (not doxycycline). Induction of enzymes (barbiturates, carbamazepin, phenytoin, primidone, chronic alcohol abuse) increases the metabolism of cyclines.

Erythromycin interacts with a great number of drugs. These interactions result from an interplay with the P-450 metabolizing enzymes in the liver. This may lead to antagonism (lincomycin, clindamycin, chloramphenicol, colistin, streptomycin, tetracycline), increased concentrations (theophylline, carbamazepine, clozapine, phenytoin, valproic acid), increased nephrotoxicity (cyclosporin A), increased concentrations, and potential toxicity (alfentanil, felodipin, bromocriptine, chinidin, disopyramide, methylprednisolone, triazolam, midazolam, tacrolimus, zopiclone, coumarin-type anticoagulants), cardial arrhythmias (astemizole, cisapride, pimozide, terfenadine), increased erythromycin concentrations (protease-inhibitors like ritonavir), increased bioavailability (omeprazole, digoxin), decreased concentration of erythromycin (cimetidine), and increased vasoconstriction (ergotamines) [42].

It is widely thought that antibiotics decrease the effectiveness of oral contraceptives. However, this is not true. In a controlled retrospective study no increased failure rate could be ascertained [47]. Large reviews concluded that available scientific and pharmacokinetic evidence does not support the hypothesis that antibiotics (with the exception of rifampicin) lower the contraceptive efficacy of oral contraceptives [48, 49].

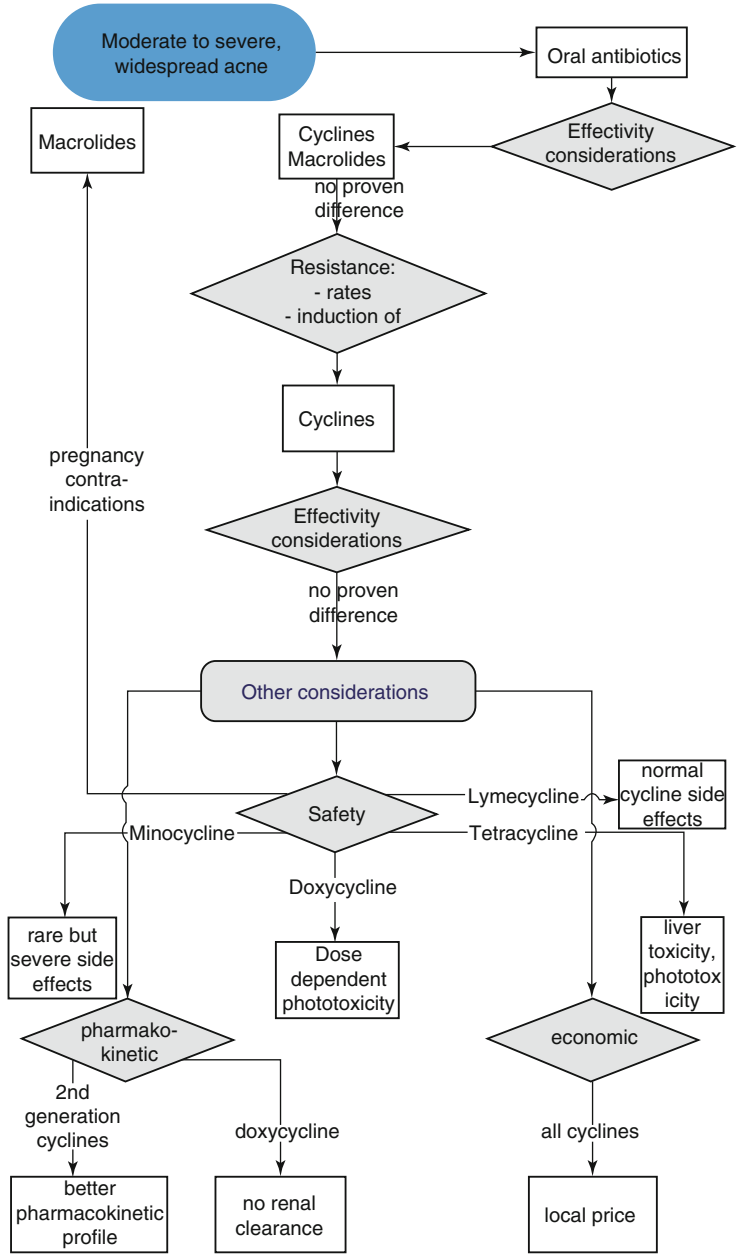
### 60.5.4 Other Effects on the Patient

Antibiotic therapy was associated with an increased carriage of *Streptococcus pyogenes* in the oropharynx (OR 3.5; CI 1.4–8.6). The carriage rate of *S. aureus* was not increased [50], it may even be decreased [51]. Patients using

antibiotics had an increased risk for upper respiratory tract infections (URTI), but not urinary tract infections. As most URTI are caused by viruses, this association is difficult to explain [15]. Household contacts of patients with acne had a slightly increased risk for URTI (OR 1.43, CI 1.33–1.51). However the risk was not increased if these acne patients were treated with antibiotics and was significantly lower when the acne patient had had an URTI and was treated with an antibiotic (OR 0.86, CI 0.8–0.9; [52]). So these associations need clarification in the future.

## 60.6 Clinical Use

The following algorithm may help to choose the optimal oral antibiotic for the individual patient (after [26]).



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# The Antibiotic Resistance in Acne

# 61

Cristina Oprica

## Contents



**Core Messages**

- *Propionibacterium acnes* (*P. acnes*) is a Gram-positive bacterium that belongs to the normal microflora. This bacterium plays an important role in the pathogenesis of acne vulgaris.
- Long courses of antibiotics have been used in acne treatment. The consequence has been the development of antibiotic-resistant *P. acnes*.
- More than 50 % of antibiotic-treated acne patients are colonized by erythromycin- and clindamycin-resistant *P. acnes* strains and more than 20 % are colonized by tetracycline-resistant *P. acnes* strains.
- There is a correlation between the presence of antibiotic-resistant *P. acnes* strains and clinical response with antibiotic treatment.
- The resistance seems now to move from acne patients to the community. *P. acnes* resistant strains have been found not only in acne patients and their close contacts, but also in the general community.
- The general perception was that *P. acnes* is a microorganism with low virulence but during the last years the prevalence of severe infections caused by *P. acnes* has increased.
- Antimicrobial resistance has emerged among *P. acnes* isolates from different severe, life-threatening infections.

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- Antibiotic treatment should be used only when necessary.
- Antibiotic treatment should not be administrated as monotherapy. Use always antibiotic treatment in combination with topical retinoid +/– topical benzoyl peroxide.
- Antibiotic treatment should be stopped when there is no further improvement. Do not use continuous antibiotics over 3–4 months.
- Use benzoyl peroxide concomitantly or pulsed as an anti-resistance drug.
- Reuse the same antibiotic in case of relapse.

## 61.1 Introduction: *P. acnes* General Susceptibility to Antibiotics

*P. acnes*, as well as the other *Propionibacterium* species, are generally but not universally susceptible to a large variety of antimicrobials [1–3]. *Propionibacterium* species are generally resistant to 5-nitroimidazole agents (metronidazole, tinidazole, and ornidazole), aminoglycosides, and mupirocin [4, 5].

*P. acnes* is the major target of antibacterial treatment, even though the reduction in bacterial numbers does not correlate with the clinical efficacy [6].

## 61.2 The Problem of Antibiotic Resistance in Acne Patients

Antibiotics have been prescribed for acne treatment for more than 40 years. The first report of resistant *P. acnes* strains collected from acne patients was published in the USA in 1979 [7]. Since then reports about *P. acnes* resistance collected from acne patient have been published in many parts of the world [8, 9]. It has been demonstrated that between 1991 and 1997 the proportion of patients carrying resistant bacteria in the UK doubled, consequently 60 % of patients in Leeds region were found to carry resistant strains [10]. The decrease of colonization rates during late 1989 and 1999 may be explained by a change in prescribing practices due to publicity about development of resistance. However during 2000 the resistant rates started to increase again [11].

In acne patients, isolates resistant to clindamycin and erythromycin are more common than isolates resistant to tetracycline. A survey conducted in Europe showed that 50 % of acne patients are colonized by clindamycin- and erythromycin-resistant *P. acnes* strains and 20 % by tetracycline-resistant *P. acnes* strains [9].

## 61.3 *P. acnes* Resistance Mechanisms

Ross et al. [12] have shown the genetic base of resistance against erythromycin and clindamycin in cutaneous *P. acnes* and classified different resistance phenotypes according to the patterns of cross resistance to MLS antibiotics: **m**acrolides (14- and 16-member rings), **l**incosamides, and type B **s**treptogramins.

The most prevalent mechanism was due to three different point mutations in genes encoding domain V, the peptidyltransferase loop of the 23S rRNA, and it has been demonstrated that each of these mutations is associated with a specific cross-resistance phenotype to MLS antibiotics.

A mobile resistance element, the corynebacterial transposon Tn 5432 carrying *erm*(X) resistance gene has been detected in *P. acnes* strains highly resistant to MLS antibiotics [13]. *Erm* (*e*rythromycin *r*ibosome *m*ethylase) genes encode for methyl transferases that methylate the $N^6$ position of *Escherichia coli* (*E. coli*) A2058 in the 23S rRNA. This position represents the overlapping binding site for MLS antibiotics and is responsible for cross resistance to these antibiotics (Table 61.1) [14]. The *Erm*(X) gene confers resistance to higher concentrations of MLS antibiotics than the point mutations do. It is therefore possible that the incidence of the

**Table 61.1** Genetic mechanisms of MLS antibiotic-resistance in *P. acnes* isolates

| | 23S rRNA base mutation/ resistance gene | Resistance phenotype |
|---|---|---|
| Group I | A→G transition at *E. coli* equivalent base 2058 | MLS resistance |
| Group II | *erm*(X) gene | High level MLS resistance, especially to telithromycin and clindamycin |
| Group III | G→A transition at *E. coli* equivalent base 2057 | Low level resistance to 14-membered ring and susceptibility to 16-membered-ring macrolides |
| Group IV | A→G transition at *E. coli* equivalent base 2059 | Resistance to 14- and 16-membered-ring macrolides; elevated but variable resistance to lincosamides |

The individual nucleotides are enumerated in the order of their occurrence based on the equivalent 23S rRNA sequence of *E. coli* [12, 13]

transposon will increase if topical antibiotics are widely used and mutational resistance may not be sufficiently protective in vivo against the antibacterial substances [13].

In general, resistance to tetracycline has been shown to be associated with resistance to erythromycin and clindamycin. A single G–C transition in the 16S rRNA of the small ribosomal subunit at *E. coli* equivalent base 1058 was found to be responsible for clinical tetracycline resistance in *P. acnes* [15]. Tetracycline-resistant isolates may display various grades of cross resistance to minocycline and doxycycline [16].

Experts recommend starting therapy with a full therapeutic dose that will permit achievement of a sufficiently high concentration. Isolates with reduced susceptibility will then be affected and may not survive by acquiring new mutations [17], although the physicians should be aware of possible side effects [18].

Trimethoprim/sulfamethoxazole resistant *P. acnes* strains have seldom been isolated [8] and propionibacteria with reduced susceptibility to chloramphenicol and fusidic acid have evolved [16].

In addition to these mechanisms, the microbiological principle of biofilms has been proposed to be applicable in acne [19]. Microorganisms within biofilms have a natural antibiotic resistance not apparent on agar plates, being 50 to 500 times more resistant to antimicrobial therapies than free-floating bacteria [20].

## 61.4 Effects of Resistance on Acne Outcome

It is still an open question how much of the antibiotic efficacy in acne is due to the antipropionibacterial or to the anti-inflammatory effect [21]. Biological actions of tetracyclines affecting inflammation, proteolysis, angiogenesis, apoptosis, metal chelation, and bone metabolism have been demonstrated [22].

In addition, each acne lesion behaves as a separate infection, independent of the other lesions, and each follicle may contain a mixture of susceptible, moderately resistant, and highly resistant *P. acnes* strains. It is unlikely that all follicles will have resistant bacteria, and therefore carriage of resistant *P. acnes* strains will not lead to total failure, but to a limited response [21]. Consequently, the clinical response will be highly dependent on these factors.

There are studies which have proved a correlation between the presence of erythromycin or tetracycline antibiotic-resistant *P. acnes* strains and the clinical response to orally administered erythromycin or tetracycline, respectively [23–25]. The clarification of the correlation found between erythromycin- resistant *P. acnes* and the clinical response to erythromycin resides in the fact that the MIC of erythromycin for resistant strains was much higher (512–2,048 mg/L) than the concentration reached in follicles after oral administration of the drug [26]. The link between resistance and treatment outcome of oral tetracycline is more difficult to prove [17]. MICs of resistant strains were 4–64 mg/L for tetracycline and 2–16 mg/L for minocycline thereby overlapping with plasma levels. As a result, the concentration in follicles may be sufficient to inhibit the resistant strains [26].

An association has been found between the occurrence of antibiotic-resistant *P. acnes* strains and the clinical response to topical antibiotics [27]. It has been shown that topical clindamycin and erythromycin can be selective or inhibitory for resistant *P. acnes* depending on the concentration or formulation of the agent [17].

## 61.5 Factors that May Promote Antibiotic Resistance Development

- Low dose of antibiotic which may promote overgrowth of resistant *P. acnes* strains or *de novo* acquisition of resistance within the normal microflora [18].
- Prescribing practices for acne may influence the resistance rates [9].
- In previously untreated patients, resistant strains appear after 12–24 weeks of treatment [10]. Courses of 4–6 months are likely to result in resistance development [18].
- Sequential or simultaneous use of chemically different antibiotics may determine the selection of multiple resistant propionibacteria [10].
- Poor treatment compliance may promote the selection of resistant isolates by altering the antibiotic pressure [10].

## 61.6 The Spread of *P. acnes* Antibiotic Resistant Strains

Acne patients are considered to be reservoirs of antibiotic resistant strains [21]. It has been shown that 41–85.7 % of untreated close contacts of acne patients who have received antibiotic treatment may carry erythromycin-resistant strains. The dermatologists who treat acne patients were found to carry resistant erythromycin and clindamycin strains [9].

The resistance seems to move from the acne patients to the community. It was unexpectedly found that clindamycin-, erythromycin-, and tetracycline-resistant *P. acnes* strains may colonize the skin of 33 % of healthy, acne-free contacts and non-antibiotic-treated subjects [21]. It has been shown that *P. acnes* can survive on different surfaces for long periods of time at room temperature in air [28] and this finding may explain the high rate of resistant bacteria in the control group through direct transfer of resistant strains from the environment [21].

## 61.7 Severe Infections Caused by Antibiotic-Resistant *P. acnes* Strains

The number of reports describing different severe, life-threatening infections in which *P. acnes* was repeatedly isolated, has abruptly augmented during the last years and this bacterium is increasingly recognized as an opportunistic pathogen [29].

It was demonstrated that antimicrobial resistance has emerged among *P. acnes* strains isolated from different severe, life-threatening infections in Europe [30]. Overall, 29 % of *P. acnes* strains were resistant to at least one antimicrobial agent. 15.1 % of the strains were clindamycin resistant, 17.1 % were erythromycin resistant, and 2.6 % were tetracycline resistant. The bacterial resistance in *P. acnes* isolates obtained from various diseases mirrored the situation with antimicrobials presently in use in different countries. Fortunately, this bacterium is usually susceptible to β-lactams or vancomycin that are used to treat serious infections [30].

## 61.8 Possible Effect on Microbial Ecology

Topical antibiotics exert selective pressure for resistance development at the site of application but probably also at other sites of the body by transfer of the product and can easily be transmitted to the patient's close contacts [10]. Oral antibiotics exert selective pressure for resistance development at all body sites where there is a normal microflora. Coagulase-negative staphylococci on the skin, *Staphylococcus aureus* in the nares, streptococci in the oral cavity, enterobacteria in the gut, etc., may also become resistant [10]. The normal microbial

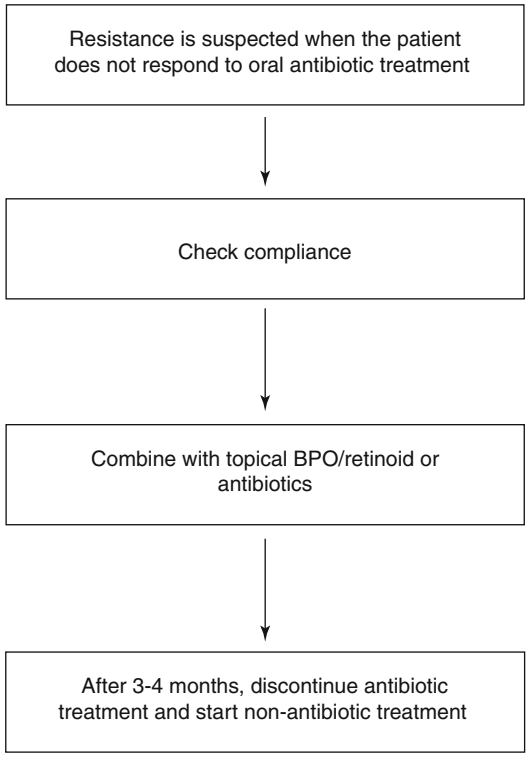


**Fig. 61.1** Measures to be taken in case *P. acnes* antibiotic resistance is suspected [18, 21]

flora may act as a reservoir for antibiotic resistance genes and under some circumstances there may be a transfer of these genes to pathogenic bacteria during their temporary colonization of the same site [31].

Published data showed that acne patients treated with antibiotics are more often colonised by tetracycline-resistant *Streptococcus pyogenes* in the oropharynx than acne patients not treated with antibiotics [32]. In addition, the risk of an upper respiratory tract infection to develop in individuals who use an antibiotic to treat acne was shown to be about two times larger than in those not using antibiotics [33].

At the present moment, methods to reduce the risk of antibiotic-resistant *P. acnes* strains include the combination of antibiotic therapy with topical benzoyl peroxide and/or topical retinoids [34, 35]. Topical benzoyl peroxide is active against susceptible and resistant P. acnes strains. [18]. Other anti-resistance drugs are represented by oral isotretinoin [36] and topical zinc acetate [37]. The measures to be taken in case *P. acnes* antibiotic resistance is suspected, are presented in Fig. 61.1.

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# Prescribing Oral Isotretinoin: The European Approach

# 62

Alison M. Layton

## Contents



**Core Messages**

- Oral Isotretinoin remains the most clinically effective anti-acne therapy producing long-term remission and/or significant improvement in many patients.
- Following the introduction of generic products of Isotretinoin in 2001, a European Directive was introduced. The implicit aims were to ensure generic prescribing was harmonised and delivered appropriately throughout the European Union and to minimise the risk of adverse effects with particular reference to teratogenicity.
- The European Directive on Isotretinoin prescribing has reviewed and introduced new guidelines on indications for use, monitoring, advice on use of physical treatments during and post-isotretinoin therapy and pregnancy prevention.
- The Pregnancy Prevention Programme includes advice on education, therapy management and control of distribution of the drug.
- Whereas the aim to prevent exposure to isotretinoin during pregnancy is highly supported by all prescribing clinicians, it is clear that the European Directive has posed some difficult clinical, ethical and economical issues for health-care workers and patients.

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## 62.1 Introduction

Oral Isotretinoin was first introduced in Europe in the early 1980s. Over 25 years later it remains a highly effective therapy for severe nodulocystic acne and cases refractory to combination treatment.

With the introduction of generic products of isotretinoin in 2001, individual preparations had to undergo a European Mutual Recognition Procedure (MRP). During this process inconsistencies were highlighted in the summary of product characteristics between different European countries.

As a result of these differences it was agreed that there would be a harmonisation process whereby the summary of product characteristics (SPC) would be considered and recommendations made on:

(a) Indications for usage
(b) Dosing
(c) Monitoring prior to and during therapy
(d) Advice on physical treatments for scarring during and post Isotretinoin therapy
(e) Pregnancy prevention

Table 62.1 outlines the changes advocated by the European Directive when prescribing oral isotretinoin.

## 62.2 Indications

The new European directive recommends that Isotretinoin should be used as second-line therapy for acne not responding to appropriate combination therapy including antibiotics and topical therapy.

There are a number of publications advocating the use of Isotretinoin for severe acne and scarring acne in the literature, hence, this new recommendation which could result in delay of isotretinoin use in certain cases may go against best and evidence based practice. With increasing clinical experience, use of the Isotretinoin has been expanded worldwide to include less severely affected patients who have not responded satisfactorily to combination therapy including long term antibiotics alongside appropriate topical, antimicrobial and retinoid therapy [1–6].

Failure to respond to conventional treatment may occur for many reasons including the emergence of antibiotic-resistant *Propionibacterium acnes* [7].

A recent review considered evidence based practical and expert opinion with respect to appropriate use of Isotretinoin and identifies poor prognostic factors as outlined in Table 62.2 [8].

**Table 62.1** Recommendations from the European Directive on isotretinoin prescribing

| | Pre-directive | Post-directive |
|---|---|---|
| Dosage | 0.5–1.0 mg/kg/day | Start 0.5 mg/kg/day |
| Indications for use | Isotretinoin recommended as first-line therapy for severe acne (nodular and conglobata) as well as acne not responding to 3 months systemic antibiotics in combination with topical | The new recommendations suggest isotretinoin should only be used in severe acne (nodular, conglobata) that has or is not responding to appropriate antibiotics and topical therapy. The inference of this being that it should now not be used at all as first-line therapy |
| Age | Previously no age limit | Not indicated in children <12 years |
| Monitoring | Liver enzymes and lipids should be checked before treatment and 1 month after the maximum dosage has been used | Baseline investigations as before but at 1 month and 3 monthly throughout the course of treatment |
| Physical treatments | It was recommended that chemical and physical peeling should be avoided during treatment and for 6 months afterwards and that wax depilation should be avoided during and 6 weeks post-therapy | All forms of peeling and wax depilation should be avoided during therapy and 6 months afterwards |
| Pregnancy prevention programme | | See text on PPP |

**Table 62.2** Prognostic factors should be taken into account and early/first-line use of oral isotretinoin considered in the following situations

| |
|---|
| • Family history |
| • Early onset |
| • Hyper-seborrhoea |
| • Site of acne (truncal acne) |
| • Psychological disabilities |
| • Scarring |
| • Persistent and late-onset acne |

## 62.3 Age Restrictions

The recommendations that isotretinoin should no longer be used in children below the age of 12 years may result in potential difficulties. Early onset and hyper-seborrhoea in young children can be indicators of more aggressive disease which requires early affective intervention [9].

Research has suggested that facial grade of scarring correlates with acne duration, hence, early effective treatment is the best way to minimise the potential for scars. By delaying treatment in young patients with aggressive acne the propensity for scarring is likely to be increased [10].

## 62.4 Dosage

The recommendation to start isotretinoin at a dose of 0.5 mg/kg/day and to titrate the dose as tolerated are well received when using Isotretinoin. However, some patients with persistent acne especially in the mature age group or cases where side effects are not tolerated at these recommended doses will require lower doses and possibly intermittent treatment [10, 11]. These approaches are not currently recognised within the new directive.

## 62.5 Monitoring

The European Directive suggests that fasting serum lipids and LFTs are performed prior to therapy, one month after starting therapy then every three months during treatment.

This contrasts with pre-directive recommendations which advocated that liver enzymes and lipids should be checked prior to treatment and one month after the maximum dosage has been achieved. Pre-treatment levels are not predictive of significant hyper-triglyceridaemia and subsequent hepatotoxicity which is thought to be idiosyncratic [12].

## 62.6 Physical Treatments

It is now recommended that peeling and wax depilation as well as laser therapy should be avoided during therapy and six months post treatment.

## 62.7 Pregnancy Prevention Programme

The regulatory authority in each European country has approved a Pregnancy Prevention Programme (PPP). This includes advice on education, therapy management and control distribution of the drug. The thrust of the PPP is to reduce Isotretinoin exposed pregnancies as almost 2000 pregnancies were reported to ROCHE Pharmaceuticals between 1982 and 2000. It is well recognised that first trimester exposure, as short as 1 week, can cause facial, cardiac, CNS malformations and mental impairment.

It has been suggested that the reason for isotretinoin exposed pregnancies relates to lack of adherence by patients and clinicians. One study has shown that 24 % patients did not recall having advice on contraceptive, 24 % had no pre treatment pregnancy test and 56 % did not have monthly testing performed [13].

The scope of the PPP suggests that it should include all females of child-bearing potential. In Europe the clinician can impose clinical judgement if they establish the patient is not currently sexually active, but it is mandatory that clinicians check carefully at each follow-up visit and record as well as act on any change in circumstance.

The education suggests that both patients and prescribers must be fully aware of teratogenicity.

The patient should acknowledge the problem by signing a consent form and should accept detailed counselling by the clinician prior to embarking on treatment.

Therapy management includes medically supervised pregnancy testing before, during and 5 weeks after a course of therapy and provides advice on contraception.

The programme suggests that where possible, patients should agree to at least one and preferably two complementary methods of effective contraception including a barrier method before therapy is initiated. The responsibility for the assessment of pregnancy tests and the administration of further prescriptions lies with the clinician.

Pregnancy testing is mandatory pre treatment and five weeks post-therapy. It has been suggested that monthly testing throughout treatment is advisable. The initial test can be done up to two weeks prior to the start of treatment providing contraception is used in those who require it. Treatment should ideally start on day 3 of the menstrual cycle.

Distribution controls suggest that only 30 days of oral isotretinoin can be supplied at one time to a female patient and the prescription will only be valid for 7 days. Dispensing restrictions do not apply to males with the process aimed at ensuring females do not get extended periods of treatment without a pregnancy test being performed.

Clinical problems related to the implementation of this approach include difficulties in females with irregular menses, potential lack of continuity of treatment due to potential unavailability of patient and/or health-care workers as well as forgotten tests. These factors may all contribute to early cessation and/or partial treatment resulting in ineffective management and associated financial burden on healthcare systems [14]. Given the potential adverse effects of oral contraceptives it may not always be appropriate to insist on patients regardless of pregnancy risk using specific forms of oral contraception.

To date there is no evidence that implementing a PPP will in fact reduce Isotretinoin exposed pregnancies. One study from America analysing the System to Manage Roaccutane related to Teratogenicity demonstrated no significant reduction in pregnancy rates [15].

To date mood change, suicidal ideation, depression and aggressive behaviour have not specifically been covered by the harmonisation process but there is an agreement to continue to monitor in view of this situation.

**Conclusions**

There have been significant changes in the indications for dosing and monitoring of Isotretinoin recommended within the European Harmonisation process.

There are now significant requirements for monitoring pregnancy risk.

A comprehensive risk assessment with clear documentation should be a routine part of prescribing isotretinoin.

If prescribing outside the product licence, it is vital that the patient, clinician and relatives are fully informed and/or records detailed. Although not specifically addressed within the European Harmonisation process, it is important to consider and act upon perceived risks and mood change.

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# Oral Isotretinoin: The US Approach

# 63

Jonathan Wilkin

## Contents



**Core Messages**

- Oral isotretinoin is at this writing the only clinically effective anti-acne therapy with the potential for producing long-term remission and/or significant improvement in patients with severe inflammatory acne.
- Progressively more complex voluntary programs to avoid fetal exposure have been insufficiently successful over the first two decades of marketing of isotretinoin, leading to a complex mandatory restricted distribution system with specific requirements for wholesalers, prescribers, pharmacies, and patients, known as iPLEDGE.
- The FDA-approved labeling for isotretinoin is understandably more detailed than the AAD recommendations for isotretinoin.
- On those issues addressed in the AAD isotretinoin recommendations, many of the recommendations are consistent with or similar to FDA-approved labeling.
- The most significant divergence in the AAD recommendations from the FDA-approved labeling is related to dosing for longer time periods. A related, yet more subtle, but still important difference is the underemphasis in the AAD recommendations on the explicit objective to seek a careful upward titration of dose as tolerated in order to shorten the duration of the treatment period.

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## 63.1 Introduction

Isotretinoin was initially approved by the US Food and Drug Administration (FDA) in May 1982. The prelaunch enthusiasm driven by key opinion leaders led many dermatologists in the USA to eagerly anticipate the delivery of isotretinoin to local pharmacies. Not only is isotretinoin effective in the narrowly defined approved indication for severe recalcitrant nodular acne, it is also effective in treating more moderate levels of severity, often leading to permanent remissions. Not surprisingly, the numbers of patients exposed to isotretinoin rapidly exceed those predicted by the prevalence of the narrowly defined FDA-approved severe subset of acne patients. Although the most severe subset of acne patients would be predictably mostly males, female patients soon accounted for approximately half of all exposed patients.

Isotretinoin was labeled Pregnancy Category X, and labeling carried strong warnings to avoid use by pregnant women, at the time of initial approval as Accutane. Pregnancy outcomes of 154 reports of isotretinoin-exposed pregnancies spurred FDA to require a boxed ("black box") pregnancy warning in 1984 [1, 2]. Additional cases continued to be reported, and the epidemiology of isotretinoin exposure during pregnancy in 433 reports was reported in 1992 [3]. More than 90 % of the identifiable prescribers were dermatologists, although a dermatologist was the initial reporter for only 40 % of the cases. 130 patients were already pregnant when they started isotretinoin. A Pregnancy Prevention Program (PPP) was introduced in 1988 which included package warning labels, an informed consent form, a PPP kit for prescribers, and a patient enrollment survey. Despite the PPP, there were still substantial numbers of reports of isotretinoin exposure during pregnancy, even including 402 among the women who voluntarily enrolled in the PPP survey [4].

The PPP was superseded by the System to Manage Accutane-Related Teratogenicity (SMART) in 2001 [5]. Voluntary reports of isotretinoin exposure during pregnancy continued to be received, suggesting that cases outside the voluntary enrollment program might be at least as prevalent. Also, reported physician behaviors were less than fully supportive, so that FDA finally replaced voluntary with mandatory actions, such as obtaining a negative pregnancy test before dispensing isotretinoin to a female patient. The new mandatory, restricted distribution program, iPLEDGE, was launched on March 1, 2006.

While exposure to even a single capsule of isotretinoin may be teratogenic in humans in the first trimester [3], a causal relationship of isotretinoin exposure to both psychiatric disorders and inflammatory bowel disease is not fully established. However, the precautionary principle should apply that physicians would consider the possibility that isotretinoin might cause or exacerbate these conditions and advise and monitor patients appropriately. Off-label use for unapproved indications in the treatment of disorders of cornification and in the chemoprevention of skin cancer in high-risk individuals is problematic in that safety for long-term use has not been clearly demonstrated. This latter fact is explicitly stated in the FDA-approved product labeling. Another potential concern related to unapproved long-term use is the finding that many of the pharmacodynamic effects attributable to isotretinoin are, in fact, due to tretinoin for which isotretinoin is a "prodrug" [6]. Systemic retinoids in smokers and even chronic topical tretinoin in a keratinocyte cancer chemoprevention trial may be associated with an excessive number of deaths [7, 8]. Further, the off-label use for unapproved long-term low dosing schedules for severe or moderate acne in women will greatly prolong the time at risk for pregnancy exposure and teratogenicity. Promoting full compliance with iPLEDGE, adopting a precautionary approach to serious conditions associated with, but not established to be causally linked to, isotretinoin, and very careful selection of patients for well thought out off-label use with additional safety monitoring may not only provide for the best care to patients but also help ensure that future patients and physicians will benefit from the availability of this very valuable medication.

The American Academy of Dermatology (AAD) has provided recommendations for use of isotretinoin in its Guidelines of Care for Acne Vulgaris Management [9]. The AAD recommendations, the European Approach (see Chap. 62), and the FDA-approved labeling for isotretinoin, for the most part, carry the same messages with some differences in emphasis.

## 63.2 Indications

FDA-approved labeling states that isotretinoin is "indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5 mm or greater…'Severe,' by definition, means 'many' as opposed to 'few' or 'several' nodules. Because of significant adverse effects associated with its use, [sic: isotretinoin] should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics."

AAD recommendations include the FDA-approved indication and add that "oral isotretinoin is also useful for the management of lesser degrees of acne that are treatment-resistant or for the management of acne that is producing either physical or psychological scarring."

## 63.3 Age Restrictions

FDA-approved labeling states that the use of isotretinoin in pediatric patients less than 12 years of age has not been studied. Labeling goes on to state that the use of isotretinoin "in pediatric patients ages 12 to 17 years should be given careful consideration, especially for those patients where a known metabolic or structural bone disease exists…adverse reactions reported in pediatric patients were similar to those described in adults except for the increased incidence of back pain and arthralgia (both of which were sometimes severe) and myalgia in pediatric patients…In a separate open-label extension study of 10 patients, ages 13 to 18 years, who started a second course of Accutane 4 months after the first course, two patients showed a decrease in mean lumbar spine bone mineral density up to 3.25 % (see **WARNINGS: Skeletal: Bone Mineral Density**)."

AAD recommendations do not directly address age as a consideration.

## 63.4 Dosage

FDA-approved labeling states that "The recommended dosage range for Accutane is 0.5 to 1.0 mg/kg/day given in two divided doses with food for 15 to 20 weeks. In studies comparing 0.1, 0.5, and 1.0 mg/kg/day, it was found that all dosages provided initial clearing of the disease, but there was a greater need for retreatment with the lower dosages. During treatment, the dose may be adjusted according to the response of the disease and/or the appearance of clinical side effects—some of which may be dose-related. Adult patients whose disease is very severe with scarring or is primarily manifested on the trunk may require dose adjustments up to 2.0 mg/kg/day, as tolerated. Failure to take Accutane with food will significantly decrease absorption. Before upward dose adjustments are made, the patients should be questioned about their compliance with food instructions." In the Information for Patients section, the labeling states that "Patients should be reminded to take Accutane with a meal…To decrease the risk of esophageal irritation, patients should swallow the capsules with a full glass of liquid." The labeling goes on to state that "The safety of once daily dosing with Accutane has not been established. Once daily dosing is **not** recommended." Finally, FDA labeling is very clear on long-term, low-dose regimens: "Long-term use of Accutane, even in low doses, has not been studied, and is not recommended. It is important that Accutane be given at the recommended doses for no longer than the recommended duration."

AAD recommendations diverge most sharply from FDA-approved labeling in allowing for longer-term, lower-dose regimens: "…initial flaring can be minimized with a beginning dose of 0.5 mg/kg/day or less. Alternatively, lower doses can be used for longer time periods, with a total

cumulative dose of 120 to 150 mg/kg. In patients who have severely inflamed acne, even greater initial reduction of dose may be required."

The case for total cumulative dose as the best (compared to days of therapy or daily dose) dosage predictor for success is strong [10]. It is also true that a minority of patients need to begin at lower daily doses; however, most of these patients would, in my view, benefit from well-planned and timely attempts at upward titration of doses, as tolerated. Were AAD to add this important caveat to their recommendations, their recommendations would move closer to the FDA-approved labeling.

## 63.5 Monitoring

FDA-approved labeling advises pregnancy tests with a sensitivity of at least 25 mIU/mL at specific times. In addition to pregnancy tests, FDA-approved labeling states that "Pretreatment and follow-up blood lipids should be obtained under fasting conditions. After consumption of alcohol, at least 36 h should elapse before these determinations are made. It is recommended that these tests be performed at weekly or biweekly intervals until the lipid response to Accutane is established. The incidence of hypertriglyceridemia is 1 patient in 4 on Accutane therapy." And, "Since elevations of liver enzymes have been observed during clinical trials, and hepatitis has been reported, pretreatment and follow-up liver function tests should be performed at weekly or biweekly intervals until the response to Accutane has been established." FDA-approved labeling also cautions that "Neutropenia and rare cases of agranulocytosis have been reported. Accutane should be discontinued if clinically significant decreases in white cell counts occur."

The AAD recommendations are that "Laboratory monitoring during therapy should include triglycerides, cholesterol, transaminase, and complete blood counts," although there are no explicit recommendations for pretreatment laboratory monitoring nor for the frequency of monitoring during therapy.

FDA-approved labeling provides specific pretreatment screening and monitoring actions during treatment that physicians should take to identify "the warning signs of psychiatric disorders to guide patients to receive the help they need." These are presented in the WARNINGS: Psychiatric Disorders and in the brochure, *Recognizing Psychiatric Disorders in Adolescents and Young Adults*: *A Guide for Prescribers of Isotretinoin*, which is part of the FDA-approved labeling.

The AAD recommends that "…treating physicians should monitor patients for psychiatric adverse events."

## 63.6 Physical Treatments

FDA-approved labeling states that "Wax epilation and skin resurfacing procedures (such as dermabrasion, laser) should be avoided during Accutane therapy and for at least 6 months thereafter due to the possibility of scarring…"

## 63.7 Pregnancy Prevention Program

FDA-approved labeling states in a boxed warning that, "**Because of Accutane's teratogenicity and to minimize fetal exposure**, **Accutane is approved for marketing only under a special restricted distribution program approved by the Food and Drug Administration**. **This program is called iPLEDGE**. Accutane must only be prescribed by prescribers who are registered and activated with the iPLEDGE program. Accutane must only be dispensed by a pharmacy registered and activated with iPLEDGE, and must only be dispensed to patients who are registered and meet all the requirements of iPLEDGE (see **PRECAUTIONS**)." FDA-approved labeling describes the iPLEDGE program requirements for wholesalers, prescribers, and pharmacists, as well as for both male and female patients. As these descriptions of the iPLEDGE program requirements are too extensive for a complete discussion here, the reader is referred to the FDA-approved labeling: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/018662s060lbl.pdf

The iPLEDGE program is adapted for use by multiple producers of isotretinoin, the innovator and all of the generic manufacturers.

The AAD recommendations observe that iPLEDGE is "mandatory" and "required."

### Conclusions

There is extensive off-label use of isotretinoin. Long-term use, once-daily dosing, use for less severe acne than the labeled indication, use in disorders of cornification, and use in chemoprevention of actinic keratoses and skin cancer fall outside FDA-approved labeling.

Failure to prevent fetal exposure, especially failure to ensure that the patient was not already pregnant when isotretinoin was first prescribed, has led FDA to impose a mandatory restricted distribution program with significant requirements for wholesalers, prescribers, pharmacists, and patients.

Laboratory testing and non-laboratory monitoring of patients, e.g., for signs of psychiatric disease, in addition to the requirements of iPLEDGE make the comprehensive risk assessment and medical records documentation a necessary and time-intensive integral part of prescribing isotretinoin.

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# Hormonal Therapy for Acne

# 64

Clio Dessinioti and Christos C. Zouboulis

## Contents



**Core Messages**

- Acne vulgaris is a multifactorial dermatosis in which high levels of androgens and/or hypersensitivity of the sebaceous glands to normal levels of androgens play a critical role.
- Indications of hormonal therapy in women include proven ovarian or adrenal hyperandrogenism, recalcitrant acne, acne not responding to repeated courses of oral isotretinoin, acne tarda, polycystic ovary syndrome, or the presence of clinical signs of hyperandrogenism such as androgenic alopecia or seborrhea/acne/hirsutism/alopecia (SAHA) syndrome.
- Hormonal treatments for acne include anti-androgens, estrogens, combination oral contraceptives, low-dose glucocorticoids, and gonadotropin-releasing hormone (GnRH) agonists.
- Anti-androgens (cyproterone acetate, flutamide, spironolactone) inhibit directly the binding of 5α-dihydrotestosterone to the androgen receptor. They may be used together to build anti-androgen oral contraceptives.
- Anti-androgen oral contraceptives exert their action either by suppressing the secretion of pituitary gonadotropins, thereby inhibiting ovarian androgen production, or by increasing liver synthesis of sex hormone-binding globulin (SHBG).

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- Contraindications of oral contraceptive use in women include a history of clotting disorder, thrombophlebitis, migraine, and smoking over age 35.

## 64.1 Introduction

Androgens play an important role in acne vulgaris [1]. High levels of androgens and/or hypersensitivity of the sebaceous glands to normal androgen levels result in an increase of sebum production which is a prerequisite for acne in all patients [1–4].

Hormonal treatments are effective in acne by lowering circulating and local androgen levels and opposing their effects on the sebaceous gland and probably on the follicular keratinocytes as well [1, 5]. Hormonal treatments include anti-androgens (androgen receptor blockers) and agents designed to decrease the endogenous production of androgens by the ovary or adrenal gland, such as estrogens, anti-androgen oral contraceptives, low-dose glucocorticosteroids, or gonadotropin-releasing hormone (GnRH) agonists (Table 64.1) [6–8]. In this chapter, we will discuss how and when hormonal therapies are used in acne.

## 64.2 How Are Hormonal Therapies Used in Acne?

**Anti-androgens** or androgen receptor blockers are defined as agents that inhibit directly the binding of dihydrotestosterone (DHT) to its receptor in a competitive way [9]. They include cyproterone acetate, drospirenone, and spironolactone. Use of all anti-androgens should be avoided in men, as they result in feminization, as well as in women during pregnancy [7, 8, 10].

Cyproterone acetate (CPA) is the only anti-androgen that also has an anti-gonadotropin action by inhibiting ovulation [4, 8]. It inhibits the production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), the ovarian function is blocked, and the serum androgen levels are reduced. It inhibits the binding of 5α-dihydrotestosterone (DHT) to the androgen receptor and it reduces the activity of 5α-reductase that catalyzes the transformation of testosterone in DHT [7, 11]. CPA (10, 50 mg) treatment has been used in acne (Table 64.2). CPA should begin on the first day of the menstrual period. It may be given alone (at a dose of 50–100 mg daily) or in combination with ethinyl estradiol (EE) in the form of an oral contraceptive (CPA 2 mg/EE 35 μg) [4, 8]. CPA (even at low doses of 12.5 mg, that is, ¼ of the 50 mg tablet) may be added to the fixed combination of CPA 2 mg/EE 35 μg during the first 10 or 15 days of the menstrual cycle, in order to avoid menstrual irregularities caused during treatment with CPA alone [7, 12, 13]. CPA/EE-containing oral contraceptives and CPA are not approved for use in the USA [4]. The most frequent side effect is amenorrhea or oligomenorrhea [7]. Other side effects include nausea, vomiting, fluid retention, leg edema, headache, and melasma. CPA has also been associated with tiredness, headache, liver dysfunction, shortness of breath, and blood clotting disorders [14, 15].

**Table 64.1** Mechanism of action of different hormonal therapies for acne

| Agent | Mechanism of action |
|---|---|
| Estrogens | Suppression of the ovarian production of androgens by suppressing gonadotropin release<br>Stimulation of hepatic synthesis of sex hormone-binding globulin (SHBG) |
| Anti-androgens | Inhibition of ovulation<br>Blocking androgen receptors<br>Inhibition of 5α-reductase |
| Anti-androgen oral contraceptives | Inhibition of ovarian androgen production<br>Stimulation of hepatic synthesis of SHBG |
| Oral glucocorticosteroids | Blocking of adrenal androgen production |
| GnRH agonists | Inhibition of ovarian androgen production |
| 5-α reductase inhibitors | Inhibition of androgen metabolism |

**Table 64.2** Indications of cyproterone acetate in female acne

- In severe acne as an alternative to isotretinoin
- In case of contraindication to ethinyl estradiol
- In case of coexisting acne and/or hirsutism, or androgenic alopecia

Spironolactone may be used for female patients with therapy-resistant acne, although it has not been approved for this disorder. It has been used in doses ranging from 25 to 100 mg daily [7, 8, 16, 17]. Most commonly, spironolactone is used in countries where no other antiandrogens are available. In general, it should be reserved for cases resistant to conventional therapy [7]. Spironolactone may be combined with an oral contraceptive [8]. It functions both as an androgen receptor blocker and an inhibitor of 5α-reductase. Response in acne may take as long as 3 months as with other hormonal therapies [7]. Adverse effects are dose dependent. Low doses such as 25–50 mg daily are generally well tolerated. It may be associated with hyperkalemia, menstrual irregularity, breast tenderness, headache, and fatigue [8]. It is contraindicated in women at increased risk of breast cancer [18]. Treatment with spironolactone during pregnancy may lead to abnormalities of the male fetal genitalia, such as hypospadias [17].

Oral contraceptives (OC) contain an estrogen (EE) and a progestin. Progestins are used in order to avoid the risk of endometrial cancer associated with unopposed estrogens [7, 8]. The progestins contained in OC include estranes and gonanes, which are derivatives of 19-nortestosterone, CPA, and a novel progestin, drospirenone [8, 9, 11]. Drospirenone, a progestin derived from 17α-spironolactone, has anti-androgenic as well as anti-mineralocorticoid activity [19]. EE may have anti-androgenic effects either by suppressing the secretion of pituitary gonadotropins, thereby inhibiting production of ovarian androgens, or by increasing liver synthesis of sex hormone-binding globulin (SHBG), which reduces the circulating free testosterone level [2, 8, 17, 20].

In Europe, the OC containing CPA 2 mg/EE 35 μg is approved for the treatment of acne. In the USA, there are three FDA-approved OC for acne therapy, namely, the combinations of norgestimate/EE, norethindrone/EE, and 3 mg drospirenone/20 μg EE. OC are approved for acne treatment in female patients older than 14 years old, and guidelines suggest that OC treatment is discontinued 3–4 cycles after acne improvement [21].

Various studies have evaluated OC for the treatment of acne [17, 20, 22, 23]. A low-dose oral contraceptive containing 100 μg levonorgestrel/20 μg EE was associated with a positive correlation between a reduction in lesion counts and reductions in androstenedione, bioavailable testosterone, and DHEAS levels after 6 cycles of treatments [22]. A study with drospirenone 3 mg/EE 30 μg showed a higher efficacy in total acne lesion reduction compared to norgestimate/EE 35 μg and a similar efficacy to CPA 2 mg/EE 35 μg [24]. A randomized, placebo-controlled study of drospirenone 3 mg/EE 20 μg for 6 months in 538 women (14–35 years old) with moderate acne showed efficacy in both inflammatory acne lesions and comedones [25].

Breast examinations and Papanicolaou smears may be recommended for women receiving chronic estrogen therapy, but recommendations vary from country to country [8, 18]. Oral contraceptives are contraindicated in women with a history of clotting disorder, thrombophlebitis, cerebrovascular disease, coronary occlusion, abnormal vaginal bleeding, impaired liver function, migraine, in smokers over age 35, and in individuals at increased risk of breast cancer [7, 10, 18]. The most serious side effect of oral contraceptives, thromboembolism, has largely been eliminated by the reduced doses of estrogen used in modern formulations, The incidence of other serious adverse effects, such as hypertension that follow the use of estrogens, is rare in young healthy females [8]. Frequently reported adverse effects include metrorrhagia, nausea, vomiting, breast tenderness, headache, edema of the venous system of the lower extremities, and weight gain. These are often transient and resolve after the first few months of therapy [8, 22].

In case of combination therapy with oral antibiotics and oral contraceptives, there is no scientific evidence supporting the ability of antibiotics to reduce either blood levels and/or the

effectiveness of oral contraceptives, with the exception of rifampin (rifampicin)-like drugs [12]. There was no difference in contraceptive failure rates in dermatologic patients who received OC together with antibiotics and in individuals who took OC alone [17, 26–28].

## 64.3 Less Commonly Used Hormonal Treatments: Oral Glucocorticosteroids, GnRH Agonists, and 5α Reductase Inhibitors

Low-dose oral glucocorticosteroids may be useful in therapy of acne in patients with well-documented adrenal hyperandrogenism [4, 29] (Table 64.3) in order to suppress adrenal activity [28, 30]. Low-dose glucocorticoids are most commonly used to treat male or female patients with classic or late-onset congenital adrenal hyperplasia [29] (see Chap. 31). In such cases, low-dose prednisolone (2.5–5 mg/day) or low-dose dexamethasone (0.25–0.75 mg) can be given orally at bedtime), although the latter incurs a higher risk of adrenal suppression [8].

Gonadotropin-releasing hormone (GnRH agonists), such as buserelin, nafarelin, or leuprolide, block androgen production in the ovary. They block ovulation by interrupting the cyclic release of FSH and LH from the pituitary. They are available in injectable and nasal spray forms and have proven to be efficacious in treating acne and hirsutism, but drawbacks that limit their use include the high cost and side effects [8].

5-α reductase inhibitors can be classified as type 1, type 2, and type 1/2 dual inhibitors, depending on which isoenzyme of 5α-reductase they inhibit [31]. 5-α reductase (5-αR) is the enzyme that catalyzes the conversion of testosterone to DHT, which is 2–10 times stronger than testosterone in androgenicity [6]. Type 1 5α-reductase exists predominantly in the skin, where its activity is concentrated in the sebaceous glands and is significantly higher in sebaceous glands from the face and scalp compared with nonacne-prone areas [32, 33]. Type 2 5α-reductase exists predominantly in the prostate and within hair follicles [6]. Finasteride, a specific type 2 5α-reductase competitive inhibitor, has not been reported to be effective in acne [4].

**Table 64.3** Indications of oral glucocorticoids in acne

| |
|---|
| • In patients (male or female) with elevated serum DHEAS, and an 11- or 21-hydroxylase deficiency |
| • In acute flare of acne for a short period of time |
| • In very severe acne for a short period of time |

## 64.4 When Is Hormonal Therapy Recommended for Acne?

Hormonal therapy may be useful for acne in selected cases [8]. It is indicated for women (Table 64.4), when oral contraception is desirable, when repeated courses of isotretinoin are needed to control acne, and when there are clinical signs of hyperandrogenism, such as in SAHA syndrome [7, 34]. Also, hormonal therapy can be proposed for late-onset acne (acne tarda) and for cases of proven ovarian or adrenal hyperandrogenism [8, 35]. It is important to note that hormonal therapy can be very effective in females with acne whether their serum androgens are abnormal or not [8, 17].

In men (Table 64.4), acne may be the only clinical sign of androgen excess, in the context of

**Table 64.4** Indications of hormonal therapy for acne in females and males

| |
|---|
| Females |
| • When oral contraception is desirable |
| • As an alternative when repeated courses of isotretinoin are needed |
| • Women whose acne is not responding to conventional therapy |
| • Polycystic ovary syndrome |
| • When there are clinical signs of hyperandrogenism, such as androgenic alopecia and seborrhea/acne/hirsutism/alopecia (SAHA) syndrome |
| • Late-onset acne (acne tarda) |
| • Proven ovarian hyperandrogenism |
| • Proven adrenal hyperandrogenism |
| Males |
| • Low-dose oral glucocorticoids may be used in cases of proven adrenal hyperandrogenism |

congenital adrenal hyperplasia (see Chap. 31). Therapy of male acne patients with biochemical signs of adrenal androgen overproduction relies on low-dose glucocorticoids [10, 30] (Table 64.4).

Polycystic ovary syndrome (PCOS) may present with acne as a marker of hyperandrogenism, or even acne may be the sole clinical cutaneous manifestation of PCOS [18] (see Chaps 31 and 76). An oral contraceptive pill therapy is the first-line therapy for hirsutism and acne in women with PCOS. Drospirenone/EE- and CPA/EE-containing oral contraceptives are effective in PCOS-associated acne therapy [18].

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# Less Common Treatments

# 65

Ana Kaminsky

## Contents



**Core Messages**

- The aim of this review is to report on a series of both new and old drugs for topical and systemic use and also to disclose certain schemes or physical treatments which, although not commonly used, should be taken into account since they are inexpensive and affordable methods to underprivileged sectors of the population, in both emerging and industrialized countries.
- The topical drug group includes agents such as sulfur, alpha and beta hydroxyl acids, and dapsone, whereas the systemic group includes zinc sulfate, corticosteroids, ibuprofen, clofazimine, and dapsone.
- Beta- and alpha-hydroxy acids may be used for non-inflammatory acne and mild inflammatory acne. Lower concentrations of alpha-hydroxy acids (AHAs) are useful to remove comedones and prevent their formation.
- Dapsone in a gel formulation at 5 % concentration is a "new–old" drug, which may be promising in the treatment of acne. However, the experience available about its use is limited.
- Ibuprofen, associated with tetracyclines, may be used in the treatment of very inflammatory acne.

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- The association of isotretinoin and corticosteroids prevents the occurrence of acne fulminans (pseudo acne fulminans).
- Microdermabrasion is a painless noninvasive adjuvant procedure, which facilitates the action of therapeutic agents in the treatment of comedones.

## 65.1 Introduction

Due to recent advances in the etiology and pathogenesis of acne, new therapeutic options have become available. As a result, the medication spectrum to treat this condition, which is prevalent among adolescents, has widened.

At present, topical and systemic antibiotics and retinoids, the recently released adapalene or tazarotene, both exhibiting retinoid properties, and the use of a bacteriostatic such as benzoyl peroxide have proven useful and effectively change disease progression.

This chapter includes an overview of some of the less commonly used acne treatments related to the topical, systemic, and physical varieties and inexpensive methods affordable to underprivileged sectors of the population, in both emerging and industrialized countries.

## 65.2 Topical Acne Treatments

### 65.2.1 Sulfur

Sulfur used to be the most common ingredient in antiacne formulations. However, it has now fallen into disuse mainly because of its odor, although it exhibits comedogenic and presumably comedolytic properties as well.

Sulfur-containing formulations have been found to be comedogenic both in the rabbit ear model and in humans when used under occluded conditions for 6 weeks [1]. Nevertheless, these findings on the potential comedogenicity of sulfur-containing preparations have not been reproduced [2]. Although sulfur is no longer used, it may eventually be found in some preparations in combination with benzoyl peroxide, resorcinol, and other compounds. Recommended concentrations range between 1 and 5 %.

Vleminckx solution and Ress solution, two sulfur-containing formulations, are of interest and still have their advocates.

Vleminckx's solution: (Sublimed sulfur 250 g, calcium oxide 165 g, water to 1,000 ml). A spoonful of this solution is dissolved in 250 ml of hot water and applied with stupes for 20 min [3]. The solution may also be applied pure at night. The time required for application and mainly the unpleasant odor of this solution are drawbacks when compared to other treatments. This solution has proven highly effective in the treatment of both moderate and severe inflammatory acne.

Ress solution: [Precipitated sulfur/zinc sulfate (equal parts) 3.6, sodium borate/zinc oxide (equal parts) 6.0, acetone 30.0, camphorated water/rose water (equal parts) 120.0] [4]. It is applied locally on inflammatory lesions.

### 65.2.2 Hydrogen Peroxide

Hydrogen peroxide cream has been lately compared with fucidic acid in the treatment of impetigo. The new cream formulation has been shown to stabilize hydrogen peroxide and therefore avoids fast degradation and exerts a protracted antimicrobial effect. This formulation is based on crystalline lipids, and it is effective against both Gram-positive and Gram-negative bacteria. Consequently, it may be an adjuvant topical treatment in particular for patients with Gram-negative folliculitis [5].

### 65.2.3 Hydroxy Acids

#### 65.2.3.1 Beta-Hydroxy Acid

Salicylic acid: This is the most well-known keratolytic agent in dermatologic therapy. It is a skin desquamation promoter which acts on the stratum corneum producing dissolution of the intercellular cement and, sometimes, moderate

peeling [6]. It acts on the interfollicular epidermis and on the acroinfundibulum. In acne therapy, it is found as an active ingredient in a range of cleansers and astringent lotions and has a mild comedolytic and anti-inflammatory effect. It is used in concentrations of 1–3 %. A concentration of 5 % salicylic acid in propylene glycol may also prove useful [7].

In comparison with tretinoin and isotretinoin, it is a mild comedolytic agent. In concentrations of 2 % it is well tolerated probably due to its anti-inflammatory effects [8]. At present, it is used in peeling lotions in concentrations ranging between 15 and 35 %, as a complement to the treatment of non-inflammatory acne.

#### 65.2.3.2 Alpha-Hydroxy Acids

The alpha-hydroxy acid family includes different compounds used to treat several types of skin diseases. These compounds are weak organic acids and, structurally, all of them include one hydroxyl group attached to the alpha position of the acid. Although they are found in nature, the alpha-hydroxy acids used to manufacture dermatologic and cosmetic products are usually produced synthetically. The mechanism of action has not been elucidated yet. However, it has been shown that, at low concentrations, alpha-hydroxy acids decrease corneocyte cohesion at the lower levels of the stratum corneum. It has also been suggested that this is due to the interference with the formation of ionic bonds [9].

Typically, these acids induce dry scale shedding from the skin surface in an exfoliative process by dissolving adhesions between cells in the upper skin layers.

In lower concentrations, alpha-hydroxy acids reduce follicular corneocyte adhesion, leading to the elimination of comedones and preventing their formation. In higher concentrations they cause pustule unroofing and loosening of the corneocytes lining the follicular epithelium [4, 10].

The most frequently used agent in superficial peeling is glycolic acid. It is used for brief exposures, in concentrations of 30, 50, and 70 %. However, it is considered a complement therapy rather than a treatment in itself.

### 65.2.4 Corticosteroids

A few topical preparations contain weak corticosteroids; evidence of their efficacy is still not available. Clobetasol propionate is a potent corticosteroid that may help reduce inflammation in nodular acne when applied twice a day for 5 days [11].

### 65.2.5 Dapsone

Dapsone (diaminodiphenylsulfone or DDS) is an aqueous gel formulation at 5 % concentration which appears to be a new and promising agent for the treatment of moderate to moderately severe acne. It has been approved for the treatment of mild-to-moderate acne vulgaris. It features a rapid onset of action and is effective for protracted regimens. This drug is delivered transdermally in two stages with preferential immediate uptake of the drug in the skin oil located in and near the pilosebaceous follicle, followed by the slow release of a suspension of microparticles in the surrounding region. Since dapsone is given topically, systemic absorption is expected to be considerably lower than that observed with the oral administration. Therefore, any adverse hematological effects are avoided. This was confirmed in a clinical study which evidenced that total systemic exposure to dapsone and its metabolites was approximately 100 times lower for dapsone gel than for oral dapsone at a therapeutic dose level [12]. Some clinical studies performed to date have shown that the number of both inflammatory and non-inflammatory lesions decreased by 50 % after a 28-day treatment period.

## 65.3 Systemic Acne Treatment

The administration of antibiotics, isotretinoin, or hormonal regimens is the most relevant systemic treatment, depending on each case. Other less common acne treatment modalities are discussed below.

### 65.3.1 Corticosteroids

Patients with severe inflammatory acne vulgaris, acne fulminans, and pyoderma faciale should be given oral prednisone (0.5–1.0 mg/kg daily) for 4–6 weeks; then the dose should be tapered. In acne fulminans and pyoderma faciale it is preferable to use steroids for 3–4 weeks before administering isotretinoin. Similar oral doses are also indicated for patients whose acne flares up remarkably while on isotretinoin [13].

Acne worsening observed between the third and the sixth week may oftentimes be very severe and even trigger genuine manifestations of acne fulminans. However, this should more appropriately be called "pseudo" acne fulminans, since systemic features are minimal or almost absent, and no pyrexia occurs. Baseline hematologic and biochemical parameters are within normal ranges. Some patients with previously demonstrated type III and IV hypersensitivity to *P. acnes* develop an altered immunological reaction to this organism. Another theory is that altered neutrophil function may result in severe acne flares. *P. acnes* destruction is thought to result in mediator release, inducing neutrophil chemotaxis, which may be responsible for flares detected during isotretinoin therapy. Patients who develop severe flares may be exhibiting an exaggerated response [14].

It has also been suggested that isotretinoin induces increased fragility of the pilosebaceous duct, which leads to a massive contact with *P. acnes* antigens [15].

A long-term study showed that the simultaneous use of isotretinoin and corticosteroids in very inflammatory and severe acne from the start of therapy avoided the early exacerbation phenomenon that an antigen–antibody reaction may trigger.

The therapy scheme applied included weight-dependent doses (e.g., 80 kg) of an initial isotretinoin dose of 20 mg/day for a week, with slow dose increases until the desirable dose of 1 mg/kg/day was reached on the sixth week, which amounts to a total dose of 150 mg/kg. Methylprednisolone was prescribed at a starting dose of 40 mg every other day for 6 weeks, progressively decreasing to discontinuation of the corticosteroid in the tenth week, and to then continue with isotretinoin as sole course of therapy (Fig. 65.1).

With the simultaneous administration of isotretinoin and corticosteroids for the most severe types of inflammatory acne (nodules, abscesses, cysts), this serious manifestation may be prevented. Consequently, this combination therapy prevents the development of "pseudo" acne fulminans as a complication derived from the use of isotretinoin [16].

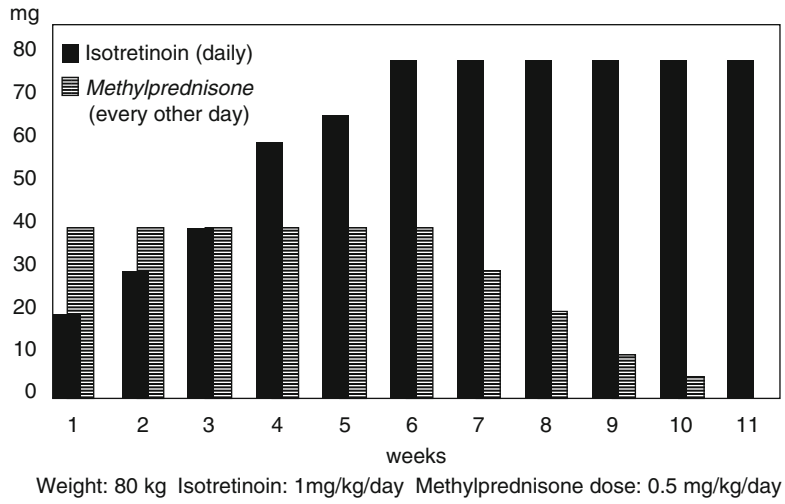


**Fig. 65.1** Combination of isotretinoin and methylprednisone in very severe inflammatory acne

### 65.3.2 Zinc Sulfate

Zinc sulfate appears to have limited therapeutic efficacy. In a double-blind clinical trial it was demonstrated that zinc sulfate capsules, 220 mg/day, corresponding to 50 mg of elemental zinc three times daily with food intake, may provide benefits in selected patients with mild-to-moderate pustular acne. However, the authors are reluctant to recommend oral zinc sulfate for the treatment of acne vulgaris due to the high incidence of gastrointestinal side effects. They consider that the incidence of nausea would be lower had they used gluconate zinc (200 mg/day) instead of zinc sulfate [17].

### 65.3.3 Ibuprofen

As inflammatory acne lesions are infiltrated with neutrophils, the use of an anti-inflammatory drug (NSAID) was suggested. Ibuprofen was selected for its properties.

Ibuprofen effectively decreases inflammation by inhibiting cyclo-oxygenase, a pivotal enzyme in the arachidonic acid cascade leading to the formation of the pro-inflammatory prostaglandin products. Thus, ibuprofen may inhibit human leukocyte chemotaxis and the formation of the inflammatory lesions observed in acne.

The use of ibuprofen tablets (2,400 mg/day) associated with tetracycline hydrochloride capsules (1,000 mg/day) was effective when administered for 2 months to patients with moderately severe acne [18]. Other authors combine minocycline capsules (150 mg/day) and ibuprofen tablets (1,200 mg/day) with an excellent clinical response and the additional benefit of fewer side effects at low ibuprofen doses [19].

### 65.3.4 Clofazimine

Clofazimine has both antimicrobial and anti-inflammatory activity. The exact mechanism of action of clofazimine is unknown, but neutrophils and monocytes appear to be the primary sites of action. As both cystic acne and acne fulminans may present a granulomatous component, clofazimine was found to be effective in cases of recurrence after several courses of isotretinoin [20].

### 65.3.5 Dapsone

Dapsone (DDS) has been found to be effective in the management of nodulocystic acne, but the few studies available are based on a limited number of cases [21, 22].

In 1974, 484 acne patients were reported to have been treated with oral DDS. Patients with acne featuring papules, pustules, and occasional cysts accompanied by inflammatory lesions did not respond to drug therapy. However, some exhibited a slight improvement not comparable with the one obtained with tetracycline, and therefore DDS was discontinued. The cystic, tuberous, and phlegmonous acne cases, as well as very severe manifestations of acne, improved remarkably when treated with DDS (50–100 mg/day) for 3 months. The condition gradually resolved to remission; only a few low-intensity relapses were detected [23].

At present, DDS has undoubtedly been replaced by isotretinoin. However, due to its affordable cost, DDS is more likely to be used in emerging countries.

When using Dapsone, its adverse effects must also be weighed. Some of them are pharmacologic and predictable, but allergic and idiosyncratic reactions occur as well. Most patients with glucose-6 phosphate dehydrogenase (G6PD) deficiency tolerate this drug well, except when very high doses are administered. Follow-up examinations and laboratory testing should be performed according to the monitoring guidelines. Complete blood count (CBC), a chemistry profile, a urinalysis (UA), and G6DP level tests should be performed [24].

## 65.4 Physical Treatment

Many abrasive materials, usually based on polyethylene and aluminium oxide, are of limited value.

### 65.4.1 Comedone Extraction

Mechanical extraction of open comedones is performed by exerting some light pressure on individual lesions with a comedone extractor. This technique may prove useful. A large variety of specially shaped tools, particularly for blackhead removal, are available.

### 65.4.2 Electrocauterization

Light cautery after a local anesthetic with EMLA cream (0.025 % lidocaine and 0.025 % prilocaine) for 60–90 min under an occlusive dressing has been shown to help patients with multiple macro-whiteheads and blackheads larger than 1.5 mm in diameter [25]. The electrocautery is used at a very low setting so as to produce slight pain or no pain at all. The aim of this technique is to produce very low-grade thermal damage so as to stimulate the body's own defence mechanisms to eliminate the comedones.

### 65.4.3 Cryotherapy

The beneficial effects of the use of low temperatures in the treatment of skin diseases have long been known. Cold compresses as well as carbonic snow, whether alone or in combination with sulfur and acetone used to ameliorate inflammatory acne, are used to treat sequelae of superficial scars.

### 65.4.4 Cryoslush Therapy

Solid carbon dioxide is mixed with acetone to produce a slush-like mixture that is brushed over the skin. This technique is used to produce erythema and desquamation. The degree of erythema and peeling is determined by the time the slush is in contact with the skin.

### 65.4.5 Liquid Nitrogen

Superficial freezing with liquid nitrogen will hasten the resolution of chronic fluctuant nodular lesions and is comparatively painless. Two 15-s freeze–thaw cycles are recommended. This technique produces cold damage to the fibrotic cyst wall, resulting in chemotaxis of polymorphs, whose proteases will subsequently destroy the wall and allow healing [26].

### 65.4.6 Intralesional Corticosteroids

An intralesional injection of corticosteroids (triamcinolone 2.5 mg/ml) may be used to treat nodular lesions. It may be administered using a syringe with a 30-gauge needle. If given too superficially or too deeply, it may lead to atrophy.

### 65.4.7 Microdermabrasion

Microdermabrasion is a technique used to produce an abrasion of the skin with a high-pressure flow of aluminium oxide crystals or with a diamond fraise. Crystal microdermabrasion systems are the best therapeutic option and include tiny crystals blasted onto the skin which carry out the exfoliating process. Microabrasion is used as an adjuvant treatment for non-inflammatory acne and in facial scarring [27].

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# Risk Factors of Acne Relapse

# 66

Brigitte Dréno

## Contents



**Core Messages**

- Acne is a chronic disease posing the problem of relapses.
- The risk factors of acne relapses after treatment are still partially known.
- Acne relapse can be related to either the profile of acne itself, with five main factors having been identified (early onset, duration of acne, extension, hypersebrrhea, heredity), the management of acne by the dermatologist, the patient himself, or finally the type of drug used.
- The identification of risk factors by the dermatologist remains important and indicates the necessity of follow-up and maintenance therapy after clinical improvement.

## 66.1 Introduction

Acne is a chronic inflammatory disease, which means that "relapses" can be associated with the evolution of this illness after stopping treatments. Although for a long time now, the literature tries to determine the risk factors for acne relapse, at the moment these factors are not yet completely identified. There is a mix of experience of acne experts with scientific data [1]. Moreover, the time for acne relapse after stopping treatment, the frequency of relapse, and the intensity and duration of the relapse can be different among

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**Table 66.1** Main risk factors associated with acne relapse

| Risk factors of acne relapse |
|---|
| 1. Related to the profile of acne |
| a. Heredity |
| b. Early Onset |
| c. Long duration of acne |
| d. Hyperseborrhea |
| e. Extension of acne lesions |
| 2. Related to the management of acne |
| a. Interest of maintenance therapy by topical retinoids |
| 3. Related to the patient |
| a. Bad adherence |
| b. Severe Psychological impact |
| 4. Related to the drug |
| a. Less frequent with isotretinoin than other systemic treatments |

acne patients and remain difficult to predict. At a practical level, these risk factors of acne relapses can be divided into factors related to either the profile of acne, the management of acne, the patients themselves, or the drug used (Table 66.1).

### 66.1.1 Risk Factors Related to the Profile of Acne

#### 66.1.1.1 Family History

Recent research strongly supports the fact that genetic factors may play an important role in the development of acne and relapses [2]. Various studies conducted in twins suffering from acne showed that the disease was attributable to additive genetic effects. A recent paper performed in China evaluated that the risk of acne vulgaris occurring in a relative of a patient with acne vulgaris was 4.05 higher (95 % confidence interval (CI): 3.45–4.76, $P < 0.001$) than for the relative of an unaffected individual [3]. In addition another study comparing two subpopulations of acne patients (with and without history of acne family) confirms the importance of heredity as a prognostic factor for acne and that a family history of acne is associated with earlier occurrence of acne, increased number of retentional lesions, and therapeutic difficulties with more relapses [4].

#### 66.1.1.2 Persistent and Late-Onset Acne

Patients suffering from acne for a long period of their life have often unsuccessfully received multiple courses of antibiotics over many years. Reasons for this persistent or late-onset acne may be hormonal, but in the majority no etiological factors are found. A study conducted by Goulden et al. could show that in relatives of acne patients older than 25 years, the risk of adult acne was significantly greater ($P < 0.001$) with more relapses than that of relatives of unaffected individuals [5].

#### 66.1.1.3 Early-Onset Acne

Biro et al. demonstrated throughout a clinical trial that those girls who had more comedonal and inflammatory lesions as early as 10 years, as well as 2.5 years prior to menarche, developed more severe acne in adolescence with more frequent relapses [6]. These results confirmed an investigation conducted by Chew et al. in 1990 showing that there is a trend towards greater severity, higher incidence of acne vulgaris, and more frequent relapses in teenagers with a history of infantile acne compared to their peers [7].

#### 66.1.1.4 Hyperseborrhea

Several studies have demonstrated that subjects with severe acne tend to have a higher sebum excretion rate than those with either physiological or moderate acne. Greenwood et al. suggested that severe acne would respond significantly less well than moderate acne with more relapses and that the follicular level of antibiotic may be a relevant factor in determining improvement in acne [8]. Further, Eady et al. suggested that follicular levels of antibiotic vary inversely with sebum excretion rates. Thus, a high sebum excretion rate would result in a dilution of the antibiotic so that the treatment will be below an optimum therapeutic concentration increasing the risk of acne relapse [9].

#### 66.1.1.5 Location of Lesions

Investigations on the treatment success of acne located in different areas of the body demonstrated differences in results. When treating systemically papulopustular acne lesions with the

second-generation cyclines in combination with benzoyl peroxide for 6 months, Mobacken found that results were better on the face than on the trunk with more relapses [10]. Goulden et al. demonstrated that the incidence of relapse with a treatment regimen of isotretinoin, 0.5 mg/kg per day for 1 week in every 4 weeks for a total period of 6 months, was significantly higher in patients with predominantly truncal acne ($P = 0.01$) than for patients with acne on the face [5].

### 66.1.2 Risk Factors Related to the Management of Acne by Physician

The risk of relapses is directly correlated to the persistence or the development of new retentional lesions after stopping treatment. The target is more specifically the microcomedone [11], representing the clinically non-visible central precursor lesions of acne. Thus not taking into account these acne lesions is associated with an increased risk of relapses. At the scientific level, only one molecule has shown an effect for maintenance therapy: topical retinoid. Two recent randomized trials have indeed demonstrated that topical retinoids can prevent acne relapses after stopping systemic treatments [12, 13]. Thus, topical retinoid monotherapy should be considered for maintenance to help minimize the risk of acne relapse.

### 66.1.3 Risks Factors of Relapses Related to the Patient Himself

#### 66.1.3.1 Poor Adherence

Poor adherence to treatment is associated with a higher risk of less efficacy of treatment on acne lesions and relapses [14, 15]. A recent study on 1,389 dermatology patients revealed that 44 % of them complied poorly with treatment [16], confirming the importance of this factor for the success of treatment. Another large-scale observational study used a simple, validated questionnaire (ECOB, Elaboration d'un outil d'evaluation de l'observance des traitements medicamenteux) to assess the risk of poor adherence in 33,339 patients worldwide. Overall there was a poor adherence rate of 50 %. Poor adherence was found to be associated with young age, occurrence of side effects, lack of improvement, previous systemic therapy, lack of knowledge about acne treatment, and lack of patient satisfaction with treatment. On the other hand, factors that had a positive effect on adherence included more severe acne, use of cosmetics, use of either topical therapy alone or oral isotretinoin, good clinical improvement, patient satisfaction with therapy, and knowledge of acne treatment [15, 17].

#### 66.1.3.2 Psychological Impact

Severe acne may lead to scarring and disfigurement, aggravating the already present psychosocial aspects of this condition. Tan provided evidence throughout recent investigations on the impact of acne on psychosocial health, including psychological abnormalities such as depression, suicidal ideation, anxiety, psychosomatic symptoms, including pain and discomfort, embarrassment, and social inhibition. Effective treatment of acne was accompanied by improvement in self-esteem, affect, embarrassment, body image, social assertiveness, and self-confidence [18]. Rapp et al. associated anger with quality of patients' life and with treatment satisfaction [19]. Thus at the clinical level, it is now well known that stress and psychological disturbance are associated with a high risk of relapse and with excoriations being often mixed with acne lesions. At the physiological level, it has been shown that substance P stimulates sebaceous secretion [20]. It is produced by peri-sebaceous nerve endings that are more numerous in acne skin than in healthy skin. Thus, substance P stimulates the production of sebum and formation of acne lesions. Stress is associated with an increase of substance P production.

### 66.1.4 Risk of Relapses Related to the Drug

No clinical study has determined the risk factors and the frequency of relapses with topical

treatment, but the clinical experience demonstrates that they are often linked with the severity of acne and the different factors described in the section "profile of acne." Strangely, systemic treatment with cyclines is used for more than 30 years now and no study has explored the frequency and the main risk factors of relapses, but clinical experience in a manner similar to topical treatments shows that the percentage of relapse is more than 50 % and is also influenced by the profile of the acne patient. The same applies with hormonal treatment and zinc salts which are treatment alternatives. All these treatments are in fact suspensive not curative.

For oral isotretinoin, the situation is different. It is the only drug able to induce a partial or complete atrophy of sebaceous gland. Clinical studies show a percentage of relapse only between 23 % [21] and 38 % [22]. In addition, a recent prospective study identified in multivariate analysis that several factors significantly increase the risk of relapses at the end of a treatment by isotretinoin: severe seborrhea and high score of inflammatory lesions, an early age, family history of acne, prepubertal acne, acne extended to the trunk and arms, and curiously notion of previous treatment by topical retinoids [23]. Thus this profile of acne patients requires a particular attention by dermatologists and a posttreatment follow-up (Table 66.2).

In conclusion, many factors seem to be associated with risk of acne relapse. They can be related to the management of acne (maintenance therapy), the patient himself (adherence, psychological impact), drugs, and also to the profile of acne itself. Concerning this last point the main identified risk factors for relapse are heredity, early onset, long acne duration, hyperseborrhea, and extension of acne lesions.

**Table 66.2** Main risk factors of relapse after stopping oral isotretinoin

| |
|---|
| 1. Early age of patient |
| 2. Family history of acne |
| 3. Pre-pubertal acne |

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# Acne Maintenance Therapy

# 67

Lee T. Zane

## Contents



**Core Messages**

- The primary goal of acne maintenance therapy is to prolong remission of acne vulgaris following more aggressive therapy.
- Preferred maintenance regimens should emphasize efficacy in preventing relapse, cost effectiveness, and long-term safety, both in terms of adverse effects and potential for generating antimicrobial resistance.
- Rational maintenance therapy is directed at proximal factors in acne pathogenesis.
- Current clinical evidence supports the efficacy of topical retinoids in maintaining remission following combination therapy with topical retinoids and oral antibiotics.
- Clinicians should emphasize the importance of prevention to maximize adherence to acne maintenance regimens.

## 67.1 Introduction

As a chronic condition that may be characterized by progressive worsening and flares of increased activity, acne requires rational therapy tailored to the natural history of the disease. Appropriate therapeutic choices generally balance the efficacy for reducing disease severity against the

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patient's and physician's tolerance for risk and cost. During periods of greater severity, efficacy and potential for rapid clearance may be emphasized over long-term safety concerns, while issues of tolerability, safety, cost, and convenience may be favored over clearance efficacy during periods when the acne is clear or mild. In the absence of viable and reasonable "cures" to produce permanent clearance of acne, much of the management of chronic acne consists of alternating periods where treatment is aimed at aggressively inducing remissions with hopefully longer periods of remission where therapy is intended to prevent relapse. This chapter will focus on maintenance therapy following conventional acne therapy. Hormonal treatment and isotretinoin therapy will be discussed in other chapters.

## 67.2 Principles of Acne Maintenance Therapy

Broadly, the term "maintenance therapy" for a chronic disease refers to treatment regimens intended to maintain a disease-free or disease-limited remission. Generally, maintenance therapy follows more aggressive initial treatment which, while intended to clear or substantially reduce disease activity, may also carry risks of side effects or toxicity which preclude safe long-term aggressive therapy (Fig. 67.1).Specifically for the conventional treatment of acne vulgaris, many of the concerns regarding long-term aggressive therapy have centered on the use of oral antibiotic agents.

For many years, it had been common practice to use long-term oral antibiotics as maintenance therapy for acne. However, more recently, increasing awareness of the potential consequences of long-term antibiotic use has led to widespread efforts to avoid this practice [1–3]. Antibiotic overuse has almost certainly led to an increasing prevalence of antibiotic-resistant strains of *Propionibacterium acnes* not only on the skin [4], but in the blood as well [5]. Widespread resistance has in turn led to reduced clinical efficacy for many antibiotic agents in the treatment of acne [6]. In addition to world-wide concerns about antibiotic resistance, epidemiologic observations describing putative links between long-term antibiotic use and breast carcinoma [7], upper respiratory tract infections [8], and lupus erythematosus [9] have heightened worry about their overuse.

Acne is a chronic disease with lesions of limited duration. Most acne treatment, therefore, is designed to prevent new lesions from replacing current ones. Similarly, the overall goal of the maintenance phase is prevention of disease

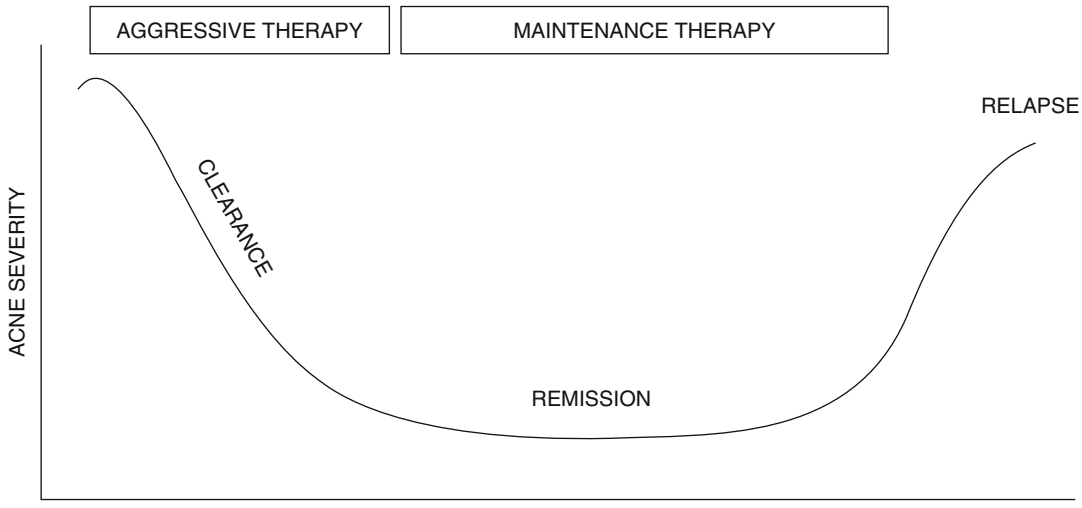


**Fig. 67.1** Stages of acne severity through aggressive and maintenance therapy phases

progression. From a pathogenetic standpoint, it is therefore reasonable that rational maintenance therapy should target the most proximal steps of acne lesion development, namely microcomedogenesis. Recent findings suggest that subclinical inflammation is present in the follicular sebaceous unit prior to the infundibular keratinocyte proliferation characteristic of microcomedo formation [10, 11]. Following this rationale, most of the published literature on acne maintenance therapy has focused on the use of topical retinoids, given their ability to normalize keratinocyte desquamation in the infundibulum and their anti-inflammatory activity [12]. By the same token, other agents which suppress the subclinical inflammation preceding microcomedogenesis or inhibit the hormonal signals that promote sebocyte growth/overactivity and abnormal follicular keratinocyte proliferation could also be considered potential candidates for maintenance therapy if they have a suitable long-term safety profile. Because of its preventive function, maintenance therapy should be instituted early and used continuously following the initial treatment phase in order to prevent lesion initiation and progression, not implemented in reaction to disease worsening.

## 67.3 Assessment of the Evidence

At the time of this writing, five clinical trials examining the efficacy of topical maintenance therapy have been published [13–17], all with a similar two-phase design. Subjects are treated with more aggressive therapy during an initial treatment phase followed by a maintenance treatment phase during which a topical regimen is assessed for its ability to maintain the clinical gains achieved during the initial treatment phase. The regimens employed during the initial treatment phase have included oral antibiotics in three of these trials [13–15] and strictly topical medications in two [16, 17]. All have included a topical retinoid in the maintenance treatment phase and all have been industry sponsored.

Thiboutot and colleagues [15] conducted a multicenter, randomized, double-blind, vehicle-controlled trial comparing the efficacy of adapalene 0.1 % gel vs. gel vehicle applied at bedtime for 16 weeks in maintaining at least 50 % lesion count reductions among 253 patients with facial acne who had experienced at least moderate improvement during a preceding 12-week treatment period with doxycycline, 100 mg daily, with or without adapalene 0.1 % gel. Of the 215 patients completing the maintenance phase of the study, 109 had been randomized to the adapalene arm and 106 to the vehicle arm. In the intent-to-treat (ITT) population, 75 % of patients randomized to adapalene 0.1 % gel successfully maintained at least 50 % of the improvement in total lesion count achieved during the preceding treatment period (vs. 54 % of patients randomized to gel vehicle, $P<0.001$). Similar success rates were seen for inflammatory and noninflammatory lesion counts. Following lesion counts longitudinally over time, adapalene 0.1 % gel and gel vehicle groups demonstrated statistically similar counts during the first 12 weeks of maintenance therapy. It was not until week 16 that the treatment arms diverged with statistically significant separation; in gel vehicle-treated patients lesion counts (total, inflammatory, and noninflammatory) continued to worsen while those in adapalene 0.1 % gel-treated patients remained relatively constant. The authors suggest that such a divergence would be expected to widen with extended maintenance therapy. Local tolerability scores remained comparable between adapalene 0.1 % gel and gel vehicle throughout the course of the maintenance phase.

Contemporaneously, Leyden and colleagues [14] implemented a multicenter, randomized, double-blind, parallel-group trial comparing the efficacy of three different 12-week maintenance regimens in 110 patients with moderate-to-severe facial acne who had achieved at least 75 % global improvement from tazarotene 0.1 % gel + oral minocycline 100 mg twice daily during the initial 12-week treatment phase. In the maintenance phase, patients were randomized in a modified factorial design to receive tazarotene 0.1 % gel + oral placebo, oral minocycline 100 mg + gel vehicle, or tazarotene 0.1 % gel + oral minocycline 100 mg for 12 weeks. Patients were instructed to perform topical applications at bedtime and to ingest oral agents twice daily

A treatment arm consisting of no active therapy (gel vehicle + oral placebo) was not included in the study design due to ethical considerations. Outcomes were analyzed only in the per protocol populations: of the 90 patients who completed the study, 28 completed treatment with tazarotene 0.1 % gel and 31 each completed therapy with minocycline 100 mg or minocycline 100 mg + tazarotene 0.1 % gel. All three maintenance regimens were deemed effective in preserving improvements observed during the initial treatment phase and no statistically significant differences were cited among them for multiple efficacy parameters: mean overall disease severity score, proportion of patients maintaining ≥50 % or ≥70 % global improvement, mean percentage change from baseline in noninflammatory or inflammatory lesion counts, or proportion of patients maintaining ≥70 % or ≥90 % reduction in noninflammatory or inflammatory lesion counts. Caution should be exercised in inferring from the inability to detect statistically significant differences between the treatment arms to mean that they are truly equivalent, particularly in the setting of the smaller sample sizes in each arm. Nonetheless, regardless of the maintenance regimen to which they were randomized, at least 81 % of patients in this study maintained ≥50 % global improvement at the end of the maintenance phase, with at least 54 % maintaining ≥75 % global improvement.

A subsequent European study by Alirezai and colleagues [13] employed a similar design, but employed oral lymecycline in the initial treatment phase. Described as a multicenter, investigator-blind, randomized, controlled study, this trial compared 12 weeks of once-daily application of adapalene 0.1 % gel to gel vehicle in its ability to maintain at least 50 % of the lesion count reductions seen in a prior trial of combination therapy. The combination therapy phase treated 242 patients with moderate-to-moderately severe acne with 12 weeks of oral lymecycline 300 mg once-daily plus either adapalene 0.1 % gel or gel vehicle. Of the eligible subjects who experienced at least moderate (25–49 %) improvement from the combination therapy, 136 were randomized in the maintenance phase. Outcomes were analyzed using the ITT population. At the end of the 12-week maintenance phase, a statistically significantly higher proportion of patients randomized to adapalene 0.1 % gel achieved maintenance success than those assigned vehicle for both total lesions as well as noninflammatory lesions (85 % success rates for both; for inflammatory lesions, point estimates for success were higher for the adapalene group, but did not achieve statistical significance). Point estimates for percent reduction in lesion counts at week 12 were superior with adapalene for total, inflammatory, and noninflammatory lesion counts, but none achieved statistical significance vs. vehicle at this time point. This is consistent with the Thiboutot study [15] where statistically significant separation from vehicle was not seen until week 16.

Two studies using topical combination therapies in the initial treatment phase have been published, both examining adapalene in the maintenance phase. A study in China published by Zhang and colleagues [17] began with an initial 12-week treatment phase of either adapalene 0.1 % gel + twice-daily clindamycin 1 % solution or twice-daily clindamycin 1 % solution alone. Subjects with at least moderate improvement were randomized to receive 12 weeks of either adapalene 0.1 % gel or no treatment (not gel vehicle). While adapalene 0.1 % gel maintenance therapy was found to be superior to no treatment at all, the incomplete blinding and lack of a vehicle control make it difficult to draw strong inferences from the study's results. A more recent, smaller, single-center study by Thielitz and colleagues [16] treated 54 subjects in a noncontrolled initial combination phase with adapalene 0.1 % gel in the morning and benzoyl peroxide 2.5 % gel at bedtime for 8 weeks. All subjects who successfully completed the initial phase (49 subjects) regardless of level of improvement were randomized to one of three 12-week maintenance regimens: adapalene 0.1 % gel daily, gel vehicle daily, or adapalene 0.1 % gel alternating every other day with gel vehicle. Unlike the other studies so far discussed, the primary efficacy outcome for this study was maintenance of at least 50 % reduction in microcomedo counts as assessed using cyanoacralate strips on the forehead. Differences in success rates for this primary outcome were not found to be statistically significant

between groups, though median counts for both adapalene groups were numerically lower than that for the vehicle group. Differences in success rates for total, inflammatory, or noninflammatory lesion counts were similarly not found to be statistically significant.

Several methodological issues should be considered when evaluating such studies of acne maintenance therapy and when designing future trials. First, in studies using the two-phase design, carryover effects from the initial treatment phase (particularly those induced by oral antibiotic therapy) may contribute to the early persistent reductions observed in the maintenance phase. Sufficiently long maintenance phases might better highlight treatment differences. Second, in the two-phase studies which restrict the maintenance phase sample to those experiencing substantial clinical improvement in the initial combination therapy phase, the generalizability of the maintenance results may potentially be limited only to those subjects who respond robustly to combination therapy with the same agent that will be used for maintenance (e.g., good responders to a particular topical retinoid). Third, unlike other chronic conditions such as asthma and depression where the success of suppressive therapy is evaluated based on time to recurrence and severity of disease at recurrence [18, 19], currently no standard criteria have been set for successful maintenance therapy for acne. Lastly, it could be argued that topical benzoyl peroxide should be used as a comparator for other candidate maintenance regimens instead of vehicle. Benzoyl peroxide was shown to be the most efficacious and cost-effective therapy among 5 antimicrobial regimens tested in a very large, well-designed study in Europe [20] and may also serve to ameliorate antimicrobial resistance risk following oral antibiotic use in the combination treatment phase.

## 67.4 Putting it into Practice: Helping Patients Adhere to Maintenance Therapy

Acne maintenance therapy may be easier to conceptualize and justify than it is to implement effectively in the clinical setting. As acne therapy relies heavily on patient adherence to treatment regimens outside the physician's office, ensuring adequate patient compliance with maintenance therapy poses certain challenges.

First, the patient who achieves excellent results from their aggressive clearance regimen may be reluctant to switch away from a treatment that is working well and/or resist trading the ease of taking an oral medication for the inconvenience of applying a topical one. In these situations, prescribers of acne maintenance therapy would do well to highlight the shift in priority toward long-term safety concerns, both in terms of systemic risks as well as broader risks such as global patterns of antimicrobial resistance. Second, since maintenance therapy regimens often include medications of lower potency than those used for clearance, some patients may recall having used such a medication in the past and its limited efficacy at that time (hence the escalation to more aggressive clearance therapy), and may be understandably reluctant to use a medication that "didn't work before." Here, it is important for the physician to emphasize to the patient that the suitability of some medications depends on the current severity of the patient's acne and what may have not been ideally suited for a previous severity may now be the most appropriate therapy (i.e., medications required to "*get* you clear" may be substantially different from those intended to "*keep* you clear").

Third, patients may find it difficult to remain motivated during their maintenance therapy. Without the incentive of seeing continued improvement in their acne, patients may wonder why they should continue treatment when they are already clear or nearly clear. Emphasizing the importance of prevention and "not losing ground" gained during clearance therapy may be a useful approach with the patient. Fourth, unlike the goal of achieving clearance, the lack of defined clinical endpoints for maintenance therapy success may leave patients concerned about how long they will need to stay on their suppressive regimen if they are already clear ("How long will I have to stay on this medication? I don't want to take it for the rest of my life."). Unfortunately, the unsatisfying answer is that patients should stay on maintenance therapy as long as it is necessary,

safe, and desired. It may not be known how long any given patient will remain clear after maintenance therapy is stopped, until it is actually stopped. Similarly, if the cost or inconvenience of continued maintenance therapy begins to outweigh the perceived benefit, patients may be well justified in wishing to discontinue therapy. Fifth, on the flip side of the previous point, it is also not always clear when maintenance therapy should be deemed failing and abandoned in favor of escalating therapy. While it is important to remind patients to expect typical frequent small vacillations of severity during maintenance that they may have experienced previously, the astute clinician should also attempt to discern whether a brief period of worsening is representative of a minor perturbation or the harbinger of a true relapse. Often, candid input from the patient will aid in drawing this distinction.

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# Cosmetics and Cleansers in Acne

# 68

Zoe Diana Draelos

## Contents



**Core Messages**

- Acne is a common condition that is increasingly being treated in the OTC market. Cleanser, moisturizers, and cosmetics are being developed to supplement acne therapy.
- This chapter examines over-the-counter (OTC) cleansers and cosmetics in the framework of acne treatment. An evaluation of cleansers is presented, to include surfactants, various cleanser forms, and active ingredients incorporated into OTC cleansers.
- Acne cleansers are based on surfactants that are useful in removing sebum and normalizing the acne biofilm. Cleansers include soaps (true soaps, syndets, combars) formulated either as solid bars or as liquid emulsions.
- Other variations marketed to offer additional cleansing benefits include facial scrubs composed of polyethylene beads, aluminum oxide, ground fruit pits, or sodium tetraborate decahydrate granules, or the addition of active ingredients, like benzoyl peroxide (up to 10 %), salicylic acid (up to 2 %), sulfur (3–8 %), and hydroxy acids, in the formulation.
- Rinse-off formulations of benzoyl peroxide or salicylic acid have less effects compared to the leave-on formulations.

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- Acne patients may wish to use moisturizers to counter the dryness and flaking that inevitably accompanies the use of topical acne medications containing skin irritants, such as benzoyl peroxide and/or retinoids.
- The realm of colored cosmetics is presented to provide ideas for the selection of facial foundations, powders, and ancillary colored facial products in the acne patient who may desire camouflaging, but must select products that do not worsen the facial acne.

## 68.1 Introduction

Acne is a condition that is impacted to a greater or lesser degree by all substances that touch the skin surface. Sebum, eccrine secretions, bacteria, cosmetics, cleansers, and moisturizers all impact the skin of patients afflicted with acne. While prescription dermatologic care remains the mainstay of acne therapy, an important contribution to the success or failure of acne treatment is the concomitant use of cleansers and cosmetics. This chapter examines over-the-counter (OTC) cleansers and cosmetics in the framework of acne treatment. The discussion opens with an evaluation of cleansers to include surfactants, various cleanser forms, and active ingredients incorporated into OTC cleansers to assist the dermatologist in formulating cleanser recommendations to patients. Following the use of cleansers, acne patients may wish to use moisturizers to counter the dryness and flaking that inevitably accompanies the use of topical acne medications containing skin irritants, such as benzoyl peroxide and/or retinoids. Finally, the realm of colored cosmetics is presented to provide ideas for the selection of facial foundations, powders, and ancillary colored facial products in the acne patient who may desire camouflaging, but must select products that do not worsen the facial acne.

## 68.2 Acne Cleansers

Acne cleansers utilize the same surfactants found in cleansing products for the general population, but may focus on increased sebum removal. Cleansers are based on surfactants that are useful in removing sebum and normalizing the acne biofilm. Soaps are some of the major cleansers used in acne. These include true soaps that are composed of long-chain fatty acid alkali salts, pH of 9–10. Many of the milder acne soaps are composed of synthetic detergents, known as syndets. These cleansers contain less than 10 % soap with a more neutral pH adjusted to 5.5–7.0 [1] Some of the most popular soaps for acne patients are combars composed of alkaline soaps to which surface active agents have been added, pH of 9–10. These combars also contain triclosan, a potent antibacterial helpful in acne that is considered an acne treatment in Europe, but is not listed in the Acne Monograph in the USA. These cleansers can be formulated as solid bars or as liquid emulsions.

In additional to traditional acne bar and liquid cleansers, other variations are marketed to offer additional cleansing benefits. Facial scrubs contain the cleansing ingredients previously discussed, but may add physical scrubbing granules designed to aid in removal of comedonal plugs composed of polyethylene beads, aluminum oxide, ground fruit pits, or sodium tetraborate decahydrate granules [2]. Polyethylene beads are the most popular. These smooth spheres do not damage the skin surface, but provide mechanical exfoliation throughout the cleansing process. A more mild scrub utilizes sodium tetraborate decahydrate granules, which dissolve during the scrubbing process when mixed with water limiting the length of time the granules can produce exfoliation.

Surfactants are effective at removing the sebum, bacteria, and environmental dirt, but may be supplemented by a variety of acne treatment ingredients that may be added as active ingredients in the formulation. These ingredients include benzoyl peroxide, salicylic acid, sulfur, and hydroxy acids.

1. Benzoyl Peroxide

   Benzoyl peroxide is a commonly used additive in acne cleansers. In Europe these

cleansers are considered drugs, but in the USA benzoyl peroxide cleansers up to 10 % are considered OTC products. Benzoyl peroxide is an organic peroxide consisting of two benzoyl groups joined by a peroxide group prepared by reacting sodium peroxide with benzoyl chloride to yield benzoyl peroxide and sodium chloride. It is a radical initiator and highly flammable, explosive, a possible tumor promoter, and mutagen accounting for the divergent regulatory policies regarding this highly effective acne treatment ingredient.

Benzoyl peroxide has many properties pertinent to acne, including antibacterial, anti-inflammatory, and comedolytic effects [3]. When benzoyl peroxide touches the skin, it breaks down into benzoic acid and oxygen. It has antimicrobial properties against *Propionibacterium acnes* as demonstrated by a 2-$\log_{10}$ decrease in *P. acnes* concentration after 2 days of 5 % benzoyl peroxide topical application [4]. This type of bacterial killing may not be seen with benzoyl peroxide cleansers that have a short skin contact time; however, benzoyl peroxide cleansers can suppress the development of resistant organisms [5]. Further, benzoyl peroxide also acts as an anti-inflammatory agent by reducing oxygen radicals, which may produce reduced consumer pain and redness [6]. Again, it should be emphasized that the rinse off formulations of benzoyl peroxide cannot have as dramatic an effect as the leave-on formulations.

2. Salicylic Acid

The other major comedolytic used as an active in OTC cleansers is salicylic acid in concentrations up to 2 %, as allowed by the United States Acne Monograph [7]. Salicylic acid is a colorless crystalline oil soluble phenolic compound originally derived from the willow tree *Salix*. It is a beta hydroxy acid where the OH group is adjacent to the carboxyl group. Synthesis of the compound involves the treating of sodium phenolate, the sodium salt of phenol, with carbon dioxide at 100 atm pressure and 390 K temperature followed by acidification with sulfuric acid. Salicylic acid is chemically known as 2-hydroxybenzoic acid, has a rich history in medicine.

Salicylic acid can penetrate into the follicle and dislodge the comedonal plug from the follicular lining [8]. It does not kill *P. acnes*, however, and does not prevent the development of antibiotic resistance. The effects of salicylic acid in a cleanser formulation are less than a leave-on formulation due to the reduction in contact time. Some salicylic acid formulations try to overcome this brief contact by using smaller particle size and depositing the material into the pores during facial rinsing [9].

3. Sulfur

The oldest treatment for acne predating benzoyl peroxide and salicylic acid is sulfur, which is bacteriostatic [10]. It is a yellow, nonmetallic element that has been used in OTC acne preparations. The mechanism of action for sulfur is not totally understood, but it is thought to interact with cysteine in the stratum corneum causing a reduction in sulfur to hydrogen sulfide. Hydrogen sulfide in turn degrades keratin producing the keratolytic effect of sulfur [11]. Sulfur has been labeled as a comedogen, but this is controversial [12]. Sulfur is available in concentrations of 3–8 % in OTC acne formulations, but has a characteristic foul odor and yellow color. Decolorized, deodorized sulfur is available, but it is not commonly used in acne cleansers. However, with the trend toward natural and green skin care products, sulfur is making a slight comeback as an OTC acne cleanser active.

4. Hydroxy Acids

Hydroxy acids, such as glycolic acid, have also been used in acne treatments as desquamating agents. Glycolic acid is the smallest alpha hydroxy acid appearing as a colorless, odorless, hygroscopic crystalline solid. While glycolic acid can be obtained from the fermentation of sugar cane, it is more commonly synthesized by reacting chloroacetic acid with sodium hydroxide followed by re-acidification. No acne claims can be made regarding hydroxy acids in the USA because glycolic acid is not listed on the Acne Monograph.

The efficacy of glycolic acid in treating acne is related to the free acid concentration [13]. The free acid is able to dissolve the ionic bonds between the corneocytes forming the stratum corneum. This desquamation can remove the comedonal plugs; however, the water-soluble glycolic acid cannot enter the oily milieu of the pore. For this reason, salicylic acid cleansers are more popular than glycolic acids.

## 68.3 Acne Moisturizers

In addition to cleanser, moisturizers are also marketed for acne prone skin in the OTC market. These moisturizers may contain monographed ingredients to treat acne, such as salicylic acid and rarely sulfur, previously discussed. However, other ingredients, such as retinol and tea tree oil, may also be used, but acne claims cannot be made. One of the main uses of moisturizers in acne is to smooth skin scale and prevent skin irritation induced by topical retinoids and benzoyl peroxide. These moisturizers for acne-prone skin are based on dimethicone, which is noncomedogenic, and forms the basis for the oil-free claim because dimethicone is a silicone and not obtained from mineral oil or vegetable oil. Dimethicone is an excellent emollient, meaning that it can intercalate between desquamating corneocytes and smooth down the edges of the scale. This makes the skin smooth and soft immediately after cleansing until sebum production acts as a natural emollient. Oil-free moisturizers can improve the tolerability of irritating acne topicals.

The discussion now turns to active ingredients that may be incorporated into skin care lines for individuals with acne. Acne claims cannot be made for these ingredients and the formulations that contain them are considered cosmetics and not OTC drugs.

1. Retinol
   Vitamin A derivatives, known as retinoids, are used in the treatment of acne. A variety of OTC retinoids exist that may be helpful in acne. These retinoids include retinol and retinaldehyde. Retinol can be absorbed by keratinocytes and reversibly oxidized into retinaldehyde. Retinaldehyde is irreversibly converted into all-trans retinoic acid, known as tretinoin, a potent prescription retinoid. Tretinoin is transported into the keratinocyte nucleus modulating cellular behavior. Large multicenter double-blind placebo-controlled studies on the OTC retinoids have not been conducted. However, retinol has been shown to be twenty times less potent than topical tretinoin but exhibits greater penetration than tretinoin [14].
2. Tea Tree Oil
   Another OTC topical nonmonographed agent used in botanical products for acne-prone skin is tea tree oil. Tea tree oil, obtained from the Australian tree *Melaleuca alternifolia*, contains several antimicrobial substances including: terpinen-4-ol, alpha-terpineol, and alpha-pinene [15]. It appears as a pale golden oil with a fresh camphoraceous odor. It is used for medicinal purposes as an antiseptic, antifungal, and antibacterial [16].

   The antibacterial activity of 10 % tea tree oil has been shown against *Staphylococcus aureus*, including methicillin-resistant staphylococcus aureus (MRSA), without resistance [17]. Lower concentrations, however, have demonstrated bacterial resistance. Tea tree oil has been found to be as effective in the treatment of acne as 5 % benzoyl peroxide based on a reduction in comedones and inflammatory acne lesions; however, the onset of action was slower for tea tree oil [18]. The tea oil group did experience fewer side effects than the benzoyl peroxide group. Another randomized 60 subject placebo-controlled study in subjects with mild to moderate found 5 % topical tea tree oil produced a statistically significant reduction in total lesion count and acne severity index as compared to placebo [19]. Tea tree oil may also reduce the amount of inflammation present around acne lesions thereby reducing redness [20].

   Tea tree oil is toxic when swallowed. It also has produced toxicity when applied topically in high concentrations to cats and other animals [21]. It use in low concentration

topically for the treatment of acne has not produced toxicity problems. However, tea tree oil is a known cause of allergic contact dermatitis. An Italian study of 725 subjects patch tested with undiluted, 1 %, and 0.1 % tea tree oil found that 6 % of subjects experienced a positive reaction to undiluted tea tree oil, 1 subject experience an allergic reaction to 1 % tea tree oil, and no subjects experienced a reaction to the 0.1 % dilution [22]. Thus, the incidence of allergic reactions to tea tree oil is concentration dependent.

3. Miscellaneous Acne Ingredients
   An ingredient of some interest in moisturizers for acne-prone skin is zinc. Zinc has been used in topical moisturizer formulations, since zinc salts are bacteriostatic to *P. acnes* [23]. A study by Dreno et al. demonstrated that zinc salts in the culture media of *P. acnes* prevented the development of organisms resistant to erythromycin. Since many *P. acnes* organisms are resistant to topical erythromycin, which has been largely replaced by topical clindamycin, this may be an important mechanism for preventing bacterial resistance [24].

   Another miscellaneous acne moisturizer ingredient is nicotinamide [25, 26]. Topical nicotinamide 4 % was shown to be comparable to clindamycin gel 1 % in the treatment of moderate acne [27].

**Table 68.1** Standard list of possible comedogenic substances

| |
|---|
| Butyl stearate |
| Cocoa butter |
| Corn oil |
| D&C red dyes |
| Decyl oleate |
| Isopropyl isostearate |
| Isopropyl myristate |
| Isostearyl neopentanate |
| Isopropyl palmitate |
| Isocetyl stearate |
| Lanolin, acetylated |
| Linseed oil |
| Laureth-4 |
| Mineral oil |
| Myristyl ether propionate |
| Myristyl lactate |
| Myristyl myristate |
| Oleic acid |
| Oleyl alcohol |
| Olive oil |
| Octyl palmitate |
| Octyl stearate |
| Peanut oil |
| Petrolatum |
| Propylene glycol stearate |
| Methyl oleate |
| Petrolatum |
| Safflower oil |
| Sesame oil |
| Sodium lauryl sulfate |
| Stearic acid |

## 68.4 Cosmetics

Following cleansing and moisturizing in the acne patient, camouflage with cosmetic products may be an additional need. It is important that acne patients avoid contact with comedogenic ingredients [28]. Table 68.1 lists the traditional substances thought to worsen acne; however, not all patients may develop acne when exposed to these substances. A quick review of the list demonstrates that many of the ingredients are commonly used in skin care formulations. Avoidance of substances on this list also does not automatically guarantee noncomedogenicity [29]. All formulations designed for patients with acne should be comedogenicity tested prior to making this claim [30].

Patients with acne may wish to use facial foundations to camouflage acne lesions and aid in oil absorption. A facial foundation is a pigmented moisturizer applied over the entire face after cleansing. It contains iron oxide and zinc oxide to pigment the skin with a semitranslucent film. Acne patients generally do best with an oil-free or low oil facial foundation. The facial foundation can be finished by dusting a loose pigmented powder on top to increase coverage, which is the ability of the cosmetic to camouflage the skin, and also improve oil control. Most facial powders contain talc and kaolin, excellent oil absorbers, accompanied by iron oxide, the brown pigment that can be adjusted to match the patient's skin color.

Some facial foundations are labeled as acne treatment cosmetics because they include salicylic acid, a monographed acne ingredient in the USA. The salicylic acid facial foundations have prolonged contact with the skin as leave-on formulations and may be able to positively impact acne treatment.

### Conclusions

Acne is a common condition that is increasingly being treated in the OTC market. Cleanser, moisturizers, and cosmetics are being developed to supplement acne therapy. The formulations may provide benefit in some patients when combined with more traditional prescription orals and topicals. In some regards, cleansers remain the mainstay of acne therapy and are appropriate both in systemized OTC acne treatment lines and always used as part of prescription therapy. Moisturizers and cosmetics can also supplement good skin habits in the acne patient.

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# Chemical Peeling in Acne

# 69

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## Contents



**Core Messages**

- Chemical peeling (CP) in acne treatment which is equivalent to the use of topical retinoids, is underappreciated.
- Superficial CPs used for acne include Jessner's solution, α-hydroxy acids (AHA) such as 70 % glycolic acid, pyruvic acid, and salicylic acid (SA) peels.
- A newly developed agent, salicylic acid in polyethylene glycol, affects only the stratum corneum, and is safe and suited for acne treatment.
- This novel formulation suppresses skin tumor development by normalizing the keratinocyte differentiation.
- Pre-peel evaluation of the patient and post-peel care contribute to optimal results and minimize the risk of complications.

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## 69.1 Introduction

Chemical peeling (CP) is not a novel treatment option for acne and has long been widely used in the world. In Japan, topical retinoids had not been approved until 2008, and thus Japanese dermatologists had made every effort to explore treatment options for comedones because only sulfur solution was available. There were several reasons why topical retinoids had not been

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approved in Japan (1) Severe skin irritation of Japanese sensitive skin resulted in stoppage of a clinical trial for tretinoin in 1980s and (2) fears for teratogenicity still remained because etretinate for psoriasis was the only available retinoid in Japan.

Since adapalene was approved in 2008, a breakthrough of the acne treatment has been introduced in Japan. However, CP will be continuously used for acne treatment because new formulation of CP agent has been developed and accepted as a safe and effective therapy for acne. In this chapter, CP including Jessner's solution and α-hydroxy acids (AHA) such as 70 % glycolic acid peels used for acne treatment will be briefly reviewed, and the clinical evaluation of salicylic acid in polyethylene glycol (PEG) will be introduced.

## 69.2 The Rationale for CP in Acne

CP is an in-office procedure which consists of the application of chemical exfoliating agents to the skin, and which is classified by the peeling depth based on the histological degeneration as superficial, medium, or deep CP. Superficial peels penetrate the epidermis only, medium-depth peels damage the entire epidermis and papillary dermis, and deep peels reach the level of the midreticular dermis. Subsequent regeneration and rejuvenation of the tissues follows. Clinical indications for different type of peels are summarized in Table 69.1 [1]. Many variables can affect the depth of the peel, including the nature and concentration of the selected peeling agent, the number of coats applied, the type of the patient's skin, and the anatomical location of the peel (Table 69.2).

**Acne peeling** has been preferably accepted by many dermatologists because a series of **superficial CP** can give a dramatic improvement in active acne over a short period of time. A wide variety of agents have been shown to be effective for superficial CP. These include Jessner's solution, α-hydroxy acids (AHA) such as 70 % glycolic acid and lactic acid, pyruvic acid, and a β-hydroxy acid (salicylic acid) peel [1–3]. Among these, glycolic acid and Jessner's solution are the most commonly used in acne [4]. Of note, glycolic acid and Jessner's solution peels should not be used in inflammatory acne [3]. As superficial peels penetrate the epidermis only, they are usually suitable for all skin phototypes with minimal to no "downtime." Serial procedures are required for optimal results and the use of home care products is advisable [1].

Superficial peels are commonly used in acne, causing epidermal remodeling and desquamation, which lead to clinical effects confirmed by

**Table 69.1** Main clinical indication for chemical peels

| Type of peel | Clinical indication |
|---|---|
| Superficial peels<br>*A-hydroxy acid peel (70 % glycolic acid, lactic acid)*<br>*B-hydroxy acid peel (salicylic acid)*<br>*Jessner's solution*<br>*Trichloroacetic acid peels (TCA)10–20 %*<br>*Pyruvic acid 40–50 %* | Active acne<br>Actinic keratoses<br>Superficial dyschromias<br>Improvement of skin texture |
| Medium-depth peels<br>*TCA 35 %*<br>*Jessner's peel + TCA 35 %*<br>*Glycolic acid 70 % + TCA* | Dyschromias (Ephelides, lentigines simplex, senile lentigines, flat seborrheic keratoses, melasma, postinflammatory hyperpigmentation)<br>Multiple solar keratoses<br>Improvement of skin texture<br>Fine wrinkles |
| Deep peels<br>*Phenol* | Dyschromias (solar lentigines)<br>Fine, coarse wrinkles<br>Actinic keratoses<br>Acne scars |

**Table 69.2** Factors that may influence the depth of CP

- The patient's skin type
- The patient's medicsal history
- The site to be peeled
- The skin preparation procedure in the weeks preceding the peel
- Cleansing and defatting the skin before the CP
- The type and concentration of the peeling agent
- The application method
- The number of coats applied
- The duration of contact

computer analysis as well as histological examinations [5, 6]. In particular, it has been suggested that the effect of glycolic acid in acne may be mediated via unroofing of papules and pustules and correction of the abnormal keratinization seen in acne [7]. The mechanism of action of salicylic acid, which is a component of Jessner's solution, may be due to its excellent keratolytic and comedolytic action. Also, it penetrates easily in the pilosebaceous unit due to its lipophilic nature [8].

No effect of 30 % glycolic acid peels and Jessner's solution peels on facial sebum secretion was found in patients with facial acne after two peels. However, the authors suggest that the cumulative effect of more than two peels should be further evaluated before definite conclusions can be drawn [4].

There have been several randomized controlled trials (RCT) published with high evidence levels using glycolic acid, Jessner's solution and salicylic acid in acne [9–11]. A recent split-face, double-blind, randomized, controlled study comparing the efficacy of alpha-hydroxy acid CP (30 % glycolic acid) and beta-hydroxy acid CP (30 % salicylic acid) in the treatment of mild to moderate facial acne, reported no significant differences in efficacy between the two peels. Both CP were applied every 2 weeks for a total of 6 treatments, and they showed significant improvement by the second treatment [12].

For these reasons, the guideline for CP of the Japanese Dermatological Association recommends that acne should be an absolute indication for CP.

Medium-depth and deep chemical peels are useful treatment modalities for acne scarring and will be discussed in detail elsewhere in this book.

## 69.3 Pre-peel and Post-peel Considerations

Careful selection of patients and individualization of the CP, are essential for optimal results (Table 69.3).

In order to minimize potential post-peel complications, a thorough pre-peel evaluation of the patient is needed, including a medical history and determination of Fitzpatrick's skin type, skin oiliness, and thickness.

**Table 69.3** Pre-peel and post-peel considerations

| | |
|---|---|
| Before the peel | • Obtain medical history<br>History of recurrent herpes infection<br>Concomittant disorders<br>Use of medications: isotretinoin<br>Previous cosmetic procedures<br>Keloid formation<br>• Discuss with the patient<br>• Consider patient's lifestyle<br>• Establish skin phototype<br>• Prepare skin with topical retinoids or bleaching creams or AHA |
| After the peel | • Sun avoidance<br>• Sunscreen application<br>• Make up |

Oral antiviral prophylaxis (acyclovir) for a patient with a history of herpes simplex in the case of a superficial peel is not required, unless the patient has had herpetic lesions within 2 weeks prior to the CP [3].

Pigmentation complications after a CP may be more frequent in patients who take oral contraceptives and other medications that may be photosensitizing. The risk of scarring after a CP is increased in patients with a history of prior treatments such as radiation or oral isotretinoin, which reduce the number of epithelial appendages, thus disrupting re-epithelialization. It is recommended that at least 12 months pass after oral isotretinoin treatment is completed before considering a CP, in order to reduce the risk of complications [13].

A discussion should be made with the patient, highlighting that a deeper peel results in better results, but also in greater inconvenience and higher risk for complications.

Priming the skin is crucial in order to improve results and reduce the risk of complications. A pretreatment with topical retinoids and/or AHA for a period of at least 15 days before the peel, enhances the penetration of the peel. The pretreatment should last longer, in case of darker skin types [13].

After the peel, clear instructions should be given to the patient on the need of sunscreen application during the post-peel period, on sun avoidance for 6 weeks after the peel, as well as on the use of make-up (Table 69.3) [1].

Nevertheless, reactive hyperpigmentation may occur after any depth of chemical peels [1]. Other potential complications include hypopigmentation, persistent erythema, scarring, infection, and acneiform exanthems [13].

## 69.4 CP in Acne Treatment

### 69.4.1 Jessner's Solution

Classical Jessner's solution consists of resorcinol (14 %), lactic acid (14 %), and salicylic acid (14 %) in alcoholic solution (ethanol). Its shelf life is 2 years and should be kept in a dark container. It darkens with age and exposure to light and air [3, 13]. It is used alone for superficial peels in the treatment of acne. It has a low risk of complications but may cause intense burning sensation and exfoliation to the patient [3].

Cleansing the skin before CP to remove makeup or oils, using ether, acetone or isopropyl alcohol, is essential in order to prevent uneven penetration of the peeling agent [13]. Then, Jessner's solution is applied in a triple-layer [1, 13]. Post-peel erythema is always self-limiting and may be treated with a mild topical steroid and emollients, which will also relieve feelings of stinging and discomfort [13].

### 69.4.2 α-Hydroxy Acid Peels in Acne Treatment

α-hydroxy acids (AHA) at low concentrations (<30 %) reduce corneocyte cohesion and result in exfoliation of the epidermis. At higher concentrations, they have a destructive action via keratinocyte detachment and epidermolysis [14]. Glycolic acid penetrates the skin easily and thus is the most commonly used AHA peel. Since glycolic acid peels are associated with efficacy, low risk of adverse events and ease of use, they represent a frequent choice for acne treatment [7]. Glycolic acid peels have keratolytic, anti-inflammatory, and antioxidant effects, which are mediated by thinning the stratum corneum, enhancing epidermolysis, dispersing basal layer melanin, and increasing collagen gene expression [15].

The skin is cleaned as already described. Then the solution is applied on the skin in a thin layer. As AHA are weak acids, they do not induce enough coagulation of the skin proteins and therefore cannot neutralize themselves. So they need to be neutralized once the skin achieves uniform erythema [1]. The appearance of frosting presents no additional benefit, except increased risk of postinflammatory hyperpigmentation and scarring. So, if frosting is observed in any particular area it should be immediately neutralized with water or sodium bicarbonate [3].

The peeling is performed once every 4 weeks and 6 sessions are usually required. Topical glycolic acid home care products ranging from 8 to 15 % concentrations are recommended between treatments, starting no sooner than 1 week after the peel [16].

### 69.4.3 β-Hydroxy Peels in Acne Treatment: Salicylic Acid Peel

Since the first introduction of SA peeling by Unna in 1882, SA has long been used in dermatological treatment However, higher concentration of SA resulted in toxic adverse effects, such as tinnitus, deafness, dizziness, and headaches, presumably due to the excessive absorption of SA (salicylism or salicylic acid intoxication) [17].

In 1997, Kligman introduced 30 % SA in ethanol, reporting no risk of SA toxicity [18, 19]. SA has a strong comedolytic effect, lipophilic nature, and anti-inflammatory properties, and therefore is indicated for noninflammatory and inflammatory acne vulgaris, as well as for postinflammatory pigmentation. An important advantage of SA CP is that it is a safe and efficacious treatment for acne in patients with skin types V and VI (Fitzpatrick's classification) [3]. SA peels are done every 2 to 4 weeks and 6 sessions are usually required. Clinical improvement appears after three peels. After cleansing and defatting of the skin as for other peels, the solution is applied using cotton-tipped applicator or gauze sponge. It is left for approximately 3 min according to the

skin reaction and then is washed off the face. It does not need to be neutralized [16]. A white precipitate of the salicylic acid appears after 1 min, but this is not real frosting [1].

This noninflammatory peel with SA is reported to be safe; however, this preparation may induce irritation such as dryness, scaling, burning sensation, erythema, and crusting in darker skinned individuals [20], most of which are tolerable.

### 69.4.4 Newly Developed 30 % SA Formulation in PEG

In Japan, a novel formulation of CP agent has been investigated because CP equivalent to the use of the topical retinoids is really required for acne treatment in the absence of approved topical retinoids. Furthermore, high incidence of adverse side effects using other CP agents including SA in ethanol resulted in many claims from patients. These issues prompted Japanese dermatologists to explore the development of non-inflammatory CP agents that are safely used for Asian sensitive skin.

#### 69.4.4.1 Advantages of PEG as a Vehicle for SA

CP agents for acne treatment are preferably expected to work only in epidermis without affecting dermal or systemic components. However, excessive absorption of SA may lead to salicylism resulting in systemic side effects. Ueda et al. paid special attention to the effect of various vehicles on the percutaneous absorption of SA reported in 1960 [21]. Examining the absorption and distribution of $^{14}$C-SA in PEG applied topically to hairless mouse skin [22], they found from plasma concentration of radioactivity that SA in PEG was little absorbed through the intact skin of hairless mice and that microautoradiograms of the skin revealed the highest level of radioactivity in the cornified cell layer without distribution in the dermis. Although lipophilic SA is absorbed via the sebaceous gland, SA in PEG is not absorbed through the sebaceous gland because SA has a strong affinity to PEG and is little released. Since the plasma levels of radioactivity were extremely lower than the toxic level, they concluded that SA in PEG appeared to be safe for use without severe side effects as a CP agent.

#### 69.4.4.2 Mechanism of Action of SA in PEG

SA is considered to cause a detachment of the cornified cells on the surface of the skin and in the hair follicles by removing the intercellular lipids and extracting integral proteins from the desmosomes. Histological studies in the skin of hairless mice following CP with SA in PEG also suggested that the architecture of the epidermis and the papillary dermis can be regenerated by simply injuring the cornified layer without degeneration or inflammation [23]. Further studies using sun-damaged skin model in hairless mice demonstrated that reorganization of the epidermis and a rebuilding of the superficial dermal connective tissues occur with no evidence of producing inflammatory infiltrates [24]. These findings support the concept that SA in PEG can be used safely as a CP agent with no risk of salicylism.

#### 69.4.4.3 Clinical Evaluation of SA in PEG

Excellent clinical results with 30 % SA in PEG have been reported without notable side effects or hyperpigmentation (Fig. 69.1). Patients with acne received a single application of 30 % of SA in PEG at 2-week interval. Five minutes after application, the skin was thoroughly rinsed with water, cooled with cotton gauze soaked in ice water, and gently wiped dry with cotton gauze. Hashimoto et al. treated 16 Japanese patients, finding that the serial superficial CP treatment yielded dramatic improvement within a period of 10 weeks with only mild burning sensation and erythema in 3 patients [25]. They concluded that SA in PEG peels appear to have a good safety profile that is comparable to topical retinoids offering ease of treatment on an outpatient basis. More recently, Dainichi et al. reported an excellent outcome in 436 acne patients with minimal side effects, thus concluding that SA in PEG is an ideal preparation for Asian patients who tend to develop hyperpigmentation and keloids [26].

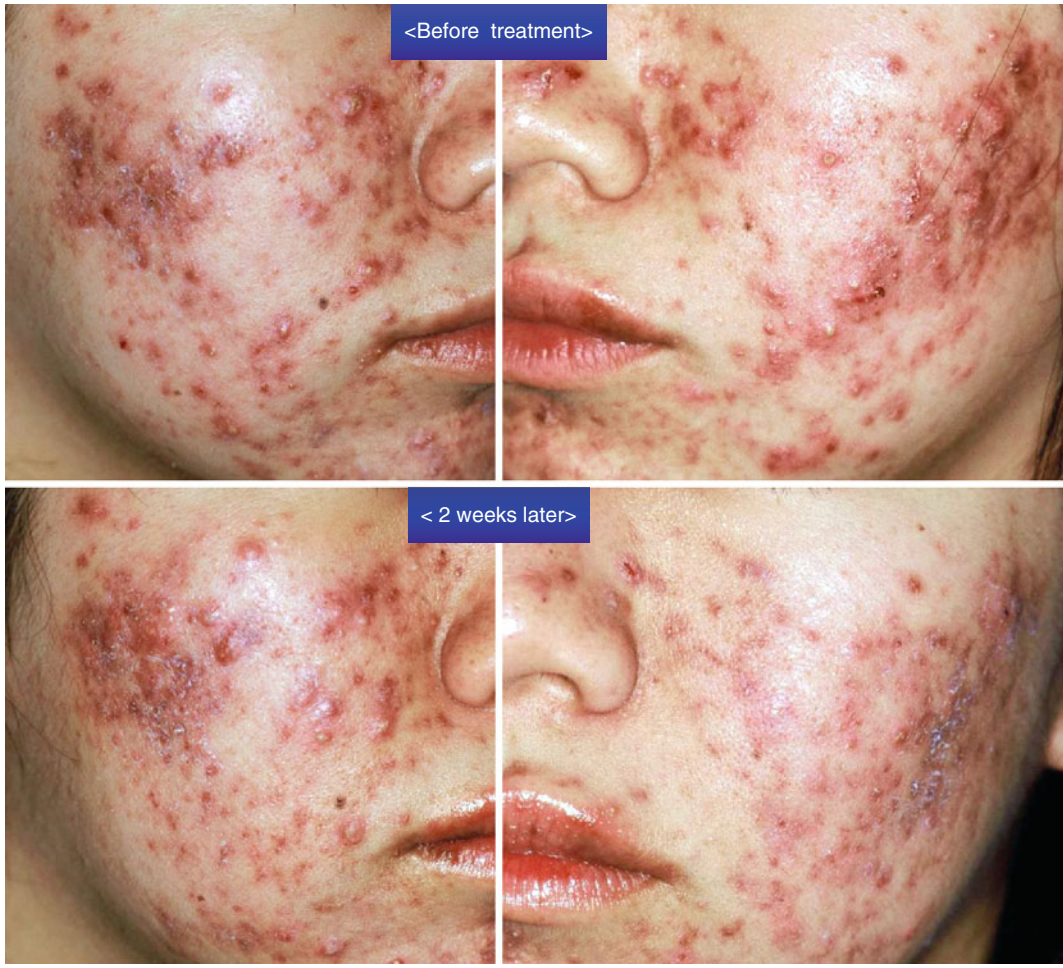


**Fig. 69.1** Clinical effect of a single application of SA in PEG on inflammatory acne. The patient started to take oral antibiotics (minocycline 200 mg/day) and received a single application of CP with SA in PEG only on the *left side* of the face. Note a remarkable improvement on *left side* 2 weeks after the treatment. *Right side* was not treated with CP. Photographs are provided courtesy by Dr. S. Ueda

#### 69.4.4.4 Novel Effects of SA in PEG

CP with SA in PEG, which specifically acts on the stratum corneum, has been reported to suppress UVB-induced skin tumor development in hairless mice [27]. The structural atypia and expression of p53 protein in keratinocytes induced by UVB irradiation were intensely suppressed. Furthermore, incomplete expression of filaggrin and loricrin was also improved. Since the immature cornified envelopes (CEs) are reported to be replaced with mature CEs by the fourth week after treatment with SA in PEG, this CP may normalize the keratinocyte differentiation leading to the suppression of skin tumor development. This fact also indicates that the stratum corneum plays a protective role against carcinogenesis and may provide a novel strategy for the prevention of photoinduced skin tumors [28]. CP with SA in PEG may yield some other unexpected effects in the future.

## 69.5 Perspective on CP in Acne Treatment

Although CP has been developed for the treatment of acne in Japan under the special circumstances where topical retinoids were unavailable, the value of CP which is equivalent to the use of

topical retinoids seems to be underappreciated in most countries except Japan. Especially, newly developed SA in PEG was scientifically investigated for its action mechanism revealing that it is uniquely suited for acne therapy even for patients with darker skin. This novel formulation removes the cornified cell layers without inducing inflammation which is the desired histological effect without SA-related toxicity. Superficial CP with SA in PEG is a good indication for those who cannot tolerate the use of retinoids. This safe CP may recall attention of dermatologists as another option of acne treatment popularizing SA in PEG as the first choice agent.

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# Lasers and Phototherapy in Acne

# 70

Leihong Flora Xiang and Harald P.M. Gollnick

## Contents



**Core Messages**

- Acne is a multifactorial disease causing a polymorphous clinical picture in the active and in the post-active stages.
- Lasers and blue light can be used as adjunctive treatment in the active stage.
- Lasers are ideal instruments for the physical post-acne sequelae such as scarring and postinflammatory hyperpigmentation.
- UV-light has no place in the treatment of active acne.
- Photodynamic therapy needs careful pretreatment considerations.

## 70.1 Introduction

Depending on the clinical course and the type of lesions and the post-acne sequelae, the use of light and of lasers needs to be carefully weighed up. The evidence of light and lasers in the active stages of acne is low, however, in the status with scarring and postinflammatory lesions of post acne sequelae its use is of high value and the evidence-based data are much more convincing (Fig. 70.1).

## 70.2 Active Stages of Acne

The so-called induction therapies in the active stages of acne are evidence-based topical and systemic drug treatments; however, UV-light,

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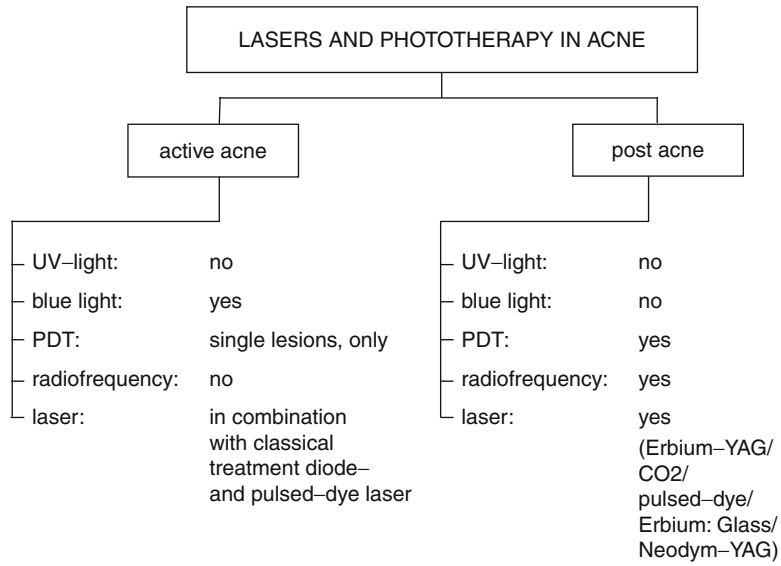


**Fig. 70.1** Administration of LASERs and phototherapy in acne treatment

visible light, lasers, photodynamic therapy, or radiofrequency are belonging to the so-called adjunctive treatment procedures. Those can be used in addition to the classical therapy in acne to further speed up the treatment result or even to improve the final outcome.

### 70.2.1 UV-Light

There are a few reports and no evidence-based clinical trials. UVA, i.p. artificial suntanning is comedogenic, therefore obsolete. UVA promotes the oxidation of squalene to squalene-peroxide which in turn promotes comedogenicity. UVB and natural suntanning have a camouflage effect with melanocytic pigmentation which reduces the aspect of inflammatory erythema of acne lesions. However, high dose UVB and erythematous burns lead to a superficial desquamation, which may have a slight comedolytic effect in the uppermost part of the follicular plugging. In contrast, any additional increase of cumulative erythematous UVB doses may lead to an increased carcinogenic life long risk and will increase the chance of earlier skin aging [1–4].

### 70.2.2 Visible Lights

Visible lights range from 400 to 750 nm in the electromagnetic spectrum.

#### 70.2.2.1 Blue Light

Blue light ranges from 420 to 480 nm. There are a few evidenced clinical trials reported which speak toward an additional therapeutic effect. The proposed effect by which these wavelengths are working is a stimulation of the synthesis of bacterial porphyrins and the release of free oxygen radicals with consecutive destruction of *Propionibacterium acnes* (*P. acnes*).

In two well-controlled studies a moderate efficacy could be demonstrated, and additional case reports support the method. Usually eight treatment cycles, of which each consists of twice weekly for 4 weeks. The dose applicated is about 40 J/cm$^2$, which may, depending on the light source, last for 20–30 min. The efficacy is directed toward the inflammatory lesions and has been proven in acne papulopustulosa. Therefore a combination with a retinoid with low UV sensitivity at night seems to be preferable. One of the trials compared Blue Light with BPO 5 % with a similar outcome [5–7].

### 70.2.3 Photodynamic Phototherapy

Photodynamic therapy is a new method in the treatment of acne by activating molecules that could absorb light, producing singlet oxygen and eventually destroying bacteria. These molecules called photosensitizer can be either applied externally (exogenous) or occur naturally within the body (endogenous). In 1990 Kennedy et al. introduced the use of topical ALA photosensitizing agent for the treatment of skin diseases [8].

ALA is a kind of exogenous precursor metabolized by the hemoglobin synthesis pathway to protoporphyrin IX (PpIX) taken up by the pilosebaceous units, possessing the potential to cause reversible damage to sebaceous glands. Two types of ALA are commercially available: Levulan (DUSA Pharmaceuticals, Wilmington, Massachusetts), which consists of 20 % ALA solution, and 5-methylated ALA (MAL) in a cream base (Metvix, Photocure ASA, Oslo, Norway). ALA powder (Fudan Zhangjiang Pharmaceuticals, Shanghai, China) is also available, which could be prepared as different percent solutions.

Divaris et al. injected ALA intraperitoneally into albino mice and showed that red fluorescence characteristic of PpIX was present in the sebaceous glands, weak in the epidermis and hair follicles [9]. This study showed that ALA selectively accumulates in sebaceous glands after intraperitoneal injection. ALA is applied to the skin and allowed to incubate for 30 min or longer, depending on the condition being treated as ALA penetrates inflammatory lesions more rapidly than it enters normal tissue [10]. When sufficient ALA has entered target tissue, residual ALA is wiped away and the treated area is exposed to wavelengths of light in the absorption spectrum of PpIX.

#### 70.2.3.1 Photodynamic Therapy with Blue Light

*P. acnes* are known to produce endogenous intracellular porphyrins, the major component of which are coproporphyrin III and protoporphyrin IX [11]. Blue light (415 nm) is the most effective wavelength activating porphyrin, and protoporphyrin IX could be activated with significantly lesser peaks at 509, 544, 584, and 635 nm. The BLU-U Blue Light Photodynamic Therapy Illuminator (Dusa Pharmaceuticals, Inc.) is FDA cleared for the treatment of moderate inflammatory acne vulgaris.

Changes in pH by formation of a proton pump and thus dissipation of pH gradients affect *P. acnes* viability and also stimulate tissue regeneration. Irradiation of *P. acnes* colonies with blue visible light leads to photoexcitation of the bacterial porphyrins, production of singlet oxygen, and destruction of *P. acnes* responsible for inflammation.

Akaraphanth et al. investigated 20 patients with moderate to severe acne on the face who were treated with four sessions of topical ALA-PDT with blue light (415 nm, 48 J/cm$^2$, density power 40 mw/cm$^2$) on the right side of face compared with blue light alone on the left side of the face [12]. Ten percent of topical ALA was applied to acne lesions on the right side of the face with 1 h incubation, avoiding light exposure. The mean percent reduction in inflamed lesions counts tended to be higher in the ALA-PDT side; it was 32 %, 50.9 %, 65.9 %, and 71.1 %, respectively, compared with the blue light alone side at 4, 8, 12, and 16 weeks after the beginning of treatment. There was no significant change in sebum excretion, erythema, or the melanin index after treatment. The side effects were stronger on the ALA-PDT-treated side, such as pain, stinging, peeling, erythema, pruritus, etc.

#### 70.2.3.2 Photodynamic Therapy with Red Light

Red light is less effective of activating porphyrin, but has good tissue penetration and anti-inflammation and regeneration effects. Red light induced cytokines releasing from macrophages and stimulated proliferation of fibroblasts.

Xiang et al. have investigated the efficacy and adverse effects of photodynamic therapy, employing low concentration of photosensitizer, short incubation time, and red light source in the treatment of acne (unpublished data). Thirty

patients with facial acne were randomized into two groups. In the one group, patients were applied with 5 % 5-aminolevulinic acid (ALA) on the facial lesions of the right side and with placebo agent on left side as control. In the other group, 5 % ALA were applied on the facial lesions of the left side and with placebo agent on right side as control. All patients were irradiated with red light once a week for four sessions. The lesions count, adverse effects, sebum-secreting level, and pigmentation index were recorded at each visit. The study revealed that in 25.9 % of the patients, 60 % or more of the lesion were improved at the ALA-treated side 2 weeks after the last treatment, while at the control side did not. The efficacy analysis of the ALA-treated side was superior to the control side ($p < 0.05$). Compared to the baseline which denotes acne lesions before treatment, it showed a reduction in all kinds of lesions on the ALA-treated side ($p < 0.05$); however, there was only a reduction of pustules and total lesion counts on the control side ($p < 0.05$). It was concluded that both 5 % ALA-PDT and red light alone can be effective in the treatment of acne. The effective rate and efficacy analysis of 5 % ALA-PDT was superior to using red light alone. Hong et al. enrolled eight patients with mild to moderate acne vulgaris on the face treated with one session of 20 % topical ALA with 4 h occlusion and red light (630 ± 63 nm) irradiation. It also showed a higher reduction of inflamed lesions in the ALA-PDT-treated side compared to red light alone side [13]. ALA-PDTP with red light had affected three of the four pathogenic factors, post-treatment reduction in sebum excretion rates, the suppression of bacterial PpIX fluorescence produced by colonization of *P. acnes* in sebaceous follicles, and damage to sebaceous glands, which were associated with acne vulgaris development.

### 70.2.4 Adverse Effects of ALA-PDT

Side effects included transient hyperpigmentation, superficial exfoliation, and crusting, all of which resolved without scar formation [14]. Pigmentation after topically applied ALA-PDT is caused by melanogenesis, which is a photodynamic reaction to the accumulation of PpIX in the epidermis. While a decrease in sebum production often leads to dry skin, 1 month after PDT treatment, the level of sebum secretion recovers [15].

Irradiation with green, yellow, or red light of delta aminolevulinic acid applied to the skin either as non-esterified or esterified cream or solution after different time spans of 2–4 h leads to the formation of protoporphyrin IX which produces a bacterio-cytotoxic effect with destruction of *P. acnes* and *Staphylococcus aureus* in the follicular canal, anti-inflammatory effects by leucocytotoxicity, and, dependent on the dose irradiated a temporarily or irreversible destruction of the sebaceous gland with consecutive decrease of seborrhea. Controlled studies support the efficacy; however, long-term effects with mis- or nonfunction of the endocrine sebaceous gland need to carefully consider the use of PDT in active acne stages. New formulations of delta-ALA are coming up in the near future and may give more security to this treatment procedure. Single nodular lesions obviously respond to PDT, what may give evidence to use the PDT in severe nodular acne for single lesions as a supportive measurement [12–14, 16–21].

### 70.2.5 Intense Pulsed Light

Pulsed light sources with different filter systems using visible and infrared spectra induce with high energy output with PDT effects. The use without photosensitizer seems to be non-efficacious. The mechanism is similar to PDT and may have the same adverse effect profile.

Intense pulsed light (IPL) sources covered a wide range of the visible light spectrum and near-infrared. The visible output spectrum matched to the absorption spectrum of the target porphyrins and also the deeper penetrating green, yellow, and red bands are exploited. The near-infrared pulse is optimized to create controlled thermal damage in the dermis [10].

### 70.2.6 Laser

Many current therapies have drawbacks involving patient compliance, systemic toxicities, and bacterial resistance. Lasers are now established options in the armamentarium to treat acne, including 532 nm potassium titanyl phosphate laser, 585 and 595 nm pulsed dye lasers, 1,450 nm diode laser, and 1,540 nm erbium glass laser, intensive pulsed light, etc.

Green light (532 nm KTP laser) is well absorbed by bacterial porphyrins and could penetrate to a depth of 1–2 mm in the skin [22]. Eleven patients with mild to moderate acne were recruited in the prospective randomized split-face trial. Four treatments were completed with fluences of 7–9 J/cm$^2$ per pulse for spot of 4 mm and duration time of 20 ms. At 1 month follow-up, the acne lesion count score on the laser treated side decreased by 35.9 %, and the untreated side increased by 11.8 %. Sebum production decreased by 28.1 % on the treated side, compared to increased by 6.4 % on the untreated side at fourth week after last treatment.

Long-term improvement of inflammatory acne has been achieved after one low-fluence pulsed-dye laser treatment [23]. Forty-one patients with mild-to-moderate facial inflammatory acne were enrolled in the double-blinded randomized controlled trial. Patients were randomized to either receive PDL or placebo treatment. Total lesion counts fell by 53 % in PDL group and 9 % in controls. On the other hand, it was reported that low fluence pulsed dye laser therapy didn't result in significant improvement of facial acne [24].

The 1,450 nm diode laser was the first to receive FDA clearance for treatment of acne which had deep penetration [25]. The selective heat damaged sebaceous gland, improve the structure of sebaceous gland, regulate the secretion of sebum, and stimulate proliferation of fibroblasts and collagen synthesis. Dynamic Cooling Device synchronizes to protect the epidermis from heat damage. The treatment was given spaced 3 weeks apart, and the average treatment fluence was 18 J/cm$^2$. Lesion counts decreased 37 % after one treatment, 58 % after two treatments, and 83 % after three treatments. The 1540 Erbium:glass Aramis laser is FDA cleared for treatment of acne on the back.

The use of lasers in post acne sequelae is well evidenced; however, its use in active acne is lacking appropriate evidence-based studies.

Those lasers which have an action spectrum in the visible range may have influence on bacterial porphyrins and therefore may become destructive similar to blue light. Furthermore it is possible that they destroy leucocytes in the perifollicular infiltrate. Infrared lasers act anti-inflammatory and are in addition producing thermal damage to the sebaceous gland.

One controlled study with a pulsed dye laser produced good results in active acne, a second one showed no efficacy. KTP laser are of no value. However, diode lasers with 1,450 nm seem to be effective on inflammatory lesions [26–29].

### 70.2.7 Radiofrequency

Radiofrequency devices are effective by producing irreversible destruction of the sebaceous gland. They like PDT or destructive laser wave length cannot be recommended in active inflammatory acne.

## 70.3 Post-acne—Inactive Stages

Inactive stages of acne consist of scarring of different types and postinflammatory hyperpigmentation [30].

### 70.3.1 Scarring

#### 70.3.1.1 Ablative $CO_2$ and Erbium YAG Laser

The Erbium-YAG laser is preferentially indicated for the superficial varioliforme-like scarring lesions [31]. A half-sided comparison in this indication of Erbium-YAG with $CO_2$ laser showed equivalent results with a better adverse reaction profile. However, the $CO_2$ laser shown by Alster and West better results in the more

deeper lesions with up to 80 % good to very good results [32]. A further smoothening of the scar surrounding areas appears shortly after the procedure. About 2–3 sessions are necessary for an optimal outcome [33].

Both laser types can also be used in combination shown by Weinstein in $n=78$ patients with good (50–70 %) to very good (70–90 %) results. The local post-laser erythema, however, was prolonged with about 8–10 days [34].

#### 70.3.1.2 Fractioned Photothermolysis

The ablative characteristic of the $CO_2$ laser (10,600 nm) combined with fractional photothermolysis allows the ablation of epidermis and dermis in a small-circumscribed micro area (microablation) with an excellent protection of the surrounding skin.

Thirteen and in a second study $n=25$ patients with moderate to severe post-acne scarring were treated over up to 2 months in 2–3 sessions [35, 36]. Almost all showed very good results with a shorter adverse reaction profile with crusting falling off already after 2 days. Erythema persisted up to 1–3 months.

#### 70.3.1.3 Non-ablative Lasers

This group of lasers in post-acne scarring consists of the Neodynium-YAG (1,064, 1,320 nm), Diodes (1,450 nm), pulsed-dye (585 nm), and the Erbium:Glass (1,550) laser types.

In the situation of atrophic scars the Neodynium-YAG laser showed a quite good result after 2–17 sessions [37, 38]. In a half-sided comparative study both laser types were equivalent.

In another study the Diodes laser and Neodynium-YAG were compared in a half-face split study. After three sessions with a schedule of 4 weeks each, only a moderate result could be achieved.

Erythematous and vascularized hypertrophic scars can be treated quite efficiently by the Pulsed-dye laser [39].

Fractional photothermolysis by the Erbium: Glass laser is a new and promising technique with good to very good results and a short recovery time of the skin with regard to patients comfort and off time. Two studies with $n=53$ and $n=29$ patients mild to moderate scars could be treated successfully in 90 % with >50–75 % improvement [40, 41].

#### 70.3.1.4 IPL Technique

In a larger study on $n=109$ patients with keloids and with hypertrophic scars in the average of eight sessions [6, 7, 12–14, 16–21, 26–33] more than 90 % of the individuals recognized less erytheme, diameter, and consistence of the scars [42].

#### 70.3.1.5 Postinflammatory Hyperpigmentation

Lasers are two sided in the situation of postinflammatory hyperpigmentation. Due to an inflammatory reaction an enhancement of pigmentation can occur, therefore a worsening; this is particular in skin types III to VI. Q-switched lasers such as Ruby, Alexandrite, and Neodynium-YAG or IPL may have a better effect. First good results have been reported in single cases with non-ablative fractional photothermolysis Erbium:Glass laser)[43].

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# Treatment of Acne Scarring

# 71

Greg J. Goodman

## Contents



**Core Messages**

- If a delay of as little as 3 years between acne onset and adequate treatment, scarring may be inevitable.
- There is a continuing battle between the safety of the patient and efficacy of the procedure in many cases of post-acne scarring.
- There are no methods of totally removing acne scarring hence everything is a compromise and often many techniques need to be combined.
- Manufacture for the patient a set of realistic expectations. It is vital that the patient realizes the impossibility of complete removal of the scars.
- Educate the patient about the nature of acne scarring, the apparent "memory" that the skin as to the position and severity of scarring and its seeming reluctance to alter with therapy. This is most apparent with techniques that rely upon "collagen remodeling" such as ablative, non-ablative, and fractional resurfacing. Incomplete results and the requirement for multiple treatments and ongoing therapies categorize this group of techniques and processes.
- Listen to the patient. Try to understand the patient's acceptance of temporary versus permanent, their acceptance of risk, and a prolonged treatment process,

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the limitations of the patient's budget, intellect, social circumstances, and work requirements (including the ability to stay out of the sun during any required healing phase).

- Even predictable morbidity can be difficult for a patient who is not anticipating this and often despite information both written and verbal patients often underestimate the postoperative phase of even relatively mild procedures.
- A carefully mapped out plan of action is required in most patients with an understanding that a "one-size-fits-all" model is not satisfactory for most cases. This requirement increases with the complexity of the scar types and the disease burden of the patient.
- The most efficacious procedure may not be practical or may be too likely to produce unsatisfactory complications or excess morbidity. This may have to be passed over in favor of a less effective treatment if the patient is inappropriate for a more aggressive one. It is also important for the physician to realize his own or her own limitations. If the patient's condition requires expertise in an operation that is outside the physician's capability or requires equipment that the physician does not have then referral should occur to a more appropriate clinic.

## 71.1 Introduction

### 71.1.1 Methods of Assisting Post-acne Scars

Altering the appearance of post-acne scars is difficult. The scars seem to retain a memory of their depth and severity and must be unwillingly coerced into improvement.

There are only a limited number of ways to help acne-scarred skin. One can:

*Cut out the scar*. This is necessary when the scar is dystrophic, has a white base or is in the middle of a bearded area. This category also includes a variety of "punch" techniques (punch elevation, excision, or grafting). These techniques are useful in treating punched out and ice pick scars.

*Fill up the scar*. This includes autologous (autologous collagen, dermal, and fat grafting) and non-autologous temporary, semipermanent, and permanent augmentation techniques and agents.

*Alter its color*. Color may be the main visual clue to the presence of scarring whether macular, atrophic, or hypertrophic scar. The technique employed is dependent on the offending color. Brown marks and scars are often a manifestation of postinflammatory hyperpigmentation and are responsive to medical therapy with bleaching preparations and light chemical skin peeling. Erythematous scars and marks usually require home care, vascular laser, and time. Hypopigmented marking is more difficult and may require pigment transfer techniques.

*Induce* (*or reduce*) *collagen*. This is the most common but least efficient method. Inducing collagen formation is a common pathway used by all resurfacing techniques from the most minor home care through to superficial treatments such as microdermabrasion, light chemical skin peeling through to all deeper methods of resurfacing.

Common to all collagen altering therapies, the effect is often delayed for some months after the treatment; there is often a peak and a later decline following therapy. The degree of collagen remodeling seems proportional to the severity of the injury and there is often a reliance on multiple therapies or ongoing treatment to maximize the result.

Similar (but opposite) considerations seem to apply to hypertrophic scars with multiple and often periodically repeated therapies required to change the apparent "memory" of the excessive fibroblast produced dermal fibrosis.

*Relax the region*. Excessive muscle activity acting on thinned, atrophic skin of the forehead, chin, or lower jaw line may amplify the appearance of scarring. Botulinum toxin may be used to modify this skin puckering.

### 71.1.2 Literature Review

One of the few epidemiology studies on the prevalence of post-acne scarring suggests that the type and extent of scarring was in part correlated to the site of the acne, the previous acne severity, and its duration before adequate treatment. Facial scarring affected both sexes equally and occurred in up to 95 % of cases. If a delay of as little as 3 years between acne onset and adequate treatment, scarring seemed inevitable [1].

Critical reviews and meta-analysis studies are generally lacking in the acne-scarring literature. No truly randomized prospective comparative studies (level A) exist. Occasional articles are prospective, some retrospective but usually are descriptive case reports and case series [2, 3], and descriptions of procedures without a formal study being conducted (level C evidence). Most studies on post-acne scarring have been uncontrolled, unblinded, and not randomized even if prospective.

Some limited comparative studies have been described for lasers and acne scarring (level B).

The difficulty in the evaluation of acne scarring is manifold. There is no simple clinically reproducible method for evaluating the volume of deficiency or excess of a single acne scar or an acne-scarred area.

Devices to measure specific lesion volume such as silicon profilemetry or 3D photography, confocal microscopy, or cutaneous ultrasound are outside the abilities of usual practice. Photography has often been poorly taken with respect to uniformity of the normal camera variables of using the same camera, same settings, same backdrop, same lighting, same patient angle, distance, and magnification. Photography inherently is a two-dimensional tool and the volume of scarring is a three-dimensional issue. Turning the patient's profile ever so slightly will completely alter the ability of the observer, no matter how blinded, to determine improvement.

Often studies estimate a percentage subjective or objective improvement analyzing baseline photographs and post-treatment photographs for comparison. Patient and/or observer are asked just to estimate percentage improvement. Often a relatively simple grading system is used such as 0 % no improvement, 25 % mild improvement, 50 % moderate improvement, 75 % excellent improvement, 100 % complete eradication, or similar scale. Yet what this percentage improvement refers to remains ill defined (depth of scar, number of scars, change of scar type, global cosmetic improvement). Patient satisfaction rating is another scale used and probably has been as accurate and more important as any objective method used; yet this is open to many biases making it a less than desirable benchmark.

Long-term follow-up studies are required with many of the ablative technologies in regard to long-term efficacy and complications such as hypopigmentation.

Unfortunately there remains no agreed classification on the morphology or severity of acne scarring. Limited morphological classification of acne scarring has been attempted, but further consensus in morphological description would be useful to allow us to compare articles that discuss a patient's scar type and response to therapy.

There has also been no agreed objective quantitative or qualitative scoring system of estimating global severity or the burden of disease presented by post-acne scarring. Such classification would allow discussion and comparison of patients and their response to therapy (or that of a cohort) and for the purposes of further comparative studies.

Without adequate classification and measure of disease it is hard to perceive how we may compare different patients, their response to treatments and studies performed by different practitioners or investigating units.

### 71.1.3 Evidence for Ablative and Fractionated Resurfacing Technologies for the Treatment of Post-acne Scarring

#### 71.1.3.1 Laser Skin Resurfacing

Despite the above comments, there has been an excellent systematic review of the treatment of post-acne scarring by laser resurfacing [4, 5]. In this analysis the authors identified no controlled

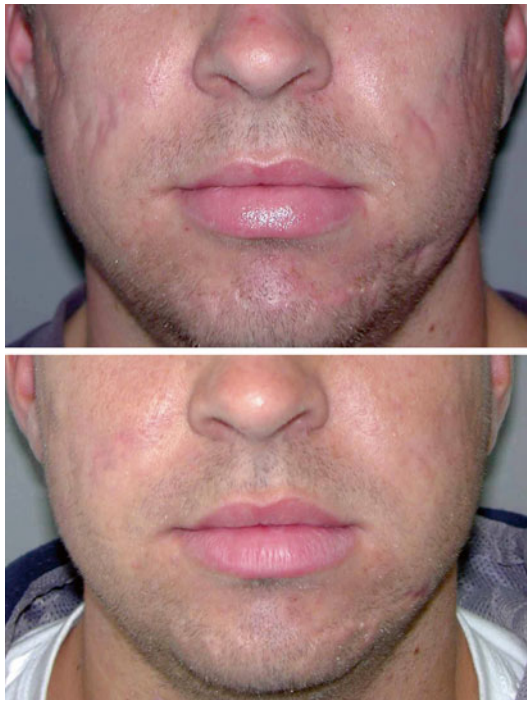

**Fig. 71.1** Patient before and after subcision, fat transfer, and combined CO2 and erbium laser resurfacing

studies and only 16 case series illustrating the effects of $CO_2$ [6–18] or erbium YAG lasers [19, 20] or a combination of $CO_2$ and erbium lasers [21] for the treatment of post-acne scarring patients (Fig. 71.1). The authors could find no studies of reasonable quality. In terms of temporary morbidity, they did find that pigmentation as a side effect was common being evident, even transiently, in up to 44 % of patients. The duration of pigmentary change was said to range between 1 and 6 months with $CO_2$ laser and 2–3 weeks with erbium laser. The length and erythema in the 14 studies averaged 6–16 weeks (CO2 laser) and for 1–3 months (Erbium laser). The mean improvement in scarring was 25–81 % for the CO2 laser and between 50 and 70 % for the erbium YAG laser. Photography with disparate attempts at blinding observers was used in most studies.

Three studies [3, 13, 15] have discussed the use of ablative lasers in the skin of color which is often more problematic.

These studies showed erythema and hyperpigmentation to be common but these adverse effects predictably settled. However, this took 3 months or more to do so in some. Hypopigmentation was very uncommon but sometimes was long term.

#### 71.1.3.2 Dermabrasion

A reasonably effective acne scar corrective procedure over the last 50 years; dermabrasion has been suggested by some studies to be less likely to cause pigmentary and other sequel [22, 23] than other resurfacing procedures. I could find no actual studies or case series to show this. Cold injury caused by the cryo anesthesia used in conducting dermabrasion was thought to increase pigmentary abnormalities. To lessen this complication and to limit blood splatter, tumescent anesthesia was suggested and may be effective [24]. There were experiential reports of experienced physicians suggesting that morbidity associated with dermabrasion is predictable in all skin types [25, 26].

#### 71.1.3.3 Chemical Peeling

A number of case series have been presented on the use of medium and deep chemical peeling in the treatment of post-acne scarring [27, 28]. This technique is also followed by an incidence of postinflammatory hyperpigmentation that seems to settle in most patients over the first 3 months. One paper utilizing a modified phenol peel on 46 Asian patients [28] (11 of whom had acne scarring as their prime indication) suggested that this treatment was effective with 7 of these patients improving by 51 % or more. Over 74 % of all patients developed postinflammatory hyperpigmentation. In 11 % of patients, postoperative erythema lasted longer than 3 months.

Medium strength trichloroacetic acid peel was used in 15 patients with acne scarring and showed improvement in all but one patient and moderate or marked improvement in 9 of these patients [27]. 73 % suffered from transient hyperpigmentation. The authors concluded that this is a safe and effective modality in dark skin patents for the treatment of post-acne scarring.

A variation of chemical peeling involving the use of 60–100 % trichloroacetic acid [29, 30] (termed the CROSS technique) has excited interest of in the treatment of smaller “ice pick” and

poral-type scars which have always been difficult. Basically this modality scars the inside of the cylindrical scar making it cosmetically more appealing. A similar concept was discussed with the use of high energy $CO_2$ laser [31]. This treatment was discussed in study of 65 patients [29]. The authors divided the patients into two treatment arms of using 65 % and close to 100 % trichloroacetic acid in dark skin individuals of Fitzpatrick skin type 4 to 6. The study showed no significant incidence of complications.

#### 71.1.3.4 Plasma Skin Resurfacing

At the time of this writing there has been no manuscript in the literature on this new method of resurfacing in regard to acne scarring. This technology utilizes a plasma cloud of electrons originating from nitrogen atoms and radiofrequency stimulation of these atoms and from personal experience it may be useful in post-acne scarring.

#### 71.1.3.5 Fractional Resurfacing

Fractionated photothermolysis produces small vertical zones of full thickness thermal damage by a mid-infrared laser [32]. This is akin to sinking posts or drilling holes of thermal damage with areas surrounding these posts left free of damage, significantly limiting morbidity and risk. There have been a number of recent studies suggesting its efficacy in post-acne scarring. One study [33] showed that increased density of the small vertical zones of damage cause more swelling, redness, and hyperpigmentation as against higher fluences or energy of these zones. Patient satisfaction seen to be higher when treated with higher fluences but not higher densities.

A prospective case series of 53 patients [34] with atrophic acne scarring using blinded observers showed 51–75 % improvement and 90 % of patients. No incidence of dyspigmentation or scarring was noted. Importantly, clinical response rates were independent of age gender photo skin type.

A number of smaller studies and case reports have also looked at acne scarring, hypopigmented, and postsurgical scarring [35–37] also suggesting satisfactory outcome.

This technology may allow treatment for extra-facial scarring which has not been accessible with other resurfacing technologies.

### 71.1.4 Evidence or Efficacy and Safety of Non-ablative Technologies for Atrophic Acne Scarring

#### 71.1.4.1 Manual Skin Needling or Rolling

In a concept not dissimilar to fractionated resurfacing, manual needling or skin rolling may be used when expensive machinery is not available. In its simplest form one may employ a 30-gauge needle introduced into the skin to a controlled depth with the aid of a small artery forceps held at about 2–3 mm from the tip to stab the skin repeatedly, but this is only appropriate for small areas of scarring. For larger areas a tattoo gun without pigment may be used or a needle-studded rolling pin [38] may be rolled over the face or extra-facially. Although adequate studies into this technology are entirely lacking at present, it appears that the dermal trauma heals with collagen remodeling and may be responsible for improvement in atrophic scarring.

#### 71.1.4.2 Non-ablative Resurfacing

Non-ablative lasers may have a role in the treatment of minor atrophic acne scarring. Comparative studies between laser systems have been performed [39] and different conditions utilizing the same laser system also being compared [40, 41]. The major lasers for this purpose have been the mid-infrared lasers at wavelengths of 1,320 nm, 1,450 nm, and 1,540 nm appropriately cooled to protect the epidermis while targeting dermal water [2, 4, 39–42]. These lasers used conducted heat from the chromophore to produce a diffuse dermal injury heating to above 50 ° C inducing collagen remodeling. Repeated treatments are required and longevity of result is still largely unknown.

This technology seems safe [2, 41], although postinflammatory hyperpigmentation can be seen if blistering occurs. There appears to have a

reasonable level of patient satisfaction and perception of efficacy [40] but objectively and on histology there may be somewhat less efficacy [41].

## 71.1.5 Evidence for Augmentation and Similar Procedures in Atrophic Post-acne Scarring

### 71.1.5.1 Fat Transfer

For grossly atrophic disease with destruction of the deeper tissues, fat remains the optimal replacement agent (Fig. 71.1). Fat is an excellent deeper augmentation material. It is cheap, readily available, will not be rejected, nor suffer allergic reactions. It is easy to work with and is without risk of communicable disease. The issue of permanence has gradually been resolved [43]. Some anecdotal reports attest to it efficacy in treating post-acne scarring [44, 45], but adequate studies are lacking. .

### 71.1.5.2 Subcision

Subcision of scars appears to work by breaking up the attachments of atrophic acne scars releasing the surface from the deeper structures. Successive treatments appear to produce further improvement [46, 47]. The technique usually involves the insertion of a sharp hypodermic needle. It has become a first-line treatment for many isolated moderate bound down atrophic scars. This is despite a lack of controlled studies although one split face designed study utilizing subcision on one side alone compared to a non-ablative laser combined with subcision on the other side, showed the relative efficacy of the combined side [48] suggesting synergy between these two modalities.

### 71.1.5.3 Punch Techniques

Punch techniques such as punch excision [49], grafting [50], and elevation or float techniques [51] have been useful and probably remain the gold standard for punched out scars probably up to 3–4 mm in width (deep "box car" and larger "ice pick" scars). These techniques were described many years ago and have not been studied with any scientific rigor.

### 71.1.5.4 Non-autologous Tissue Augmentation

For patients with few atrophic scars, there is now quite an array of injectable fillers including human collagen and hyaluronic acid among the short-term agents and many agents of a longer term nature with the reintroduction of silicon and variations of polyacrylamides for longer correction. However there are no controlled trials in acne scarring.

## 71.1.6 Evidence for Cytotoxic and Vascular Laser Therapy in the Treatment of Hypertrophic Post-acne Scarring

### 71.1.6.1 Cytotoxics

High strength intralesional corticosteroids are commonly used in the treatment of hypertrophic and keloidal acne scars. Recently reports have appeared of intralesional cytotoxics fluorouracil [52–54], bleomycin [55, 56], and mitomycin [57, 58] as treatments of hypertrophic and keloidal scars. Fluorouracil is usually utilized at a concentration of 50 mg/ml and has been mixed 80:20 with low strength intralesional steroid (Fig. 71.2). However, it may be used alone [59]. Recently the molecular basis of the action of Fluorouracil (5-FU) has been elucidated [60].

### 71.1.6.2 Vascular Lasers

In 1995, it was reported that Flashlamp pumped pulsed dye tunable laser was useful in the treatment of keloid sternotomy scars with improvement in scar height, skin texture, erythema, and pruritus in the laser-treated scars [61]. This initial work has been borne out by more recent studies [62, 63]. Its effects on erythematous acne scars can only be extrapolated at this stage.

## 71.1.7 Directions for the Future and Conclusions

The treatment of acne scarring is evolving and doing so in a way that is comforting to both the patient and the practitioner. Ablative technologies

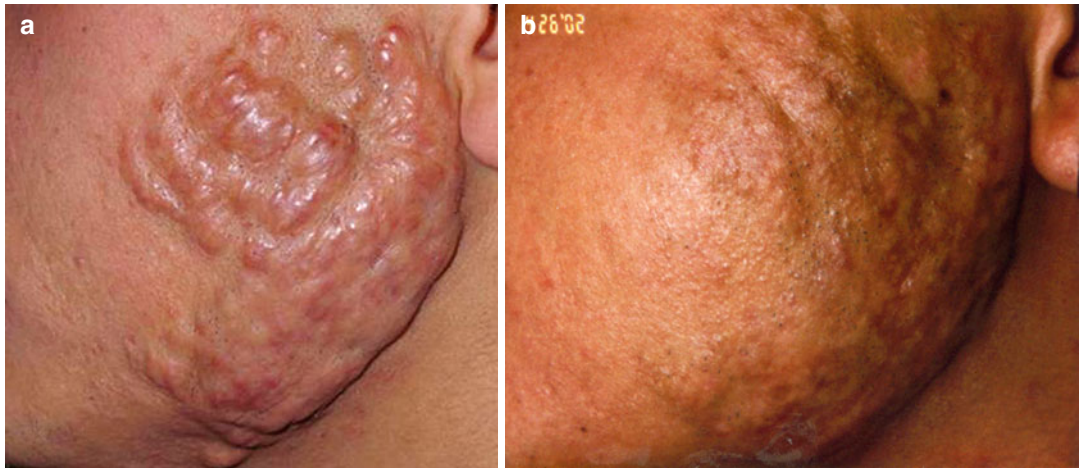


**Fig. 71.2** Patient with very severe keloidal post-acne scarring on the left jaw line before (26a) and after (26b) multiple fluorouracil treatments

are on the wane due to a relative intolerance to the twin evils of downtime and adverse events. Replacements for these treatments must provide meaningful improvement to the patient. The advent of first manual skin rolling, focal TCA peeling, and then fractional resurfacing have been major advances but one should not forget very useful techniques from the past such as punch techniques, excisional surgery, and subcision.

Pendulums swing and mildly ablative resurfacing is making a comeback in the form of plasma skin resurfacing and mid range erbium laser resurfacing. These ablative technologies are trying to occupy the halfway house between downtime and complications on one hand and efficacy on the other. They offer more rapid healing and more limited morbidity and may have a place in the future.

Fractional resurfacing without doubt seems to be the most useful new technology and new fractional wavelengths will be added over the coming years. We will probably see a convergence between these technologies pushing the boundaries of patient tolerance and efficacy. It has also added an ability to treat unusual forms of scarring gleaned from the experience of treating post-acne scarring.

Dermal augmentation and our understanding of what can be achieved with it is now increasing rapidly and one could envisage safer, longer term, and elegant materials to work with in the future for the correction of focal atrophic acne scarring disease.

The treatment of hyperplastic post-acne scarring continues to be disappointing and we await an improved understanding of its pathogenesis. However, some improvements have been made in this treatment such as new cytotoxic therapies but we still have a long way to go.

## 71.2 Tabulated Treatment Plans

The first rule, I feel, is to give patients hope that their condition can be improved but not false hope they their scars can be completely abolished. Patients require a treatment plan together with an understanding of their condition will take time and patience and possibly multiple therapies to settle.

In Tables 71.1, 71.2, 71.3, and 71.4, treatments will be suggested according to the patient's scar severity or burden of disease. Those considered relatively safe will appear in italics (*Relatively safe treatment modalities in most patients*). Relatively less safe but acceptable procedures will appear underlined (Relatively less safe treatment modalities). These latter procedures will be those that require more patient discussion and risk acceptance.

**Table 71.1** Grade 1—abnormally colored, macular disease: Erythematous, hyper-, or hypopigmented flat marks visible to patient or observer at any distance

| Examples of scars | Treatment plan |
|---|---|
| Erythematous flat marks | *Time and optimized home skin care (retinoids, topical anti-inflammatories), often supplemented by vascular lasers* |
| Hyperpigmented flat marks (postinflammatory marks) | *Optimized home care (bleaching, sun protection etc) and light strength peels ± microdermabrasion*<br>*Supplemented by pigment lesion lasers or intense pulsed light (IPL) only if required* |
| Hypopigmented macular scars | *Pigment transfer procedures (blister grafting, autologous cell transfer) maybe fractional resurfacing* |

**Table 71.2** Grade 2—mildly abnormally contoured disease: Mild atrophy or hypertrophy that may not be obvious at social distances of 50 cm or greater and may be covered adequately by make up or the normal shadow of shaved beard hair in males or normal body hair if extra-facial

| Examples of scars | Treatment plan |
|---|---|
| Mild rolling atrophic scars | If localized<br>*Consider skin needling or rolling or microdermabrasion and/or superficial dermal fillers* |
| | If generalized<br>*Multiple treatments of non-ablative lasers, fractional resurfacing often complimented by the localized treatment modalities either simultaneous or as follow-up treatments* |
| Small soft popular | *Fine wire diathermy (FWD). Maybe fluorouracil injections if FWD unsuccessful* |

**Table 71.3** Grade 3—moderately abnormally contoured disease: Moderate atrophic or hypertrophic scarring that is obvious at social distances of 50 cm or greater and is not covered easily by make up or the normal shadow of shaved beard hair in males or body hair if extra-facial, but is still able to be flattened by manual stretching of the skin (if atrophic)

| Examples of scars | Treatment plan |
|---|---|
| More significant rolling, shallow "box car" | If generalized<br>*Medical skin rolling or fractionated resurfacing*<br>If unavailable consider ablative lasers or dermabrasion *or plasma skin resurfacing,* |
| | If localized<br>*Dermal fillers or subcision* |
| Mild to moderate hypertrophic or papular scars | *Intralesional corticosteroids and/or fluorouracil and/or vascular laser. Combine with silicon sheeting* |

**Table 71.4** Grade 4—severely abnormally contoured disease: Severe atrophic or hypertrophic scarring that is obvious at social distances greater than 50 cm and is not covered easily by make up or the normal shadow of shaved beard hair in males or body hair if extra-facial, and is not able to be flattened by manual stretching of the skin

| Examples of scars | Treatment plan |
|---|---|
| Punched out atrophic (deep "box car"), "ice pick" | *If very numerous, deep and small consider focal trichloroacetic acid (CROSS technique) maybe combined with fractional resurfacing*<br>*If fewer and broader but still <4mm in diameter consider punch techniques (float, excision grafting), with or without subsequent fractional* or ablative resurfacing techniques |
| Bridges and tunnels, dystrophic scars | *Excision* |
| Marked atrophy | *Fat transfer,* stimulatory fillers such as PLA, hydroxyapatite, silicon (if fat not feasible), occasionally rhytidectomy |
| Significant hypertrophy or keloid | *Intralesional corticosteroids steroids or fluorouracil and/or vascular laser* |

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# Concepts of Future Acne Treatment

# 72

Clio Dessinioti and Christos C. Zouboulis

## Contents



**Core messages**

- Research of the molecular events implicated in acne pathogenesis has led to the introduction of agents and compounds with potential use as "targeted" future acne treatments.
- Future acne treatments discussed in this chapter include ectopeptidase inhibitors, 5-lipoxygenase inhibitors, inhibitors of lipogenic enzymes, a tripeptide derivative of α-melanocyte-stimulating hormone ($K_D$PT), peroxisome proliferator-activated receptor activators, lauric acid, Toll-like receptor-2 (TLR2) blockers, and *Propionibacterium. acnes* vaccines.
- Emerging anti-inflammatory agents may represent an effective option to treat antibiotic-resistant acne and/or to prevent antibiotic resistance development by limiting antibiotic use for acne.

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## 72.1 Introduction

Current treatment options for acne do not stand up to the challenge of an optimal treatment. Indeed, there is no topical therapy that effectively targets all four major pathogenetic factors implicated in acne, namely, increased seborrhea, follicular hyperkeratinization, *Propionibacterium acnes* (*P. acnes*) hypercolonization, and inflammation;

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**Table 72.1** Future concepts of acne treatment

| Treatments regulating lipogenesis/sebum | Anti-inflammatory agents |
|---|---|
| Ectopeptidase inhibitors | Ectopeptidase inhibitors |
| 5-lipoxygenase inhibitors (zileuton) | 5-lipoxygenase inhibitors (zileuton) |
| PPAR activators | Inhibitors of lipogenic enzyme SCD |
| | α-MSH derivative ($K_D$PT) |
| | Lauric acid |
| | TLR2 blockers |
| | *P. acnes* vaccines |
| | Cathelicidin-BF |
| | APRC11 |

*PPAR* peroxisome proliferator-activated receptor activators; *SCD* stearoyl-coenzyme A desaturase; *TLR2* Toll-like receptor-2

it may be its multifactorial etiology that makes acne challenging to treat. Furthermore, many patients with acne have clinically relevant *P. acnes* resistance limiting the use of antibiotics, and some patients may be intolerant to second- or third-line therapies, such as minocycline and oral isotretinoin [1].

Research in the molecular events implicated in acne pathogenesis has led to the introduction of agents and compounds with potential use as future "targeted" acne treatments. Future acne treatments that will be discussed in this chapter include ectopeptidase inhibitors, 5-lipoxygenase (5-LOX) inhibitors, stearoyl-coenzyme A desaturase (SCD) inhibitors, a tripeptide derivative (KdPT) of α-melanocyte-stimulating hormone (α-MSH), lauric acid, Toll-like receptor-2 (TLR2) blockers, and *P. acnes* vaccines (Table 72.1).

## 72.2 Ectopeptidase Inhibitors

Ectopeptidases are ubiquitously expressed and have pleiotropic functions including proteolytic activity and effects on various key biological processes such as growth, apoptosis, differentiation, adhesion, motility, invasion, cell–cell interaction, angiogenesis, and transformation [2]. The ectopeptidase neutral endopeptidase (NEP;CD10; EC 3.4.24.11), which is often coexpressed with dipeptidyl peptidase IV (DP IV) (EC 3.4.14.5, DP IV, CD26) and aminopeptidase N (APN) (EC3.4.11.2, membrane alanyl-aminopeptidase [m AAP], APN, CD13) in vivo, has been reported to be significantly upregulated in sebaceous glands of acne patients while it is not detectable in healthy subjects [3]. The pharmacological inhibition of DP IV and APN affects growth, cytokine production, and typical functions of human peripheral T cells both in vitro and in vivo [4, 5].

In particular, inhibitors of DP IV have potent immunosuppressive and anti-inflammatory effects in various disease models and are undergoing phases II and III clinical trials for type II diabetes (NCT00676338) [6] and psoriasis (NCT00824980) [7]. APN inhibitors have shown therapeutic efficacy in analgesia models and tumor neoangiogenesis, while both DP IV and APN are expressed on human keratinocytes in vivo and are upregulated in hyperproliferative skin diseases, such as psoriasis [8, 9]. Inhibitors of DP IV and APN suppress keratinocyte proliferation in vitro [10, 11] and partially restore keratinocyte differentiation in vivo [12]. Also, DP IV, CD26, APN, and CD13 are expressed on human SZ95 sebocytes at the mRNA and protein level and exhibit enzymatic activity [2]. Inhibitors of DP IV Lys[Z($NO_2$)]-thiazolidide and Lys[Z($NO_2$)]-pyrrolidide and APN inhibitors actinonin and bestatin suppressed proliferation, enhanced terminal differentiation, and slightly decreased total neutral lipid content in SZ95 sebocytes in vitro. Also, the anti-inflammatory and differentiation-restoring cytokine interleukin (IL)-1 receptor antagonist was significantly upregulated in SZ95 sebocytes and the HaCaT keratinocyte cell line in the presence of these inhibitors [2].

## 72.3 5-LOX Inhibitors

Leukotrienes (LT), a family of highly potent biological substances derived from arachidonic acid (AA), play an important role in the development of tissue inflammation, including inflammation in acne (see Chap. 16). The rationale for use of LTB4 inhibitors in acne treatment is based on the

implication of the AA pathway in the development of acne inflammation [13]. Also, the polyunsaturated fatty acid AA leads to sebaceous lipogenesis and enzymes involved in the biosynthesis of the pro-inflammatory lipids LTB4 and prostaglandin E2 are activated in sebaceous glands of acne lesions. 5-LOX controls the synthesis of LTB4 and LTB4 is a 5-LOX/LTA4 hydrolase product of AA metabolism. AA induces LTB4 and IL-6 release and enhances lipid synthesis in cultured human sebocytes [13]. Since 5-LOX catalyzes LTB4 production, inhibition of 5-LOX provides an attractive target for downregulation of inflammatory processes in the sebaceous gland.

The role of zileuton, an oral 5-LOX inhibitor, at a dose of 600 mg four times daily for 3 months, was evaluated in moderate inflammatory acne in 10 patients. Zileuton is approved for the treatment of asthma in the USA (Zyflo™, Cornerstone Therapeutics, Cary, NC, USA), showing a good safety record. A gradual and time-related reduction in inflammatory lesions and acne severity was observed. The mean reduction in inflammatory acne lesions was 71% at 12 weeks, with a significant improvement seen by week 2. LTB4 levels in the blood were not affected by the treatment. The reduction of inflammatory lesions was strongly associated with the reduction of total sebum lipids and free fatty acids [14]. This effect may be explained by the fact that LTB4 is a natural ligand for peroxisome proliferator-activated receptor (PPAR)-α, which in turn regulates lipid and lipoprotein metabolism, inflammatory response, cell proliferation, differentiation, and apoptosis of sebaceous gland cells. It has been suggested that zileuton has no effect on microorganisms, thus indicating that non-antimicrobial therapy alone can markedly reduce inflammatory lesions [14].

Furthermore, in one patient, zileuton 600 mg four times daily for 2 weeks transiently reduced sebum synthesis with a similar potency compared to a subsequent low-dose isotretinoin therapy [15].

In vitro, zileuton prevented the activation of the leukotriene pathway and AA-induced lipogenesis in human SZ95 sebocytes. In particular, pretreatment of SZ95 sebocytes with zileuton partially prevented the AA-induced LTB4 and IL-6 release and increased neutral lipid content. IL-6 release and neutral lipid content were also reduced with long-term zileuton treatment [16, 17].

## 72.4 Inhibitors of Lipogenic Enzyme SCD

SCD is an endoplasmic reticulum-bound, key enzyme in fatty acid biosynthesis that catalyzes the Δ-9*cis*-desaturation of saturated fatty acids. The resulting monounsaturated fatty acids (MUFA) are incorporated in membrane phospholipids, triglycerides, wax esters, and cholesterol esters. SCD is expressed in human sebocytes at the mRNA level in vivo and in vitro. Induction of TLR2 in SZ95 sebocytes results in upregulation of SCD mRNA expression and a potent inflammatory response via increased IL-6 and IL-8 production. These findings highlight the significance of sebaceous lipid synthesis in the regulation of the inflammatory cascade in acne. A single treatment with a SCD inhibitor/ligand regulated SCD by selectively inhibiting abnormally increased SCD mRNA levels. The compound diminished the linoleic acid (LA)-enhanced IL-8 secretion but did not reduce sebaceous lipids in SZ95 sebocytes when cells were maintained in culture medium supplemented with testosterone and LA. These data may indicate that inhibition of the SCD pathway in human sebocytes results in an anti-inflammatory but not in a lipostatic effect [18].

## 72.5 $K_D$TP: An α-MSH Derivative

α-MSH, a tridecapeptide hormone, exerts pigmentary and anti-inflammatory effects in vitro and in vivo via melanocortin receptors (MCR), which belong to the superfamily of G protein-coupled transmembrane receptors [19, 20]. MC1R and MC5R have been detected in sebocytes in vitro and they may regulate lipogenesis. α-MSH has weak inhibitory effects on IL-1β-induced secretion of IL-8 in human sebocytes in vitro [21]. However, α-MSH induces lipogenesis

in primary human sebocytes and exerts pigment-inducing activity, which limit its use as a potential anti-inflammatory agent in acne patients [19–21].

$K_D$PT (Lys-D-Pro-Thr) is a derivative of the C-terminal sequence of α-MSH in which the second amino acid, proline, is replaced by its D-enantiomer and the third amino acid, valine, is exchanged for threonine. Potent anti-inflammatory effects of $K_D$PT were shown in human SZ95 sebocytes on IL-1β-mediated IL-6 and IL-8 expression. These effects of $K_D$PT were independent of MC1R binding, thus not inducing melanogenesis (cutaneous pigmentation). This agent has been proposed as promising future agent in the treatment of inflammatory diseases, including acne [20].

## 72.6 PPAR Activators

It has been found that activators of PPAR have the potential to modulate lipogenesis. The impact of isoform-specific synthetic PPAR activators (rosiglitazone, a PPAR-γ activator; L-165.041, a PPAR-δ activator; WY14643, a PPAR-α activator) on basal and induced apoptosis in immortalized human SZ95 sebocytes has been studied in vitro. No effect on DNA synthesis or membrane integrity was noted at tested concentrations of these agents. However, significant inhibition of histone-associated DNA fragments (a late event in cell apoptosis) was detected after 24 h for all three PPAR activators in a concentration-dependent manner. PPAR activators may exhibit a sebostatic effect, not by acting directly on lipogenesis but by protecting cells from apoptosis and holocrine secretion [22].

## 72.7 Lauric Acid

Sebum free fatty acids (FFA) may have antibacterial activity against a range of Gram-positive bacteria (see Chap. 23). Lauric acid comprises only 1–2% of total sebum free fatty acids (FFA), but it is one of the most active antimicrobial FFA. Lauric acid exerts potent antimicrobial activity against *P. acnes* in vitro and in an in vivo mouse model, and it has been proposed as an alternative treatment for antibiotic therapy of acne [23]. It inhibits the growth of *P. acnes* at a concentration 15 times lower than that of benzoyl peroxide. In addition, lauric acid did not show cytotoxicity when cultured with human SZ95 sebocytes [23].

Lauric acid exhibits antimicrobial activity against methicillin-resistant *S. aureus [*24]; it may lead to less frequent development of spontaneous resistant bacteria strains compared with tetracycline treatment [25] and it is efficient on biofilm-formed bacteria [26], thus emerging as a potential useful treatment for antibiotic-resistant acne.

## 72.8 TLR2 Blockers

The induction of inflammatory mediators, such as cytokines, chemokines, and metalloproteinases (MMP) by *P. acnes*, occurs via a TLR2-dependent pathway (see Chap. 16). These results provide logical support for the use of anti-inflammatory regimens, such as blockers of TLR2 in the treatment of acne [1]. It was found that treatment of primary human monocytes with all-*trans* retinoic acid (atRA) downregulates TLR2 and that atRA is able to reduce *P. acnes-induced* release of inflammatory cytokines, including IL-12 and tumor necrosis factor-α [27]. Adapalene, a synthetic topical retinoid, reduced expression of TLR2 by keratinocytes from normal skin or acne explants in vitro, a finding that may explain the anti-inflammatory activity of this agent in acne [28].

Also, zinc salts may inhibit TLR2 expression by keratinocytes in vitro, although this inhibition does not modify IL-8 secretion by keratinocytes [29]. The development of agents that selectively inhibit or block TLR2 may provide a "targeted" anti-inflammatory treatment in the future.

## 72.9 *P. acnes* Vaccines

It has been widely accepted that inflammation in acne lesions may be induced by host immune reactions to *P. acnes* (see Chaps. 16 and 18). The

suppression of *P. acnes* by anti-*P. acnes* antibodies has been proposed as a potential treatment for acne. Killed strains of *P. acnes* and/or *Staphylococci* have been used as acne vaccines (Acnevac™ or autovaccines); however, their potency in inhibiting the production of pro-inflammatory cytokines in human skin cells has not been elucidated [30].

Inactivation of *P. acnes* with heat was employed to create a *P. acnes*-based vaccine. Intranasal immunization in mice with this vaccine provoked specific antibodies against two *P. acnes*-specific proteins with molecular weights at approximately 64 and 250 kDa. Protective effects of vaccination with heat-killed *P. acnes* on *P. acnes*-induced inflammation have been demonstrated in vivo and in vitro. Antibodies elicited by inactivated *P. acnes* attenuated pro-inflammatory IL-8 production in human sebocytes, while having no effect on *P. acnes* growth. The clinical improvement observed in this *P. acnes* inflammatory murine model highlights inactivated *P. acnes*-based vaccines as a novel treatment for acne vulgaris based on their anti-inflammatory properties in the absence of an antibacterial effect [31, 32].

On the other hand, some antibodies against *P. acnes* induce pro-inflammatory mediators and cause cytotoxicity and tissue injury. It has been shown that some patients have antibodies against *P. acnes*, with positive correlations between antibody titers and the severity of acne [33]. Thus, the design of vaccines against specific *P. acnes* antigens may represent a promising future acne treatment [32].

## 72.10 Other Anti-Inflammatory Agents: Cathelicidin-BF and APRC11

Cathelicidins together with defensins represent the two major vertebrate antimicrobial peptides. Cathelicidin-BF has been purified from the snake venom of *Bungarus fasciatus* and it is the first identified cathelicidin antimicrobial peptide in reptiles. Cathelicidin-BF showed anti-inflammatory effects combined with potent antimicrobial activity against *P. acnes* and $O_2^-$ production inhibition in vitro and in an in vivo mouse model [34].

Various markers of inflammation such as chemokines, MMP, or pro-inflammatory cytokines are commonly studied as acne "targets." A rhamnoside is a glycoside of rhamnose, sugars found in plant glycosides. The effect of a new rhamnoside derivative, APRC11 ($C_{17}H_{34}O_5$) (Pierre Fabre, Toulouse, France) or undecyl-rhamnoside, was studied on the modulation of inflammation markers. Pre-incubation of normal human keratinocytes with APRC11 resulted in inhibition of *P. acnes*-stimulated IL-1α, IL-8, and MMP-9 as well as in upregulation of IL-1R expression, at the mRNA and the protein level, in vitro [35]. An interesting point commented on by the authors was the strong variability of keratinocytes in their response to *P. acnes* stimulation and also in their response to anti-inflammatory treatment, underlying the importance of an individualized approach to the acne patient [35].

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# Part X

# Impact of Acne on Quality of Life

# Acne and Quality of Life

# 73

Uwe Gieler, Volker Niemeier, and Jörg Kupfer

## Contents



**Core Messages**

- Patients with acne may develop psychological problems as a consequence of their condition. Emotional problems due to the disease should be taken seriously into account during the treatment plan in order to improve outcomes. Even mild-to-moderate disease can be associated with significant depression and suicidal ideation, and psychological change does not necessarily correlate with disease severity.
- Acne patients suffer from social discomfort and reduced quality of life.
- Psychological comorbidities in acne are probably greater than generally assumed. Attention should be paid to psychosomatic aspects especially if there is suspicion of depressive-anxious disorders, particularly with evidence of suicidal tendencies, body dysmorphic disorders or also in disrupted compliance. Therefore, patients who report particularly high emotional distress or dysmorphic tendencies due to the disease should be treated adequately, if possible, by interdisciplinary therapy. The dermatologist must have some knowledge of the basics of psychotherapy and psychopharmacology, which sometimes must be coupled with systemic and topical treatments of acne in conjunction with so-called psychosomatic basic treatment.

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## 73.1 Introduction: Impairment and Quality of Life

While the role of the psychosomatic component in the pathogenesis of acne is variably assessed, secondary emotional impairment due to disfigurement by the disease is almost undisputed [1–3]. The psychogenic impairment due to acne was pointed out by Sulzberger and Zaidens [4]: "There is probably no single disease which causes more psychic trauma, more maladjustment between parents and children, more general insecurity and feeling of inferiority and greater sums of psychic suffering than does acne vulgaris". Nevertheless psychological aspects are often neglected in the therapy of acne patients, which may result in deficient compliance and discontent with treatment [5–7]. Koo [8] warns against considering acne merely as a "cosmetic problem" and neglecting psychosocial aspects. Nearly 70 % of 4,597 acne patients questioned report psychosocial rejection [9]. The psychosocial rejection does not appear to be only a subjective experience, since 18–30-year-old acne patients are considerably more often unemployed than persons with healthy skin [10]. From psychosocial research it is well known that more qualities like "friendly", "socially skilled" and "intelligent" are attributed to physically attractive strangers than to physically unattractive strangers [11].

Motley and Finlay [12] interviewed 100 patients with acne by means of a standardized questionnaire (ADI = Acne Disability Index), inquiring about how much they felt impaired by their disease and demonstrated that the ADI was correlated with the severity of acne. The ADI correlated with the severity of facial acne, chest and back acne. Measures were made of the financial value to patients of acne treatment: when hypothetically offered either a cure for their acne or £500, 87 % of patients preferred treatment to the money. All 13 patients who stated a preference for the £500 had minimal acne. There was no correlation between the clinical grading of acne and the amount patients would be prepared to pay for a hypothetical cure, but there is a correlation between the acne disability score and the amount patients would pay [12].

A positive association was found between poor self-image and the severity of acne compared to controls [13].

Mallon et al. [1] interviewed 111 acne patients using a questionnaire on the quality of life (SF-36) and compared the results to the responses of patients with other serious organic diseases. The acne patients reported levels of social, psychological and emotional problems that were as great as those reported by patients with chronic disabling asthma, epilepsia, diabetes, back pain or arthritis. Only patients with cardiac diseases reported higher values with respect to psychosocial limitations [1]. Furthermore, although acne patients denied that they were ill, they reported emotional and social problems on a par with those reported by patients who would generally be considered as "seriously ill" patients (Asthma, Chronic Pain, Diabetes, Epilepsia, Rheuma). Acne patients apparently do not see themselves as physically handicapped, but give a high degree of impairment to quality of life regarding social issues [1].

In a study of Rapp et al. [14] with 479 individuals with acne using the Skindex showed that high Trait Anger was unrelated to acne severity or frequency of face washing. Anger was significantly related to both global quality of life and skin-related quality of life as well as to satisfaction with treatment and adherence to treatment advice. Regression analyses revealed that high Trait Anger remained a significant predictor of global and skin-related quality of life and satisfaction with treatment, but not adherence to treatment advice after controlling for covariates. The authors pointed out that anger is associated with the quality of patients' lives and with their satisfaction with treatment. Care of acne patients should include attention to anger and other chronic emotional states, to quality of life as well as to clinical severity. Simple guidelines are suggested for how clinicians might approach this important aspect of care (Table 73.1).

In a study with 120 South African acne patients [15] the quality of life measures such as feelings, social activities, performance at work or school, activities of daily living and overall mental health were found to be associated with

**Table 73.1** INVOTE [14]

| |
|---|
| • **I**nquire about how acne affects the patient's social life, emotions, self-esteem, ability to do their work (or studies), and their leisure activities |
| • **V**alidate their experience by acknowledging the importance of these impacts of acne on them and the quality of their life |
| • **O**ffer to discuss ideas for reducing the negative impact and for finding additional resources (e.g. readings, referral) to help further |
| • **T**ell patients that you are committed to helping them with symptom management as well as the negative impact that acne has on their QOL |
| • **E**valuate QOL when you monitor the other outcomes such as severity, adherence, and satisfaction with treatment |

distress but not with acne severity. The authors mentioned that South African patients with acne vulgaris suffer significant psychological distress which affects their quality of lives. Nearly the same results showed a recent study with 1,878 acne patients in Spain measuring Quality of life with Skindex-29 cared by 252 clinicians. The Skindex-29 showed worse quality of life in women, older patients and those with more severe clinical disease [16].

## 73.2 Psychological Abnormalities in Acne Patients

None of the studies on general personality factors performed in the 1960s revealed a significant difference between acne patients and the healthy control group [17,18]. As already demonstrated for other diseases, there is thus no characteristic personality structure of acne patients [19].

Polenghi et al. [20] showed in 33 examined acne patients that these were especially patients with depressed and conformist personality traits. The authors did not, however, provide information on patient selection or the acne severity. Moreover, these were older patients with a mean age of more than 27 years, so possibly several patients with persistent acne were included in the study.

However, emotional problems may arise during the course of acne, which are frequently independent from its severity. Picardi et al. [21] found a high psychiatric comorbidity (>30 %) in patients with acne using the 12-item General Health Questionnaire (GHQ-12). Patients with truncal disease express greater levels of disability which correlate with the severity of their disease [22].

Using the State-Trait-Anxiety Inventory, Garrie and Garrie [23] observed significantly higher scores in acne patients compared to a control group. However, Medansky [24] did not find higher anxiety scores in patients with severe acne.

Acne patients are less depressive than pain patients or patients with a depressive disorder [25]. However, when acne patients are compared to other skin patients using a depression test inventory, acne patients are found to be almost equally depressive as hospitalized psoriasis patients [26].

Sayar et al. [27] compared 31 acne patients with 25 skin-healthy controls and observed increased trait anxiety and depression levels in the acne patients. The authors conclude that the high level of trait anxiety may be due to the long-standing disability caused by acne in social circumstances. In addition, lower self-esteem was found in psychological testing of acne patients. Gupta and Gupta (2001) describe psychiatric comorbidities of acne patients [28]. They pointed out that the depressed acne patient should always be assessed for suicide risk.

## 73.3 No Correlation Between Subjective and Objective Severity

Welp and Gieler [29] and Medansky [24] did not find a significant correlation between objective clinical findings and significant psychometric variables. Gloor et al. [30] reported that the objective severity of disease is not necessarily indicative of motivation for therapy. Mosam et al. [15] pointed out in a recent study the same fact that clinical severity was not associated with patient perception or psychological distress which was also stated in a recent study [16]. A possible explanation of this phenomenon would be that patients who are generally

concerned about their appearance are already affected by the occurrence of minor lesions and are increasingly worried about discrimination. By contrast, patients with severe acne may feel less disfigured if they are accepted by their environment and are given a steadfast self-image, e.g. because of other abilities and a special personality. In this case, fear of discrimination or anxiety about uncontrollability of the disease is lower.

The effect of facial acne on interpersonal relationships is undoubted, but psychological parameters have only shown little correlation with the severity of acne [31–33]. Only in patients with truncal acne levels of disability correlate with severity of acne [22].

## 73.4 Which Acne Patients Seek Medical Treatment?

Only about 17–22 % of patients with acne seek any form of medical treatment [7,34]. The subjective severity of the acne is the central predictive criterion for seeking medical advice [35]. Kramer and Garralda [36] found that 38 % of teenagers aged 13–16 years under treatment by a general practitioner had a psychiatric disorder, although only 2 % had presented with psychiatric symptoms. Acne was the most common presenting complaint associated with such covert psychiatric disorders. In adolescents the frequency of treatment seeking is low. In a Netherlands study [37], 594 adolescents between 14 and 18 years were examined for acne. Only 13 % used topicals and 5 % systemic drugs. Multivariate logistic regression models demonstrated that girls were about twice as likely to have used topical agents. Those with more inflammatory lesions on the face and with more extensive acne used topical and/or systemic acne therapy more.

## 73.5 Therapy Expectations, Self-Management of Acne, and Help-Seeking Behaviour

Acne patients often have too high expectations towards therapy [38]. In an earlier study by Rasmussen and Smith [39], 86 % of patients consider care with water and soap alone to be sufficient. Smithard et al. [40] examined a representative sample of 317 pupils between 14 and 16 years attending a UK comprehensive school. 50 % were rated as having acne. They reported that the most frequently reported method in managing skin problems was to wash more often (82 %), 50 % drank more water, 21 % changed diet, 35 % had used a concealer, and 9 % had used over-the-counter creams. Only nine participants (3 %) reported that they had used prescribed products for the skin. Fewer than a third of participants with definite acne had sought medical advice [40]. In the treatment of acne patients, the development of a good physician–patient relationship is an essential basis in order to understand the individual situation, social environment, and depressive reactions. The importance of considering the patient's subjective ideas for improved compliance was also pointed out by Stangier [41].

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# Instruments of Measurement of Quality of Life in Acne

# 74

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## Contents



**Core Messages**

- Patient-reported outcomes are increasingly used in clinical practice and research due to the awareness of the role of patients in clinical management decisions.
- For a comprehensive assessment of the burden of acne, subjective measurement of the psycho-social impact is necessary in addition to the objective measurement of the disease severity.
- Quality of life in acne patients can be measured by the use of a generic, dermatology-specific or an acne-specific measure.
- Generic measures are used to assess the effects of health or disease on general well-being and are applicable to both the normal population and patients but lack specificity to the unique quality of life (QoL) effects of a particular disease.
- Dermatology-specific measures assess specific impacts of skin diseases on QoL and are more relevant to dermatology patients than generic measures, but may not be useful to cover specific issues of a particular skin condition.
- Acne-specific measures are designed to capture the impact of acne on patient's life and are more responsive to change than generic or dermatology-specific

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measures, but are unable to discern the impact of the disease on a patient's general well-being and do not allow a cross-condition comparison.
- Combining a generic measure with a dermatology-specific or acne-specific measure provides more in detail data than those obtained by their use separately.
- Among the dermatology-specific measures, Skindex and the DLQI have established data in favour of their practical application in acne patients while DSQL has shown some potential.
- Of the six acne-specific measures, Acne-Specific Quality of Life Questionnaire (Acne-QoL) has the most impressive evidence of psychometric data especially pertaining to its responsiveness to change and the availability of minimal clinically important difference (MCID) data, making it particularly useful as an evaluative tool in clinical trials. However, the fact that it was originally designed and validated for facial acne only may limit its wider application in clinical research.
- Because of their compact design, CADI and Acne Quality of Life Scale (AQLS) may be more feasible for use in the routine clinical setting.

## 74.1 Introduction

Increased emphasis on patient empowerment and the growing interest in patient–centred care have encouraged health-care professionals and researchers to incorporate patient-reported outcomes such as quality of life (QoL) measures in routine clinical practice and outcome research.

Acne is a chronic skin disease that is associated with a great deal of psychological, social and physical impact on patients' lives, as discussed in the previous chapter. For comprehensive assessment of the burden of this disfiguring condition accurate measurement of its psychosocial handicap is very important. Although physiological measures are useful in providing information to clinicians, they are of little interest to patients and often correlate poorly with the well-being and functional capacity of the patient.

Subjective assessment of QoL provides more in-depth data than that obtainable from clinical data [1]. However, quality of life assessment is a challenging and complex exercise in itself. This complexity is based on differences in individuals' perceptions, expectations and values and above all the very subjective nature of the concept of quality of life. A number of different methods have been adopted over the years to obtain information regarding the QoL of patients including face-to-face interviews, telephone interviews, focus groups and questionnaires. *Interviews and focus groups*, although valuable in providing rich data, are time-consuming and expensive and are also less likely to be practical in a clinical setting. On the other hand, the more common use of *questionnaires* offers a more practical approach to measuring QoL. Standardised questionnaires for self-rating by the respondents are very useful for recording QoL not only because of their ease of use but also because they allow data recording independent of the investigator, thus avoiding the influence of the examiner on the respondent [2]. A number of measures have been described to quantify the psychological, physical and social impacts of a disease on an individual's QoL. These instruments either encompass all the ways that patients' lives could be affected by any disease (*generic measures*) or are specific to diseases of a particular organ system (*specialty-specific measures*), such as the skin, or to individual diseases (*disease-specific measures*) [3, 4]. However, in order to cover the full range of QoL issues, the application of both a generic and a dermatology-specific or disease-specific instrument has been recommended [2, 5]. This has been shown to help facilitate the comparison between populations (generic instrument) as well as to explore specific areas of problems experienced by different patient groups (disease-specific instrument) [6].

Three types of QoL instruments have been used to evaluate the QoL impact in acne patients: generic, dermatology-specific and acne-specific. A brief account of these three categories of instruments and their use in acne patients is presented below.

## 74.2 Generic Measures

These measures provide a comprehensive and broad perspective of health which allows them to be used both in a normal population and across patients with a variety of disorders enabling comparison between different population groups. Since these measures focus on common elements of health or illness, they are likely to lose specificity to the unique constellations of QoL impacts of a particular disease such as acne. Moreover, most of them are lengthy and hence time-consuming and rather impractical for routine use in a busy outpatient clinic environment. A number of generic instruments have been used, either alone or in combination with other dermatology-specific or acne-specific measures to evaluate the QoL impact in acne.

### 74.2.1 Euro-QoL (EQ-5D)

This is a 5-item generic QoL instrument which enquires about pain or discomfort, mobility, self-care, usual daily activities and depression or anxiety [7]. Each question has three possible response formats: no problem = 1; some problem = 2; extreme problem = 3. EQ-5D also has a global question about patient-rated current health state on a 0–100 visual analogue scale (VAS) where 0 represents worst imaginable health and 100 represents best imaginable health. Although the EQ-5D has mostly been recognised to be more appropriate for economic evaluations, its brevity and simplicity of use may make it a useful and feasible instrument even in a clinical dermatology setting. Using the EQ-5D, acne patients were found to have significantly greater impairment in pain/discomfort and anxiety/depression dimensions compared to a normal population [8]. This study also demonstrated that the EQ-5D was responsive to change in patients' QoL after successful therapy of their acne, although not to the same extent as a dermatology-specific measure. On the 0–100 global question VAS, acne patients scored 76 which was 10 points lower than for a normal population sample as found by a previous study using the EQ-5D [9].

### 74.2.2 SF-36

This is one of the most commonly used generic QoL measures being incorporated worldwide into health status surveys, in monitoring of medical care outcomes and in clinical research [10]. It has 36 items which are contained in 8 subscales (physical functioning, social functioning, mental health, energy and vitality, role limitations due to physical problems, role limitations due to emotional problems, pain and general health perception) or 2 summary scales: a Mental Summary Scale and a Physical Summary Scale. Each item is scored on a 0–100 scale where 0 represents worst health and 100 represents perfect health. Acne patients were found to have worse scores in mental health than patients with asthma, epilepsy, diabetes, arthritis, back pain and coronary heart disease [11]. For the social functioning domain, the results were the same except for patients with coronary heart disease whose scores were worse than for acne. In another study, the SF-36 responded to an improvement in acne patients' QoL following successful treatment [8]. However, the degree of improvement was smaller than that shown by a dermatology-specific measure, the Dermatology Life Quality Index (DLQI).

### 74.2.3 General Health Questionnaire

This self-administered generic instrument was originally developed to screen individuals for mental and psychological problems to provide appropriate health-care services for them [12]. Using a 28-item version of the General Health Questionnaire (GHQ), 41 % of acne patients were found to have some sort of non-psychotic

psychiatric illness as compared to 31 % of the general population [11]. Although not statistically significant, women (49 %) in this study had greater psychological impairment than men (36 %). The GHQ has also been used to assess the effectiveness of acne therapy in parallel with other dermatology-specific and generic measures [13]. In a Japanese study of acne patients, the use of proper make-up over a period of 2–4 weeks was shown to decrease the GHQ score from 9 to 5 ($p < 0.01$) [14].

### 74.2.4 UK Sickness Impact Profile

This generic measure is the UK-adapted version [15] of the original American Sickness Impact Profile or SIP [16] which was primarily designed to be a general health survey to assess the burden of illness on patients' daily activities and behaviour. Total scale score is expressed as a percentage. The UK Sickness Impact Profile (UKSIP) is quite a lengthy questionnaire with 136 items (grouped into 12 subscales, e.g. physical activities, social activities, rest and sleep, home management, recreation, work and eating); this has limited its use in routine clinical settings. Nevertheless, it has been used in a small number of studies in dermatology including one study of acne patients where it was used in parallel with two acne-specific quality of life measures (i.e. ADI and CADI) [15]. The overall UKSIP mean score of acne patients was 5.6 % as compared to 0.45 % for normal controls.

### 74.2.5 Preference-Based Measures or Utility Measures

These instruments, which are generic in nature, are designed to assess the value that an individual places on his/her disease, by directing comparative questions related to finance, time or other disease states. A utility instrument may, for example, generate a single health utility score on a scale, which ranges from 0 (representing death) to 1 (representing perfect health). This single score compares the individual's current health state to death and reflects the relative value of this health state to the individual [17]. A number of instruments or techniques are available for the measurement of health state utilities; the three most commonly used are time trade-off, standard gambles and rating scales [18].

Few QoL studies in dermatology have incorporated utility measures and these have been mainly focused on atopic eczema and psoriasis [19]. In a small sample of six acne patients, using paper standard gamble technique (PSG), the mean utility score was found to be 0.999 [20]. In a slightly larger sample of 28 acne patients, using a different technique called the time trade-off, acne patients' mean utility score was found to be little bit worse at 0.938 [21]. In another study, the utility approach was used to assess the cost-effectiveness of isotretinoin therapy in acne patients [22]. The concept of "Willingness-to-Pay" (WTP) can be used to explore individuals' attitudes to the value placed by patients on a hypothetical cure for their disease. Acne sufferers show a very wide range of values [23].

## 74.3 Dermatology-Specific Measures

These are specifically developed for the assessment of skin conditions and therefore assess specific impacts of skin diseases on QoL and can be used for the comparison of QoL in one skin disease with another. These questionnaires meet with greater acceptance than generic questionnaires because these are perceived as more relevant by the dermatology patients [24]. A brief introduction to some of the dermatology-specific measures which have been incorporated in acne-related studies is presented below.

### 74.3.1 Dermatology Life Quality Index

The DLQI is the most commonly used dermatology-specific QoL measure in dermatology [25]. It was developed as a simple measure for routine use in a busy clinical setting [26].

Over the years, it has been extensively validated and used in over 36 different skin diseases in a large number of epidemiological studies and clinical trials [27].

The DLQI is a self-administered questionnaire and consists of 10 items, each having four possible response options (not at all = 0; a little = 1; a lot = 2; very much = 3). The total scale score is derived by summing the individual item scores and ranges from 0 to 30, 0 indicates no impact on QoL and 30 indicates maximum impact. The questions cover six dimensions—symptoms, daily activities, work or study, personal relationships, social or leisure activities and effect of treatment. A simple series of descriptor "bands" have been described to allow easy interpretation of DLQI scores [28].

The DLQI has been used in a number of cross-sectional [29] and longitudinal studies to assess the efficacy of acne therapies [13]. Zaghloul et al. demonstrated that in acne patients treatment adherence was inversely correlated to the DLQI scores [30]. The responsiveness of the DLQI to change was demonstrated in a study showing that the proper use of cosmetic camouflage in acne patients was associated with an improvement in their DLQI scores [31]. In fact, the DLQI was found to be more responsive to change in acne patients' QoL compared to two generic measures, the EQ-5D and SF-36 [11].

### 74.3.2 Skindex

Skindex, a dermatology-specific tool, was originally designed to detect differences between cohorts of patients in various populations and also in individual patients following changes in their skin diseases. A number of versions of Skindex have been described over the years, e.g. Skindex-61 [32], Skindex 1.1 [33], Skindex-29 [34], Skindex-16 [35] and Skindex-17 [36]. Skindex-61 has eight subscales—cognitive effect, social effect, depression, fear, embarrassment, anger, physical discomfort and physical limitations. The responses are standardised from 0 to 100; 0 indicates no effect and 100 maximal effect. The scale score is the average of responses to questions for each subscale. Skindex-29 is a refined version of Skindex-61 resulting from psychometric analysis. It consists of three subscales (emotions, functions and symptoms) and one item on adverse effects from treatments. The results are presented either separately for the three subscales or as a composite mean score for the overall scale.

Skindex has been used in a number of studies of acne patients. Lasek and Chren found that acne patients had greater impairment of emotions, functioning and symptoms as compared to patients with benign lesions and to normal controls [37]. However, compared with psoriasis patients, acne patients experienced similar emotional effects but fewer effects related to functioning and physical symptoms. Older patients reported greater impact of acne on their lives than younger patients. No difference in QoL impairment was found between men and women. Interestingly, in another study, using a Spanish version of the Skindex-29, women were found to have greater impairment of their QoL as compared with men [38]. The16-item version of Skindex-16 consisting of 3 scales (symptoms, emotions and functioning) has also been successfully used in a community-based study of acne patients in parallel with a battery of other measures [39].

### 74.3.3 Dermatology Quality of Life Scales

This is also a self-administered questionnaire designed for descriptive purposes and to enable comparisons between different skin diseases and patient groups [40]. Each of its 29 items is rated on a 5-point Likert scale and enquires about patients' current experience about the impact on their lives. The Dermatology Quality of Life Scales (DQLS) includes four subscales under a psychosocial domain—despair, embarrassment, distress and irritableness, and four subscales under an activities domain—social, everyday, summer and sexual. In patients with acne and psoriasis, the mean DQLS scores were higher for acne patients in the psychosocial domain and for psoriasis patients in the activities domain [40].

### 74.3.4 Dermatology-Specific Quality of Life Instrument (DSQL)

The DSQL was designed to be a comprehensive but brief instrument for general use in clinical trials and observational research [41]. Its questions cover five subscales—physical impact, activities of daily living, work difficulties, social functioning and self-perception. It also includes two subscales from the SF-36 and eight global items. Two aspects of QoL impact from skin disease (over the last month) are assessed by the DSQL: the frequency of limitations on patient's well-being (on a 0–4 scale) and the level of intensity of such limitations or impact (assessed on a 1–10 scale). The scale scores are calculated by the simple means of the raw item scores which range from 0 (i.e. not at all) to 4 (i.e. constantly). The instrument has two forms: the 52-item version was originally developed to measure the impact of contact dermatitis while the 53-item version was developed for acne patients. It has, however, also being used to evaluate the QoL impact of other dermatoses including chronic lichen sclerosus in women [42]. The responsiveness of the scale to change was determined in a placebo-controlled randomised clinical trial of 12 weeks of acne treatment [43]. Within treatment groups, the DSQL was able to discriminate clinically meaningful changes associated with small and moderate effect sizes. There were also significant differences between the DSQL total scores of active and placebo groups. In a study of African patients with acne, using the GHQ and the DSQL, clinical acne severity was not found to have any relationship with psychological distress or patient perception, but an association was seen between psychological distress and QoL aspects such as activities of daily living, social activities and overall mental health [44].

### 74.3.5 Children's Dermatology Life Quality Index

This simple instrument was developed for use in daily clinical practice and clinical trials to assess the impact of skin diseases on the health-related quality of life of school-age children [45]. The Children's Dermatology Life Quality Index (CDLQI) has 10 items covering symptoms and feelings, school, holidays, leisure, personal relationships, treatment and sleep. The total scale score ranges from 0 to 30; a higher score indicates greater QoL impairment. The scores can also be expressed as the percentage of the maximum score. A cartoon version of the CDLQI was developed in 2003, which was easier and quicker to complete and thus favoured by children as well as by their parents [46].

In the original study, the mean CDLQI scores for acne patients ($n$ = 40) were 5.7 while they were highest in scabies patients (mean score = 9.5) and lowest in patients having naevi (means core = 2.3). However, in a community-based cross-sectional survey of teenagers with acne, the mean CDLQI scores were found to be 1.7, indicating a low QoL impact in the community [47]. There was no significant difference in the mean scores between boys and girls. The CDLQI was also shown to have a good correlation with an acne-specific measure, i.e. Cardiff Acne Disability Index (CADI) [47].

## 74.4 Acne-Specific Quality of Life Instruments

Disease-specific measures of QoL are used to evaluate a patient's experience of a specific disease [48]. These tools are more responsive to change and are able to detect small changes in the most relevant dimensions of a particular disease [49]. Their sensitivity to identify tangible benefits of interventions makes them particularly useful in health outcomes research [50]. On the other hand, since they are so specific and less comprehensive, they may not be able to discern the impact of the disease on a patient's general well-being and functioning [51]. Moreover they do not allow a cross-condition comparison. Six acne-specific instruments have been described to quantify the QoL impact in acne patients.

### 74.4.1 Acne/Cardiff Acne Disability Index

ADI, a self-administered acne-specific questionnaire, has 48 questions which cover eight dimensions—psychological (14 items), physical (4 items), employment (3 items), recreation (3 items), social reaction (14 items), self-awareness (3 items), financial aspects (4 items) and skin care (3 items) [23]. Its scores have been found to correlate with the clinical severity of acne as well as the amount that a patient was willing to pay for a cure [23]. It has been used to assess the impact that acne has on the QoL of college students [52]. A 5-item condensed version of the ADI, the Cardiff Acne Disability Index (CADI), which is easier to use, was later developed that has 4-point Likert scale response categories (0–3) [53]. The total score ranges from 0 to 15, which can also be expressed as a percentage of the total score. The CADI has shown some evidence of reliability and validity [15] and of sensitivity to change after successful treatment [54]. Studies have shown that the instrument is useful in routine clinical practice [54] and is easily understood and quickly completed even by young school-age children [47]. The CADI has also been translated and validated for use in France [55].

The more compact structure of CADI makes it more suitable than the ADI for clinical assessment and patient monitoring in routine practice [15].

### 74.4.2 Acne-Specific Quality of Life Questionnaire

This acne-specific instrument was specifically developed for use in clinical trials to assess the QoL of patients with facial acne [56]. The instrument consists of 19 questions which assess the effect of acne on certain QoL aspects of patients' lives during the previous week on a 7-point scale (0 = extremely, 6 = not at all); a higher score indicates better QoL. The items of the questionnaire cover four domains: acne symptoms, self-perception, role-emotional and role-social. The domain scores are calculated by summing the scores of items in that domain. The measurement characteristics of the Acne-QoL, assessed in a subsequent study, were found to be optimal [57]. The responsiveness of the Acne-QoL was demonstrated by its ability to detect both small and moderate treatment effects in a randomised, double-blind, placebo-controlled study [58]. This study further strengthened the evidence of validation of the Acne-QoL and supported its subscale structure. It was confirmed in a later study, describing the minimal clinically important difference (MCID) for the Acne-QoL scores, that the statistically significant treatment advantage shown by the above study was also clinically significant [59]. Although a reliable, valid and responsive instrument, the Acne-QoL has a major limitation which is the restriction of its use to facial acne only (for which it was originally validated).

A shorter version of the Acne-QoL consisting of only four items, intended to promote its utility in busy clinical practice, has been developed and validated [60]. However, the brevity of Acne-QoL 4 inevitably compromises the detail of information otherwise extractable through the use of the more comprehensive original measure.

### 74.4.3 Acne Quality of Life Scale

This acne-specific questionnaire was developed to assess QoL in patients with mild-to-moderate acne and is claimed to be sensitive to changes in acne severity and its associated psychological morbidity [61]. It has a 4-point rating scale with 0 indicating "not at all" and 3 indicating "very markedly". The total score is calculated by adding the scores for individual items; a higher score indicates greater QoL impairment. The original 12-item scale was found to have two subscales, social quality of life impact (containing 9 items) and vocational quality of life impact (containing 3 items). However, only the 9-item social impact subscale was found to be valid and its use was recommended by the authors to evaluate the QoL impact associated with acne particularly for assessing the effectiveness of therapies for acne.

In an open-label study to assess the efficacy of combination therapy with benzoyl peroxide/clindamycin topical gel, AQLS scores (normal range = 0–27) were shown to be significantly improved from 2.8 at baseline to 0.8 after 8 weeks of therapy ($p < 0.001$) [62]. However, the clinical significance of this improvement was not determined in the study.

AQLS has been shown to positively correlate with both subscales of the Hospital Anxiety and Depression Scale or the HADS (i.e. anxiety and depression) in patients with acne [63]. However, no correlation was found between acne severity and AQLS scores. There was also no difference between male and female patients with regard to QoL impairment. Moreover, this study demonstrated that, irrespective of the degree of severity of skin lesions, acne patients had greater levels of anxiety and depression compared with the normal population.

### 74.4.4 Acne Quality of Life Index

This is a 21-item acne-specific QoL measure which has been developed to be used in clinical practice and research [64]. An item pool was collected from focus groups of acne patients which was reduced to 21 items based on the results of factor analysis as well as qualitative analysis of the original item pool. The final questionnaire has been shown to have an adequate reliability and validity profile. However, its responsiveness to change needs to be determined before it could be incorporated into clinical trials.

### 74.4.5 Assessment of the Psychological and Social Effects of Acne

This 15-item questionnaire was one of the earlier instruments developed specifically to assess the psychosocial impact of acne [65]. The contents of the questionnaire were based on responses of seven psychological questionnaires sent to acne patients and normal control subjects. However, it was not fully validated and its use has been rarely reported. In one small study of acne patients, Assessment of the Psychological and Social Effects of Acne (APSEA) was used in parallel with the DLQI and the CDLQI and demonstrated high correlation with these dermatology-specific measures [66].

#### Conclusions

The quality of life of acne patients can be affected due to a number of clinical, psychological and social reasons [29]. Although objective measures of acne severity are crucial for the clinical assessment of the disease, they fall short in the assessment of the psychological and social effects of the disease on patients. The use of QoL measures helps to capture a complete picture of the overall impact of acne and its treatment on patients' lives from their own perspective. Use of such measures may also help to identify patients vulnerable to develop psychological complications due to their skin conditions, thereby prompting the treating physician to take timely therapeutic actions individualised to patients' particular needs. That is why the use of simple QoL measures has been recommended as part of the integral clinical strategy during acne patients' clinical management planning [47]. However, in order to promote the wider use of QoL instruments in routine clinical practice, it is important to improve the level of knowledge about available instruments as well as to provide formal training to dermatologists in the proper use of these instruments.

Generic instruments, because of their limited coverage of the unique constellations of QoL issues of skin disease patients, are better used in combination with dermatology or disease-specific instruments [67]. Combined use of such instruments can provide insight into those aspects of patients QoL which are not covered either when used alone. The complementary information gathered by their use can then be used not only to aid clinical care and in research but also by health managers and politicians while making critical decisions regarding health policy and resource allocation.

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# Part XI

# Acne in Systemic Disease

# The SAHA Syndrome

# 75

Christos C. Zouboulis and Clio Dessinioti

## Contents



**Core Messages**

- The SAHA syndrome encompasses the association of **S**eborrhea and **A**cne with **H**irsutism and/or androgenetic **A**lopecia in women.
- It highlights the major cutaneous features indicating peripheral hyperandrogenism in young females.
- The SAHA syndrome is classified into familial, ovarian, adrenal, and hyperprolactinemic types.
- Hyperandrogenism, insulin resistance, and acanthosis nigricans form the HAIRAN syndrome that may be classified as a variant of SAHA with polyendocrinopathy.
- The diagnosis of the SAHA syndrome requires a thorough history, physical examination, and appropriate laboratory investigations (including DHEA sulfate, free testosterone, prolactin, and 17-OH progesterone) to rule out androgen excess.
- Management of the cutaneous hyperandrogenism-associated manifestations of the SAHA syndrome includes lifestyle modifications for weight loss and oral and/or topical treatments for acne. In women, additional treatment options include oral contraceptives and/or antiandrogens and insulin-sensitizing medications for hirsutism, androgenetic alopecia, and menstrual irregularities.

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## 75.1 Introduction

The association of **s**eborrhea and **a**cne with **h**irsutism and/or androgenetic **a**lopecia in women was defined in 1982 as SAHA syndrome [1]. The term highlights the major cutaneous features indicating peripheral hyperandrogenism in young females [2–4]. The SAHA syndrome has common clinical characteristics with the polycystic ovary syndrome (PCOS) [4].

## 75.2 Pathogenetic Background

The sebaceous gland is an important organ of active androgen formation, expressing all the necessary enzymes for the de novo biosynthesis of testosterone [5, 6]. Androstenedione and dehydroepiandrosterone (DHEA) are converted to testosterone and further to 5α-dihydrotestosterone by the intracellular enzyme 5α-reductase. In women, up to 50 % of the total circulating testosterone is produced in the skin and in other peripheral organs. Androgens, by binding to the nuclear androgen receptors in the cells of the skin, affect several cutaneous functions, such as growth and differentiation of pilosebaceous units and epidermal barrier homeostasis [5, 6].

Androgen excess can increase the size and number of lobules per sebaceous gland as well as sebum excretion [7, 8]. Most acne patients have normal circulating androgen levels, which do not correlate with acne severity [7]. Acne is the result of a local hyper-responsiveness of the sebaceous gland to normal androgens or the result of a local overproduction of androgens in the skin [7].

Hirsutism and oligo/amenorrhea are commonly associated with hyperandrogenemia [4]. Patients with hirsutism often exhibit increased activity of 5α-reductase and higher levels of androstenedione and DHEA sulfate (DHEAS) [9]. Androgen excess acts differently on the hair of the scalp, inducing shortening of the follicular anagen phase and progressive conversion of terminal hair to intermediate ones, leading to androgenic alopecia [10, 11].

SAHA syndrome includes the dermatological manifestations of androgen excess in women, either on the basis of high circulating androgen levels (hyperandrogenemia) or due to the capacity of the pilosebaceous unit to respond with increased sensitivity to normal circulating androgen levels (hyperandrogenism) [4, 11].

## 75.3 Clinical Characteristics

The SAHA syndrome is classified into familial, ovarian, adrenal, and hyperprolactinemic types (Table 75.1) [4].

**Table 75.1** Types of the SAHA syndrome (from [9])

| Types of SAHA | Clinical manifestations | Laboratory abnormalities |
|---|---|---|
| Familial | Facial hirsutism<br>Mild facial inflammatory acne | Normal hormonal blood levels |
| Ovarian | Young, obese women<br>Menstrual irregularities<br>Significant seborrhea<br>Inflammatory acne with scarring<br>Facial, mammary, central body hirsutism<br>Androgenetic alopecia | Increased LH/FSH ratio, increased free testosterone levels |
| Adrenal | Non-obese patients<br>Significant seborrhea<br>Severe nodulocystic facial/truncal acne with scarring<br>Female androgenetic alopecia<br>Central hirsutism | Increased DHEAS, cortisol |
| Hyperprolactinemic | Similar with adrenal SAHA, with or without galactorrhea | Increased serum prolactin |
| HAIRAN syndrome | SAHA with polyendocrinopathy: hyperandrogenism, insulin resistance, acanthosis nigricans | Increased serum insulin, glucose, cortisol, progesterone, and androgens |

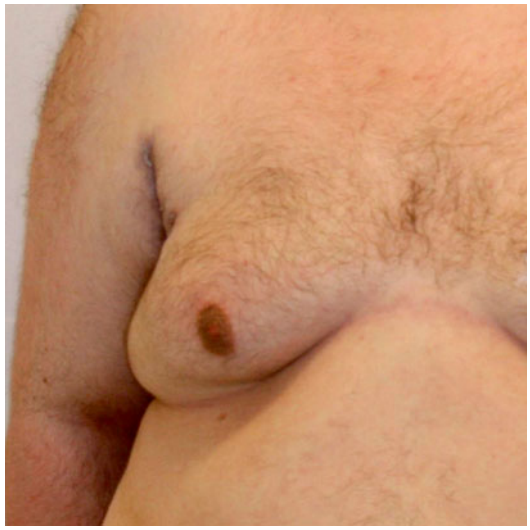

**Fig. 75.1** Hirsutism on the breast area of a 29-year-old female with ovarian SAHA syndrome

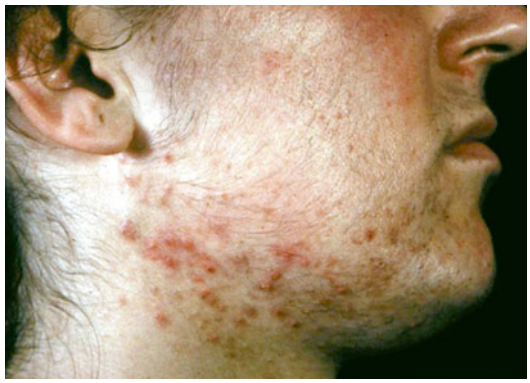

**Fig. 75.2** Facial acne and hirsutism in a 30-year-old female with adrenal SAHA syndrome

Familial SAHA represents the familial occurrence of clinical signs of peripheral hyperandrogenism, such as facial hirsutism and mild facial inflammatory acne, possibly due to a genetically determined increased androgen receptor sensitivity and/or enhanced androgen metabolism in the skin. Hormonal blood levels are usually normal [4].

Ovarian SAHA represents the clinical expression of functional ovarian hyperandrogenism. Ultrasound of the ovaries shows absence of findings in mild cases and enlarged ovaries with hyperthecosis and large persistent follicular cysts in more severe cases. Laboratory abnormalities, such as increased luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio and increased free testosterone levels, may be present. Patients are usually young, obese women, with menstrual irregularities, significant seborrhea, inflammatory scarring acne, facial, mammary, and central body hirsutism, and androgenetic alopecia (Fig. 75.1) [4].

Adrenal SAHA represents anatomical or functional adrenal hyperplasia. Increased DHEAS and, in more severe cases, increased cortisol blood levels may be present. It affects thin patients and presents with significant seborrhea, severe nodulocystic facial and truncal acne with scarring, female androgenetic alopecia, and central hirsutism (Fig. 75.2). Linear extension of the pubic triangle over the abdomen up to the thorax may be present [4].

Hyperprolactinemic SAHA represents a manifestation of increased serum prolactin and presents with similar findings with adrenal SAHA, including nodulocystic acne and central hirsutism, with or without galactorrhea [4].

Hyperandrogenism, insulin resistance, and acanthosis nigricans form the HAIRAN syndrome that may be classified as a variant of SAHA with polyendocrinopathy (Table 75.1). HAIRAN syndrome affects young, obese patients and presents with seborrea, mild inflammatory acne, hirsutism, androgenetic alopecia, acanthosis nigricans, and insulin-resistant diabetes mellitus (Fig. 75.3). Blood insulin, glucose, cortisol, progesterone, and androgens may be increased [4].

SAHA syndrome can be associated with polycystic ovary syndrome, cystic mastitis, obesity, insulin resistance, and infertility [3]. Seborrhea and acne which are the two most frequent signs in SAHA are induced by androgen activity [4]. The clinical pattern of the syndrome varies depending on the presence of clinical characteristics. Each of the four clinical characteristics can be differentially present, with all four being present in approximately 20 % of the patients; seb orrhea is always present, and androgenetic alopecia occurs in 21 % of the cases, acne in 10 %, and hirsutism in 6 % of the patients [4]. The diagnosis of the SAHA syndrome requires a thorough history, physical examination, and appropriate laboratory investigations (including DHEAS, free testosterone, prolactin, and 17-OH progesterone) to rule out androgen excess (Fig. 75.4) [4, 6].

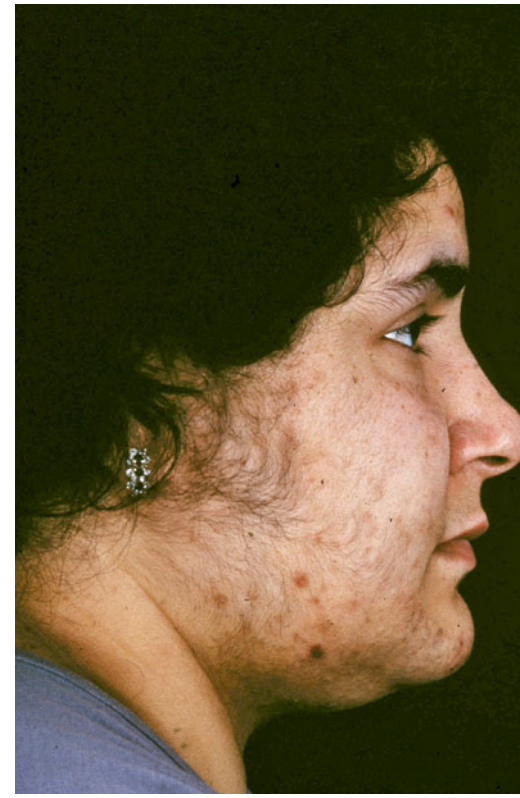

**Fig. 75.3** Facial hirsutism and acne in a 22-year-old obese female with HAIRAN syndrome

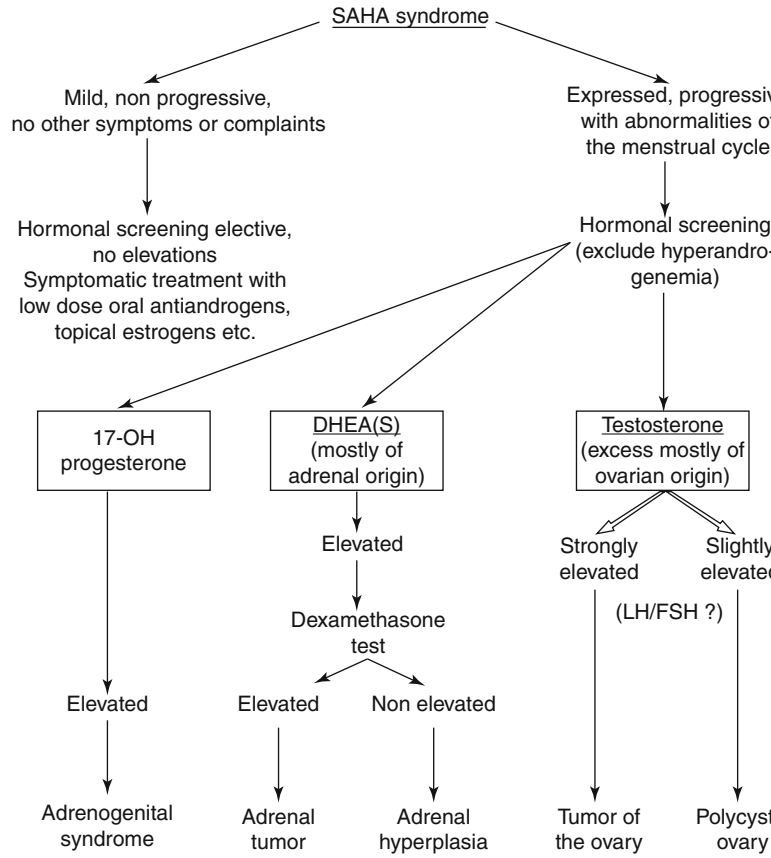


**Fig. 75.4** Peripheral hyperandrogenism in females and its differential diagnosis (androgenetic vs. androgenic etiology) (from[ 12])

## 75.4 Treatment

Management of the cutaneous hyperandrogenism-associated manifestations of the SAHA syndrome includes lifestyle modifications for weight loss and oral and/or topical treatments for acne. In women, additional treatment options include antiandrogen oral contraceptives and/or antiandrogens and insulin-sensitizing medications for hirsutism, androgenetic alopecia, and menstrual irregularities [7, 11, 13, 14]. Moreover, oral glucocorticoids are indicated for adrenal SAHA. A 6-month treatment with 2-month regimens of 10 mg (0-5-5), then 5 mg (0-0-5), and finally 2.5 mg (0-0-2.5) prednisolone has been suggested [13]. Bromocriptine (2.5–7.5 mg/day), a dopaminergic agonist, is used for the treatment of hyperprolactinemic SAHA [4].

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# The Polycystic Ovary Syndrome and Acne

# 76

Joseph L. Pace

## Contents



**Core Messages**

- The polycystic ovary syndrome (PCOS) was first described by Stein and Leventhal who defined a syndrome consisting of obesity, amenorrhea, hirsutism, and infertility associated with enlarged polycystic ovaries.
- Hyperandrogenism is crucial to acne development and in women it can be caused by various conditions, the most prevalent of which is PCOS.
- Common dermatologic manifestations of PCOS include hirsutism, acne, acanthosis nigricans, and androgenic alopecia.
- Persistent, severe, or acne of late onset in women is highly suggestive of PCOS.
- Key factors in the pathogenesis of PCOS include androgens and increased insulin resistance.
- Lifestyle modifications remain the first-line therapy for all obese women with PCOS.
- Hormonal treatments used for females with acne include anti-androgens (androgen receptor blockers) or agents designed to decrease the endogenous production of androgens by the ovary or adrenal gland, such as oral contraceptives, low-dose glucocorticoids, or gonadotropin-releasing hormone (GnRH) agonists.

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DOI 10.1007/978-3-540-69375-8_76, © Springer-Verlag Berlin Heidelberg 2014

## 76.1 Introduction

The polycystic ovary syndrome (PCOS) was first described by Stein and Leventhal [1] who defined a syndrome consisting of obesity, amenorrhea, hirsutism, and infertility associated with enlarged polycystic ovaries. This syndrome is associated with menstrual disorders, acne, and hirsutism. In the majority of cases, a familial trait is obvious, but the responsible genes have yet to be identified. Low birth weight and a family history of diabetes are strong risk factors for PCOS. However, the pathophysiology of the syndrome causing overproduction of ovarian androgens is now becoming clearer. The early diagnostic signs are often mistakenly dismissed as normal changes of adolescence, but it is important to make an early diagnosis in order to prevent early and late complications of the syndrome [2].

## 76.2 PCOS and Acne

In 1990, PCOS or hyperadrenalism were reported to occur in 10 % of patients with late-onset acne [3] and women with severe acne may have PCOS. Modern imaging techniques have revealed the presence of polycystic ovaries in normal women [4] and mildly polycystic ovaries in hirsute women with normal menses [5]. The latter finding has led to the inclusion of women who were previously labeled as having idiopathic hirsutism under the diagnosis of PCOS. An estimated one-third of women in the UK have polycystic ovaries [6]. The increase in PCOS has been linked to childhood obesity (*American Association of Clinical Endocrinologists* Position Statement on Childhood Obesity Linked to Early Development and PCOS in Young Girls – September 13, 2005), eating disorders, and increasingly stressful lifestyles (no exercise, increased body weight) [7, 8].

Hyperandrogenism is crucial to acne development and in women it can be caused by various conditions, the most prevalent of which is PCOS. Common dermatologic manifestations of PCOS include hirsutism, acne, acanthosis nigricans, and androgenic alopecia (Figs. 76.1 and 76.2).

Acne is generally considered a disorder of adolescence, but it can also affect adults [9, 10].

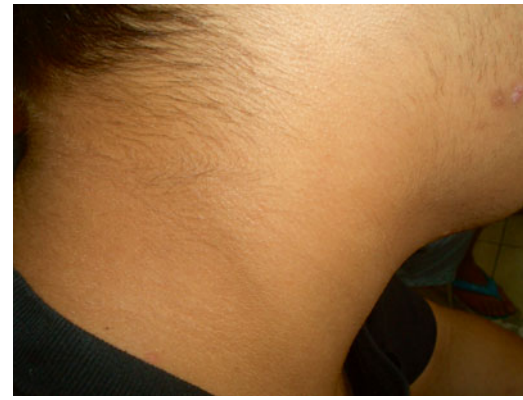

**Fig. 76.1** PCO patient with beginning hirsutism

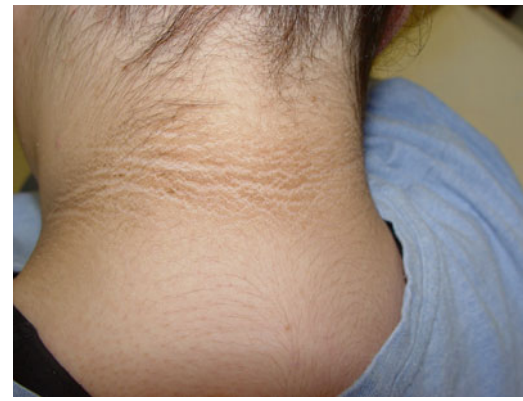

**Fig. 76.2** PCO patient with mild signs of acanthosis nigricans

It appears that post-adolescent acne is increasing in incidence, although a very limited number of studies have focused on this point. 12 % of women continue to have significant persistent acne until the age of 44 [11], but less severe degrees of acne are even more common. Observations of post-adolescent acne reveal the presence of two distinct clinical forms: persistent acne and late-onset acne. They both affect predominantly the face, and persistent acne is a more common form [12].

Persistent, severe, or acne of late onset in women is highly suggestive of polycystic ovary syndrome (PCOS). Initial clinical presentation of PCOS can occur in the second or third decade, frequently precipitated by excessive weight gain [13]. PCOS may present with acne as its sole clinical manifestation. Many studies showed a

high prevalence of PCOS in acne patients. PCOS is also prevalent in women with late-onset acne, persistent acne, and acne resistant to conventional therapies [14]. Furthermore, 83 % of women with acne had polycystic ovaries (not PCOS) compared with 19 % in a control group without acne [15] and approximately 80 % of women with severe acne, 50 % with moderate acne, and one-third with mild acne have some elevation of plasma androgens [13].

## 76.3 Etiology of PCOS

### 76.3.1 Androgens

Numerous factors contribute to the development of acne, foremost being the requirement for androgens [16], and androgenic stimulation of sebaceous glands is necessary for the development of acne. A number of female patients with acne may have at least one abnormal hormone level, although it is clear that the majority of acne patients in general do not have an endocrine disorder [17].

Androgens enhance sebum production from sebaceous glands and cause abnormal follicular epithelial cell desquamation, both of which contribute to the development of a comedone. There is evidence that both circulating serum androgens and locally produced androgens play a role.

Some studies have reported a positive correlation between acne severity and circulating serum androgen levels. Women with acne have been reported to have elevated serum levels of total testosterone, free testosterone, dehydroepiandrosterone (DHEAS), 3α-androstanediol glucuronide, and androstenedione, as well as low levels of sex hormone-binding globulin (SHBG) [18, 19].

Androgens produced and secreted locally within the sebaceous gland also play a major role in acne formation. The enzyme 5$\alpha$-reductase converts testosterone to the more potent androgen dihydrotestosterone within the sebaceous glands. It is likely that genetic factors may determine abnormal follicular keratinization or sebaceous gland androgen response in individuals with persistent acne [16]. Individuals who have acne tend to have a higher rate of sebum excretion than those who do not have acne [20] Moreover, adult patients with acne have been found to have higher sebum excretion rates than did age-matched controls [21].

### 76.3.2 Associated Insulin Resistance

Hyperinsulinemia plays a key role in the pathogenesis of PCOS [2]. It has been proposed that hyperandrogenemia may contribute to insulin resistance in PCOS and that hyperinsulinemia can promote hyperandrogenism. The results of pharmacological modification studies have suggested that the latter mechanism is more operative than the former. PCOS is perhaps the most common disorder in which the association between insulin resistance and ovarian function appears to be important.

The metabolic syndrome, a constellation of interrelated risk factors for cardiovascular disease and type 2 diabetes mellitus, has become a major public health concern against the backdrop of increasing rates of obesity. Insulin resistance plays a pivotal role as the underlying pathophysiological link of the various components of the syndrome, as well as between PCOS and metabolic syndrome [22].

Consequently, several studies recommend that women with PCOS should undergo comprehensive evaluation for the metabolic syndrome and recognized cardiovascular risk factors and receive appropriate treatment as needed [23, 24]. An approximate fourfold increase in the prevalence of the metabolic syndrome is found in women with PCOS compared with the general population, consistent with the proposed major role of insulin and obesity in the syndrome, implying a greater risk of cardiometabolic disease in women with PCOS. However, this estimate is likely to vary according to PCOS definition, ethnicity (in Malta, for example, 10 % of population have late-onset diabetes mellitus compared to 2–3 % in Europe generally) [25], and different etiological pathways to PCOS [26].

Acanthosis nigricans (AN) is a cutaneous marker of insulin resistance. Studies have reported that acanthosis nigricans is present in

50 % of obese women with PCOS and 5–10 % of normal weight women with PCOS [27]. The mechanism is unknown, but it is believed that hyperinsulinemia stimulates the growth of keratinocytes and/or dermal fibroblasts and produces the skin changes characteristic of acanthosis nigricans. Milder forms of AN may be found in many more patients when carefully looked for.

Increased insulin-like growth factor 1 (IGF-1) levels in addition to androgens may influence acne in adult men and women. While IGF-1 appears to have a stronger effect on acne in women, androgens may play a greater role in acne for men. However, in both men and women these hormones are interrelated, possibly owing to reciprocal effects on hormone production [28].

#### 76.3.2.1 Links Between Hyperinsulinemia and Increased Androgen Production

These include:

- Direct stimulation of ovarian androgen secretion by insulin.
- Direct stimulation of luteinizing hormone (LH) secretion by insulin or sensitization of LH-secreting pituitary cells to GnRH stimulation.
- Decreased levels of SHBG, with concomitant elevation of free androgens.
- The synergistic growth- and cyst-promoting action of insulin and LH.

## 76.4 Diagnosis of PCOS

The diagnosis of PCOS requires a complete history,[1] physical examination with emphasis on evidence of androgen excess, and appropriate laboratory investigation to exclude other causes of hyperandrogenism. There is consensus agreement that for a diagnosis of PCOS any two of the following three criteria should be present:

- Clinical or biochemical evidence of hyperandrogenism
- Chronic anovulation
- Imaging of polycystic ovaries, using specific ultrasonographic criteria, and other diagnoses excluded

Investigations

1. Free testosterone level
   (In PCOS: high normal or slightly elevated serum free and total testosterone levels are expected)
2. 17-$\alpha$ hydroxyprogesterone (to screen for congenital adrenal hyperplasia)
3. Dehydroepiandrosterone sulfate (reflecting mainly adrenal cause of hyperandrogenism)
4. Prolactin, LH/FSH levels
   (*The OC may be contraindicated if prolactin is raised. The LH/FSH ratio is not considered as important a diagnostic point as thought previously*)
5. Fasting glucose
6. Serum insulin levels (not routine test)
7. Pelvic ultrasound

## 76.5 Management of PCOS

PCOS is treatable, but not curable, with medications, diet, and exercise. Early detection and careful management can prevent many serious PCOS-related complications. Management is best carried out by a multidisciplinary team also including endocrinologist/gynecologist/dermatologist/psychologist/dietician, since lifestyle adjustment is vitally important where indicated. In addition, full patient information on available treatments and the expected timeline to see improvement are all important in achieving and maintaining the patient's trust and compliance.

Traditionally, management of PCOS consisted mainly of ovulation induction, treatment of acne and hirsutism, and prevention of endometrial cancer. However, with mounting evidence showing that PCOS is associated with dysmetabolic syndrome and an increased risk for developing diabetes and heart disease, this can no longer be our sole focus. Current data

[1] Valproate therapy for epilepsy is associated with weight gain in approximately 50 % of women patients. Hyperinsulinemia and high serum levels of insulin-like growth factor-binding protein 1 may lead to hyperandrogenism and polycystic ovaries [29].

**Table 76.1** PCOS with acne: initial management

| |
|---|
| Lifestyle management |
| *The hormones* |
| OC with drospirenone OR Cyproterone acetate |
| *The insulin resistance* |
| Metformin (alone if OC contraindicated—patient desires pregnancy, heavy smoker, age OR in combination with OC) |
| **It is CRUCIAL to continue hormonal and/or insulin resistance measures on a long-term basis. This limits recurrence of acne and reduces possibility of long-term sequelae from metabolic syndrome** |

support a strong recommendation that women with PCOS should undergo comprehensive evaluation for diabetes and recognized cardiovascular risk factors and receive appropriate treatment as needed (Table 76.1). Lifestyle modifications remain the first-line therapy for all obese women with PCOS. However, many obese women with PCOS find weight loss difficult to achieve and maintain, and this is not an option for lean women with PCOS. For these reasons, insulin-sensitizing drugs are proving to be a promising and unique therapeutic option for chronic treatment of PCOS [24].

The different and often interrelated factors that must be addressed to achieve successful outcome both in the short- and long-term include:

1. Lifestyle and psychological (stress and anger) issues
2. Hyperandrogenism
3. Insulin resistance

### 76.5.1 Lifestyle and Psychological (Stress and Anger) Issues

A crucial step for the patient is to lose weight if overweight, to exercise, and to stop smoking (an additional risk factor for thrombosis if an oral contraceptive is considered, and also a risk factor for long-term cardiovascular complications) if a smoker. Most patients will find this difficult to achieve and do not seek expert help.

Psychological comorbidity in acne is often its most disabling feature [30]. Stress (and anger) [31] can be major factors in both provoking acne and perhaps aggravating PCOS as well as making successful outcomes more difficult. IVOTE is a recognized method of dealing with these factors **and** can be applied to ALL patients before they become angry:

**I**nquire about how acne affects the patient's social life, emotions, self-esteem, ability to do their work (or studies), and their leisure activities.

**V**alidate their experience by acknowledging the importance of these impacts of acne on them and the quality of their life.

**O**ffer to discuss ideas for reducing the negative impact and for finding additional resources (e.g., readings, referral) to help further.

**T**ell patients that you are committed to helping them with symptom management as well as the negative impact that acne has on their QOL.

**E**valuate quality of life (QOL) when you monitor the other outcomes such as severity, adherence, and satisfaction with treatment.

### 76.5.2 Hyperandrogenism

The primary goal of pharmacologic therapy for cutaneous disorders of hyperandrogenism is reduction of androgen production and action. Hormonal treatments can be effective for females with acne whether or not their serum androgen levels are abnormal [9, 12].

They include anti-androgens (androgen receptor blockers) or agents designed to decrease the endogenous production of androgens by the ovary or adrenal gland, such as oral contraceptives, low-dose glucocorticoids, or gonadotropin-releasing hormone (GnRH) agonists. Hormonal therapies will be briefly outlined, as they are discussed in detail elsewhere in this book.

Anti-androgens, or androgen receptor blockers, are defined as agents that inhibit directly the binding of dihydrotestosterone (DHT) to its receptor in a competitive way. They include cyproterone acetate, drospirenone, spironolactone, and flutamide.

#### 76.5.2.1 Oral Contraceptives with Cyproterone Acetate or Drospirenone

Combined oral contraceptives exert their action either by suppressing the secretion of pituitary gonadotropins, thereby inhibiting ovarian androgen production, or by increasing liver synthesis of sex hormone-binding globulin (SHBG). Some progestins (*cyproterone and drospirenone*) may have potential added advantages due to specific anti-androgen effects. Cyproterone acetate is combined with ethinyl estradiol 35 μg but may also be used separately or in addition [32] Drospirenone is combined with ethinyl estradiol 30 μg. Both agents similarly resulted in 60 % reduction in acne [33].

Oral contraceptives (OCs) can be initiated in patients with no contraindications. This approach may not be appropriate in mature females because of increasing thromboembolic risks [12]. A pelvic exam and Pap smear are no longer required for the initiation of hormonal contraception in most women of childbearing potential [34]. In case of combination therapy with oral antibacterials and oral contraceptives, there is lack of scientific evidence supporting the ability of antibiotics to reduce either blood levels and/or the effectiveness of oral contraceptives, with the exception of rifampin (rifampicin)-like drugs [35]. If the patient's acne has not significantly improved with an OC after 3–6 cycles, an androgen receptor antagonist (cyproterone, spironolactone, flutamide) or insulin sensitizers such as metformin can be added [36], but these agents can also be used in combination initially.

#### 76.5.2.2 Androgen Blockers

Spironolactone has both anti-androgenic and antimineralcorticoid properties and is effective at doses of 50–200 mg daily. Side effects include occasional irregular menstrual bleeding and breast tenderness. Because of its potential for causing abnormalities in fetal development (particularly in male genitalia development), spironolactone should be avoided in women desiring pregnancy or combination oral contraceptives should be used in conjunction for contraception and synergistic effects.

Spironolactone functions both as an androgen receptor blocker and an inhibitor of 5-α reductase. In doses of 50–100 mg twice daily, taken with meals, it has been shown to reduce sebum excretion rate by 30–50 % and improve acne. However, many women with sporadic outbreaks of inflammatory lesions or isolated cysts respond well to 25 mg twice daily, and some even respond to just 25 mg/day [37]. In addition, it is contraindicated in women at increased risk of breast cancer [14].

#### 76.5.2.3 Low-Dose Corticosteroids

They can be used in case of adrenal hyperandrogenism or in patients with severe inflammatory acne on a short-term basis.

### 76.5.3 Insulin Resistance

#### 76.5.3.1 Diet

Diet is a crucial part of management in overweight patients. Given the current recommendation for insulin sensitizers, interest in dietary management with low glycaemic index regimens has re appeared [38], although genetic factors are also very relevant in this regard [39].

#### 76.5.3.2 Insulin Sensitizers: Metformin—Thiazolidinediones

Insulin-sensitizing agents have been reported to be effective as off-label treatment in treating hirsutism. Insulin-sensitizing agents not only improve the menstrual and metabolic abnormalities associated with PCOS, but may decrease hyperandrogenism. Insulin-sensitizing drugs have been shown to decrease free serum testosterone levels by reducing ovarian androgen synthesis and increasing sex hormone-binding globulin levels [40–43].

Women with PCOS treated with combination therapy involving oral contraceptive pills, anti-androgen, and insulin-sensitizing agents also have improvements in multiple metabolic

abnormalities in addition to improvements in hirsutism and circulating serum androgen levels.

In other studies, PCOS patients treated with metformin alone showed improvement in acne and hirsutism score, restarted normal menstrual cycles, some fulfilled their wish to conceive when previously unsuccessful, and attained a decrease of insulin, glucose, and androgen levels. These improvements occurred in both obese and lean individuals [44, 45].

Pharmacological treatment of hyperinsulinemia, such as with insulin sensitizers like metformin, has consistently improved circulating androgen levels.

Side effects of metformin [46] include nausea and other upper gut symptoms, which are common and the most frequent treason for discontinuation of therapy. Dosage should start at the lower end 500 mg once daily after food and increased gradually. Doses of up to 1,700 mg daily are commonly used. Patients should be advised that gastrointestinal problems often abate after a week or two, but a significant number still have to discontinue therapy on this account. Occasional mild episodes of hypoglycemia may occur in a small number of patients.

**Prevention of Lactic Acidosis**
**(The Most Serious Potential Complication of Biguanide Drugs)**

During treatment, renal function should be monitored regularly especially during significant intercurrent illness with the potential to alter renal function (dehydration, shock, and sepsis) or increase the risk of tissue hypoxia and acidosis (such as acute myocardial infarction, pulmonary embolism, and cardiac failure). All these can trigger lactic acidosis, and the dose of metformin should be significantly reduced or the drug discontinued altogether. Furthermore metformin be withheld for 24–48 h before the use of iodinated contrast agents and be recommenced 48 h afterwards.

**Table 76.2** PCOS with acne: management of relapses

| Lifestyle management |
|---|
| *The hormones* |
| *REINSTITUTE IF DISCONTINUED* |
| OC with drospirenone OR Cyproterone |
| *The insulin resistance* |
| Metformin (alone if OC contraindicated—patient desires pregnancy, heavy smoker) |

## 76.6 PCOS and Acne Relapse

While relapses after isotretinoin are not infrequent [47] women with PCOS may experience only partial emission with isotretinoin therapy and are more prone to relapse if the hormonal problem is not adequately addressed [48, 49]. This has clear implications for both initial and follow-up management. This may be due to failure to manage hormonal problem (in females) and lifestyle issues on a long-term basis (Table 76.2).

To prevent acne relapse, continuing with an OCP such as cyproterone acetate 2 mg/ethinyl estradiol 35 μg and/or metformin may reduce recurrence of acne in the female acne patient.

### 76.6.1 PCOS in Teenagers: Frequently Asked Questions

Some questions may arise depending on the age of onset and comorbidities of untreated PCOS:

Q: Even when the diagnosis of PCOS has been well established, should the condition be managed symptomatically or prophylactically at a young age?

Are those to whom the adolescent is referred sufficiently aware of the importance of lifestyle intervention for the symptoms and possible sequelae of the syndrome?

More specifically, is there a place for long-term treatment with insulin sensitizers starting in adolescence?

A: The hormonal abnormalities inherent in PCOS often begin in adolescence and include hyperinsulinemia and rapid LH pulse frequency, both of which mediate ovarian and adrenal overproduction of androgens.

Recognizing and reducing androgen levels in adolescence are critical given their association with the metabolic syndrome, diabetes, and infertility in adulthood [50].

"For how long?—still up for debate but getting longer and longer … and longer!"

## Conclusions

PCOS is prevalent in women with late-onset acne, persistent acne, and acne resistant to conventional therapies. PCOS may present with acne as its sole clinical manifestation and many studies showed a high prevalence of PCOS in acne patients. The increase in PCOS has been linked to increasing stress in everyday life and childhood obesity.

The associated insulin resistance is of prime importance as hyperinsulinemia plays a key role in PCOS pathogenesis. Growing evidence indicates that elevated serum insulin induces hyperandrogenism; thus both androgens and insulin resistance need to be managed. PCOS is thus the most common disorder in which the association between insulin resistance and ovarian function appears to be important. Androgens and stress [32] both stimulate the pilosebaceous unit—microcomedo, inflammation, colonization with *P. acnes*. Androgens may be increased, by hyperinsulinemia as found in PCOS. Stress may also be an important factor in triggering the PCOS from relatively benign polycystic ovaries [7, 8].

The primary goal of pharmacologic therapy for cutaneous disorders of hyperandrogenism is reduction of androgen production and action. Certain OC with specific antiandrogen effects, spironolactone, and metformin given alone or in combination have proved useful, with metformin now acknowledged as a primary off-label treatment for PCOS. Even after isotretinoin therapy, long-term "hormonal control" with OC and/or metformin (as sole therapy if patient wishes to become pregnant) may reduce possibility of relapse and also address potential long-term problems such as the metabolic syndrome. The PCOS is treatable, but not curable, with medication, diet, and exercise. Early detection and careful management can prevent many serious PCOS-related comorbidities from occurring later in life.

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# The SAPHO Syndrome

# 77

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## Contents



**Core Messages**

- The acronym SAPHO (synovitis, acne, pustolosis, hyperostosis, and osteitis) was coined in 1987 to designate a syndrome combining musculoskeletal and skin disorders of which the most common are palmoplantar pustolosis and severe acne.
- The etiopathogenesis of the SAPHO syndrome is unknown. The two major theories currently proposed include (1) a form of spondyloarthritis and (2) infection, in particular with *Propionibacterium acnes*.
- The SAPHO syndrome is strictly related to the spondyloarthitides, in particular to psoriatic arthritis, and many SAPHO cases meet the classification criteria for these diseases.
- The pathogenetic role of *P. acnes* in the SAPHO syndrome is still sub judice. Some studies frequently isolated the bacterium in bone lesions and synovial tissue and fluid of patients with the syndrome. Others found the microorganism only occasionally.
- The musculoskeletal manifestations of the SAPHO syndrome include hyperostosis, osteitis, and synovitis.
- The skin conditions observed in the SAPHO syndrome include palmoplantar pustolosis, pustular psoriasis, acne

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fulminans, acne conglobata, and hidradenitis suppurativa. These are observed only in one-third of the patients.
- Treatments thought to be beneficial include antibiotics, calcitonin, bisphosphonates, and anti-tumour necrosis factor α (TNFα) agents.
- Bisphosphonates and anti-TNFα agents are considered today the most efficacious drugs against the musculoskeletal manifestation of the SAPHO syndrome. These are often effective on skin lesions.

## 77.1 Introduction: Definitions

The SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome describes an association between skeletal disorders consisting of bone lesions and arthritis and various dermatologic conditions; the most frequent of these are palmoplantar pustolosis and severe acne. The acronym SAPHO was firstly proposed by Chamot and co-workers [1]. Although typical cases have been described in several countries beginning from 1961, under more than 40 different acronyms and denominations including acne induced arthritis, arthro-osteitis associated with severe acne, and recurrent multifocal osteomyelitis [2–4]. Diagnostic criteria proposed by the French authors include (1) osteoarticular manifestations of palmoplantar pustolosis, severe acne (conglobata or fulminans), or hidradenitis suppurativa; (2) hyperostosis of anterior chest wall, spine, pelvis, or limb, with or without dermatosis; or (3) chronic recurrent multifocal osteomyelitis with or without dermatosis [2, 5].

## 77.2 Epidemiology

The SAPHO syndrome has long been considered a rare condition and its exact prevalence is unknown. It must be more frequent than it was thought since many cases are not recognised. Most reports are from Japan [6, 7] and western and northern continental Europe [1–5, 8–13]. There are relatively few reports from the UK, the USA, Canada, and Australia [14, 15]. It is unknown if these discrepancies are due to differences in the incidence of the disease or to difficulties in making the diagnosis. The disease can occur in all age groups but is more frequent in children and in young and middle-aged subjects. There is a female preponderance in the forms associated with palmopustular hyperostosis [6–8, 10–12, 15] and a male predominance in those occurring together with acne conglobata [1, 2, 4].

## 77.3 Aetiology and Pathogenesis

The etiopathogenesis of the SAPHO syndrome is unknown. The two major theories currently proposed include (1) a form of spondyloarthritis and (2) infection, in particular with *Propionibacterium acnes*, a gram-positive anaerobic bacillus component of the normal flora of the skin and mucosae.

The spondyloarthritis complex includes diseases with common manifestations and shared genetic predisposition linked to the HLA-B27 antigen [16, 17]. These are ankylosing spondylitis, reactive arthritis, psoriatic arthritis, arthritis associated with inflammatory bowel diseases, and forms that fail to meet criteria for definite categories, which are designated as undifferentiated spondyloarthritis. The SAPHO syndrome shares clinical manifestations with spondyloarthritis. Sacroiliitis, spondylitis, and peripheral enthesitis are common in patients with SAPHO syndrome. Pustular psoriasis, psoriasis vulgaris, and inflammatory bowel disease have been described in several patients. The frequency of HLA-B27 is higher in patients with the SAPHO syndrome than in the general population. Two French studies evaluated the performance of the classification criteria for all forms of spondyloarthritis in patients with SAPHO syndrome [9, 18]. In the first, 7 out of 21 patients met the European Spondylarthritis Study Group (ESSG) criteria [9]. In the second, 7 out of 15 patients met the Amor criteria [18]. If palmoplantar pustolosis is considered a psoriatic criterion, the number of

patients meeting the criteria rises to 11 (55 %) in the first study and to 10 (67 %) in the second. Therefore, psoriasis was suggested to be the missing link between SAPHO syndrome and spondyloarthritis.

The pathogenetic role of *P. acnes*, a bacterium implicated in the pathogenesis of comedones and acne, relies on several reports documenting culture of the microorganism from biopsy specimens of involved bones. Eduld et al. [19], Wagner et al. [20], and Kircoff et al. [21] isolated *P. acnes* from bone specimens in 7 out of 15, 7 out of 11, and 8 out of 14 patients with the SAPHO syndrome, respectively. In contrast, other studies have only occasionally found the microorganism [8, 10, 22]. There are also contrasting data on the efficacy of antibiotic therapy. Therefore, the role of *P. acnes* in the pathogenesis of the SAPHO syndrome remains under consideration.

## 77.4 Clinical Manifestations

### 77.4.1 Musculoskeletal Manifestations

The musculoskeletal manifestations of the SAPHO syndrome include hyperostosis, osteitis, and synovitis. Hyperostosis is a consequence of abnormal osteogenesis. It becomes visible on X-rays with bony enlargement, sclerosis, and increased bone density [5]. Osteitis is the histopathologic finding in the involved bones [4]. In the early phase of the disease evolution, there is an infiltration of polymorphonuclear cells indistinguishable from that of bacterial osteomyelitis. Bone scans routinely revealed increased uptake of $^{99m}$Tc-phosphonate in the affected areas. Subsequently, the mononuclear cells become prevalent, and in the late stages of the disease course, osteoclasts and osteoblasts are seen around the sclerotic and enlarged bone trabeculae.

The most frequent site of involvement is the upper anterior chest wall [1, 7–9, 12, 15] (Fig. 77.1). Any of the local structures may be involved including the sternoclavicular joints, costomanubrial and costochondral joints, or the manubriosternal joint, the sternum, the clavicles, and the anterior portion of the ribs [4, 5]. Pain, tenderness, and swelling over the affected joints and bones are the hallmark of the syndrome [4, 5]. The pain may be diffuse and severe and needs to be differentiated by other causes of chest wall pain. Other sites of the axial skeleton that may be involved in isolation, or in addition to the chest wall, include the ilium and the vertebrae [5, 9, 15]. Vertebral involvement occurs in up to one-third of cases and presents itself as chronic lumbosacral, dorsal, or cervical pain. Radiographically, spondylodiscitis consisting in erosion of the vertebral plates with reactive sclerosis is the most common feature. Other findings include isolated vertebral sclerosis, syndesmophytes, and paravertebral ossification [1, 7, 9, 12]. Sacroiliitis is seen in up to one-third of patients and, unlike that observed in ankylosing spondylitis, is primarily unilateral and associated with hyperostosis [7, 9, 12]. Long tubular bones, especially those of the lower limbs, can also be the sites of hyperostotic and sclerotic lesions of the SAPHO syndrome [4, 5]. Similarly to the axial skeleton involvement, symptoms

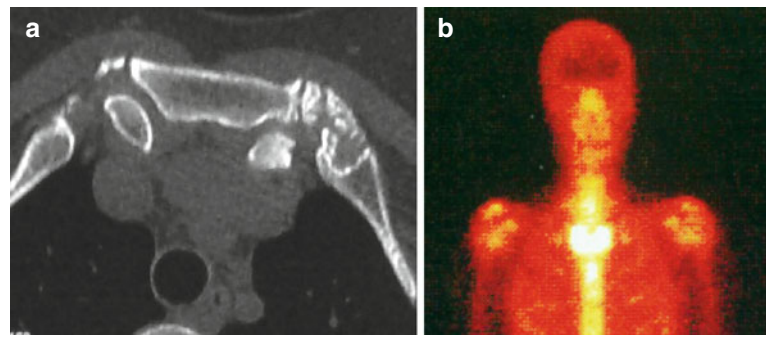


**Fig. 77.1** The SAPHO syndrome involving the chest wall. (**a**) CT scan showing hyperostosis, sclerosis, and erosion at the right sternoclavicular joint. (**b**) the scintigraphic scan demonstrating increased uptake at the same affected areas

include pain, tenderness, and swelling. Synovitis occurs in about one-fifth of cases and usually affects few larger joints asymmetrically [5, 7, 9].

## 77.5 Cutaneous Manifestations

About two-thirds of patients with the SAPHO syndrome have skin involvement [1, 12]. The characteristic skin condition of the SAPHO syndrome is palmoplantar pustolosis which affects about half the patients. The other half has acne fulminans, acne conglobata, pustular psoriasis, hidradenitis suppurativa, and, rarely, Sweet's syndrome and pyoderma gangrenosum [4, 5]. The course of skin and musculoskeletal lesions are not necessarily synchronous, with pustular skin lesions noted up to 20 years after bone lesions. Skin lesions may be absent or so mild to go unrecognised [23, 24]. Terms such as sterno-costo-clavicular hyperostosis, chronic recurrent multifocal hyperostosis, and the acquired hyperostosis syndrome have been utilised to describe the skeletal manifestations occurring in the absence of cutaneous lesions [4, 5].

## 77.6 Treatment

The treatment of the SAPHO syndrome is empiric [5, 8, 15]. Since no large controlled trials have been reported, the choice of medications in clinical practice has been based on anecdotal experiences or small case–control cases. Non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics are the first choice but have limited efficacy. Oral corticosteroids can be used in the most severe forms. Some patients respond and the dosage can be tapered after the resolution of the flare. Local injections of steroids can be useful for the management of peripheral arthritis and peripheral enthesitis. Second-line drugs, including sulphasalazine, cyclosporine, methotrexate, and leflunomide, have been tried with contradictory results [4, 5, 8, 15].

Treatments thought to be beneficial include antibiotics, calcitonin, bisphosphonates, and anti-tumour necrosis factor α (TNFα) agents.

Antibiotics have been tried after the reported isolation of *P. acnes* from the bone biopsies of patients with the SAPHO syndrome [19, 20]. The inefficacy of antibiotic treatment in patients whose bone cultures grew *P. acnes* suggests that the process is not totally septic and that *P. acnes* may act as an antigen provoking an immunological reaction [19]. Tetracycline [25], clindamycin [26], and macrolides [27] are thought to be of some benefit. Macrolides, especially azithomycin, have been effective in some cases, possibly as a result of their anti-inflammatory and immunomodulating properties [27].

Calcitonin, which reduces bone turnover, was beneficial in some cases of the SAPHO syndrome [28, 29]. This depends probably on the increased bone turnover, observed in biopsy specimens of the SAPHO syndrome. In the last few years, bisphosphonates, which are synthetic analogues of pyrophosphate and potent inhibitors of bone resorption, have been studied in the SAPHO syndrome [30–33]. There is also evidence that bisphosphonates may exert beneficial anti-inflammatory properties by suppressing interleukin-1β, TNFα, and interleukin-6 [34].

There is today great evidence suggesting that anti-TNF agents are highly effective in the spondyloarthritides, especially in ankylosing spondylitis and psoriatic arthritis [35]. All the three available drugs, infliximab, adalimumab, and etanercept, have been approved for ankylosing spondylitis and psoriatic arthritis. On the basis of this background we treated two patients affected by refractory SAPHO syndrome with infliximab [36, 37]. Both patients had chest pain limiting normal activity despite adequate treatment with NSAIDs and had failed second-line therapy. Both received three intravenous infusions of infliximab (5 mg/kg) at weeks 0, 2, and 6. In both cases, pain and local signs of inflammation on the clavicles and sternum disappeared. In one patient, severe acne dramatically improved. The results were maintained in the following 18 months. Wagner and his co-workers have reported a sustained clinical effect of TNFα blockage over a 9-month period in other 2 patients with SAPHO syndrome [38]. They have found significant amounts of TNFα production in biopsy

specimens from different sites. The efficacy of infliximab on the acne fulminans of SAPHO syndrome has also been reported by Iqbal and Kodney [39]. More recently, Massara et al. have treated with infliximab four patients with SAPHO poorly responding to conventional therapy [40]. A complete remission of osteoarticular manifestations was obtained and maintained for 12 months. Palmoplantar pustolosis relapsed in two patients during treatment, suggesting that cutaneous involvement responds less favourable than the rheumatological manifestations. Infliximab achieved also excellent results in two young patients with chronic multifocal osteomylitis localised in facial bones [41] and clavicula [42], respectively. Both cases have been resistant to steroid therapy. In the first patient, the anti-TNFα agents interrupted a disease course of 10 years. The therapy of the SAPHO syndrome with anti-TNF blocking agents has recently been reviewed [43]. In conclusion, the results of these studies suggest that TNFα blockage is efficacious in the SAPHO syndrome and that the positive effects may also persist for a long time even after the end of the treatment.

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# The PAPA Syndrome

# 78

Mosaad Megahed, Melanie Wosnitza, and Claudia N. Renn

## Contents



**Core Messages**

- **P**yogenic aseptic **a**rthritis, **p**yoderma gangrenosum, and **a**cne (abbreviated PAPA) form the PAPA syndrome, which belongs to the hereditary autoinflammatory disorders.
- PAPA syndrome is characterized by unprovoked recurrent systemic inflammatory episodes involving mainly joints and skin. This is due to a primary dysfunction of the immune system that originates from an autosomal dominant inherited defect of the CD2-binding protein (CD2BP1). CD2BP1 is mainly expressed on neutrophils, the inflammatory cells most implicated in this syndrome.
- Patients with PAPA syndrome suffer from early onset of destructive, recurrent pyogenic arthritis, often occurring spontaneously or after minor trauma and leading to serious joint destruction.
- Cutaneous symptoms present at the time of puberty and include severe acne conglobata and pyoderma gangrenosum.
- The PAPA syndrome should be considered in the differential diagnosis of patients presenting with pyoderma gangrenosum or severe acne conglobata. Early onset of serious courses of acne, pyoderma gangrenosum, or optional seronegative arthritis with unremark-

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able laboratory findings is highly suggestive of the PAPA syndrome.
- Complementary genetic analysis is useful in the management of these patients, and treatment should be commenced early in order to prevent severe scarring, joint destruction, and avoidable complications.
- Treatment comprises of corticosteroids and biological response modifiers, such as etanercept, infliximab, anakinra, and mycophenolate mofetil. However, treatment recommendations in the PAPA syndrome still vary from report to report, and further studies are necessary before specific guidelines for the management of this complex condition can be formulated.

## 78.1 Introduction: Definition and Synonyms

The PAPA syndrome is a very rare autoinflammatory disorder and is a clinically allotropic syndrome affecting both joints and skin (OMIM #604416). Depending on the clinical manifestations, some authors use the term familial recurrent arthritis (FRA) as a synonym for PAPA syndrome, if early childhood arthritis and joint destruction are the dominant clinical features [1].

The PAPA syndrome is listed in the section "rare diseases" by the Office of Rare Diseases of the National Institute of Health (NIH) in the USA. It is inherited in an autosomal dominant manner with variable expression and discriminative clinical phenotypes without sex predilection. Until today only a few families worldwide have been discovered to suffer from PAPA syndrome (2 in the USA, 1 in Germany, 1 in Italy, 1 in the Netherlands, and 1 in New Zeeland) [1–9]. Several reports can be found in the literature about an association of severe acne, hidradenitis suppurativa, and pyoderma gangrenosum with seronegative arthritis [10–12]. This suggests that previous cases of PAPA syndrome may have existed.

## 78.2 Pathogenesis

The PAPA syndrome is characteristically self-limiting and belongs to a group of syndromes called "hereditary autoinflammatory syndromes" or "familial periodic fever syndromes," even though there is no intrinsic periodicity to the inflammatory episodes. All syndromes in this group share a common phenotype including unprovoked autoinflammation with various symptoms.

Due to systemic inflammation lacking high-titer autoantibodies, pathogens, or self-reactive T cells, these disorders can be distinguished from autoimmune diseases [13]. Although the precise pathogenesis is only partly understood, the autoinflammatory process is believed to be due to a primary dysfunction of a protein that regulates inflammation in the native immune response. The defect is caused by a missense mutation in the proline–serine–threonine phosphatase interacting protein 1 (PSTPIP1) gene located on chromosome 15q (Fig. 78.1). This gene encodes for the CD2-binding protein (CD2BP1) [1, 8, 9]. CD2BP1 is primarily expressed on hematopoietic cells and displays a CD2 cytoplasmic tail-binding protein which is involved in the regulation of the actin cytoskeleton. The defect is transmitted in an autosomal dominant fashion with variable expression but complete penetrance at the point of adolescence. Affected patients are karyotypically normal and show no association to histocompatibility locus antigens (HLA) regions.

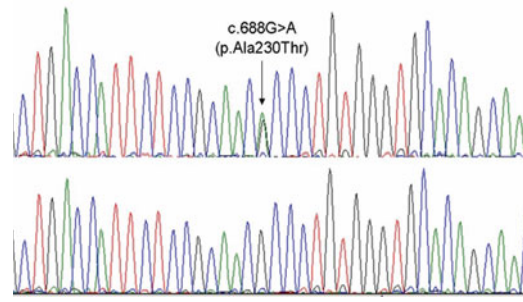


**Fig. 78.1** Missense mutation in the CD2BP1 gene (c.688G>A, p.Ala230Thr) in a PAPA syndrome patient (With courtesy from T. Kleefstra, MD, PhD, Department of Human Genetics, Radboud University Nijmegen Medical Centre, Netherlands)

The PAPA-associated PSTPIP1 gene is highly expressed in neutrophilic granulocytes and PSTPIP1 mutants are very effective in inducing pyrin activation. This in turn leads to increased production and activation of interleukin-1 beta (IL-1β), a potent inflammatory protein [14–17]. The wide range of effects of IL-1β comprises participation in tumor necrosis factor alpha (TNF-α) production [2], fever induction, extravasation of neutrophilic granulocytes, and inhibition of neutrophilic granulocyte apoptosis [18]. Further mutants of CD2BP1 can also result in decreased apoptosis [13]. This explains the autoinflammatory phenotype seen in PAPA syndrome which is dominated by neutrophilic dermatoses and neutrophil-rich sterile effusions of the joints [1, 19]. Pyrin and CD2BP1 are moreover part of an inflammatory pathway associated with the familial Mediterranean fever (FMF), a prototypic disease in the group of auotinflammatory disorders [16].

## 78.3 Symptoms in PAPA Syndrome

The variegated manifestations of the PAPA syndrome are primarily characterized by neutrophilic predominance in the inflammatory lesions. Cutaneous symptoms exhibit strong neutrophilic infiltrations in affected areas [19]. Dermatologic findings include severe cystic acne with subsequent scarring in untreated patients. Peculiar early onset before puberty and persistence into late adulthood is a feature as well. Patients are affected to a variable degree by pyoderma gangrenosum including pathergy as a characteristic feature (Fig. 78.2). This refers to the predisposition of developing new pyoderma gangrenosum lesions at the sites of slight trauma, biopsy, or needle sticks. Sterile abscesses at the site of parenteral injection and hidradenitis suppurativa have been documented in some family members.

Major features also include a multigenerational involvement of relapsing, aseptic, pauciarticular, nonaxial, destructive arthritis, beginning in childhood [1, 5, 7]. Often the inflammatory episodes occur unprovoked or after minor

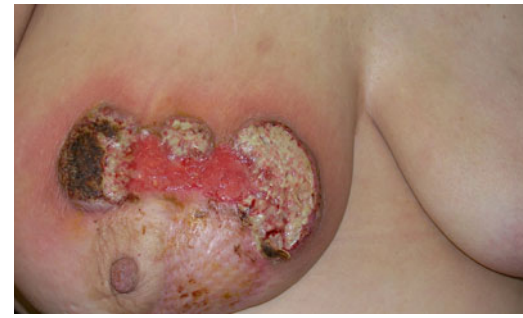

**Fig. 78.2** Pyoderma gangrenosum in a patient with PAPA syndrome

trauma leading to synovial inflammatory episodes dominated by neutrophils. Drained synovial fluid is seropurulent or purulent, but examinations for bacterial or fungal infection as well as laboratory investigations for autoantibodies or antigen-specific T cells are all negative [5, 6, 20]. Radiological findings demonstrate periosteal proliferation, osteophytes with diffuse joint space narrowing, cyst formation, and subchondral sclerosis, leading to ankylosis of the affected joints or cervical spine in some patients [5, 7]. Characteristically, inflammatory episodes of arthritis persist in the majority of cases until treated with surgical drainage, intraarticular steroids, or biological response modifiers [3, 8].

Affected patients may not exhibit the whole spectrum of PAPA symptoms clinically since manifestation is dependent on the individual expression.

## 78.4 Diagnosis and Evaluations

Personal and familial history reveals relapsing aseptic arthritis resulting in joint destruction. Skin symptoms include ulcer formation after minor trauma with rapid extension within a few days. Additionally patients have a history of severe acne starting early before puberty and lasting into adulthood. Scarring can be noted at the sites of former ulceration or acne.

In some cases laboratory findings reveal elevated inflammatory markers such as elevated CRP, IL-1β, and TNF-α levels but are otherwise unremarkable. Laboratory evaluations exhibit

negative results for ANA, ENA, ANCA, anti-ds DNA, rheumatoid factor, lupus anticoagulant, rapid plasma reagin, and cryoglobins. Serum alfa1-antitrypsin levels, total complement levels, C3, C4, and coagulation studies are likewise normal. Drained synovial fluid is sterile and cultures of skin tissue do not grow any mycobacteria, atypical mycobacteria, or fungi. X-ray studies of involved joints reveal characteristics of severe destructive arthritis. This comprises typical signs like osteophytes, diffuse joint space narrowing, subchondral sclerosis, and cyst formation. Additionally ankylosis can be a feature. Genetic analysis demonstrates a normal karyotype and a missense mutation in the PSTPIP1/CD2BP1 gene located on chromosome 15q.

**Skin biopsy**

In skin biopsy, the cutaneous ulcerations in PAPA syndrome show histologically features which are consistent with pyoderma gangrenosum, namely, inflammatory edematous infiltrate of lymphocytes and neutrophils. Endothelial swelling and fibrinoid necrosis of vessel walls may also be present.

## 78.5 Differential Diagnosis

In cases with pyoderma gangrenosum as the dominant clinical feature, differential diagnoses include other conditions that can cause severe ulcerations similar to that of pyoderma gangrenosum. These conditions are summarized in Table 78.1.

Differential diagnosis in patients with acne conglobata comprises mainly rosacea, perioral dermatitis, folliculitis, and pseudofolliculitis barbae.

In addition juvenile idiopathic arthritis [1], familial Mediterranean fever syndrome, and synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome range among differential diagnoses in patients with joint involvement [22, 23]. Arthritis in PAPA syndrome differs from juvenile idiopathic arthritis in (a) its recurring episodes of pyogenic, (b) aseptic joint involvement, (c) in the association with skin symptoms, and (d) in its autosomal dominant inheritance. Familial Mediterranean fever is characterized by its irregular periodicity of attacks with fever, monoarthritis, sacroiliitis, and polyserositis and its autosomal recessive inheritance. Skin lesions are seen in some patients and present as erysipelas-like rash, scrotal pain, and swelling. SAPHO syndrome is an acronym for synovitis, acne, pustolosis, hyperostosis, and osteitis syndrome revealing cutaneous symptoms like palmoplantar pustulosis, severe acne conglobata, and hidradenitis suppurativa. In adults with arthritis and fever, systemic lupus erythematosus (SLE) and other causes of arthritis as rheumatoid arthritis or ankylosing spondylitis should be excluded as well.

**Table 78.1** Conditions causing severe ulceration ([21], modified)

| | |
|---|---|
| Vascular occlusive or venous disease | • Venous stasis ulceration<br>• Antiphospholipid-antibody syndrome<br>• Livedoid vasculopathy<br>• Small-vessel occlusive arterial disease<br>• Type I cryoglobulinemia |
| Vasculitis | • Polyarteritis nodosa<br>• Cryoglobulinemic vasculitis<br>• Wegener's granulomatosis |
| Cutaneous involvement of malignant process | • Lymphoma<br>• Leukemia cutis<br>• Langerhans'-cell histiocytosis |
| Primary cutaneous infection | • Deep fungal infection<br>• Herpes simplex virus type 2<br>• Cutaneous tuberculosis<br>• Amebiasis cutis |
| Drug-induced tissue injury | • Hydroxyurea<br>• Injection-drug abuse |
| Exogenous tissue injury | • Factitial disorders<br>• Munchhausen's syndrome |

## 78.6 Treatment of PAPA Syndrome

So far only a few families with PAPA syndrome have been identified. However, there are numerous different approaches how to treat the disease.

In relation to the dominant symptom and its severity in expression, topical or systemic treatment is chosen. Treatment options primarily comprise corticosteroids and biological response modifiers, such as etanercept, infliximab, anakinra, and mycophenolate mofetil.

In the case of severe pyogenic arthritis, synovial fluid of the affected joint should be drained along with intra-articular steroid injections. Prednisone orally can also be considered, optionally in combination with other drugs such as azathioprine [5, 24]. Even though high-dose glucocorticoids work well on arthritis and pyoderma gangrenosum [5, 9], such a treatment is often associated with a flare of acne [5]. Disease-modifying antirheumatic drugs (DMARDs) should be used in young patients with early onset of arthritis to anticipate full expression and further joint destruction. Tallon et al. used sulfasalazine and leflunomide in a young child and were successful in preventing complete expression of his family's phenotype [7]. Shenefelt et al. also treated with sulfasalizne in a PAPA syndrome case [25]. Patients with the PAPA syndrome were found to have aggressive cytokine responses, of both TNF-α and IL-1β. Targeting this pathogenic mechanism, Cortis et al. reported on successful treatment of PAPA syndrome with the TNF blocker etanercept in a glucocorticoid-resistant patient. Etanercept is effectually used in various other diseases with elevated TNF levels as well. Infliximab, a TNF-α monoclonal antibody, is another drug specifically addressing the pathogenic pathway of the PAPA syndrome. Stichweh et al. reported dramatic improvement in a PAPA patient with pyoderma gangrenosum after one infusion of infliximab. A second infusion led to its full clinical remission [26]. Shoham et al. applied anakinra, an IL-1 antagonist, in two patients with PAPA syndrome and induced transient responses [16]. To cut down steroid-resistant flares of PAPA syndrome arthritis, anakinra can be implemented for a period of about 1 week. Dierselhuis et al. treated a 16-year-old boy with anakinra subcutaneously for 1 week and obtained full remission of the arthritis flare [3]. Renn et al. applied a combination of prednisolone and mycophenolate orally together with topical treatment in a PAPA patient demonstrating relapsing episodes of pyoderma gangrenosum. The ulceration healed within 3 months [6].

In addition to systemic treatment in the PAPA syndrome patient with pyoderma gangrenosum, topical treatment can help to relieve symptoms. Topical ulcer treatment may include cautious debridement with silver nitrate, potassium permanganate, or Burrow's solution. Topical and intralesional corticosteroids, topical tacrolimus, and intralesional cyclosporin A have been reported to cause improvement as well. Additionally, bacteriostatic wet dressings may be applied. In cases of pyoderma gangrenosum alone without flaring arthritis, systemic treatment includes glucocorticoids as prednisone or cyclosporin A. In case of resistance to therapy azathioprine is an alternative.

Severe acne conglobata may require systemic treatment with tetracycline antibiotics or isotretionin [25]. In cases of severe scarring dermatosurgery, chemical peelings, and intralesional glucocorticoid injections may help to correct persisting lesions.

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# Acne in Transplantation Patients

# 79

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## Contents



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**Core Messages**

- Acne is a common skin disease in transplant recipients. It is directly related to pharmacological properties of immunosuppressive drugs.
- The average prevalence of acne in transplant recipients is 20–25 %.
- Acne in transplant recipients impairs physical appearance and quality of life. A cause of graft failure among transplant recipients is noncompliance with drugs, particularly in adolescents, who are very concerned by their appearance.
- The clinical aspects of acne in transplantation are different from acne *vulgaris*, and "acne-like eruption" name should be used.
- Three drugs are responsible for acne in transplantation: steroids, cyclosporine, and sirolimus.
- Steroid acne is a folliculitis which develops within the first weeks of treatment and disappear with reducing dosages.
- Cyclosporine acne has a comedonal aspect and develops 2 months after cyclosporine introduction. It is not dose dependent.
- Sirolimus acne is a folliculitis associated with scalp location. It develops within the first weeks of treatment.

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- Isotretinoin can be used starting with low dosages.
- Long-term antibiotics (erythromycin, clindamycin, and cyclines) must be used with care because of potential risk for bacteria to develop antimicrobial resistance.

## 79.1 Introduction

For transplant specialists, the main preoccupation during the first year after transplantation is graft rejection. Then chronic pathologies are dominated by infections and cancer prevention. As the survival of organ transplanted patients improves, prevalence of secondary complications such as mucocutaneous pathologies increases. The two main skin complications, infection and tumoral skin diseases, are induced by chronic immunosuppression. Acne is a common side effect which touches 20–25 % of transplant recipients. It is directly related to pharmacological properties of immunosuppressive drugs.

A cause of graft failure among transplant recipients is noncompliance with drugs, particularly in adolescents, who are very concerned by their appearance. In a recent study, impact of skin diseases following transplantation on quality of life has been evaluated in 173 renal transplant recipients. For 16 % of patients, skin diseases had a significant impact on the quality of life. The greatest impact was in patients who were younger, female, and with multiple skin problems. Acne, itch, and sebaceous hyperplasia were the three skin diseases found to have a significant impact on the quality of life in a multifactorial model of quality of life outcome [1]. In a few publications, severe acne was responsible for drug discontinuation [2]. So, active care of acne is necessary, mainly in adolescents and young adults, first to increase quality of life and also to get a better compliance with immunosuppressive drugs.

Three drugs used in transplantation are known to induce acne: steroids, cyclosporine, and sirolimus. These acnes differ from acne *vulgaris* by their appearance, their evolution, and their physiopathology. They are often considered as acne-like eruption more than true acne. It develops generally during the posttransplant period and tends to regress.

After a brief reminder on the main immunosuppressive drugs used to prevent graft rejection, we will detail the acne caused by the immunosuppressive drugs and try to clarify their management.

## 79.2 Immunosuppressive Drugs in Organ Transplantation

From the 1960s, azathioprine and steroids were referred as conventional immunosuppression for chronic graft rejection. Since the 1980s, cyclosporine has become the most effective and widely used immunosuppressive drug. After 20 years, new immunosuppressive drugs are available in organ transplantation such as tacrolimus, mycophenolate mofetil (MM), and rapamycines. Polyclonal antibodies and recently monoclonal antibodies are used for rejection prevention and treatment of steroid-resistant rejection.

The conventional immunosuppressive regimen (cyclosporine-azathioprine-steroids), have been used for 30 years with good results. The aims of new protocols (new drugs, new immunosuppressive protocols) are to reduce acute and long-time graft rejection, toxicity, and to improve quality of life of organ transplant patients.

### 79.2.1 Azathioprine

Azathioprine is a purine analogue. It is incorporated into cellular DNA and inhibits synthesis and metabolism. It inhibits gene replication and consequent T cell activation. It inhibits the primary immune response and is effective in preventing the onset of acute rejection. The most important side effect is hematologic since the drug is a broad myelocyte suppressant.

### 79.2.2 Calcineurin Inhibitors

#### 79.2.2.1 Cyclosporine

Cyclosporine is a cyclic undecapeptide isolated from the fungus *Trichoderma polysporum*. Its

immunosuppressive effect depends on the formation of a complex with cyclophilin. The complex bind to the calcineurin-calmodulin complex, inhibits the phosphatise activity of calcineurin, and inhibits the phosphorylation of the cytoplasmic subunit of the nuclear factor of activated T cells (NF-TA), a transcription factor required for transcription of interleukin 2 gene and other T-cell activation genes. Nephrotoxicity is the most important side effect of cyclosporine.

#### 79.2.2.2 Tacrolimus

Tacrolimus is a macrolide lactone synthesized by *Streptomyces tsukubaensis*. Its mechanism of action is similar to that of cyclosporine, and it is more immunosuppressive than cyclosporine. Side effects are similar to those of cyclosporine.

### 79.2.3 Mycophenolate Mofetil

The active compound of MM is mycophenolate acid. It is an inhibitor of inosine-monophosphate dehydrogenase, a critical rate-limiting enzyme in de novo synthesis of purine. As lymphocytes are highly dependent on de novo pathway, the antiproliferative action of mycophenolate acid is directed mostly to lymphocytes. Main side effects are digestive (diarrhea) and hematologic (anemia).

### 79.2.4 Rapamycines

#### 79.2.4.1 Sirolimus

Sirolimus was the first drug to be recently licensed in the rapamycine group of immunosuppressive therapy used in renal transplantation. It is a macrolide antibiotic structurally related to tacrolimus and synthesized by *Streptomyces hygroscopicus* fermentation. Its mechanisms of action differ from those of the calcineurin inhibitors. Like tacrolimus, sirolimus binds to FKBP12 immunophilin, but instead of calcineurin inhibitors, it inhibits mTOR (mammalian Target Of Rapamycin), a key protein kinase involved in the transduction signal of cytokines such as interleukin 2 and growth factors. Sirolimus therefore inhibits the T lymphocyte proliferation that occurs in response to stimulation by antigens and cytokine. Recent data suggest that sirolimus could have a protective effect against skin cancer and Kaposi's sarcoma.

Everolimus is a new rapamycine. It has been developed more recently in graft rejection prevention in organ transplantation.

## 79.3 Epidemiology of Acne in Transplantation Patients

It is difficult to really evaluate the prevalence of acne in transplant recipients. It's admitted that it is a "frequent" side effect of immunosuppressive drugs by most dermatologists. Prevalence of acne varies from 2 % in a study of 52 renal transplant recipients from New Zealand [3] to 75 % of men in a group of 80 French renal transplant recipients on sirolimus-based therapy [2]. The average prevalence is 20–25 % (Table 79.1).

The first explanation for these differences of prevalence is that clinical trials are rarely managed by transplant physicians. The prevalence of acne is often lower than post-marketing studies managed by dermatologists. Acne is probably underestimated in clinical trials because only severe aspects are generally reported. A systematic in-depth evaluation of the patients by dermatologists may increase the frequency of acne observed in post-marketing studies. For example, it has been shown in a survey that transplant specialists underestimated frequency of acne, by comparing to the perception of their patients. While transplant specialists considered 23 % of their patients to have acne, 37 % of these patients reported this side effect [20].

But other explanations may be proposed for these large variations of acne prevalence:

- In most studies, there is no definition of what is considered as «acne».
- Immunosuppressive regimens have changed over the last 40 years: new drugs and evolution of drug regimens in maintenance therapy may explain some of the differences.
- Publications refer to quite different populations. They are different according to age, sex-ratio, organ transplanted, immunosuppressive regimens, and duration of transplantation. All these factors can influence the prevalence of acne.

**Table 79.1** Frequency of acne in of organ transplanted patients (studies which focused on skin problems in transplant recipients)

| | Nb of patients | Mean age (y), male/female | Organ transplanted (Nb) | Mean time (m) from transplantation | Immunosuppressive regimens (% of patients) | Percentage of patients with acne or acne-like eruption |
|---|---|---|---|---|---|---|
| *Clinical evaluation* | | | | | | |
| Children | | | | | | |
| Menni S, Italy, 1991 [4] | 32 | 12.8, 12/20 | Kidney | 32 | Cy (34), Cy-St (25), Cy-Aza-St (19), Aza-St (12), Cy-Aza (9) | **16**<br>Only children on steroids<br>Children aged from 12 to 16 y |
| Halpert E, USA, 1991 [5] | 16 | 11, 12/4 | Kidney | 19 | Cy-Aza-St (75), Aza-St (25) | **25**<br>Only adolescent on Cy |
| Euvrad S, France, 2001 [6] | 145 | ni, 75/70 | Kidney (117), liver (14), heart (14) | NI | Cy-Aza-St (78), other (22) | **5** (+14)[a]<br>Only in adolescents |
| Adults (or children + adults) | | | | | | |
| Koranda FC, USA, 1974 [7] | 200 | 30, 122/78 | Kidney | 35 | Aza-St (100) | **63**<br>21 % with maintenance regimen |
| Bencini PL, Italy, 1983 [8] | 105 | 35, 64/41 | Kidney | 40 | Aza-St (100) | Incidence decreases after 3 months |
| Bencini PL, Italy, 1986 [9] | 67 | 34.6, 37/30 | Kidney | 3 | Cy-St (100) | **15** |
| O'Connell BM, USA, 1986 [10] | 107 | | Heart | | | **55** |
| Lugo-Janer G, Puerto-Rico, 1991 [11] | 82 | 35, 51/31 | Kidney | 35 | Cy-Aza-St (65), Aza-St (21), Cy-St (10), CP-St (2), Cy-CP-St (2) | **31**<br>Delay/transplantation: <12 m: 61 %; 12–60 m: 30 %, >60 m: 5 % |
| Lesnoni La Parola I, Italy, 1992 [12] | 140 | 34, 84/56 | Kidney | NI | Cy-St (100) | **27** |
| Hepburn DJ, New Zealand, 1994 [3] | 52 | 43.5, 27/25 | Kidney | 116 | Aza-St (71), Cy-Aza-St (29) | **2** |
| Jensen P, Norway, 1995 [13] | 140 | 47.7, 113/27 | Heart | 60 | Cy-Aza-St (95), Cy-St (4), Cy-Aza (1) | **9** |
| Barba A, Italy, 1996 [14] | 285 | 44.7, 185/100 | Kidney | 87 | Cy-Aza-St (42), Cy-St (36), Aza-St (21) | **9** |
| Salard D, France, 2002 [15] | 86 | 56.7, 55/31 | Liver | 60 | Cy-Ste (85), Tac-St (15), ± Aza (3) | **8**<br>Male > female[$p < 0.05$] |
| Prakash J, India, 2004 [16] | 54 | 37.8, 50/4 | Kidney | 124 | Cy-Aza-St (100) | **6** |

| | | | | | | |
|---|---|---|---|---|---|---|
| Alper S, Turkey, 2005 [17] | 111 | 34, 66/45 | Kidney | 42 | Cy-Aza-St (71), Cy-St (8), Aza-St (7), Tac-Aza-St (6), Cy-Aza (4), MM-Tac-St (3) | **14** |
| Tăranu T, Romania, 2005 [18] | 56 | 27/29 | | | | **20** |
| Belloni Fortina A, Italy, 2005 [19] | 217 | 19.9, 131/86 | Kidney (166), liver (19), heart (28), lung (1), kidney+liver (2), kidney+heart (1) | 79 | Cy-Aza-St (50), Cy-St (18), Tac-St (16), other (16) | **40**<br>Male: 47 %/female: 29 %$^{p = 0.01}$<br>Age at transplantation: <6 y: 17 %/6–12 y: 30 %/>12 y: 52 %,$^{p < 0.0001}$<br>Male: 47 %/female: 29 %$^{p = 0.01}$ |
| Mahé E, France, 2006 [2] | 80 | 48, 48/32 | Kidney | 59 | Sir (100)+MM-St (86)/Aza-St (5)/Tac-St (2)/St (5)/Aza (1) | **46**<br>Male: 75 %/female: 6 %$^{p < 0.0001}$ |
| *Evaluation by a survey* | | | | | | |
| Peters TG, USA, 2004 [20] | 554 | 49.5, 291/263 | Kidney | | Cy-St (100)+Cyc (60), Tac (26), Sir (10) | **37** |

*Nb* number; *ni* no information; *M*/*F* male/female; *m* months; *y* years; physician specialty: *derm* dermatologist, *nephr* nephrologist, *ped* pediatrician; Immunosuppressive drugs: *Aza* azathioprine, *CC* cyclophosphamide, *St* steroid, *Cy* cyclosporine, *MM* mycophenolate mofetil, *Sir* sirolimus, *Tac* tacrolimus

[a]14.5 % of adolescents had acne. Authors considered this acne not associated to immunosuppressive therapy but to age

### 79.3.1 Lack of Evidence: Problems of Definition

In the transplantation literature, there is confusion in the term «acne». Acne, acne-like eruption, sebaceous hyperplasia, and folliculitis can be used indifferently. In some studies, acne is included in "cushingoid changes." In studies concerning adolescents, no distinction is made between acne *vulgaris* and drug-induced acne [4, 17] with the exception of one study. But in this study, authors don't explain the differences [6]. In a study on acne in renal transplant recipient on sirolimus-based therapy, we tried to give a definition to acne: "Acne was defined as the presence of follicular papules or pustules, comedones, or nodules in usual sebaceous areas." Finally, we concluded that sirolimus induces acne-like eruption but not acne [2].

### 79.3.2 Evolution of Immunosuppressive Regimens

In older studies, steroids, azathioprine, and cyclosporine were the only drugs used for maintenance therapy. Populations were homogenous for immunosuppressive regimens. Recently, with new drugs—i.e., tacrolimus, mycophenolate mofetil, and sirolimus—in a same study, different regimens were included [15, 17, 19, 20]. In one study, the inclusion criterion to be evaluated was to receive sirolimus-based therapy, but in fact patients were on five different drug regimens [2]. In fact, even in homogenous regimens, we can observe large difference in prevalence. If we compare only studies including patients on cyclosporine, azazthioprine, and steroids, the prevalence of acne varies from 2 to 63 % [3–5, 7, 9, 12, 13, 16].

### 79.3.3 Influence of Age and Sex

#### 79.3.3.1 Acne and Age in Transplant Recipients

No acne or acne-like eruption has been reported in preadolescent children in transplant literature [4–6]. The immaturity of pilosebaceous apparitus may explain it. In young adults (mean age: 19.9 years), acne is associated with a higher age at transplantation [19].

#### 79.3.3.2 Acne Is More Frequent in Males

Three studies report a higher prevalence of acne in males than in females [2, 15, 19]. Two studies evaluated kidney or renal transplant recipients with different immunosuppressive regimens [15, 19]. The last one evaluated 80 patients on sirolimus-based therapy. The prevalence was very important, 6 % of female versus 75 % of males, and was explained by downregulation of testosterone synthesis by sirolimus [2]. It was not observed in adolescent populations [4–6].

### 79.3.4 Influence of the Time Period Posttransplantation

Acne induced by steroids and/or cyclosporine seems to be more prevalent in the months following transplantation. The average time period between transplantation and dermatological evaluation vary from 3 months to10 years (Table 79.1). In an Italian study of renal transplant recipients on azathioprine steroids, acne was almost always present during the first weeks or months after transplantation and tended to disappear thereafter [8]. In a second study, the same team evaluated 67 renal transplant recipients on cyclosporine and steroids. The acne was seen with greatest frequency between the 2nd and the 6th posttransplant months [9]. A Porto Rican study showed that prevalence of acne declines as the time posttransplantation increased. Prevalence of acne was 61 % if transplantation had been performed during the last 12 months, while it was only 5 % if transplantation had been performed more than 60 months before. Immunosuppressive regiments included steroids, cyclosporine, azathioprine, and cyclophosphamide [11].

## 79.4 Drug-Induced Acne and Acne-Like Eruption

Three immunosuppressive drugs have been associated with acne or acne-like eruption in transplantation: steroids, cyclosporine, and sirolimus.

**Table 79.2** Characteristics of immunosuppressive drug-induced acne or acne-like eruption

| Drug | Clinical aspects | Dose dependent | Delay between drug introduction and acne | Evolution | Associated lesions |
|---|---|---|---|---|---|
| Steroids | Comedones | Yes | A few weeks | Dose-dependent | Cushingoid changes |
| Cyclosporine | Comedones | No[a] | 2 months | Regression within 6 months | |
| Sirolimus | Folliculitis | No | A few weeks | No regression | Scalp folliculitis |

[a]The acne is associated to skin concentration of cyclosporine

Because these drugs are used together in maintenance regimens, acne was initially attributed mostly to the use of steroids. The clinical aspects of drug-induced acne, its evolution and its pathogenesis are different from acne *vulgaris*. These properties are detailed in Table 79.2. So, the name "acne-like eruption" should be used.

### 79.4.1 Steroids

Adults and adolescents are more commonly affected by steroid acne, even if children can be also affected. Steroid acne can result from systemic or topical administration of steroids. It appears within 2 weeks of systemic steroid therapy, or even earlier if acne is active before transplantation, and regress upon discontinuation. This acne differs from juvenile acne. The lesions are more monomorphous with papules and papulo-pustules scattered on the face, upper trunk, and upper limbs. Steroid-induced cutaneous manifestations are dose dependent. So, acne prevalence tends to disappear after the first month of posttransplantation due to reduction of steroids [8, 11, 19]. It can recur after steroid pulses given for acute graft rejection episodes [6]. An increased frequency of acne in post-pubertal organ recipients is consistent with a possible steroid-induced facilitation of the sebaceous gland response to androgens.

### 79.4.2 Cyclosporine

Cyclosporine-induced acne has been documented during the very first use of this treatment. In first reports, authors attributed most of the cases to the concomitant use of steroids. The role of cyclosporine was confirmed by two lines of evidence. (1) Acne has been induced by cyclosporine taken alone either in transplantation or in dermatological conditions such as in atopic dermatitis (Fig. 79.1) [21]; (2) discontinuation of cyclosporine in acne in transplant recipient is associated with rapid improvement of acne despite steroid continuation [22]. Cyclosporine-induced acne developed within the first trimester after drug introduction [5]. The clinical aspect is comedonal acne with frequent inflammatory component (Fig. 79.1). Severe acne, such as nodulocystic acne or nuchal acne keloidalis, has been reported [21].

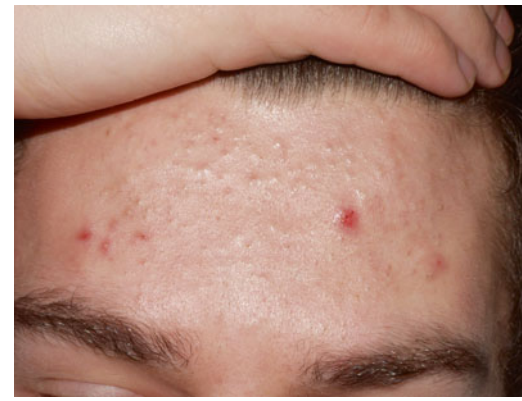

**Fig. 79.1** Cyclosporine-induced acne in an 18-year-old boy with atopic dermatitis (no acne before cyclosporine introduction). Acne was treated efficiently with adapalene

The skin is one of the main sites of accumulation of cyclosporine. The drug is very lipophilic and is eliminated through the sebaceous glands. It extends the anagen phase of the follicular cycle and induces toxic follicular dystrophy at higher

tissue concentration. This particular toxicity is usually seen after months of treatment. This may explain the high incidence of side-effects on the pilosebaceous follicle: acne, hypertrichosis, infundibular cysts, keratosis pilaris, sebaceous gland hyperplasia, acne keloidalis nuchae, or follicular eruptions; and why "acne" develops only 2–3 months after cyclosporine introduction. The skin concentration does not correlate with the blood levels. It may explain why cyclosporine acne is not dose-dependent.

### 79.4.3 Sirolimus

In trials of sirolimus, the frequency of acne was estimated at 15–25 %. In a recent systematic evaluation of renal transplant recipients we showed than 45 % of patients who received high doses of sirolimus suffered from acne-like eruption. It occurred predominantly in males with 75 % of males with renal transplant recipients develop acne versus 6 % of women. In men, acne was more frequent in patients with history of severe acne *vulgaris* [2].

This eruption develops soon after sirolimus initiation, generally during the first month after initiation. Clinically, sirolimus-induced acne differs from acne *vulgaris*. Only inflammatory lesions are generally observed. Sebaceous areas are involved, but the lesions frequently extend to the forearms, internal surface of the arm, cervical area, and scalp (Fig. 79.2) [2, 23]. In at least a few cases, severe, painful, nodular, edematous lesions on the neck and face have been observed suggesting a specific pathogenic role for sirolimus (Fig. 79.3). Bacteriological and histological examinations suggest a nonspecific folliculitis. After discontinuation of sirolimus, acne regressed in a few weeks [2]. Other diseases of the pilosebaceous apparatus are frequent in patients on sirolimus-based therapy: hidradenitis suppurativa, furuncles, and chronic folliculitis, and changes in hair aspects (scalp alopecia or skin hypoertrichosis) [24].

The most likely explanation for the role of sirolimus in the pathogenesis of acne is that sirolimus inhibits the epidermal growth factor (EGF) pathway, as is suggested by three lines of evidence (1) It has been demonstrated that sirolimus inhibits EGF action by inhibiting the mTOR pathway. (2) Anticancer therapies that specifically inhibit EGF cause cutaneous toxicity, especially acne, and this toxicity is very similar to that caused by sirolimus as it induces ingrowing paronychia inflammation, aphtous ulceration, epistaxis, and xerosis. And (3) testosterone upregulates EGF receptor synthesis, and sirolimus down-regulates testosterone synthesis. Sirolimus might therefore induce acne because of its direct inhibition of EGF action (i.e., the TOR pathway) and do so predominantly in males because of the downregulation of the EGF receptor by testosterone suppression [2].

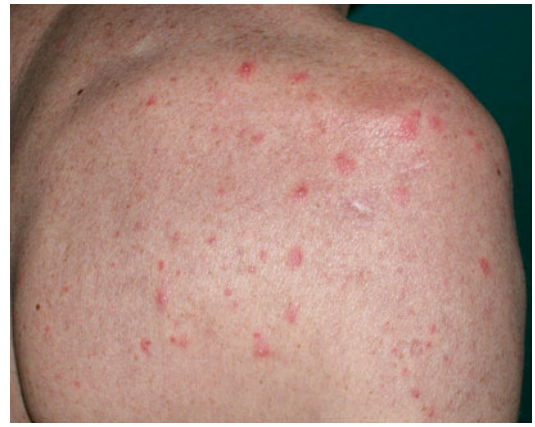

**Fig. 79.2** Diffuse folliculitis (acne-like eruption) in a renal transplant patient on sirolimus

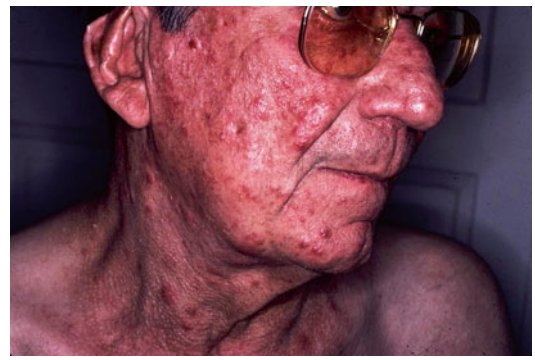

**Fig. 79.3** Nodular inflammatory acne-like eruption of the face in a renal transplant patient on sirolimus

### 79.4.4 Tacrolimus

In clinical trials comparing tacrolimus and cyclosporine associated to steroids, acne was reported significantly less frequently in the tacrolimus treatment group. It may be explained by a low accumulation of tacrolimus in skin. Recently, localized acne in areas treated with topical tacrolimus has been reported in an 18-year-old woman with vitiligo. She had no history of acne prior to tacrolimus introduction. She was treated, during 3 months for a vitiligo with topical 0.1 % tacrolimus [25]. Like with cyclosporine, only high concentration of tacrolimus in sebaceous gland may induce acne. This high concentration could not be reached by systemic administration but only with long time topical application.

**Azathioprin** and **mycophenolate mofetil** have not been associated to acne in clinical trials in transplant recipients.

## 79.5 Treatments

The management of acne in transplant recipient has to take into account many parameters including characteristics of the acne and of the patient and the foreseeable toxicity of the treatment.

### 79.5.1 Topical Treatment

Usual topical treatments of acne *vulgaris*—i.e., topical retinoids and benzoyl peroxide—can be used in transplant recipients. Xerosis is a frequent side effect of immunosuppressive drugs and may be exacerbated by topical treatments of acne. Topical retinoids are indicated in mild or moderate cyclosporine-induced acne, with predominant comedonal aspects, and are generally considered as efficient in steroid acne and sirolimus acne.

### 79.5.2 Antibiotics

No study evaluates efficiency of cyclines or topical antibiotics (erythromycin and clindamycin) in acne of transplant recipients. Only, efficiency of doxycyline in acne-like eruption induced by sirolimus was reported with an efficiency reported in 50 % of patients. In all the cases, doxycycline was associated with local treatment [2]. In reports of the use of cyclines for acne or infections, tolerance was good with no pharmacological interaction with immunosuppressive drugs [2, 22, 23, 26–28].

Prevention of severe infections is one the main preoccupation of transplant specialists. When a dermatologist treats the acne of a transplant recipient patient with topical or oral antibiotics, the risk for bacteria to develop resistances to antibiotics has to be taken into account with the transplant specialist. There is no information about acquired antibiotic resistance because of long time antibiotics for acne in immunosuppressed patients. In acne vulgaris, antibiotic resistance to local antibiotics induced by long term or sequential antibiotherapy for acne has been documented with acne for *Propionobacteium acnes* and *Streptococcus pyogenes*. These results should be borne in mind when deciding on possible treatment with long-term antibiotics.

### 79.5.3 Isotretinoin

In the 1970s, experimental evidence has shown than isotretinoin may increase the likelihood of allograft rejection. Since these reports, clinical and experimental data show that isotretinoin may protect against acute and chronic allograft rejection, is efficient, and generally well tolerated.

In a model of rats with acute renal allograft rejection, isotretinoin shows interesting results on renal functions in acute and chronic allograft rejection. In an acute kidney allograft rejection model, low dose (2 mg/kg/day) or high dose (20 mg/kg/day) of isotretinoin was administered subcutaneously during 7 or 14 days to the rats. It was started the day of transplantation and was continued daily until the end of the experiment. In this model, isotretinoin significantly ameliorates functional, vascular, glomerular, and tubulo-interstitial lesions of acute

**Table 79.3** Common toxicity of isotretinoin and main immunosuppressive drugs used in organ transplantation

| | Skin and mucosal toxicity | General toxicity |
|---|---|---|
| Steroid | Skin fragility | Hyperlipidemia, glucose intolerance |
| Azathioprine | Alopecia | Thrombocytopenia, leucopenia, anemia, hepatitis |
| Cyclosporine | Paronychia, alopecia, stomatitis | Hyperlipidemia, thrombocytopenia, anemia, hepatotoxicity, myalgia |
| Tacrolimus | Alopecia, stomatitis, pruritus | Glucose intolerance, thrombocytopenia, leucopenia, anemia, hepatotoxicity |
| Mycophenolate mofetil | Alopecia | Glucose intolerance, thrombocytopenia, leucopenia, anemia, hepatotoxicity |
| Sirolimus | Xerosis, pruritus, nail change, paronychia, cheilitis, stomatitis, epistaxis | Hyperlipidemia, glucose intolerance, thrombocytopenia, leucopenia, anemia |

renal allograft rejection [29]. These results were confirmed in a chronic allograft model (8 weeks experiment) by the same authors: isotretinoin monotherapy, low and high doses, administered orally, led to significant preservation of renal function and decreased rejection phenomena. It inhibits development of graft rejection if it was started immediately after graft, and it inhibits progression of rejection phenomena when it was started 14 days after renal allograft. The action appears directly immunosuppressive and anti-fibrotic [30]. Authors of these studies suggest that isotretinoin represents a therapeutic option in transplantation in the treatment of acute rejection and in the prevention of chronic allograft.

Experience with the use of isotretinoin in transplant recipients is limited in the literature. A few cases of patients with severe acne treated with isotretinoin have been reported in renal [2, 26–28, 31, 32] and heart [33, 34] transplant recipients. In all these cases, with low or high doses of isotretinoin, from 0.2 to 1 mg/kg/day, a dramatic improvement of the acne was generally observed. When blood levels of immunosuppressive drug were recorded, cyclosporine [22, 34] or sirolimus [2], no significant modification of drug blood level has been reported. In none of these observations, authors observe any deterioration of allograft function. In a few reports severe acne remained well controlled after withdrawal of isotretinoin [27].

Tolerability of isotretinoin is a major factor limiting its use [35]. The main explanation is the in common skin, mucosal, and general toxicity of isotretinoin and immunosuppressive drugs (Table 79.3). Severe hyperlipidemia, hepatotoxicity, diabetes mellitus, and pancreatitis have been reported after isotretinoin introduction in transplant recipients.

**Table 79.4** Isotretinoin therapy in transplant patients with acne [36]

| | |
|---|---|
| Liver transplant recipients | 20 mg once a week regimen with gradual dose increase (20 mg/week) |
| Other transplant recipients | Half the standard dose regimen initially, with gradual increase to standard dose |

We must be especially careful in liver transplant recipients. No case of acne treated by isotretinoin or case of skin prevention with retinoids has been reported in liver transplant recipients. Because of the hepatotoxicity of isotretinoin, use of this drug in liver transplant patient may be used with caution and in all case with consent of the transplant specialist.

Because of these in common toxicity and risk of hepatotoxicity in liver transplant recipients, it has been proposed by Cunliffe [36] two dosing schedules of isotretinoin therapy according to organ transplanted (Table 79.4).

In all cases:

- It is necessary to inform transplant specialist of isotretinoin introduction.
- Patients must be carefully monitored with regard to their increased risk of adverse side effects from potential drug interactions.

### 79.5.4 Two Steps: Dermatologist, Transplant Physicians

For steroids, cyclosporine, or sirolimus, discontinuation of the treatment induces rapid regression of the acne. So, if the treatment of acne fails, or has to be stopped because of severe side effects, the solution can come from the transplant clinician. Finally, modification of treatment, either the decrease of the dosage of the drug or the switch to other drug, has to be considered as a therapeutic option in severe and treatment-resistant cases.

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# Part XII

# Pathogenesis of Rosacea

# Rosacea: The State of the Art

# 80

Albert M. Kligman and Christos C. Zouboulis

## Contents



**Core Messages**

- Rosacea has a high psychological impact.
- Cathelicidins play a major role in the development of rosacea's cutaneous lesions.
- Rosacea as an actinic lymphatic vasculopathy.

## 80.1 Controversies in Rosacea

Hundreds of papers have been published in the worldwide literature on rosacea in the last 10 years alone [1–4]. What quickly becomes evident to the novitiate is the high frequency of controversial, confusing, contradictory reports regarding almost every aspect of this common disease; viz., epidemiology, classification, prevalence, natural course, pathogenesis, etc. Reports on treatment dominate the literature, supported largely by the skin care industry subject to the usual marketing biases. As regards funding for basic science investigations, rosacea is an orphan disease. Funding has been notably scanty to nonexistent.

It is illuminating to take a cursory look at the multitudinous issues that are the sources of so much disputation.

Marks was the first to highlight the controversial issues in an entertaining but informative paper

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entitled "Rosacea: hopeless hypotheses, marvelous myths and dermal disorganization," noting impiously that clinicians ought to be as red-faced as their patients in their disputes on rosacea [1–3]. Marks enumerates the areas that provoke the most disagreements, viz., the role of sunlight (is it good or bad), blood flow (increased or decreased), therapies (some help, others hurt), how do we know it is rosacea and not acne, etc [4].

These and other disputatious issues vex and embarrass us to this very day. To get a flavor of the numerous controversies which afflict the subject, it is instructive to examine the text of a large study of more than a hundred rosacea patients by Sibange and Gawkrodger [5], whose opinions largely coincide with main stream reports but often clash starkly with our own, as follows.

1. Half of their patients had migraine headaches, regarded as plausible by many experts since both involve abnormalities of the vasculature. In our extensive experience with many hundreds of subjects, migraine headaches are uncommon, not more than 5 % and possibly not different than in the general population.
2. Only 45 % exhibited episodes of flushing, which we regard as a prerequisite for a diagnosis. It is surprising how often patients will deny flushing until persistent questioning establishes otherwise. The triggers for flushing (not simple blushing) are often not obvious and may be due to vasodilating drugs prescribed for hypertension or erectile dysfunction, even foods such as parmesan cheese. Other eminent authorities such as Prof. Frank Powell in Ireland and Prof. Alfredo Rebora in Italy also contend that flushing is not an obligatory prerequisite for the diagnosis of rosacea. We have yet to see a rosacea patient in whom a history of flushing cannot be flushed out.
3. Only half exhibited telangiectasia. Other writers also consider that dilated vessels are often absent, especially in early cases. Telangiectasia may not be apparent by ordinary inspection. Under polarized light, however, telangiectasia can be demonstrated, in all cases, even in childhood rosacea. We hold that telangiectasia are an obligatory diagnostic feature of rosacea but may also occur in the photoaged face. Other facial dermatoses should be considered in their absence; for example, contact dermatitis and lupus erythematosus. Telangiectasia may also occur in the photoaged face which may be difficult to differentiate from rosacea.
4. The prevalence of rosacea was equal in men and women. In fact, rosacea is probably 3–5 times more common in women, though solid epidemiologic data are lacking. In fact, rosacea tends to be far more severe in men, not noted by Sibange and Gawkrodger [6].
5. Papular-pustular rosacea was the dominant subtype with a prevalence of 80 % in males and 60 % in females, which we regard as astonishingly exaggerated figures. In this respect, most would agree that erythemato-telangiectatic rosacea is by far the most common subtype; though again, as in most opinions about rosacea, solid figures are not available. In the Philadelphia, USA, population, papulo-pustular rosacea is relatively uncommon. Actually it is only intermittently present in afflicted persons. We forbear to comment about those authors, favorites of industry supported therapeutic trials, who seem to have no trouble recruiting 50 or more new volunteers with papulo-pustular rosacea every few months.
6. A family history was present in only 6 %. While again there are no valid family pedigree studies, our figure is closer to 25 % and may be higher still. It is not uncommon to find 2 or 3 siblings in a family of five who have rosacea. Incomplete dominance is the probable mode of transmission. It should be an easy matter to settle this question.
7. Incidentally, demodectic mites were found in only 2 of 20 normal subjects. We know in fact that these mites are ectoparasitic residents found in nearly 100 % of normal adults. This is simply a matter of proper technique, of which the cyanoacrylate follicular biopsy procedure is the most reliable. The role of Demodex folliculorum in the etiology of rosacea is, as usual, the object of furious debates. In our view, demodectic mites do not cause rosacea but may aggravate the symptoms, especially sensory discomforts such as itching, burning, and dryness.

8. Ocular rosacea is another aspect which has engendered extreme controversy. In the ophthalmologic literature the prevalence is said to be as high as 50 % of patients with associated cutaneous diseases and perhaps half that number in patients seen by dermatologists. In series of Dr. Kligman of nearly 60 women with classical centro-facial rosacea, an ophthalmologist could establish a diagnosis of ocular rosacea in only two cases, who complained of gritty eyes that showed minor signs of eyelid blepharitis.

In view of the above dissensions we agree with Marks that "intense confusion surrounds the disorder known as rosacea" [7]. While this situation is scandalous, we have reason to hope that we are on the cusp of a new wave of scientific investigations which will put these controversies to rest.

## 80.2 Recent Advances in Studies of Rosacea

Practicing dermatologists have provided most of the information we possess about the nature of rosacea. Much effort has been devoted to therapeutics with little regard to more basic scientific enquiries.

Funding for research has been meager and scanty. The National Institutes of Health has been notable for its immense disregard of the psychosocial sufferings of rosacea patients. It has not funded a single scientific study! The implication is that rosacea is merely a cosmetic nuisance centered on appearance, a domain which falls to the cosmetic industry to support.

Happily, the status of rosacea as an orphan disease is undergoing change, with a new emphasis on basic studies of pathogenesis, epidemiology, quality of life assessments, and genomics. The recent formation of a new society, The American Acne and Rosacea Society (AARS), is a meritorious development which will bring knowledge of rosacea up to parity with acne vulgaris, a disease about which a great deal is known and for which treatment is both rational and effective. The AARS is committed to serious funding.

The following section furnishes a synopsis of some impressive advances in our understanding of rosacea and its impact on health and psychological well-being.

## 80.3 A Quality of Life Instrument for Rosacea

It has been increasingly recognized that the burden of skin disease entails more than their cutaneous manifestations. For many patients the psychological comorbidities may have a greater impact on the patient than the visible signs of the disorder.

The psychological impact of disease has come to be recognized as so important that the Food and Drug Administration has issued guidelines for their inclusion as secondary endpoints in therapeutic trials. Rosacea specialists and the National Rosacea Society have been keenly aware that rosacea patients suffer enormously from the psychosocial impacts of this incurable, embarrassing, distressing disorder, driving many patients to seek psychological help for depression and anxiety. Loss of self-regard and confidence are almost inevitable.

Quality of life instruments have long been available to measure the psychosocial impact of diseases such as atopic dermatitis and psoriasis. Every dermatologist categorizes the importance of PASI scores for objectively evaluating therapeutic efficacy. Doctors are traditionally focused on the clinical signs of disease, which they go to great pains to measure, while patients tend to pay greater attention to how the disease affects their enjoyment of life and their capacity for enjoying social relationships.

At long last, a thoroughly validated rosacea quality of life instrument has been developed by Nicholson et al. [8], which they designate Rosa Quel, and whose value is inestimable.

After intensive interviews, a highly qualified team of investigators at Chapel Hill, North Carolina came up with a 21-item quality of life instrument. This was an enormous enterprise which required the dilution of more than 30 other features that lacked specificity and sensitivity. It is exceedingly interesting that the highest median

scores (3 and 4) of the 21-item list pertained to concerns relating to appearance (the red face), cosmetic concealments, and awareness of having "sensitive skin," making them susceptible to sensory discomforts such as burning, stinging, and itching.

This contribution to the well-being of rosacea sufferers has the secondary benefit of providing ammunition against managed care insurance companies who all too often refuse payment for medical treatment on the grounds that rosacea is merely a cosmetic problem. Insurance companies have little awareness of the dreadful psychosocial consequences of rosacea and are badly in need of the education that Rosa Quel provides.

Recent studies on the high prevalence of depression among rosacea sufferers emphasize the seriousness of this distressing disease. A recent USA national survey among 14 million visits for rosacea to private offices and hospital clinics, between 1995 and 2002, found that 1 % had a comorbid psychiatric diagnosis [6]. Of these, 70 % had a major depressive order. The odds ratio of depression was a startling 4.81. These are alarming figures and should put to rest any lingering notion that rosacea is simply an uncomfortable condition and that cosmetologists rather than dermatologists should be the major source of help.

## 80.4 Cathelicidins Are Key Elements in the Pathogenesis of Rosacea

Cathelicidins are antimicrobial peptides universally distributed in living organisms that are part of the innate immune defense system, affording immediate protection against infections by bacteria, fungi, viruses, and parasites. Two groups of antimicrobial peptides have been identified in skin, β-defensins and cathelicidins. These are rapidly released in response to infection and epidermal injury, immediately stimulating cytokine production by keratinocytes, initiating an inflammatory defensive reaction.

Recent work by Gallo and his associates in San Diego make it possible not only to measure these cationic peptides but to show in detail how they probably mediate the inflammatory process in rosacea. This work provides new insights into the pathogenesis of rosacea [9, 10].

Yamasaki et al. took biopsies from the nasolabial cheeks of rosacea patients and found tenfold higher concentrations of the active cathelicidin LL-37. This was undetectable in the skin of normal subjects. In addition, specific proteases, required for the activation of cathelicidins, were 1,000-fold greater than in normals [11].

In an elegant and meticulous study they injected cathelicidin into transgenic cathelicidin knock-out mice. No response ensued. By contrast, normal mice showed a brisk reaction with erythema, vesicular dilatation, neutrophilic infiltration, and increased IL-8 and serum protease, closely mimicking the pathologic events in rosacea.

In addition to these antimicrobial activities, cathelicidins are known to have many other functions that may be influential in the pathogenesis of rosacea; viz., promotion of leukocyte chemotaxis, angiogenesis (which might explain the origin of telangiectasia), and the increase in metalloproteinases, which degrade the dermal matrix, as evidenced by loss of collagen and elastosis, prominent features of advanced rosacea.

An exciting, unanticipated revelation in this study lies in providing the rationale for the current practices of using sub-antibacterial concentrations of a tetracycline derivative, doxycycline hydrate, for the treatment of rosacea. It turns out that doxycyline inhibits the proteases which are required for the activation of cathelicidins. This opens the way for pharmacologists to search for protease inhibitors as an alternative to antibiotic therapy.

These studies have far-reaching implications for understanding the pathogenesis of rosacea. More than 20 antimicrobial peptides have been identified in skin which not only protect against infection but also alert the host and stimulate elements of the defense system, including barrier repair and recruitment of inflammatory cells. These multiple signaling activities have received the designation, quite appropriately, as "alarmins."

## 80.5 Rosacea as an Actinic Lymphatic Vasculopathy

Recently, ultraviolet (UV) light-induced skin changes, such as solar elastosis and vessel dilatation as well as immunosuppression, have been accused to contribute in the development of rosacea [12, 13].

The most-cited pathogenic theory about rosacea centers on inherent abnormalities in cutaneous vascular homeostasis [12]. According to it, erythema is controlled by two vasodilatory mechanisms: humoral substances and neural stimuli [12, 14]. Cytokines and neuropeptides probably communicate within the network made of the endocrine, nervous, and immune systems. The apparent inflammatory reaction in rosacea is likely the result of altered communication and/or reciprocal modulation between them [15].

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# The Vascular Concept

# 81

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## Contents



**Core Messages**

- The most-cited pathogenic theory about rosacea centers on inherent abnormalities in cutaneous vascular homeostasis.
- Rosacea start as an *actinic vasculopathy*, probably of the lymphatic vessels, thereby corroborating Kligman's postulate that rosacea should be viewed as a UV-induced dermatosis.
- Ultraviolet (UV) light-induced skin changes, such as solar elastosis and vessel dilatation as well as immunosuppression, have been accused to contribute in the development of rosacea.
- UVB irradiation of human skin resulted in pronounced dermal angiogenesis accompanied by upregulation of the potent angiogenic factor vascular endothelial growth factor (VEGF) and downregulation of the endogenous angiogenesis inhibitor thrombospondin-1.
- The dermal damage permits vasodilation and vascular pooling. Angiogenesis seems to play an important role in the pathogenesis especially of the more severe clinical form of rosacea.
- Newly formed blood vessels facilitated the infiltration of inflammatory cells into dermal tissue, resulting in the damage of dermal matrix components.

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- Neurogenic mediators contribute to inflammation and immunosuppression following UV irradiation of the skin.

## 81.1 Introduction

The phenotypic expressions of rosacea have been suggested to be caused by divergent pathogenetic factors. Although its precise etiology remains unknown, various factors have been suspected of contributing to this condition (Table 81.1). Recently, familial cases of rosacea have been reported, and a genetic predisposition to the disease has been suggested. In addition, ultraviolet (UV) light-induced skin changes, such as solar elastosis and vessel dilatation as well as immunosuppression, have been accused to contribute in the development of rosacea [1].

The most-cited pathogenic theory about rosacea centers on inherent abnormalities in cutaneous vascular homeostasis. According to it, erythema is controlled by two vasodilatory mechanisms: humoral substances and neural stimuli [2, 3]. Cytokines and neuropeptides probably communicate within the network made of the endocrine, nervous, and immune systems. The apparent inflammatory reaction in rosacea is likely the result of altered communication and/or reciprocal modulation between them [4, 5]. The major neuropeptide probably involved in rosacea is substance P (SP) [6], while the involvement of vasoactive intestinal peptide (VIP) and calcitonin-gene-related peptide is uncertain [7, 8]. Apart from their proinflammatory properties, neuropeptides and neurohormones are also potent downregulators of immunity.

**Table 81.1** Current aspects of the pathogenesis of rosacea

- Abnormalities in cutaneous vascular homeostasis
- Chronic excessive light exposure
- Dermal matrix degeneration
- Regular alcohol consumption
- Pilosebaceous unit abnormalities in combination with the organism *Demodex folliculorum*
- Emotional stress
- Hormonal influence

## 81.2 UV Light-Induced Skin Changes

UV radiation is an initial stress factor for the development of inflammatory lesions in rosacea. Histological findings in rosacea, in particular fluffy edema and slight perivascular lymphocytic infiltrate, and dilation of lymphatic vessels, present strong evidence that almost all variants of rosacea start as an *actinic lymphatic vasculopathy*, thereby corroborating Kligman's postulate that rosacea should be viewed as a UV-induced dermatosis [9].

Indeed, there is a general consensus among clinicians that rosacea is at least a photoaggravated disorder. Pathophysiologic processes induced by UV radiation, which are processes similar to those seen in photoageing, contribute to the signs and symptoms of rosacea [10]. The pivotal role of sunlight is supported by the distribution of erythema and telangiectases on the facial convexities. Sun-protected areas, such as the supraorbital and submental areas, are typically spared. In contrast, epidemiologic studies demonstrate that only 17–31 % of rosacea patients report worsening of symptoms by sunlight [11]. Several photoprovocation studies in rosacea patients have failed to show heightened skin sensitivity to the acute effects of ultraviolet radiation.

Interestingly, identical changes of lymphatic vascular morphology may be found in the vicinity of basal cell and squamous cell carcinomas from the face of older patients without any clinical signs or previous history of rosacea. This may be taken as an indication that solar elastosis and concomitant lymphatic vessel alterations are indeed a direct consequence of severe UV damage rather than an idiopathic and specific phenomenon of early rosacea. Yano et al. [12] could show that UVB irradiation of human skin resulted in pronounced dermal angiogenesis accompanied by upregulation of the potent angiogenic factor vascular endothelial growth factor (VEGF) and

downregulation of the endogenous angiogenesis inhibitor thrombospondin-1. These newly formed blood vessels facilitated the infiltration of inflammatory cells into dermal tissue, resulting in the damage of dermal matrix components. Although not expressed by endothelium, VEGF was found to be present in epithelial cells and was expressed by infiltrating cells in rosacea-involved skin [13]. In contrast, expression of VEGF receptors was observed both by vascular endothelium and infiltrating mononuclear cells. VEGF receptor-ligand binding may contribute to the vascular changes and cellular infiltration that occurs in rosacea.

At the molecular level, various chromophores have been identified, whereas DNA remains the major chromophore in the skin. Epidermal Langerhans cells (LC) are considered as the main targets of UV, since UV inhibits their antigen-presenting activity and their capacity to stimulate allogeneic type 1 T cells. Keratinocytes are also a target of UV light, and they produce and release numerous soluble and immunosuppressive mediators. In human skin, IL-10 is mainly produced in the dermis. CD11β+ macrophages and neutrophils infiltrate epidermis after intense UV. UV-induced immunosuppression is transferable with suppressor T cells, whose phenotype is still debated (natural killer T cells and T regulatory type 1 cells). Although the mechanisms by which immune regulatory suppressor T cells act still remain unclear, there is increasing evidence that apoptosis of epidermal LC or reactive T cells may play an important role through the Fas/FasL system [14].

Recent studies have shown that UV radiation also stimulates angiogenesis, which promotes telangiectasia [15]. Kosmadaki et al. [16] demonstrated an increased expression of VEGF mRNA levels after in vitro irradiation of cultured keratinocytes, an effect that appeared to be independent from tumor necrosis factor-α. Microarray analysis from Howell et al. [17] revealed 57 genes of human keratinocytes were upregulated, and 27 genes were downregulated after UVB exposition. One downregulated gene was thrombospondin-1, whereas the platelet-derived endothelial cell growth factor—an angiogenesis activator—was upregulated. These results suggest a gene expression mechanism by which UVB induces an angiogenetic switch in keratinocytes. This may represent an important early event promoting neovascularization, growth of cutaneous neoplasms, and vascular and inflammatory lesions in rosacea. The vessels involved seem to be the lymphatic skin vessels, as described above.

Even at suberythemal doses, UVB reduces LC density, migration, and maturation in the epidermis and regional lymphoid tissue. It has been suggested that this immunosuppressive effect is in large part due to the effects of UVB in modulating cytokine gene expression in keratinocytes [18]. In addition, moderate doses of UVB can induce an increase of cyclooxygenase-2 (COX-2) expression in keratinocytes to cause a potent induction of the eicosanoid prostaglandin E2 [19].

## 81.3 Dermal Matrix Degeneration

Much interest has surrounded the dermal connective tissue and its role in the pathogenesis of rosacea. Histopathologic studies have demonstrated both endothelial damage and matrix degeneration in skin specimens of affected patients [20, 21]. In a study of UV light effects on rats, dilated and tortuous vessels were detected well before matrix abnormalities became apparent [22]. Solar radiation may alter lymphatic and blood vessel function via damage to the dermal support network of elastic and collagen fibers. This matrix-centered theory holds that telangiectasia, persistent erythema, profound flushing, and edema are all caused by poor connective tissue support for cutaneous vessels, resulting in the pooling of serum, inflammatory mediators, and metabolic waste. Despite prominent ectasia, vessels in rosacea maintain the ability to dilate and to constrict in response to local (ethylnicotinate privine and dimethyl sulfoxide) and systemic (adrenaline, noradrenaline, histamine and acetylcholine) vasoactive agents. These findings provide some support for the central role of matrix degeneration, since vessel reactivity remains intact. Neumann et al. [23] identified structural changes leading to the formation of telangiectasias; the

deranged connective tissue is secondary to damaged capillaries. The primary damage may be evoked mostly by environmental influences, mainly by the sun. Infections, infestations, and granulomatous changes are not primary factors in the development of rosacea.

The presence of elastolytic granulomas, along with the fact that rosacea mostly occurs in areas exposed to the sun, is a strong indication of a causal link between chronic exposure to the sun and rosacea development. Ramelet and Perroulaz [24] postulated a pathogenic role for degenerated elastic fibers in rosacea, and Ozkaya-Bayazit and Buyukbabani [25] described granulomas centered by altered collagen and phagocyting elastic fibers in rosacea specimens. UV irradiation in susceptible individuals may cause distortion of collagen structure. Palisaded granulomas represent a reaction to altered collagen. This reaction occurs throughout the superficial and deep dermis in contrast to elastolytic granulomas, which usually occur in the superficial dermis [26]. We speculate that the doughnut-shaped neutrophilic granulomas may form around traces of unidentified foreign-body material, possibly of keratinous origin. Rosacea fulminans (pyoderma faciale) in this context presents as an exaggerated suppurative variant with large confluent dermal abscesses.

Aroni et al. [27] reported that histological changes are not confined to the upper dermis but often involve the deeper dermis and subcutaneous fat (dilatation of vessels, presence of inflammatory infiltrate). Furthermore, they showed that even clinically normal-looking skin in patients with rosacea exhibits histological changes, especially dilatation of the vessels and solar elastosis, though to a lesser degree compared to lesional skin. Many investigators have supported that these two factors are the earliest dermal changes that influence the onset and progression of rosacea [3]. In all cases of normal-looking skin, mild lymphocytic infiltrate was noticeable around the vessels and near the follicles, implying that this infiltration is an early event in the inflammatory procedure. At last, there is no histological pattern unique to rosacea, supporting the multifactorial origin of the disease.

## 81.4 Neuropeptides Mediate Effects of UV Radiation-Induced Immunosuppression

There is accumulating evidence that neurogenic mediators contribute to inflammation and immunosuppression following UV irradiation of the skin. Originally, neuropeptides were defined as endogenous substances synthesized in nerve cells and/or involved in nervous system functions [28]. The interaction between peripheral nerves and the immune system is mediated by different types of cutaneous nerve fibers that release neuromediators and activate specific receptors on target cells in the skin such as keratinocytes, mast cells, LC, microvascular endothelial cells, fibroblasts, and infiltrating immune cells. Among the best-studied neuropeptides are CGRP, SP, and α-melanocyte stimulating hormone (α-MSH). These neuropeptides are capable of mediating cutaneous neurogenic inflammation by induction of vasodilation, plasma extravasation, and augmentation of cytokine, chemokine, and cellular adhesion molecule expression [29]. Legat et al. [30] examined the possibility that UV modulation of the cutaneous neurosensory system and CGRP may contribute to local immunosuppression in mice mediated by repeated subinflammatory UV irradiation. The number of epidermal nerve fibers (ENFs) immunoreactive for CGRP in skin increased without altering the total number of ENFs.

SP, thought to induce flushing in carcinoid, has been mentioned in previous rosacea studies [6, 7]. SP is prominent in atopic lesions, inducing mast cell degranulation with histamine and leukotriene release, leukocyte–endothelial adhesion, and neutrophil activation. Other proposed mediators have included VIP [31], serotonin, histamine, and prostaglandins. VIP is known to induce histamine release in human skin and to include a nitric oxide-dependent vasodilation in human skin [28], but it is unlikely to be involved in rosacea pathogenesis [7]. Pierard-Franchimont et al. [32] reported about the possible modulatory role of somatostatin in the outcome of rosacea. Four patients presenting long-standing recalcitrant facial rosacea were treated with octreotide for diabetic retinopathy. Rosacea improved rapidly and

**Table 81.2** Molecular targets and related therapies[a] for rosacea

| | Strategic approach to target | Expected outcome of intervention at target | Therapies in trial |
|---|---|---|---|
| SP | Reduction of SP expression, no effect on CGRP and VIP | Diminishing of neurotrophic factors and density of nerve fiber | Flashlamp pulsed dye laser, clinical trial [7] |
| CGRP | Inhibition of calcineurin | Release of neuropeptides from sensory nerve fibers | Tacrolimus[b] [33]<br>Pimecrolimus[b] [5]<br>Cyclosporine A[c]<br>Topical application, clinical trials |
| α1-adrenergic receptor | Oxymetazoline[d], [e]selective α1-adrenergic receptor agonists | Improvement of erythema and flushing | Topical application |
| Inflammation (unspecific) | Submicrobial doses of doxycycline or minocycline (several preparations) | Improvement of clinical signs (unspecific) | Systemic administration, clinical trials [36] |
| | Isotretinoin | Improvement of inflammation | Systemic administration, registered [37] |

*SP* substance P, *CGRP* calcitonin-gene-related peptide, *VIP* vasoactive intestinal polypeptide
[a]Azelaic acid, dapsone, and metronidasole applied topically; zinc sulfate and somatostatin administered systemically have been shown to be active or are currently studied for their efficacy in rosacea without known molecular target
[b]Ineffective
[c]No published results, clinical trial (http://www.ClinicalTrials.gov)
[d]Clinical trials [34]
[e]Registered [35]

even cleared without any recurrence in three of the patients. The beneficial effect might be attributed to inhibitory actions on the sebaceous gland, the neovascularization, and/or on the inflammatory process. In particular, somatostatin plays a prominent role in neuroendocrinological aspects of the skin [4] and may help to clear some inflammatory dermatoses including rosacea (Table 81.2).

## 81.5 Corticotropin-Releasing Hormone: the Response to Peripheral Stress

Corticotropin-Releasing Hormone (CRH) is the most proximal element in the hypothalamic–pituitary–adrenal (HPA) axis, which coordinates the response to systemic stress. The response to peripheral stress (e.g., solar irradiation) is supposed to be mostly mediated by epidermal melanocytes, which are responsible for the pigmentary reaction. CRH and related urocortin I–III peptides act as central coordinators for neuroendocrine and behavioral responses to stress and in peripheral organs amongst others as modulators of local immune and vascular functions. The general mechanism of action of these peptides in mammalian systems involves interactions with membrane-bound CRH receptors type 1 (CRH-R1), type 2 (CRH-R2), and CRH-binding protein (CRH-BP) [38, 39]. In human skin, CRH-R1 and CRH-BP are expressed in all major cellular populations of epidermis, dermis, and subcutis with CRH-R1α being the most prevalent isoform. The CRH-R2 was localized predominantly in hair follicles, sebaceous and eccrine glands, muscle, and blood vessels [40]. The incubation of normal epidermal melanocytes with CRH triggers a functional cascade structured hierarchically and arranged along the same algorithm as in the HPA axis. CRH activation of CRH-R1 stimulates cAMP accumulation and increased pro-opiomrelanocortin (POMC) gene expression and production of adrenocorticotropic hormone (ACTH). CRH and ACTH also enhance the production of cortisol and corticosterone, and cortisol production is also stimulated by progesterone. POMC gene silencing abolished the stimulatory effect of CRH on corticosteroid synthesis, indicating that this effect is indirect and mediated by production of ACTH. Thus, the melanocyte response to CRH is highly organized along the same functional hierarchy as the HPA axis [41].

Stress or an abnormal response to stressors and the participation of neuropeptides has been found in the pathophysiology of several skin disorders [8]. Flint et al. [42] reported a mild, acute restraint stress activation of the cutaneous CRH-POMC axis. A number of studies have also indicated that CRH can cause marked increases in vascular permeability in the skin microcirculation through the degranulation of mast cells, an action mediated via CRH-R1 receptors [43]. Degranulation of mast cells involves the release and stimulation of numerous vasoactive molecules including histamine and NO. CRH-induced vasodilation in human skin appears to be mediated, at least in part, by mast cell-derived histamine. Human mast cells synthesize and secrete both CRH and urocortin in response to immunoglobulin E receptor cross-linking. Mast cells also express CRH receptors, activation of which leads to the selective release of cytokines and other proinflammatory mediators [44]. Acute stress increases skin CRH that can trigger mast cell-dependent vascular permeability, effects inhibited by certain histamine-1 receptor antagonists, possibly acting to reduce intracellular $Ca^{2+}$ ion levels [45].

Nevertheless, the specific pathogenetic role of stress in skin diseases still remains unclear. Interleukin (IL)-18, a member of the IL-1 family, is a key mediator of peripheral inflammation and host defense responses and is secreted by human keratinocytes. Park et al. [46] demonstrated by inhibition of p38 MAPK that CRH regulates IL-18 production through the MAPK signaling pathway in human keratinocytes. Zbytek et al. [47] reported that CRH stimulates nuclear factor-kappa B (NF-κB) activity. CRH also stimulates basal IL-6 and IL-8 secretion in human sebocytes [48]. Specificity of the CRH effect was demonstrated by the use of CRH-R antagonist antalarmin and α-helical CRH. CRH-dependent stimulation of NF-κB activity is consistent with accumulated data about the role of CRH in the regulation of local epidermal homeostasis (Fig. 81.1).

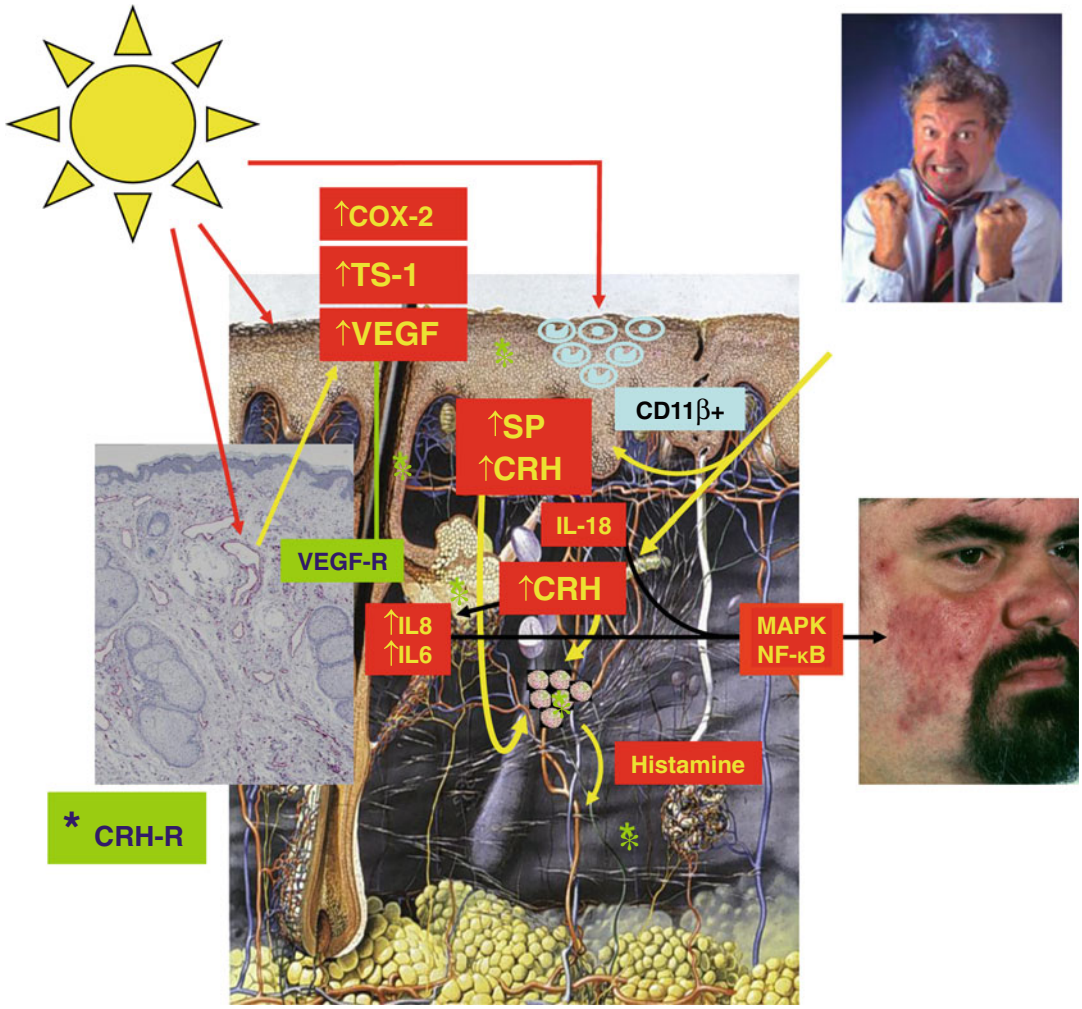


**Fig. 81.1** Mechanisms of rosacea pathogenesis. UV irradiation induces pronounced dermal changes compatible with rosacea, presenting strong evidence that rosacea starts as an *actinic lymphatic vasculopathy*. *COX-2* cyclooxygenase-2, *CRH* corticotropin-releasing hormone, *CRH-R* CRH receptor, *LYVE-1* lymphatics-selective antibody, *TS-1* endogenous angiogenesis inhibitor thrombospondin-1, *SP* substance P, *VEGF* vascular endothelial growth factor, *VEGF-R* VEGF receptor

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# Rosacea and Neuropeptides

# 82

Maeve A. McAleer and Frank C. Powell

## Contents



**Core Messages**

- The cutaneous nervous system includes neuropeptides produced by cutaneous sensory nerves and skin cells, target cells, neuropeptide-degrading peptidases and other inflammatory mediators such as cytokines and neurotrophins. These components interact to allow adaptation to the external environment but, if uncontrolled, can also contribute to neurogenic inflammation and disease.
- The cutaneous neurovascular system may play a role in the pathogenesis of rosacea, as suggested by symptoms such as flushing, stinging, itch, and exacerbation by UV radiation or emotional stress experienced by many patients.
- Cutaneous neurogenic inflammation involves nerves, skin cells, neuropeptides, neuropeptide receptors, neuropeptide-degrading enzymes and inflammatory mediators.
- Cutaneous neuropeptides including Substance P (SP), Calcitonin Gene Related Peptide (CRGP), Corticotrophin-releasing hormone (CRH), Vasoactive Intestinal Peptide (VIP) and Somatostatin (SST) have been studied in rosacea.
- Serum SP levels were increased in rosacea patients, and SP immunoreactive neurons were increased around the

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blood vessels in lesional skin of rosacea patients.
- Erythematotelagectatic rosacea patients treated with pulsed dye laser had decreased facial sensitivity, reduced superficial nerve fibre density and a reduction in neurons immunoreactive to SP after the laser treatment.
- An increased density of VIPR positive cells were demonstrated in the endothelium and perivascular cells in rhinophyma patients.
- An analogue of SST has been reported to improve papulopustular rosacea.
- Rosacea patients had significantly more post-prandial flushing compared with controls.
- Epithelial skin cells respond to environmental stress from UVB radiation by increased CRH production, and this may play a role in rosacea pathogenesis.

## 82.1 Introduction

Rosacea is a common cutaneous disorder that has diverse clinical manifestations ranging from facial vascular hyperreactivity to sebaceous gland hyperplasia. It has been postulated that neurovascular interactions with release of proinflammatory and vasodilatory neuropeptides could be intergral to the pathogenesis of certain subtypes of this disorder. Stress, ultra-violet light or microbial antigens may stimulate release of these neurotransmitters and contribute to the flushing and erythema seen in some patients with rosacea. Study of the neurovascular interactive network in rosacea has provided understanding and insights in to the vascular reactivity which is a feature of the clinical disorder in some patients with rosacea.

The cause of rosacea is unknown. There is an increased frequency of flushing in some rosacea patients [1], and some report increased vascular reactivity to triggers such as hot beverages, spicy foods, and increases in environmental temperature [2]. One theory of pathogenesis is frequent facial flushing which causes vascular dilation that produces the erythema and telangiectasies of rosacea. Subsequently, dilated vessels leak fluid and proinflammatory mediators resulting inflammatory papules and pustules [3]. Individuals with rosacea can also complain of increased sensitivity of the facial skin with symptoms of burning, stinging, and itch, especially in response to some topically applied agents [4].

These rapid responses of flushing, stinging, and itch experienced by rosacea patients suggest that the cutaneous neurovascular system plays a role in the condition.

The temporal relationship between the onset and exacerbation of inflammatory skin conditions and psychological stress suggests a connection between the central nervous system and the peripheral cutaneous neuro-immune systems (Fig. 82.1). 60–91 % of individuals with rosacea associated the onset or flares of their condition with emotional stress [5, 6] and hypnosis was found to be helpful for the treatment of established rosacea [7].

The cutaneous nervous system involves the complex interplay between neuropeptides produced by cutaneous sensory nerves and skin cells, receptors on target cells, the activation state of target cells, the presence of neuropeptide-degrading peptidases and other inflammatory mediators such as cytokines and neurotrophins that maintain sensory nerve function [8]. After release into their microenvironment, cutaneous neuropeptides act via paracrine, juxtacrine or endocrine pathways [7, 9]. Interdependent communications exist between the cutaneous neuroimmune system and the central nervous system via a ‘neuropeptide language’. The central and peripheral cutaneous neurovascular network allows adaptation to the external environment but can also contribute to neurogenic inflammation and disease when uncontrolled [9, 10] (Fig. 82.1).

Cutaneous neuropeptides including Substance P (SP), Calcitonin Gene Related Peptide (CRGP), Corticotrophin-releasing hormone (CRH), Vasoactive Intestinal Peptide (VIP) and Somatostatin (SST) have been studied in rosacea.

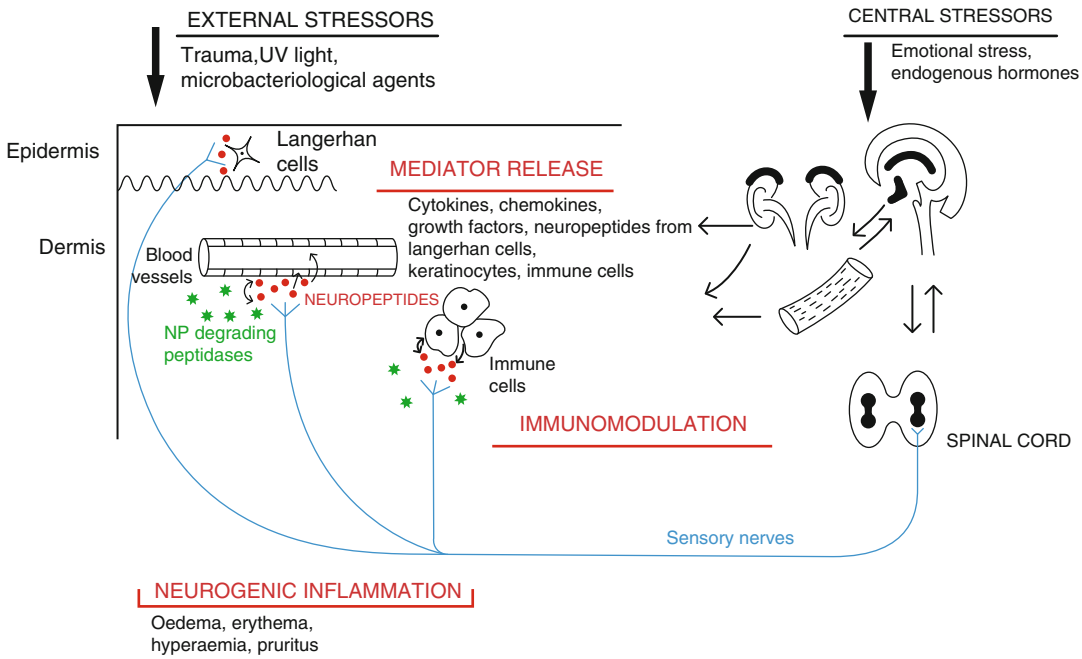


**Fig. 82.1** Peripheral and central stressors acting on the cutaneous neuroendocrine system can result in neurogenic inflammation

## 82.2 Substance P

Substance P (SP) is an undecapeptide of the tachykinin family. In the skin SP is found predominantly at the dermoepidermal junction but also intraepidermally. The effects of SP have been described on keratinocytes, including hair follicles, mast cells, fibroblasts, and endothelial cells. SP causes the release of inflammatory mediators, such as TNFα and histamine, upregulation of cell and blood vessel adhesion molecules, cytokine production, recruitment of neutrophils and eosinophils, the release of chemokines, such as IL1 and IL8, and the promotion of fibroblast chemotaxis and proliferation [7, 9] (Table 82.1).

Individuals with rosacea have been shown to have increased serum SP compared with a control group. When the SP level was measured in 23 rosacea patients, 9 had elevated levels, compared with none of the control group [11]. It was suggested that this might be related to increased local production or reduced metabolism of the released neuropeptide. In addition, SP immunoreactive neurons were increased around the blood vessels of lesional skin in nine rosacea patients, compared with non-lesional skin in the same individuals [12]. Further evidence to suggest SP plays a role in the pathogenesis of rosacea was reported by Lonne-Rahm et al. [4]. They investigated the effects of flashlamp pulsed dye laser treatment on 31 patients with erythematotelangectatic rosacea with regard to skin sensitivity, nerve density, contacts between nerves and vessels, and the expression of the neuropeptides SP, Calcitonin-Gene related peptide (CGRP), and Vasoactive Intestinal Peptide (VIP) [4]. Three months after pulsed dye laser treatment was completed, a significant number of patients had decreased facial skin sensitivity. There was also a significant reduction in superficial nerve fibre density and a reduced number of neurons immunoreactive to SP.

**Table 82.1** The main sources and effects of cutaneous neuropeptides and their characterisation in rosacea

| Neuropeptide | Receptors | Main sources in the skin | Effects | Characterisation in rosacea |
|---|---|---|---|---|
| SP | Tachykinin receptors | – Sensory nerves | – Erythema, oedema and itch<br>– Histamine release from mast cells<br>– Vasodilatation<br>– T cell and macrophage activation, neutrophil chemotaxis<br>– KC and fibroblast proliferation<br>– ↑ Cell adhesion molecules<br>– ↑ IL, TNF-α, leukotrine $B_4$, prostaglandin<br>– Sebaceous gland regulation | – Increased serum SP in rosacea [11]<br>– Increase in SP immunoreactive nerves in lesional skin of rosacea patients [12]<br>– Following pulsed dye laser rosacea patients had reduced stinging and a reduction in neurons immunoreactive to SP [4] |
| VIP | VPAC receptors | – Sensory nerves<br>– Merkel cells | – Pro and anti-inflammatory effects<br>– Sweat secretion<br>– Histamine release from mast cells<br>– Induces NO synthesis<br>– Vasodilation and blood vessel function<br>– Keratinocyte migration and proliferation<br>– Involved in IL, chemokine, TNF-α release | – Denser distribution of VIP receptor positive cells in the endothelium and perivascular large cells of patients with rhinophyma compared with the control group [13] |
| CGRP | CGRP receptors | – Sensory nerves | – Vasodilatation<br>– Mast cell degranulation<br>– Histaimine & TNF-α release<br>– Pro and anti-inflammatory effects<br>– Release of nitric oxide<br>– Regulation of keratinocyte and endothelial cell proliferation | – No significant change in CGRP immunoreactive neurons after pulsed dye laser treatment [4] |
| SST | SST receptors | – Sensory nerves | – Histamine release from mast cells<br>– Regulation of T and B cell proliferation<br>– Antiproliferative actions | – Case reports of patients with papulopustualar rosacea responding to octreotide (SST analogue) [14] |
| NKA | Tachykinin receptors | – Sensory nerves | – Histamine release from mast cells<br>– ↑ Keratinocyte nerve Growth factor expression | – Post prandial flushing was observed in 48 % of rosacea patients compared to 0 % of controls. Post prandial NKA levels were increased on 7 % of rosacea patients and 26 % of controls. No association between flushing and neuropeptides or rosacea and neuropeptides was demonstrated [15] |
| CRH | CRH receptors | – Keratincytes<br>– Pilosebaceous unit<br>– Melanocytes | – Proinflammatory<br>– Mast cell degranulation; release of histamine, TNF-α, cytokines and VEGF from mast cells<br>– Fibroblast proliferation, anti-proliferative in keratinocytes<br>– Stimulates steroid production | – Epithelial cells respond to environmental stress by increased production of CRH and this has direct effects on vessel wall function [16] |

*SP* substance P, *VIP* vasoactive intestinal peptide, *CGRP* calcitonin gene related peptide, *SST* somatostatin, *NKA* neurokinin A, *CRH* corticotrophin releasing hormone, *IL* interleukin, *TNF* tissue necrosis factor

## 82.3 Vasoactive Intestinal Peptide

Vasoactive intestinal peptide (VIP) is present in gastrointestinal and in neural tissues. It is detected in nerve fibres associated with dermal vessels, sweat, apocrine, and meibomian glands, hair follicles, and Merkel cells. VIP immunoreactive fibres are found in close anatomic relation to mast cells and sweat glands. VIP mediates vasodilatation by inducing nitric oxide synthesis, which has been shown to be increased in the skin of some patients with rosacea. VIP receptor (VIP-R) positive cells studied in the biopsies of five patients with rhinophyma [13]. Rhinophyma patients had a more dense distribution of VIP-R positive cells within the endothelium and perivascular large cells compared with the control group [13].

## 82.4 Calcitonin Gene Related Peptide

Calcitonin gene related peptide (CGRP) is 37 amino-acid neuropeptide. CGRP expression has been detected in the CNS, in cutaneous neurons associated with blood vessels and free nerve endings in the skin [17]. CGRP is also found in association with smooth muscle cells and blood vessels. It is one of the most prominent neuropeptides in the skin and is often co-localised with either SP or SSM. CGRP modulates immune responses and inflammation, predominantly through anti-inflammatory and neurotrophic effects. It has been shown to have a pro-inflammatory effect in early inflammation. CGRP is one of the most potent vasodilatory mediators. It acts on small and large vessels directly, and it potentiates microvascular permaeability and oedema formation caused by SP or NKA. It also causes the release of nitric oxide from endothelial cells. Intraveneous injection of CGRP in rats caused increased vasodilatation and skin temperature in a dose-dependant manner [9]. When investigating the effects of flashlamp pulsed dye laser on erythematotelangectatic rosacea, Lonne-Rahn et al. [4] found vascular-related CGRP positive fibres in the dermis of rosacea patients. Following the pulsed dye laser treatment there was a no significant decrease in the numbers of CGRP positive fibres compared with before treatment [18].

## 82.5 Somatostatin

Somatostatin (SST) activity has been demonstrated in Merkel cells associated with sweat glands, in keratinocytes, Langerhan cells, suprabasal cells of the epidermis and in dendritic cells and neurons [19]. Four patients with papulopustualar rosacea that responded to octreotide, a long acting somatostatin analogue, have been reported. It was postulated that the inhibitory effects of SSM on the granulomatous response and on neurogenic inflammation helped treat the papulopustular rosacea [14].

## 82.6 Neurokinin A

Murphy et al. [15] investigated facial vasomotor instability and the release of neuropeptides in 27 patients with untreated rosacea (16 papulopustular, 9 erythematelangectatic) and 27 age-, sex- and socioeconomic-matched psoriasis control patients. 81 % of the rosacea group reported a history frequent flushing compared with none of the control group. Fasting and post-prandial plasma levels of CGRP, VIP, SST and neurokinin A (NKA) and gastrin were measured. A standard measure of carbohydrate at 60 °C was administered orally, and post-prandial flushing was induced in 48 % of rosacea patients but none of the controls. Fasting and post-prandial VIP, CRGP and SST were normal in all subjects. Post-prandial NKA levels were elevated in 26 % of controls and 7 % of rosacea patients. Post-prandial gastrin levels were elevated in 33 % of rosacea patients and 22 % of the control group. There was no association between a history of gastrointestinal upset, post-prandial flushing and elevated gastrin or NKA levels. As expected there was more post-prandial flushing in rosacea patients but no correlation between neuropeptide release and rosacea or post-prandial flushing [15].

## 82.7 Corticotrophin Releasing Hormone

Corticotrophin releasing hormone (CRH) is a 41 amino-acid peptide. It is released from the pituitary following stimulation by corticotrophin-releasing factor derived form the hypothalamus. CRH is also a key mediator in the neuroimmunoendocrine axis. It is responsive to chronic stress and aggressors such as UV radiation and cytokines. It has both proinflammatory and anti-inflammatory effects. It can induce mast cell degranulation and therefore increase vascular permeability, inhibit keratinocyte proliferation and induce keratinocyte differentiation. Fimmel et al. [16] investigated the influence of UV irradiation on the synthesis of the angiogenic factor VEGF and CRH in human dermal micrvascular endothelial cells, keratinocytes, fibroblast and a sebaceous gland cell line SZ95. They reported that following exposure to a physiological dose of UVB radiation CRH synthesis significantly increased in keratinocytes, fibroblasts and moderately in the sebocytes while CRH levels decreased in the endothelial cells. They suggest that epithelial skin cells respond to environmental stress by increased CRH production, and this has direct effects on vessel wall function and, hence, could be involved in rosacea pathogenesis [16].

A greater understanding of the skin as a neuroimmunoendocrine organ, and its possible role in the pathogenesis of roscaea could lead to novel treatments for this common dermatosis.

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# Rosacea and *Demodex folliculorum* 83

Noreen Lacey and Frank C. Powell

## Contents



**Core Messages**

- *Demodex* mites are ubiquitous in normal adults.
- Mites are increased in number in patients with papulopustular rosacea (PPR).
- The relevance of the increased numbers of mites in rosacea patients is unknown.
- Patients immunosuppressed by disease or therapy have increased numbers of facial mites.
- Some otherwise healthy adults (mainly females) develop an abundance of *Demodex* mites on their facial skin (demodicosis) that may be related to innate immune tolerance enhanced by inadequate facial cleansing techniques and give rise to minor symptoms of pruritus, stinging, and facial erythema.
- Anti-mite therapy has been reported to successfully clear the clinical lesions in some patients with PPR.
- When mites cause inflammation this may be initiated by immune mechanisms, mechanical blockage, through associated mite-related bacteria, or other mechanisms as yet unknown.
- Several non-invasive methods can be used to extract mites from human skin. The optimal techniques to provide representative numbers of viable mites have yet to be fully defined.

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- Microbiological studies of mite-related bacteria have revealed specific agents that may explain the role of antibiotic therapy in the management of inflammatory rosacea.
- Diseases caused by *Demodex* mite infestation in animals (called demodectic mange in dogs and demodicosis in other animals) are often serious and affect the animals' general health. They are more likely to occur in immunosuppressed animals. Because of the easy availability of many mites on the surface of such animals' skin, these animals can provide material for study of their biologic functions.

## 83.1 Introduction

The possible role of *Demodex* mites in human disease remains a matter of controversy. Several studies have shown there is a higher number of *Demodex folliculorum* in the centrofacial skin of rosacea patients in comparison to control subjects. We propose potential pathogenic mechanisms by which *Demodex* mites may contribute to the development of inflammatory lesions in papulopustular rosacea (PPR).

## 83.2 Background

"*Demodex folliculorum*" mites were first described in human skin by Henle [1]. Descriptive illustrations and measurements were provided by the German dermatologist Carl Gustav Simon the following year [2]. Akbulatova [3] suggested there were two subspecies and subsequently two distinct species of *Demodex* mites were confirmed to exist in man. Both species were redescribed using statistical methods for meristic data and by standard morphological criteria for each life stage; histological data showed that both had a discrete niche in the pilosebaceous unit [4]. The larger of these, *Demodex folliculorum* is located mainly in the upper third of pilosebaceous follicle of the face (often in clusters). The smaller species, *Demodex brevis*, takes residency in the lower third of the follicle and in sebaceous and meibomian glands usually as solitary organisms [5]. *D. folliculorum* mites (~300–400 μm) have a long abdominal segment which is well suited to the follicular canal and infundibulum. *D. brevis* (~200–300 μm) is shorter and terminates in a pointed end. Both possess four pairs of short legs with claw-like appendages (Fig. 83.1), enabling slow movement. It has been proposed that sebum is the mite's main food source [6, 7] but the specialized piercing mouthparts suggest that feeding on follicular and glandular epithelial cells takes place through disruption of cellular walls and draining of their contents [4, 8]. The mite body is almost transparent, but may have a distinctive brownish colour in the abdominal region (the reason for which is unknown). Both *D. brevis* and *D. folliculorum* have distinctive spiral rings encircling the abdomen, (more obvious in *D. folliculorum*) which give these mites a resemblance to an earthworm. Due to this appearance *Demodex folliculorum* mites are sometimes called "sebaceous worms" [5, 7, 9]. A genital opening is found dorsally in the anterior portion and an anus is lacking. Crystalline wastes are thought to be stored in large cells of the abdomen [5, 9, 10]. The life cycle of *Demodex folliculorum* is approximately 14 days from an ovum to the final adult stage [7, 10, 11].

## 83.3 Prevalence in Man

Both *Demodex* species are ubiquitous in the human adult population. The mite is usually not present in neonates; its population is sparse in children and adolescents, with numbers increasing with the host's age [4, 5, 12]. Mites are thought to be transmitted by direct contact from adults to children and predominantly occupy areas rich in sebaceous glands, such as facial skin, the neck, scalp, eyelids and upper chest.

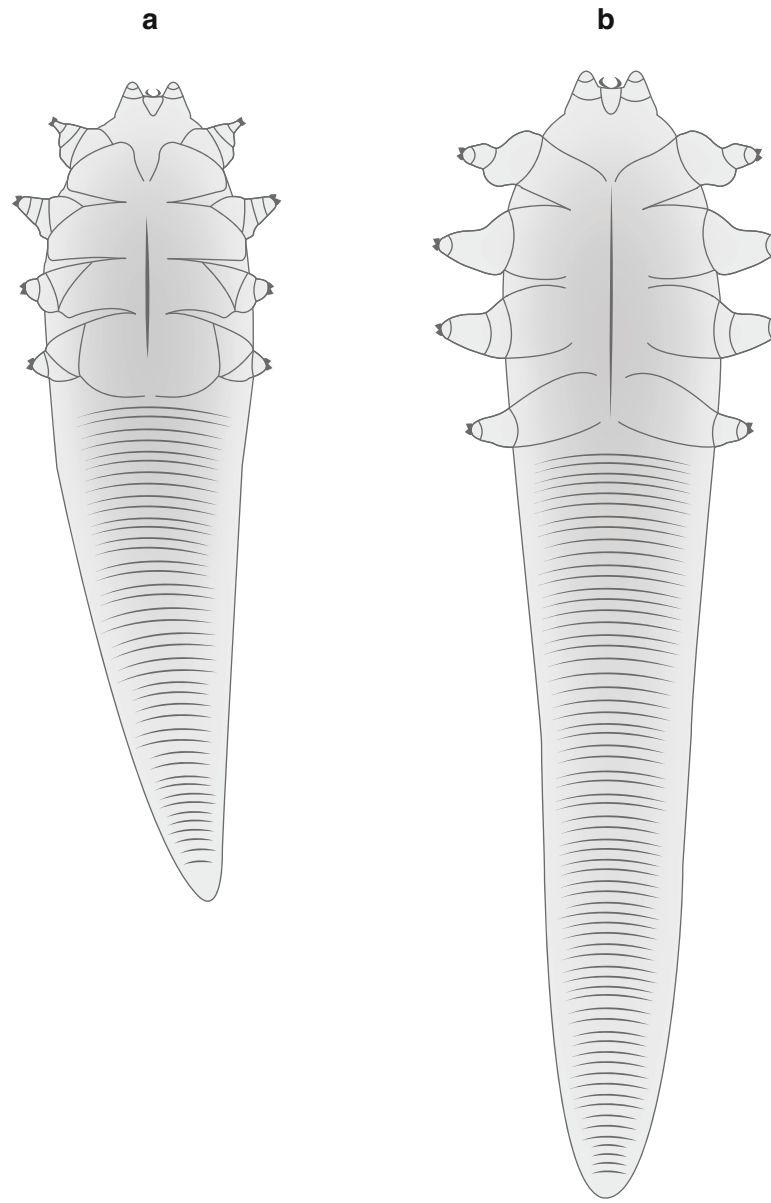


**Fig. 83.1** Illustration of adult *Demodex folliculorum* (**b**) and *Demodex brevis* (**a**) mites showing relative size and morphology

Mites are rarely found elsewhere on human skin in healthy individuals.

*Demodex* are considered by most investigators to be commensal organisms in human skin as in most individuals they produce no clinical signs or symptoms of inflammation. However, the role these mites play in the biology of human skin is unknown and their potential for a beneficial function (as mutualistic organisms) has not been investigated [13].

## 83.4 *Demodex* in Animals

In veterinary medicine, *Demodex* mites are recognised as being pathogenic parasites. *Demodex canis* (which is ubiquitous in dogs), is recognised as the cause of "canine demodicidosis", a disorder where mites proliferate in large numbers. The mild localised form causes small patches of scaly alopecia of their hairy coat [especially around the eyes and paws

**Table 83.1** *Demodex* mites in animals

| *Demodex* species | Animal infected | Associated disorder |
|---|---|---|
| *Demodex canis*<br>*Demodex cornei*<br>*Demodex injai* | Dogs | Canine Demodicosis Erythematous, scaly patches of alopecia, most common on face and legs but can develop to cover large areas of the body |
| *Demodex cati*<br>*Demodex gatoi* | Cats | Feline Demodicosis<br>Patchy erythema, scaling and alopecia |
| *Demodex ovis* | Sheep | Ovine demodicosis<br>Alopecia, erythema and scaling of the face, neck shoulders and back |
| *Demodex equi* | Horses | Equine Demodicosis<br>Alopecia and scaling over the face, neck, shoulders and forelimbs. Papules and pustules may be seen |
| *Demodex bovis* | Cattle | Bovine Demodicosis<br>Nodules, granulomatous inflammation, formation of scar tissue |
| *Demodex caprae* | Goats | Caprine Demodicosis Follicular papules and nodules on face, neck, shoulders and sides |
| *Demodex phylloides* | Pigs | Swine Demodicosis<br>Alopecia, presence of abscesses in the facial region, pruritus and weight loss |

(peripheral regions) with erythema]. Generalised demodicosis (complicated by bacterial infection) is the most severe canine skin disease, covering large areas of the body with marked crusting and can often prove fatal for the animal [14]. Although mites infest the terminal follicles of animals such as dogs, they are not usually seen in human scalp biopsies where terminal hairs are present, but they can be found in the miniaturised follicles of patients with male pattern alopecia and PPR [15]. Other animals affected by *Demodex* mites include cats (*D. cati*, *D. gatoi*), sheep (*D. ovis*), horses (*D. equi*, *D. caballi*), cattle (*D. bovis*), goats (*D. caprae)* and pigs (*D. phylloides*) [14, 16] (Table 83.1). In some animals such as dogs *(D. canis*, *D. cornei*, *D. injai)*, cats (*D. cati*, *D. gatoi*), horses (*D. equi*, *D. varia equi*), rats (*D. ratti and D. manus*) and hamsters (*D. aurati*, *D. criceti*) more than one *Demodex* species has been identified [17].

## 83.5 *Demodex* and Rosacea

The tendency for rosacea to develop after 30 yrs of age is paralleled by an increase in *Demodex* numbers. *Demodex* numbers increase in spring and summer months, when rosacea may be exacerbated [10, 18]. *Demodex* infestations as a causative role in rosacea have been implied since 1932 [19].

## 83.6 Counting Mites in Human Skin

Several studies have shown that there is a higher number of *Demodex* mites on the face of rosacea patients when compared to age- and sex-matched control subjects [18, 20–23]. A recent report using meta-analysis of previous studies has shown a statistically significant association between *Demodex* species infestation and the development of rosacea [24]. Varied sampling methods have been utilised by researchers in the extraction and identification of *Demodex* mites (Table 83.2). These include epilating hairs (eye lashes), expressing sebum from the depth of the follicle using a comedo extractor, adhesive bands (Cellotape) applied to the skin surface over a variable period, skin scrapings (suitable only when there is marked infestation), keratin plug extraction (in *Demodex folliculorum* particularly), and skin biopsies. These methods are not very suitable to be utilised for quantification purposes.

A recommended technique for the detection and quantification of these organisms is the standardised skin surface biopsy method (SSSB) [20, 21, 25–27], a non-invasive technique which collects the superficial part of the horny layer and extracts the contents of the upper part of the pilosebaceous follicle [28]. SSSB involves

**Table 83.2** Methods of studying *Demodex* mites in human skin

| Method | Technique | Limitations |
|---|---|---|
| Skin biopsy | 3–4 mm punch biopsy under local anaesthetic. Specimens are processed and stained with haematoxylin and eosin | This method cannot be used in quantitative studies as the sample area is limited to the diameter of the punch and some biopsies may not contain any follicles. *Demodex* are difficult to detect as they shrink and become transparent in preparations |
| Standardised skin surface biopsy | A drop of cyanoacrylic adhesive on a microscope slide applied to the skin and gently removed once dry. A standard surface area, generally 1 $cm^2$, is studied microscopically at standard magnifications | Mites deep in follicles or mites that have penetrated into the dermis are not detected in preparations. False negatives or reduced numbers of mites being detected may be due to bad adherence of the adhesive to the skin, due to sebum in between |
| Expression of sebum from the depth of the follicle | Follicular content and sebum are extracted by squeezing the affected skin (mostly the cheeks and nasolabial folds). Extracts are smeared on a microscope slide with a drop of mineral oil and examined microscopically | This method cannot be used as a quantitative measurement of mites, as variable numbers of follicles are sampled and the whole follicular content may not be retrieved |
| Adhesive bands (Cellotape) | Adhesive bands or sellotape are placed firmly on the skin, gently removed, placed on a slide and viewed microscopically | This method is not as sensitive as the SSSB method. Mites deep in the follicles will not be detected |
| Skin surface scrapings | Skin scrapings taken from suspect regions of the face, are placed on a slide, followed by drops of KOH to digest debris. Samples are viewed microscopically immediately | This is not a standardised quantitative measurement. Mites deep in follicles will not be present in samples. KOH will kill *Demodex* potentially making it harder to identify them with no movement |
| Epilating hairs | Lashes are epilated (generally three from each eyelid), placed on a slide with a drop of mineral oil and examined microscopically | This method cannot be used as a quantitative method |

placing a spot of cyanoacrylate adhesive on a clean microscope slide and placing the adhesive bearing side of the slide on the skin for approximately 1 min to allow it to polymerise, before gentle removal by an initial "rocking" movement with the slide to loosen its adherence to the skin, and then a gradual peeling effect while the surrounding skin is kept stretched with the fingers of the other hand. To standardise this technique, a surface area of 1 $cm^2$ is pre-drawn on the slide and only mites in this area are counted [21, 22]. Some researchers recommend pre-cleaning the area of skin to be sampled with ether [26, 27]. The material on the surface of the slide that has been in contact with the skin appears as a whitish circular crust and contains both the adhesive and the surface keratin as well as the upper follicular contents. A drop of immersion oil can be added to help clarify the sample. Application of a cover slip prior to microscopy helps to disperse the sample on the same plane and facilitates microscopic evaluation. For easy identification of mites, slides are studied microscopically at a magnification of ×40 and ×100 [26] (Fig. 83.2a–c). *Demodex folliculorum* mites extracted by this method can be easily visualised and counted. *D. brevis* is found deeper in the sebaceous gland [22] and is thus not usually present in such samples. Repeated skin surface biopsies at the same site on the skin is generally well tolerated (up to three times) and provides an improved yield of mites [26].

As has been pointed out earlier the identification of *Demodex folliculorum* mites in a sample taken by skin surface biopsy is not necessarily an indication of their pathogenic potential. It has been proposed that mite numbers more than 5 per $cm^2$ has pathogenic implications [16, 18, 27]. Forton and Seys [22] demonstrated high numbers of *D. folliculorum* on the cheeks of rosacea patients, using the SSSB method (mean = 10.8 Df/$cm^2$) particularly in

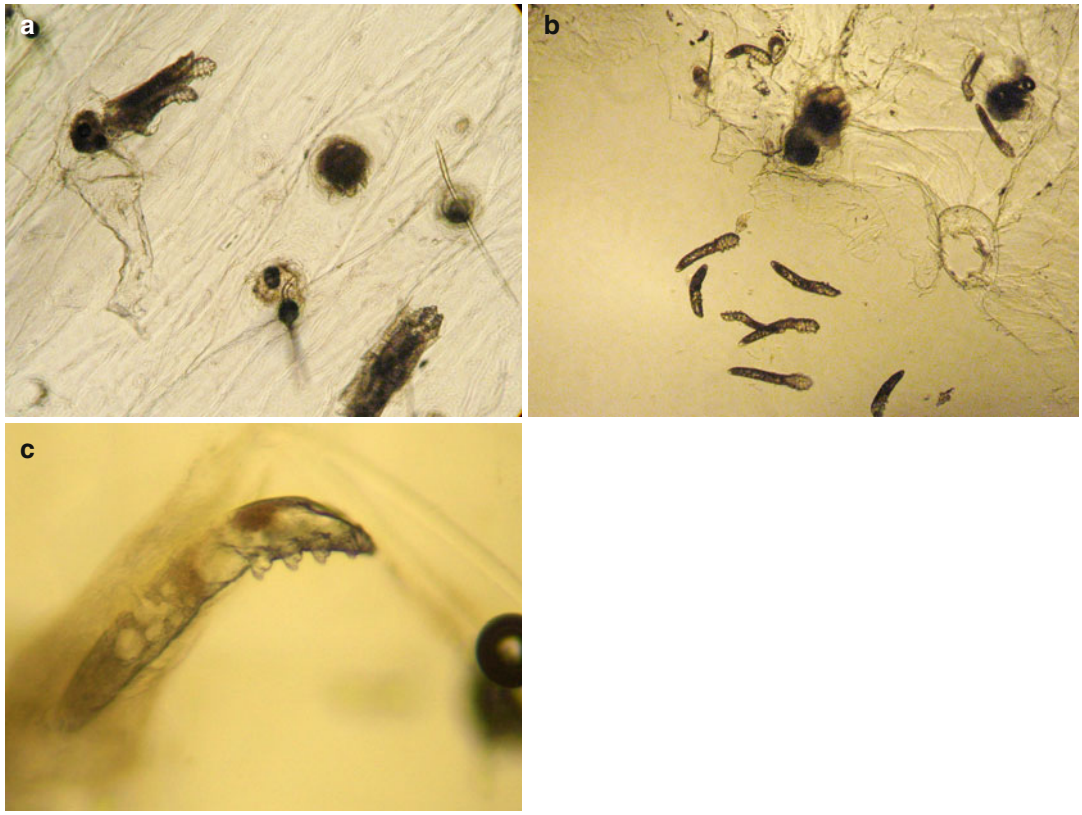


**Fig. 83.2** (**a**) An image of a SSSB sample clarified with 1–2 drops of immersion oil and viewed at magnification ×40. (**b**) Many free moving *Demodex folliculorum* mites can also be visualised using the SSSB method. (**c**) A *Demodex folliculorum* mite extracted from the face of a patient with rosacea using the SSSB method (original magnification ×100)

papulopustular rosacea patients (mean = 12.8 Df/cm$^2$) in comparison to a mean of 0.7 Df/cm$^2$ in controls. Bonnar et al. [21] showed that there were a higher number of *Demodex* mites in an area of 10 cm$^2$ in rosacea patients (49.8 Df) than control patients (10.8 Df). Georgola et al. [23] again detected more *D. folliculorum* mites in rosacea subjects (90.2 %) than age- and sex-matched controls (11 %). Rufli et al. [29] isolated large numbers of mites in 16 out of 18 rosacea cases. Symptoms were cleared by acaricide application in all affected patients in this study. Ayres and Anderson [19] also noted increased numbers of *Demodex* mites in cases of acne rosacea. Subjects admitted infrequent use of soap and water and instead used cleansing creams. Again symptoms were cleared with use of antiparasitic ointment. Shelley et al. [30] observed that symptoms of unilateral demodectic rosacea were suppressed with use of oral metronidazole but there was no reduction in the *Demodex* mite population. Only after miticidal treatment with topical crotamiton, were *Demodex* eliminated and eruptions cured.

## 83.7 *Demodex* in Other Clinical Settings

Studies are also showing that there is an increase of *Demodex* in subjects (>5/cm$^2$) with some form of immunosuppression: children with leukaemia receiving chemotherapy [31], patients with HIV infection and AIDS [32–34], patients undergoing phototherapy [35], and patients on chronic dialysis [36]. *Demodex* infestation has

also been associated with clinical entities: pityriasis folliculorum [25, 27, 37, 38], pustular folliculitis of the face [11], scalp eruptions [39], blepharitis [40–43], spinulosis of the face [44], granulomatous rosacea [45], and perioral dermatitis [46]. The term demodicosis remains controversial but the pathogenic role of *Demodex* in these dermatosis is indirectly confirmed when in almost all cases symptoms were cleared with use of acaricidal ointments. Demodicosis is generally manifested by mild symptoms, fine follicular scaling, erythema and superficial papules and pustules with some granulomas developing. Rosacea patients tend to have a previous history of flushing, persistent erythema prior to the development of papulopustules and the scaling is rather flaky [16, 27].

Since several studies have shown that symptoms in patients with rosacea or rosacea-like eruptions are alleviated with acaricidal treatment, the potential role of *Demodex* mites in the pathogenesis of rosacea cannot be disregarded.

## 83.8 Treatment

The mainstays of therapy and maintenance for papulopustular rosacea remain as systemic or topical antibiotics, such as topical metronidazole (0.75 % gel; 1 % cream), azelaic acid (20 % cream; 15 % gel), erythromycin (2 % solution), tretinoin (0.025 % cream or lotion; 0.01 % gel) and systemic oxytetracycline [47]. It is thought antibiotics work through their anti-inflammatory properties; however, their mode of action is unknown. Cases of demodicosis have been treated successfully with metronidazole [48, 49]. Shelley et al. [30] controlled "rosacea like dermatitis" with this antibiotic. This could not be attributed to its anti-parasitic properties as it is not thought to be miticidal [25], only with crotamiton (which has miticidal activity against the scabies mite, *Sarcoptes scabiei*) were *Demodex* and the eruptions completely cleared. Other treatments successful in cases of demodicosis include salicyclic acid, lindane, sublimed sulphur, oral ivermectin and topical permethrin.

## 83.9 Possible Role of *Demodex* in Rosacea

Several pathogenic mechanisms have been postulated by which *Demodex* mites may initiate inflammatory lesions of PPR (Table 83.3).

### 83.9.1 Cutaneous Microenvironment

The cutaneous microenvironment of rosacea patients may prove conducive for the proliferation of *Demodex* mites. Rosacea affects Caucasians most commonly with Skin type I and type II. These skin types may have increased sensitivity and abnormal barrier function which facilitates a high population of *Demodex* mites. At a critical number, a host immune response may be triggered to attempt to reduce mite numbers to an acceptable level. Studies have indicated individuals with Human leucocyte antigen (HLA) CW2 phenotype appear to be more susceptible to demodicidosis while the HLA A2 phenotype demonstrated resistance to increase in *Demodex* numbers [50].

### 83.9.2 Obstruction of Sebum Flow

Histology of biopsy material show large numbers of mites suggesting that mites may mechanically block hair follicles and sebaceous ducts by either their increased numbers or by initiating hyperkeratinisation of the infundibular keratinocytes and epithelial hyperplasia [37], obstructing normal sebum flow. We have regularly observed groups of mites (>6) in a brown drop of gelatinous-type readily adhesive material possibly a mixture of skin surface lipids, follicular keratinocytes and keratin, which may have the effect of plugging a follicle and producing microcomedones as have been observed in patients with rosacea [51]. Resulting stagnation could promote bacterial overgrowth (*Staphylococcus epidermidis* organisms have been frequently isolated from pustules of patient with rosacea) inducing inflammatory lesions [52, 53].

**Table 83.3** Possible role of *Demodex* mites in rosacea

| Possible action | | Potential consequences |
|---|---|---|
| 1 | Altered cutaneous microenvironment | The cutaneous microenvironment of rosacea patients may prove conducive for the proliferation of *Demodex.* At a critical number the host immune response may be triggered to reduce numbers to an acceptable level |
| 2 | Mechanical blockage of follicles | The number of mites could obstruct normal sebum flow and cause stagnation. Resultant host immune stimulation or bacterial overgrowth of *P. acnes* or other bacteria may induce inflammatory lesions |
| 3 | Alteration of sebum composition | *Demodex* mites may alter sebum composition; by selectively ingesting particular constituents, by changing the pH of sebum or by facilitating normal flora overgrowth |
| 4 | Alter local immune reactivity | *Demodex* may be able to downregulate the host's immune response, only becoming an opportunistic pathogen with the host's immune system is altered. The aberrant innate immune response in rosacea patients could allow the proliferation of *Demodex* to a critical number where the adaptive immune response is initiated and cutaneous inflammation occurs |
| 5 | Damage to follicular epithelium by mites | *Demodex* mites may rupture follicular epithelial lining cells by way of their specialised mouth pieces, with subsequent inflammatory reaction. Rupture of follicles with granulomatous reaction could occur in severe cases |
| 6 | Release of waste products by mites | Large numbers of dying mites could release crystalline waste products into follicular canal initiating inflammation |
| 7 | Release of endogenous enzymes | *Demodex* mites have been shown to possess enzymes such as lipase to facilitate digestion of lipids. Release of these may facilitate inflammation. *Demodex* may have other proteases that may dysregulate the endogenous protease/protease inhibitor balance in the skin |
| 8 | Endobacterial release from degenerating mites | Mites may have symbiotic endobacteria which cause immune reaction in host when released from dead mites |
| 9 | Surface bacterial transportation | Mites may transport bacteria on their outer surface from other follicles initiating inflammation |

### 83.9.3 Alteration of Follicular Milieu

Our preliminary studies have shown that patients with papulopustular rosacea have increased facial pH and reduced skin surface hydration levels [54]. The fatty acid profile of the skin surface lipid layer in PPR is also altered, with reduced levels of long chain saturated fatty acids [55]. The feeding habits of *Demodex* could potentially alter sebum composition: by selectively ingesting particular constituents, by changing the pH of sebum or by facilitating normal flora overgrowth.

### 83.9.4 Alteration of Local Immune Reactivity

Any potential role *Demodex* may play in the biobalance of normal skin has been largely ignored as they do not normally induce any inflammatory reaction and appear to function as commensals. These mites could be of benefit to the host (as mutualistic organisms) by ingesting bacteria or other organisms in the follicular canal, only becoming an opportunistic pathogen when their numbers increase due to a reduced host immune response as has been found for other commensal microorganisms [13, 53].

The host's immune response appears to tolerate these mites when their numbers are low. It can be postulated that mites are capable of downregulating the host immune response in some way to avoid elimination. The innate immune response may be triggered when the numbers increase beyond a critical point and result in a decrease in the mite population without inducing clinical inflammation. Histologic sections of clinically normal skin sometimes show a mild lymphocytic infiltrate surrounding follicles in which *Demodex* mites are present. In rosacea-prone patients there appears to be an aberrant innate immune response which results in the overexpression of cathelicidin peptides and its processing enzyme which

have been experimentally shown to result in the production of erythema and inflammatory lesions in a mouse model [56]. This immune hyperreactivity may be triggered by an increase in the follicular mite population in rosacea patients.

### 83.9.5 Trauma and Foreign Body Reaction

*Demodex* mites have highly specialised mouth parts capable of puncturing cells. As mites numbers increase in each follicle, their feeding regime may rupture the follicular epithelium, allowing penetration of the mites into the dermis or the diffusion of *Demodex*-related antigens across the epithelial surface, initiating an immune response. Histological examinations of skin biopsies taken from rosacea patients show inflammation occurring around infested and within follicles. Forton and Seys [22] have shown a statistically significant relationship between the presence of *Demodex* and perifollicular lymphohistiocytic inflammation. The immune response may be a cell-mediated or humoral immune reaction or both. Georgala et al. indicated a delayed hypersensitivity reaction in subjects with papulopustular rosacea, possibly triggered by antigens of follicular origin, most likely related to *Demodex folliculorum.* They demonstrated that $CD_4$ helper T cells predominated in dermal infiltrates from inflamed *Demodex* infested follicles, with an increase in macrophages and Langerhans cells also being noted [23]. Grosshans et al. [57] indicates a humoral response for the inflammatory reaction, showing that patients with rosacea have *Demodex*-specific antibodies to *D. caprae*, by assuming cross-antigenicity between *Demodex* species.

### 83.9.6 Toxic Waste

With an increase of mites in each pilosebaceous unit, large numbers of dying and dead mites could release their crystalline waste products into a damaged follicular canal, promoting an inflammatory response. In addition there may be a host inflammatory reaction stimulated by their chitinous exoskeletons or related chitinase enzymes. Similar host inflammatory reactions have been seen in patients with asthma in relation to house dust mites and their related products [58].

### 83.9.7 Enzymatic Actions

It has been shown that *Demodex* mites possess enzymes such as lipase to aid in digestion of lipids [59]. These enzymes may also initiate an immune response when released into the follicular canal. *Demodex* may also have other proteases that could interfere with the normal protease/protease inhibitor balance in the skin [60]. A study has shown numerous *Demodex* coated by alpha-1-antitrypsin and alpha-1-antichymotrypsin in biopsy specimens of facial skin lesions, suggesting these serum protease inhibitors are acting as a protective host response to these mites [61]. Bevins and Liu [62] have suggested that *Demodex* numbers may influence expression levels of cathelicidin (an antimicrobial peptide, found to be elevated in rosacea patients) by way of enzyme activity to activate host protease-activated receptors (PARS) which induce the expression of antimicrobial peptides and the upregulation of pro-inflammatory cytokines.

### 83.9.8 Endobacteria

*Demodex* mites may have an endosymbiotic relationship with bacteria, which cause an inflammatory response, when released into damaged follicles from dead mites. A study has shown that a bacterium (*Bacillus oleronius*) isolated from a *Demodex* mite is capable of stimulating inflammatory cells in rosacea patients. Antigenic preparations from this bacterium induced significantly more Peripheral Blood Mononuclear Cell (PBMCs) stimulation in rosacea patients (73 %) than control subjects (29 %) suggesting prior sensitisation of PBMCs from patients with rosacea to these bacterial antigens [63]. Studies on inflammatory ocular conditions have also implicated *B. oleronius* and *Demodex* mites as co-

pathogens in the development of blepharitis. One such study showed a statistical significant correlation between ocular *Demodex* infestation, facial rosacea and serum immunoreactivity to antigens of this bacterium [64, 65]. The presence of other endosymbiotic bacteria cannot be ruled out; *B. oleronius* may represent just one of many different or closely related species present in mites.

### 83.9.9 Surface Bacteria

The mites act as vectors for bacteria [17]. Various electron microscopy studies have shown bacteria adherent to the chitinous exoskeleton of mites, allowing these mites to transport bacteria from follicle to follicle, which could initiate inflammation [16, 22, 53].

## 83.10 Practical Observation

To date we have evaluated over 400 live *Demodex* mites, predominately extracted from the facial skin of PPR patients using SSB method. Through our studies we have encountered various difficulties with extracting clean (glue free), intact live *Demodex* mites for further investigations on their antigenic/inflammatory potential in cell culture experiments. Our observations and recommendations below may prove useful to investigators interested in studying these mites.

- **Visualising and identifying mites in samples:** A key aspect that aids in identifying these mites microscopically is by viewing their motility. In a SSB, the mites abdomen is often found stuck in the cyanacrylate glue and their upperbody, where their four pairs of legs and mouth parts are found (podosoma and gnathosoma, respectively), sways in gentle motion (almost like they are waving!). However, these mites are very prone to desiccation once removed from their follicular niche and die quickly. Clarifying a sample with oil and covering with a coverslip reduces this problem. Investigators should note that visualising for prolonged periods under a light microscope will also kill these mites as the sample becomes overheated from the microscope light. This can become obvious as the mites move/sway faster as the sample heats up prior to dying. Recommended viewing time per each sample is less than 10 min, before removal to a humidified chamber and ambient temperature, discussed below.
- **Removal of live *Demodex* mites from SSB:** To remove live intact *Demodex* mites from SSB, the sample cannot be clarified with oil and covered with a coverslip and viewed under a normal light microscope. The problems encountered here include: that the mites are covered in oil which will not be suitable in future cell culture experiments and once the coverslip is removed the sample needs to be re-examined to identify the area mites were visualised in, as focus and position are lost. This will also not work for light microscopes with long objective lens as there is no room for manoeuvring and manipulation of mites from samples.

  To aid in the extraction of live mites, we obtained a very fine forceps with a 0.1 mm sized tips (Moria forceps, Fine Science Tools). To remove the issue of space to gently manipulate mites from samples, we began to use a dissecting stereomicroscope (×90). The samples were also raised above the light source on a transparent platform to reduce the heat reaching the sample while maintaining the light through the sample.

  To overcome the problem of desiccation and death through removal from the skin, we store SSB slides as soon as possible post-extraction in a humidified chamber (simply, sterile cotton wool soaked in sterile water placed in the bottom of a petri dish, with the slide placed above balancing on two plastic tips) in an incubator. We also found through various experiments by altering the incubator temperature (37 °C, 30 °C, 28 °C, 25 °C) that 28 °C seems optimal and mites have remained live and motile for up to 9 days. Other investigators suggest 5 °C as maintenance temperature and between 16 and 20 °C as optimal conditions [66].
- **Preparation of *Demodex* mites for cell stimulation studies:** We have used both live

and lysed *Demodex* mites in cell stimulation studies (normal human keratinocytes and immortalised sebocytes (SZ95 line), respectively) to evaluate their inflammatory effect [67, 68]. Removal of mites from SSB is tedious and very gentle manipulation of keratin plugs and removal of mites by using the tip of the forcep is critical. The abdominal section of these mites (opisthosoma) is easily ruptured and care must be taken when placing the mites in medium for cell culture experiments. A major ongoing problem when working with these mites is the loss of approximately 50 % of mites during wash steps and on addition to cell experiments. The cuticle of these mites seems to stick to the sterile plastic tips (even when coated with a silicone base which should reduce protein binding) when washed with PBS and cannot be washed off. Mites stuck on the inside of the pipette tip can be easily visualised using the stereomicroscope. Investigators should be aware of this and only live mites visualised in the cell experiments can be taken as the "stimulation amount".

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# 84 The Role of Adenosine Triphosphate in the Pathogenesis of Rosacea: An Explanation for the Mode of Action of Tetracyclines for the Treatment of Rosacea

Albert M. Kligman

## Contents



**Core Messages**

- The triad of rosacea management includes patient education, skin care, and appropriate treatment.
- Systemic (oral) treatments for rosacea include antibiotics such as tetracyclines, macrolides, and metronidazole, as well as oral isotretinoin.
- The only FDA-approved systemic treatment for papulopustular rosacea is anti-inflammatory dose doxycycline 40-mg.

## 84.1 Introduction

Tetracylines have been used to treat acne vulgaris and rosacea for many decades; they share some common clinical manifestations. Their efficacy has usually been attributed to their antimicrobial activity, especially in the case of acne.

## 84.2 Tetracyclines and the Dermal Matrix

The antimicrobial explanation proved to be insufficient when it came to be known in 1980 that tetracyclines also had the capacity to inhibit the mammalian collagenase enzymes. This discovery led to the widespread use of tetracyclines for the

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treatment of periodontal disease. Collagenases can also degrade the dermal matrix, as commonly happens in photoaging and in rosacea, an interesting connection for this story. In fact, a host of empirical studies have shown that tetracylcines can be effective for the treatment of a variety of unrelated dermatologic disorders, viz, dermatitis herpetiformis, bullous diseases, especially bullous pemphigoid, certain autoimmune diseases such as lupus erythematosus, scleroderma, parapsoriasis, mastocytosis, and even a variety of non-dermatologic disorders, including rheumatoid arthritis [1].

## 84.3 Current Developments

Bacterial pathogens are not causative in any of these disorders. Capping all these developments was the unexpected discovery that a tetracycline derivative, doxycline hyclate, was effective in clearing the inflammatory and noninflammatory lesions of acne vulgaris at oral doses which were considerably below the concentrations that suppressed *Propionibacterium acnes*. These submicrobial doses also had the added benefit of not inducing resistance. It subsequently became known that a submicrobial dose of doxycline hyclate, 40 mg/day, was just as effective for the treatment of rosacea as full 1,000 mg doses of first generation tetracyclines. Doxycycline has acquired a major market share for the treatment of rosacea.

The successful use of submicrobial doses of a tetracycline for the treatment of rosacea sets the background for a study by Dr. Richard Granstein's group at the Weill Medical School of Medicine in New York City which proffers a different explanation of why tetracyclines work in rosacea. The recent report of this group centers on the potential role of adenosine triphosphate in causing the persistent centrofacial erythematous inflammatory reaction, which is the hallmark of rosacea.

## 84.4 Adenosine Triphosphate

Adenosine triphosphate (ATP) is a neuropeptide present in all living tissues, supplying chemical energy. The Weill group focused on the endothelial cells of the dermal microvasculature, using a human dermal microvascular cell line. A prior study showed that ATP upregulated the release of a number of pro-inflammatory factors. Endothelial cells are chief participants in all inflammatory disorders because they synthesize and secrete a variety of pro-inflammatory cytokines. Among these, they chose to study two potent ones, interleukin (IL)-8 and a growth regulated oncogene. These investigators had already demonstrated that tetracyclines inhibited the production of these cytokines in their endothelial cell like model in vitro. It was also known that chemical, physical, and bacterial perturbations invariably released ATP into the extracellular environment, acting there as danger signals for alerting other cells to migrate into the area of injury or infection. IL-8 was known to be a potent chemotactic agent for attracting neutrophils to the site of injury.

Putting all these events together, the authors postulated that drugs that could inhibit the release of pro-inflammatory cytokines would prevent the inflammatory process. This reasoning was no longer a hypothetical speculation since it had been convincingly demonstrated that tetracycline hyclate was an effective treatment for rosacea [2, 3].

This study nicely illuminated another feature related to the well-known fact that psychological stress precipitates and aggravates the episodic flushing and the persistent erythema so characteristic of the clinical profile of rosacea. ATP is a neuropeptide which is known to be a sympathetic nerve co-transmitter. Accordingly, stress would likely excite its release by neurons of the sympathetic system, inaugurating the release of pro-inflammatory cytokines.

The same variety of injuries is known to cause barrier disruption, a finding common to all chronic inflammatory conditions. The role of ATP-mediated cytokine release in rosacea invites a similar study of atopic dermatitis and perhaps even psoriasis.

This study, along with that of Dr. Gallo's group in San Diego, validates the value of basic science investigations for revealing the mechanisms by which drugs exert their therapeutic benefits.

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# Part XIII

# Classification and Clinical Types of Rosacea and Differential Diagnoses

# Standard Grading System for Rosacea

# 85

Gregor B.E. Jemec

## Contents



**Core Messages**

- No fully validated score for grading of rosacea severity is available, but the Standard Grading System provides basic framework for disease quantification.
- Patient input is important to the Standard Grading System.

## 85.1 Introduction

Apart from life and death very few biological things are absolute, and in a more practical perspective clinical medicine deals almost exclusively with likelihoods. The likelihood that a patient has a given disease is based on the presence of diagnostic factors, and differential diagnoses are always possible—if not always likely. The likelihood that a given treatment will work is established on the basis of randomised controlled trials essentially giving a chance that a treatment is better than placebo. This is reflected by the scarcity of true pathognomonic tests. Most often a disease is the result of a complicated interplay between many different endo- and exogenous pathogenic factors.

In this world of biological relativism, the correct assessment of disease severity is a prerequisite for the development of specific knowledge. In this context correct is taken to mean a true representation of the magnitude of the disease. Except for lethal diseases it is important to know "how

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much disease" is present. Quantification of disease severity makes it easier to establish likelihoods of co-occurrence through showing quantitative relationships, which are so important in biological systems. This holds true for predispositions, risk factors and treatment effects. It is therefore also useful in the development of dermatology as a science. A good example of this is the transformation of rheumatology into a modern science. This feat was achieved not only through a better understanding of immunology, but as much through a better description of the clinical reality allowing rheumatologists to establish clearer associations between risk factors or disease markers and a better definition of treatment outcomes.

## 85.2 Technological Options for Measurement of Disease Severity in Rosacea

When no biochemical markers exist for the quantification of a disease, a "black box" approach has been used, simply describing physical changes in the skin, e.g. how hot, red or thick the skin is [1]. Such physical measurements of physiological phenomena in the skin can give important information about skin diseases when collected under standardised conditions and may often do so at an early stage before the changes become clinically obvious. The data are furthermore continuous and most often correlate well with clinical assessment [2].

A hallmark of rosacea is erythema, and measurement of erythema through simple reflectance spectroscopy has been used to quantify the disease [3]. A similar approach has been made in atopic eczema where erythema has been shown to correlate well with other measures of disease severity [2]. Other rosacea hallmarks may be more difficult to measure precisely, but it may be speculated that the teleangiectasia can be measured using laser doppler flow imaging; and papular, oedematous or phymatous lesions may be suitable for ultrasound or optical coherence tomography imaging.

The technology most commonly used for grading rosacea is, however, standardised photography. Clinical photography allows both physicians and patients to assess changes over time better than unaided memory alone. When used in actual trials, however, the procedure needs to be standardised. Commercially available systems fulfil the stringent requirements. Photographs can subsequently be compared or graded by independent observers, where needed [4].

## 85.3 Clinical Staging Versus Grading

Staging and severity assessment are not identical procedures, as one is essentially static and the other dynamic. Quantification of disease may be undertaken for several reasons. It may serve as a classification of patients into groups with different prognosis as is done in oncology, or it may serve accurately to describe the amount of pathology seen by the physician or experienced by the patients.

In rosacea the classical staging has been proposed by Plewig and Kligman [5] (Table 85.1). This is a staging very suitable for classifying a population of rosacea patients in relevant clinical terms; it may be used to describe the long-term evolution of patients and is very useful to establish the overall comparability of groups in clinical trials. It is, however, similar to, e.g. the Hurley staging of hidradenitis suppurativa, which also offers categories of disease severity, while it is not sufficiently capable to monitor the short-term changes in progress or remission of individual patients.

For dynamic monitoring different systems are necessary. A review of the systems used before 2004 suggests not only great ingenuity of individual authors but also great diversity of methods [6]. Various combinations of counting or scoring prominent features of rosacea have been proposed, either in the entire face or in selected areas, and either alone or in combination with other measures. No uniform grading system was, however, described, and most papers described outcomes without reference to any validity testing of the proposed method(s).

Generally, the clinical grading of all inflammatory skin lesions can be composed of individual grading of erythema, induration, desquamation and area on a Likert type scale, typically ranging from 0 to 3. The prototypical score is the PASI

score, and one might therefore expect it to be a generic score, but it is not [7, 8]. Although the parameters are generic, not every inflammatory skin disease can be assessed using the PASI score and disease-specific differences occur, which necessitate the development and validation of separate disease-specific scores.

**Table 85.1** Plewig and Kligman Staging of Rosacea

| Stage | Description |
|---|---|
| I | • Prolonged erythema/cyanosis<br>• Teleangiectases<br>• Sensitive skin (stinging) |
| II | • Appearance of inflammatory papules/pustules<br>• Oedematous papules<br>• Prominent pores<br>• More frequent attacks of inflammatory papules/pustules<br>• Involvement of larger areas of the face |
| III | • Appearance of large inflammatory nodules (furunculoid elements)<br>• Tissue hyperplasia<br>• Oedema<br>• Phymata |

Which parameters are needed and included in these scores is usually determined by expert consensus, although patients may also be involved in the process by describing the most prominent symptoms [9]. In rosacea the hallmarks of the disease are well established and have formed the basis of the proposed standard grading system for the disease.

## 85.4 Standard Grading System for Rosacea

Grading systems estimate the relative effects of predispositions, risk factors and treatments in a quantitative manner appropriate for clinical medicine. Based on the consensus classification system of rosacea published by the National Rosacea Society Expert Committee, a grading system has been proposed, although not yet validated [10, 11] (Table 85.2). At present, this expert consensus effort represents the best attempt in standardising disease severity grading

**Table 85.2** Standard grading system for rosacea

| Feature | | Score | | | |
|---|---|---|---|---|---|
| Primary features | Flushing (transient erythema) | Absent | Mild | Moderate | Severe |
| | Non-transient erythema | Absent | Mild | Moderate | Severe |
| | Papules and pustules | Absent | Mild | Moderate | Severe |
| | Telangiectasia | Absent | Mild | Moderate | Severe |
| Secondary features | Burning or stinging | Absent | Mild | Moderate | Severe |
| | Plaques | Absent | Mild | Moderate | Severe |
| | Dry appearance | Absent | Mild | Moderate | Severe |
| | Oedema | Absent | Mild | Moderate | Severe |
| | – If present | Acute | Chronic | | |
| | – If chronic | Pitting | Non-pitting | | |
| | Ocular manifestations | Absent | Mild | Moderate | Severe |
| | Peripheral location | Absent | Present | | |
| | – If present, list locations | | | | |
| | Phymatous changes | Absent | Mild | Moderate | Severe |
| Global assessment by physician | Subtype 1: Erythematotelangiectatic | Absent | Mild | Moderate | Severe |
| | Subtype 2: Papulopustular | Absent | Mild | Moderate | Severe |
| | Subtype 3: Phymatous | Absent | Mild | Moderate | Severe |
| | Subtype 4: Ocular | Absent | Mild | Moderate | Severe |
| Global assessment by patient | | Absent | Mild | Moderate | Severe |

in rosacea, although considerable space for improvement exists.

The system is based on a scorecard listing three different elements in disease severity: Primary features, secondary features and subjective features. The primary features are flushing (transient erythema), permanent erythema, papules/pustules and teleangiectasia. The secondary features are: burning/stinging, plaques, dry appearance, oedema, ocular manifestations, peripheral location and phymatous changes. The subjective features are: physician rating by subtype (erythemotelangiectatic, papulopustular, phymatous or ocular) and patients' global assessment.

A total of 19 parameters are listed and assessed on a Likert type scale. Of these, 15 are assessed on a four point scale: absent–mild–moderate–severe, and for several of these definitions are suggested. The score of edema and peripheral location is, however, unclear as points are awarded for binary choices only: acute or chronic oedema and for pitting or non-pitting oedema. For peripheral location the locations are listed, giving an open-ended score. The overall score ranges from 0 to 45+ the contribution from the binary and open-ended scores. No specific instructions for how to add these have been provided. A list of suggestions is also given for the use of the instrument in a research setting, essentially adding more precise descriptions of the factors scored.

The obvious strength of the grading system is the strong anchoring in the disease definition and the comprehensive clarity of the features to be assessed. It is also strength that subjective elements are included, particularly the patient's assessment of eye involvement and overall severity add to the value of the grading system.

Validation tests are, however, necessary to establish the statistical limitation of the proposed system.

## 85.5 Trends in Disease Severity Assessment Methods

Further developments are not only possible but likely. With the increased complexity of clinical science required by large randomised controlled therapeutic and diagnostic trials, the need for structured research into disease quantification is gaining importance. Different trends are becoming apparent.

One trend is the measurement of specific biological markers through either genetic or immunological methods. The dream that a simple blood test will replace the clinical assessment is rarely achieved in dermatological diseases. Even the development of extensive biophysical measurement techniques has not proven useful in daily clinical practice, although some of the methods are well advanced and routinely used in trials. It may be speculated that future improved image processing and automated analysis systems will enable the conversion of standardised photographs into continuous scores reflecting at least erythema.

Another trend is that of patient involvement through composite scores [12]. In psoriasis research, a trend has been seen over the last 20 years, suggesting a movement towards the use of combined measures integrating both physician and patients assessed parameters in the overall evaluation of disease [13]. In rosacea this appears particularly important, as it has been shown that patients focus more on papules/pustules, whereas clinicians focus on erythema [14]. This is to some degree already done in the Standard Grading System, but explicit identification of the specific subjective complaints is lacking as a background for the patients' subjective input.

Finally a conservative trend also exists. The global assessment either in a Likert type scale, a verbal form or in the form of a Visual Analogue Scale score. This is often pursued by regulating authorities but has some support in specific research as well. In atopic eczema it appears to correlate well with biophysical measures, clinical scores and patients' self-reported disease severity and quality of life [2]. The lure of simplicity is great; even though it may not develop and improve the understanding of the individual disease as would a more specific grading system. Anchored global physician and patient assessment still form the backbone of clinical trials, but the standard grading system in rosacea may yet form a more exact and responsive alternative for the benefit not only of research but routine monitoring as well.

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# Classical Clinical Presentations of Rosacea

# 86

Uwe Wollina

## Contents



**Core Messages**

- Rosacea is typically described as a common chronic-recurrent facial dermatosis affecting predominantly adults.
- The term "rosacea" does not refer to a single entity and is characterized by multiple clinical presentations that are best defined as major subtypes and variants. Subtypes of rosacea may or may not share common clinical features and/or pathophysiologic associations.
- Common clinical findings of rosacea, described as primary features, include transient erythema (flushing), nontransient erythema, inflammatory lesions, and telangiectasias. Depending on the rosacea subtype, a given patient may present with some or all of these features.
- Other clinical findings of rosacea, described as secondary features, may include dry facial skin appearance, fine scaling, edema, plaque formation, phymatous changes, ocular manifestations, and involvement of extrafacial sites.
- The predominant subtypes are inflammatory (papulopustular) rosacea and erythematotelangiectatic rosacea. Other subtypes include phymatous, glandular, and ocular rosacea. A given patient with rosacea may present with features of more than one subtype, and the severity of signs and symptoms may vary.

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- Facial symptoms are commonly reported by patients with rosacea, primarily the inflammatory and erythematotelangiectatic subtypes. These symptoms reflect an inherent background of "sensitive skin" secondary to an increase in central facial transepidermal water loss. The most commonly noted symptoms are stinging, burning, and pruritus.
- Disorders characterized by a rosacea-form facial eruption which may simulate rosacea include topical corticoisteroid-induced rosacea-like eruption, demodecidosis, and perioral dermatitis.

## 86.1 Introduction

Rosacea is typically described as a common, chronic-recurrent, usually symmetrical facial dermatosis primarily affecting adults. In fact, rosacea is not a single entity, but rather is inclusive of multiple clinical presentations that are best characterized as subtypes [1–3]. A suggested classification of rosacea subtypes is depicted in Table 86.1 and Figs. 86.1–86.5 [1, 2]. It is important to recognize that patients "do not read dermatology textbooks and journals." As such, the signs and symptoms among individual patients may vary considerably and do not always fit neatly into a single description of a rosacea subtype. Over time, severity, frequency of exacerbations, and duration of remissions are also highly variable among affected patients. Although most common in fair-skinned Caucasians, rosacea is an "equal opportunity disorder" that may affect all ethnicities.

Although use of disease classifications may at times create some controversy, the recognition of rosacea subtypes provides a framework to work from when globally assessing a patient clinically [1–5]. From a management perspective, assessing subtype characteristics and capturing individual signs and symptoms are crucial, as response to different treatments vary depending on the subtype of disease and individual clinical features [3–5]. For example, patients with inflammatory rosacea presenting as multiple facial papules, pustules, and predominantly perilesional erythema respond very favorably to currently available medical therapies in terms of reduction in inflammatory lesions and perilesional erythema, although telangiectasias remain unchanged [5, 6]. On the other hand, patients with nontransient

**Table 86.1** Subtype classification and clinical features of rosacea

| Subtype | Clinical features |
|---|---|
| Erythematotelangiectatic | Transient facial erythema (flushing and blushing)<br>Persistent erythema (Erythema congestivum)<br>Telangiectasias<br>Edema<br>Dermatitis |
| Papulopustular (i.e., inflammatory) | Persistent erythema (Erythema congestivum)<br>Papules and pustules<br>Plaques (cellulitis)<br>Telangiectasias<br>*Demodex* folliculitis |
| Phymatous | Localized skin tissue hypertrophy (inflamed or not inflamed)<br>Sebaceous gland hyperplasia +/– fibrosis<br>Hyperplastic phymas: rhinophyma (nose), chin (gnathophyma), forehead (metophyma), ears (otophyma), and/or eyelids (blepharophyma)<br>Mucinous phymas<br>Pseudorhinophyma |
| Ocular | Conjunctival hyperemia: Telangiectasia of conjunctiva and lid margin<br>Corneal injury: Sensation of foreign body in the eye—Corneal complication (punctate keratitis, marginal keratitis, infiltrates, ulcers)<br>Blepharitis<br>Chalazion or hordeolum |
| Sensory | Painful (burning and stinging), pruritus, sensation of dryness, light sensitivity |

macular erythema and fine linear telangiectasias involving the nose and cheeks with absence of inflammatory lesions (erythematotelangiectatic rosacea) tend to respond much less favorably to available topical and systemic therapies and often warrant treatment with physical modalities such as laser and light sources [5, 6]. Well-developed phymatous changes, such as rhinophyma, also respond poorly to medical therapy, necessitating use of a physical modality approach [6].

The clinical assessment of the patient with rosacea is not a static process as the disorder is chronic and recurrent. The major clinical presentations of rosacea have been purposefully defined as subtypes and not stages as there is no definitive evidence that these clinical forms of rosacea are stages that progress from one to another [1, 2]. However, the clinical features of rosacea may vary in their severity and typically wax and wane in intensity. Over time, a given patient may develop features of more than one rosacea subtype [1–4]. As a result, it is not uncommon for clinicians to combine therapies, including, topical agents, oral agents, and physical modalities, in order to optimize treatment of specific clinical features affecting a given patient [5, 6].

## 86.2 Major Rosacea Subtypes

The diagnosis of rosacea is made based on history and physical examination [1, 2]. Although histologic features of rosacea have been noted, the diagnosis of rosacea is not often confirmed based on these findings [1, 3–5]. As a result, it is important to observe the signs and symptoms that may be associated with different clinical presentations of rosacea in order to discern what may be problematic for an individual patient and to make correlations with the degree of response to various therapeutic options.

In 2002, a subtype classification of rosacea was published which now serves as a valuable starting point for assessing patients, discussing clinical presentations, and directing therapies more accurately in order to target what is affecting individual patients (subtype-directed therapy) [1]. Prior to the definition of subtypes, clinicians would often discuss approaches to "rosacea" in articles or at conferences without clearly defining the clinical subtype of the disease, as if the term "rosacea" referred to a single entity [6]. The observation in 1989 that rosacea may represent more than one disease entity was very astute and clinically applicable [7]. In fact, all rosacea patients "are not created equal" and any discussion of rosacea is not complete without a more specific description of involved subtypes and specific clinical features. The predominant cutaneous subtypes are erythematotelangiectatic rosacea and papulopustular (inflammatory) rosacea with other defined subtypes including phymatous, ocular, and glandular rosacea [1–4].

The cardinal clinical features of erythematotelagiectatic rosacea are nontransient erythema involving the central face and a history of flushing, with telangiectasias also present in most cases [1–3] (Figs. 86.1 and 86.2). The erythema is diffuse and of variable intensity, with sparing of periocular skin. Flushing, unassociated with sweating or palpitations, is more commonly reported in patients with erythematotelangiectatic rosacea as compared to the inflammatory subtype [4, 8]. Importantly, flushing in and of itself does not imply the presence of rosacea as it may occur as a constitutional response to external heat, exercise, embarrassment, or nervousness or in association with underlying medical disorders such as carcinoid syndrome and systemic mastocytosis [1, 4, 9]. Flushing associated with rosacea is slower in onset and more prolonged than

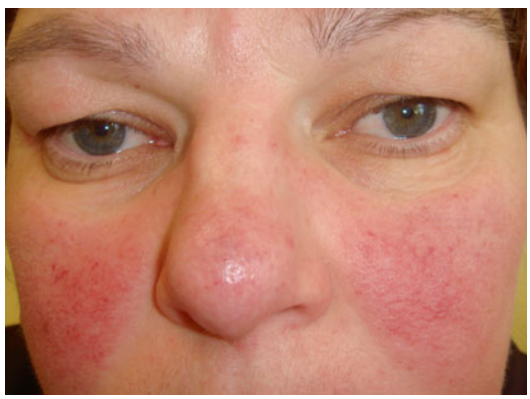

**Fig. 86.1** Erythematotelangiectatic rosacea subtype

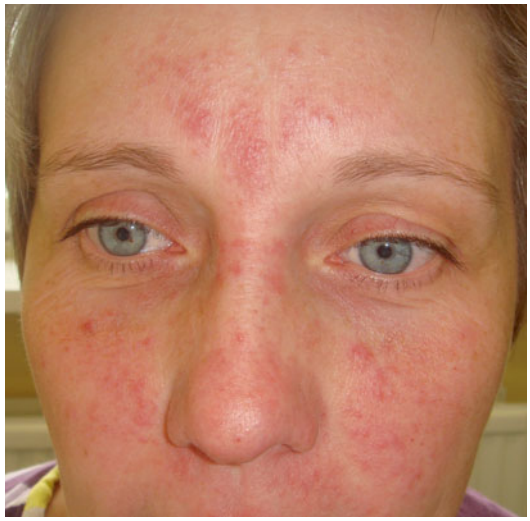

**Fig. 86.2** Erythematotelangiectatic subtype

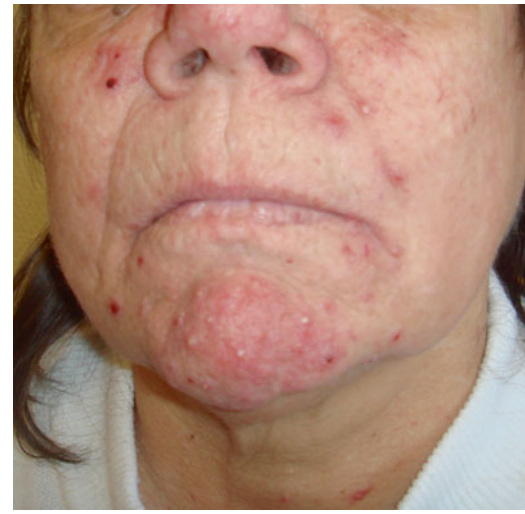

**Fig. 86.3** Papulopustular subtype

constitutional flushing [4]. Stinging and itching are frequently reported by patients with erythematotelangiectatic rosacea and are also common in those with the inflammatory subtype. Trigger factors that may exacerbate rosacea are well described in the literature and include heat, alcohol, some foods, weather changes, and vasodilatory medications [1, 3].

Inflammatory (papulopustular) rosacea presents with variable intensity of central facial erythema and a variable number of erythematous papules and pustules [1–3] (Fig. 86.3). Erythema associated with this subtype may be diffuse, more concentrated around inflammatory lesions (perilesional erythema), or both. Interestingly, facial erythema characteristically spares the periocular skin often with sharp demarcation ("raccoon eyes"). Telangiectasias are typically present, but are often subtle, and may be obscured by background erythema [3, 4]. Edema is usually subtle when present during episodic flares but may be more severe in some cases. Repeated exacerbations may lead to phymatous skin thickening or to the rare but dramatic complication of solid facial edema, most commonly observed in men [3, 4]. Intermittent episodes of flushing may be reported by some patients but is less consistently a feature of the inflammatory subtype as compared to erythematotelangiectatic rosacea [1, 3, 4, 8]. It has been reported that increased central facial transepidermal water loss is not as marked in inflammatory rosacea as compared to the erythematotelangiectatic subtype [10]. This at least partially explains why signs of "rosacea dermatitis" such as facial skin scaling and "sensitive skin" symptoms such as stinging, burning, and pruritus are not as consistently observed or as severe in intensity in patients with inflammatory rosacea as compared to those affected predominantly by the erythemato-\telangiectatic subtype.

"Sensitive skin" characterized by symptoms of stinging, burning, and pruritus, and a low threshold for development of signs and symptoms of skin irritation after application of many topically applied substances is very common in patients with erythematotelangiectatic rosacea [1, 4, 8–14].

## 86.3 Other Clinical Presentations of Rosacea

In addition to the two most common subtypes, other presentations have been noted. Phymatous rosacea, described as a distinct subtype, is reviewed in more detail in Chap. 87. The word *phyma* means growth. This form of rosacea most commonly affects the nose and presents as localized tissue hypertrophy, skin thickening, surface

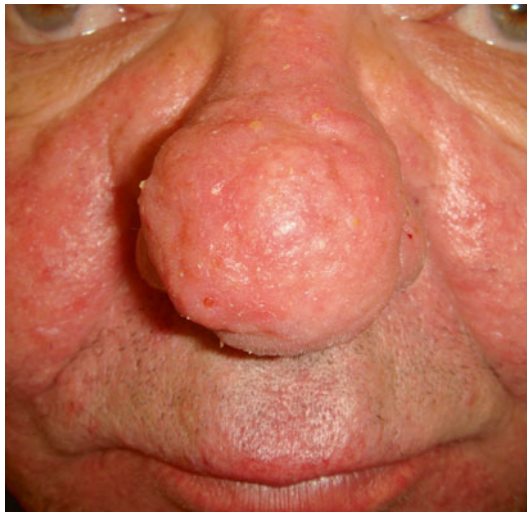

**Fig. 86.4** Phymatous subtype

nodularity, and patulous follicles often filled with clearly visible debris (rhinophyma) [1, 2]. Surface texture may vary, ranging from soft to fibrotic, and visible inflammation may or may not be present at any given point in time. Four types of phymatous changes associated with rosacea have been described: glandular, fibrous, fibroangiomatous, and actinic [15]. Phymas also occur on the chin (gnathophyma), the mid forehead (glabellaphyma), and the cheeks (malaphyma) (Fig. 86.4). In the hyperplastic type, sebaceous glands enlarge, and their ducts clog with keratinous debris. Inflammation is usually present, even when skin color is normal or similar to that of the surrounding ruddy complexion.

Ocular rosacea, also designated as a rosacea subtype, is a common disorder which may precede or be concurrent with cutaneous rosacea [4, 16]. Most cases present as conjunctivitis and blepharitis, with recurrent chalazion noted to be associated with ocular rosacea [4, 17, 18]. On examination, conjunctival hyperemia, telangiectasias ("bloodshot eyes"), and eyelid inflammation are often observed. Symptoms of ocular rosacea include burning, stinging, itching, photophobia, a dry sensation and/or foreign body sensation, and blurred vision [3, 4]. More severe potential complications are rare and may include punctuate keratitis, marginal keratitis, corneal infiltrates, corneal ulcers, iritis, scleritis, and

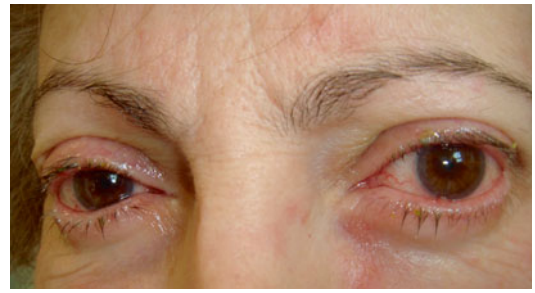

**Fig. 86.5** Ocular subtype

impaction of the meibomian glands (Fig. 86.5) [4, 17, 18].

The term glandular rosacea was proposed to described a clinical rosacea variant seen most commonly in men [4]. Glandular rosacea presents as thick sebaceous skin texture with edematous papules, pustules, and some nodulocystic lesions concentrated on the central and inner cheeks. In females affected by this phenotype, the chin is most commonly affected [4]. The background erythema in glandular rosacea is not often a brisk pink or red, but rather exhibits a hue of rust. However, the raised inflammatory lesions are distinctively erythematous and edematous. Over time, with repeated inflammatory exacerbations, chronic edema of the central face may occur. Flushing and features of "sensitive skin" are less commonly noted in patients with glandular rosacea [4].

The term sensory rosacea is not accepted by the experts committee [1, 2]; it has been used to describe the clinical picture in patients who report burning, stinging, and itching or even outright pain in facial skin.

Extrafacial lesions of rosacea have been described in the literature [19, 20]. Acneiform eruptions involving the central chest, scalp, neck, and extremities have also been reported [19, 21].

Granulomatous rosacea is another clinical presentation that has been described as a rosacea variant [1]. This form of rosacea presents as monomorphic papules or nodules involving the periorificial regions which exhibit a red, brown, or yellow hue. Involvement is often periocular and may be unilateral [4]. In most cases, nontransient facial erythema, predominance of central

facial involvement, and flushing are notably absent. Crawford et al have suggested that granulomatous rosacea has to be removed from under the umbrella of rosacea and that it should be renamed granulomatous facial dermatitis [4].

## 86.4 Rosaceaform Clinical Presentations

Prolonged facial application of topical corticosteroids may produce the characteristic signs and symptoms of rosacea and may be correctly termed topical corticoisteroid-induced rosacea-like eruption [22, 23]. The clinical presentation is usually most consistent with the inflammatory subtype [4]. The eruption occurs at sites where the topical corticosteroid has been applied on the face, may occur in any patient using the therapy over a prolonged period, and may be more likely to occur in individuals who are inherently susceptible ("rosacea-prone") [24, 25]. Upon discontinuation of topical corticosteroid application, a marked exacerbation of the rosacea-like eruption, referred to as rebound, frequently occurs.

The role of *Demodex* mites (*D. folliculorum*, *D. brevis*) in the pathophysiology of rosacea remains controversial [3, 4]. Nevertheless, demodecidosis has been shown to produce papulopustular and rosacea-like eruptions which simulate inflammatory rosacea [26–29].

As perioral dermatitis may sometimes simulate rosacea, it has been considered by some to fall under the umbrella of rosacea [4]. However, its distinctive clinical appearance, distribution, and usual pattern of few or no recurrences after successful treatment resulted in its exclusion from the list of rosacea subtypes [1].

Facial scaling and flaking is inherently associated with either erythematotelangiectatic or inflammatory rosacea, likely related to increased central facial transepidermal water loss [10, 30, 31]. The clinical signs of facial dryness, scaling, and flaking, determined not to be concurrent seborrheic dermatitis, have been noted to affect approximately 40 % of patients with inflammatory rosacea at baseline prior to initiation of therapy [30, 31]. These findings are believed to be a component of rosacea dermatitis [8, 31]. True seborrheic dermatitis presenting with classic involvement of the scalp, hairline, eyebrows, paranasal region, and melolabial folds has been reported to occur as an "overlap" in 22 % of patients with inflammatory or erythemato-telangiectatic rosacea [32]. This overlap is believed to be the concurrent presence of two common disorders in the same patient and is distinct from rosacea dermatitis [32].

The dermal matrix degradative effects of chronic photodamage are believed to contribute to the pathogenesis of rosacea [4, 8, 33, 34]. Nontransient erythema and telangiectasis are features common to both rosacea and chronic photodamage. However, not all individuals with chronic photodamage presenting as facial erythema with telangiectasias have rosacea. It is important to clinically differentiate chronic facial photodamage from rosacea, especially the erythemato-telangiectatic subtype, although the two may coexist. The distinction is clinically significant as patients who only have photodamage may be erroneously diagnosed with rosacea and may undergo unnecessary treatment. Unlike rosacea, the erythema and telangiestasias of chronic photodamage are more typically diffuse, with a tendency to evenly involve the lateral face, with extension onto the neck region and ear helices. Poikiloderma, especially involving the lateral neck and upper central chest, is a common finding in patients with chronic photodamage.

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# Rhinophyma: A Variation of Rosacea?

87

Uwe Wollina and Shyam B. Verma

## Contents



**Core Message**

- Rhinophyma is a part of phymatous rosacea affecting males 20 times more than females.
- Rhinophyma pathogenesis includes sebaceous gland hyperplasia, vascular sprouting, and dermal fibrosis.
- Rhinophyma presents in four major types, i.e., glandular, fibrous, fibroangiomatous, and actinic type.

## 87.1 Introduction: Definitions

Rhinophyma is part of rosacea stage III or phymatous rosacea in the classifications according to Plewig and Kligman [1] and the US National Rosacea Society Expert Committee on the classification and staging of rosacea [2].

## 87.2 Epidemiology

In general, rhinophyma is uncommon. The onset of rhinophyma usually occurs between the ages of 30–50 years, but rhinophyma is a disease more common in the second half of life. As in other types of rosacea Caucasians are more often affected although exact numbers have not been collected. Also in Indians rhinophyma is not a rarity in contrast to black Africans [3] or Japanese [4].

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## 87.3 Genetics

No genetic associations are known that prone patients to rhinophyma. However, the rarity in certain populations such as black Africans or Japanese argues for a genetic background [3, 4].

## 87.4 Clinical Manifestations

Rhinophyma is a disfiguring condition known for a long time as documented in masterpiece paintings [5]. The clinical presentation of rhinophyma is not completely different from other phymas except its location on the nose and the pronounced hyperplasia of sebaceous follicles. Indeed rhinophyma may be accompanied by either (papulopustular) rosacea or any other type of phymas like gnatophyma (chin), metophyma (forehead), ears (otophyma), eye lids (blepharophyma), or zygophyma (cheeks) [6]. In some patients rhinophyma is the one and only presentation of rosacea, in most rhinophyma is accompanied by facial and ocular rosacea.

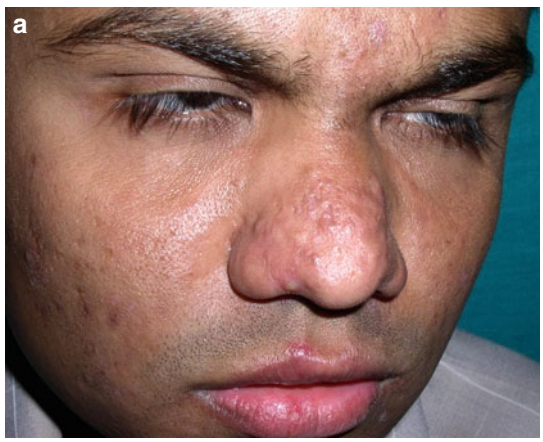
The affected skin often shows some degree of sun damage such as solar elastosis. Mild to moderate to most severe types of rhinophyma are known. Giant pendulating variants have been seen leading to an elephant-like facial appearance a social recluse. Most often affected are middle-aged or older males. Occasionally, a rhinophyma can develop in adolescents [7]. In rare cases of a female rhinophyma, they present with a mild type. The male to female ratio has been estimated as 20:1 [8].

Rhinophyma has been classified into four subtypes (Table 87.1, Figs. 87.1 and 87.2) [9].

There is a long list of differential diagnoses in rhinophyma (Table 87.2). In particular in

**Table 87.1** Classification of rhinophyma (Jansen and Plewig [9])

- Glandular type with increased sebum excretion
- Fibrous type with dominance of connective tissue overgrowth
- Fibroangiomatous type with edema and venous teleangiectasia
- Actinic type with nodular masses of elastic tissue



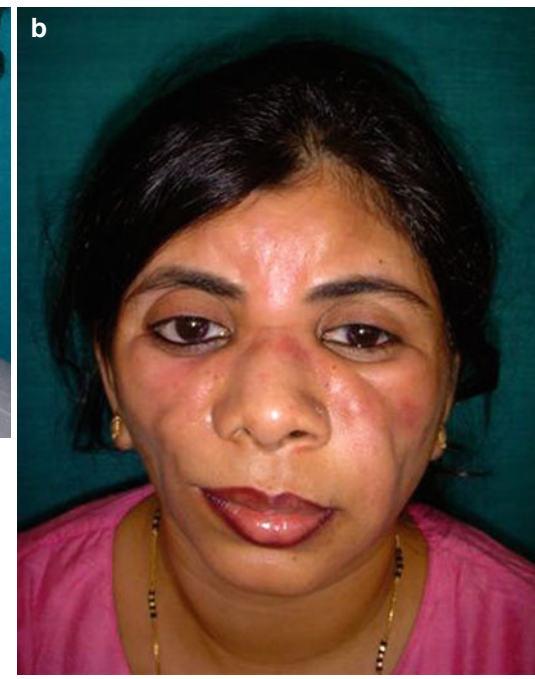
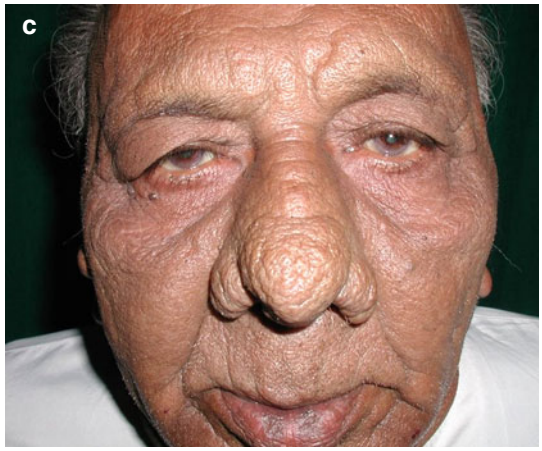




**Fig. 87.1** Types of rhinophyma. (**a**) Glandular type of early onset, (**b**) fibromatous type in combination with metophyma and zygophyma, (**c**) fibroangiomatous type and (**d**) actinic type with pendulating masses



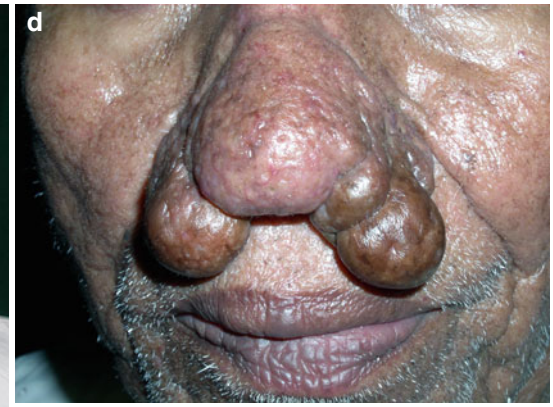




**Fig. 87.1** (continued)

**Table 87.2** Differential diagnoses of rhinophyma

| Diagnosis | References |
|---|---|
| Amelanotic melanoma | Peterson and Rowley [17] |
| Angiosarcoma | Mentzel et al. [18] |
| | Aguíla and Sánchez [19] |
| Cutaneous B-cell lymphoma | Stanway et al. [20] |
| Granuloma faciale | Requena et al. [21] |
| Leprosy | |
| Metastatic carcinoma | Nesi and Lynfield [22] |
| Microcystic adnexal carcinoma | Bewer et al. [23] |
| Sarcoidosis | Leonard [24] |
| Xanthoma disseminatum | Celić et al. [25] |

cases with rhinophyma only but no other manifestations of rosacea differential diagnosis has to be checked including histological investigation from deep skin biopsies.

## 87.5 Etiology and Pathogenesis

The skin surface shows irregularities, large pores, and a tumor-like growth. The tissue seems to be fibrotic. Indeed, histopathology demonstrates dermal fibrosis and elastosis, sebaceous hyperplasia, tortuous blood vessels, ectatic lymphatic vessels, and a variable degree of dermal lymphohistiocytic inflammation and edema. The dermal fibroblasts are Factor XIIIa positive, but S100 negative [10].

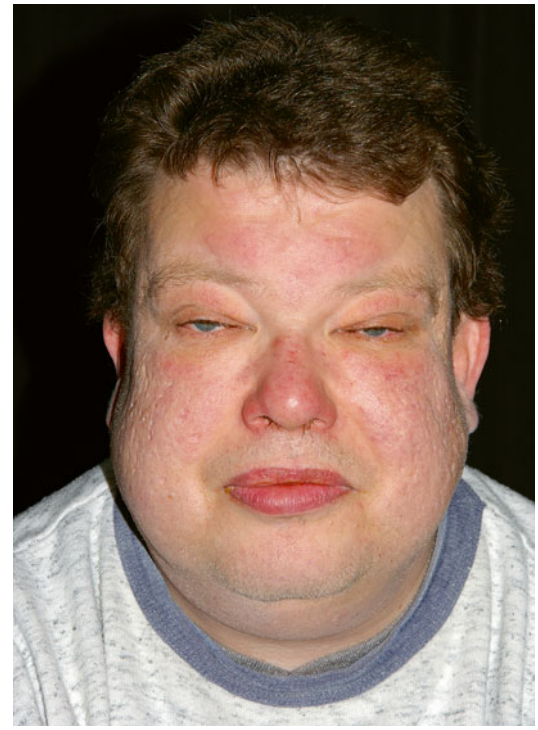


**Fig. 87.2** Metophyma, zygophyma and blepharophyma and nasal telangectasia without rhinophyma in a 45-year-old Caucasian

A persistent up-regulation of fibrogenic isoforms of transforming growth factor beta (TGF-beta) like TGF-beta-1 and -2, but not TGF-3 contributes to increased fibroblast

function [11]. In vitro, tamoxifen decreased TGF-beta-2 and fibroblast hyperactivity [12]. In severe types of rhinophyma mucin accumulation as been described [13].

Rhinophyma has been characterized by increased expression of vasoactive intestinal peptide-receptor (VIP-R) in dermal vessels and large perivascular cells. In addition neuroglandular antigen expression was seen in the connective tissue. This could contribute to the abnormal vascular response to various stimuli in rhinophyma [14].

## 87.6 Laboratory Findings

There is no specific or confirmatory laboratory test in rhinopyhma.

## 87.7 Trigger Factors

Trigger factors of rhinophyma are the same as in rosacea in general, i.e., UV-irradiation, cold and hot temperature, hot spices, alcohol, medications, and so on. In contrast to common myths rhinophyma does not show a positive association to alcohol consumption [15]. A very rare complication of rhinophyma is secondary localized cutaneous amyloidosis [16].

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# Ocular Rosacea

# 88

Dietrich Trebing

## Contents



**Core Messages**

- Ocular rosacea is a common associate of rosacea; 3–58 % of patients suffering from skin rosacea have an ocular manifestation.
- Ocular involvement seems to be independent of the degree of cutaneous involvement.
- Ophthalmological diagnoses are blepharitis with or without conjunctivitis, iritis, iridocyclitis, hypopyoniritis, and keratitis.
- Most common cutaneous signs are teleangiectasia, irregularity of lid margins, and meibomian gland dysfunction.
- Main symptom is a foreign body sensation and dry, irritated eyes, burning, itching, and tearing.
- Local treatment of ocular rosacea consisted of eyelid hygiene and topical erythromycin or metronidazol gel combined with oral tetracycline or doxycycline.

## 88.1 Introduction

Rosacea is a chronic inflammatory condition of vasomotor instability [1].

Ocular rosacea is a common associate of rosacea. It is often misdiagnosed, because ophthalmologists do not carefully examine the face of the patient and dermatologists do not routinely enquire for ocular symptoms. So, the range of an

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ocular involvement differs between 3 and 58 % [1–5]. The involvement of the eyes can be isolated or in combination with cutaneous rosacea. Rosacea-associated ophthalmic complications are independent of the severity of facial cutaneous rosacea. The disease of skin comprises 4 stages: flushing, erythema with teleangiectasia, papulopustular rosacea, and the most severe stage of edema and sebaceous gland hyperplasia leading to cutaneous changes such as rhinophyma [4].

## 88.2 Epidemiology

Rosacea generally affects between 2 and 5 % of adults in Germany, quarter of those suffering from ocular rosacea [6]. Rosacea occurs in adults, peaking between 40 and 50 years of age [7], rarely in the childhood [1, 7]. In northern Europe, dominated by fair-skinned, red-headed people, the prevalence is 10 % and in southern Europe 2 % [7].

## 88.3 Etiology and Pathogenesis

The etiology of ocular rosacea is unknown. The pathophysiologic mechanisms remain unclear, but various factors have been implicated in both ocular and cutaneous rosacea, such as climatic exposures, vascular changes, matrix degeneration, pilosebaceous unit abnormalities or microbial organisms, and, more recently, inflammatory mediators. In ocular rosacea, a meibomian gland dysfunction leads to thickened secretions, glandular dropout, and thickened eyelid margins.

## 88.4 Clinical Manifestations

Conjunctivitis (Fig. 88.1) and keratitis are predominating ocular symptoms [3].

Further blepharitis with meibomian gland inflammation and relapsing chalazions, ocular redness, superficial punctuate keratopathy, episcleritis, iritis, and corneal ulcers, vascularization (Fig. 88.1), and scarring [1, 4]. Main symptom is a foreign body sensation and dry, irritated eyes, burning, itching, and tearing [5].

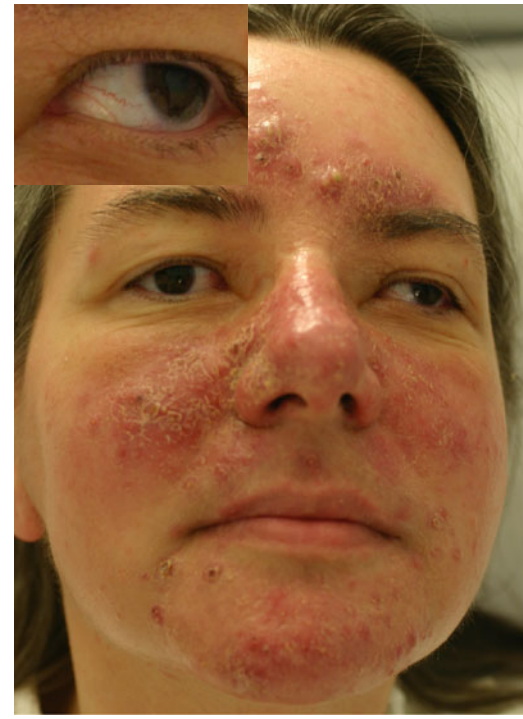

**Fig. 88.1** Severe pustular and granulomatous rosacea of the face with concomitant conjunctivitis

Without treatment, ocular rosacea can lead to blindness.

## 88.5 Treatment

Treatment of the various forms of rosacea should be adapted to the stage and phase of the disease. Rosacea is not curable, but the symptoms can for the most part be effectively controlled, thus preventing permanent damage to the skin, such as scarring and permanent edema [7]. Local treatment of ocular rosacea consisted of eyelid hygiene and topical erythromycin or metronidazole gel [1]. Further, warm compresses, artificial tears, and washing the area around the eye with warm water, including the eyelids, can be used to help alleviate symptoms. Additionally, oral antibiotics, typically doxycycline, may be prescribed. Some patients feel that dietary restrictions of caffeine, spicy foods, and alcoholic beverages may reduce or eliminate symptoms [3, 5].

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# Childhood Rosacea

# 89

Clio Dessinioti

## Contents



**Core Messages**

- Rosacea rarely affects children.
- Childhood rosacea may present with facial erythema, telangiectasias, flushing, papules and pustules, localised to the cheeks, chin and the nasolabial folds.
- Ocular manifestations in children include blepharitis, meibomianitis, recurrent chalazia, episcleritis, iritis and corneal ulceration, vascularisation and scarring.
- In contrast to adult rosacea, the phymatous form has not been reported in children.
- Differential diagnosis of rosacea in childhood includes steroid rosacea, acne and systemic lupus erythematosus.
- Childhood granulomatous rosacea needs to be differentiated from childhood granulomatous perioral dermatitis (CGPD), lupus disseminatus miliaris faciei (LMDF), granulomatous rosacea (GR) and sarcoidosis.
- Treatment does not differ from that used for adult rosacea and includes topical metronidazole and azelaic acid, and when indicated, oral tetracyclines for children >8 years old, or oral erythromycin for younger children.

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## 89.1 Introduction

Rosacea is a condition commonly affecting adults 30–50 years old (see relevant chapters), but can present at any age and has rarely been reported in children [1, 2].

## 89.2 Clinical Characteristics of Childhood Rosacea

Similarly to adult rosacea, rosacea in childhood is characterized by facial erythema, telangiectasias, flushing, papules and pustules, localised to the cheeks, chin and the nasolabial folds. However, contrary to adult rosacea, the phymatous form has not been reported in children [3].

Ocular rosacea may develop alone or in association with cutaneous manifestations. It presents with blepharitis, meibomianitis, recurrent chalazia, episcleritis, iritis and corneal ulceration, vascularisation and scarring [3].

Childhood granulomatous rosacea (GR) is considered a variant of rosacea [4]. It belongs to a group of idiopathic facial granulomatous dermatoses of childhood, that is, those which cannot be attributed to any known infective or noninfective agents. It presents with red to yellow-brown papules over the face and is characterized by a granulomatous lymphohistiocytic infiltrate on histopathologic examination [4]. GR has been reported in children infected with the human immunodeficiency virus, in which case Demodex mites were observed [5]. A possible case of juvenile rosacea has been presented by Savin et al. in which the lesions resolved after a median of 1 year [6].

According to the National Rosacea Society Expert Committee on the classification of rosacea, the typical symptoms of rosacea may be absent in GR and are not needed for diagnosis [4]. So, GR patients often do not have persistent facial erythema; the lesions are not confined to the convexities of the face, may be unilateral, and usually do not flush [7].

Rosacea during childhood is a chronic condition that often persists into adulthood.

## 89.3 Differential Diagnosis of Rosacea in Childhood

Childhood rosacea needs to be differentiated from a plethora of conditions.

**Steroid rosacea** is a term used for rosacea-like features due to the use of topical or inhaled corticosteroids. It presents with monomorphic papules, pustules and telangiectasias that may be accompanied with atrophy [3].

**Systemic lupus erythematous** may present with a malar (butterfly) erythema. Differential diagnosis will be based on positive antinuclear and anti-DNA antibodies, and the histology [3].

**Childhood granulomatous perioral dermatitis** has initially been described by Gianotti et al., who called it Gianotti-type perioral dermatitis' [8]. It is a rare disease of unknown aetiology [9]. It has been described in prepubertal children aged 9 months to 13 years old. It has predominance for skin of color [10], but cases of white-skinned children [11, 12] have been also described. It presents with asymptomatic, small, dome-shaped, monomorphous, flesh-coloured papules and micronodules 1–2 mm of diameter. Diascopy shows an 'apple-jelly' colour. It primarily affects the periorificial parts of the face: the perioral, periorbital and perinasal areas. Also, it can affect the ears, upper eyelids, cheeks, chin, forehead and nose. Blepharitis has been reported [11, 12]. Histopathology reveals a dermal non-caseating granulomatous infiltrate surrounded by variable numbers of lymphocytes and histiocytes, with some predilection for the perifollicular and interfollicular dermis, in a manner reminiscent of granulomatous acne rosacea [9, 11, 12]. It has been proposed that the presence of granulomas is not a prerequisite for diagnosis and that it could represent a late or secondary phenomenon related to disorder of the hair follicle, like in granulomatous rosacea [10]. In fact, CGPD has been proposed to be a variant of GR [12] as they present many similarities. They both present clinically with erythematous or yellow-brown, dome-shaped papules in the face and histologically with perifollicular lymphohistiocytic or granulomatous infiltrate. Further similarities include the possibility of blepharitis, conjunctivitis,

extrafacial lesions and the response to systemic tetracycline and topical metronidazole [12, 13]. In a subset of patients, CGPD may be the first manifestation of a rosacea diathesis [12].

**Childhood sarcoidosis** is rare and is nearly always associated with the involvement of another organ [14, 15]. Screening for systemic sarcoidosis is warranted, in case of any granulomatous skin lesion without apparent diagnosis [15].

**Lupus miliaris disseminatus facei (LMDF)**, also known as facial idiopathic granulomas with regressive evolution [16], is of unknown aetiology. It affects adults and adolescents. Rare cases of LMDF have been reported in Japanese children, and it has been suggested that they represent cases of CGPD under the name of LMDF [17]. LMDF presents with yellow-brown, dome-shaped papules, mainly in the convexities of the face: lower eyelids, lower part of the glabella, cheeks, nasolabial folds and perioral area. Diascopy shows an 'apple-jelly' colour. Occasionally the neck, axillae, shoulders, arms, hands, groins and legs are affected [17]. Typical histopathologic findings include epithelioid granulomas with caseation. It runs a chronic course, resolving spontaneously within 1–3 years, usually with scarring. LMDF has been considered to be a distinct condition, a manifestation of the papular type of rosacea, or a form of GR [13, 18].

**Acne** can be differentiated from rosacea based on the presence of comedones.

## 89.4 Treatment of Childhood Rosacea

Treatment of rosacea in childhood is similar to that in adult rosacea. Emphasis should be given to avoidance of triggering factors, such as sun exposure, hot beverages or hot baths. As the skin of the rosacea patient can be more sensitive to topical treatments, the daily use of emollients and gentle cleansers is advised [3].

Topical treatments include metronidazole 0.75 % cream, or metronidazole 0.75 % or 1 % gel, which are effective to treat erythema, papules and pustules. Azelaic acid (20 % cream or 15 % gel) has been reported to be efficacious, with mild side effects including stinging and burning sensation. In adult rosacea, a randomised controlled trial showed that pimecrolimus 1 % cream, a calcineurin inhibitor, had similar efficacy compared to metronidazole 1 % cream, for the inflammation and erythema, with a good tolerability profile [19]. On the other hand, there have been reports of a rosaceiform eruption after pimecrolimus application [20]. There are no such studies in children with rosacea.

For moderate-to-severe cases of childhood rosacea, the treatment of choice is systemic tetracyclines. Tetracyclines are however contraindicated in children younger than 8 years of age, as they can cause dental staining and temporary depression in bone growth. Alternative options are oral or topical erythromycin [2].

Ocular rosacea is managed with adequate eyelid hygiene, including cleansing eyelids with warm compresses, and the use of topical erythromycin or bacitracin ointment. Systemic antibiotics may be required for more severe cases, in which case the child should be referred to an ophthalmologist [3].

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# Differential Diagnosis of Rosacea

# 90

M. Badawy Abdel-Naser

## Contents



**Core Messages**

- Rosacea is a common chronic skin disorder characterized by several stages or subtypes and each must be differentiated from a number of different cutaneous and systemic disorders.
- Examination of the face must be completed by examination of the skin of the rest of the body including scalp, nails, and mucous membranes.
- Diagnosis of rosacea is mainly based on characteristic clinical features, namely, erythema, telangiectasia, papules, swelling, and pustules; however, rarely skin biopsy may be needed to exclude other similar conditions.
- Acne vulgaris, steroid-induced acne, seborrheic dermatitis, perioral dermatitis, and lupus erythematosus are among the most common dermatoses that can be confused with well-established erythematotelangiectatic and papulopustular rosacea.
- It is not uncommon that rosacea may coexist with other disorders, such as seborrheic dermatitis, acne vulgaris, and lupus erythematosus.

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## 90.1 Introduction

Rosacea is best regarded as an inflammatory facial skin disorder. As already mentioned in previous chapters, it is heralded usually by frequent episodes of flushing (stage I, pre-rosacea, subtype 0) followed in 81 % of patients by persistent erythema (erythrosis) and telangiectasia (stage II, erythematotelangiectatic, subtype 1) in the center of the face, which may proceed in a minority of patients (19 %) to formation of papules and pustules (stage III, papulopustular, subtype 2) and even nodules (stage IV, phymatous, subtype 3) [1, 2]. This variable clinical presentation makes differential diagnosis rather wide according to presenting symptoms and signs (Table 90.1). Sometimes, biopsy is needed to establish the diagnosis.

## 90.2 Differential Diagnosis Related to Acne Stages and Subtypes

### 90.2.1 Stage I. (Pre-rosacea—Subtype 0)

Transient or temporary erythema (flushing, blushing) may occur in several unrelated conditions. Taking a careful history always discloses the cause. Exercise, embarrassment, anger, stress, anxiety, guilt feelings, pregnancy, menopause and peri-menopause, strong emotions, heatstroke, sunburn, sex, alcohol, fever, spicy food, and monosodium glutamate (MSG) in Chinese food are common causes of flushing [3]. Drugs and toxins can also cause facial erythema with or without affection of the whole body. The common red alcoholic face is due to vasodilatation and telangiectasia. Disulfiram produces flushing of the face associated with an unpleasant feeling when administered with alcohol, an adverse reaction used as a therapy for the alcoholics. Cephalosporins, griseofulvin, metronidazole, and sulfonylureas are other drugs that may also produce flushing with alcohol. The red man syndrome following intravenous vancomycin is the most known example of a red face developing in a patient following medication; similarly cyclosporine A may result in flushing with anaphylactic symptoms [4]. Food allergens, sulfites, MSG, tartrazine, and scombroidosis (and other seafood poisoning) cause the restaurant flushing syndrome.

A history of atopy and ingestion of known food allergens, such as peanuts, egg, fish, and walnuts, together with positive results of skin tests or RAST to these foods, suggests food allergy. Rapid onset, within minutes, of symptoms consisting of flushing, bronchospasm, and hypotension is consistent with a sulfite reaction. Burning, pressure, and tightness or numbness in the face, neck, and upper chest following ingestion of Chinese food are due to MSG. Presently, the use of these substances has been eliminated from most restaurants. Bronchospasm and urticaria in a patient with a history of aspirin intolerance suggest tartrazine sensitivity. Flushing, urticaria, pruritus, gastrointestinal complaints, or bronchospasm developing in everyone ingesting a fish meal indicates scombroidosis, ciguatera, or other seafood poisoning. Severe headache or hypertension together with facial erythema can result from ingestion of naturally occurring amines, such as tyramine (cheese, red wine) and phenylethylamine (chocolate) [5]. Flushing is also a side effect of calcium channel blockers (nifedipine,

**Table 90.1** Summary of the differential diagnosis of rosacea

| Common | Uncommon |
|---|---|
| Seborrheic dermatitis | Flushing disorders (drugs, physical factors, systemic and skin diseases) |
| Acne vulgaris | Cardiac diseases, lymphomas and polycythemia vera |
| Erythromelanosis faciei and keratosis pilaris rubra | Dermatomoysitis and systemic scleroderma |
| Lupus erythematosus | Contact dermatitis and photosensitivity |
| Demodex folliculitis | Atopic dermatitis |
| Steroid-induced acne and perioral dermatitis | Sarcoidosis (papular—lupus pernio) |

verapamil, diltiasim), quinidine, vasodilator drugs (nitroglycerine, amyl nitrite, butyl nitrite), opiates, cholinergic drugs, and contrast media. The same phenomenon, however, can also be seen in diseases, such as pheochromocytoma, carcinoid tumor, and systemic mastocytosis [6].

### 90.2.2 Stage II (Erythematotelangiectatic—Subtype 1)

Angioneurotic edema or urticaria may affect the face and is manifested by facial erythema; however, lesions develop rapidly, usually asymmetric and evanescent. The presence of swollen lips in addition to the facial erythema occurs in Melkersson Rosenthal syndrome (cheilitis granulomatosa). Steroids, both systemically and topically, are the most commonly described drugs that can result in facial erythema. The condition is not only due to vasodilatation as in case of Cushing's syndrome but also as a result of steroid-induced rosacea and perioral dermatitis; both are not easy to distinguish from rosacea and careful history taking helps in establishing the diagnosis. Steroid addiction is a term given to the rebound phenomenon of intense redness, scaling, crusting, and sometimes pustulation following cessation of steroids after long-term topical usage [3, 4, 7]. MARSH syndrome is characterized by melasma, acne, rosacea, seborrheic eczema, and hirsutism [8]. Rubeosis diabeticorum is a peculiar form of facial redness occurring in 30 % of those who take chlorpropamide and alcohol simultaneously. Flushing and redness begin around the eyes and spread to the forehead and may be associated with nausea and dyspnea. The predisposition to this reaction is probably inherited as an autosomal dominant trait [9].

Exposure to wind, dust, and sandstorms induces facial erythema in all exposed individuals particularly atopics (Fig. 90.1) and, likewise, exposure to cold during winter sport activity and heat, burn, X-ray, and ultraviolet radiations

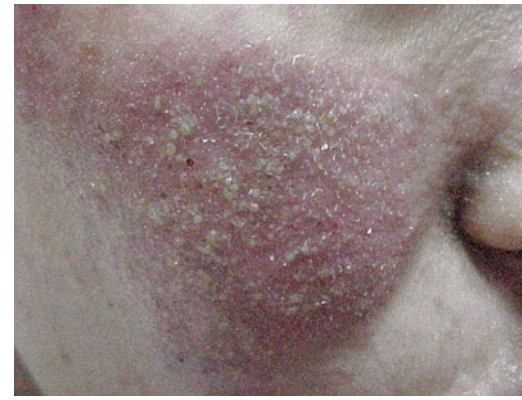
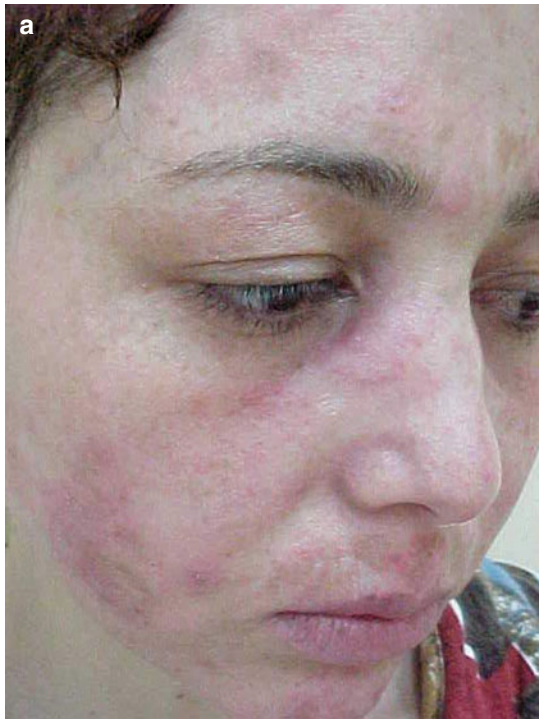


**Fig. 90.1** Contact dermatitis with superimposed infection in an atopic patient showing bilateral and almost symmetrical diffuse ill-defined erythema and papulopustular lesions on the face

[10, 11]. In addition to Hodgkin's disease, hyperthyroidism, superior vena caval obstruction, and polycythemia vera are diseases that are associated with flushing and/or plethoric face [12, 13]. Autoimmune connective tissue diseases are other disorders causing facial erythema. Malar erythema or discrete maculopapular eruption with fine scaling on the butterfly area and lacking pustules is a common manifestation of systemic lupus erythematosus (Fig. 90.2a, b). Lupus patients may have coexistent rosacea that flares as systemic steroids are tapered [13]. Dermatomyositis with or without myositis (dermatomyositis sine myositis) is manifested by heliotrope or dusky red erythema of the face and upper chest that together with Gottron's sign is regarded as pathognomonic signs [14]. Facial erythema may occur in maxillary sinusitis and congestive heart diseases, e.g., mitral valve stenosis. Chronic obstructive air way diseases, e.g., chronic asthmatic bronchitis and emphysema, result in chronic oxygen deprivation with a plethoric facies. In HIV infection facial erythema is common and is mostly due to psoriasis or seborrheic dermatitis [15, 16]. Photosensitive dermatitis that involves face and sun-exposed parts in addition to dementia and diarrhea characterizes pellagra due to niacin or tryptophan deficiency as a result of alcoholism, anorexia nervosa, isoniazid therapy, carcinoid



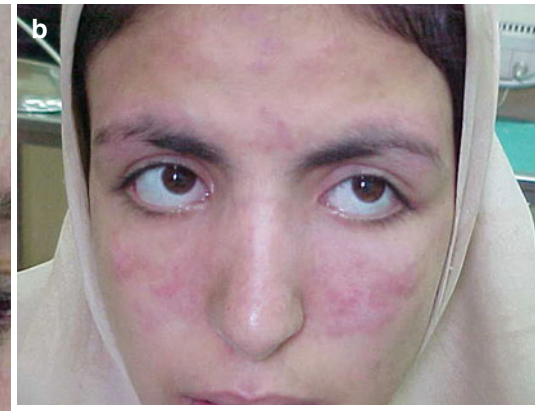




**Fig. 90.2** (**a**, **b**) Two different cases showing similar features in the form of erythema characteristically involving the butterfly (malar) area of the face, one of the American Rheumatism Association criteria for the diagnosis of systemic lupus erythematosus

tumor, or 5-fluorouracil therapy [17]. The presence of telangieactasias and similar lesions on the extremities indicates lupus pernio. Cutaneous lymphoma in particular Sezary's syndrome, which is characterized by erythroderma, represents an example of T-cell lymphoma with facial erythema [18]. Diagnosis of facial erythema in these cases depends on the associated findings rather than on the character of the erythema itself.

### 90.2.3 Stage III (Papulopustular—Subtype 2)

Several other conditions may simulate any of the stages of rosacea. Seborrheic dermatitis often coexists with rosacea and it is differentiated by the presence of greasy scale in seborrheic sites. Ocular rosacea is frequently misdiagnosed as blepharitis of seborrheic dermatitis and is thus improperly treated [15]. Acne vulgaris is the classic differential diagnosis of rosacea. It typically occurs in a younger age group and is characterized by white and black comedones as well as inflammatory lesions. A family history of acne, the presence of scars, and the absence of blushing and telangiectasia are in favor of acne. Patients in their 20s and 30s may have both diseases simultaneously [19]. Perioral dermatitis is distributed around the mouth sparing the vermilion border. Lesions are tiny papules or papulovesicles and with no diffuse background erythema. Other conditions to be considered include bromoderma, iododerma, sarcoidosis, pustular folliculitis, and papular syphilid [20]. Granulomatous rosacea (acne agminata) (Fig. 90.3a, b) is not easy to distinguish from lupus vulgaris and sarcoidosis and histopathological examination may be required (Fig. 90.4a, b) [21]. Erythromelanosis faciei and keratosis pilaris rubra show erythema of the lateral cheeks. The presence of tiny follicular papules and keratotic plugs distinguishes these disorders. The associated follicular atrophy and scarring alopecia seen in keratosis pilaris atrophicans faciei (ulerythema ophryogenes) are quite distinctive [22].

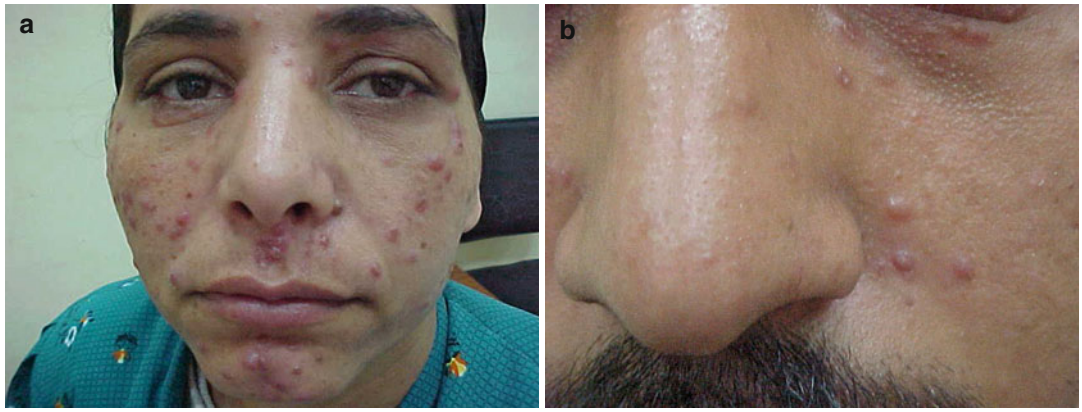



**Fig. 90.3** (**a**, **b**) Two different cases of granulomatous rosacea showing multiple skin-colored or slightly erythematous papules and small nodules on the face characteristically involving also the eyelids

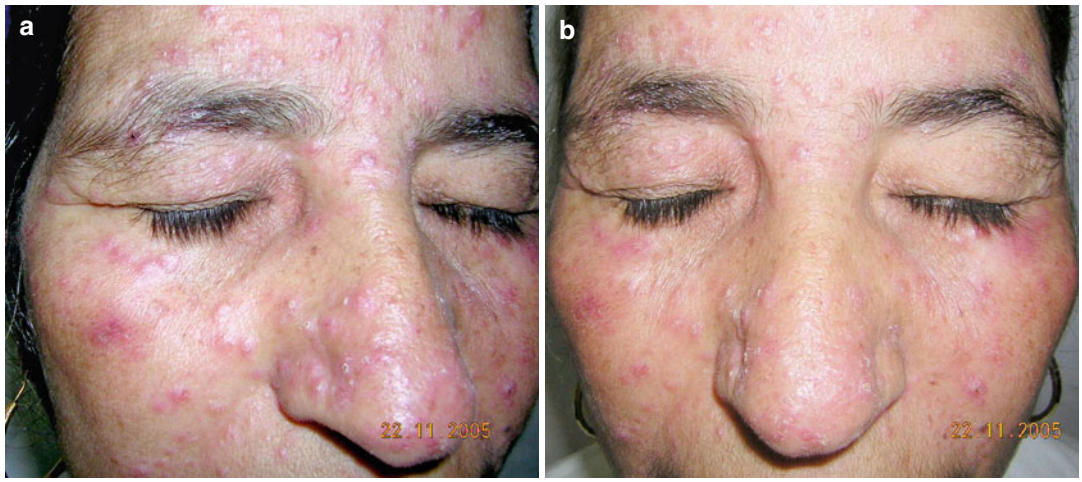



**Fig. 90.4** (**a**, **b**) Extensive papular eruption on the face is sometimes not easy to diagnose. Differential diagnosis includes sarcoidosis, granulomatous rosacea, and lupus vulgaris. Physical examination, appropriate laboratory tests, and skin biopsy settle the diagnosis

Haber's syndrome is presumably an autosomal dominant disease with an early onset and persistent rosacea-like dermatosis of the face. Erythema and telangiectasia can be admixed with comedones, pitted atrophy, and small papules. Later in life, scattered keratotic plaques develop on the trunk and extremities. In some patients, an overlap with Dowling–Degos disease has been observed [23]. Demodex folliculitis, a rosacea-like facial eruption of erythematous follicular papules and pustules, may occur due to demodicosis mostly in immunocompromised individuals, e.g., leukemia and HIV infection. Skin scrapings reveal numerous *Demodex* mites [16].

### 90.2.4 Stage IV. (Phymatous—Subtype 3)

Some conditions may result in soft tissue enlargement of the nose. Sarcoidosis (Lupus pernio) can closely mimic phymatous and granulomatous rosacea by producing red papules on the face, but the disease will also manifest itself in other organs. Other conditions include leonine facies of lepromatous leprosy (Fig. 90.5) or leukemia (Fig. 90.6a, b) which are manifested by similar lesions elsewhere in the integument, familial nevoid hyperplasia, Melkersson Rosenthal syndrome, deep fungal infections (Fig. 90.7), and acromegaly [24, 25].

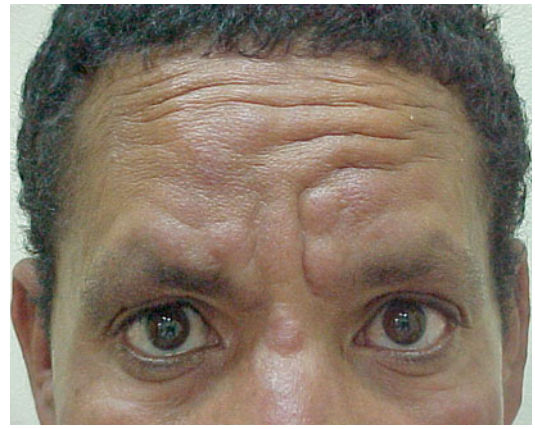
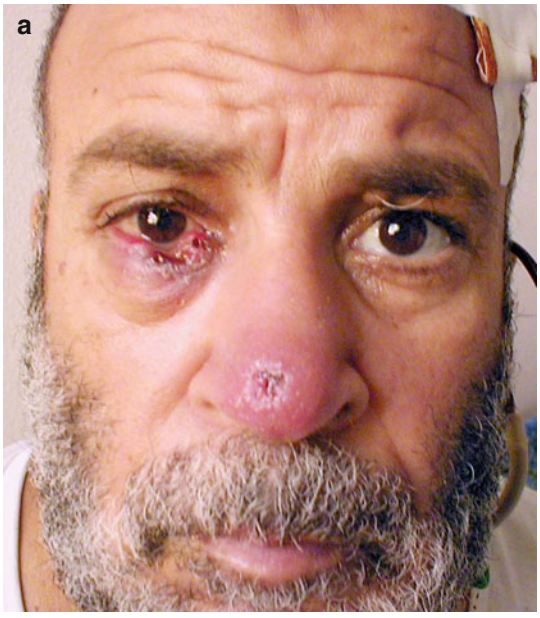


**Fig. 90.5** A case of lepromatous leprosy showing diffuse swelling of facial skin and multiple erythematous nodules with accentuation of normal skin markings. Loss of the outer third of the eyebrows is characteristic



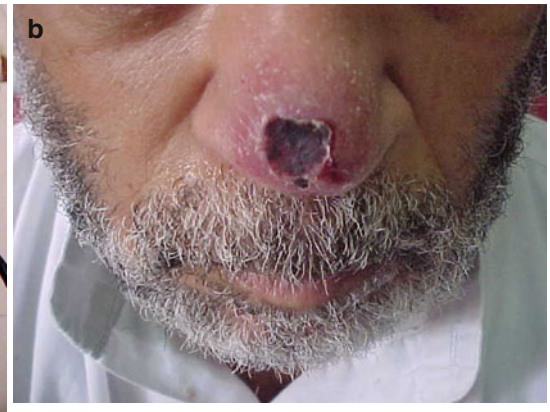




**Fig. 90.6** (**a**, **b**) Leukemia cutis (**a**) showing multiple flesh-colored papules and nodules on the face. Similar lesions were seen on the scalp, trunk, and arms. The nodules rapidly ulcerate and (**b**) on the nose result in its enlargement

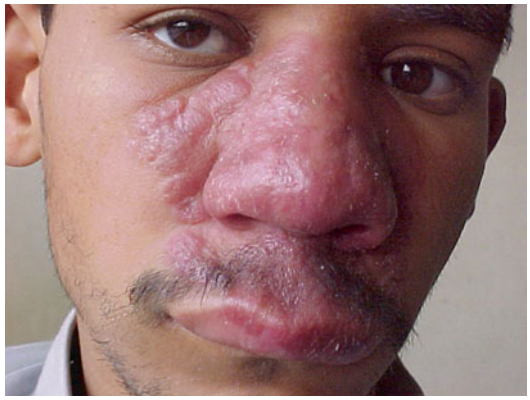


**Fig. 90.7** Deep fungal injection (zygomycosis) resulting in a diffuse enlargement of the nose mimicking rhinophyma; however, adjacent facial skin including upper lip and nasal sinuses are also affected

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# Part XIV

# Management of Rosacea

# A Treatment Strategy for Rosacea

# 91

Mark V. Dahl

## Contents



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## Abbreviation

FDA Food and Drug Administration

**Core Messages**

- In order to define the treatment regimen identify subtypes and elements of rosacea—No one treatment works for all patients.
- Only a few treatments have been proved effective in randomized clinical trials—Most treatment require the off-label use of available medications approved for other conditions.
- Topical treatments are preferred to systemic ones.
- Combination therapies may be needed.
- The decision to use any systemic treatment requires consideration of its risks and benefits.
- Any consideration of the severity of rosacea and the benefit of a particular treatment should also include consideration of how rosacea affects the patient's quality of life.
- Remission in some patients can be maintained by the daily application of topical treatments.

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## 91.1 Introduction

The cause of rosacea is speculative [1, 2]. Regardless of theories about its pathogenesis, no single therapeutic strategy successfully treats all types of rosacea and all patients with rosacea [3–5]. This chapter explores the therapies in various subsets of rosacea. Evidence-based studies and other reports are cited [6]. The efficacy of these treatments often has not been supported by the highest levels of evidence, namely, randomized controlled trials and meta-analyses of randomized controlled trials.

The "treatment ladder" (i.e., preferred order for use in treatment) presented herein is based also on personal experience, and it may be more or less arbitrary. Thus, preferences for treatment should be considered my opinion. Other rank orders for treatment preference may be equally safe and effective. Only a few topical products have been approved by the United States Food and Drug Administration (FDA) for use in patients with rosacea. The only approved oral drug for rosacea is low-dose doxycycline. Thus, most treatment recommendations reported in this chapter are recommendations for off-label use. Other chapters cover many treatments for rosacea in greater detail.

Treatment can be aimed at specific elements of rosacea affecting a given patient [6]. The subtypes and their elements are described in Chap. 86. A less detailed "scorecard" for use in a physician's office [7] can be modified to include other elements.

This outline bases treatment on rosacea subtypes and elements and encourages physicians to direct therapies to them. Topical and systemic treatments can be used, either individually or together. Treatments must be selected after considering the severity of disease, the effects of rosacea on quality of life, cost, risk of adverse effects, probable duration of treatments, and comorbid conditions of the patient. For all these reasons, many treatment regimens are unique; there is no one best way to treat all patients.

## 91.2 Erythematotelangiectatic Rosacea

The several conditions in erythematotelangiectatic rosacea may be interrelated, and treatment of any element may help another.

The facial skin of the rosacea patient blushes red continuously, but the shades of red fluctuate as vessels dilate and contract in response to various "trigger factors." With exercise, the red central facial complexion of a patient may stay red long after stopping the exercise (i.e., erythema congestivum). Another patient may telegraph emotions by blushing from embarrassment or flushing red from anger or rage. Patients do not like this reaction but find it difficult to avoid triggers, which are often of little use and of hateful consequence. Patients just want to be "normal" by interacting with their friends without fear of blushing or flushing, eating what they want without looking sunburned, or sipping alcohol without looking like an alcoholic.

Erythematotelangiectatic rosacea is difficult to treat medically, with laser or intense pulsed light therapy sometimes used as first-line treatment. As a general rule, it is usually better and cheaper to attempt medical treatment before surgery, especially if there is any danger of permanent cosmetic disability from a surgical therapy.

### 91.2.1 Erythema and Persisting Erythema

Most clinical trials count inflammatory papules and pustules as a primary end point. Many topical treatments seem to lessen erythema, but results may be biased; a decreased number of inflammatory lesions make skin seem less red even in "uninvolved" areas of skin among the papules and pustules. This effect might not be observed in clinical trials of patients with pure erythematotelangiectatic rosacea.

That said, most dermatologists often prescribe either topical metronidazole or topical azelaic acid as first-line therapy. In clinical

trials, both treatments have shown decreasing erythema [8–10], and both are reasonably well tolerated by most patients, especially given the spectrum of available vehicles [11–13]. Many patients simultaneously start a controlled regimen of skin care that minimizes irritation, controls chemicals, supplies sunscreen, and moisturizes the skin [14, 15].

Some of the redness of rosacea skin is probably due to subtle eczematous dermatitis that has been called *rosacea dermatitis* [1]. It is manifested by redness, sensory change, and fine scale. It results from the same pathogenic factors present in follicles, probably related to bacteria, bacterial toxins, breakdown products of sebum, skin temperature, or other factors. If this is indeed true, one might predict with reasonable surety that effective treatments for the inflammation that causes papules and pustules would also be effective for the mild dermatitis among them—as they are. Not only does the redness decrease, but the "dryness" (e.g., the roughness and flaking) goes away as well.

Often, though, these treatments are not enough. Patients who continue to be red want more help. Topical adrenergic agonists may be available soon, but, in their absence, many patients and their physicians resort to intense pulsed light therapies [16] or treatment with vascular lasers [17–23]. Both pulsed light therapy and the use of vascular lasers seem to help many patients, although treatments must often be repeated.

Cover-up or color-correcting gels, creams, or powders can be helpful [24]. A dusting of green powder can blunt redness nicely without any telltale sign of makeup. Men can use such products, too, if they have a mind to do so. Opaque, skin-tinted foundations also can help a great deal if applied in sufficient quantity.

### 91.2.2 Flushing and Blushing

Blushing occurs mostly from embarrassment, and the embarrassment upon blushing makes the redness even worse. There is no effective treatment for flushing or blushing; however, the blushing skin can be covered with cosmetics. Biofeedback and psychiatric manipulations rarely help alleviate the disorder, but both approaches may help patients to accept their condition.

Flushing occurs in overlapping varieties, namely, wet or dry and episodic or constant [25, 26]. These distinctions are not of much help to treaters. Wet flushing wets the patient with sweat due to the activation of sweat glands by autonomic nerves such as might occur with fever, stress, migraine headache, or dumping syndrome.

Flushing is caused by a large array of mediators, including tyramine, histamine, sulfites, nitrites, alcohol, capsaicin, and monosodium glutamate in foods, and vasoactive mediators in the body (Table 91.1) [27]. It comes as no surprise that flushing from various causes is variable, that different flushes have different causes and consequences, and that no single antagonist can effectively treat all causes. However, it is useful to identify causes, especially treatable ones. Several reviews are available [27]. For flushing due to high central body temperatures, patients may benefit from moving to a cool place, sucking on ice chips, and applying cool compresses. Topical therapies are of little or no help.

Systemic treatments are also unsatisfactory, both to prevent flushing and to avoid side effects. The α-adrenergic agonists such as clonidine hydrochloride or β-blocking agents such as propranolol HCl favor vasoconstriction [28, 29]. Anticholinergic drugs such as glycopyrrolate may also help.

### 91.2.3 Edema

Although solid facial edema and persistent orbital edema occur [30, 31], transient edema from vasodilation is far more common. Dermatologists seldom diagnose transient edema, because edema is rather subtle and often appears at times other

**Table 91.1** Topical treatments

| Subtype | Treatment |
|---|---|
| Erythematotelangiectatic | |
| Erythema | Metronidazole<br>Azelaic acid<br>Cover-ups |
| Erythema congestivum (i.e., persisting erythema) | Metronidazole<br>Azelaic acid<br>Cover-ups<br>Intense pulsed light |
| Flushing or blushing | Cool compresses |
| Edema | Cool compresses<br>Control flushing |
| Telangiectases | Intense pulsed light (for small vessels)<br>Vascular laser |
| Papulopustular | |
| Papules and pustules | Metronidazole<br>Azelaic acid<br>Sulfacetamide or sulfur<br>Benzoyl peroxide<br>Benzoyl peroxide or clindamycin<br>Clindamycin<br>Tretinoin |
| Cellulitis | Intralesional steroids |
| *Demodex* folliculitis | Sulfacetamide<br>Sulfur<br>Permethrin |
| Dermatitis | Metronidazole<br>Ketoconazole<br>Sulfacetamide or sulfur |
| Phymatous | |
| Hyperplastic phymas | Ablative laser<br>Electrosurgery |
| Mucinous phymas | Metronidazole<br>Topical corticosteroids |
| Pseudorhinophyma | Remove heavy glasses |
| Ocular | Eyelid hygiene (i.e., use baby soap wash)<br>Topical sulfacetamide |
| Sensory | |
| Pain (i.e., burning, stinging) | Wash face (i.e., use cleanser and water)<br>Moisturize (i.e., use bland emollients)<br>Sulfur |
| Itching | Calcineuron inhibitors<br>Hydrocortisone |

than during office appointments. Hot environments and exposure to radiant heat are especially likely causes. A face mask containing a cooling gel (available without prescription) can be worn whenever edema might be precipitated, such as by working over an open fire (e.g., as a restaurant cook).

### 91.2.4 Telangiectases

Chronic flushing and vasodilation seem to induce capillaries, venules, and arterioles to enlarge into visible telangiectases. At this point, vasoconstriction is of little help; instead, destruction of dilated vessels by vascular lasers or intense pulse light treatments is the primary therapy [32, 33].

### 91.2.5 Dermatitis

The redness from subtle inflammation in the skin in rosacea patients tints down after topical application of anti-inflammatory agents such as the calcineuron inhibitors pimecrolimus and tacrolimus [34] or topical corticosteroids such as hydrocortisone. However, long-term use of such agents is associated with side effects that include cutaneous atrophy (leading to a redder appearance) and papules of steroid rosacea. Happily, redness also tints down after applications of metronidazole or ketoconazole, after barrier repair by irritant avoidance, after moisturization, and after administration of systemic antibiotics such as tetracycline.

## 91.3 Papulopustular (Inflammatory) Rosacea

Inflammatory rosacea can be treated effectively with many topical and systemic treatments. Controlled clinical trials document the efficacy of these treatments. There are numerous safe and effective first-line therapies. The rosacea subtype can often be treated with topical agents alone.

### 91.3.1 Topical Therapies

#### 91.3.1.1 Metronidazole

Metronidazole is safe and effective [35–37], and it is probably more cosmetically acceptable than sulfacetamide or sulfur preparations, which tend to smell. Patients can apply creams, lotions, and gels once daily [38, 39]. One meta-analysis suggested that lotion may be the most effective form [40]. The maximum solubility of metronidazole in water is 0.75 %. Chemists have devised formulations to boost the concentration to 1 %, but the boosted amount has not yet been shown to represent a substantial enough therapeutic advance to justify a higher cost [41]. Most metronidazole gels used for rosacea are water based, so they tend not to dry or irritate the skin. Applications of metronidazole gel are more likely to prolong remissions than are applications of its vehicle [42]. Metronidazole is widely assumed to help alleviate *Demodex* folliculitis, but other drugs such as sulfur may produce better results.

#### 91.3.1.2 Azelaic Acid

Topical products containing azelaic acid decrease papules and pustules [43–48]. Azelaic acid comes in gel (15 %) and cream (20 %) forms, but the gel works better, probably because it is absorbed better into the skin. In head-to-head studies, its efficacy is similar to that of topical metronidazole gel [9, 49]. Some patients have mild sensory or other irritation, but most can continue to use it anyway.

#### 91.3.1.3 Sulfacetamide or Sulfur

The old preparation of sulfacetamide or sulfur still works [50, 51]. Sulfacetamide (10 %) probably works as an antibiotic, and sulfur (5 %) probably works as an antiseptic, antiparasitic, and antiseborrheic agent [52]. Many different preparations are available. Different types contain sunscreen, urea, precipitated sulfur, colloidal sulfur, green tints, or cover-up powders [50]. All emit a characteristically unpleasant sulfur smell that is sometimes blocked (more or less) by other additives. Fortunately, many patients and their spouses are unable to smell its odor.

#### 91.3.1.4 Clindamycin

Although one study showed the efficacy of clindamycin [53], this drug is probably less effective than either metronidazole or azelaic acid. It is often relegated to second-tier therapy. The common resistance of skin bacteria to clindamycin may be relevant to treatment success. Creams, lotions, foams, gels, and solutions provide different vehicles for special situations and specific anatomic locations.

#### 91.3.1.5 Benzoyl Peroxide

An anti-acne warrior, the antiseptic benzoyl peroxide also fights "acne rosacea" [54]. Benzoyl peroxide tends to be more irritating than other agents, but resistance to it is unlikely to develop. If tolerated, a topical product combining both benzoyl peroxide and clindamycin may provide additional advantages [55, 56].

#### 91.3.1.6 Tretinoin and Adapalene

Since systemic retinoids benefit patients with rosacea, topical ones such as tretinoin and adapalene might also help [57–59]. Unfortunately, topical retinoids tend to irritate the skin and make it redder. Their place in the hierarchy of rosacea treatment is still controversial [4, 57].

### 91.3.2 Systemic Therapies

Systemic therapy is often a first-line therapy used in conjunction with a topical product [60] (Table 91.2). The tetracyclines and macrolide antibiotics are first-choice drugs.

#### 91.3.2.1 Tetracycline, Doxycycline, or Minocycline

As a systemic therapy, oxytetracycline is quite effective, but it is not available in the USA [61].

Tetracycline is remarkably effective as well [53, 62]. In one study, 113 patients with 8 or more papules and pustules received tetracycline

**Table 91.2** Systemic treatments

| Subtype | Treatment |
|---|---|
| Erythematotelangiectatic | |
| Erythema | Tetracycline<br>Doxycycline |
| Erythema congestivum (persisting erythema) | Tetracycline<br>Doxycycline |
| Flushing or blushing | β-Adrenergic blocking agents<br>α-Adrenergic agonists<br>Anticholinergics |
| Edema | Isotretinoin (for solid facial edema) |
| Telangiectases | None available |
| Dermatitis | Tetracycline |
| Papulopustular | |
| Papules and pustules | Tetracyclines (e.g., tetracycline, oxytetracycline, doxycycline, or minocycline)<br>Macrolide antibiotics (e.g., erythromycin, azithromycin, clarithromycin)<br>Ampicillin<br>Trimethoprim-sulfamethoxazole<br>Metronidazole<br>Isotretinoin |
| Cellulitis | Doxycycline<br>Intralesional or systemic corticosteroids |
| *Demodex* folliculitis | Ivermectin |
| Phymatous | |
| Hyperplastic phymas | Isotretinoin (temporary) |
| Mucinous phymas | Doxycycline |
| Ocular | Doxycycline<br>Tetracycline |
| Sensory | |
| Pain (e.g., burning) | Nonsteroidal anti-inflammatory agents<br>Doxepin |
| Itching | Hydroxyzine |

500 mg twice daily and applied topical metronidazole gel 0.075 % daily [42]. Within 3 months, all papules and pustules were eliminated in 67 patients (59 %), and there were fewer lesions in 104 patients (92 %). Common side effects are vaginal yeast infections, photosensitivity, and alleged failure of oral contraceptives.

Doxycycline and minocycline are probably equally effective, but head-to-head studies are lacking. The side effects associated with minocycline (e.g., lupus-like syndromes, hepatotoxicity, and skin pigmentation) relegate it to second tier. Patients treated with once-daily, extended-release minocycline may be less likely to develop dizziness or other vestibular adverse effects [63].

An unorthodox cycline has received FDA (Oracea) and EMEA (Oraycea) approval for treatment of rosacea [64]. This pill combines long-acting and short-acting forms of doxycycline in low doses to allow once-daily administration without affecting mouth or vaginal bacteria.

#### 91.3.2.2 Erythromycin, Azithromycin, or Clarithromycin

Of the macrolide antibiotics, erythromycin is most widely used, but there are no good studies to document its efficacy. Although the resistance of *Propionibacterium acnes* to erythromycin is well known, the role of *P acnes* as a cause of rosacea is speculative. Erythromycin is the oral antibiotic of second choice.

#### 91.3.2.3 Other Conventional Antibiotics

Ampicillin can be used safely over long periods. Trimethoprim-sulfamethoxazole works well, but drug allergy to sulfa medications is common, and occasional suppressive effects of the drug on blood cell counts (red and white blood cells) necessitate more careful informed consent and monitoring. Clindamycin is rarely used because of worries about pseudomembranous colitis.

#### 91.3.2.4 Metronidazole

Since metronidazole works well topically, it comes as no surprise that it works systemically, too. Studies of its efficacy are lacking. Convulsions and neuropathies are associated with higher doses. Gastrointestinal side effects, metallic taste, and neutropenia are other problems relegating metronidazole.

After remission is obtained with any regimen, patients often can discontinue all therapy without recurrence. Rosacea inflammation seems to feed on itself, and exacerbations are characterized by

the sudden appearance of crops of papules that are often rather localized to one area of the face. For most patients, the daily application of metronidazole is recommended to help maintain remission, on the basis of a study that showed success with that strategy [42]. Some patients require either intermittent courses of systemic antibiotics or continuous suppressive therapy. Because of some success in individual patients, topical retinoids may help maintain remission.

#### 91.3.2.5 Nicotinamide or Zinc

Although safe in low doses, nicotinamide or zinc has scant evidence of clinically relevant efficacy [65, 66].

#### 91.3.2.6 Isotretinoin

Isotretinoin is effective for rosacea [67, 68]. However, concerns about birth defects, depression, and other side effects limit its use mostly to refractory inflammatory rosacea.

### 91.3.3 Plaques (Cellulitis)

In contrast to the inflammation of acne vulgaris, that of rosacea tends to spread widely beyond the follicle to form tender nodules and plaques. These respond slowly to systemic therapy. Sometimes a small amount of intralesional triamcinolone (2.5–5 mg/ml) can be injected into plaques to hasten resolution. Occasionally, prednisone may be indicated.

### 91.3.4 Demodex *Folliculitis*

The ability of *Demodex* mites to cause papules and pustules of rosacea is controversial, but treatments that eliminate these mites can sometimes help [69]. Products containing sulfur are the first-tier treatment for *Demodex* folliculitis. Topical metronidazole seems to help, yet the organism has survived it in vitro [70]. Also effective, permethrin is becoming more popular [71]. Systemic ivermectin may work, too, but most evidence supporting its use is reports of its success in individual patients who also applied permethrin.

## 91.4 Phymatous Rosacea

### 91.4.1 Hyperplastic Phymas

There is no role for topical therapy for hyperplastic rhinophyma, either to retard progression or to shrink the enlargement. Treatment is surgical. Systemic antibiotics such as doxycycline may decrease inflammation and have mild benefit. Isotretinoin shrinks sebaceous glands and the swelling in the nose as well, but the glands and the nose promptly enlarge when treatment is discontinued. Resculpturing the nose is usually the treatment of choice [31]. This can be done with an ablative laser such as a carbon dioxide laser or an erbium:YAG laser [72] or with electrosurgery [73, 74].

### 91.4.2 Mucinous Phymas

In the mucinous form of rhinophyma, inflammation is more pronounced. The nose is smooth, boggy, bulbous, and violet. Mucin adds to nose volume. This form of rosacea responds to systemic antibiotics such as doxycycline, but the response is slow and incomplete.

### 91.4.3 Pseudorhinophyma

In pseudorhinophyma, heavy eyeglasses rest on the lymphatic vessels that drain the nose, causing typical phymas often in the absence of other current or previous signs of rosacea. Coagulation factor XIII causes fibrosis and it is present in edema. Perhaps that is the pathogenic link. Unfortunately, the appearance of the nose does not change after heavy eyeglasses are replaced with lighter ones or contact lenses. Surgical ablative sculpturing of the nose is the treatment of choice, as with the hyperplastic subtype.

## 91.5 Ocular Rosacea

Ocular rosacea [75] responds reliably to systemic tetracyclines [76–78]; currently, doxycycline seems to be the treatment of choice. The scales and

secretions along the lid margins can be washed off with 1-to-10 dilution of baby shampoo to water, which is used as a scrub solution on a cotton-tipped applicator. Refractory or severe symptoms necessitate referral to an ophthalmologist.

## 91.6 Sensory Rosacea

The subgroup of sensory rosacea has not been recognized by the expert committee [79]. The avoidance of triggers, such as radiant heat, may help some patients [80]. When stinging or burning is due to barrier disruption, the daily moisturizing of the skin with oils or creams containing humectants (if tolerated) is essential for eventual alleviation. When due to dermatitis, sensory rosacea may respond to weak topical steroids (e.g., hydrocortisone 1 %) or calcineurin inhibitors (e.g., pimecrolimus), which reduce inflammation. When the condition is due to *Demodex* species overgrowth, precipitated sulfur or topical pyrethrums may help.

### Conclusions

The wide array of possible combinations for the treatment of rosacea makes each case different. Successful treatment takes all elements into account. Usually a set of treatments is needed that includes the avoidance of triggers, the use of daily skin care regimens, the use of topical or systemic agents, and physical modalities (e.g., intense pulse light or vascular laser treatments).

Rosacea appears on the face, and it is there for all to see. For this reason and others, the disease can interfere with a high-quality life [81, 82]. By rationally choosing among the many potential treatments, clinicians can help most patients.

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# Topical Treatment of Rosacea

# 92

Uwe Wollina

## Contents



**Core Messages**

- Topical treatment is a cornerstone in the management of all stages of rosacea.
- Topical rosacea treatments include metronidazole (0.75, 1 %), sodium 10 % with sulfur 5 %, azelaic acid (15, 20 %), benzyol peroxide, clindamycin, and erythromycin.
- Topical treatment with metronidazole or azelaic acid is recommended for mild to moderate rosacea. Both compounds can be used in maintenance therapy.
- Moisturizers may help to reduce redness and symptoms of dryness, burning, irritation, and itch.
- Topical cyclosporine A is an established treatment in ocular rosacea.

## 92.1 Introduction

Topical treatment is a cornerstone of rosacea management in all stages of the disease. Topical treatment aims to reduce signs of inflammation (redness, pustules), prevent common relapses, and avoid triggers such as skin irritation and ultraviolet (UV)-irradiation.

There is an absolute need to avoid topical corticosteroids. One of the possible severe adverse effects of these drugs is the induction of pyoderma faciale. Also, topical steroid treatment is not efficacious as withdrawal of steroids commonly leads to relapses [1, 2].

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## 92.2 Topical Metronidazole

Topical metronidazole is a cornerstone of topical medical treatment of rosacea. It is available in various formulations such as gel, cream, or ointment, and the vehicle used may also have an impact on the efficacy and tolerability of topical metronidazole [3].

Treatment of rosacea with the 0.75 % gel formulation showed a 65.1 % reduction of papules and pustules in a randomized split-face double-blind pair-controlled trial after 8 weeks [4]. In a double-blind, multicenter trial, 0.75 % metronidazole gel reduced the papules and pustules significantly better than the excipient over 3 months. The authors stated that gel formulation was poorly tolerated with frequent complaints of dry skin [5]. In such cases the cream formulation might be more convenient. New gel formulations with hydrosolubilizing agents have been developed that are much better tolerated [6]. Topical metronidazole has no effect on telangiectasias [7].

The phase IV, open-label, multicenter trial CLEAR included 582 rosacea patients, and metronidazole gel 0.75 % was applied twice daily for 12 weeks. The inflammatory papules and pustules decreased significantly over 12 weeks. The mean erythema score declined by nearly 50 %; itching, pain, soreness or stinging were reduced by 25 % [8]. Based on a recent Cochrane review of rosacea treatment, topical metronidazole gel is more effective than placebo in controlling inflammatory rosacea [9]. Topical metronidazole 0.75 % gel maintains remissions of rosacea [10]

## 92.3 Topical Azelaic Acid

Topical azelaic acid is available in gel (15 %) and cream (20 %) formulations. Azelaic acid has been shown to suppress ultraviolet-light-induced cytokine release and induces peroxisome proliferation-associated receptor gamma [11].

Numerous clinical trials of azelaic acid use for rosacea treatment have been performed. In two phase III trials 664 patients were enrolled. A clear superiority of the azelaic acid gel over vehicle was demonstrated for inflammatory lesions and erythema. Azelaic acid was well tolerated and no severe adverse effects were observed [12].

A split-face study of azelaic acid 20 % cream, metronidazole 0.75 % cream, and permethrin 5 % cream demonstrated that azelaic acid has the strongest effect on inflammatory lesions but not erythema [13]. A multicenter, double-blind, randomized parallel-group trial of 251 patients with papulopustular rosacea compared 15 % azelaic acid gel with 0.75 % metronidazole gel. Azelaic acid gel was superior to metronidazole in the reduction of both inflammatory lesions and erythema. Neither treatment had any effect on telangiectasias [14]. In a recent Cochrane systematic review the drug has been rated, after metronidazole, as the second most effective topical drug in rosacea [9]. Topical azelaic acid can be used in maintenance therapy [15].

Compared to metronidazole gel 1 and 0.75 %, azelaic acid gel 15 % has a greater irritation potential [16].

## 92.4 Topical Calcineurin Inhibitors

Topical calcineurin inhibitors, pimecrolimus and tacrolimus, have been used off-label for rosacea although some case reports of rosacea induction have been published. Topical calcineurin inhibitors may be the treatment of choice when preexistent atopic dermatitis is complicated by rosacea [17–19].

In a randomized open-label trial 1 % pimecrolimus cream was compared with 1 % metronidazole cream in papulopustular rosacea. In week 12 both compounds achieved a relief of inflammatory lesions in the same range. Neither treatment improved telangiectasias [20].

Pimecrolimus 1 % cream was studied for the treatment of steroid-induced rosacea in an 8-week split-face trial, and it was found to be effective in the reduction of inflammatory lesions [21].

In contrast, another randomized, single-blind, split-face placebo-controlled trial in 25 patients with papulopustular rosacea did not show a significant advantage of pimecrolimus compared to placebo after 4 weeks treatment. Only erythema improved better with the verum [22]. Another randomized vehicle-controlled double-blind trial

in 40 patients with papulopustular rosacea for 4–8 weeks further supported these findings [23].

## 92.5 Topical Antibiotics Other Than Metronidazole

There are a number of other topical antibiotics than metronidazole that have been evaluated for rosacea over the years.

An investigator-blinded study with 43 rosacea patients compared topical clindamycin lotion twice daily to oral tetracycline. After 12 weeks, both treatments demonstrated comparable overall efficacy to reduce inflammatory facial lesions but the topical agent was more effective in the reduction of pustules [24].

Topical benzoyl peroxide 5 %/clindamycine 1 % gel once daily was investigated in a randomized, double-blind, vehicle-controlled study over 12 weeks. At the end of treatment a significant reduction of papules and pustules was seen. At week 12 7.7 % of patients were "clear or nearly clear" [25]. Another double-blind, randomized, vehicle-controlled study of once-daily benzoyl peroxide/clindamycin topical gel with 53 patients with moderate to severe rosacea demonstrated a 71.3 % reduction of inflammatory lesions in the verum and of 19.3 % in the vehicle group at week 12. In addition, flushing and blushing significantly improved [26].

Topical erythromycin/benzoyl peroxide gel has been investigated in a clinical trial and compared to topical metronidazole gel. At the end of treatment, there were significantly more patients with clinical improvements in the topical erythromycin group but almost threefold more patients with complete remission in the metronidazole group [27].

Topical azithromycin 2 % was evaluated in a phase II trial compared to erythromycin 2 % gel. The efficacy was comparable between the two compounds but less pronounced than in acne vulgaris [28].

Omiganan pentahydrochloride is a new cationic antimicrobial peptide that can be formulated as 1 % gel for topical use [29]. Because of its broad antimicrobial efficacy, it could be a potential drug for topical therapy in rosacea.

## 92.6 Vitamin-Receptor Antagonists

Patients with rosacea are characterized by high levels of cathelicidins (antimicrobial peptides) in affected skin leading to increased protease activity. This has been linked to the formation of vascular abnormalities like persistent erythema and facial telangiectasia [30]. Vitamin $D_3$ is capable to regulate cathelicidin expression in skin, which might be another option to control cutaneous inflammation [31].

## 92.7 Other Topical Compounds

Topical tretinoin 0.025 % in a cream worked slower than oral isotretinoin low-dose therapy but achieved the same final outcome after 16 weeks of treatment. Adverse effects were milder compared to the oral treatment [32].

Another retinoid is adapalene available as 0.1 % topical gel. A randomized prospective trial ($n=55$) using adapalene compared to metronidazole gel 0.75 % demonstrated comparable efficacy and safety/tolerability [33].

Permethrin is a pyrethroid compound used for scabies and other infestations. It has been introduced into rosacea treatment to control *Demodex folliculorum* infestation and the growth of the commensal *Bacillus oleronius*. Other compounds working in the same directions are topical crotamiton and topical tetracylines [34].

Topical sodium-sulfacetamide 10 %/sulfur 5 % emollient foam produced significant clinical improvement in a small clinical trial involving eight patients with papulopustular rosacea [35]. The combination with sunscreen is branded as Rosac Cream. This product was compared to metronidazole 0.75 % gel in 152 patients with inflammatory rosacea in an investigator-blinded, randomized, parallel-group study over 12 weeks. The reduction in inflammatory papules and pustules and erythema reduction was significantly better in the Rosac Cream-group [36]. The drug is an FDA-approved treatment in the USA [37].

A topical formulation of dapsone is known by the name of aczone (Allergan, Irvine/CA). Phase II trials in rosacea have been promising [38].

Terbinafine is an allylamine compound with antimycotic and anti-inflammatory activities. Fourty-four patients with mild to moderate papulopustular rosacea were enrolled in the 8-week trial. There was no statistical difference in outcome measures between the terbinafine and the metronidazole group. Local side effects were mild and transient with a comparable frequency in both groups [39].

Extracts of the plant *Quassia amara* have shown antiparasitic and anti-inflammatory activity. A topical gel containing 4 % of *Quassia amara* extract was used for 30 rosacea patients in an open-label study. A 6-week treatment was considered to be effective and safe. The effect was in the range of what can be achieved with metronidazole or azealic acid, although no direct comparison was made [40].

Other natural compounds are under investigation such as antioxidative and anti-inflammatory substances, such as green tea, licorice, arbutin, soy, acai berry, pomegranate, turmeric, feverfew, and niacinamide [41, 42]. Recently, a *Chrysanthellum indicum*-based moisturizing cream has been evaluated in 246 patients with moderate rosacea over a 12-week period. The self-applied treatment resulted in a significant improvement in erythema and overall rosacea severity [43].

Silymarin/methylsulfonilmethane improved signs of inflammation and erythema in 46 patients with mild to moderate rosacea. In addition, hydration of skin and itching were improved. The best effect was seen in mild, erythematotelangiectatic rosacea [44].

## 92.8 Topical Cleansers and Moisturizers

Facial skin in rosacea is sensitive to irritation and often dry. There is lacking evidence that cleansers can improve rosacea significantly. However, whenever cleansers are indicated, they should be mild, nonalkaline, and may contain ceramides or polyhydroxy acid. Skin care with moisturizes is an accepted adjunctive treatment of the dry facial skin in rosacea. Their pH should be neutral to mild acid. Unnecessary ingredients should be avoided especially barrier disrupting emulsifiers and potential allergens. The best products aim to decrease dryness and irritation [45, 46].

Recently, a moisturizing lotion containing furfuryl tetrahydropyranyladenine 0.125 % has been investigated in mild to moderate rosacea patients. The moisturizer was used twice daily for 48 weeks. The product reduced erythema by 44 % and inflammatory lesion count by 89 % at week 48. In addition telangiectasias and dryness were reduced. Treatment was well tolerated without any severe adverse effects [47]. Skin barrier function improves as measured by transepidermal water loss (TEWL) and characteristic symptoms like stinging and burning were progressively reduced [48].

## 92.9 Topical Sunscreens

Ultraviolet irradiation is a known trigger factor for rosacea. Therefore, the use of sunscreens has been recommended but scientific evidence for a therapeutic or prophylactic value is sparse [49].

## 92.10 Topical Treatment in Ocular Rosacea

Topical cyclosporine A solution is an effective treatment for ocular rosacea. There is an FDA-approved 0.05 % ophthalmic emulsion on the market (Restasis, Allergan, Irvine/CA). After 3 months of treatment there is a significant increase in Schirmer scores with improvement of the mean tear break-up time score [50]. The first choice in ocular rosacea still remains systemic therapy [9, 51].

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# Systemic Treatment of Rosacea

# 93

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## Contents



**Core Messages**

- The triad of rosacea management includes patient education, skin care, and appropriate treatment.
- Systemic (oral) treatments for rosacea include antibiotics such as tetracyclines, macrolides, and metronidazole, as well as oral isotretinoin.
- The only FDA-approved systemic treatment for papulopustular rosacea is anti-inflammatory dose doxycycline 40 mg.
- Doxycycline inhibits the activity of matrix metalloproteinases (MMPs) in human skin. So, it prevents the tryptic KLK activation by MMPs and the production of the active antimicrobial peptide LL-37 (cathelicidin).
- Oral zinc salts have been evaluated in a small number of studies with conflicting results.
- Systemic treatments may be combined with topical treatment for faster and better clinical response.
- Topical maintenance treatment after oral therapy discontinuation is essential to maintain remission in rosacea patients.
- Sebum modifying treatments may emerge as future key players to effectively treat rosacea.

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## 93.1 Introduction

Rosacea is a common chronic inflammatory dermatosis affecting the central face, characterized by intermittent periods of exacerbation and remission. It affects both sexes, and it typically presents after 30 years of age [1–3]. Reported prevalence rates of rosacea range from 0.09 % to 10 % [4]. A Greek study reported a prevalence of 1.22 %, with 0.88 % prevalence for ETT and 0.34 % for PPR [3].

Although the pathogenesis of rosacea has not been elucidated, it has been proposed that it may represent a *Demodex*-associated perifollicular inflammatory reaction [5, 6], an activation of the innate immune response in the skin [6, 7] and/or increased vascular reactivity [4, 7]. Recent data highlight a key role for *Demodex folliculorum* in the inflammatory response of the pilosebaceous unit in rosacea [6, 8]. A study in 50 rosacea patients compared to controls showed increased density of *Demodex folliculorum* by PCR, increased expression of proinflammatory cytokines (IL-8, IL-1, TNF-α), and increased expression of the antimicrobial peptide cathelicidin (LL-37) in skin samples. Cathelicidin may in turn play a role via induction of neovascularisation and inflammation [6].

Clinical manifestations of rosacea are primarily distributed on the convexities of the central face, including the cheeks, nose, chin, and central aspect of the forehead [7]. The National Rosacea Society Expert Committee has classified rosacea into four subtypes based on the predominant clinical features in each patient: erythematotelangiectatic rosacea (subtype 1), papulopustular rosacea (PPR, defined as multiple small dome-shaped erythematous papules and pustules on a background of erythema in a centrofacial distribution) (subtype 2), phymatous rosacea (subtype 3), and ocular rosacea (subtype 4). Granulomatous rosacea is considered a variant of rosacea [1].

## 93.2 Overview of the Treatment Principles

Although there is no curative therapy for rosacea, treatment strategies recommended to control underlying signs and symptoms include a combination of skin care, patient education to avoid triggering factors, photoprotection, topical agents, oral (systemic) therapy, and light-based modalities [9].

There are no published guidelines for the treatments of rosacea. The choice of treatment seems to depend on various factors, such as the rosacea type as well as associated symptoms and signs, the patient's medical history, and his/her preferences for therapy.

Treatments for rosacea aim to improve skin erythema and reduce papules and pustules, to reduce symptoms such as irritation, burning, scaling, to sustain remission, to avoid exacerbations, and to improve the patients' quality of life [10].

Precipitating or exacerbating factors should be avoided, such as strenuous exercise, hot and humid atmosphere, emotional upset, alcohol, hot beverages/meals, spicy foods, sun exposure, astringents and scented products containing hydroalcoholic extracts, cleansers containing acetone or alcohol, abrasive or exfoliant preparations, intense rubbing of the skin, and toners or moisturizers containing glycolic acid [11].

Patients should be reassured about the benign nature of the disorder and the rarity of rhinophyma (particularly in women). Web sites such as those of the National Rosacea Society (http://www.rosacea.org) and the American Academy of Dermatology (http://www.aad.org) are available with relevant information [11].

## 93.3 Systemic Therapies for Rosacea

### 93.3.1 Antibiotics: Tetracyclines, Macrolides, Metronidazole

Tetracycline hydrochloride was discovered in the 1960s as a product of *Streptomyces aureofaciens* and was later shown to be bacteriostatic through inhibition of bacterial protein synthesis. Tetracyclines are broad-spectrum antibiotics with coverage of both gram-positive and gram-negative species, including *Mycoplasma*, *Chlamydia*, *Staphylococcus*, and *Streptococcus* [12]. Oral tetracycline derivatives, including tetracycline (250–1,000 mg/day), doxycycline (100–200 mg/day),

and minocycline (50–100 mg/day), have used for the treatment of papulopustular rosacea, often in combination with topical treatments such as metronidazole, azelaic acid, or sodium sulfacetamide sulfur [9, 11]. Also, they have been used for moderate to severe ocular signs and symptoms of rosacea [9]. Limitations with their use for rosacea treatment include the lack of well-designed randomized, controlled studies to evaluate their efficacy and their association with increased bacterial resistance in *Propionibacterium acnes* [13], as well as *Staphylococcal* and *Streptococcal* strains [14].

Anti-inflammatory dose doxycycline 40 mg once daily (containing 30 mg immediate-release and 10 mg delayed-release doxycycline beads) is the only tetracycline approved by the US Food and Drug Administration (FDA) for the treatment of inflammatory papules and pustules in rosacea. Based on single-dose pharmacokinetics, conventional formulations of doxycycline that are not controlled-release and administered at a dose of 40 mg or higher achieve serum levels that may produce selection pressure against susceptible bacterial strains based on minimum inhibitory concentration evaluations [15].

As the pathogenesis of rosacea appears to be multifactorial, anti-inflammatory dose antibiotics are used not for their antibacterial effects but for their anti-inflammatory properties. The cathelicidin peptide LL-37 participates in innate defense against microbes, promotes leykocyte chemotaxis and angiogenesis, and alters the expression of extracellular matrix components. LL-37 is produced after the proteolytic activation of its inactive precursor protein hCAP18, by tryspin-like serine protease kallikrein 5 (KLK5) [16]. Doxycycline has been reported to nonselectively inhibit matrix metalloproteinases (MMPs) by binding to zinc and calcium atoms and causing conformational changes, and by suppressing gene expression in skin keratinocytes. Doxycycline was shown to prevent cathelicidin activation via inhibition of the activation of tryptic kallikrein-related peptidases in live keratinocytes *in vitro* [16].

Once daily anti-inflammatory dose doxycycline 40-mg has been shown to be as effective as the 100 mg dose and to have a lower risk of adverse effects [17].

Anti-inflammatory dose, doxycycline 40 mg for 16 weeks, was evaluated for the treatment of papulopustular rosacea in two phase 3, parallel-group, multicenter, randomized, double-blind, placebo-controlled studies ($n = 537$). In both studies, treatment resulted in significant reduction in the mean lesion count at week 16 (mean decrease from baseline n lesion count in the doxycycline group was 11.8 in one study and 9.5 in the other study), compared to placebo ($p < 0.001$). Anti-inflammatory dose doxycycline was well tolerated and the most common adverse events were nasopharyngitis (4.8 %), diarrhea (4.4 %), and headache (4.4 %) [15].

Once daily sub-antimicrobial-dose doxycycline 40 mg in patients with PPR resulted in improvement of the investigator's global assessment score (IGA) to clear or near clear [18, 19]. Also, it has been proposed that combination of systemic with topical therapies may increase benefit in rosacea patients. Systemic doxycycline, including anti-inflammatory dose doxycycline 40 mg once daily, may be combined with topical metronidazole or azelaic acid to faster control a flare in PPR patients [20].

Macrolide antibiotics including erythromycin (250–1,000 mg daily), clarithromycin, and azithromycin, as well as metronidazole (an imidazole derivative) (200 mg twice daily), have all been used for the treatment of rosacea. Disadvantages of these treatments include gastrointestinal side effects, the risk of bacterial resistance, the need for alcohol avoidance in the case of metronidazole, and the higher cost of the newer second-generation macrolides [9].

## 93.4 Isotretinoin

Oral isotretinoin has been used as an off-label treatment for rosacea. Treatment with isotretinoin results in a decrease of the sebaceous gland size and of the sebum production [21]. Also, isotretinoin has been shown to have immunoregulatory properties in patients with acne (decreasing TNF-α, IL-4, IL-17, and IFN-γ serum levels) that may also account, at least in part, for its beneficial effect in rosacea [22].

In several studies isotretinoin has been found to be effective at doses of 0.5–1 mg/kg or 40–60 mg/day. However, treatment was poorly tolerated by these patients due to xerosis of the skin and conjunctivae [23]. The efficacy of intermediate-dose isotretinoin (20 mg/day, followed by 20 mg per every other day for 2 months, 20 mg twice weekly for the next 2 months, and 20 mg once weekly for the last 2 months) was studied in 25 patients with refractory papulopustular rosacea. Clinical improvement was noted from the first month of treatment. Treatment was generally well tolerated [24]. Low dose, 10 mg/day, oral isotretinoin is an effective alternative treatment for papules and pustules [25, 26]. For isotretinoin, 0.1–0.3 mg/kg/day has been proposed as the optimal dose for papules and pustules, while 0.1–1.0 mg/kg/day has been reported for treating nodules and plaques [9, 26].

A multicenter, double-blind, randomized study of 537 patients with rosacea subtypes II and III evaluated isotretinoin (0.1 mg/kg, or 0.3 mg/kg, or 0.5 mg/kg), or doxycycline (100 mg daily for 14 days, then 50 mg daily) or placebo, for 12 weeks. Among the different dosage regiments of isotretinoin, low-dose 0.3 mg/kg/day was the most effective dose. Isotretinoin 0.3 mg/kg showed similar reduction of lesions compared to doxycycline [27].

Follow up showed that 45 % of patients had a relapse within a median of 11 months [24]. Longer remission times have been reported with higher isotretinoin doses (0.5–1 mg/kg, for 3–6 months) [28]. Similar to the acne, remission times in rosacea may be related to the cumulative dose. Isotretinoin 10 mg/day for 4 months led to 75 % decrease in papulopustular lesion count and 38 % decrease in erythema, which were preserved at 4 months of follow-up [29]. Continuous "micro-dose" isotretinoin at a dose of 34.2 mg/week kept the disease under control; however, there was immediate recurrence when the individually determined dose was stopped [26].

Oral isotretinoin has been shown to decrease nasal volume in rhinophyma due to the ability of oral isotretinoin to markedly reduce sebaceous gland size [30].

Oral isotretinoin should not be combined with oral tetracyclines due to the risk of benign intracranial hypertension [9]. Another important limitation that should be considered with oral isotretinoin is the associated teratogenesis in women of reproductive potential, who consist of the "typical" rosacea patients.

## 93.5 Oral Zinc Sulfate

Zinc sulfate has been used for the treatment of acne vulgaris [31]. It has been evaluated in the treatment of rosacea as an inexpensive and safe therapeutic option. Zinc is a free radical scavenger [32] and it possesses antibacterial properties [33], but its potential mechanism of action in rosacea is not known.

A randomized, placebo-controlled, double blind, cross-over study evaluated oral zinc sulfate 100 mg three times daily, in the treatment of rosacea in 25 patients. After 3 months of treatment with oral zinc, there was a statistically significant decrease in erythema, papules, and pustules but no effect on telangiectasia (individual score was given for each type of lesions). Response was sustained at 3 months of follow-up. There were no side effects apart from mild gastric upset [32]. Another randomized placebo-controlled study evaluated oral zinc sulfate 220 mg (equivalent to 50.8 mg elemental zinc) twice daily for 3 months in 53 patients. There was no statistically significant improvement with oral zinc compared to placebo in a total rosacea severity score that included grading for flushing, erythema, papules, pustules, and telangiectasia [34].

## 93.6 Other Oral Therapies

Oral β-blockers nadolol and propranolol (20–40 mg, 2–3 times a day) have been used for flushing of rosacea, but side effects such as hypotension and bradycardia are important limitations. Carvedilol, a nonselective β-adrenergic blocker with α1 blocking activity and antioxidant activity, is indicated for the treatment of mild to

moderate congestive heart failure. A case of refractory ETR was successfully treated with carvedilol [35]. Also, a retrospective study reported treatment with oral carvedilol (3.125–6.25 mg, 2–3 times a day, titrated up to 31.25 mg/day) in 11 normotensive patients with refractory ETR. Treatment resulted in significant improvement in facial erythema and cheek temperature within 3 weeks. Treatment duration ranged from 1 week to 28 months. Treatment was discontinued in one patient due to asymptomatic mild hypotension [36].

## 93.7 Systemic Therapies for Rosacea: Where Do We Stand?

The ROSacea International Expert Consensus Group (ROSIE) proposed that the treatment approach should be based on symptoms and signs of rosacea, rather than on the rosacea stage or subtype, as patients often experience a range of symptoms spanning more than one subtype [9].

A recent Cochrane systematic review included 58 randomized controlled trials of treatments for moderate to severe rosacea. Among systemic treatments, there was some evidence to support that doxycycline 40-mg is effective and safe for short-term use for papulopustular rosacea [37].

At present, there are no topical or oral agents that are FDA approved for erythematotelangiectatic rosacea or for facial erythema of rosacea in the absence of inflammatory lesions. Most studies have evaluated the effect of systemic treatments on papules and pustules and on the overall severity of rosacea, whereas erythema or telangiectasia was not studied. So, there is no data regarding the effect of systemic therapies on erythema or telangiectasia [37, 38].

Relapse after systemic therapy occurs in approximately 25 % of patients, and the ROSIE underlines the necessity of topical maintenance therapy, usually around six months, in order to maintain remission. Then alternate day or twice weekly topical therapy is advised [9].

### 93.7.1 Future Perspectives

Several pieces of evidence point to a possible role of sebum modifying treatments for the management of rosacea. Firstly, the beneficial effect of oral isotretinoin in PPR and the diminution of sebaceous gland size and decreased sebum production in treated rosacea patients suggests that sebaceous gland dysfunction may play a role in rosacea pathogenesis [21]. Also, the sebaceous microenvironment may permit the increased proliferation of *Demodex* mites implicated in rosacea [39]. Interestingly, sebaceous lipids have both pro- and anti-inflammatory properties and sebum regulates the innate immune response of the skin which is altered in rosacea. Sapienic acid, lauric acid, palmitoloeic acid, and oleic acid have antibacterial properties. A case–control study showed an abnormal fatty acid composition of the skin surface lipid layer in 25 patients with PRP compared to 24 controls. Myristic acid (C14:0) was statistically significantly increased in PRP, while the SFA arachidic acid (C20:0), behenic acid (C22:0), tricosanoic acid (C23:0), lignoceric acid (C24:0), and the monounsaturated fatty acid cis-11-eicosenoic acid (C20:1) were decreased in PRP. Decreased long chain fatty acids result in dysregulated skin barrier function and increased transepidermal water loss. Also, minocycline 100 mg once daily for 6 weeks decreased the concentration of oleic acid in PPR patients [39].

Moreover, serine protease inhibitors have been proposed as a potential treatment for rosacea as they can directly control the processing of LL-37 from hCAP18 by tryptic KLKs such as KLK5 [16].

Unmet challenges in rosacea treatment include therapies to improve erythema and telangiectasia and new agents with anti-inflammatory properties that may be used in the context of long-term continuous therapy with no risk of antibacterial resistance.

A further elucidation of the factors implicated in the pathogenesis of rosacea will pave the way for causal treatments aiming to effectively treat rosacea rather than simply alleviate the associated signs and symptoms.

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# Laser and Light Therapy of Rosacea

# 94

Dae Hun Suh

## Contents



**Core Messages**

- Though oral and topical therapies in rosacea are effective, erythema and persistent flushing often plateau after long-term treatment. Lasers have been shown to be effective in vascular lesions . Thereby erythema has been main target of laser and light therapy of rosacea. Many vascular lasers and intense pulsed light (IPL) have been applied to reduce erythema and telangiectasias seen in rosacea. They can be very useful as alternatives to topical and oral therapies in the erythematotelangiectatic subtype and may be an adjunctive option in the papulopustular subtype.
- Faster and more complete symptom resolution can be achieved by laser and IPL when they are paralleled with topical and oral rosacea treatment agents. Though high cost is a practical problem in clinics, these non-ablative lasers are well tolerated and have little side effects. In addition to erythema, these laser therapies may induce remodeling of abnormal dermal connective tissue by thermally induced fibroblast or endothelial damage.

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## 94.1 Vascular Laser

In early 1980s, argon laser (488–514 nm) was applied for red nose and rhinophyma by rosacea [1, 2]. However, argon laser could leave hypertrophic or atrophic scar along the treated vessels [3, 4]. Ever since 1980, there have been many evolutions in vascular lasers to become a safer and more effective therapy. Currently employed vascular laser devices for the treatment of rosacea are pulsed dye laser with short pulse duration (585 or 595 nm; 0.45 and 1.5 ms), long-pulsed dye laser (595 nm, 0.5–40 ms), potassium-titanyl-phosphate laser (532 nm, 1–50 ms), and diode-pumped frequency doubled laser (532 nm) [5–8]. Light emitted by these lasers are selectively absorbed by oxyhemoglobin which has peak absorption at 541 and 577 nm in superficial vessels. Both short pulsed and long pulsed dye laser with 585 or 595 nm have been regarded as treatment of choice in rosacea, for their promising results confirmed in prospective study [9]. Effectiveness of laser wavelengths corresponds to the absorption peak of oxyhemoglobin. These short wavelength lasers target small superficial vessels and are best suited for treatment of superficial erythema and telangiectasia.

High selectivity of these lasers decreases the destruction of surrounding tissue. Longer pulse duration delivered energy at low rate of vessel heating with minimum tissue trauma and purpura. In addition, epidermal precooling with epidermal cooling gel or spray provides epidermal protection that leads to minimized adverse response like pain, erythema, edema, and scar formation. Dynamic cooling device such as cryogen cooling spray allowed more effective epidermal precooling and protection resulting in further decrease of the collateral tissue damage [10].

In a report with 585 nm pulsed dye laser at 450 μs pulsed width, fluence of 6.0–7.5 J/cm$^2$ and a 5 mm spot in the treatment of rosacea patients with persistent erythema and telangiectasia, good or excellent reduction was achieved in 24 of 27 patients after 1–3 laser sessions spaced 6–12 week apart [11]. However, overall disease severity and inflammatory lesion count were not changed after 2–6 sessions of pulsed dye laser utilizing 450 μs pulsed width and fluence of 5.5–7.5 J/cm$^2$ in other prospective study [9]. In another study, after mean 2.4 sessions of pulsed dye laser treatment with typical purpuric setting (585 nm, 450 μs, 6.0–6.75 J/cm$^2$), 37 of 40 patients scored above moderately effective. Six patients showed post-inflammatory hyperpigmentation which resolved with hydroquinone and hydrocortisone. No other severe adverse reactions, like scarring, were observed [6].

Pulsed dye laser incorporating cooling device enables high energy transmission with epidermal protection. Tan treated 16 patients with 595 nm pulsed dye laser with purpuragenic dose (1.5 ms pulsed width, 9.5–11.5 J/cm$^2$, and a 7 mm spot) for 2 sessions spaced 8 weeks [12]. Significant improvement of symptom, quality of life, and erythema was shown in all patients. However, all patients experienced postoperative purpura, and there were more severe adverse effects including transient hyperpigmentation (31 %) crusting (25 %). Another study employed subpurpuric dose (6 ms, 7–90 J/cm$^2$, 7 mm spot) reported that 2 of 12 patients had 75 %, 2 had 50–75 %, and 5 had 25–50 % improvement after one treatment session. No complications were observed [13]. On the whole, two or four sessions are required to achieve the best outcome with pulsed dye laser.

Treatments with purpuric dose induce quick response. However, postoperative purpura and long downtime limited usefulness of pulsed dye laser. Though treatments with subpurpuric dose need more sessions, they are getting popularity for their safety. Stacking pulse technique may improve clinical result in subpurpuric setting [14].

After KTP laser treatment in 47 patients with rosacea, one session achieved 70 % or greater reduction in 38 % of patients. Two sessions of KTP laser treatment brought same result in 70 % of patients [15]. For eradication of deeper facial vessel, longer wavelength lasers are required. Because hemoglobin has spectral peak absorption at 800 nm and above 1,000 nm, diode laser (810 nm, 1–1,000 ms), long-pulsed alexandrite laser (755 nm; 3–20 ms), and long-pulsed neodymium:yttrium-aluminum-garnet (Nd:YAG; 1,064 nm, 1–100 ms) lasers can be effective

in deeper bruise-like vessels [16]. Erythema associated with aging was successfully treated by a recently developed combined laser that combined pulsed dye laser (585 nm) and long-pulsed Nd:YAG laser (1,064 nm); thus it can be another option for effective erythema and telangiectasia associated with rosacea [17].

## 94.2 Intense Pulsed Light

The light from IPL is multichromatic and noncoherent and composed of multiple wavelengths ranging from 550 to 1,200 nm. Flashlamp light from device is filtered by two kinds of filters which establish short end and high end. Filter and setting vary depending on the device. Thus, fluence and pulse duration also vary with the system adopted. There are some benefits in IPL device compared with vascular laser. The light emitted by IPL device has multiple wavelength and thus can penetrate various skin layer and target various chromophores including hemoglobin and melanin. Multiple targeting enables IPL to treat various skin conditions such like pigmented lesion, vascular lesion, hair removal, and photoaging [18–21]. IPL device allows for a large spot size to facilitate treatment of large area quickly. Generally, IPL is well tolerated and has no downtime.

For its safety and efficacy to various skin conditions, IPL is one of the frequently used devices for skin rejuvenation. IPL may induce cytokine activation and other biological active factor release by thermal heating. This biological action leads to stimulate fibroblast to increase collagen production and thus to bring out dermal remodeling and vascular and elastic tissue rejuvenation [22, 23].

Many successful treatments of vascular lesion with many models of IPL device have been reported [20, 24, 25]. IPL has broadened treatment possibilities and has been used for the treatment of erythema in rosacea patients. In a large study, 174 of 188 patients (74 with rosacea) demonstrated a facial clearing of 75–100 % after mean 2 sessions of IPL treatment (515–1,200 nm, 50–60 J/cm$^2$) [26]. Three rosacea patients who had been previously treated unsuccessfully with pulsed dye or copper vapor laser experienced 75–100 % clearance after only a single treatment. There were 34 adverse events such as bruise and edema. There was no permanent adverse effect like scarring. In other previous study, IPL was given to 28 evaluable patients at 2.4/4.0 ms double pulse with a 20 ms delay time. Fluence ranged from 32 to 36 J/cm$^2$ with 570 nm filter or from 27 to 32 J/cm$^2$ with 560 nm filter. The average number of treatment was 3.6 spaced a minimum 3 weeks apart. Patient-evaluated responses in questionnaire are that redness was better or much better for 83 %, flushing and skin texture were better or much better in 75 %, and acneiform breakouts were better or much better in 64 % of patients [27]. There was an attempt to quantify the improvement of rosacea-associated erythema with scanning laser Doppler before and 1 month after IPL [28]. Four patients were treated five times with IPL (515 nm filter, a single pulse duration of 3 ms, fluence of 22–25 J/cm$^2$). A 30 % decrease in blood flow and a 29 % in blood flow decrease in actual area of the cheek occupied by telangiectasia were noted. A 21 % decrease in the intensity of erythema was also noted. Recent study with 60 patients presenting with telangiectasia owing to facial rosacea reported mean clearance of 77.8 % and maintenance 51.6 months without recurrence [29]. Mean number of treatment was 4.1 with pulse duration between 4.3 and 6.5 ms and fluence of 25–35 J/cm$^2$.

Photodynamic therapy with IPL, pretreated with topical aminolevulinic acid (ALA), is established as effective therapy in acne [30]. Selective penetration of ALA to sebaceous gland was previously demonstrated. Thus, this treatment can be helpful in rosacea patient with concomitant photodamage [31]. Further studies are necessary to evaluate the efficacy of this treatment.

## 94.3 Other Laser Therapies in Rosacea

Some ablative lasers have been used for correction of rhinophyma which is disfiguring condition resulting in nasal obstruction. Argon laser

has also been found to treat rhinophyma through direct coagulation and shrinkage of connective tissue up to a depth of 0.5 mm [1]. However, many potential adverse effects including atrophy, scarring, hyperpigmentation and insufficient efficacy limits its use.

Carbon dioxide ($CO_2$) laser facilitates accurate sculpting and provides effective hemostasis for blood vessels up to 0.5 mm in diameter [32]. Two to three passes appear sufficient for mild rhinophyma, whereas four to five passes are required for moderate and severe rhinophyma [33]. Re-epithelization may be completed over 3–8 weeks [33, 34]. Acute postoperative complications like milia and small pustules can be shown [33]. Erythema may persist for several months [35, 36]. Hyperpigmentation that usually subsides within 6–16 weeks has been reported to occur in 5–83 % of patients after $CO_2$ laser resurfacing; it's more common in darker skin types [35]. Ultrapulse $CO_2$ lasers that have faster repetition rates shorten tissue exposure time, thereby minimize thermal damage of collateral tissue [37, 38].

The erbium:yttrium aluminum garnet (Er:YAG) laser allows better depth control of tissue destruction than $CO_2$ laser [35]. Fine resurfacing maintains the good cosmetic result and reduces healing time of 7–14 days and duration of erythema of 1–4 weeks [39]. Pigmentary change and scarring can be observed. A disadvantage of Er:YAG laser is intra-operative failure of hemostasis. However, dual-mode Er:YAG that provides the controlled ablative mode for tissue reduction and excellent intra-operative hemostasis can achieve better results [40].

Neodymium:yttrium aluminum garnet (Nd:YAG) lasers can be used to treat rhinophyma [41, 42]. Sculpturing the rhinophyma with Nd:YAG laser and then 3 months later following fine excision can lead to good cosmetic result comparable to that seen with $CO_2$ laser [42]. Postoperative edema and exudates may develop but resolve within 2 weeks. A 1,450 nm diode laser may also exert as effective treatment to mild and moderate rhinophyma with minimal complication [43].

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# Nonclassical Treatments

# 95

Uwe Wollina

## Contents



**Core Messages**

- Rosacea is a multifactorial disease that needs a stage- and severity-dependent treatment.
- Most patients can successfully be treated by standard therapy.
- Emerging treatments result from anti-inflammatory activity of certain compounds like zinc, neurophysiological activity like oxymetazoline or ondansetron, or probably from antifibrotic compounds in the future.

## 95.1 Introduction

Rosacea is a multifactorial disease with a variable course. Although most patients can be treated by standard therapy, the search for new treatment modalities is going on. Some of the nonclassical treatments discussed in this chapter highlight the neurophysiological background of rosacea.

## 95.2 Treatment of Flushing

The use of alpha-2 agonists such as clonidine hydrochloride 0.05 mg twice daily or nadolol 40 mg once a day were insufficient to suppress induced flushing in rosacea [1, 2]. Naloxone is a morphine antagonist interacting with opioid receptors. Naloxone 0.8 mg in 2 ml saline injected

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subcutaneously before provocation suppressed the flushing reaction in five patients [3].

Oxymetazoline is a sympathomimetic imidazole derivate and a selective alpha-1-adrenergic receptor agonist. Its alpha adrenergic activity results in vasoconstriction for up to 12 h if applied topically to the nasal mucosa. Recently, it was shown that it exerts anti-inflammatory activity by inhibition of proinflammatory cytokines [4]. Oxymetazoline has been used topically with success in a patient to treat erythema and flushing [5].

Carvedilol is a beta-adrenoreceptor antagonist and vasodilatator. The substance has been used to improve refractory flushing and persistent erythema in a patient with rosacea [6].

## 95.3 Treatment of Teleangiectasias and Vascular Sprouts

Angiogenic growth factors such as fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) are involved in neoangiogenesis. Dobesilate is an inhibitor of FGF [7]. In a 33-year-old female rosacea patient topically applied dobesilate improved erythema and teleangiectasia after 2 weeks [8].

Twenty-four patients with papulopustular or teleangiectatic rosacea were treated with 0.1 % tacrolimus ointment twice daily for 12 weeks. In this open trial erythema improved significantly, whereas papulopustules were not significantly improved [9].

## 95.4 Treatment of Papulopustules (Inflammatory Rosacea)

Topical calcineurin inhibitors have been occasionally reported to be successful in individual rosacea patients [10]. Topical pimecrolimus has been investigated in a randomized-vehicle controlled double-blind trial. Forty patients with rosacea were enrolled and achieved either 1 % pimecrolimus cream or placebo twice daily for 4 to 8 weeks. In this trial there was no statistic significant difference between pimecrolimus and the vehicle; both resulted in some improvement [11]. In three patients with corticosteroid-induced rosacea, topical tacrolimus 0.075 % ointment was effective in the reduction of inflammatory signs with 10 days [12].

Terbinafine is an antimycotic drug with anti-imflammatory activities. Topical 1 % terbinafine cream was compared to 0.75 % metronidazole gel in a single-center, single-blinded 8-week trial. Terbinafine was found as effective as metrodiazole [13].

Azithromycin is a macrolide antibiotic showing antioxidative efficacy with potency for rosacea therapy. In a randomized open trial azithromycin 500 mg three times a week (first months), followed by half the dosage (second months), and 250 mg twice weekly (third months) was compared to 100 mg doxycycline per day for three months. Sixty-seven patients had been included. At the end of the study arithromycin was at least as effective as doxycycline [14]. Azithromycin was used successfully in pregnant patients [15].

Azithromycin has been evaluated in a 2 % topical formulation vs. 2 % erythromycin topically in a phase I trial. It was reported that although topical azithromycin showed anti-inflammatory activity erythromycin was superior [16].

In rats, plasma and liver choline levels were decreased in response to nicotinamide (NAM) administration. It was concluded that chronic NAM administration resulted in a group deficiency state due to the greatly increased need for methylation of NAM [17].

An oral formulation containing NAM 750 mg, zinc 25 mg, copper 1.5 mg, and folic acid 500 µg (Nicomide®, DUSA Pharmaceuticals, Inc., Wilmington, MA) resulted in significant improvement of inflammatory signs of rosacea after 4 and 8 weeks [18]. The addition of oral antibiotics did not achieve an additional benefit [19]. In this trial it was not investigated weather any single constituent would have a beneficial effect on rosacea.

Acne and dissecting folliculitis have both been treated successfully with oral zinc [20].

Twenty-five rosacea patients participated in a double-blind, placebo-controlled, cross-over study getting either 100 mg zinc sulfate or placebo three times per day for 3 months. Zinc decreased the rosacea score significantly but only after the fourth months. No major adverse effects were noticed [20].

Herbal medicine may show a mixed response in inflammatory rosacea [21]. However, herbal medicine as an adjunct to traditional medicine might add an additional benefit for patients. In a randomized trial 68 women with rosacea were treated either with minocycline or spironolactone alone or in combination with a traditional Chinese recipe, Chibixiao recipe, for 8 weeks. The response/cure rate was 45.0 % in the first group and 87.5 % in the group that received Chinese herbals as well ($p<0.01$). The suggested mechanism was a lowering of testosterone levels in circulation [22]. There are no data, however, that would suggest a higher incidence of rosacea in patients with hyperandrogenism.

In a single-center open-label study 30 patients with rosacea were treated topically with a gel containing 4 % Quassia amara extract. After 6 weeks of treatment efficacy was in the range of standard drugs as metronidazole and azelaic acid. The formulation had an excellent tolerability and safety [23].

There is a long controversy about the possible pathogenetic role of *Helicobacter pylori* (Hp) infection of the stomach. Eradication of Hp by triple therapy, however, can result in a significant improvement in about two-third of patients with papulopustular rosacea [24]. This is supported by another study in 25 patients with rosacea and Hp, in whom eradication resulted in a decrease in rosacea severity during eradication [25].

Another study covering 44 patients with Hp infection treated with a double-therapy (clarithromycin and omeprazole for 2 weeks) evaluated inflammatory signs of rosacea. Sixty days after treatment the severity of rosacea was not different from a control group [26]. From these studies no final conclusions can be drawn but one might expect that triple therapy is more effective in control of inflammatory rosacea than double therapy.

Ivermectin (MK-0933, 22,23-dihydroderivative of avermectin $B_1$) is a synthetic derivative of a broad-spectrum antiparasitic class of macrocyclic lactones known as avermectins. Pharmacokinetic study of ivermectin shows good bioavailability. It is absorbed rapidly, metabolized in the liver, and excreted in the feces (98 %) and urine (1 %). Ivermectin acts by binding selectively to specific neurotransmitter receptors that function in the peripheral motor synapses of parasites. It has an endectocidal effect causing paralysis of parasites by suppressing the conduction of nervous impulses in the nerve-muscle synapses of the arthropods and insects [27].

The role of ectoparasitosis demodecidosis in rosacea is controversial. However, in some special situations, like human immunodeficiency virus infection or AIDS, a single dose of ivermectin can improve rosacea-like eruptions [28, 29].

## 95.5 Treatment of Phymas

In phymas a significant fibrosis can develop depending on the subtype of disease. In an experimental setting tamoxifen was shown to decrease TGF-beta-2 secretion of rhinophyma fibroblasts in vitro [30]. Tamoxifen has some actions that make its use problematic in rosacea patients in vivo. It was demonstrated that tamoxifen hampers cutaneous wound healing in elderly postmenopausal women [17]. In mice, tamoxifen induced increased skin fragility and blistering due to interaction with plectin, a structural protein of stratified epithelia [31]. Therefore, there is a need of further research in antifibrotic compounds.

## 95.6 Treatment of Ocular Rosacea

Ocular rosacea is characterized by inflammation of the eye lid margins, conjunctivitis, and keratitis including dry eye complex.

Cyclosporine A is a calcineurin inhibitor that has been shown to possess anti-inflammatory properties. It is capable of inhibiting lipopolysaccharide-induced NF-kappaB activation and acts as an

uncompetitive inhibitor of the chymotrypsin-like activity of the 20S proteasome in vitro [32]. Cyclosporine 0.05 % ocular emulsion is effective in dry eye caused by autoimmune connective tissue disease and has a potential in ocular rosacea as well [33].

Azithromycin improves rosacea-associated conjuctivity and other ocular symptoms [34]. In patients with Hp infection eradication therapy results in improvement of ocular rosacea. In a study with seven patients ocular rosacea responded even better than cutaneous rosacea [35].

Serotonin (5-HT) has been shown to act as a morphogen in craniofacial and heart development and in the migration of neural crest derivatives. Some of these structures are capable of capturing 5-HT during development. Human ocular tissues differentially expressed mRNAs for the various serotonin 5HT receptor subtypes. Studies suggest a diverse range of possible physiological and pharmacological functions of 5HT receptors in these human ocular tissues. The serotonin receptor 5HT2 occurs in ocular tissue with the least amount in ciliary epithelium and most amount in retina. 5HT2 receptor subtype mRNAs were the most abundant with 5HT2A and 5HT2B being the most predominant in the retina, ciliary body, ciliary epithelium, choroid, conjunctiva, and iris [36].

Ondansetron, a selective serotonin antagonist, has antipruritic effects when given at dosages of 8–12 mg/day p.o. [37]. The compound has no effect on thermoregulation in a hot environment [34]. Ondansetron given at a dosage of 12 mg intravenously improved ocular rosacea in a 56-year-old woman after only 4 days. She responded as well after a relapse. Flushing was also improved [38].

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# Cosmetics in Rosacea

# 96

Zoe Diana Draelos

## Contents



**Core Messages**

- Rosacea patients form a subset of sensitive skin due to barrier defects requiring special formulations and testing.
- The barrier defects manifest as stinging, burning, and vasodilation requiring the avoidance of sensory provoking and irritant ingredients in cosmetics.
- Skin care products and cosmetics can be valuable in the rosacea patient to complement prescription therapies and provide redness camouflage.
- Cleansers for rosacea patients should preserve the intercellular lipids while maintaining a healthy biofilm.
- Moisturizers for rosacea patients should assist in barrier repair and provide broad-spectrum photoprotection.
- Cosmeceuticals with anti-inflammatory properties may be a useful adjunct to traditional therapy in some rosacea patients.
- In general skin care products and cosmetics selected for rosacea patients should possess no volatile substances, no irritants, no sensitizers, minimal ingredients, no barrier damaging ingredients, and no unnecessary ingredients.

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## 96.1 Introduction

Rosacea patients form a subset of sensitive skin, making the selection of skin care products and cosmetics problematic. Ingredients that typically cause no difficulty in the average patient can cause severe stinging and burning in the rosacea patient. Sometimes the adverse reaction can be invisible; more typically, it is characterized by the rapid onset of facial flushing. For this reason, developing a methodology for product recommendations in the rosacea patient becomes important. This chapter will discuss a rationale for the selection of cleansers, moisturizers, cosmeceuticals, and facial cosmetics in the rosacea patient.

## 96.2 Sensitive Skin and Rosacea

Many skin care and cosmetic products are labeled as appropriate for sensitive skin. What exactly does this mean? There is no standardization as to the meaning of this term; however, most manufacturers will test sensitive skin care products on a population consisting of at least 30 % rosacea sufferers. Of the entire population, approximately 40 % consider themselves to possess the characteristics of sensitive skin [1]. Sensitive skin can be defined in both subjective and objective terms. Subjective perceptions of sensitive skin are derived from patient observations regarding stinging, burning, pruritus, and tightness following various environmental stimuli. These symptoms may be noticed immediately following product application or delayed by minutes, hours, or days [2]. Furthermore, the symptoms may only result following cumulative product application or in combination with concomitant products. Objective perceptions of sensitive skin include the onset of facial flushing and/or inflammatory papules following application. An adverse reaction to a cosmetic or skin care product may elicit subjective and/or objective signs in a rosacea patient.

## 96.3 Facial Product Testing for Sensitive Skin

Skin care and cosmetic products designed for rosacea patients must be specially tested as appropriate for sensitive skin. One method of testing is simply to employ an in-use model by enrolling 40–60 subjects with mild-to-moderate rosacea and ask them to use the newly developed product for 4 weeks while recording their perceptions in a diary. A dermatologist investigator can also assess the state of the subject's rosacea at 2-week intervals for improvement or worsening related to the study product.

Another method of evaluating product appropriateness for rosacea is to use a modification of the lactic acid facial stinging test [3]. This test provokes a flare of rosacea by exposing the skin to an irritating chemical accompanied by heat. The test is performed by placing the rosacea patient in a warm facial sauna for 15 min or until profuse sweating and redness appear followed by an application of a 5 % aqueous solution of lactic acid at room temperature to one randomized nasolabial fold using brisk rubbing strokes of a cotton-tipped applicator. The product in question is applied to the other nasolabial fold and the subject is asked to rate the stinging of both application areas. The subject is blinded as to the identity of the applied products, so as not to bias the stinging response. The patient rates the stinging at 2.5 and 5 min after application on an ordinal 4-point scale (0 = no stinging, 1 = slight stinging, 2 = moderate stinging, 3 = severe stinging) [4, 5]. Even though this test is quite artificial, it appears to correlate well with skin care and cosmetic products that might cause difficulty in rosacea patients, but this remains controversial [6].

The most important part of product testing for rosacea patients is the need to expose the facial skin during a rosacea flare when the inflammation in active. Vasodilation and inflammatory mediator release must be present to get an accurate assessment. Products that sting on the face of a rosacea patient may provoke a flare, which is undesirable, and should not be marketed as

appropriate for sensitive skin. In general, rosacea patients can use skin care and cosmetic products from reputable manufacturers that are labeled as appropriate for sensitive skin.

## 96.4 Facial Cleansers

Proper skin care can enhance rosacea treatment or, in some cases, totally negate a positive effect. No skin care act is more important than cleansing. Since demodex and *Propionibacterium acnes* may be contributory in some forms of rosacea, skin cleansing is the first step to restoring and maintaining a healthy biofilm. Thorough cleansing is also necessary to control the growth of pityrosporum species in patients with the overlap syndrome of rosacea and seborrheic dermatitis. In short, the goals of cleansing in a rosacea patient are to remove excess sebum, environmental debris, desquamating corneocytes, unwanted organisms, and old skin care and cosmetic products while leaving the skin barrier untouched. This can be a challenge since cleansers cannot distinguish between sebum and intercellular lipids meaning that products that clean too well may be problematic. This discussion focuses on the use of the cleansers in rosacea patients with a variety of skin needs to include oily, normal, and dry skin (Table 96.1). Cosmetic removal, cleansing devices, and problematic products are also discussed.

**Table 96.1** Cleansing Categories for Rosacea Patients

| Rosacea skin type | Cleanser type | Formulation |
|---|---|---|
| Oily skin | Soap | Long-chain fatty acid alkali salts with a pH between 9 and 10 |
| Normal skin | Syndet | Synthetic detergents contain less than 10 % soap, adjusted pH of 5.5–7 |
| Dry skin | Lipid-free cleanser | Liquids that clean without fats |

1. Oily Skin

   Many rosacea patients with highly sebaceous skin produce abundant sebum. Even though the skin is oily, over cleansing will result in shiny, flaky skin. This is due to the barrier disruption created by removal of the intercellular lipids causing premature corneocyte desquamation followed by the subsequent accumulation of sebum. The face is over dry immediately after cleansing, but oily again 2–4 h after cleansing. This is a challenging situation, since cleansing does not reduce sebum production; it only removes the sebum present at the time of cleansing. This observation accounts for the ill-founded belief of some rosacea patients that skin cleansing produces redness and increased sebum.

   The most basic cleanser for oily skin is soap, created as a reaction between a fat and an alkali resulting in a fatty acid salt with detergent properties [7]. Soap is composed of long-chain fatty acid alkali salts with a pH between 9 and 10 [8]. The high pH thoroughly removes sebum, but can also damage the intercellular lipids. For persons with extremely oily skin, this type of cleanser may be appropriate (Ivory, Procter & Gamble). Aggressive scrubbing with a washcloth or other implement should be avoided when trying to remove copious sebum, since the manipulation of the skin may provoke a rosacea flare. A better solution is to wash the face twice, each time removing more sebum. Gentle massaging of the cleanser into the skin with the hands followed by lukewarm water rinsing is best. It is important to avoid exposing the face to water temperature extremes, which could provoke flushing.

2. Normal Skin

   There is no definition of normal skin; however, for this discussion the term will refer to patients without oily or dry skin. Soap may remove too much sebum in this population, making syndet cleansers the preferred choice. Syndets, also known as synthetic detergents, contain less than 10 % soap with an adjusted pH of 5.5–7. The neutral pH, closer to the natural pH of the skin, produces less irritation.

In general, all beauty bars, mild cleansing bars, and sensitive skin bars are of the syndet variety (Oil of Olay, Procter & Gamble; Dove, Unilever; Cetaphil Bar, Galderma). The most commonly used detergent is sodium cocoyl isethionate. These cleansers also possess excellent rinsability, meaning that a soap scum film is not left behind on the skin when used with water of varying hardness. This is an important property in the sensitive skin rosacea patient where the soap film might produce irritation.

For rosacea patients who are concerned about body odor and desire a "squeaky-clean" skin feel, another type of cleanser, known as a combar, is available. Combars are produced by combining an alkaline soap with a syndet to produce less aggressive sebum removal than a soap but more aggressive sebum removal than a syndet. Most of the combars also add an antibacterial, such as triclosan, to provide odor control properties. These cleansers are commonly labeled as deodorant soaps (Dial, Dial Corporation; Irish Spring, Colgate Palmolive) [9]. For rosacea patients with abundant sebum production and difficult to control pustules, this type of cleanser may be beneficial. Triclosan is not approved as an acne ingredient in the USA, but is used in Europe for this purpose. For patients with normal sebum production, the deodorant cleanser can be used once daily or once every other day to provide antibacterial effects without overly aggressive sebum production.

3. Dry and/or Sensitive Skin
   Many rosacea patients possess sensitive skin that must be gently cleaned due to limited sebum production. These patients are usually mature postmenopausal women. Lipid-free cleansers represent a cleansing alternative for this population. Lipid-free cleansers are liquids that clean without fats, which distinguishes them from soaps (Cetaphil Cleanser, Galderma; CeraVe, Coria; Aquanil, Person & Covey). The cleanser is applied to dry or moistened skin, rubbed to produce a slight lather, and rinsed or wiped away. These products may contain water, glycerin, cetyl alcohol, stearyl alcohol, sodium laurel sulfate, and occasionally propylene glycol. They leave behind a thin moisturizing film, but do not possess strong antibacterial properties. For this reason, lipid-free cleansers are excellent for the dry face, but are not recommended for cleansing the groin or armpits. They also are not good at removing excessive environmental dirt or sebum.
4. Cosmetic Removal
   Lipid-free cleansers may also be used to remove cosmetics in the rosacea patient. They can be applied dry and rubbed over the eyelids, cheeks, and lips to remove both water-removable and water-resistant cosmetics following by lukewarm water rinsing. If necessary, another cleanser can be used for additional cleaning. Many of the commercially marketed cosmetic removers contain solvents that are volatile and damaging to the intercellular lipids, thus provoking rosacea.

   Another product for cosmetic removal is cleansing cream. Cleansing cream is composed of water, mineral oil, petrolatum, and waxes (Abolene) [10]. The most common variant of cleansing cream, known as cold cream, is created by adding borax to mineral oil and beeswax (Pond's Cold Cream) [11]. These products are popular among mature women as they provide cosmetic removal and mild cleansing in one step.
5. Cleansing Devices
   Cleansing devices combine a cleanser with an implement for washing the skin. The most common cleansing device is a disposable cleansing cloth impregnated with a cleanser. The cloth is composed of polyester, rayon, cotton, and cellulose fibers, which are heated to produce a thermobond. Additional strength is imparted to the cloth by hydroentangling the fibers with high-pressure jets of water, eliminating the need for adhesive binders. This creates a soft durable cloth. The cloth can be packaged dry or wet typically with a syndet cleanser. Dry cloths are wetted before use.

   The amount of sebum removal produced by the cloth can be varied by the amount of cleanser, but also by the weave of the cloth. There are two types of fiber weaves used in facial cloths: open weave and closed weave.

Open weave cloths possess 2–3 mm windows between adjacent fiber bundles. These cloths are used in persons with dry and/or sensitive skin to increase the softness of the cloth and decrease the cleansing surface area. Closed weave cloths, on the one hand, are designed with a much tighter weave and provide a more thorough cleansing, but also induce exfoliation. The exfoliation is intended to remove desquamating corneocytes. While this may be beneficial in some rosacea patients, it may be problematic in others. The degree of exfoliation achieved is dependent on the cloth weave, the pressure with which the cloth is stroked over the skin surface, and the length of time the cloth is applied. Individuals with sensitive skin may wish to consider using an open weave cloth gently over the face once weekly for mild exfoliation.

Moisturizing cleansing cloths are also available and may be the preferable choice in rosacea patients. The cloth contains two sides, which may be differently designed to deliver different benefits. The moisturizing cloths contain a cleanser on the textured side and a moisturizer on the smooth side. The cloth is activated with water and the textured side is used first to clean and gently exfoliate the skin following by rinsing of the cloth. The rinsed cloth is then turned over and the face is rinsed and moisturized simultaneously. This cloth technology can also be used for cosmetic removal in some patients.

A variant of the cleansing cloth is the cleansing pouch. Fusing two cleansing cloths around skin cleansing and conditioning ingredients creates the cleansing pouch. A plastic membrane is placed between two fibered cloths containing holes of various diameters to control the release of ingredients onto the skin surface. Many times the cleansing pouches contain a variety of botanicals, which may be problematic in the rosacea patient.

6. Problematic Cleansers and Cleansing Implements

Other cleansers and cleansing implements may also be problematic in the rosacea patient. Products that induce aggressive exfoliation, such as abrasive scrubs, may provoke flushing. Abrasive scrubs incorporate polyethylene beads, aluminum oxide, ground fruit pits, or sodium tetraborate decahydrate granules to induce various degrees of exfoliation [12]. The most aggressive exfoliation is produced by irregularly shaped aluminum oxide particles and ground fruit pits, which should be avoided by the rosacea patient. Milder exfoliation is produced by polyethylene beads, which possess a smooth rounded surface. The least aggressive exfoliation is produced by sodium tetraborate decahydrate granules, which soften and dissolve during use.

Another form of aggressive exfoliation is produced by sponges composed of nonwoven polyester fibers (Buf Puf) [13]. These sponges are too aggressive for most rosacea patients. Rosacea patients have sensitive skin that must be handled gently like a fine silk scarf. Pulling, tugging, rubbing vigorously, and strong cleansers will ruin a silk scarf immediately and are not recommended for the rosacea patient with sensitive skin. Some rosacea sufferers will scrub their face mercilessly hoping to cleanse away the inflammatory lesions and redness, when in actuality they are only worsening the barrier damage. However, barrier damage repair can be facilitated with moisturizers, the next topic for discussion.

## 96.5 Facial Moisturizers

Moisturizers are important to provide an environment suitable for barrier repair in the rosacea patient. Facial moisturizers are the most important cosmetic in the prevention of a facial rosacea flare. These moisturizers attempt to mimic the effect of sebum and the intercellular lipids composed of sphingolipids, free sterols, and free fatty acids. They intend to provide an environment allowing healing of the stratum corneum barrier by replacement of the corneocytes and the intercellular lipids. Yet, the moisturizing substances must not occlude the sweat ducts, or miliaria will result, must not produce irritation at the follicular ostia, or an acneiform eruption will result, and must not initiate comedone formation. Furthermore, the facial moisturizer must not

produce noxious sensory stimuli, which may also provoke a rosacea flare.

Moisturizers are used to heal barrier-damaged skin by minimizing transepidermal water loss (TEWL) and creating an environment optimal for rosacea control. There are three categories of substances that can be combined to enhance the water content of the skin including occlusives, humectants, and hydrocolloids (Table 96.1). Occlusives are oily substances that retard transepidermal water loss by placing an oil slick over the skin surface, while humectants are substances that attract water to the skin, not from the environment, unless the ambient humidity is 70 %, but rather from the inner layers of the skin. Humectants draw water from the viable dermis into the viable epidermis and then from the nonviable epidermis into the stratum corneum. Lastly, hydrocolloids are physically large substances, which cover the skin thus retarding transepidermal water loss.

The best moisturizers to prevent facial rosacea flares combine occlusive and humectant ingredients. For example, a well-formulated moisturizer might contain petrolatum, mineral oil, and dimethicone as occlusive agents. Petrolatum is the synthetic substance most likely intercellular lipids, but too high a concentration will yield a sticky greasy ointment. The aesthetics of petrolatum can be improved by adding dimethicone, also able to prevent water loss, but allowing a reduction in the petrolatum concentration and a thinner more acceptable formulation. Mineral oil is not quite as greasy as petrolatum, but still an excellent barrier repair agent that further improves the ability of the moisturizer to spread, yielding enhanced aesthetics. The addition of glycerin to the formulation will attract water from the dermis speeding hydration. It is through the careful combination of these ingredients that facial moisturizers can be constructed to prevent a rosacea flare.

## 96.6 Facial Cosmeceuticals

Cosmeceuticals are over-the-counter moisturizers with a variety of active ingredients designed to enhance the appearance of the skin. Most of the cosmeceuticals designed for rosacea patients contain anti-inflammatory agents intended to reduce redness. The anti-inflammatories are botanical extracts that may complement prescription therapy in the maintenance phase of rosacea treatment. Commonly used botanical anti-inflammatories in the current marketplace include ginkgo biloba, green tea, aloe vera, allantoin, feverfew, and glycyrrhiza inflata. Their rationale for use in currently marketed cosmeceuticals for redness reduction is discussed (Table 96.2).

1. Ginkgo biloba
   Ginkgo biloba leaves contain unique polyphenols such as terpenoids (ginkgolides, bilobalides), flavonoids, and flavonol glycosides with anti-inflammatory effects [14]. These anti-inflammatory effects have been linked to antiradical and antilipoperoxidant effects in experimental fibroblast models. Ginkgo leaves are also purported to alter skin microcirculation by reducing blood flow at the capillary level and inducing a vasomotor change in the arterioles of the subpapillary skin plexus. Taken together, these changes may lead to decreased skin redness.
2. Green Tea
   Green tea, also known as Camellia sinensis, is another anti-inflammatory botanical containing polyphenols, such as epicatechin, epicatechin-3-gallate, epigallocatechin, and eigallocatechin-3-gallate. The term “green tea” refers to the manufacture of the botanical extract from fresh leaves of the tea plant by steaming and drying at elevated temperatures avoiding oxidation and polymerization of the polyphenolic components. A study by Katiyar et al. demonstrated the anti-inflammatory effects of topical green tea application on C3H mice [15]. A second study by the same authors found topically applied green tea extract containing epigallocatechin-3-gallate reduced UVB-induced inflammation as measured by double skin-fold swelling [16]. Green tea extracts are the most commonly used cosmeceutical botanical anti-inflammatory at the time of this writing.
3. Aloe Vera
   The second most commonly used anti-inflammatory botanical is aloe vera. The

mucilage is released from the plant leaves as a colorless gel and contains 99.5 % water and a complex mixture of mucopolysaccharides, amino acids, hydroxy quinone glycosides, and minerals. Compounds isolated from aloe vera juice include aloin, aloe emodin, aletinic acid, choline, and choline salicylate [17]. The reported cutaneous effects of aloe vera relevant to rosacea include reduced inflammation, decreased skin bacterial colonization, and enhanced wound healing. The anti-inflammatory effects of aloe vera may result from its ability to inhibit cyclooxygenase as part of the arachidonic acid pathway through the choline salicylate component of the juice. However, the aloe vera final concentration in any moisturizer must be at least 10 % to achieve a cosmeceutical effect relevant to the rosacea patient.

4. Allantoin
   Allantoin is oldest anti-inflammatory ingredient added to many moisturizers labeled as appropriate for sensitive skin. It is naturally found in the comfrey root, but usually synthesized by the alkaline oxidation of uric acid in a cold environment [18]. It is a white crystalline powder readily soluble in hot water, making it easy to formulate in cream and lotion moisturizers designed for sensitive skin. It is termed as a skin protectant, which may be helpful in redness reduction.
5. Feverfew
   Feverfew is a small bush with citrus scented leaves used as a traditional medicinal herb. It has been used to treat headaches, arthritis, and digestive problems. The anti-inflammatory benefits of this plant have been attributed to parthenolide and tanetin, which are thought to decrease the release of serotonin and prostaglandins [19]. It also induces vasoconstriction. These are the mechanisms that may allow feverfew to reduce redness in rosacea. A new skin line (Aveeno, Johnson & Johnson) was introduced that was based on parthenolide-free feverfew, since parthenolide can induce allergic contact dermatitis.
6. Glycyrrhiza inflata
   Glycyrrhiza inflata is a member of the licorice family, known for containing a variety of anti-inflammatory botanicals. One extract isolated by heating from the root of the Glycyrrhiza inflata licorice plant is licochalcone A. It possesses anti-inflammatory properties as evidenced by its in vitro ability to inhibit the keratinocytes release of $PGE_2$ in response to UVB-induced erythema and the lipopolysaccharide-induced release of $PGE_2$ by adult dermal fibroblasts [20]. Licochalcone A is the active agent in one of the largest product lines currently sold internationally for redness reduction (Eucerin, Biersdorf).

**Table 96.2** Facial cosmeceuticals for redness reduction

| Botanical ingredient | Active agent | Skin functional effect |
|---|---|---|
| Ginkgo biloba | Terpenoids (ginkgolides, bilobalides), flavonoids, flavonol glycosides | Decrease circulation at the capillary level, reduce inflammation through antiradical and antilipoperoxidant effects |
| Green tea | Polyphenols such as epicatechin, epicatechin-3-gallate, epigallocatechin, epigallocatechin-3-gallate | Reduces UVB-induced inflammation by functioning as an antioxidant |
| Aloe vera | Aloin, aloe emodin, aletinic acid, choline, choline salicylate | Salicylate derivative inhibits cyclooxygenase pathway |
| Allantoin | Diureide of glyoxylic acid | Enhances the water holding capacity of the extracellular matrix improving barrier function |
| Feverfew | Parthenolide, tanetin | Inhibits the release of prostaglandins and serotonin |
| Glycyrrhiza inflate | Licochalcone A | Inhibits keratinocytes release of prostaglandins in response to UVB-induced erythema |

## 96.7 Facial Camouflaging Cosmetics

Many times complete redness reduction with pharmaceuticals and skin care products is impossible due to the presence of telangiectasias, which cannot be addressed with either treatment modality. This leaves colored cosmetics as a viable alternative for all female rosacea patients, and possibly some males. The cosmetics can camouflage the underlying redness by either blending colors or concealing the underlying skin to achieve a more desirable appearance.

The art of blending colors to minimize facial redness utilizes the complementary color to red, which is green. Moisturizers with a slight green tint are applied after the prescription medication and well blended. Since the mixture of red and green produces brown, the sheer green tint will tone down bright red cheeks. Sometimes the green tint is followed by application of a tan facial foundation that matches the desired skin color. The green tint allows a sheer facial foundation to better camouflage the red tones. If the red remains apparent, a more translucent or even opaque facial foundation can be used.

## 96.8 Facial Cosmetics and Skin Care in the Problem Patient

Occasionally a rosacea patient will present who cannot use any topical medications and skin care or cosmetic products without an adverse effect. The dermatologist may at first think that the patient is histrionic, since these patients present with a basket full of problematic products and have usually seen multiple dermatologists. In this case, it may be worthwhile to embark on a logical elimination scheme to determine which products can and cannot be tolerated. This discussion introduces an algorithm for dealing with these difficult patients, based more on the art of medicine than the science that first discontinues all unnecessary products and then reintroduces them systematically. The algorithm is presented in Table 96.3.

**Table 96.3** Skin care treatment algorithm for problematic rosacea patient

| | |
|---|---|
| 1. | Discontinue all topical cosmetics, over-the-counter treatment products, cleansers, moisturizers, and fragrances. Use only a lipid-free cleanser and a bland moisturizing cream for 2 weeks |
| 2. | Discontinue all topical prescription medications for 2 weeks. Especially avoid medications containing retinoids, benzoyl peroxide, glycolic acid, and propylene glycol. Oral medications for rosacea may be continued |
| 3. | Eliminate all sources of skin friction by selecting loose, soft clothing |
| 4. | Discontinue any physical activities that involve skin friction, such as weight lifting, running, horse back riding, etc |
| 5. | Evaluate the patient at 2 weeks to determine if any improvement has occurred or if any concomitant dermatoses are present. If underlying dermatoses, such as seborrheic dermatitis, psoriasis, eczema, atopic dermatitis, or perioral dermatitis appear, treat as appropriate until 2 weeks after all visible signs of the newly diagnosed skin disease have disappeared |
| 6. | Patch test patient to elicit any allergens with the standard dermatologic patch test substances. Determine which of these allergens are clinically relevant and make avoidance recommendations |
| 7. | Evaluate the patient's mental status especially noting signs of depression, menopause, or psychiatric disease |
| 8. | Allow the female patient to add one facial cosmetic in the following order: lipstick, face powder, and blush |
| 9. | Test all remaining cosmetics used by the patient by applying nightly to a 2 cm area lateral to the eye for at least five consecutive nights. Cosmetics should be tested in the following order: mascara, eye liner, eyebrow pencil, eye shadow, facial foundation, blush, facial powder, and any other colored facial cosmetic |
| 10. | Lastly, test all topical rosacea medications by applying nightly to a 2 cm area lateral to the eye for five consecutive nights |
| 11. | Analyze all data and present the patient with a list of medications, skin care products, and cosmetics that are appropriate for use |

This is indeed a time-consuming undertaking, but it is a thorough approach to determining the topical products that are appropriate for the challenging patient.

### Conclusions

The rosacea patient may pose a challenge to the dermatologist aiming to give practical advice on the selection of skin care and cosmetic products. This chapter has discussed the variety of cleansers, moisturizers, and cosmeceuticals in the current marketplace that may or may not be appropriate for the rosacea patient. Key to success is customizing a skin treatment regimen for each patient. Identifying skin needs and matching products to those needs will result in a satisfied patient. An approach for identifying products suitable for the problematic patient has also been presented. The ideas discussed in this chapter should provide ideas for supplementing traditional rosacea therapy with skin care and cosmetic products.

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# Treatment of Rhinophyma

# 97

Uwe Wollina and Shyam B. Verma

## Contents



**Core Message**

- The cornerstone of drug therapy of rhinophyma in milder cases is systemic isotretinoin.
- The more advanced cases of rhinophyma need a surgical approach. Healing by secondary intention is the gold standard with superior cosmetic outcome.

## 97.1 Introduction

Treatment of rhinophyma includes avoidance of triggers (Chap. 87), drug therapy and surgery.

## 97.2 Retinoid Therapy

In early stages oral isotretinoin monotherapy is established. The standard dosage is 0.2–0.5 mg/kg body weight and day, but lower dosages as low as 10 mg/day are safer and often better tolerable in particular with ocular involvement. Isotretinoin is contraindicated in patients taking tetracyclines since there is a risk of the development of pseudotumour cerebri. Other strict contraindications are gravidity and lactation, hypervitaminosis A, renal or liver failure and allergies against any constituent of the drug formulation. Since most patients are males teratogenicity of retinoids is not such a huge problem in

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clinical practice. Of course women in their reproductive years need a strict contraception during isotretinoin therapy. A monthly pregnancy test for women is recommended in Germany. Monitoring includes regular laboratory investigations of blood count, liver enzymes, cholesterol, and triglycerides (in a 3-month interval) and in women beta-human chorionic gonadotropin (once a month) [1].

## 97.3 Antifibrotic Treatment

Since dermal fibrosis is a leading symptom antifibrotic therapy might be an option for the future. Tamoxifen, an anti-oestrogen approved for breast cancer, has yet been used in an experimental approach only [2].

## 97.4 Ablative Treatment

In more advanced cases surgery is a need. Surgery can be performed under general or regional anaesthesia or in tumescent anaesthesia. The latter does provide the advantage of less bleeding [3].

Cryosurgery with liquid nitrogen spray is an option for mild-to-moderate rhinophyma. Several freeze-and-thaw cycles are used [4].

Electrocautery using a bipolar electrosurgical unit or radiosurgery (high-frequency electrosurgery) with a loop attachment can both be used to remove the tissue in thin layers [5, 6]. Radiosurgery is less painful than conventional electrosurgery and much less expensive than laser [7]. By this means haemostasis can be provided as well. Some authors use a combination of debulking by tangential excision, sculpturing with scissors and final contouring by dermabrasion [8, 9].

Tangential excision and razor blade ablation are useful, safe and quick procedures in the hand of the experienced surgeon [10]. Electrocautery is used in conjunction for haemostasis. Another haemostatic option is FloSeal® (Baxter, USA), a gelatine-thrombin co-mixture, to be applied on the denuded nose [11].

Ultrasonic scalpels offer the combination of sculpturing and haemostasis by the same tool [12]. The decortation has to respect the dermal tissue. If it is too deep, injuries to perichondrium or cartilage may develop and scar formation may develop.

Lasers can be used as well. Mostly used are CO2, Erb:YAG and Nd:YAG laser. The $CO_2$ laser offers a bleedless operation field but needs an extensive operation time compared with conventional surgery. The Erb:YAG has a disadvantage since this laser does not coagulate and rhinophymas can show a lot of bleeding during ablation. On the other hand the thermal injury is much less than with a CO2 laser. Decortication of rhinophyma with a combined Erb:YAG/CO2 laser may produce improved results. The Nd:YAG shows good cosmesis although temporary oedema and proteinous discharge may develop after the procedure [13–16]. Apikian et al. [2] reported on successful treatment of mild-to-moderate rhinophyma with a 1,450-nm diode laser in five patients. The laser was used four times in a monthly interval [17].

There does not appear to be an increased risk of scarring in rhinophyma laser therapy, but the conventional surgical methods are much more rapid. Since there is rapid spontaneous re-epithelialization within a couple of weeks, there is no need of skin grafting. In the long run both split skin grafts and full skin grafts on the nose have the tendency to shrink. The cosmetic outcome is much better in secondary healing despite the longer downtime for patients [17].

The use of hydrocolloid dressings may improve the healing when applied as early as in the operation theatre. Another option described in recent literature is the use of radiotherapy. A 72-year-old male patient was treated successfully with 90-kV photons to a total dosage of 40 Gy in 20 daily fractions [18]. Such a treatment would not be recommendable in younger patients.

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# The Future of Rosacea Treatment

# 98

Frank C. Powell and Maeve A. McAleer

## Contents



**Core Messages**

- Future treatments of rosacea are dependent on advances in the understanding of the aetiology and pathogenesis of each subtype of rosacea.
- Technological advances in intense pulsed light sources and pulsed dye lasers should result in greater potential for treating the telangiectasias in erythematotelangiectatic rosacea (ETT).
- The erythema observed in ETT has been shown to respond to the topical application of an alpha1-adrenergic receptor agonist.
- Increased understanding of the cutaneous neurovascular system may result in novel treatments.
- Some complementary and alternative medicines have effects, such as anti-inflammatory and antimicrobial actions, that may impact on rosacea.
- Low-dose antimicrobial agents, topical benzoyl peroxide, trichloroacetic acid skin peels and photodynamic therapy have been shown to be effective in papulopustular rosacea (PPR).
- The development of drugs directed at sebaceous gland hypertrophy may aid patients with phymatous rosacea.

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- The skilful clinician will identify the rosacea subtype and adapt therapy to suit the rosacea variant and the individual patient's requirements, being mindful of both established and novel treatments for rosacea.

## 98.1 Introduction

The future of rosacea treatment will depend on developing an understanding of the aetiology and pathogenesis of the various components that result in this common cutaneous disorder. Appropriate therapy can then be directed at causative factors with the objective of preventing the development of the more florid manifestations of the disease. Until that knowledge is available treatment will be directed at the different clinical features that present in rosacea patients.

To adequately treat rosacea today and into the immediate future the first step requires the recognition of its various clinical manifestations and classification into its appropriate subtype by the physician [1]. The skilful clinician will then adapt therapy to suit the morphological variant of the disorder and individualise the treatment to suit the particular patient. Some of the subtypes of rosacea can be treated today in a relatively straightforward fashion with a predicted good response (e.g. papulopustular rosacea (PPR) responds well to topical and/or systemic antibiotics), while other subtypes (e.g. erythematotelangiectatic rosacea (ETTR) and flushing) are difficult to treat as adequate therapeutic modalities have, as yet, not been developed.

## 98.2 Classification of Rosacea

Rosacea has been classified into four different subtypes based on the primary morphological features that are present, recognising that clinical overlap may occur [12] Table 98.1. *Erythematotelangiectatic rosacea* (subtype 1) is characterised by the presence of persistent centrofacial erythema often associated with the presence of multiple facial telangiectasias and a tendency to flushing. *Papulopustular rosacea* (subtype 2) presents with an eruption of multiple small dome-shaped erythematous papules, some of which have surmounting central pustules, which usually arise in a central facial distribution and on a background of erythema. These patients may also have a tendency to flush and may have facial telangiectasias. Subtype 3 rosacea is also referred to as *phymatous rosacea (PR)*. Patients with this subtype most often have rhinophyma, where the nose is enlarged and distorted due to sebaceous gland hyperplasia and fibrosis. This condition predominantly affects male patients. Incorrectly described by some as "end stage rosacea", rhinophyma can arise in patients with surprising little preceding inflammatory changes. Gnathophyma, metophyma, otophyma and blepharophyma are other, much rarer variants of phymatous rosacea. *Ocular rosacea (OR)* is the fourth subtype of this disorder. It is a frequent accompaniment of papulopustular and ETTR and may precede the onset of cutaneous changes. It is difficult to diagnose with certainty in the absence of skin involvement as the ocular inflammatory changes (conjunctivitis, blepharitis, chalazion, hordeolum, etc.) are not specific for rosacea and there is no diagnostic test that will confirm this or any other subtype of the disorder.

Some patients have more than one subtype of the disorder at any given time (e.g. PPR and OR) and the numerical delineation of subtypes from 1 to 4 does not imply disease progression in this sequence. In fact there is some evidence that subtypes 1 and 2 are distinct cutaneous disorders with overlapping clinical features, and phymatous changes are not limited to patients with rosacea as similar findings can be seen in patients with actinic damage or acne vulgaris.

## 98.3 Present Treatments and Future Options

Because the aetiologies of the various subtypes of rosacea are unknown, therapeutic choices are dictated by the established responses of the

**Table 98.1** Subtypes of rosacea with current and possible future therapies

| Rosacea subtype | Clinical features | Current treatment | Potential future treatments |
|---|---|---|---|
| ETTR / I | – Persistent centrofacial erythema and frequent flushing<br>– Telangiectasias are common | – Measures to minimise flushing<br>– Sunscreening agents and cosmetic camouflage<br>– Pulsed dye laser and intense pulsed light | – Addition of therapeutic agents such as "Green tea" to topical products [2].<br>– Further developments in laser and intense pulsed light technology [3].<br>– Topical alpha-1-adrenergic receptor agonist [4]. |
| PPR / II | – Centrofacial papules and pustules and erythema | – Systemic antimicrobial therapy.<br>– Topical metronidazole or azelaic acid | – Longer term low-dose antimicrobial therapy.<br>– Photodynamic therapy [5]<br>– Alternative topical agents such as benzyl peroxide or menthol [6, 7]<br>– Trichloroacetic acid skin peel [8]<br>– Anti-demodectic therapy |
| PR / III | – Thickened skin with prominent pores and surface irregularities | – Surgery<br>– Electrocautery<br>– CO2 laser. | – Drugs directed at sebaceous gland growth<br>– Photodynamic therapy |
| OR / IV | – Symptoms of irritation<br>– Ocular inflammation | – Regular eyelid hygiene<br>– Topical fusidic acid or metronidazole<br>– Systemic antimicrobial therapy | – A diagnostic test would aid the recognition of the OR and allow further research into the pathogenesis |
| All subtypes | – | – | – Complementary and alternative medicines [6, 9–11]<br>– Treatments targeted at the cutaneous neurovascular system |

clinical lesions to treatment modalities rather than a cause-directed approach. As the knowledge base relating to the aetiology of rosacea grows, it is hoped that treatments will increasingly be designed to target etiological factors rather that selected on an empirical basis. Based on current trends the future of rosacea treatment will probably involve a combination of drugs and devices [13] Table 98.1.

### 98.3.1 Erythematotelangiectatic Rosacea (Subtype 1)

This disorder occurs almost exclusively in subjects with Fitzpatrick skin phototypes I or II, actinic damage is a constant feature of the histopathology of the skin, and many patients notice deterioration of their facial erythema with exposure to sunlight. However, surveys have shown that understanding of the adverse effects of sunlight and "weathering" on sensitive skin among the general public is poor. Therefore susceptible members of the public should be educated in the importance of *avoidance of undue outdoor exposure and the daily use of protection and appropriate sun block creams* all year round. This message is separate from that related to the risk of skin cancer, and it should be emphasised that these measures are designed to prevent the development of actinically induced telangiectasias and facial erythema. Tinted sunblock creams, those whose vehicle formulations contain dimethicone and cyclomethicone, and preparations which combine sun-blocking properties with medication to treat rosacea or reduce erythema are often favoured by patients because of their cosmetic acceptability, low irritant potential or ease of application.

"Natural" products such as *Green tea* are often favoured by the public and are likely to be increasingly used in the future. Green tea possesses antioxidant anti-inflammatory properties and has been shown in human volunteers to cause a dose-dependent reduction in erythema after simulated solar irradiation [2]. Further evaluation of these properties is required.

The telangiectatic element of subtype 1 rosacea can be treated successfully by *lasers* using various light sources and it is likely that further technical developments in this field will lead to more selective therapy options in the future. The lasers primarily in use at present include the *sub-purpuric long-pulsed dye lasers* which appear to increase compliance when compared with some of the older lasers, but require multiple treatment sessions, while *intense pulsed light therapy* allows for targeting different sized vessels at different depths and has the added benefit of treating the solar damage that is an important component of this subtype of rosacea [3]. The long-term remission rate of lesions treated by the various forms of laser needs to be established so that treatment options can be guided.

Following ablation of the telangiectatic vessels the degree of facial erythema often diminishes but does not fully clear and an effective therapy for this element of ETTR is required. The use of *oxymetazoline hydrochloride 0.05 % solution* applied topically daily to the affected areas of the face has been recently reported to result in reduced facial erythema within 2–3 h, an effect that was sustained for the entire day. This drug appears to act through direct stimulation of adrenoreceptors resulting in vasoconstriction, but it may have additional anti-inflammatory effects [4]. There is obvious potential for the use of this drug in the treatment of the erythematous component of ETTR and other subtypes of rosacea either as a sole agent or in combination with other active therapies if the possible problems related to absorption, tachyphylaxis, and rebound vasodilatation can be successfully addressed.

The increased understanding of *the interactive dermal neurovascular environment* in patients with photodamage and ETTR opens the possibility that agents which inhibit the release of vasoactive neuropeptides from nerve endings or block their receptors on blood vessels or that increase their metabolism by neuropeptidase enzymes may have a role in the management of this subtype of rosacea in the future (Fig 98.1).

Although several agents, ranging from beta blocking agents to clonidine, have been proposed as potential therapies of the *flushing* often associated with ETTR, none of these are successful to a significant degree and many have potentially

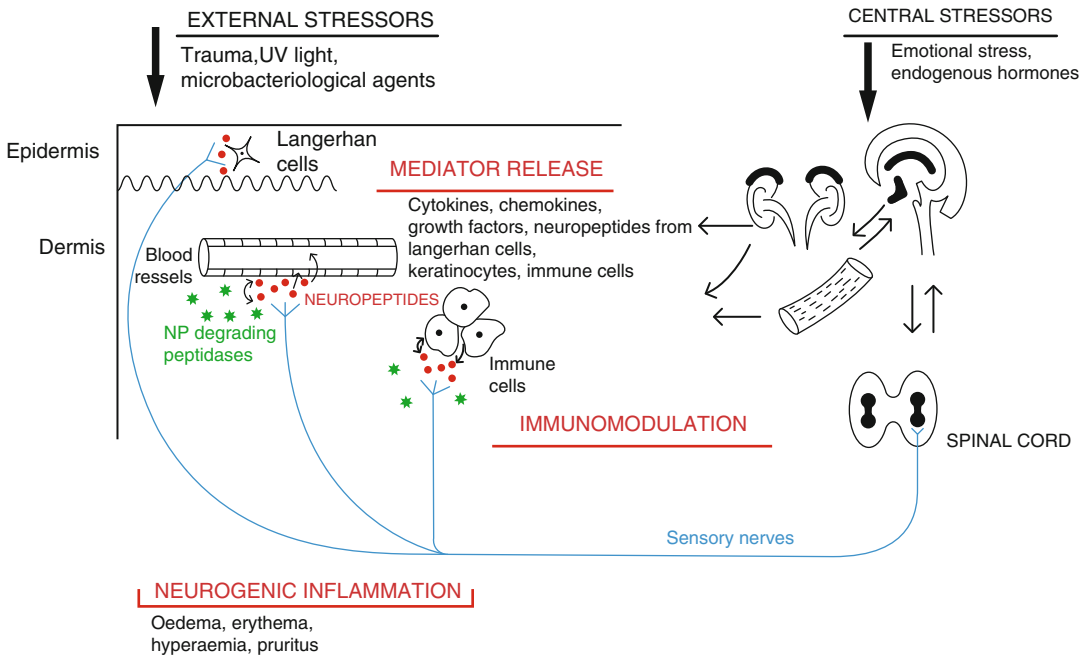


**Fig. 98.1** Diagrammatic representation of the possible mechanism of neurogenic inflammation in the skin precipitated by external stressors such as ultraviolet light

serious side effects which make their use difficult to justify for what is essentially a benign condition. While treatments for postmenopausal flushing have improved in recent years, the flushing seen in patients with rosacea is of a different pathogenic mechanism and similar advances have not been reported for this element of rosacea. *Highly selective sympathectomy* has been shown to be effective in large numbers of patients [14], but potential side effects will limit its use to those with socially disabling flushing only. Less invasive and destructive surgical approaches in combination with medical treatment of the typically associated anticipatory anxiety may provide more symptomatic relief for these patients in the future.

### 98.3.2 Papulopustular Rosacea (Subtype2)

The papules and pustules of subtype 2 rosacea respond well to a variety of topical and systemic antibiotic treatments. Currently used medications including topical metronidazole, topical azelaic acid and oral tetracyclines have substantial clinical evidence to support their continued use into the future. Sub-antimicrobial dose doxycycline also appears to be effective and reduces the amount of pills a patient is required to take. Topical calcineurin antagonists such as tacrolimus and pimecrolimus initially showed promise as agents to treat PPR, but may in fact induce rosacea-like eruptions so their use is restricted in this group of patients.

However antibiotic therapy is often required repeatedly for these patients and there is increasing concern about the potential public health issue relating to bacterial resistance in the community which may result in restriction of antibiotic usage for conditions such as rosacea. In addition patient preference is often for non-antibiotic treatments, and they often use *complementary or alternative medicines* including herbal therapies [9]. Some of these agents have been shown to reduce inflammation (Licorice), have photoprotective properties (Green Tea), and have antimicrobial (Tea Tree Oil) or

anti-demodectic activities (Camphor Oil) [10]. *Topical kinetin 0.1 % (N6-furfuryladenine) lotion* (an essential plant growth factor) applied over 12 months in combination with a sunscreen was shown to decrease facial erythema and improve skin dryness but did not affect inflammatory papules or pustules in an open study of 18 patients with "moderate" rosacea [11]. Such an agent may have a role when used in combination with antibacterial therapy for PPR. *Menthol*, which has antibacterial and antifungal properties in addition to synergy with tetracyclines [6], is another "natural" agent that may have a role in topical rosacea management in the future. Its pleasant smell may also add to patient compliance with therapy. The use of these agents should be evaluated in a scientific fashion to determine whether they have a role in the future management of PPR.

*Low strength trichloroacetic acid peel* was shown to be well tolerated and to reduce facial erythema and papulopustular lesions and improve skin texture in a small group of Brazilian patients with ETTR and PPR [8]. *Topical benzoyl peroxide* has potent antimicrobial activity and has been used extensively in the treatment of acne vulgaris. It has been reported to be effective in the clearing of the papules and pustules of PPR [7], and its low cost and lack of bacterial resistance make it a potentially attractive agent. However, the sensitive skin of most rosacea sufferers is intolerant of irritating agents and its use may be limited to those exceptional patients with PPR who have oily, less easily irritated skin.

*Photodynamic therapy (PDT)* is a modality that is increasingly used to treat a range of inflammatory, malignant and premalignant skin conditions [15]. It has been used to treat some patients with PPR with successful results [5], but long-term follow-up studies are required to determine the duration of remission before this can become a first-line treatment of PPR.

Some patients with PPR and others who have a rosacea-like eruption due to local or systemic immunosuppression or other reasons develop an overabundance of demodex folliculorum mites in the skin. The facial skin of such patients appears slightly scaly (described as having a "frosted" appearance) and the term pityriasis folliculorum is often used for this eruption which is part of the rosacea spectrum. Such patients benefit from *anti-demodetic therapy (such as permethrin or benzyol peroxide)* which reduces the mite population in the skin with subsequent clearing of the papules and pustules. With increasing recognition of these patients, possibly by use of diagnostic aids such as dermatoscopy or skin surface biopsy, selective use of topical or systemic anti-mite therapy may be increasingly useful in the future for a subgroup of patients currently classified as having PPR.

### 98.3.3 Phymatous Rosacea (Subtype 3)

The use of *isotretinoin* to treat the early changes of rhinophyma has been suggested [16], but results have varied. Those patients with poral prominence, oily skin and inflammatory lesions may benefit most from this therapy. The majority of rosacea patients are poorly tolerant of the drying effect of isotretinoin on skin and eyes, and low dosages (less than half the dose used to treat acne vulgaris patients) should be used. Drugs which specifically affect sebaceous gland growth or differentiation may prove more helpful for patients in this subtype.

The sebaceous gland hypertrophy of established rhinophyma can be treated with surgical excision, *cryosurgery*, or *electrocautery* or with the use of *ablative lasers such as* $CO_2$. The results are often cosmetically favourable and patients are usually pleased with the outcome [17]. These modalities are likely to form the backbone of treatment of rhinophyma in the future. Long-term follow-up studies remain to be done to determine the duration of remission from rhinophyma following these forms of intervention.

*PDT* (as described for PPR) has also been used to treat rhinophyma, but sufficient patients have not yet been reported to evaluate the effectiveness of this form of therapy which may hold promise for the future.

There is no effective treatment for the other forms of phymatous rosacea and none for the recalcitrant upper facial edema accompanied by persistent erythema that is sometimes referred to

as "edematous rosacea" or Morbihan disease. The prominence of mast cells in the dermal inflammatory infiltrate in these patients suggests that antihistamine therapy should be helpful, but results to date have been largely disappointing in individual patients. Until the pathogenesis of these unusual conditions and their relationship (if any) to rosacea are understood it is unlikely that further progress will be made on their treatment.

### 98.3.4 Ocular Rosacea (Subtype 4)

Dermatologists should become more aware of the presentations of ocular rosacea and their treatments in order to optimise care in the future. Crusting of the eye lids and keratin "cuffing" of the bases of the cilia (eyelashes) are common (anterior blepharitis), so that *regular eye hygiene* is important (gentle cleaning of the lid margins with tepid water, sometimes with the addition of a very mild detergent such as baby shampoo diluted 1 in 10 in cooled boiled water). To ensure that this is carried out routinely cleansing should be done at the same time as applying topical medication to the face. Inadequate tear secretion can lead to impetiginisation of the lid margins as manifested by yellow crusting (staphylococcal blepharitis) and *topical fucidic acid*; *chloramphenicol or metronidazole gel* can be applied to clear this infection. Because reduced tear secretion and reduced tear break-up time are common features of ocular rosacea due to meibomian gland dysfunction (posterior blepharitis), *artificial tears* are an important component of the treatment of these patients and will remain important for the future. Chalazia or hordeolia usually require the use of *systemic antibiotic therapy*, such as tetracyclines, erythromycin or minocycline, and sometimes surgical incision may be necessary, especially if meibomian cysts develop.

While the above treatments can be effective the topical therapies are unpleasant to apply and in some patients prolonged courses of systemic antibiotics are necessary. Improved treatment of ocular rosacea probably requires a better understanding of the pathogenesis of this common rosacea subtype and ideally a diagnostic aid or test to confirm that the ocular changes are in fact related to rosacea.

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# Part XV

# Rosacea and Quality of Life

# Impact of Rosacea on Quality of Life

99

Mohammad Khurshid Azam Basra
and Andrew Y. Finlay

## Contents



**Core Messages**

- Impact of rosacea on quality of life is mainly due to its disfiguring lesions on the aesthetically most important area of the body, i.e. the face.
- The impact of rosacea may extend far beyond the physical lesions into the psyche of patients.
- Low self-esteem, low self-confidence, social anxiety, depression and social avoidance behaviour are important ways in which a rosacea patient's quality of life may be impacted.
- Emotional distress can both be a triggering factor as well as a consequence of rosacea.
- The magnitude of quality of life impact may vary with different types of rosacea.
- These is no compelling evidence to suggest that rosacea is related to alcohol abuse.
- Successful treatment may lead to improvement in patient's quality of life.
- Use of subjective measures of quality of life is important to capture the complete impact of rosacea from a patient's perspective as well as to monitor the efficacy of therapeutic interventions.
- Health-care providers ought to address the psychosocial needs of rosacea patients as much as its physical symptoms.

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- For the best medical outcomes, there is a need to improve the doctor–patient relationship and the use of quality of life measures provides an easy and practical way to achieve this.

## 99.1 Introduction

Healthy skin plays an important role in an individual's physical and psychosocial well-being. Skin diseases, although not generally life-threatening, frequently have a major impact on patient's psychological and social life as well as everyday activities [1]. The 1989 UK Household Survey estimated that 16 of every 1,000 persons were affected by a long-standing skin disorder sufficiently severe to limit their activities [2]. Another survey of disability amongst 14,000 adults in the mid-1980s also found that 1 % of complaints causing disability in private households and 2 % in communal establishments were due to skin disorders [3].

Many skin diseases are chronic and incurable; the resulting impact on patients' lives is subjective and related to individual circumstances. The quality of life (QoL) impact of skin disease is complex, unpredictable and plays a major influence in decision taking. This makes measurement of QoL particularly important in dermatology [4]. The physical, social and emotional consequences of skin diseases are substantial and myriad as shown by a number of studies [1, 5]. These include negative emotions, loss of self-esteem, stress, stigma, shame, embarrassment, social impact, relationships, employment, daily activities and physical discomfort. In addition, some chronic skin diseases pose a significant financial burden to the patients and their families and to the health services in the form of hospital care, physician visits, prescription drugs and over-the-counter products as well as incurring indirect costs to society caused by loss in productivity.

Because of the visible nature of many skin diseases, the psychological aspects of patients' lives are frequently affected. These include fear of disfigurement or dysmorphophobia, unintentional and sometimes excessive manipulation of skin lesions, social anxiety and social avoidance behaviour or social phobia. Approximately 30 % of dermatology patients have at least one psychological co-morbidity [6]. The perception of not having a "perfect" body image can have serious consequences ranging from social isolation to suicidal thoughts and even suicide [7]. The psychiatric morbidity in these patients does not necessarily have to have a linear correlation with the site or severity of their skin disease [8]. Mere presence of facial blemishes has the potential to cause significant impairment of a patient's QoL. Studies have not found any difference in QoL due to facial blemishes based on their types or size of the affected area [9].

Rosacea is one such condition which is always accompanied by visible skin manifestations and often bothersome symptoms. Not only can these two aspects be highly frustrating for the patients, but they are also emotionally and socially unacceptable and have been associated with significant psycho-emotional problems and impairment of patients' QoL [10, 11].

## 99.2 Quality of Life Impact of Rosacea

The main lesions of rosacea, i.e. erythema, telangiectasia, papules and pustules (and rhinophyma, if present), are located on the face, an area which is considered to be the most important area of the body from an aesthetics perspective. Although most patients do experience some discomfort and soreness in the involved area, what is actually more disturbing for the patients is the cosmetic aspect of rosacea. The striking redness, swelling and blemishes can have a devastating impact on a patient's emotional well-being. The negative emotions generated as a result of one's unsightly appearance may lead to a multitude of emotional and social problems. As the disease progresses and facial features change from localised redness and telangiectasia to more widespread papules, pustules and swelling, the magnitude of these emotional effects also increases.

Studies have demonstrated that patients with rosacea report having low self-confidence and suffer from feelings of diminished self-esteem, guilt and shame [10, 12]. The presence of mere facial flushing in some patients is enough to cause embarrassment and anxiety in social situations. The anxiety in these patients may well resemble panic disorder and ultimately result in social avoidance behaviour [12]. The occurrence of social inhibition has also been described in some early studies [13]. Patients with rosacea frequently report being the subjects of stares, rude comments, jokes and misconceptions, all because of their skin appearance [14]. In addition to social phobia, a higher incidence of depression has also been observed in these patients [15, 16]. Surveys on large sample of rosacea patients found that 76 % respondents reported having low self-esteem and self-confidence due to the effect of rosacea on their personal appearance, 69 % felt embarrassed, 65 % felt frustrated, 50 % reported that it had diminished their outlook on life, 41 % suffered from anxiety, 38 % had to cancel their social engagements and meetings because of their appearance, 35 % felt helpless, 25 % had depression and 18 % felt that they were isolated [14, 17]. In addition to the aforementioned psychological aspects, rosacea patients may face difficulties in their professional career advancement as well as experiencing impaired sexual desirability [18, 19].

Stigmatisation is another aspect associated with rosacea and further contributes to patients' emotional sufferings. The red face and enlarged nose of patients are often wrongly associated with poor hygiene and alcohol abuse [20]. However, controlled studies have not found any compelling evidence that links rosacea with alcohol abuse [21, 22].

The magnitude of QoL impact may differ in patients with different types of rosacea, e.g. erythematotelangiectatic, papulopustular or rhinophyma. A German study using the Dermatology Life Quality Index (DLQI, German version) found different QoL scores in patients with papulopustular rosacea (mean DLQI = 7.0, SD = 4.9; normal range = 0–30; higher scores indicate worse QoL), erythematous lesions only (mean DLQI = 4, SD = 2.8) and rhinophyma (mean DLQI = 5.6, SD = 3.6). The study concluded that patients with papulopustular rosacea had greatest QoL impairment [23].

Poor response to treatment in some patients is frustrating and yet another factor contributing to poor quality of life. On the other hand, however, successful treatment seems to improve the QoL. Treatment of telangiectatic rosacea using pulsed dye laser resulted in a significant improvement in patients' QoL determined by the DLQI [24]. The DLQI scores decreased from the baseline scores of 7.8 to 1.9 after 2 treatments showing a 75.6 % improvement in QoL ($p < 0.01$). The authors concluded that the significant improvement in QoL was the result of reduction in flushing achieved by destruction of excessive cutaneous vasculature due to rosacea. Patients felt that they were less self-conscious of their skin appearance in public places after the treatment and did not feel the need to hide their face under make-up [24].

## 99.3 Measurement of Quality of Life in Rosacea Patients

In order to quantify the overall morbidity caused by rosacea in a patient, it is important to measure both the clinical severity of physical symptoms and the quality of life impact of the disease. A grading system has been developed to measure the clinical severity of rosacea symptoms [25]. However, carrying out only objective clinical assessment by a physician carries the risk of underestimation of the overall impact of a skin disease. Not only that, studies have shown that clinicians' and patients' assessment of clinical severity of rosacea differ significantly; clinicians tend to focus more on erythema while patients' primary focus is papules and pustules [26]. Therefore, for optimal evaluation, objective measures of disease severity should always be supplemented by subjective measures of the impact of disease on patients' lives. Inclusion of patient-administered measures such as QoL measures in clinical

practice helps health-care professionals to be aware of their patients' problems and needs. This also helps patients feel that they are actively involved in clinical management decisions by allowing them to express their feelings and concerns about the illness and its treatment in a structured way.

Three types of QoL instruments have been used in dermatology: generic, dermatology-specific and disease-specific. As described in chapter 2.9.2 *generic* instruments aim to measure QoL in any population regardless of the underlying conditions, while *specific* (dermatology- and disease-specific) instruments are suited for evaluating a patient's experience of a particular organ system or disease [27].

In addition to these main categories of QoL instruments, a number of instruments are available to capture exclusively the emotional aspects of aesthetically disfiguring illnesses such as rosacea. Examples are Body Image Avoidance Questionnaire [28], Appearance Schemas Inventory [29] and Derriford Appearance Scale (DAS59) [30]. Although these instruments have the potential to be used in dermatological patients, based on their item content, they have not been formally validated for use in dermatology yet.

Studies using a dermatology-specific measure, i.e. the DLQI [31], have found a mild-to-moderate degree of QoL impairment [32] of rosacea patients ranging from 4 to 7.8 (normal DLQI score range = 0–30) [24, 33, 34]. However, a dermatology-specific measure may lack sensitivity to the nature of the specific issues and severity of psychosocial distress which patients with rosacea experience in their day-to-day life. This may consequently make the measure less responsive to change in QoL following therapeutic interventions. In order to highlight specific aspects of rosacea-related QoL from the patient's perspective, a rosacea-specific instrument, Rosacea-specific Quality of Life Instrument or RosaQoL, has been developed [35, 36]. Its 21 items cover a range of aspects of a rosacea patient's QoL such as symptoms, embarrassment, frustration, botheration due to skin appearance, need to cover the lesions, worry about the side effects of medication and need to avoid certain environments. The contents of the questionnaire were derived from six in-depth interviews with patients having rosacea. Initial results of reliability and validity are encouraging. However, responsiveness to change was only partially confirmed in the original study. A subsequent open-label observational study of 583 patients with mild-to-moderate rosacea demonstrated a significant improvement in patients' QoL after using azelaic acid gel [37].

A rosacea-specific instrument has a number of clinical implications, e.g. it could highlight the most bothersome aspects of the disease from the patient's perspective. This would potentially enable the treating physician to customise the treatment to the specific needs of the patient. It could also help in monitoring the response to treatment based on changes in patient's QoL. Moreover, a rosacea-specific measure could be used as an additional outcome measure in clinical trials to assess the efficacy of different therapies.

## Conclusions

While managing a disfiguring disease such as rosacea, physicians should bear in mind that it is not enough to treat the physical symptoms of the disease, as its psychological and social consequences and its profound impact on QoL also need ongoing attention. The importance of appearance for normal psychological functioning of an individual and its consequent impact on QoL cannot be overemphasised. Proper and timely attention to this under-recognised aspect can go a long way in preventing the emotional and behavioural problems that many of these patients develop during the course of their illness. Discussing these issues with patients can help strengthen the doctor–patient relationship and promote patient satisfaction. Both these factors have been shown to play a key role in improving medication adherence [38, 39]. An improvement in patient adherence will eventually result in better health outcomes [40].

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# Erratum

## Pathogenesis and Treatment of Acne and Rosacea

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Constantin E. Orfanos has authored the Introduction (pages xxv–xxviii)
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