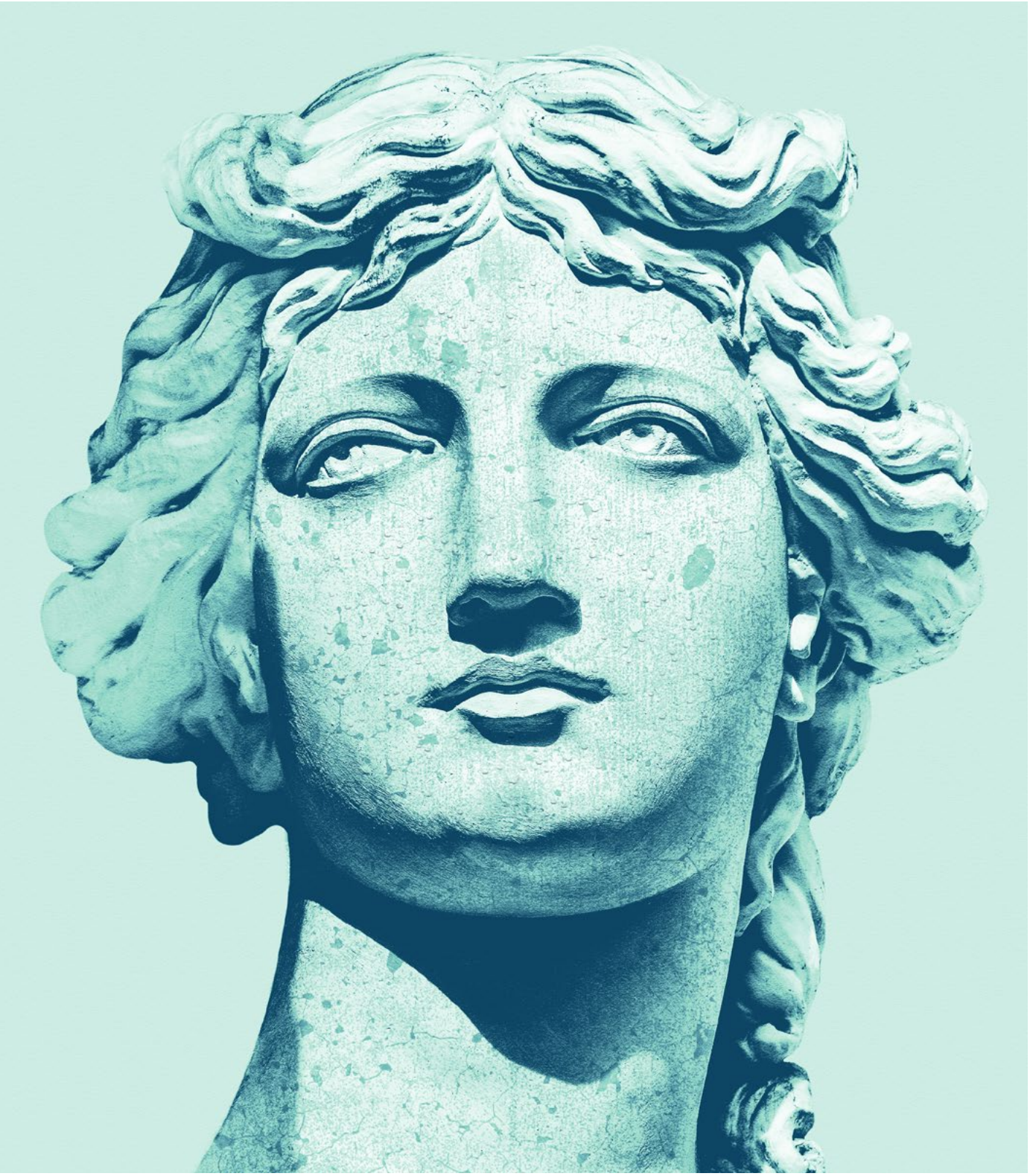
Australasian Society of Cosmetic Dermatologists

IN THIS ISSUE

ACNE 1

OPINIONS AND PROGRESS IN

Cosmetic Dermatology



VOLUME 02 / ISSUE 02 / JULY 2022

Australasian Society of Cosmetic Dermatologists

GALDERMA

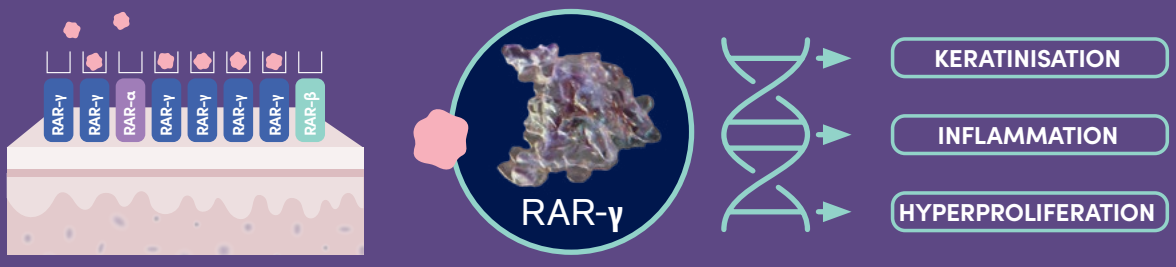
EST. 1981

PRECISION WHERE IT MATTERS. PERFORMANCE IN ACNE CARE.[1–3]

Watch the AKLIEF® mechanism of action video

This patient image has been digitally altered to reflect potential presentation of varying degrees of acne.

THE FIRST-OF-ITS-KIND RAR-γ-SELECTION TREATMENT FOR PATIENTS WITH FACIAL AND TRUNCAL ACNE[1,2,4-6]



PLEASE REVIEW THE PRODUCT INFORMATION BEFORE PRESCRIBING, AVAILABLE VIA THE FOLLOWING QR CODE.

AKLIEF® (trifarotene) Cream, 0.005%

PBS information: This product is not listed on the PBS.

References: 1. Aubert J, *et al. Br J Dermatol* 2018;179(2):442–56. **2.** Tan J, *et al. J Am Acad Dermatol* 2019;80(6):1691–99. **3.** Blume-Peytavi U, *et al. J Eur Acad Dermatol Venereol* 2020;34(1):166–73. **4.** Thoreau E, *et al. Bioorganic Med Chem Lett* 2018;28:1736–41. **5.** Stein Gold L & Dirschka T. *Dermatol Ther* 2021;11:661–4. **6.** Wilson C, *et al. EADV* 2018 (Poster P0044).

Australasian Society of Cosmetic Dermatologists

www.ascd.org.au/medical_journal

OPINIONS AND PROGRESS IN
Cosmetic Dermatology
VOLUME 02 / ISSUE 02 / JULY 2022

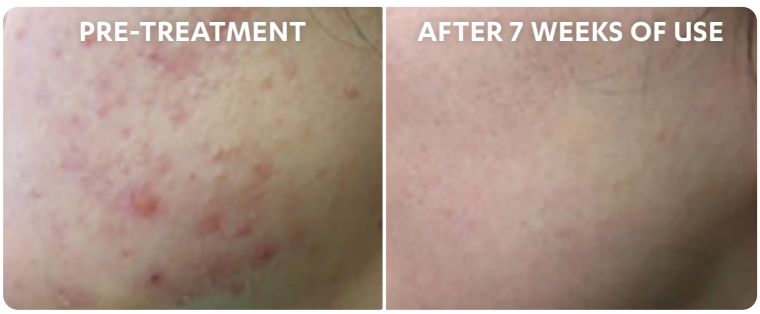
The ASCD follows guidelines on ethical publishing, including editorial independence, produced by the International Committee of Medical Journal Editors (http://www.icmje.org/recommendations/), the World Association of Medical Editors (http://www.wame.org/about/policy-statements) and the Committee on Publication Ethics (http://publicationethics.org/resources).

Say goodbye to acne with BIRETIX

cantabria labs

Specially-designed formulations to help prevent and reduce the characteristic signs of acne-prone skin in adolescents and adults.

Thanks to the combination of Retinsphere® Technology and Biopep-15, BIRETIX improves the condition and appearance of acne-prone skin.



New stockist deals available now. For more information visit:
www.dermocosmetica.com.au

dermocosmètica.

Photos courtesy of Fabbrocini G et al, Eur J Acne, 2012. 2. Manfredini M et al. Hi. Tech Dermo, 2013.

Biretix is distributed in Australia by Dermocosmètica ABN 52152881019 Unit 8, 14–16 Lens Street, North Coburg VIC 3058
T: +61 3 9354 0898 F: +61 3 8692 6923 E: info@dermocosmetica.com.au

Australasian Society of Cosmetic Dermatologists
www.ascd.org.au/medical_journal

OPINIONS AND PROGRESS IN
Cosmetic Dermatology
VOLUME 02 / ISSUE 02 / JULY 2022

Welcome to **the Acne Issue**

We are thrilled to have Dr Jo-Ann See, a leading Australian dermatologist on acne, join us as guest editor for this issue.

We are excited to collaborate with Dr See and the not-for-profit organisation she co-founded: All About Acne. All About Acne is well regarded by doctors, industry, and the community and we are fortunate to be working with Dr See and her colleagues. This issue is indeed about active acne and will be followed by Issue 6 that will focus on acne scarring and repair.

The recent ASCD Annual Symposium in Melbourne was a heart-warming reintroduction of face-to-face conferencing the 'old-fashioned' way. Many of us have started to venture overseas to catch up with family, friends and attend international meetings. It appears that we have transitioned reasonably well into a COVID-normal world, ready to reconnect and reinvigorate, but also ready for any new challenges in our collective COVID trajectory.

It is a great privilege to remain a part of your continuing education activities and we hope you enjoy this issue.

Co-Editors in Chief
Dr Adrian Lim
Clinical Professor Saxon D Smith

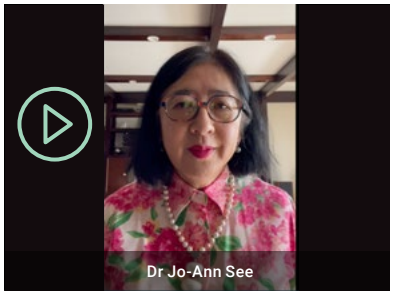
Contents

Acne 1 — Guest editorial

Guest Editor: Dr Jo-Ann See[1]

1. Central Sydney Dermatology, Sydney, NSW, Australia

Correspondence: Dr Jo-Ann See Joseederm@bigpond.com



CLICK IMAGE TO LINK TO VIDEO DURATION_01:21

See J-A. Acne 1 – Guest editorial. Opin Prog Cosmet Dermatol 2022;2(2):1.

I am honoured to be the guest editor for this first acne issue of the journal. In this issue we will focus on the medical aspects of acne and the subsequent issue will look at the physical therapy approach to management such as chemical peels and lasers.

As we all know, acne is one of the most common dermatological disorders but it is often misunderstood by our patients as a "rite of passage" where everybody suffers from it at some stage in their lives and everybody receives advice often from nonmedical sources. As medical specialists, we acknowledge that acne is a medical disease and manage it with the benefit of a scientific background.

It is wonderful to have been able to collaborate with so many outstanding dermatologists and their co-authors from around the country to bring you an up-to-date, informative review.

As always, we start with a historical perspective with an amusing article from Clinical Professor Saxon Smith who reminds us that acne sufferers have been documented since Egyptian times circa 1500BC. This is not a new disease!

We then fast forward to an up-to-date review of acne pathogenesis. Lee-Mei Yap and co-author, Andrew Awad describe the paradigm shift in a new understanding of acne pathogenesis by the major role inflammation plays, the powerful immune response that is triggered and influences on comedogenesis. The role of the microbiome and its new found importance is discussed further by Mina Kang and co-authors Phillip Tong and Nicholas West in "Good skin takes guts". Gut metabolic end products may have systemic immunomodulatory, metabolic and endocrine effects on our skin.

I have the pleasure of including an article from the Brisbane team about diet and acne which you will find fascinating with its explanation of acne-good and acne-bad foods, as well as an acne eating plan!

Authors Lori Zhang and A/Prof Kurt Gebauer discuss the differential diagnosis of acne and acneiform eruptions that are occurring with the newer Janus kinase inhibitors. Their article highlights the negative medical impact of acne which is discussed at length in the excellent article "The psychological burden of acne" by Georgina Heddie, Sally Tregenza and Emma Ryan. This must-read article looks at the relationship of stress and acne and the psychological burden associated with having acne, isotretinoin, and social media with implications for management.

Acne is not just a teenage problem and we look at paediatric and adult acne subgroups. The team from South West Sydney discuss pre-pubertal acne and the need for early diagnosis as well as timely and effective management. Adult female acne is eloquently explored by the team from Canberra with particular reference to the specific challenges of treatment which may often require long term maintenance.

Mei Tam and I discuss the investigations that you may want to order with regards to prescribing oral isotretinoin or if you are considering a diagnosis of hormonal acne. We would like to emphasise the need for tests that are clinically important and the timeframe when they should be performed.

Hannah Gribbin and Lisa Byrom provide us with an excellent review of topical preparations and the importance of individualising treatment according to the patient's skin type and acne subtype. Annabel Stevenson tackles systemic therapies and some of the controversy regarding prescribing oral antibiotics, retinoids and hormonal therapy.

Of course, no issue on acne would be complete without an "update on isotretinoin" by Haady Fallah and A/Prof Marius Rademaker who review the current evidence of the ongoing controversies associated with this drug and give their practical recommendations.

I hope you enjoy reading this edition and that you can pick up some pearls that may not only interest you but benefit your day-to-day practice.

That filtered lens – a historical perspective to acne

Saxon D Smith[1, 2, 3]

1. ANU Medical School, ANU College of Health and Medicine, Australian National University, Canberra, ACT, Australia
2. Sydney Adventist Hospital, Wahroonga, NSW, Australia
3. The Dermatology and Skin Cancer Centre, St Leonards, NSW, Australia

Correspondence: Saxon D Smith dr.saxon.smith@gmail.com

Disclosures: *none*

Smith SD. That filtered lens – a historical perspective to acne. Opin Prog Cosmet Dermatol 2022;2(2):2-3.

In the age of rapid fire non-stop social media, you would be forgiven in thinking that acne was a newly discovered skin disease selectively affecting all sufferers on the night of their year 12 formal or Tinder™ date. It is true that over 80% of adolescents and young adults can be afflicted with some degree of severity of acne.[1] Furthermore, the substantial negative psychological impacts of this highly visible skin disease continue to be well explored.[2] In fact, acne has deep roots set in a history longer than TikTok™ pimple popping videos.

In the famous Ebers Papyrus (circa 1500BC), the ancient Egyptians recorded the first reference to a condition known as 'aku-t' which described boils, pustules, or inflamed swellings.[3] Some of the earliest references to acne as a skin condition occurring in puberty can be seen with the Greek fathers of medicine, Aristotle and Hippocrates, use of the Greek word 'ionthoi'.[3] In particular, the singular form of 'ionthoi' translates to mean 'the onset of beard growth'.[3] On the other hand, Roman physicians, such as Celsus, used the term 'varus' to describe a similar skin condition.[3] Furthermore, both Greek and Roman physicians wrote that the condition appeared in puberty only.[3] It is perhaps these historical references which laid the foundation for the current term of 'acne vulgaris' which has been used since the 1800s.[3]

Whilst the term for acne perhaps appears to have been fairly stable throughout history, the same cannot be said for the understanding of its pathogenesis. The ancient Greeks thought illness was from an imbalance in the four "humors" which existed as liquids within the body: blood; phlegm; black bile; and, yellow bile. They attested that skin diseases were a manifestation of internal imbalances of these "humors" as the pores in the skin were regarded as orifices through which "humors" could pass.

By the 17th century, physicians had started to think about a tentative association with the endocrine system. In 1638, Riolanus associated acne with menstrual disorders. Whilst Johnston, in 1648, linked acne with a pattern of heterosexual behaviour:

> *"vari are little hard tumours on the skin of the face curdled up of a hard thick juice. They are known easily. They are of the bigness of hemp seed, and they infect young people that are inclined to venery and fruitful, but chast withal and continent"*
> (as translated by Culpepper).[3]

However, by the 18th century, the writings of Daniel Turner (1714) suggested that most physicians considered it beneath their dignity to treat such minor conditions.[3] Over time, this reluctance to treat must have shifted. By the 19th century, two of the fathers of modern dermatology, Willan and Bateman, divided acne into three categories based on the three types of lesions that occur: simplex; punctata; and, indurata.[4] Willan and Bateman also included a fourth category 'acne rosacea' in their types but made pains to differentiate this subtype from the other three categories because of different demographics and presentation. Importantly, Willan and Bateman appear to be the first to apply the word 'acne' as an overarching term for this condition.[3]

The clinical advancement in terminology for acne was paralleled by technology to better understand its pathophysiology. In 1846, Carl Zeiss, a German scientific instrument maker and optician, formed

Carl Zeiss AG to mass produce microscopes and other optical instruments.[5] This allowed for the identification of skin glands and their subsequent study. By 1903 the aetiology of acne remained uncertain. However, Von Jacobi (1903) wrote that "many morbid processes conspire to favour the existence of the disease," but that "a peculiar seborrhoeic condition is frequently present, which gives rise to the formation of comedones." Furthermore, he stated that the "specific significance attributed to various bacteria found in the pus of acne pustules is contestable."

The pathophysiology of acne is now well understood. In fact, there is a complex interplay that involves: sebum lipid composition; *Cutibacterium acnes* (formerly *Proprionibacterium acnes*) overgrowth; infundibular plug formation from the biofilm produced by *C. acnes* contributes to comedone formation and hyperkeratinisation; local pro-inflammatory cytokines driving epithelial hyperproliferation; and, increased androgen levels and sensitivity to androgens.

History has delivered us the origins of the terminology, clinical classification and pathophysiology of acne vulgaris. However, the quick and easy application of photo filters through your preferred social media platform has given us the means to ensure that desired 'picture perfect' formal photo is ready for sharing with all and sundry.

References

1. Tan J, Bhate KA. Global perspective on the epidemiology of acne. Br J Dermatol 2015;172(1):3-12.
2. Stamu-O'Brien C, Jafferany M, Carniciu S, Abdelmaksoud A. Psychodermatology of acne: Psychological aspects and effects of acne vulgaris. J Cosmet Dermatol. 2021;20(4): 1080-3.
3. Grant RN. The History of acne. Proc R Soc Med. 1951;44:647-52.
4. Bateman T. Practical synopsis of cutaneous disease according to the arrangement of Dr Willan. Philadelphia (1824), p260-72.
5. https://www.zeiss.com.au/corporate/about-zeiss.html (accessed 17 April 2022).
6. Mahmood NF, Shipman AR. The age-old problem of acne. Int J Women's Dermatol. 2017;3:71-6.

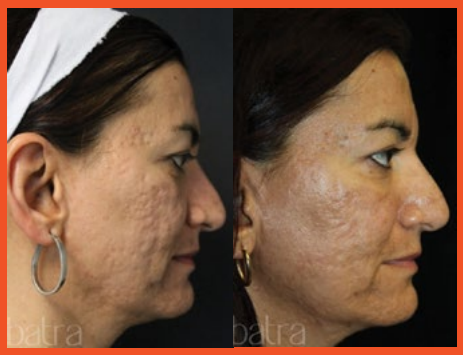
LEARN WHY MORE DERMATOLOGY PRACTICES AROUND AUSTRALIA ARE INVESTING IN THIS INNOVATIVE TECHNOLOGY

THE GO TO DEVICE FOR ACNE AND SURGICAL SCARRING

Highly customizable parameters for a wide range of skin conditions

Safe for all skin types*

BEFORE **AFTER**



VENUSVIVAMD

Venus Viva™ MD is a highly effective and customizable skin ablation and resurfacing device, and it now comes with two tip options for treating a range of mild to severe skin conditions. Treat milder skin texture irregularities with the 160 pin tip, or treat more severe acne scars, scars, and deep rhytides with the 80 pin tip. This device uses NanoFractional Radio Frequency (RF) technology, offering patients a safer, lower downtime, lower risk alternative to traditional skin resurfacing options, while providing equal results. A published clinical study showed that 100% of patients rated their satisfaction with the results of their NanoFractional RF™ treatments as "Excellent," "Very Good," or "Good."

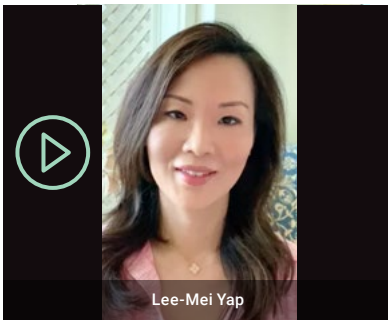
*The Venus Viva™ MD is cleared by TGA, FDA, and Venus Viva™ (using the Viva™/Viva™ MD applicators) is licensed for the use in dermatological procedures requiring ablation and resurfacing of the skin.

Before and After images and consent supplied by Dr Sonia Batra

Call Blake Williams on M. 0418 119 344 or visit www.venusconcept.com to find out more

VENUSCONCEPT
delivering the promise

Pathogenesis of acne: An overview



CLICK IMAGE TO LINK TO VIDEO DURATION_00:40

Lee-Mei Yap[1,2], Andrew Awad[3]

1. Department of Dermatology, St. Vincent's Hospital, Melbourne, VIC, Australia
2. The Dermatology Institute of Victoria, Melbourne, VIC, Australia
3. Sinclair Dermatology, Melbourne, VIC, Australia

Correspondence: Lee-Mei Yap ylmei@yahoo.com

Disclosures: *none*

OUTLINE: Acne is a common inflammatory pilosebaceous disease which typically presents with a pleomorphic array of lesions at various inflammatory stages. Its pathogenesis involves key elements such as follicular hyperkeratinisation, a pro-inflammatory sebaceous lipid profile, *Cutibacterium acnes* and hormones (e.g., androgens, insulin-like growth factor-1). These interdependent factors interact to produce changes in the cutaneous microenvironment, leading to inflammation and powerful immune responses that promote acne development.

The microcomedone is considered the precursor of all clinical acne lesions. Its formation is a result of increased sebum production and abnormal follicular keratinisation, which is primarily hormonally regulated, around the onset of puberty. Sebum is not only produced in excess in acne, but its composition is altered with an accumulation of oxidised squalenes and a deficit in linoleic acid, creating an inflammatory milieu.

Recent research has produced a paradigm shift in our understanding of acne pathogenesis. Inflammation is now believed to precede abnormal keratinisation and microcomedone formation rather than being a secondary event. Immunohistochemical studies have demonstrated the presence of inflammation in all stages of lesion development including preclinical microcomedones.

The cutaneous microbiome is another emerging area of interest. In a balanced cutaneous microbiome, *Staphylococcus epidermidis* plays a beneficial role in limiting *C. acnes* overcolonisation hence disequilibrium of the microbiome can trigger activation of the innate immunity and inflammation. *C. acnes* activates the innate immunity via the expression of toll-like receptors, protease activated receptors, tumour necrosis factor-α and the production of pro-inflammatory cytokines such as interleukin-1, interferon-γ and matrix metalloproteinases.

We present an updated view on acne pathogenesis and discuss the processes that influence comedogenesis and sebum production, the role of the cutaneous microbiome, as well as novel concepts of inflammation involved in acne.

KEYWORDS: Acne, sebaceous gland, sebum, *Cutibacterium acnes,* cutaneous microbiome

Yap L-M, Awad A. Pathogenesis of acne: An overview. Opin Prog Cosmet Dermatol 2022;2(2):5-10.

Introduction

Acne is a common chronic inflammatory disease of the pilosebaceous unit which is characterised by comedones, papules, pustules, nodules, cysts, and potential scarring. It affects approximately 85% of teenagers but can affect most age groups, and can persist into adulthood.[1] There is significant physical and psychological morbidity associated with acne, including permanent scarring, poor self-esteem and body image, and depression and anxiety.[2]

The current understanding of acne pathogenesis is continually evolving. The main pathogenic factors are (1) follicular hyperkeratinisation; (2) sebum alterations resulting in a pro-inflammatory lipid profile; (3) *Cutibacterium acnes* (*C. acnes*, formerly *Propionibacterium acnes)*; and (4) inflammation driven by both innate and acquired immunity (Figure 1). These factors are further influenced by environmental factors such as diet and stress, and genetic factors.

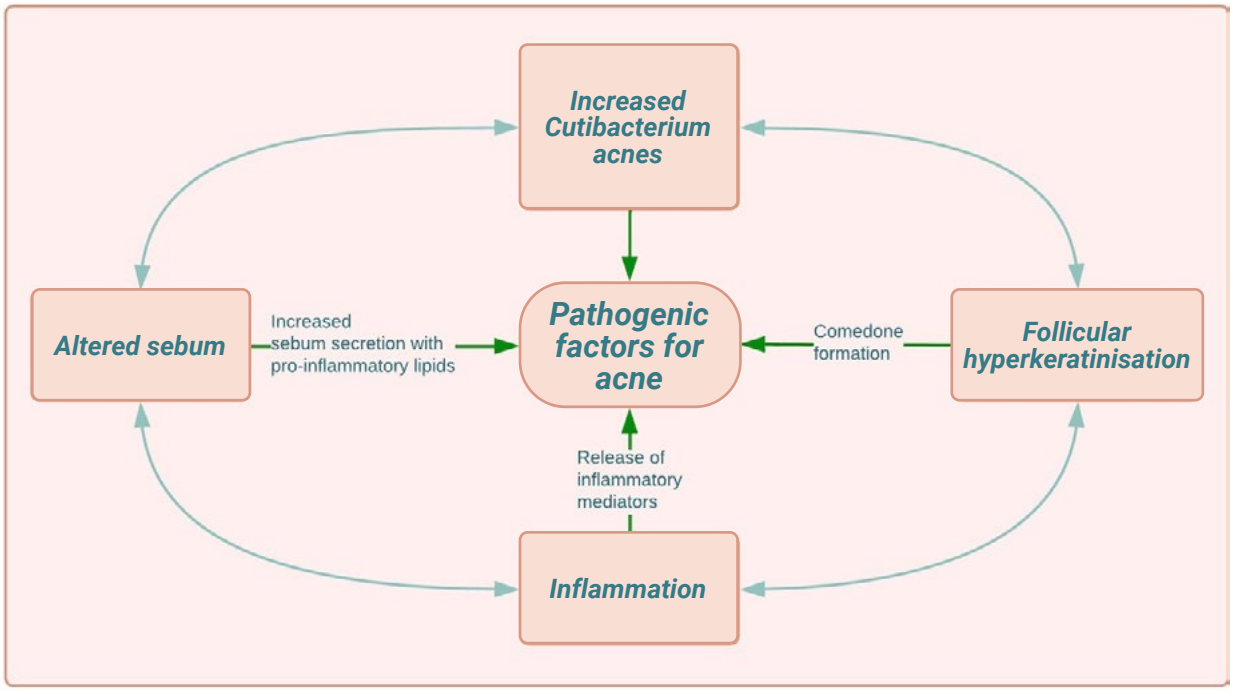


Figure 1. *The major factors involved in the development of acne lesions.*

The exact sequence of events in acne pathogenesis is not fully understood but the aetiological factors are all interrelated. Recent research has led to a greater understanding of sebaceous gland homeostasis, and the cellular and molecular mechanisms involved in the multiple inflammatory cascades that result in the formation of acne. These insights will hopefully lead to more targeted therapies for acne in the future.

Follicular hyperkeratinisation

The first step in acne development is widely believed to be the formation of the microcomedone, which is the precursor to comedones, papules and pustules.[3,4] It is not visible to the naked eye and is formed in the lower part of the infundibulum (infrainfundibulum). Normally, keratinocytes are shed in the hair follicle lumen as single cells and then discarded. In acne, increases in both follicular keratinocyte proliferation and corneocyte cohesiveness lead to the development of a hyperkeratotic plug containing keratin, sebum and bacteria, which then obstructs the follicular lumen to produce a microcomedone.[5]

The exact process by which microcomedones evolve into other acne lesions remains to be determined. The microcomedone continues to fill up with more sebum, keratin and bacteria, and evolves into visible comedones, papules, pustules and cysts. This distension eventually results in follicular wall rupture, and the extrusion of the contents induces a brisk inflammatory response. Within 24 hours of comedone rupture, CD4+ lymphocytes are found around the pilosebaceous unit, and CD8+ cells are found around the dermal vasculature. One to two days after comedonal rupture, neutrophils become the predominant cell type in the inflammatory dermal infiltrate.[6]

The initiating event for microcomedone formation is unclear. Follicular keratinocyte proliferation may be stimulated by interleukin (IL)-1α, androgens and the effects of *C. acnes*. Low levels of linoleic acid, an essential fatty acid in the skin, have been reported to stimulate follicular hyperkeratinisation and the production of inflammatory cytokines. IL-1α induces follicular keratinisation and comedogenesis, whereas IL-1 receptor antagonists have been shown to inhibit microcomedone formation. Fibroblast growth factor receptor (FGFR)-2 signalling plays an important role in follicular proliferation by increasing production of IL-1α and 5-α reductase.[7]

The sequence of events and mechanisms involved in comedogenesis was revisited by Saurat, who described a phenomenon called the "comedo switch".[8] It was postulated that comedones do not arise from follicular hyperkeratinisation as widely believed, and may result from abnormal differentiation of sebaceous progenitor cells in the junctional zone. Undifferentiated sebocytes in acne are thought to differentiate into sebaceous duct cells as well as infundibulum keratinocytes, resulting in abnormal keratinisation of the follicular infundibulum.

Role of the sebaceous gland

Structure and function of sebaceous gland

A sebaceous follicle consists of four parts: the sebaceous gland, the keratinised follicular infundibulum, the sebaceous duct that connects the gland to the infundibulum, and the hair follicle. The pilosebaceous unit comprises the hair follicle, sebaceous gland and the arrector pili muscle (Figure 2). Sebum plays an important role in skin barrier function, and has been shown to have both pro- and anti-inflammatory properties.[5] Sebum is composed of a complex mixture of triglycerides, wax and sterol esters, squalene and free fatty acids. Sebocyte turnover is 14 days and sebum secretion is holocrine, that is the sebocytes disintegrate and release sebum as they migrate towards the sebaceous duct.[5]

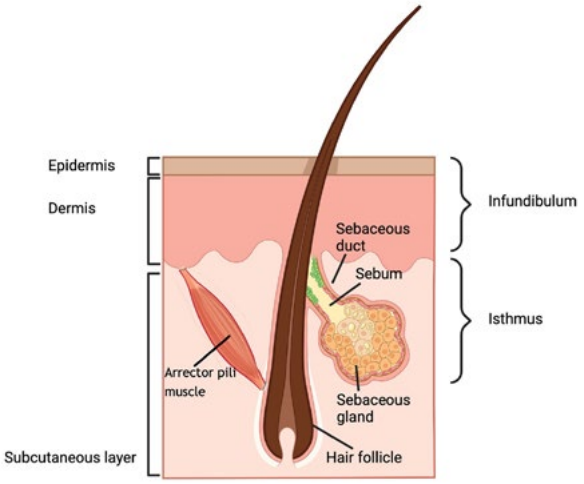


Figure 2. *Structure of the pilosebaceous unit*

Triglycerides, the main component of sebum, are converted into free fatty acids, which then promote *C. acnes* colonisation and inflammation. Lipoperoxides in sebum also induce inflammatory cytokines and activate the peroxisome proliferator-activated receptors pathway to increase the production of sebum.[7] The sebum composition in acne is distinct with higher levels of squalenes and monounsaturated fatty acids but less linoleic acid.[5, 9]

Acne patients have a higher amount of lobules per sebaceous gland and the overall size of the sebaceous follicles is increased leading to seborrhoea (increased sebum production).[10] The secretion rates of sebum have been reported to correlate with the severity of acne.[7]

Hormonal regulation of the sebaceous gland

Regulation of sebaceous gland growth and sebum production is complex. Similar to their effects on keratinocytes, androgens, in particular dihydrotestosterone (DHT), play an important role in the proliferation and differentiation of sebocytes. Sebum production is mediated by different receptors expressed by the sebaceous gland including (1) the DHT receptor, activated by androgens; (2) the histamine receptor, activated by histamines; and (3) the neuromodulator receptor, predominantly the substance P and corticotrophin-releasing hormone receptor, which are activated by stress.[11]

Androgens are produced both inside and outside the pilosebaceous unit. The onset of adrenarche, usually at 7-8 years, is associated with a rise in circulating levels of dehydroepiandrosterone sulfate (DHEAS) produced by the adrenal gland. DHT is converted from DHEAS by 5-α reductase and 17-β hydroxysteroid dehydrogenase (Figure 3). DHT is regarded as the principal androgen regulating sebum production, with 10-fold greater affinity than testosterone for the androgen receptor.[5]

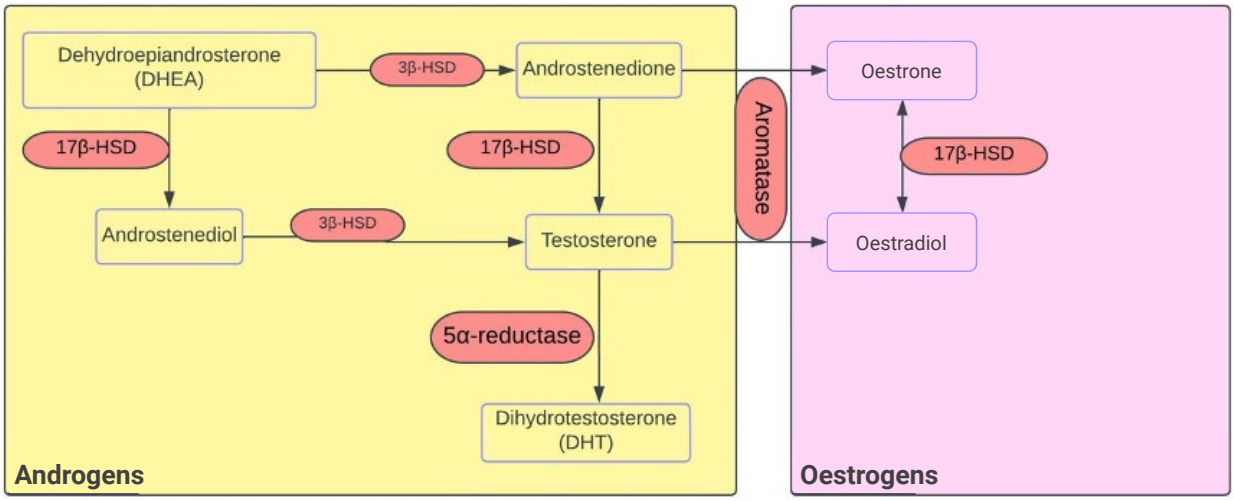


Figure 3. *Steroid biosynthesis pathway*
HSD = hydroxysteroid dehydrogenase

5-α reductase, the enzyme responsible for converting testosterone to DHT, has the highest activity in areas on the body with the highest density of pilosebaceous units such as the face, chest and back. Conversion of testosterone to DHT has been reported to be 30 times higher in acne skin compared to normal skin.[7]

Although androgens have been widely accepted as the main hormonal trigger in acne during puberty, recent evidence suggests that insulin growth factor (IGF)-1 plays a crucial role. IGF-1 may promote acne via several mechanisms including stimulation of androgen synthesis, in particular DHT. IGF-1 may also cause desaturation of sebum triglycerides and fatty acids, resulting in a pro-inflammatory lipid profile.[12]

Inflammation in acne

Inflammation plays a crucial role in all stages of acne pathogenesis. The classic concept of acne pathophysiology is that inflammation follows follicular hyperkeratinisation. This sequence of events has been challenged by compelling evidence that dermal inflammation may precede comedone formation. Compared with skin of patients without acne, the clinically uninvolved skin of acne patients showed increased numbers of CD4+ T cells and macrophages, in addition to increased expression of IL-1α, E-selectin and vascular adhesion molecules. The main initiator for this inflammatory cell infiltration remains unknown but these findings suggest that inflammation precedes hyperkeratinisation and is present in all acne lesions, including pre-clinical microcomedones.[13] Thus, the classical distinction of non-inflammatory (microcomedones, comedones) and inflammatory (papules, pustules, nodules, cysts) theory may need to be revised.

The type of inflammatory response determines the clinical lesion and the potential for scarring.[5] In early lesions, neutrophils predominate to cause suppuration, resulting in a pustule. Inflamed papules, nodules and cysts arise from an influx of lymphocytes (predominantly T helper cells), neutrophils and foreign body-type giant cells. Scar formation correlates with the severity of the inflammatory response. Early non-specific inflammation is thought to be associated with less severe scarring and delayed specific T cell responses may influence the outcome of scar formation.[5, 7] However, in mild to moderate acne, there is no direct correlation of severity of disease and scar formation.[7]

C. acnes and the cutaneous microbiome

C. acnes is an anaerobic, gram positive rod and is the dominant inhabitant of the pilosebaceous unit, accounting for 90% of the microbiome in sebum rich sites due to their ability to thrive in an anaerobic, lipid-rich environment.[14] The cutaneous microbiome is a unique microbial fingerprint which controls the balance of the microbiota and of the transient microbial colonisation. The normal flora of sebaceous glands includes bacteria (*C. acnes*, *Staphylococcus epidermidis*), fungi (e.g., *Malassezia spp*) and demodex mites. *C. acnes* is largely considered a normal skin inhabitant rather than a pathogen *per se*.[5]

Recent research indicates that acne development is related to an unbalanced equilibrium between *C. acnes* and *S. epidermidis*.[15] *S. epidermidis* is a skin commensal which plays a beneficial role in acne by limiting *C. acnes* overgrowth and inflammation by suppressing *C. acnes*-induced IL-6 and tumour necrosis factor (TNF)-α from keratinocytes.[14] The cutaneous microbiome in acne patients is associated with a decrease in number of *S. epidermidis* and an overcolonisation by selected *C. acnes* phylotypes.[15] Conversely, *C. acnes* can also exert beneficial effects by limiting the proliferation of pathogens *Staphylococcus aureus* and *Streptococcus pyogenes*. Any alterations in the equilibrium of the skin microbiome can therefore trigger the activation of the innate immunity and result in inflammation.[11]

There is a significant increase in *C. acnes* colonisation at puberty but its density has not been found to correlate with acne severity. This may be due to differences in the pathogenicity of *C. acnes* strains and variable host immune response to *C. acnes*. Certain ribotypes of *C. acnes* (types 4 and 5) are more commonly associated with acne, indicating that these strains are more capable of triggering acne or better suited to survive in an acne environment.[5]

C. acnes and innate immunity

Within the skin, both innate and adaptive immunity contribute to the host immune function. The innate immune system constitutes first line defence against microbial pathogens, and is dependent on a large family of pattern recognition receptors that detect specific molecular structures on the surface of pathogens.

Keratinocytes play a central role in innate immunity via expression of pattern recognition receptors such as toll-like receptors (TLR) and protease-activated receptors. *C. acnes* activates the TLR-2 pathway to stimulate the production of cytokines (IL-1α, IL-8, IL-12) and TNF-α, antimicrobial peptides (AMPs) and chemokines. The inflammatory cytokines additionally induce matrix metalloproteinases which cause dermal matrix destruction and scarring. IL-8 stimulates neutrophil recruitment, the release of lysosomal enzymes and resultant disruption of the follicular epithelium while IL-1α promotes remodelling and comedogenesis of the pilosebaceous unit.[5, 11]

C. acnes can also incite inflammation via inflammasomes, which are innate immune receptors that regulate the activation of caspase-1. *C. acnes*

has been shown to promote the secretion of proinflammatory cytokines IL-1 β and IL-18 by activating the inflammasomes in the cytoplasm of both neutrophils and monocytes.[16, 17]

The role of AMPs is another emerging area of interest. Sebum free fatty acids such as linoleic acid have antimicrobial activity via stimulation of AMPs production. AMPs, in particular human β-defensin-2 are upregulated in keratinocytes during inflammation then accumulated in the skin. Via their antimicrobial action, AMPs provide important defence against *C. acnes*, possibly offering a new target of acne therapy.[11]

C. acnes and adaptive immunity

C. acnes has been shown to trigger the adaptive response by stimulating IL-17A and IFN-γ secretion by CD4+ T cells in early acne lesions. Prominent T helper-1 and -17 responses have also been demonstrated in *in vivo* and *in vitro* studies.[7]

C. acnes and biofilm

C. acnes has recently been shown to be present in the infundibulum of sebaceous follicles in biofilms, which are aggregations of microbiomes surrounded by extracellular polysaccharides.[18] Buckhart et al. proposed that the same biological glue that allows the cohesion of the biofilm may be responsible for inducing the cohesiveness of keratinocytes to follicular walls, leading to the formation of a comedone.[18] Biofilms also allow *C. acnes* to cluster together to prevent attack from host immune cells and antibacterial agents as well as inducing resistance to antibiotics.

Genetic factors

The exact role of genetics factors in acne pathogenesis remains unclear. The size, number and activity of sebaceous glands is inherited. It is widely believed that the tendency to have severe (including nodulocystic) acne runs in families, and an association between moderate to severe acne and a family history of acne has been reported.[5] Possible genes involved in acne include those encoding regulation of androgen metabolism and components of the transforming growth factor (TGF)-β pathway.[5]

Diet and acne

The link between diet and acne is an emerging area of interest. Prospective studies have shown a link between acne and high glycaemic index diets, saturated fats and dairy products.[5] Both refined carbohydrates and dairy products are thought to worsen acne by increasing insulin and IGF-1 expression, which results in increased androgen activity and sebocyte modulation.[5, 7] More recently, the use of whey protein supplements for body building and B12 supplementation has been found to trigger or exacerbate acne.[5]

Diet-mediated changes in sebum production and composition may also promote *C. acnes* growth and biofilm formation, further exacerbating the inflammation in acne. *C. acnes* can also produce lipase, which increases levels of free palmitic and oleic acids, creating a pro-inflammatory sebum lipid profile.

Recent studies have identified leptin as a novel sebaceous gland regulator. Leptin is a hormone secreted by the adipocytes that regulate body weight. In adipocytes, it has been shown to activate pro-inflammatory enzymes and cytokines (IL-6 and 8), resulting in an inflammatory lipid profile.[11]

Summary

A complex interplay of multiple factors is implicated in the development of acne especially follicular hyperkeratinisation, alterations in sebum production and composition, *C. acnes*, alterations in the cutaneous microbiome, and inflammation. It is also important to appreciate the role of environmental factors such as diet and stress.

Inflammation and immune activation play a pivotal role in all stages of acne development. Inflammation is now regarded as an early process, occurring even before follicular hyperkeratinisation and the development of clinically visible lesions. Hormones, especially androgens and IGF-1, play a key role in increasing sebum production and promoting a more comedogenic and inflammatory lipid profile. These changes result in *C. acnes* overgrowth and trigger multiple inflammatory cascades, activating both innate and adaptive immune responses. Disruptions in the equilibrium of the cutaneous microbiome can lead to overgrowth of pathogenic *C. acnes* strains. However, not all *C. acnes* strains are considered pathogenic, and some have anti-inflammatory effects. These insights into the multifaceted pathogenic factors can translate into novel therapeutic approaches for acne.

References

1. Bhate K, Williams HC. Epidemiology of acne vulgaris. Br J Dermatol. 2013;168(3):474-85.
2. Ramrakha S, Fergusson DM, Horwood LJ, Dalgard F, Ambler A, Kokaua J, et al. Cumulative mental health consequences of acne: 23-year follow-up in a general population birth cohort study. Br J Dermatol. 2016;175(5):1079-81.
3. Gollnick H, Cunliffe W, Berson D, Dreno B, Finlay A, Leyden JJ, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. J Am Acad Dermatol. 2003;49(Suppl 1):S1-37.

4. Harper JC, Thiboutot DM. Pathogenesis of acne: recent research advances. Adv Dermatol. 2003;19:1-10.
5. Zaenglein AL, Thiboutot DM. Acne Vulgaris. In: Bolognia J, Schaffer JV, Cerroni L. Dermatology. Fourth ed. Philadelphia: Elsevier; 2018. p.588-603.
6. Norris JF, Cunliffe WJ. A histological and immunocytochemical study of early acne lesions. Br J Dermatol. 1988;118(5):651-9.
7. Goh C, Cheng C, Agak G, Zaenglein AL, Graber EM, Thiboutot DM, et al. Acne Vulgaris. In: Kang S, Amagai M, Bruckner A, Enk AH, McMichael A, et al. Fitzpatrick's Dermatology.Volume One. Ninth ed. New York: McGraw-Hill Education; 2019. p. 1392-417.
8. Saurat JH. Strategic Targets in Acne: The Comedone Switch in Question. Dermatology. 2015;231(2):105-11.
9. Clayton RW, Göbel K, Niessen CM, Paus R, van Steensel MAM, Lim X. Homeostasis of the sebaceous gland and mechanisms of acne pathogenesis. Br J Dermatol. 2019;181(4):677-90.
10. Gollnick HP. From new findings in acne pathogenesis to new approaches in treatment. J Eur Acad Dermatol Venereol. 2015;29 Suppl 5:1-7.
11. Dréno B. What is new in the pathophysiology of acne, an overview. J Eur Acad Dermatol Venereol. 2017;31 Suppl 5:8-12.
12. Tan JKL, Stein Gold LF, Alexis AF, Harper JC. Current Concepts in Acne Pathogenesis: Pathways to Inflammation. Semin Cutan Med Surg. 2018;37(3s):S60-62.
13. Jeremy AH, Holland DB, Roberts SG, Thomson KF, Cunliffe WJ. Inflammatory events are involved in acne lesion initiation. J Invest Dermatol. 2003;121(1):20-7.
14. Grice EA, Kong HH, Conlan S, Deming CB, Davis J, Young AC, et al. Topographical and temporal diversity of the human skin microbiome. Science. 2009;324(5931):1190-92.
15. Claudel JP, Auffret N, Leccia MT, Poli F, Corvec S, Dréno B. Staphylococcus epidermidis: A Potential New Player in the Physiopathology of Acne? Dermatology. 2019;235(4):287-94.
16. Kistowska M, Gehrke S, Jankovic D, Kerl K, Fettelschoss A, Feldmeyer L, et al. IL-1β drives inflammatory responses to propionibacterium acnes in vitro and in vivo. J Invest Dermatol. 2014;134(3):677-85.
17. Qin M, Pirouz A, Kim MH, Krutzik SR, Garbán HJ, Kim J. *Propionibacterium acnes* Induces IL-1β secretion via the NLRP3 inflammasome in human monocytes. J Invest Dermatol. 2014;134(2):381-8.
18. Burkhart CG, Burkhart CN. Expanding the microcomedone theory and acne therapeutics: *Propionibacterium acnes* biofilm produces biological glue that holds corneocytes together to form plug. J Am Acad Dermatol. 2007;57(4):722-4.

Acne: Diagnosis and differential diagnosis

CLICK IMAGE TO LINK TO VIDEO DURATION_00:40

Lori Zhang[1], Kurt Gebauer[1, 2, 3]

1. University of Western Australia, Perth, WA, Australia
2. Probity Medical Research Inc, Waterloo, Ontario, Canada
3. Fremantle Dermatology, Fremantle, WA, Australia

Correspondence: Lori Zhang zhangloriy@gmail.com

Disclosures: *none*

OUTLINE: This article discusses acne vulgaris with particular emphasis on differential diagnosis that may be confusing to practitioners. As this is a broad topic, the article provides vignettes and references for further review of the diseases discussed. There is a focus on how to distinguish acne from its differential diagnoses using the cutaneous features of the disease as well as patient demographics, triggers for the disease and the natural history of the disease. The article also examines medications that induce acne, including the newly emerging class of Janus kinase inhibitors. Also highlighted is the significant negative mental health impact of the disease, hence the need for a reliable diagnosis.

KEYWORDS: Acne, acneiform eruption, drug induced

Zhang L, Gebauer K. Acne: Diagnosis and differential diagnosis. Opin Prog Cosmet Dermatol 2022;2(2):11-18.

Introduction

Acne is a medical skin condition impacting more than 70% of the population, most commonly affecting adolescents.[1] Prompt and accurate diagnosis is essential to prevent permanent scarring, as well as mitigate damage to mental health. Acne is often accompanied by anxiety and self-esteem issues so engaging empathy and compassion are key principles when treating patients with acne.

The disease is polymorphic in terms of severity, thus a strong understanding of the clinical features of acne and its differential diagnoses are essential to making the correct diagnosis. Although acne is common, clinicians must be familiar with other diagnoses that cause acneiform eruptions or secondary factors that may be causing acne. Apart from the cutaneous features of the disease, several other factors can guide a diagnosis including patient demographics, triggers for the disease and the natural history of the disease. It may also be useful for clinicians to consider the situation where skin conditions occur co-morbidly.[2]

There are a wide range of causes of acne including genetics, hormonal changes and dietary factors. Medications may also cause acne as a side effect such as steroidal medications, anti-epileptics, epidermal growth factor receptor (EGFR) inhibitors and the newly emerging class of Janus kinase (JAK) inhibitors.

Clinical features of acne

Acne is characterised by a variety of skin lesions. There are non-inflammatory lesions, such as open comedones (blackheads) and closed comedones (whiteheads), and inflammatory lesions, including papules, pustules, nodules and cysts.[1-4] Acne is related to blockage of the pilosebaceous unit so it is most commonly located where there are many hair follicles, on the face, neck, upper chest and back.[1-3] These lesions are accompanied by erythema, pain and depending on the severity, can leave significant scarring.[3] This scarring can range from hyperpigmentation, hypopigmentation, and hypertrophic and atrophic scarring. Scarring tends to be worse in Asian and dark-skinned patients, with these populations at high risk of keloid scarring.[2, 3] The triggers for acne include stress, skin products, hormones, medications and excessive ultraviolet (UV) light.

There is no globally accepted classification of acne so it is up to the clinician to use a consistent method of determining severity for their patients.[4] This article will overview one of the most comprehensive methods of classifying acne, using the Leeds Technique established by Cunliffe.[5] The clinician grades the severity of the patient's acne on a scale of 0-10 by counting how many of each type of lesion there are (Table 1).[5]

Table 1. Leeds Technique Acne Grading System[5]

	Lesion type	Name
Non-inflammatory lesions	Open comedones	Blackheads
	Closed comedones	Whiteheads
Inflammatory lesions	Superficial lesions ranging from 0.1 cm to 0.5 cm in width with minimal erythema	Papules
	Superficial lesions ranging from 0.1 cm to 0.5 cm in width that have accumulated pus underneath	Pustules
	Deep lesions which are larger than 0.5 cm	Nodules
	Scarred skin after an acne eruption that may be erythematous or have altered pigmentation	Macule

Psychological impact

In addition to the physical nature of the disease, it's psychological impact does not always correspond to the clinical severity of the disease.[6] Although acne can be clinically mild, it can have a detrimental effect on the patient's self-confidence, self-esteem and cause co-morbid anxiety and depression.[3, 6] This is often exacerbated by the social pressures of adolescence as the disease most commonly presents during puberty.[2] Most people manage acne without requiring the input of a general practitioner or dermatologist. However, patients that do seek medical advice are typically afflicted by issues beyond the physical alone. It is important to be aware of this aspect of the disease when presented with a patient with acne, to ensure treatment of their disease is holistic.[6]

Other impacts of acne on wellbeing

For some, having acne can cause hindrances other than the physical and mental. People whose job relies on their physical appearance, such as models or TV presenters, may suffer economically if they were to have severe acne. Being able to properly diagnose acne in this situation is even more important as their economic livelihood depends on it, on top of the physical and mental issues it causes. There are also particular jobs where having severe acne is a barrier to entry, for example, the air force does not accept people who have severe acne.

In 2012, there was a study on discrimination in job applications of people with facial stigmata of acne including active acne and scarring.[7] The results showed that people with facial stigmata were rated lower than those without skin blemishes and interviewers remembered less about the interviewee. There was more attention drawn to the physical appearance of the applicant rather than the content of their interview which results in being less likely to be employed successfully.

Differential diagnosis

A broad understanding of the most common dermatological diseases is integral to distinguish between typical lesions encountered in the clinical setting. The following sections describes various dermatological diseases and their differentiating features from acne.

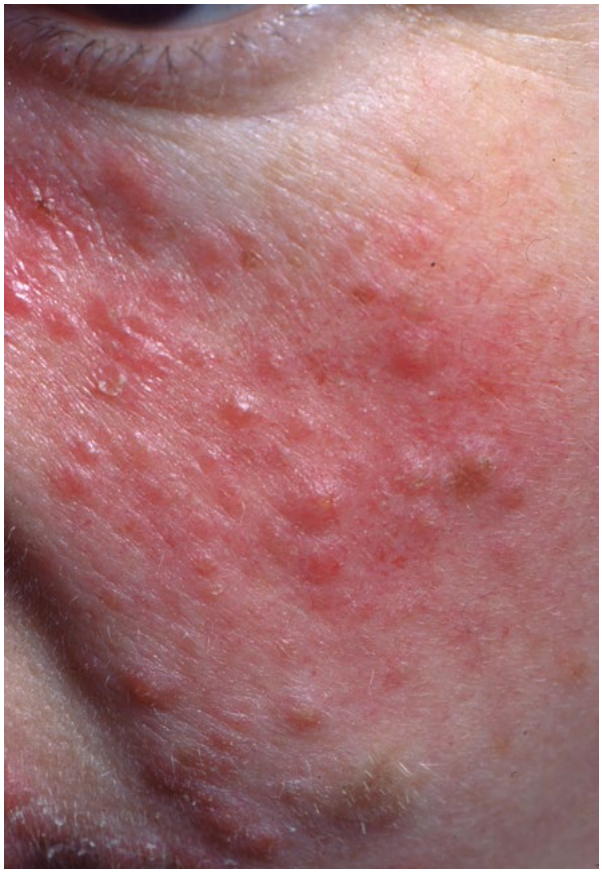


Figure 1. *Rosacea*

Rosacea

Rosacea (Figure 1) is a chronic erythematous rash of the central face that typically affects people in their 30s to 50s.[8] The papulopustular form presents with

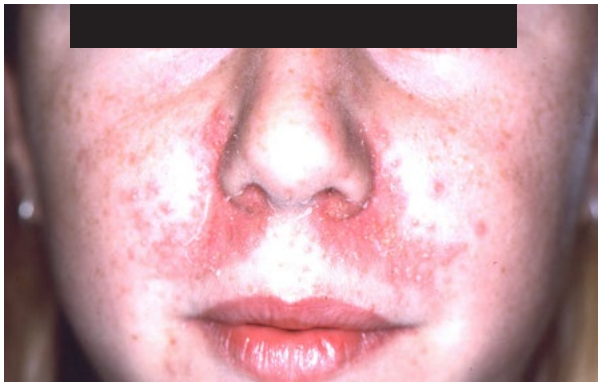


Figure 2. *Peri-orificial dermatitis*

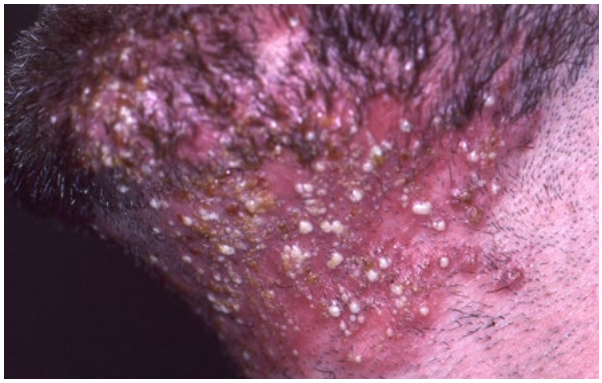


Figure 3. *Pseudomonal folliculitis*

inflammatory lesions (papules and pustules), especially in the centre of the face, that mimics acne.[2, 9] Acne and rosacea share similar triggers including UV, stress, makeup and certain skin products.[10] Patients with either condition may present with co-morbid anxiety or depression and lowered self-esteem which can complicate the treatment.

Features of rosacea that differentiate it from acne include central erythema, telangiectasia and flushing, which are exhibited in most cases of rosacea and are not present in acne.[3] Conversely, rosacea does not present with comedones and rarely has manifestations on the trunk, whereas acne does.[10] Rosacea tends to present in early to middle-aged adults whereas acne presents in adolescence and young adulthood.[9] The natural history of the disease also differs. In the later stages of phymatous rosacea patients can have hyperplasia of tissue in the centre of the face resulting in rhinophyma.[2] Rhinophyma is not a feature of acne.[10]

Peri-orificial dermatitis

Peri-orificial dermatitis (Figure 2) exhibits lesions such as papules and pustules, typically around the mouth, nose and eyes.[8, 10] People with peri-orificial dermatitis usually have a history of recent corticosteroid use, whether topical to the face or inhaled through puffers.[2, 3] However, this dermatitis has other causes that are shared with acne, such as hormonal changes (e.g., pregnancy or hormonal medication) and certain face creams or sunscreens that are patient dependent.[11] Epidemiologically, both conditions occur from teenage years till middle age.[11]

Peri-orificial dermatitis presents without comedones, nodules or cysts, which are significant features of acne.[8, 10] The lesions tend to occur in clusters around the mouth, nose or eyes, unlike acne which affects all areas of the facial skin including the cheeks, forehead and chin. There is also a characteristic clinical pattern of disease with sparing of the skin around the vermillion of the lip in peri-orificial dermatitis.[10] Thus, acne can be differentiated from peri-orificial dermatitis by both phenotype and in the patient history.

Folliculitis

Folliculitis is the name given to inflammation of the hair follicle of any cause.[12] Each inflamed follicle has a whitehead, papule or pustule on the surface that can resemble acne. The lesions tend to be erythematous, itchy and can become infected if irritated. There are many causes of folliculitis including bacterial, yeast and parasitic infections.

Bacterial folliculitis is caused by *Staphylococcus aureus*, the most common cause of folliculitis. The appearance of the lesions are very similar to acne. However, for many patients, folliculitis only occurs in areas of thick dense hair growth like the scalp, beard and buttock, which differentiates it from acne which tends to occur on the face and trunk.[10] Bacterial folliculitis can become more inflammatory over time as lesions can progress into boils and even furuncles.[12] Deeper infections can leave significant scarring which can be confused with acne scarring.[12] The natural history of these lesions differentiates it from acne, as well as the location of the lesions. Acne also presents with blackheads which bacterial folliculitis does not.

Folliculitis caused by *Malassezia* yeasts is called pityrosporum folliculitis.[13] These are a normal finding on the skin and most commonly occurs in adolescents. The disease is characterised by papules and pustules that are intensely itchy.[13] It is often misdiagnosed as acne due to the similar appearance and age group it appears in. It is associated with a tropical climate where the weather is humid, excessive sweating and the occlusion of hair follicles by clothing or sunscreen.[13] Some patients may report that their acne flares with similar triggers. The lesions appear in similar locations to acne, but on the face, they tend to occur peripherally around the cheeks, chin and forehead.[13] It also lacks comedones which are a feature of acne.

Demodex brevis are microscopic parasitic mites that live in the hair follicles of the face causing demodex folliculitis. Like *Malassezia* yeasts, they are a part of the natural flora of the skin.[8] The disease is more common in immunosuppressed individuals so those with human

immunodeficiency virus, diabetes mellitus and taking corticosteroid medications are at higher risk. The symptoms include redness, itching and follicular scales of peri-orificial regions of the face.[14] In more severe cases, there can be papules and pustules which appear like acne. However, there are no comedones, nodules or cysts. A biopsy of affected skin will reveal Demodex mites in the inflamed hair follicles, a definitive diagnosis of the disease.[14]

Gram-negative folliculitis is an acneiform disease caused by bacteria such as *Pseudomonas aeruginosa* (Figure 3), *Escherichia coli, Klebsiella* and *Proteus* species.[15] The disease often occurs with chronic usage of oral or topical antibiotics to treat acne or rosacea. The lesions mimic a severe flare of acne, typically presenting with multiple pustules in peri-oral and peri-nasal regions. Deeper skin lesions such as nodules or cysts can occur, most commonly with *Proteus* infection. This variant of folliculitis is particularly difficult to diagnose as it occurs in patients already on antibiotic medication to treat acne. If there is clinical suspicion due to non-response to standard treatments, a gram stain will show gram-negative bacteria.

Lupus miliaris disseminatus

Lupus miliaris disseminatus (Figure 4), previously known as acne agminata, is a rare granulomatous skin condition of red-brown papules and pustules of the face including the eyelids.[16] The condition presents most commonly in young adults, which is a similar age group to the onset of acne.[16] The pathophysiology of the disease is unknown and it is self-limiting, resolving within 1-2 years. It remits with significant scarring, similar to acne. The main difference between the diseases is the absence of comedones in lupus milaris disseminatus. A supplementary factor in differentiating it from acne is that lupus milaris disseminatus affects the eyelids, which acne does not.[10]

Pseudofolliculitis barbae

Pseudofolliculitis barbae (Figure 5) is a reaction of the hair follicle to trauma including shaving and less commonly, plucking.[17] It results in inflammatory erythematous acneiform papules and pustules appearing at the site of recent hair removal. This most commonly occurs in the beard area, but also the groin, pubic region and axilla. The disease is more common in people with dark skin or coarse and curly hair as the hair becomes ingrown when shaved in an incorrect manner. It is distinguishable from acne as the lesions only occur on site of hair growth, the association with shaving and the demographic that it affects. Pseudofolliculitis barbae may resolve if the patient stops the offending method of hair removal, after approximately 1 month.

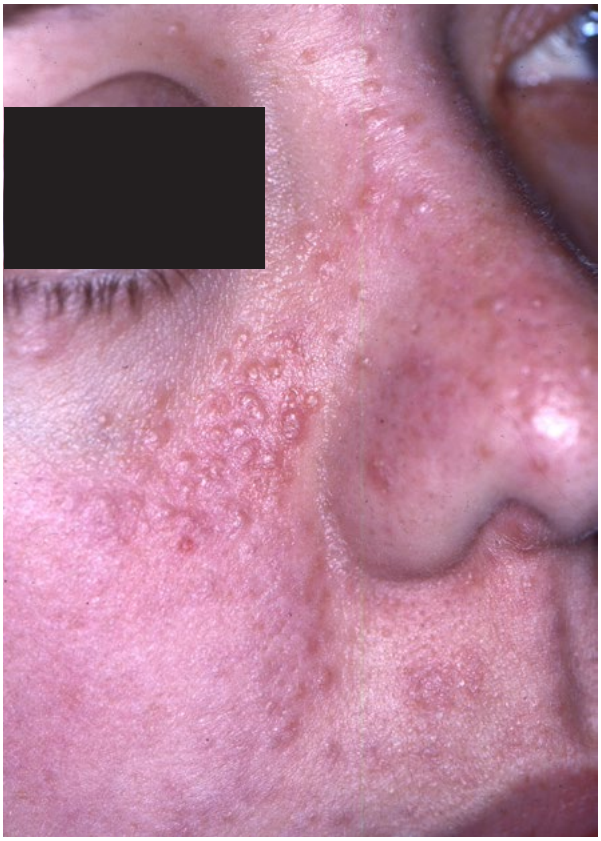


Figure 4. *Lupus miliaris disseminatus*

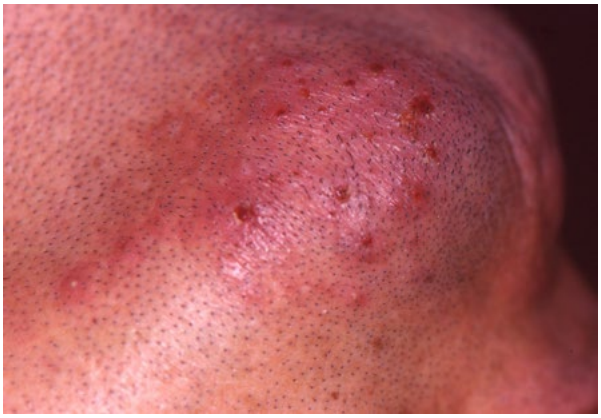


Figure 5. *Pseudofolliculitis barbae*

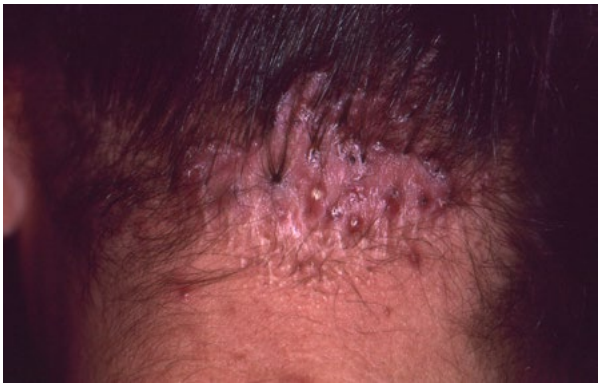


Figure 6. *Acne keloidalis nuchae*

Acne keloidalis nuchae

Acne keloidalis nuchae (Figure 6) is a form of chronic folliculitis on the back of the scalp or occipital hairline that presents with papules and pustules and results in significant scarring and alopecia in affected areas.[18] It is often preceded by irritation to the area by hair removal, a haircut or wearing tight fitting head gear. The lesions can also be pruritic, causing subsequent bleeding. Acne keloidalis nuchae can be quite devastating for individuals as the lesions and scarring leads to hair loss in the affected area. It most commonly affects men with dark skin. Despite the name of the disease, the scarring is not keloid in nature. It is different from acne as lesions only appear in the posterior neck and head areas and their subsequent scarring is characteristic of the disease.

Acne secondary to medications

Acne is a known side effect of many medications, the most common being steroidal medications, anti-epileptics and EGFR inhibitors. These are already well described in the literature so this article will briefly discuss how to determine whether acne is primary or secondary to those medications. There will be a focus on JAK inhibitors as they are an emerging therapy that clinicians need to be aware of as acne is a potential side effect. If it is determined that acne is a side effect of medication clinicians should discuss alternative therapeutic options with the patient.

Hormonal medications

Androgens are known to cause acne and increase inflammation.[3] Therefore, any medications that alter hormone levels such as hormonal forms of contraception, anabolic steroids and testosterone may alter the balance of endogenous hormones in the body resulting in new or worsening acne.[10] For certain patients, the skin changes are an unacceptable side effect of the medication resulting in non-compliance and a deterioration of the primary condition it was used to treat. For example, a patient prescribed the oral contraceptive pill for dysmenorrhoea may complain of worsening acne, discontinue the medication and suffer painful periods again. Patients should be made aware of the potential side effects of hormonal medication and suitable alternatives discussed that are acceptable to the patient. The timeline of events is key in determining if medications are the cause of acne.[10] For example, if acne started soon after the medication was started or the acne resolved when the medication was stopped.

It is also important to be aware of the patient using anabolic steroids. Patients may use anabolic steroids for their ability to build body muscle and strength quickly. Therefore, it is often used by athletes, bodybuilders, people concerned with body image and people whose job involves muscle strength. The typical demographic of users of anabolic steroids for non-medicinal purposes are men in their 30s. Some patients may be buying them illegally or may be incidentally ingesting it through other weightlifting supplements such as whey. Anabolic steroids have a medicinal function as well, used to treat delayed puberty and hypogonadism.[19] Being aware of these populations is important when presented with a patient with acne with a background of weightlifting or being treated for androgen deficiency.

Anti-epileptics

Anti-epileptics are also known to cause acne as a side effect. In particular, lithium and phenytoin can cause severe acneiform eruptions.[8, 20] Like hormonal medications, the timeline of events is important to distinguish between primary acne and acne as a side effect. The location of the lesions tends to differ from acne as lithium-induced acne occurs on the limbs and trunk rather than the face.[3] Most lesions are pustules and there are rarely comedones.[3] These features are integral in diagnosing the cause of acne, whether it is primary acne or secondary to medications.

Epidermal growth factor receptor (EGFR) inhibitors

EGFRs are tyrosine kinase receptors associated with multiple solid tumours including colorectal, lung, breast and prostate cancer.[21] They have a role in angiogenesis, cell proliferation and cell survival. Therefore, EGFR inhibitors are valuable in the treatment of EGFR-positive cancers. Another role of these receptors has been described in skin proliferation and turnover. In disrupting the normal pathway of skin homeostasis, several dermatological symptoms can present, most commonly an acneiform eruption typically on the face and trunk.[22] Erythematous papules and pustules appear around the nose and mouth, on the forehead, cheeks and chin and the upper trunk. These lesions can be pruritic and are often seen in the presence of xerosis. The acneiform rash begins within one month of beginning treatment and occurs in more than 50% of patients treated with EGFR inhibitors.[8] Hence, patients should be warned of this side effect before commencing treatment. Although the location and appearance of the lesions may be similar to acne, an acute flare of acne soon after beginning EGFR inhibitors should indicate that the symptom is a medication side effect. In addition, there are no comedones, nodules or cysts which acne can present with.[8] For some, the lesions may resolve spontaneously, or resolve within two months of cessation of the drug.[21]

Janus kinase (JAK) inhibitors

With extensive research and medical therapies utilising JAK inhibitors, their role in inflammatory disease is important to understand. The JAK signal transducer and activator of transcription (JAK-STAT) pathway is an intracellular signalling network that is involved in the growth and development of immune and blood

cells.[23] Conditions where the pathway is disrupted can result in dermatological, cancerous and autoimmune conditions. The use of JAK inhibitors to treat these conditions is underway, with upadacitinib on the pharmaceutical benefits scheme (PBS) for atopic dermatitis and tofacitinib and baracitinib on the PBS for rheumatological conditions. Their use in dermatology is growing with off-label use and studies investigating their effects in the treatment of psoriasis, alopecia and vitiligo. This section will discuss how acne has been reported as a side effect experience by patients using JAK inhibitors, focusing on upadacitinib and delgocitinib.

A phase 2b clinical trial of 167 subjects on the use of upadacitinib in atopic dermatitis has published results suggesting that acne is an adverse event.[24] The likelihood of acne as a side effect was 9.5% in subjects on the 7.5 mg dose, 4.8% in subjects on the 15 mg dose and 14% in subjects on the 30 mg dose. This is in comparison to the patients on placebo of which 2.5% of patients reported acne as a side effect (see Table 2). The reports of acne were only mild to moderate and did not result in withdrawal from the trial in any cases.

Table 2. The frequency of acne as an adverse event in the use of upadacitinib for atopic dermatitis[24]

Atopic dermatitis	Acne adverse event (%)	Number of subjects	Total number of subjects
Placebo	2.5	1	40
Upadacitinib 7.5 mg	9.5	4	42
Upadacitinib 15 mg	4.8	2	42
Upadacitinib 30 mg	14	6	42

A phase 3 double-blinded study of 154 subjects on the use of delgocitinib for atopic dermatitis has published similar findings. The trial had limited detail around the side effects but did cite 3.2% of patients reporting acne as a side effect.[25]

In differentiating acne from similar appearing dermatological diseases, one should consider a range of factors including the appearance and distribution of the lesions and associated symptoms. Apart from the clinical features of the disease, one should also consider the age of the patient, triggers for the disease and the natural history (Table 3). An important factor in the diagnosis of acne is whether acne is primary or secondary to a new medication as this is a cause of acne that is easily resolved.

Conclusion

Misdiagnosis of acne for another dermatological skin condition can result in prolonged physical suffering for the patient and potentially a deterioration of their mental health due to untreated acne. It is important to also allow for the possibility of patients having multiple skin conditions presenting co-morbidly. Clinicians should also remain vigilant to the psychological impacts of acne on patients to better treat the disease.

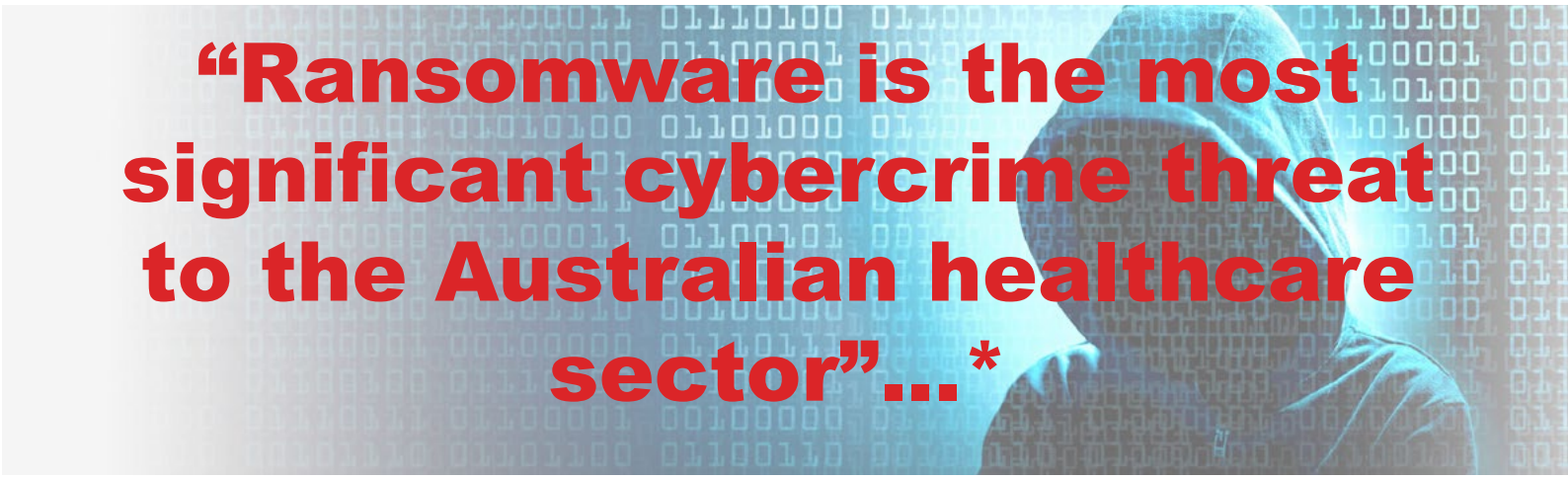
References

1. Katsambas Andreas D, Stefanaki C, Cunliffe WJ. Guidelines for treating acne. Clin Dermatol. 2004;22(5):439–44.
2. Greydanus DE, Azmeh R, Cabral MD, Dickson CA, Patel DR. Acne in the first three decades of life: An update of a disorder with profound implications for all decades of life. Dis Mon. 2021;67(4):101103.
3. Archer CB, Cohen SN, Baron SE, on behalf of British Association of Dermatologists and Royal College of General Practitioners. Guidance on the diagnosis and clinical management of acne. Clin Exp Dermatol. 2012;37(s1):1–6.
4. Strauss JS, Krowchuk DP, Leyden JJ, Lucky AW, Shalita AR, Siegfried EC, et al. Guidelines of care for acne vulgaris management. J Am Acad Dermatol. 2007;56(4):651–63.
5. Burke BM, Cunliffe WJ. The assessment of acne vulgaris—the Leeds technique. Br J Dermatol. 1984;111(1):83–92.
6. Hazarika N, Archana M. The Psychosocial Impact of Acne Vulgaris. Indian J Dermatol. 2016;61(5):515–20.
7. Madera JM, Hebl MR. Discrimination against facially stigmatized applicants in interviews: An eye-tracking and face-to-face investigation. J Appl Psychol. 2012;97(2):317–30.
8. Dessinioti C, Antoniou C, Katsambas A. Acneiform eruptions. Clin Dermatol. 2014;32(1):24–34.
9. van Zuuren EJ. Rosacea. Solomon CG, editor. N Engl J Med. 2017;377(18):1754–64.
10. Al-Natour SH. Acne mimickers: Another cause for unresponsive acne. J Saudi Society of Dermatol Dermatol Surgery. 2012;16(2):35–40.
11. Tempark T, Shwayder TA. Perioral Dermatitis: A Review of the Condition with Special Attention to Treatment Options. Am J Clin Dermatol. 2014;15(2):101–13.
12. Laureano AC, Schwartz RA, Cohen PJ. Facial bacterial infections: Folliculitis. Clin Dermatol. 2014;32(6):711–4.
13. Rubenstein RM, Malerich SA. Malassezia (Pityrosporum) Folliculitis. J Clin Aesthet Dermatol. 2014;7(3):37–41.
14. Chen W, Plewig G. Human demodicosis: revisit and a proposed classification. Br J Dermatol. 2014;170(6):1220–25.
15. Böni R, Nehrhoff B. Treatment of Gram-Negative Folliculitis in Patients with Acne. Am J Clin Dermatol. 2003;4(4):273–6.
16. Toda-Brito H, Aranha JMP, Tavares ES. Lupus miliaris disseminatus faciei. An Bras Dermatol. 2017;92(6):851–3.
17. Ogunbiyi A. Pseudofolliculitis barbae; current treatment options. Clin Cosmet Investig Dermatol. 2019;12:241–7.
18. Ogunbiyi A. Acne keloidalis nuchae: prevalence, impact, and management challenges. Clin Cosmet Investig Dermatol. 2016;9:483–9.
19. Barbonetti A, D'Andrea S, Francavilla S. Testosterone replacement therapy. Andrology. 2020;8(6):1551–66.

20. Asadi-Pooya AA, Rostaminejad M, Zeraatpisheh Z, Damabi NM. Cosmetic adverse effects of antiseizure medications; a systematic review. Seizure. 2021;91:9-21.
21. Duvic M. EGFR Inhibitor-Associated Acneiform Folliculitis: Assessment and Management. Am J Clin Dermatol. 2008;9(5):285–94.
22. Lacouture ME, Anadkat M, Jatoi A, Garawin T, Bohac C, Mitchell E. Dermatologic Toxicity Occurring During Anti-EGFR Monoclonal Inhibitor Therapy in Patients With Metastatic Colorectal Cancer: A Systematic Review. Clin Colorectal Cancer. 2018;17(2):85–96.
23. Ciechanowicz P, Rakowska A, Sikora M, Rudnicka L. JAK-inhibitors in dermatology: current evidence and future applications. J Dermatol Treat. 2019;30(7):648–58.
24. Guttman-Yassky E, Thaçi D, Pangan AL, Hong HC-H, Papp KA, Reich K, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2020;145(3):877–84.
25. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Kaino H, Nagata T. Delgocitinib ointment, a topical Janus kinase inhibitor, in adult patients with moderate to severe atopic dermatitis: A phase 3, randomized, double-blind, vehicle-controlled study and an open-label, long-term extension study. J Am Acad Dermatol. 2020;82(4):823–31.

Table 3. Summary table

	Acne	Rosacea	Peri-orificial dermatitis	Bacterial folliculitis	Pityrosporum folliculitis	Demodex folliculitis	Gram negative folliculitis	Lupus miliaris disseminatus	Pseudofolliculitis barbae	Acne keloidalis nuchae
Affected population	10 – 30 years old	30 – 50 years old	Any age	Any age	10 – 20 years old	Immuno-suppressed	Patients using antibiotics to treat acne	10 – 20 years old	Dark skin complexion, coarse and curly hair	Dark skin, male
Location of lesions	Face, neck, back, upper chest and buttocks	Face – especially centre of the face	Peri-oral, peri-nasal, peri-ocular	Face, neck, back, upper chest, buttocks	Around the chin, cheeks and forehead	Around the mouth, nose and eyes	Peri-oral and peri-nasal	Face including eyelids	Beard, groin, pubic region, axilla	Nuchal region and occiput
Triggers	Stress, skin products, hormones, medication, UV	Stress, skin products, UV, heat, spicy food	Corticosteroids		Tropical climate, humidity, occlusive clothing, sunscreen		Prolonged use of antibiotics used to treat acne – oral or topical		Hair removal including shaving and plucking	Hair removal, haircut, tight head gear
Natural history	Chronic lesions	Thickening of skin and rhinophyma	Resolves with cessation of corticosteroid	Lesions can become boils or furuncles	Chronic infection	Chronic infection	Chronic infection	Self-limiting after 1-2 years	Self-resolves after cessation of hair removal for 1 month	Chronic lesions unless trigger is removed
Lesion type										
Comedones	Y	N	N	No blackheads	N	N	N	N	N	N
Papule	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Pustules	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Nodules	Y	N	N	Y	N	N	Y	N	N	N
Cysts	Y	N	N	Y	N	N	Y	N	N	N



"Ransomware is the most significant cybercrime threat to the Australian healthcare sector"...*

Are you cyber secure?

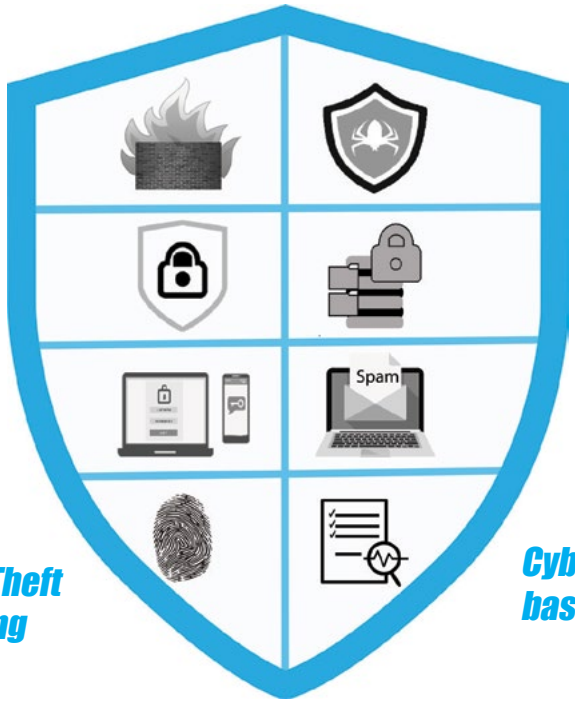
DMS Managed Cyber Security

Next Gen Firewall Protection with Intrusion Detection and Intrusion Prevention Systems

WEB/DNS Filtering Protection

Multi Factor Authentication

Credential Theft Monitoring



Next Gen Pro-Active End Point Detection and Response Protection

Immutable Online Backup for Rapid Disaster Recovery

Next Gen Email, Phishing, Anti-Spam Protection with regular staff cyber training program

Cyber Security Standards based Risk Management Framework

*https://www.cyber.gov.au/acsc/view-all-content/reports-and-statistics/2020-health-sector-snapshot

THE DMS ANTI-MALWARE GUARANTEE:

With DMS multi-layered Managed Cyber Security, any support time we spend removing malware is completely free.

DMS
DIGITAL MEDICAL SYSTEMS
CONFIDENT IT

1300 865 977
WWW.DMS-IT.COM.AU

Do we need to do any investigations for acne?

CLICK IMAGE TO LINK TO VIDEO DURATION_00:27

Jo-Ann See[1], Mei Tam[2]

1. Central Sydney Dermatology, Sydney, NSW, Australia
2. Melbourne Skin Clinic, VIC, Australia

Correspondence: Dr Jo-Ann See Joseederm@bigpond.com

Disclosures: Dr Jo-Ann See is currently on advisory boards or has consulted or received speaker's fees for Galderma, Mayne Pharma, Viatris, La Roche Posay. Dr Mei Tam has been on advisory boards for Galderma, Mayne Pharma, L'Oreal, Eli Lilly.

OUTLINE: Acne is a clinical diagnosis and laboratory investigations are not usually undertaken except for establishing triggering factors and monitoring systemic treatments. This article will focus on patients on oral isotretinoin and patients with suspected underlying hormonal acne. In the United States, monthly pregnancy tests and other laboratory tests are often performed but recently the benefit of this has been questioned in healthy patients as the changes are often minor and do not alter the course of treatment. In the majority of healthy subjects, baseline and monitoring at 2 months may be all that is necessary. An abnormal hormonal assay may alert the physician to underlying hormonal abnormalities such as polycystic ovarian syndrome in treatment-resistant female acne patients. We will briefly mention circumstances for swabbing acne lesions and monitoring patients on antibiotics or spironolactone.

KEYWORDS: Isotretinoin, investigations, hormonal, pregnancy

See J-A, Tam M. Do we need to do any investigations for acne?. Opin Prog Cosmet Dermatol 2022;2(2):20-23.

Isotretinoin

Oral isotretinoin, a vitamin A derivative is well recognised as an effective treatment for nodular cystic acne. It was approved by the United States Food and Drug Administration (FDA) for usage in 1982 and has been prescribed in Australia since then. Isotretinoin is a teratogen and is therefore contraindicated during pregnancy and lactation but other less common side effects include hyperlipidaemia and associated pancreatitis, leucopenia, thrombocytopenia and transaminitis. Barbieri comments "while laboratory abnormalities are rare and often do not influence management, frequent laboratory monitoring remains a common practice".[1]

Hence, without current standard guidelines or consensus for the laboratory monitoring of isotretinoin treatment, the frequency and tests performed can be quite variable amongst prescribing physicians.

Isotretinoin – how often and when to monitor

Monthly laboratory investigations for lipid, liver enzyme and complete blood count are frequently undertaken and critical evaluation may show that by reducing the frequency of testing this will improve the quality of care among patients and lessen the financial burden of having unnecessary tests to the patient and community.

In the United States, pregnancy tests are mandated monthly in a risk evaluation and mitigation strategy (REMS) system called iPLEDGE. This is used to ensure that no woman is or gets pregnant before or whilst taking isotretinoin. Their aim is to educate patients on the risk of isotretinoin's teratogenicity, to minimise foetal exposure and to ensure the benefits outweigh its risks.

The package insert recommends baseline fasting lipid and hepatic panels with repeated testing at weekly or biweekly intervals until response has been established. There are no specific suggestions for laboratory investigations.[1]

The European evidence-based guidelines for the treatment of acne suggest monitoring liver enzymes and lipids before treatment, at one month and every three months thereafter.[2]

A meta-analysis was performed on studies between 1960 and 2013 looking at the usefulness of monthly laboratory investigations. The final recommendation

was to reduce monitoring practices to baseline testing and a follow-up set at 4 to 8 weeks or when the daily peak dose is reached.[3]

As far back as 2003, the Global Alliance to Improve Outcomes and Acne guidelines recommended limiting laboratory investigations to baseline and 1 to 2 months after starting therapy. No further testing was needed if these tests were normal and if there were no other risk factors present.[4]

More recently in 2016, Hansen et al. concluded that "In healthy patients with normal baseline lipid panel and liver function results, repeated studies should be performed after two months of isotretinoin therapy. If findings are normal, no further testing may be required".[5] His review of 574 isotretinoin courses for 515 patients found that grade 2 (moderate) abnormalities were uncommon (0.2%-1.6% of patients) and that two thirds of these abnormalities occurred within the first 60 days of treatment.

A Delphi Consensus study (Isotretinoin Laboratory Monitoring in Acne Treatment, 2022) regarding the frequency and type of tests is soon to be published.

Of course, if any laboratory abnormalities are detected at baseline or during the monitoring phase, further investigation is warranted. A recent study has emphasised the importance of considering relevant comorbidities such as hepatic disease or alcohol use as a predictor of abnormalities during treatment rather than the value of baseline laboratory data.[8]

Comment: It seems that if there are no health concerns then monitoring at baseline and at the two-month period is all that is required. Some practitioners may wish to repeat the investigations when the daily peak dose is achieved.

Isotretinoin – what to monitor

Lipids - hyperlipidaemia has been associated with pancreatitis in patients taking oral isotretinoin.[6]

The lipid panel usually measures five different types of lipids from a blood sample and these are

i. total cholesterol – a combination of LDL, VLDL and HDL

ii. LDL or low-density lipoprotein is the "bad cholesterol" that collects in blood vessels and increases the risk of cardiovascular disease

iii. VLDL or very low-density lipoprotein

iv. HDL – high density lipoprotein or "good cholesterol" which decreases the build-up of LDL in blood vessels

v. Triglycerides – fat from food where excess amounts is associated with cardiovascular disease and pancreatic inflammation.

The monitoring of triglycerides alone may be all that is required (Delphi Consensus, 2022).

Liver function tests – a rise in transaminases (AST and ALT) has been associated with oral isotretinoin.[1, 3, 5, 8] Liver function tests often include the following parameters and it may be more cost-effective in the future to order what is clinically relevant. Monitoring of ALT may be the best parameter to measure as AST monitoring may be less specific than ALT.

Many studies have reported no significant rise in liver function tests during the course of treatment and some studies show that even in the presence of raised liver function tests some patients did not discontinue therapy or have a reduction in dosage.[3]

i. AST – aspartate aminotransferase

ii. ALT – alanine aminotransferase

iii. GGT – gamma-glutamyl transferase

iv. ALP - alkaline phosphatase

v. Bilirubin

vi. Albumin

vii. Total protein

Alkaline phosphatase changes are typically minor and of unclear significance.

Full blood count – although leucopenia and thrombocytopenia have been documented in patients taking oral isotretinoin,[5] Zane's paper suggested that blood count monitoring may be of low value.[7]

Comment: More recently, Hansen suggested that in the absence of known risk factors, complete blood count monitoring should not be undertaken.[5]

Creatine kinase (CK) is sometimes monitored due to potential elevation especially in athletes. The significance of elevated levels is unclear and true rhabdomyolysis is exceedingly rare. A mild increase in CK is well tolerated, usually transient and decreases with less physical exercise.[4, 12]

Comment: Monitoring of lipids at baseline and at 2 months or peak dose (especially triglycerides) and liver function tests (especially transaminases) is still recommended however alkaline phosphatase, creatine kinase and full blood count are probably not necessary.

Lee's review and meta-analysis[3] showed that isotretinoin therapy was associated with a very low proportion of patients tested having significant change

in the mean value of several laboratory investigations including white blood cell count, hepatic and lipid panels. However, these changes did not meet criteria for high risk and toxicity. Hence by limiting the tests and their frequency this will benefit the patient by reducing costs, the time lost in having tests done and the psychosocial burden that some patients have regarding laboratory investigations.

Hormonal investigations

When hormonal acne is suspected either because of the female patient's age and clinical features such as flaring with menses, family history or resistance to treatment, a simple laboratory investigation may uncover an increase in androgens or possible underlying polycystic ovary syndrome (PCOS).

Despite the fact that hormonal acne is commonly seen there are currently no dermatology guidelines outlining the indications for endocrinology evaluation.[9]

The pathogenesis of acne is multifactorial. Androgens promote sebum production which then plays a role in acne pathogenesis. Serum androgen levels are not correlated with acne presence or severity and it is important to remember that local tissue androgen levels and sensitivity to androgens are also important in acne pathogenesis. This may explain why some patients have clinical features of hormonal acne but normal hormonal parameters.

Several androgens are found normally in women including dehydroepiandrosterone, dehydroepiandrosterone-sulphate (DHEA-S), testosterone, dihydrotestosterone and androstenedione. These hormones are essential in the development of acne but also in other conditions such as hirsutism and female pattern hair loss. The challenge for the dermatologist is to differentiate physiological from pathological presentation of androgen mediated cutaneous disorders. Hormonal acne can be associated with these other clinical signs as well as signs of virilisation or a history of an irregular menstrual cycle.

When and what to test

Although there are inconsistencies in laboratory reference ranges and variations in androgen levels by age, day and menstrual cycle in premenopausal women, it is generally recommended to test when the serum androgen concentration is the highest. This occurs during the early follicular phase within the first seven days of the menstrual cycle.

Ideally, women should not be undergoing hormone modulating therapies such as the oral contraceptive for at least 4 to 6 weeks prior to testing.

Laboratory investigations should include total testosterone, free testosterone, sex hormone binding globulin, DHEA-S and beta human chorionic gonadotropin. The testing of androstenedione and LH:FSH ratio is controversial and may not add further information.

If PCOS is suggested then patients may be referred to an endocrinologist or gynaecologist for further assessment. The association of PCOS and metabolic syndrome will not be discussed in this article.

Brief comment on other investigations

Swabbing acne lesions – not routinely performed but may be undertaken in the presence of secondary bacterial infection or failure to respond to oral antibiotics such as in gram-negative folliculitis.

Monitoring oral antibiotics – not routinely performed except if there is a suspicion of side effects. It is generally recommended that a course of oral antibiotics should not exceed three months.

There are uncommon indications for monitoring oral antibiotics such as case reports of tetracycline induced drug hypersensitivity syndrome (DRESS) particularly in patients of African ethnicity or minocycline-related lupus may develop in patients taking a prolonged course. Monitoring may be required when sulphonamides (trimethoprim and sulfamethoxazole) are used as third-line therapy in certain situations such as renal impairment and if patients are suspected to have glucose 6 dehydrogenase deficiency.[15]

Monitoring of spironolactone

Spironolactone is an oral antiandrogen that has been used for many years in the treatment of hormonal acne. In asymptomatic young fit healthy females, there is no need for monitoring. Side effects of nausea, fatigue, or muscle weakness may indicate hyperkalaemia and would justify testing.

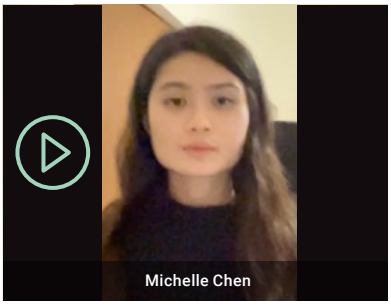
Conclusion

Limiting the number and frequency of laboratory investigations for isotretinoin monitoring will be more clinically relevant for the patient and cost saving from a health economics point of view while a hormonal assay may confirm the diagnosis of hormonal acne in a patient resistant to treatment or who has underlying PCOS.

References

1. Barbieri JS, Shin DB, Wang S, Margolis DJ, Takeshita J. The clinical utility of laboratory monitoring during isotretinoin therapy for acne and changes to monitoring practices over time. J Am Acad Dermatol. 2020;82(1):72-9.
2. Nast A, Dréno B, Bettoli V, Degitz K, Erdmann R, Finlay AY, et al. European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol Venereol. 2012;26 Suppl 1:1-29.
3. Lee YH, Scharnitz TP, Muscat J, Chen A, Gupta-Elera G, Kirby JS. Laboratory Monitoring During Isotretinoin Therapy for Acne: A Systematic Review and Meta-analysis. JAMA Dermatol. 2016;152(1):35-44.
4. Gollnick H, Cunliffe W, Berson D, Dreno B, Finlay A, Leyden JJ, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. J Am Acad Dermatol. 2003;49(1 Suppl):S1-37.
5. Hansen TJ, Lucking S, Miller JJ, Kirby JS, Thiboutot DM, Zaenglein AL. Standardized laboratory monitoring with use of isotretinoin in acne. J Am Acad Dermatol. 2016;75(2):323-8.
6. Ashraf M. Acute Pancreatitis Caused by Isotretinoin. Cureus. 2020;12(6):e8710.
7. Zane LT, Leyden WA, Marqueling AL, Manos MM. A population-based analysis of laboratory abnormalities during isotretinoin therapy for acne vulgaris. Arch Dermatol. 2006;142(8):1016-22.
8. Tkachenko E, Sharma P, Mostaghimi A. Abnormal Baseline Lab Results Rarely Lead to Treatment Modification for Patients on Isotretinoin. Dermatology. 2020;236(6):517-20.
9. Bienenfeld A, Azarchi S, Lo Sicco K, Marchbein S, Shapiro J, Nagler AR. Androgens in women: Androgen-mediated skin disease and patient evaluation. J Am Acad Dermatol. 2019;80(6):1497-1506.
10. Strauss JS, Rapini RP, Shalita AR, Konecky E, Pochi PE, Comite H, Exner JH. Isotretinoin therapy for acne: results of a multicenter dose-response study. J Am Acad Dermatol. 1984;10(3):490-6.
11. Marson JW, Baldwin HE. Elevated creatine kinase levels, exercise and isotretinoin for acne. JAAD Case Rep. 2022;21:133-5.
12. Marson JW, Baldwin HE. The creatine kinase conundrum: a reappraisal of the association of isotretinoin, creatine kinase, and rhabdomyolysis. Int J Dermatol. 2020;59(3):279-83.
13. Michałek K, Lechowicz M, Pastuszczak M, Wojas-Pelc A. The use of trimethoprim and sulfamethoxazole (TMP-SMX) in dermatology. Folia Med Cracov. 2015;55(1):35-41.
14. Plovanich M, Weng QY, Mostaghimi A. Low Usefulness of Potassium Monitoring Among Healthy Young Women Taking Spironolactone for Acne. JAMA Dermatol. 2015;151(9):941-4.
15. Ho JM, Juurlink DN. Considerations when prescribing trimethoprim-sulfamethoxazole. Can Med Assoc J. 2011;183(16):1851–8.

Paediatric acne



CLICK IMAGE TO LINK TO VIDEO DURATION_00:48

Michelle K Y Chen[1,2], Chelsea Jones[3], Li-Chuen Wong[4,5], Deshan Frank Sebaratnam[1,2]

1. South West Sydney Clinical Campuses, University of New South Wales, Sydney, NSW, Australia
2. Department of Dermatology, Liverpool Hospital, Sydney, NSW, Australia
3. The Skin Hospital, Westmead, NSW, Australia
4. Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia
5. Department of Dermatology, The Children's Hospital at Westmead, Sydney, NSW, Australia

Correspondence: Michelle K Y Chen michelle.k.chen@student.unsw.edu.au

Disclosures: *none*

OUTLINE: Acne vulgaris is a common dermatosis affecting the pilosebaceous unit, most often seen in adolescence. Paediatric acne, acne before the onset of puberty, is uncommon and encompasses neonatal acne, infantile acne, and mid-childhood acne. The clinical presentation of paediatric acne varies by age and, in some cases, may be suggestive of an underlying systemic pathology. Given the conspicuous nature of the disease, potential for permanent sequelae, and the considerable impact on quality of life, paediatric acne warrants timely and effective treatment. However, there are a limited number of guidelines for the investigation, diagnosis, and management of paediatric acne. In this article, we provide a practical overview of the clinical presentation, evaluation, and management of paediatric acne and its key differential diagnoses.

KEYWORDS: Acne, Propionibacterium acnes, paediatrics, dermatology

Chen MKY, Jones C, Wong L-C, Sebaratnam DF. Paediatric acne. Opin Prog Cosmet Dermatol 2022;2(2):24-27.

Introduction

Acne vulgaris is a common dermatosis affecting the pilosebaceous unit, most often seen in adolescence. Paediatric acne – acne before the onset of puberty – is uncommon and encompasses neonatal acne, infantile acne and mid-childhood acne. Given the conspicuous nature of the disease, potential for permanent sequelae, and the considerable impact on quality of life, paediatric acne warrants timely and effective treatment.[1,2] This article provides a practical overview of the clinical presentation, evaluation, and management of paediatric acne and its key differential diagnoses.

Paediatric acne

Neonatal acne

Neonatal acne, otherwise known as acne neonatorum, affects up to 20% of newborns.[3,4] It appears within the first two to four weeks of life and often improves by approximately four months of age.[3,5] Neonatal acne usually presents as a symmetrical distribution of closed comedones and papulopustular eruptions on the central face, which may extend to the scalp, neck and upper trunk.[3-6]

The pathogenesis of neonatal acne is multifactorial. Increased sebum excretion due to stimulation of the sebaceous glands by maternal and neonatal androgens has been suggested as a potential cause.[3,7] In male newborns, testicular androgens provide additional stimulation to the sebaceous glands, explaining why neonatal acne is more common in males by a 5:1 ratio.[3,8] Neonatal sebum excretion rates decrease over the next several months; the substantial decline in sebum production after the first six months of life provides reason for the limited period of susceptibility to neonatal acne.[3,7,9]

Diagnosis is usually clinical. Main differential diagnoses of neonatal acne include acneiform eruptions such as bacterial folliculitis, secondary syphilis, herpes simplex virus, varicella zoster virus, *Malassezia*, and naevus comedonicus.[9] Other neonatal eruptions which may present similarly are erythema toxicum neonatorum, transient neonatal pustular melanosis, milia, and miliaria.[3,9] Drug-induced acneiform reactions (e.g. to corticosteroids, lithium) during pregnancy should also be considered.[9,10]

Infantile acne

Compared to neonatal acne, infantile acne is uncommon and has a later age of onset, usually between 6–12 months with most cases resolving within one to three years.[4, 5] However, infantile acne also has a male preponderance and primarily affects the central face, chest and back.[3, 11] Clinically, infantile acne is characterised by a mixture of open and closed comedones, either alone or with inflammatory papules and pustules.[5] Suppurative nodules and cysts have also been observed (Figure 1). Infantile acne has potential to cause scarring and those with a history of infantile acne may have an increased risk of severe, refractory acne vulgaris and acne scarring during their adolescence.[1, 3, 8, 11]

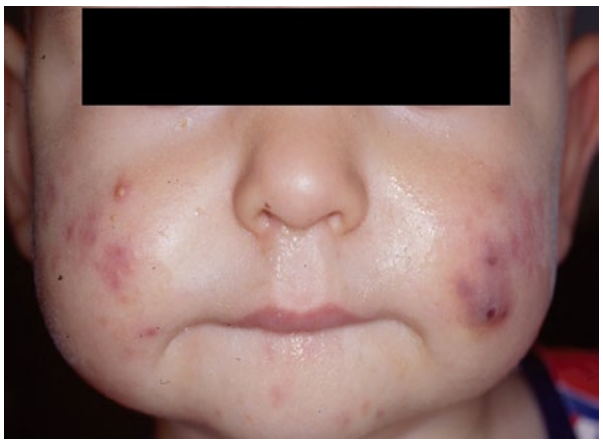


Figure 1. *Polymorphic infantile acne*

Whilst the exact aetiology of infantile acne is yet to be elucidated, genetics appear to play a strong role in its pathogenesis.[8] Factors which may influence the onset and severity of disease include chromosomal abnormalities, particular human leukocyte antigen phenotypes, mucin 1 gene, and polymorphisms of cytochrome P450 1A1.[8] Similar to neonatal acne, infantile acne is likely also related to a physiologic increase in the production of androgens by the adrenal glands and testes.[9] Infantile adrenal glands are immature with an enlarged zona reticularis that produces elevated levels of dehydroepiandrosterone, which is subsequently converted by the sebaceous gland into more potent, acne-promoting androgens, such as dihydrotestosterone.[5] Infantile acne is not commonly associated with an underlying endocrinopathy. However, unusually severe or persistent disease, and stigmata of hyperandrogenism (e.g., clitoromegaly, hirsutism) or precocious puberty (e.g., pubic hair, testicular enlargement) may warrant further investigation as well as prompt referral to a paediatric endocrinologist.[8] Other differential diagnoses in this age group include periorificial dermatitis, keratosis pilaris, plane warts and molluscum.

Mid-childhood acne

Mid-childhood acne is a rare condition referring to acne presenting in children between 1 and 7 years of age.[1] It occurs most frequently as an eruption of open and closed comedones, inflammatory papules, pustules, cysts, and nodules on the face, and less often on the chest and back (Figure 2).[11] The main differential diagnoses to consider are periorificial dermatitis, keratosis pilaris, milia, plane warts, idiopathic facial aseptic granuloma, and endocrinopathies related to hyperandrogenism.[11] Benign facial tumours such as facial angiofibromas, may also mimic acne amongst children of this age.[1]

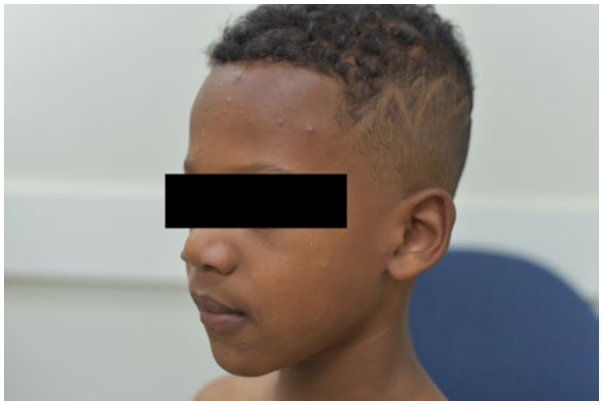


Figure 2. *Comedomal mid-childhood acne*

Treatment

Treatment is not routinely required for neonatal acne as it is often mild and spontaneously resolves without scarring within three months.[3, 8] When active treatment is sought, 2% salicylic acid (readily available in many cradle cap formulations) may be employed or a mild topical retinoid such as 0.025% tretinoin.

In contrast, early active management is often required for infantile and mid-childhood acne, even in mild disease, as scarring is common. Therapeutic options are similar to those employed for adolescent and adult patients. For mild inflammatory papules or pustules with sparse comedones, benzyl peroxide 5%, once daily, may be used. Infantile acne which presents with larger and more numerous non-inflammatory comedones may benefit from a mild topical retinoid, such as adapalene 0.1% cream or tretinoin 0.025% cream nocte.[8] Inflammatory lesions may require combination treatment with benzoyl peroxide and adapalene 2.5% + 0.1% gel. Side effects of topical therapy, which include burning, stinging, scaling, and xerosis, may be mitigated by decreasing the frequency of application, using smaller amounts of medication, and regular use of moisturisers.

Topical or systemic antibiotics (e.g., erythromycin) may be trialled for infantile or mild-childhood acne with a more severe inflammatory component. Clinical review is suggested at 3-4 months. Antibiotic therapy should be limited to 6 months, and should be prescribed in combination with benzoyl peroxide to prevent the development of antibiotic resistance.[11] It is important to note that tetracyclines are contraindicated in the treatment of neonatal and infantile acne due to the risk of permanent discolouration of teeth and altered bone growth.[3, 4, 11] Our favoured systemic agent is erythromycin ethylsuccinate at a dose of 50 mg/day in divided doses, which is available in granules that are reconstituted into an oral liquid or compounded privately.[12]

Intralesional corticosteroid injections at a weak concentration (5 mg/mL triamcinolone acetonide) into persisting large nodulocystic lesions may be helpful in resolving the lesions and preventing long term scarring. Oral isotretinoin is also occasionally required for recalcitrant or nodulocystic presentations.[8] Most published infantile cases have reported safe treatment with isotretinoin at doses ranging from 0.2 to 2 mg/kg/day.[4, 8, 9, 13]

Drug induced acne

Medications can contribute to the development of acne in children, although less commonly than in adolescents and adults. Relevant drugs in the paediatric setting include topical, inhaled, and systemic corticosteroids, anti-epileptic drugs, psychiatric medications, and immune modulating agents such as cyclosporine or sirolimus.[14-17] Inflammatory acne is also a common adverse effect of Janus kinase inhibitors, which were recently approved for the treatment of atopic dermatitis in Australia.[18, 19] If a medication is found to be contributing to acne, dose reduction or substitution can be discussed with the prescribing doctor. Topical products including emollients, makeup and sunscreen can also contribute to acne through hyperkeratinisation of the follicular epithelium and blocking of the follicular duct.[20, 21]

Acne associated with endocrine pathology

Most cases of paediatric acne are not a result of an endocrine pathology. However, it is important to recognise the clinical signs of endocrinologic abnormalities to guide investigation and referral. A thorough history and complete physical examination should be performed on children presenting with acne. Vital signs including blood pressure, height, weight, height velocity, and physical examination with a focus on signs of hyperandrogenism (clitoromegaly, hirsutism), primary sexual characteristics (testicular enlargement, thelarche, menarche), secondary sexual characteristics (body odour, oily skin and hair) or features of Cushing's syndrome (striae, central obesity, short stature, ecchymoses, skin atrophy) will help elucidate underlying endocrine abnormalities.[9, 22]

Endocrine disorders which may present with paediatric acne include central precocious puberty (due to a neurogenic tumour, trauma), precocious pseudo-puberty (due to congenital adrenal hyperplasia, adrenal tumours, or gonadal tumours), premature adrenarche, and Cushing's syndrome (pituitary tumours, ectopic hypersecretion of adrenocorticotropic hormone, adrenal overproduction or iatrogenic corticosteroids.[9, 22, 23] Infantile acne is not commonly associated with an underlying endocrinopathy, although unusually severe or persistent disease, with stigmata of hyperandrogenism, precocious puberty or Cushing's syndrome should warrant further investigation as well as prompt referral to a paediatric dermatologist and endocrinologist.[8] Mid-childhood acne is usually abnormal and therefore examination, investigation, and referral to a paediatric endocrinologist for an underlying endocrine abnormality should be considered.[1, 11]

Initial investigations for patients with clinical findings of hyperandrogenism or premature adrenarche can involve a hormonal evaluation including serum follicle stimulating hormone, luteinising hormone, dehydro-epiandrosterone, dehydroepiandrosterone sulfate, free and total testosterone, 17a-hydroxyprogesterone, and prolactin.[9, 11] If congenital adrenal hyperplasia is suspected, an adrenocorticotropic hormone stimulation test with a full range of the androgenic steroids may be helpful for diagnosis. Bone age assessment with radiographs of the left hand and wrist may be useful for the evaluation of growth and maturation.[24] Patients with signs of Cushing's or hypercortisolism may be assessed with either late-night salivary cortisol level, 24-hour urine cortisol level, or low-dose dexamethasone suppression test.[23]

Naevus comedonicus

Naevus comedonicus is a rare hamartoma of the pilosebaceous unit that usually presents before 10 years of age.[25-27] It presents as agminate, enlarged follicular openings containing comedo-like keratinous plugs.[26] White papules resembling milia, closed comedones, or deeper follicular cystic structures are occasionally observed.[5] Older children may develop painful, inflammatory cystic nodules and acneiform scarring. Most lesions are unilateral and preferentially affect the face or neck.[25] Acneiform naevi have also been reported; Blaschkolinear hamartomas composed of inflammatory acneiform lesions without the presence of comedomes.[28-30] Naevus comedonicus is rarely associated with central nervous system, skeletal,

and ocular abnormalities in naevus comedonicus syndrome.[26, 31] As naevus comedonicus is a benign disorder, treatment is not required unless for cosmesis or due to complications such as infection or scarring. Topical and systemic retinoids, topical and systemic antibiotics, as well as ablative laser treatments have demonstrated variable benefit but can be considered depending on the burden on quality of life.[26, 32] Definitive treatment necessitates surgical excision.[31] Recent research indicates that fibroblast growth factor receptor inhibitors show promise for naevus comedonicus.[26, 33]

Conclusion

While paediatric acne is uncommon, its highly visible lesions and the potential for scarring may pose a significant psychosocial burden to paediatric patients and their parents. Its early identification and treatment can be facilitated by a thorough understanding of the underlying pathogenesis, differential diagnoses, and current therapeutic options. If disease is recalcitrant to traditional agents, prompt referral to a paediatric dermatologist, and in some cases a paediatric endocrinologist, can prevent scarring and minimise the impact of uncontrolled acne on the patient's quality of life.

References

1. Ashton R, Weinstein M. Acne vulgaris in the pediatric patient. Pediatr Rev. 2019;40(11):577-89.
2. Feldstein S, Afshar M, Krakowski AC, Eichenfield LF. Filling in pediatric acne practice gaps: a prospective multicenter study of case-based education. J Adolesc Health. 2016;59(5):549-54.
3. Serna-Tamayo C, Janniger CK, Micali G, Schwartz RA. Neonatal and infantile acne vulgaris: an update. Cutis. 2014;94(1):13-6.
4. Maroñas-Jiménez L, Krakowski AC. Pediatric acne: clinical patterns and pearls. Dermatol Clin. 2016;34(2):195-202.
5. Eichenfield LF, Frieden IJ, Zaenglein A, Mathes E. Neonatal and infant dermatology e-book, (Elsevier Health Sciences, 2014).
6. Hayashi N. Clinical Features and Differential Diagnosis of Acne Vulgaris. in Acne: Current Concepts and Management (ed. Suh, D.H.) 159-167 (Springer International Publishing, Cham, 2021).
7. Barnes CJ, Eichenfield LF, Lee J, Cunningham BB. A practical approach for the use of oral isotretinoin for infantile acne. Pediatr Dermatol. 2005;22(2):166-9.
8. Greydanus DE, Azmeh R, Cabral MD, Dickson CA, Patel DR. Acne in the first three decades of life: an update of a disorder with profound implications for all decades of life. Dis Mon. 2021;67(4):101103.
9. Antoniou C, Dessinioti C, Stratigos AJ, Katsambas AD. Clinical and therapeutic approach to childhood acne: an update. Pediatr Dermatol. 2009;26(4):373-80.
10. Cantatore-Francis JL, Glick SA. Childhood acne: evaluation and management. Dermatol Ther. 2006;19(4):202-9.
11. Solman L, Layton AM. Acne in childhood. Paediatr Child Health (Oxford). 2019;29(2):85-9.
12. Monthly Index of Medical Specialities Online. E-Mycin. https://www.mimsonline.com.au.acs.hcn.com.au/Search/FullPI.aspx?ModuleName=Product%20Info&searchKeyword=erythromycin&PreviousPage=~/Search/QuickSearch.aspx&SearchType=&ID=29370002_2 (2021).
13. Admani S, Barrio VR. Evaluation and treatment of acne from infancy to preadolescence. Dermatol Ther. 2013;26(6):462-6.
14. Kazandjieva J, Tsankov N. Drug-induced acne. Clin Dermatol. 2017;35(2):156-62.
15. Boull CL, Gardeen S, Abdali T, Li E, Potts J, Rubin N, et al. Cutaneous reactions in children treated with MEK inhibitors, BRAF inhibitors, or combination therapy: a multicenter study. J Am Acad Dermatol. 2021;84(6):1554-61.
16. Strahan JE, Burch JM. Cyclosporine-induced infantile nodulocystic acne. Arch Dermatol. 2009;145(7):797-9.
17. Zamil DH, Perez-Sanchez A, Katta R. Acne related to dietary supplements. Dermatol Online J. 2020;26(8):13030/qt9rp7t2p2.
18. Chang PH, Huang SF, Chang PS, Yu Y. Safety considerations of systemic Janus kinase inhibitors in atopic dermatitis applications. J Dermatol. 2021;48(11):1631-9.
19. Awad SM, Tawfik YM, El-Mokhtar MA, El-Gazzar AF, Abdel Motaleb AA. Activation of Janus kinase signaling pathway in acne lesions. Dermatol Ther. 2021;34(1):e14563.
20. Katoulis A, Kakepis E, Kintziou H, Kakepis M, Stavrianeas N. Comedogenicity of cosmetics: a review. J Eur Acad Dermatol Venereol. 1996;2(7):115-9.
21. Maarouf M, Saberian C, Shi VY. Myths, truths, and clinical relevance of comedogenicity product labeling. JAMA Dermatol. 2018;154(10):1131-2.
22. Bree AF, Siegfried EC. Acne vulgaris in preadolescent children: recommendations for evaluation. Pediatr Dermatol. 2014;31(1):27-32.
23. Lause M, Kamboj A, Faith EF. Dermatologic manifestations of endocrine disorders. Transl Pediatr. 2017;6(4):300.
24. Satoh M. Bone age: assessment methods and clinical applications. Clin Pediatr Endocrinol. 2015;24(4):143-52.
25. Ferrari B, Taliercio V, Restrepo P, Luna P, Abad ME, Larralde M. Nevus comedonicus: a case series. Pediatr Dermatol. 2015;32(2):216-9.
26. Tchernev G, Ananiev J, Semkova K, Dourmishev LA, Schönlebe J, Wollina U. Nevus comedonicus: an updated review. Dermatol Ther. 2013;3(1):33-40.
27. Leung AK, Barankin B, Lam JM, Leong KF, Hon KL. Dermatology: how to manage acne vulgaris. Drugs Context. 2021;10:2021-8-6.
28. Torchia D. Nevus comedonicus syndrome: A systematic review of the literature. Pediatr Dermatol. 2021;38(2):359-63.
29. Melnik B, Schmitz G. FGFR2 signaling and the pathogenesis of acne. JDDG: J Dtsch Dermatol Ges. 2008;6(9):721-8.
30. Melnik BC, Vakilzadeh F, Aslanidis C, Schmitz G. Unilateral segmental acneiform naevus: a model disorder towards understanding fibroblast growth factor receptor 2 function in acne? Br J Dermatol. 2008;158(6):1397-9.
31. Timbó RPF, Gomes MK, Falcão EMM, Ramos-E-Silva M. Nevus comedonicus: case report. Case Rep Dermatol. 2017;9(3):184-9.
32. Givan J, Hurley MY, Glaser DA. Nevus comedonicus: a novel approach to treatment. Dermatol Surg. 2010;36(5):721-5.
33. Higgins R, Pink A, Hunger R, Yawalkar N, Navarini AA. Generalized comedones, acne, and hidradenitis suppurativa in a patient with an FGFR2 missense mutation. Front Med (Lausanne). 2017;4:16.

Adult female acne: A review

Diana Rubel[1,2,3], Daniel Cordas[2], Anna Elizabeth Dixon[3]

1. Australian National University, ACT, Australia
2. The Canberra Hospital, ACT, Australia
3. Woden Dermatology, ACT, Australia

Correspondence: Diana Rubel diana@wodendermatology.com.au

Disclosures: *none*

OUTLINE: Adult acne, also known as hormonal acne, predominantly affects females and can be a manifestation of underlying hyperandrogenism, or less commonly hyperandrogenaemia. Clinical variants include tender inflammatory papulonodules affecting the lower face and neck, and noninflammatory open and closed comedones of the entire face. Compared with adolescent acne, it is more likely to relapse following treatment and/or require long term maintenance therapies. Treatments include topical therapies, oral antibiotics, antiandrogen therapies with combined oral contraceptive pills or spironolactone, isotretinoin and/or physical therapies. Successful management requires us to initiate appropriate investigations when warranted, recognise the specific challenges of women requiring therapy during their reproductive years, and to administer long term maintenance regimes.

KEYWORDS: Acne, adult, hormonal, hyperandrogenism, spironolactone

Rubel D, Cordas D, Dixon AE. Adult female acne: A review. Opin Prog Cosmet Dermatol 2022;2(2):28-35.

Introduction

Acne is a chronic inflammatory disorder of the pilosebaceous unit. It is driven by androgen-mediated stimulation of sebaceous glands resulting in excess sebum production, *Cutibacterium acnes* colonisation, follicular hyperkeratosis and inflammation.[1] While acne is very common in adolescents, it is also prevalent amongst adults – either persisting from adolescence, occurring intermittently through adolescence and adulthood, or with adult onset. Adult acne is defined arbitrarily as occurring after age 25 and is sometimes called "hormonal acne" when affecting adult women. However, "hormonal acne" is a misnomer given that, firstly, a certain number of adult acne patients are male and, secondly, despite considerable efforts to analyse the possible hormonal factors contributing to adult acne, the pathogenesis of adult acne is not yet elucidated, and hormonal abnormalities are the exception rather than the norm. In this article the terms "adult acne" and "adult female acne" will be used interchangeably.

The prevalence of adult acne decreases with age and is more common in adult women across all ages. A survey consisting of 1013 university campus participants aged 20 years or older, which assessed self-reported presence of acne, found 73.3% of individuals reported ever having acne.[2] The overall prevalence of adult acne was between 15% and 50% according to decade of life, with the former prevalence estimate corresponding to participants in their 50's and the latter in their 20's. In contrast, only 3% of men were reported to experience post-adolescent acne.[3] In an earlier prevalence study of dermatology clinic presentations, most women experienced persistent acne and only 18.4% of females had acne onset after 25 years.[4] Some studies have reported a higher incidence of acne, particularly more inflammatory subtypes, in darker skin types.[3]

Clinical presentation of adult acne

Adult female acne is more likely to involve the lower face and neck, when compared with younger patients. It is also typically mild to moderate, and of more gradual onset. However, observations by several studies also show more varied patterns of presentation. A prospective observational study of 374 women aged 25 years and older with acne, who presented to an outpatient dermatology clinic, found that 90% had acne distributed over multiple facial zones, with only 11% having acne localised only to the mandibular area.[5] Additionally, there was a spectrum of lesion severity in adult female acne similar to adolescents, with most women (94%) having comedonal acne. Others have noted inflammatory (cheeks, temples, chin, forehead), mandibular, and comedonal patterns.[3] Excoriations

Figure 1: Common clinical presentations of acne

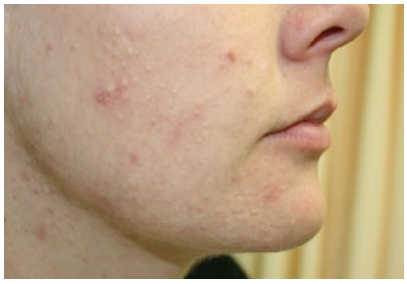


Figure 1a. *Comedonal acne*

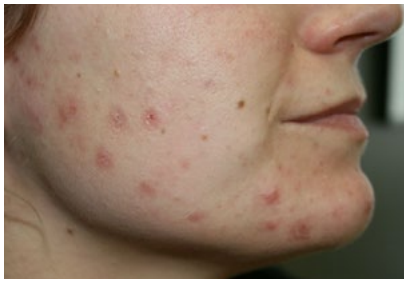


Figure 1b. *Acne excoriee*

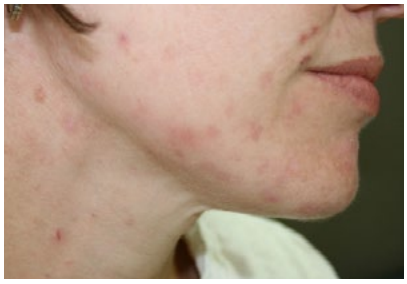


Figure 1c. *Lower face and neck acne*

may be a prominent feature and can be associated with significant stress and/or anxiety. Figure 1 illustrates the common clinical presentations of female acne.

Pathogenesis of acne

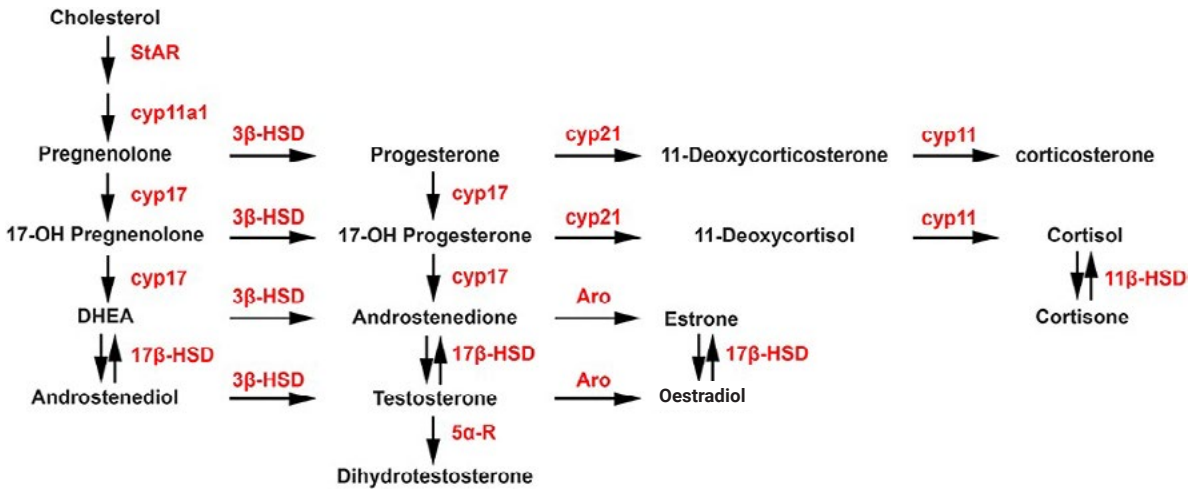
The drivers behind adult acne have not yet been fully elucidated. Understanding is hampered by absent prospective studies, and confounding factors. For instance, makeup use has been associated with adult acne, but these researchers failed to acknowledge that women with severe acne are more likely to seek camouflage options.[6] Similarly stress, diet and acne have multidirectional influences on each other, and are notoriously difficult to quantify and validate, particularly in retrospective and cross-sectional analyses. Smoking has been identified as potential factor contributing to comedone formation in adult acne.[5]

Hormonal metabolism in women

Hormones, in particular androgens, have a well-established role in the pathogenesis of acne. Activity of the sebaceous gland is dependent on the oestrogen/androgen ratio.[7] Androgens such as testosterone, androstenedione, dehydroepiandrosterone sulphate (DHEAS) and dihydrotestosterone (DHT) stimulate sebaceous gland growth and function, whereas oestrogen has the opposite effect.[7] In addition, oestrogen increases circulating sex hormone-binding globulin (SHBG), which has high affinity for testosterone over oestrogen, and can further reduce circulating androgens.[8]

Adult female androgens are derived from three major sources: the ovaries, adrenal glands, and skin.[7,9] Not all androgens are equipotent: androstenedione and testosterone are more potent androgens formed from the metabolism of DHEAS and androstenediol, respectively (Figure 2).[9] Testosterone can be further

Figure 2: Biosynthetic pathways of steroid synthesis



Abbreviations: *CYP11a1, cytochrome P450 family 11 subfamily A member 1 (P450scc); cytochrome P450 side-chain cleavage; CP17, cytochrome P450 17-α hydroxylase/ C17, 20-lyase; Aro, aromatase; 3 β-HSD, 3β-hydroxysteroid dehydrogenase D5-D4 isomerase; 5α-R, 5α reductase; 17β-HSD, 17β-hydroxysteroid dehydrogenase; CYP21, cytochrome P45021 hydroxylase; CYP11; cytochrome P450 11β-hydroxylase β1 and/or β2. StaR, steroidogenic acute regulatory proteins*

converted into DHT, which is 5 to 10 times more potent than its precursor.[8] The hair follicle can directly produce testosterone and dihydrotestosterone from circulating androstenedione, DHEA, DHEAS and oestradiol, while also synthesising androgens from cholesterol *de novo*.[9] In women, up to 50% of the total circulating testosterone is produced in the skin and in other peripheral tissues.[10]

It is important to note that most adult women with acne have normal circulating androgen levels,[11] other than slight nonspecific DHEAS elevation,[7] and that acne severity does not correlate with androgen levels. A retrospective analysis of 228 women presenting to an endocrinology clinic with cutaneous symptoms of hyperandrogenism (acne, alopecia, hirsutism) found there was no evidence to support that acne was associated with levels of androgenic hormones.[12]

Rather, it has been hypothesised that peripheral metabolism of androgens in the skin, and resulting increased sensitivity to circulating androgens, may be contributing factors to acne development where serum androgen levels are normal.[13] This peripheral sensitivity is termed hyperandrogenism, to distinguish it from hyperandrogenaemia as manifest by abnormally elevated serum levels of androgens.[14]

Laboratory investigation of suspected hyperandrogenaemia (Figure 3) should be considered in adult female acne patients who exhibit other features of hyperandrogenism (hirsutism, oligomenorrhoea, or less commonly features of virilisation). Some investigators recommend that any adult female presenting with sudden, severe acne should also undergo hormonal investigations, even in the absence of other features of hyperandrogenism. SHBG, free and total testosterone, DHEAS, luteinising hormone (LH) / follicle stimulating hormone (FSH), and 17-OH progesterone (17-OHP) plasma concentrations are helpful in diagnosing underlying hormonal pathology.

Altered hormonal states in adult acne

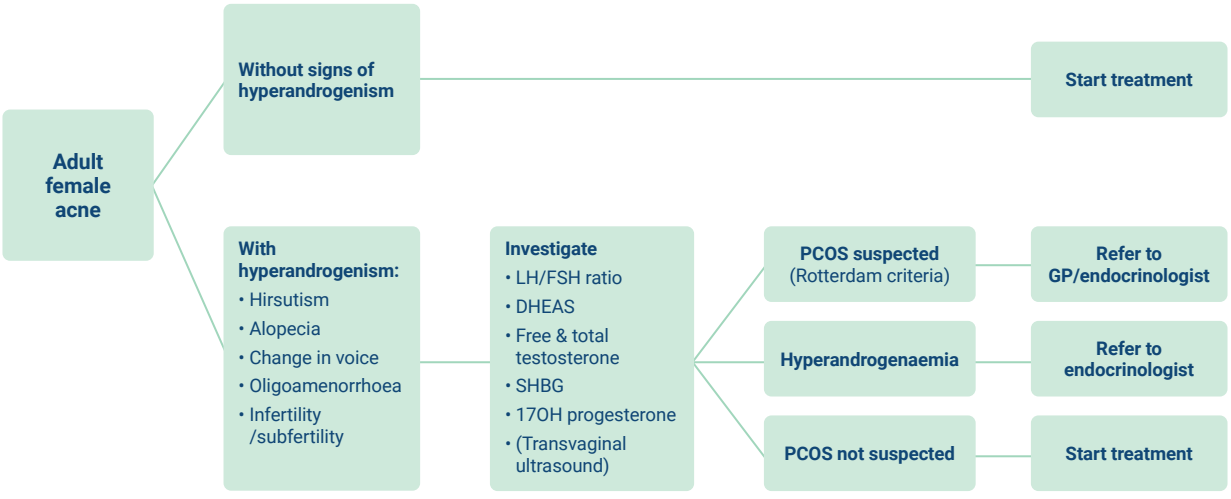
Acne is associated with several conditions with altered hormonal states, which can help provide insight into the aetiology of adult acne.

Polycystic ovarian syndrome

Polycystic ovarian syndrome (PCOS) affects 8-13% of reproductive aged women, and it is estimated that 70% remain undiagnosed.[15] A diagnosis of PCOS is made according to the Rotterdam criteria, which consists of the presence of at least two out of three criteria which are clinical or biochemical features of hyperandrogenism (acne, hirsutism, alopecia), polycystic ovaries and oligomenorrhoea.[15]

A prospective study of 120 women who presented to a dermatology clinic with acne, 31 of which had PCOS, identified hormonal aberrations associated with women with PCOS.[16] They found levels of serum anti-Müllerian hormone (AMH), total testosterone, free androgen index, LH and LH to FSH ratio were significantly raised in women with PCOS compared to women without PCOS. The hormones which were not shown to be significantly different between women with and without PCOS were SHBG, DHEAS, 17-OHP, thyroid stimulating hormone and FSH. This study also demonstrated a phenotypic difference in women with PCOS and acne. Women with PCOS had a significantly greater prevalence of truncal acne and a significantly reduced prevalence of papular acne compared to women

Figure 3: Investigation of suspected hyperandrogenaemia (adapted from Bagatin, 2019)[7]



without PCOS. No difference was found in overall acne severity as measured by the Global Acne Grading Score (GAGS) between those with and without PCOS.

A prospective cohort study of 165 women with acne aged 25 years and older measured a number of hormones thought to be implicated in acne development as well as screened for PCOS according to Rotterdam criteria.[16] PCOS was diagnosed in 26% of women. The study found that 67% of women had elevated serum 17-OHP and 61% had elevated AMH levels. The statistical relevance of this is not clear as there was no comparison made against a control group, i.e., women without acne. Additionally, it is not clear if this hormonal profile is unique to adult acne or if this is also seen in adolescent acne.

Another study consisting of 110 women with PCOS, stratified into two groups according to serum androstenedione levels (normal or elevated), found that across all women with PCOS there was a significant positive correlation between serum DHEAS and acne severity. Within each group of androstenedione levels, various correlations were reported between acne severity and serum hormone levels. Notwithstanding a lack of control group for comparison, the assessment of subgroup analyses without prior assessment of an overall effect across subgroups constitutes poor statistical methodology and the results should be interpreted with caution.

In summary, many hormones have been studied in women with PCOS, but their relevance in acne pathogenesis is yet to be fully understood. Further research, which includes patients without acne as controls, as well as comparing findings between adults and adolescents, are needed to ascertain the role of altered hormonal metabolism in PCOS and acne.

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) is a group of autosomal inherited disorders characterised by impaired cortisol biosynthesis from enzyme deficiency (usually 21-hydroxylase), and a resulting hyperandrogenic state from increased adrenocorticotropic hormone (ACTH) secretion, as there is loss of negative feedback from lack of cortisol production. This state of androgen excess results in clinical features of hyperandrogenism including acne, hirsutism and androgenetic alopecia.[14] Some forms of CAH can present later in life, termed non-classical CAH (NCAH), and notably acne may be the only presenting feature of NCAH in both women and men. NCAH is an important diagnosis to consider in patients with severe acne refractory to treatment, as it is treated with low dose oral steroids in order to provide negative feedback to the pituitary gland and thus reduce androgen production which is driving the acne.[17]

Adrenal tumours

An elevated DHEAS level suggests an adrenal source of hyperandrogenism. A high DHEAS level (>8000 ng/mL) is suggestive of an adrenal tumour, while moderately elevated DHEAS levels between 4000 to 8000 ng/mL are suggestive of congenital adrenal hyperplasia.[8]

Pregnancy

The effect of pregnancy on acne has not been assessed in detail. A prospective observational study of pregnant women with acne presenting to a dermatologist found that acne was present in 42% of women[5] and that most patients with acne had a history of acne prior to pregnancy. The study found that some women reported worsening, no change or improvement in their acne, however no statistical comparisons were made. This figure is similar to the prevalence of acne seen in the general population. Given the study cohort consists of women presenting to a dermatologist, possibly for the purposes of an acne consultation, this prevalence may not be reflective of acne in pregnant women in general. A separate study by Kumari[18] found only 15 out of 607 pregnant women had acne. Therefore, further epidemiological studies are required to evaluate the impact of pregnancy on acne.

Cessation of oral contraceptive pill

Discontinuing oral contraception was reported to worsen acne symptoms in an observational cohort study of 111 patients with adult acne.[19] This may be a confounding factor when taking a history from patients with adult acne and contraceptive use, as hormonal implant use may follow from combined oral contraceptive (COCP) cessation.

Premenstrual flares

Estimates of premenstrual flares of acne in women above 20 years old has been reported to be between 30% and 85%.[6] It is thought this could be due to a relatively lower mid-cycle peak of oestrogen in women with acne.

Hormonal implants

Progestins have androgenic potential and thus exogenous progestins present in contraceptive devices such as the intrauterine device (IUD) and subdermal implant may contribute to acne development. A review of the role of progestins in acne has suggested that levonorgestrel-containing IUDs are associated with acne flares, however high-quality evidence with randomised trials is lacking and assessment of causation is limited by varying rates of cessation of oral contraceptives prior to IUD being inserted.[20]

Recommended investigations in adult acne

Figure 3 represents a proposed algorithm for investigating and managing women with adult female acne.

Treatment of adult acne in women

Managing adult female acne can be more challenging than treating adolescents, for several reasons. Sufferers, perhaps not unreasonably, are frustrated that they have not outgrown their acne by adulthood, and they can alternate between self-blame and drastic lifestyle changes, to experimenting with expensive and unproven remedies online, beauticians, self-styled experts, and wellness peddlers. Profound psychological sequelae can result from active disease and scarring. Acne may be exacerbated by excoriations and cycles of obsessive picking and anxiety. An empathetic approach is helpful in gently dispelling myths, encouraging a healthy lifestyle such as avoiding smoking and maintaining a healthy body mass index, and general skin care advice including daily photoprotection. Studies have confirmed what experienced dermatologists have long recognised – in adult acne treatment can take longer, is more complex, may require long term maintenance (particularly with hormonal therapies), and recurrences are unfortunately not uncommon.[7] Important milestones such as career changes, travel, weddings, contraception, fertility challenges and pregnancies need to be factored into long term treatment choices.

Systemic antibiotics, mainly tetracyclines and macrolides, are often used cyclically in adult acne, and as monotherapy despite guidelines[21] recommending combination with benzoyl peroxide or topical retinoids to minimise resistance.[22] There are no studies that demonstrate superiority of any particular antibiotic in adult acne; a metanalysis of 41 prospective and controlled studies in allcomer acne patients found that superiority of any antibiotic class could not be determined, and that antibiotics should be selected on the basis of their overall safety profile and recommendations in pregnancy and breastfeeding.[23] A 2009 study found that 81% of women self-reported failure to clear acne with oral antibiotics.[24] Further, Rivera reported that neither the inflammatory nor non-inflammatory adult acne subtypes responded to topical or oral antibiotics. Given these findings, and in the interests of responsible antibiotic stewardship, oral antibiotics should not be considered for long term therapy for adult acne; additionally, there is no evidence to support switching between classes of antibiotics.

Combined oral contraceptive therapy (COCP) is effective in treating acne in adult women,[8] and are recommended as first line therapy in women with PCOS and acne.[25] Oestrogen (a) inhibits ovarian and adrenal androgen synthesis by preventing ovulation via luteinizing hormone suppression, (b) increases hepatic production of sex hormone binding globulin (reducing effective circulating androgen levels), and (c) inhibits peripheral 5-alpha-reductase to reduce conversion of testosterone into the more potent dihydrotestosterone.[26] In contrast, progestins have less impact on acne. First generation progestins can theoretically have pro-androgenic effects, so progestins belonging to subsequent classes are best suited for adult women with acne (Figure 4). Progestin-only pills should be avoided. Surprisingly, despite the variety of COCPs available, none have demonstrated superiority

Figure 4: Combined oral contraceptive pills available to treat acne in Australia (* indicated for acne treatment). Adapted from Stewart, 2015[27]

	Progesterone	Generation	Anti-androgenic effect
Ethinyl oestradiol	**Norethisterone** Brevinor/Norimin®	1st	
	Levonorgestrel Microgynons/Levlen/Trifeme/ Loette/Femmetab®	2nd	
	Desogestrel/Gestodene Marvelon/Minulet®	3rd	
	Cyproterone acetate Diane*/ Estelle*/ Brenda*/Juliet®*	3rd	++
	Drospirenone Yasmin/Yaz®*	4th	++
	Dienogest Valette®*	4th	++
Oestradiol valerate	**Dienogest** Qlaira	4th	+
Oestradiol	**Nomegestrel acetate (NOMAc)** Zoely®	4th	+

in treating acne. Choice of COCP in acne patients thus depends primarily on the safety profile. Other than rifampicin, antibiotics concomitantly given with COCP have not been shown to reduce contraceptive efficacy.[26]

Spironolactone, a steroid lactone, is an aldosterone antagonist with anti-androgenic, diuretic, and anti-hypertensive actions. It improves acne, hirsutism, and female pattern hair loss via peripheral receptor blockade of androgens at the follicle. Contraindications to its use include pregnancy, undiagnosed uterine bleeding, hyperkalaemia, and renal impairment. In Australia its use is off-label for acne and alopecia. Observational studies have confirmed its efficacy in treating female adult acne, at doses ranging from 50 to 100 mg/kg/day, with response rates ranging from 60% to 100% with good tolerability.[26]

Side effects tend to be mild and may include postural hypotension and dizziness, breast tenderness, menstrual irregularities, fatigue and headache. It is not prothrombotic and can be used in patients with a history of breast or reproductive organ tumours.[26] Despite a black box warning issued by the FDA in 2008, after reports of benign adenoma development in animals with high dose administration, long term safety data does not support tumourigenic potential in humans.[26] A retrospective analysis of 974 healthy women, who were prescribed spironolactone for acne, determined that potassium levels remained within normal reference levels and hence routine monitoring was not recommended.[28] It is prudent to ask patients about dietary intake of foods high in potassium such as coconut water, and potassium supplements.

Spironolactone is a valuable tool in the treatment of adult acne and can be combined with other modalities including topical retinoids, physical therapies, hormonal contraception, and oral antibiotics. Although its onset of action is somewhat slower than oral isotretinoin, in taking 3-6 months to see tangible clinical results, it is an excellent long-term option for maintenance treatment in women who do not wish to conceive.

Oral isotretinoin is the gold standard for severe acne and has the highest probability of long-term remission of all acne treatment options available.[7] Unfortunately, in adult acne recurrence rates are higher than adolescents. The relapse rate after an adequate isotretinoin course (variously defined as 0.5-1 mg/kg/day until acne clears, then continued for 1-2 months, or 120-150 mg/kg/day cumulative) in adult female acne can be up to 30%.[7, 24, 26] Women who did not use antiandrogen therapy after a course of isotretinoin were reported to have a 3.5 times higher risk of relapse.[29]

Low dose (5 mg/day) isotretinoin is effective in adult acne[30] and the mucocutaneous side effects are less burdensome than higher doses. Therapy must be individualised and long term, intermittent, or maintenance options reviewed as treatment progresses. Although adult female acne sufferers on isotretinoin may experience more of the usual challenges (dryness and skin sensitivity, contraception, concerns around mood changes, monitoring for lipid changes in presence of PCOS/metabolic syndrome), overall, they do not present more hurdles to dermatologists than the adolescent with severe acne. In the author's experience it can be a satisfying experience to manage these patients when done enthusiastically and empathetically, and patients' motivation for compliance often reflects the value of the therapeutic relationship.

Cyproterone acetate (pregnancy category D) is a synthesised antiandrogen with weak progestational and antineoplastic properties, and in Australia is approved for use in women with moderate to severe signs of androgenisation (defined by the TGA as alopecia, severe acne or seborrhea, or hirsutism). At doses of 50-100 mg/day it has demonstrated response rates in acne from 75% to 90%.[8] Menstrual irregularity is a common adverse effect and can be mitigated by limiting it to days 1-10 of the menstrual cycle, and/or in combination with a COCP. The side effect profile, whilst like spironolactone in nature, is more likely to lead to discontinuation. Similarly, **flutamide**, a potent antiandrogen approved only for prostate cancer, has shown efficacy in the treatment of adult female acne,[24] but its use is limited by lack of data, and adverse effects including foetal abnormalities and hepatic damage including death.

Metformin is an antihyperglycaemic agent used in type 2 diabetes. It has a complex mode of action that is still not yet fully elucidated, with differing short- and long-term biochemical effects. In acne, it is thought to act by increasing insulin sensitivity, reducing insulin-like growth factor (IGF)-1 and hence downstream antiproliferative and antiandrogenic effects.[31] Gastrointestinal side effects tend to be mild, common in the first few weeks but usually settle. Metformin is recommended in PCOS primarily for its metabolic effects.[25]

In small studies, some women with PCOS and acne improved with metformin. An open label study of metformin 500 mg three times daily for 8 weeks demonstrated a reduction in acne and hirsutism scores but no changes in insulin levels.[16] In another study, 70 women randomised to either metformin 500 mg twice daily or isotretinoin 20 mg/alternate days were assessed at 24 weeks – both groups improved significantly with superiority shown in the isotretinoin group, and better responses seen with metformin if PCOS was also present.[32] A large Cochrane review of metformin, PCOS, hirsutism and acne generally regarded the available evidence as being low to very low, with uncertainty to recommend metformin over COCP for hirsutism and acne treatment.[33]

Physical therapies such as extractions, superficial peels, light therapy (monotherapy or in combination with photoactive substances) have been utilised widely in this population of acne sufferers. Controlled data is generally lacking, and their use is dependent on availability of resources (both doctor and patient) and subspecialty interest. Results are generally less reliable than pharmacoactive preparations, but these modalities may play a role in adjunctive therapy, management of (mainly dyschromic) post acne scarring, or when pregnancy/lactation prohibit use of certain medications.

Conclusion

Adult female acne affects many women and is associated with anxiety, depression, and with a significant impact on quality of life. Its natural course, whilst decreasing steadily with age, demonstrates resistance to first-line treatment strategies often employed by primary healthcare providers, and multiple recurrences. Even though hormonal influences are incriminated, we still lack the fundamental knowledge of aetiopathogenesis of peripheral androgen sensitivity, altered innate immune responses, and genetic variations. Hormonal investigations are valuable in identifying associated pathological hormonal states, but they are not as useful in directing therapeutic choices.

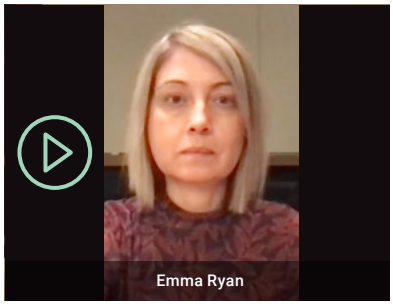
Management strategies include prompt treatment of acne that is at risk of physical and emotional scarring, utilising well known treatments such as oral antibiotics, anti-androgen agents and isotretinoin. Often management will then progress to maintenance with these agents, and intermittent interventions with higher doses or combination modalities. The need for contraception, or avoidance of certain medications in patients seeking pregnancy, complements our choices of treatment. Further studies of both pathogenesis and prospective controlled studies of epidemiology and treatment are needed to expand the knowledge base of this common disease.

References

1. Gollnick HPM. From New Findings in Acne Pathogenesis to New Approaches in Treatment. J Eur Acad Dermatol Venereol. 2015;29(55):1-7.
2. Collier CN, Harper JC, Cafardi JA, Cantrell WC, Wang W, Foster KW, et al. The Prevalence of Acne in Adults 20 Years and Older. J Am Acad Dermatol. 2008; 58(1):56-9.
3. Skroza N, Tolino E, Mambrin A, Zuber S, Balduzzi V, Marchesiello A, et al. Adult Acne Versus Adolescent Acne: A Retrospective Study of 1,167 Patients. J Clin Aesthet Dermatol. 2018;17(1):21-5.
4. Goulden V, Clark SM, Cunliffe WJ. Post- Adolescent Acne: A Review of Clinical Features. Br J Dermatol. 1997; 136(1):66-70.
5. Dreno B, Thiboutot D, Layton AM, Berson D, Perez M, Kanf S. Large-scale International Study Enhances Understanding of an Emerging Acne Population: Adult Females. J Eur Acad Dermatol Venereol. 2015;29(6):1096-106.
6. Bansal P, Sardana K, Vats G, Sharma L, Garga UC, Khuarana A. A Prospective Study Examining Trigger Factors and Hormonal Abnormalities in Adult Female Acne. Indian Dermatol Online J. 2020;11(4)544-50.
7. Bagatin E, Proenca de Freitas TH, Rivitti-Machado MC, Ribeiro BM, Nunes S, Dias da Rocha MA. Adults Female Acne: a Guide to Clinical Practice. An Bress Dermatol. 2019;94(1):62-75.
8. Ebede TL, Arch EL, Berson D. Hormonal Treatment of Acne in Women. J Clin Aesthet Dermatol. 2009;2(2):16-22.
9. Branisteanu DE, Toader MP, Porumb EA, Serban IL, Pinzariu AC, Branisteanu CI, et al. Adult Female Acne: Clinical and Therapeutic Particularities (Review). Exp Ther Med. 2022;151(23)1-7.
10. Chen WC, Zouboulis CC. Hormones and the pilosebaceous unit. Dermatoendocrinol. 2009;1(2):81-6.
11. Shaw JC. Acne. Effect of Hormones on Pathogenesis and management. Am J Clin Dermatol. 2002;3(8):517-78.
12. Karrer-Voegeli S, Rey F, Reymond M-J, Meuwly JY, Gaillard RC, Gomez F. Androgen dependence of hirsutism, acne, and alopecia in women: retrospective analysis of 228 patients investigated for hyperandrogenism. Medicine (Baltimore). 2009;88(1):32-45.
13. Preneau S, Dreno B. Female Acne- a Different Subtype of Teenager Acne? J Eur Acad Dermatol Venereol. 2011;26:277-82.
14. Chen W, Obermayer-Pietsch B, Hong J-B, Melnik BC, Yamasaki O, Dessinoti C, et al. Acne-associated Syndromes: Models for Better Understanding of Acne Pathogenesis. J Eur Acad Dermatol Venereol. 2010;25(6):637-46.
15. International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. Monash University. 2018.
16. Bansal P, Sardana K, Arora P, Khurana A, Garga UC, Sharma L. A Prospective Study of Anti-mullerian Hormone and Other Ovarian and Adrenal Hormones in Adult Female Acne. Dermatol Ther. 2020;33(6):1-9.
17. Degitz K, Placzek M, Arnold B, Schmidt H, Plewig G. Congenital Adrenal Hyperplasia and Acne in Male Patients. Br J Dermatol. 2003;148(6):1263-6.
18. Kumari R, Jaisankar TJ, Thappa DM. A Clinical Study of Skin Changes in Pregnancy. Indian J Dermatol Venereol Leprol. 2007;73(2):141.
19. Chlebus E, Chlebus M. Factors Affecting the Course and Severity of Adult Acne. Observational Cohort Study. J Dermatolog Treat. 2017;28(8):737-44.
20. Bosanac SS, Trivedi M, Clark AK, Sivamani RK, Larsen LN. Progestins and Acne Vulgaris: A Review. Dermatol Online J. 2018;24(5).
21. Dermatology 4. Therapeutic Guidelines. https://www.tg.org.au/news/dermatology-4/
22. Barbieri JS, Choi JK, James WD, Margolis DJ. Real-world Drug Usage Survival of Spironolactone Versus Oral Antibiotics for the Management of Female Patients with Acne. J Am Acad Dermatol. 2019; 81(3):848-51.
23. Bienenfield A, Nagler AR, Orlow SJ. Oral antibacterial therapy for Acne Vulgaris: An Evidence-Based Review. Am J Clin Dermatol. 2017;18:469-90.
24. George R, Clarke S, Thiboutot D. Hormonal Therapy for Acne. Semin Cutan Med Surg. 2008;4(4):6-10.

25. Teede HJ, Misso ML, Boyle JA, Garad RM, McAllister V, Downes L, et al. Translation and Implementation of the Australian-led PCOS Guideline: Clinical Summary and Translation Resources from the International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. Med J Aust. 2019;209(7):53-8.
26. Trivedi MK, Shinkai K, Murase JE. A Review of Hormone-based Therapies to Treat Adult Acne Vulgaris in Women. Int J Womens Dermatol. 2017;3:44-52.
27. Stewart M, Black K. Choosing a combined oral contraceptive pill. Aust Prescr. 2015;38:6-11.
28. Plovanich M, Weng QY, Mostaghimi A. Low Usefulness of Potassium Monitoring Among Healthy Young Women Taking Spironolactone for Acne. JAMA Dermatol. 2015;151(9):941-4.
29. Morales-Cardona CA, Sanchez-Venegas G. Acne Relapse Rate and Predictors of Relapse Following Treatment with Oral Isotretinoin. Actas Dermosifiliogr. 2013;104(1):61-6.
30. Rademaker M, Wishart JM, Birchall NM. Isotretinoin 5 mg Daily for Low-grade Adult Acne Vulgaris-placebo-controlled, Randomised Double-blind Study. J Eur Acad Dermatol Venereol. 2013;28(6):747-54.
31. Bubna AK. Metformin – For the Dermatologists. Indian J Pharmacol. 2016;48(1):4-10.
32. Behrangi E, Sadeghi S, Sadeghzadeh-Bazargan A, Goodarzi A, Ghassemi M, Sepasgozar S, et al. The Effect of Metformin in the Treatment of Intractable and Late Onset Acne: A Comparison with Oral Isotretinoin. Iran J Dermatol. 2019;22(2):47-52.
33. Fraison E, Kostova E, Moran LJ, Bilal S, Ee CC, Venetis C, et al. Metformin versus the Combined Oral Contraceptive Pill for Hirsutism, Acne, and Menstrual Pattern in Polycystic Ovary Syndrome (Review). Cochrane Database of Syst Rev. 2020;8:1-161.

The psychological burden of acne



CLICK IMAGE TO LINK TO VIDEO DURATION_01:14

Georgina Heddle[1], Sally Tregenza[2], Emma Ryan[1, 2]

1. Royal Adelaide Hospital, Adelaide, SA, Australia
2. Women's and Children's Hospital, Adelaide, SA, Australia

Correspondence: Georgina Heddle georgina.heddle@sa.gov.au

Disclosures: *none*

OUTLINE: For patients living with acne, the social and psychological impacts can be profound. Understanding the psychological burden of acne is imperative for clinicians in the assessment of acne severity and choice of acne treatment. Isotretinoin has proven efficacy for the treatment of severe acne. Widespread reporting of psychiatric consequences from isotretinoin remains contentious and continuing vigilance is recommended for prescribing dermatologists. Social media has also been shown to have an influence on psychosocial outcomes in adolescent acne patients through poor treatment guidance and a delay in seeking professional advice.

KEYWORDS: Acne, psychological burden, quality of life

Heddle G, Tregenza S, Ryan E. The psychological burden of acne. Opin Prog Cosmet Dermatol 2022;2(2):36-39.

Acne is a common, chronic, inflammatory dermatosis resulting from sebaceous gland hyperplasia, increased sebum production, follicular hyperkeratinisation and obstruction of the pilosebaceous follicle. Subsequent papules, pustules, comedones, nodules and hyperpigmentation or scarring can result. The relationship between the skin and the mind is significant but complex. Whilst not a life-threatening disease, acne can have profound impacts on an individual's social and psychological wellbeing and should not be dismissed as merely a cosmetic affliction.

Epidemiology of acne

Acne is the eighth most prevalent disease globally. The highest prevalence of acne is in adolescents aged 10-19 years, affecting up to 85% of this demographic.[1] In Australia, acne is particularly common in adolescents aged 16 to 18 years, with 93.3% of this demographic affected by acne.[2] Adolescence is a period of change associated with potential psychological distress, during which individuals are psychologically vulnerable and conscious of self-image. The onset of acne during adolescence is likely to exacerbate the emotional and psychological challenges experienced during this period. In addition to the burden of a cosmetically disfiguring skin condition that can diminish self-esteem and quality of life,[3] many adolescents experience mental illness, with 14% experiencing a mental health disorder during this time.[4]

Whilst known to be a common affliction of adolescence, the prevalence of acne in adults is increasing, particularly amongst women.[5] A survey of 1,013 adults found that the prevalence of acne was 50.9%, 35.2%, 26.3% and 15.3% among females aged 20 to 29 years, 30 to 39 years, 40 to 49 years and 50 years and older, respectively[5]. Adult acne also significantly impacts mental health,[6] with up to a 40% prevalence of psychiatric comorbidity amongst adult acne sufferers.[7]

The relationship between stress and acne

Similar to numerous other dermatoses, psychological stress is an important factor in the pathogenesis of acne. Studies have shown that the inflammatory process within the pilosebaceous unit is modulated by stress-induced production of hormones and neuropeptides.[8] Androgen secretion from the adrenal gland and cytokine production is increased by psychological stress in women resulting in sebaceous gland hyperplasia and increased sebum production, inducing and exacerbating acne.[8] Activation of the hypothalamic-pituitary-adrenal axis by emotional stress increases corticotropin-releasing hormone and cortisol which stimulate sebaceous gland lipid production and interleukin (IL)-6 and IL-11 production in keratinocytes which contribute to acne pathogenesis.[9] Furthermore, individuals that are experiencing psychological stress may pick at their acne lesions, resulting in excoriations, further inflammation, secondary infection, scarring and

hyperpigmentation.[11] Studies show that acne induced or exacerbated by psychological stress can be improved through psychological and psychiatric treatment, such as psychotherapeutic methods and medications.[11]

Acne and its psychological burden

Whilst psychological stress can induce and exacerbate acne, conversely, acne can cause significant psychological stress and morbidity. There is substantial evidence demonstrating the association between acne and negative psychological, emotional and social outcomes which have significant negative implications on quality of life.[12, 13] The degree of psychological and emotional morbidity resulting from acne is comparable to that of chronic disabling diseases such as asthma, epilepsy, diabetes and arthritis.[14] Studies show that adolescents feel pressure to meet socially perceived attractiveness and acne can subsequently be responsible for low self-esteem, anxiety and mood disorders.[15] In a study by Magin et al., patients with acne reported appearance as their primary concern and their failure to meet the ideal of perfect skin led to perceived diminished physical and sexual attractiveness. These patients also reported concern that acne sufferers were perceived as unhealthy or unhygienic.[13]

The visibility of acne, fear of scarring or disease persistence, financial costs of treatment, fear of judgment and perceived physical and sexual unattractiveness can have negative repercussions on an individual's mental health, social activities, study, work and interpersonal relationships.[16] Compared with their peers without acne, patients with acne have higher rates of dissatisfaction with appearance, low self-esteem and social dysfunction and reduced employment opportunities.[13, 17, 18] In a prospective, cross-sectional study by Hazarika et al., the dermatology life quality index (DLQI) questionnaire was employed to study the impact of acne vulgaris and its sequelae on ten different domains of daily life. The results found that acne and its sequelae had a significant impact on physical symptoms, emotions, daily and social activities, study/work and interpersonal relationships. The findings suggest that quality of life assessment tools should be employed when evaluating acne to provide the clinician a better understanding of the patient's perception of severity to guide treatment decisions.[16]

Several studies have found that acne is associated with increased rates of psychiatric morbidity, including anxiety, depression and suicidal ideation.[19, 20] In a study by Behnam et al., greater severity and duration of acne resulted in worse psychological manifestations. However, it is important to note that the psychological morbidity of acne is not always relative to its clinical severity, with findings suggesting even mild acne can result in deterioration in psychological state and quality of life.[21] Effective acne treatment has been shown to improve acne-related psychological distress and provides strong justification for treatment.[22]

Isotretinoin and psychological burden

Isotretinoin is a first-generation retinoid and is a common and highly efficacious treatment for acne.[23] Since its approval for acne treatment over 30 years ago, there have been reports of psychiatric side effects, including depression, suicide, aggression, violence, bipolar symptoms and psychosis.[23, 24] However, the relationship between isotretinoin and psychiatric effects remains contentious.

The psychiatric side effects of isotretinoin are biologically plausible and supported by the literature. Isotretinoin has been found to suppress hippocampal neurogenesis and severely disrupt learning ability in mice and decrease brain metabolism in the orbitofrontal cortex, a mediator of depression symptoms.[25] In vitro, isotretinoin alters intracellular serotonin levels and increases 5-HT1A receptors and serotonin reuptake transport levels.[26] Large scale studies of isotretinoin side effects found that 25.16% of adverse effects were psychiatric and psychiatric symptoms were reported in 1.65% of paediatric patients taking isotretinoin. Rates of depression among isotretinoin users range from 1% to 11%.[28]

Several studies have investigated the relationship between isotretinoin and depression and suicide.[12, 29] Effective acne treatment resulting in diminished self-criticism and increased self-esteem were consistently found in these studies, with several demonstrating improved quality of life.[30] Isotretinoin is an extremely effective treatment of acne and can result in significant improvement in psychological function.[12] In a meta-analysis by Li et al., isotretinoin was associated with significantly improved depression symptoms.[31] Conversely a literature review by Bremner noted that most studies found no significant increase or decrease in self-reports of depression in patients on isotretinoin.[32]

To date, there is no clear proof of association between isotretinoin and psychiatric side effects.[33] Studies have been limited by small sample size and larger prospective controlled trials are needed.

When prescribing isotretinoin, dermatologists must recognise the potential psychological adverse effects, identify risk factors that may exacerbate these risks including personal and family history, and consider the risks and benefits of isotretinoin treatment on a case-by-case basis. All patients should be informed of the potential neuropsychiatric side effects and be monitored closely. Careful follow up with

dermatology, general practice, psychology and/or psychiatry, should be organised, particularly in high-risk patients. Consultation with the patient's treating mental health clinician can be helpful and may help to decrease potential concern around use of isotretinoin. Dermatologists can screen for depression in high-risk patients before, during and after isotretinoin treatment with use of patient health questionnaires, including the Beck Depression Index (BDI) which is one of the most widely used measures of depression clinically and in research.[25]

Social media and the psychological burden of acne

In the past two decades, social media has become increasingly used, particularly amongst adolescents.[35] During this time, there has been increasing concern regarding the potential link between the use of social media and negative effects on mental health with some studies indicating that social media may be associated with detrimental mental health outcomes, such as increased self-judgement, anxiety, depression and suicidality.[35]

Social media consists predominantly of photo-sharing platforms with high value on appearance and popularity.[21] Often, images are photo-shopped or filtered leading to further negative comparisons. Studies indicate that adolescents feel pressure to meet a perceived image of attractiveness perpetuated by social media. Subsequently, when acne compromises this ideal image of attractiveness, anxiety, low self-esteem and mood disorders can ensue.[22]

Social media platforms are increasingly used to access health information, particularly in the adolescent age group, however reliability of information is variable. Studies show that treatment advice for acne on social media is prevalent and influences choice of treatment, particularly among women, adolescents and young adults.[35] Frequently the treatment advice given, particularly from non-medical professionals, is misleading, not evidence based, or incorrect. An American study on the influence of social media on acne treatment found that most treatment decisions made by patients based on recommendations provided on social media, including dietary changes and supplementation, were not supported by the American Academy of Dermatology.[35]

Implications for management and future direction

The psychological burden and social implications of acne are grossly underestimated and comparable to other debilitating chronic diseases. Acne should not be seen as an inevitable part of adolescence. Assessment of acne severity should include consideration of the effects on an individual's psychological and social wellbeing, and not be based on physical severity alone. Social media has been demonstrated to exacerbate negative psychosocial outcomes in adolescent acne patients with poor treatment guidance and a delay in seeking professional advice.

Dermatologists should adopt a holistic approach to acne management, treating the skin burden and any secondary psychological issues. Education, counselling and early initiation of appropriate treatment regimens with psychological support may prevent negative psychosocial sequalae. School-based education programs targeted at adolescents to improve knowledge and avoid erroneous social media influence is desirable.

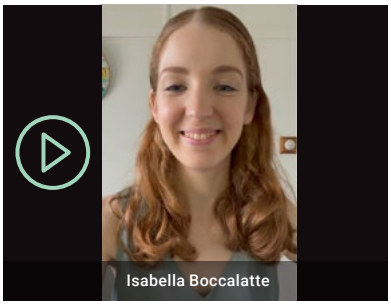
Clear evidence-based guidelines for psychological safety when treating acne with isotretinoin remain obscure. Experienced dermatologists should continue to assess patients' individual needs considering acne severity and psychosocial requirements when prescribing. Close follow-up with utilisation of broader networks of psychosocial medical specialists and tools is desirable when needed.

References

1. Alanzi M, Hammad S, Mohamed A. Prevalence and psychological impact of Acne vulgaris among female secondary school students in Arar city, Saudi Arabia, in 2018. Electron Physician. 2018 Aug;10(8):7224–9.
2. Kilkenny M, Merlin K, Plunkett A, Marks R. The prevalence of common skin conditions in Australian school students: 3. acne vulgaris. Br J Dermatol. 1998;139(5):840-5.
3. Dreno B. Assessing quality of life in patients with acne vulgaris: implications for treatment. Am J Clin Dermatol. 2006;7(2):99-106.
4. Sawyer M, Arney F, Baghurst P. The Mental Health of Young People in Australia: Key Findings from the Child and Adolescent Component of the National Survey of Mental Health and Well-Being. Aust N Z J Psychiatry. 2008;35(6):806-14.
5. Collier C, Harper J, Cafardi J, Cantrell W, Wang W, Foster W, et al. The prevalence of acne in adults 20 years and older. J Am Acad Dermatol. 2008;58(1):56-9.
6. Marks R. Acne and its management beyond the age of 35 years. Am J Clin Dermatol. 2012;5(6):459-62.
7. Rokowska-Waluch A, Pawlacyzk M, Cybulski M, Zurawski J, Kaczmarek M, Michalak M, et al. Stressful events and serum concentration of substance P in acne patients. Ann Dermatol. 2016;28(4):464-8.
8. Ganceviciene R, Graziene V, Fimmel S, Zouboulis C. Involvement of the corticotrophin-releasing hormone system in the pathogenesis of acne vulgaris. Br J Dermatol. 2009;160(2):345-52.
9. Toyoda M, Nakamura M, Morohashi M. Neuropeptides and sebaceous glands. Eu J Dermatol. 2002;12(5):422-7.
10. Alexis A. Acne vulgaris in skin of color: understanding nuances and optimizing treatment outcomes. J Drugs Dermatol. 2014;12(6):61-5.

11. Pondeljak N, Lugovic-Mihic L. Stress-induced interaction of skin immune cells, hormone, and neurotransmitters. Clin Ther. 2020;42(5):757-67.
12. Kellet S, Gawkrodger D. The psychological and emotional impact of acne and the effect of treatment with isotretinoin. Br J Dermatol. 2001;140(2):273-82.
13. Magin P, Adams J, Heading G, Pond D, Smith W. Psychological sequelae of acne vulgaris: Results of a qualitative study. Can Fam Physician. 2006;52(8):978-9.
14. Mallon E, Newton J, Klassen A, Stewart-Brown S, Ryan T, Finlay A. The quality of life in acne: a comparison with general medical conditions using generic questionnaires. Br J Dermatol. 2007;140(4):672-6.
15. Gordon R, Crosnoe R, Wang X. Physical attractiveness and the accumulation of social and human capital in adolescence and young adulthood: assets and distractions. Monogr Soc Res Child Dev. 2014;78(6):111-30.
16. Hazarika N, Archana M. The psychological impact of acne vulgaris. Indian J Dermatol. 2016;61(5):515-20.
17. Purvis D, Robinson E, Merry S, Watson P. Acne, anxiety, depression and suicide in teenagers: A cross-sectional survey of New Zealand secondary school students. J Paediatr Child Health. 2006;42(12):793–6.
18. Dalgard F, Gieler U, Holm J, Bjertness E, Hauser S. Self-esteem and body satisfaction among late adolescents with acne: results from a population survey. J Am Acad Dermatol. 2008;59(5):746–51.
19. Gupta M, Gupta A. Depression and suicidal ideation in dermatology patients with acne, alopecia arreata, atopic dermatitis, and psoriasis. Br J Dermatol. 1998;139(5):846-50.
20. Yesilova Y, Bez Y, Mehmet M, Kaya C, Alpak G. Effects of isotretinoin on obsessive compulsive symptoms, depression, and anxiety in patients with acne vulgaris. J Dermatol Treat. 2012;23(4):268-71.
21. Revol O, Milliez D, Gerard D. Psychological impact of acne on 21st-century adolescents: decoding for better care. Br J Dermatol. 2015;172(S1):52-8.
22. Gupta M. Psychosocial aspects of common skin diseases. Can Fam Physician. 2002;48:660-62.
23. Bachmann C, Grabarkiewicz J, Theisen F, Remschmidt H. Isotretinoin, depression and suicide ideation in an adolescent boy. Phamacopsychiatry. 2007;40(3):128-31.
24. Wysowski D, Pitts M, Beitz, J. An analysis of reports of depression and suicide in patients treated with isotretinoin. J Am Acad Dermatol. 2001;45(4):515-9.
25. Bremner JD, Fani N, Ashraf A, Votaw J, Brummer M, Cummins T, et al. Functional brain imaging alterations in acne patients treated with isotretinoin. Am J Psychiatry. 2005;162(5):983–91.
26. O'Reilly K, Trent S, Bailey S, Lane M. 13-cis-Retinoic acid alters intracellular serotonin, increases 5-HT1A receptor, and serotonin reuptake transporter levels in vitro. Exp Biol Med. 2007;232(9):1195–203.
27. Brzezniski P, Borowska K, Chiriac A, Smigielski J. Adverse effects of isotretinoin: A large, retrospective review. Dermatol Ther. 2017;30(4):1195-1203.
28. Marqueling A, Zane L. Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review. Sem Cutan Med and Surg. 2005;24(2):92–102.
29. Huang Y, Cheng Y. Isotretinoin treatment for acne and risk of depression: a systematic review and meta-analysis. J Am Acad Dermatol. 2017;76(6):1026-78.
30. Krowchuk D, Stancin T, Keskinen R, Walker R, Bass J, Anglin T. The psychosocial effects of acne on adolescents. Pediatr Dermatol. 1991;8(4):332-8.
31. Li C, Chen J, Wang W, Ai M, Zhang Q, Kuang L. Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis. Br Med J. 2019;9(1):117-21.
32. Bremner J. Isotretinoin and neuropsychiatric side effects: Continued vigilance is needed. J Affect Disord Reports. 2021;6:100230.
33. Droitcourt C, Poizeau F, Kerbrat S, Balusson F, Drezen E, Happe A, et al. Isotretinoin and risk factors for suicide attempt: a population-based comprehensive case series and nested case-control study using 2010–2014 French Health Insurance Data. J Eur Acad Dermatol Venereol. 2020;34(6):1293–1301.
34. Gordon R, Crosnoe R, Wang X. Physical attractiveness and the accumulation of social and human capital in adolescence and young adulthood: assets and distractions. Monogr Soc Res Child Dev. 2013;78(6):1-137.
35. Yousaf A, Hagen R, Delaney E, Davis S, Zinn Z. The influence of social media on acne treatment: A cross-sectional survey. Pediatr Dermatol. 2020;37(2):301-4.

The role of nutrition and dietetics in acne



CLICK IMAGE TO LINK TO VIDEO DURATION_00:57

Isabella Boccalatte[1, 2, 3, 4], Kelly Stewart[4], Lisa Byrom[1, 5, 6, 7, 8], Brian De'Ambrosis[1, 8, 9, 10, 11]

1. South East Dermatology, Annerley, QLD, Australia
2. Arthur House, Red Hill, QLD, Australia
3. AllSports Physiotherapy, The Gap, QLD, Australia
4. Queensland University of Technology, Brisbane, QLD, Australia
5. Dermatology Solutions, Rockhampton, QLD, Australia
6. Mater Hospital, Brisbane, QLD, Australia
7. Townsville University Hospital, QLD, Australia
8. University of Queensland, Brisbane, QLD, Australia
9. Princess Alexandra Hospital, Woolloongabba, QLD, Australia
10. Greenslopes Private Hospital, Greenslopes, QLD, Australia
11. Queensland Institute of Dermatology, South Brisbane, QLD, Australia

Correspondence: Brian De'Ambrosis bda@optusnet.com.au

Disclosures: *none*

OUTLINE: Acne is a common dermatological condition that usually appears during adolescence coinciding with puberty but can persist until, or initiate during, adulthood (the latter referred to as late adult onset). Dietary interventions to reduce acne severity have been investigated over the last decade suggesting there may be a beneficial role diet can play. Dairy products are the most researched, followed by glycaemic index and glycaemic load of carbohydrate-rich foods. Other food groups implicated in acne severity are dietary fats, fruits and vegetables. Alcohol, sugar sweetened beverages and chocolate consumption have also been linked with increased acne. There is currently no medical nutrition therapy protocol in place for health practitioners to help those living with acne. Dietary recommendations are suggested for Accredited Practising Dietitians to implement and assist those working as part of the multidisciplinary team in the acne setting.

KEYWORDS: Acne, Western diet, dairy, glycaemic index, nutrition and dietetics

Boccalatte I, Stewart K, Byrom L, De'Ambrosis B. The role of nutrition and dietetics in acne. Opin Prog Cosmet Dermatol 2022;2(2):40-44.

Introduction

Dietetic intervention utilising medical nutrition therapy for patients living with acne vulgaris is scarce in the literature. Dietetic research in the setting of acne remains largely anecdotal.[1] The lack of high quality dietetic investigations causes difficulty when applying dietary interventions at the patient level with the goal to reduce acne severity.[1] This justifies the need for rigorous dietetic research for those living with acne to provide complementary interventions with pharmaceutical treatment.

The current dietetic themes in the literature have been extensively based on the Westernised diet and its ability to increase acne severity.[2-4] The Westernised dietary pattern is characterised by energy dense, nutrient poor foods that are high in saturated fats accompanied by a high glycaemic index and load.[2] Emerging evidence around the Westernised trend of eating has been documented to aggravate acne severity.[2-4]

Acne aggravators

Glycaemic index and glycaemic load

Glycaemic index is the rate at which the carbohydrate in a food is digested, absorbed and metabolised and its subsequent effect on blood glucose.[5] This measurement allows carbohydrate-rich foods to be ranked according to quality. Glycaemic load is dependent on the glycaemic index (quality) and total available carbohydrate content (quantity) in a given amount of food.[5] Both increased glycaemic index and glycaemic load diets correlate with an increase in serum insulin like growth factor-1 (IGF-1) contributing to the acne

cascade.[6, 7] Studies have reported a reduction in IGF-1[7] and acne severity[6] with a low glycaemic index diet of two and ten weeks, respectively. More robust studies are required in this area.

Dairy products

Dairy products are a significant component of the Western diet as documented by the Australian Guide to Healthy Eating (AGHE).[8] There are limited good quality clinical trials evaluating dietary dairy intake and its association with acne. Dietary dairy intake has been investigated primarily through analysing cow's milk, not other types of dairy products such as yoghurt and cheese. Studies have consistently reported positive associations between total milk intake and acne in adolescent females and males.[9-11] It is unclear, however, if there are other components within cow's milk that exacerbate acne.

Three hypotheses have been put forward to explain how cow's milk can exacerbate acne. The first hypothesis suggests that low fat milk aggravates acne more than full fat milk. This has been supported in studies showing significant relationships between low fat milk and acne.[3, 12] The explanation for this relationship, however, is unclear. Hormonal components and bioactive molecules in milk may be responsible for this association.[11] Although, low fat milk (and other dairy) is recommended in the AGHE as the better choice for most Australians, according to these results, it may not be the ideal recommendation for acne sufferers.[8]

The second theory suggests that the quantity of milk consumed per week may increase acne severity. A longitudinal study completed in Norway found that more than two glasses of full fat cow's milk per day was associated with moderate to severe acne.[13] A further study reported that whole milk consumed on three or more days per week was associated with moderate to severe acne.[14] Neither of these studies found an association between the fat content of milk and acne.[13, 14] Consumption of more than three serves of milk per week has also demonstrated an increased risk.[3] Providing guidance on dietary restriction of cow's milk is difficult, due to the lack of data around recommended volumes across the day and week.

The third hypothesis proposes that the natural occurrence of IGF-1 in dairy promotes the acne cascade. IGF-1 can increase sebum production and hyperkeratinisation leading to acne formation.[15] An increase of milk intake has been found to increase plasma IGF-1[16] which in turn is associated with exacerbated acne.[17] Higher serum IGF-1 and more severe acne were found in adolescence compared to post-adolescence.[17] It might be possible that targeting IGF-1 through food for acne treatment is useful. More evidence, however, is required to support this before recommendations about reducing dairy intake can be made.

Lastly, there is emerging evidence suggesting that the amino acid leucine can increase acne severity. Leucine is present in cow's milk and meat, and is commonly used within whey-based protein supplements at high doses to facilitate muscle mass growth.[18, 19] Naturally occurring leucine may activate mammalian target of rapamycin complex 1 (mTORC1) promoting sebum production and hyperkeratinisation, thus, resulting in acne exacerbation.[15, 19] Again, more research needs to be conducted before recommendations about decreasing the intake of naturally occurring or supplemental leucine can be made.

Dietary fat intake

A balance of different types of fat in the diet is required for overall health. Dietary fats consist of polyunsaturated, monounsaturated, saturated and trans fatty acids. Polyunsaturated fats are found in salmon, walnuts and oils such as sunflower and safflower.[20] Saturated fats predominantly come from animal products (meat and dairy) but are also found in coconut oil and palm oil. Trans fats are those that are synthetically made through hydrogenation of vegetable oils.[20]

In a double blind, randomised controlled trial, 2000 mg of eicosapentaenoic acid and docosahexaenoic acid (omega-3 fatty acids) and 400 mg of gamma-linolenic acid (an omega 6 fatty acid) consumed daily for ten weeks were found to improve inflammatory and non-inflammatory acne lesions.[21] This study demonstrated daily polyunsaturated fatty acid supplementation reduced inflammatory markers, decreased IGF-1 and reduced acne lesions.[21] Manipulating dietary fat intake to include more polyunsaturated fatty acids, therefore, may limit inflammatory markers and may help reduce acne. More research conducted over longer time periods and with larger sample sizes is required.

Sugar sweetened beverages and alcohol

There is limited literature supporting the relationship between sugar sweetened beverages and alcohol consumption and acne severity. Huang and colleagues found that daily consumption of any sugar sweetened beverage exceeding 100 g of sugar (≈1 litre of cola) significantly increased the risk of moderate to severe acne in adolescents.[22] More studies are required to determine the applicability of these findings and to understand the association with acne in more detail.

Alcohol intake and acne has not been researched to date. Claudel et al. reported that alcohol intake increases androgens, an important acne trigger.[23] These authors suggested that acne may be exacerbated by the effect alcohol has on the body in relation to the immune system, the sweat content and the production of the bi-product acetaldehydes, all acting to increase the production of *Cutibacterium acnes* (*C. acnes*).[23]

A direct relationship between alcohol consumption and acne, however, has not been reported to date.

Chocolate

Although a very popular topic, the current body of evidence to suggest chocolate negatively effects acne is limited. One study found that adult males who were acne prone experienced a statistically significant flare in their acne after consuming 25 g of 99% dark chocolate daily over four weeks.[24] The mechanism of action was not determined, however, the researchers suggested that cocoa butter present in dark chocolate contains oleic acid which has been shown to increase keratinisation, thus contributing to acne exacerbation.[24] More evidence is required before chocolate can be attributed to acne exacerbation.

Acne saviours

Fruit and vegetable intake

The research regarding fruits and vegetables to improve acne specifically is limited and complex. As there are many components to fruits and vegetables, it is unclear as to what part directly helps with acne. Fruit and vegetable intake in addition to fish consumption was found to be significantly higher in those without acne.[25] The researchers suggested the antioxidants found in fruits and vegetables were helpful in reducing acne.[25] There is limited research supporting fruits and vegetables reduction of acne presence and severity, however, meeting fruit and vegetable intake guidelines every day supports overall health and wellbeing as per the AGHE.[8]

Potential acne eating plan

The current evidence does not support an "acne diet" per se, however, it does suggest consumption of energy dense, nutrient poor foods may contribute to acne. Consuming a well-balanced eating plan in line with the AGHE will promote overall health and wellbeing.[8] Accordingly, it is recommended that an Accredited Practising Dietitian is involved with patient care to provide specific nutritionally appropriate goals to allow acne sufferers to meet the AGHE.

The figure below demonstrates the summary of evidence in a practical form to help dermatologists determine when to refer on to a dietitian.

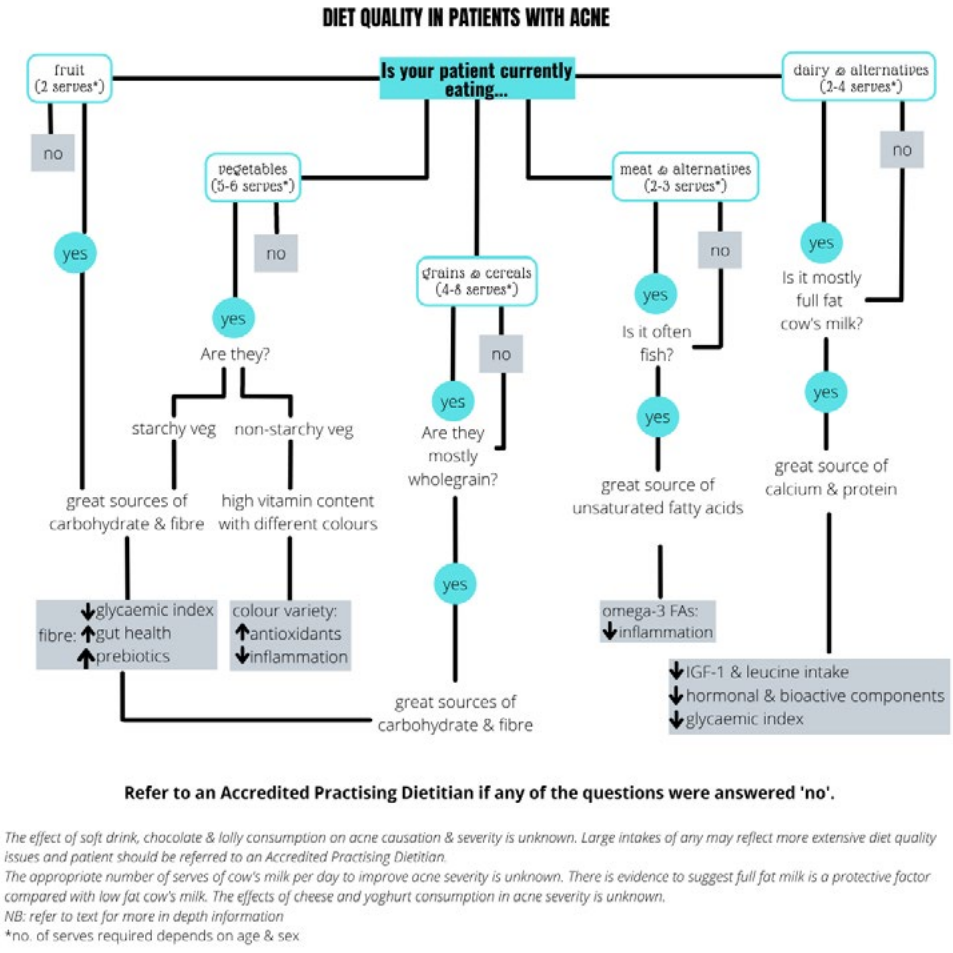


Figure 1. *A Dermatologist's Guide for Referring to an Accredited Practising Dietitian [reference to come]*

The sample meal plan below expresses in food terms, how to incorporate the evidence-based research into practice.

Acne clinic

Our experience with an acne clinic which provides holistic multidisciplinary team care to patients has been favourable. A general practitioner, dermatologist and an accredited practising dietitian are involved with psychology to be included. The primary goal is to provide the latest evidence-based research into patient care to reduce the severity of acne from all aspects of health. The clinic has been in operation since January 2020 and preliminary findings are showing positive results regarding combined medical and diet therapies.

Conclusions

The Westernised eating pattern encompasses energy dense, nutrient poor foods that may be acnegenic. To date, the consumption of full fat cow's milk over low fat milk to decrease acne severity has been evaluated but limited evidence regarding yoghurt and cheese has been reported. There is convincing evidence supporting the consumption of low glycaemic index and load diets to reduce acne severity. Dietary fats may have a role in influencing inflammatory markers, with promising evidence that polyunsaturated fats may reduce acne severity. The association of sugar sweetened beverages, alcohol and chocolate with acne exacerbation is limited with any mechanism of action still to be defined. Adequate fruit and vegetable consumption increases fibre intake, lowering the glycaemic index of the diet,

SAMPLE MEAL PLAN TO REDUCE ACNE SEVERITY

Meals should combine a low GI grain, a protein-rich food, a colour-rich food & sometimes some healthy fats

Breakfast	wholegrain cereal (e.g. oats, wheat biscuits) & 1tbs LSA (linseed, sunflower seeds & almonds) OR toast with healthy fat spread (e.g. peanut butter, avocado) + glass of full cream milk + piece of fresh fruit or some dried fruit
Lunch	1x wholegrain sandwich/toast/wrap + lean meat/chicken/tuna/eggs/legumes + 1-2 cups of salad + avocado
Dinner	wholegrain pasta/basmati rice + lean meat/chicken/salmon/legumes + ~2 cups of cooked vegetables or 2-3 cups of salad cooked with olive oil or peanut oil

The below should be included as extra parts of a meal or as between meal snacks/dessert

Extras	piece of fresh fruit or small handful of dried fruit or ½ cup of frozen fruit in a smoothie + 2 serves of either a glass of full cream milk or a small tub of yoghurt or 2 slices of cheese (in any combination) + handful of raw nuts or a small tin of baked beans or a boiled egg

Fluids: ~2L of water per day

Note:
a) Naturally occurring protein should be spread evenly throughout the day as this is best for good health and muscle mass gain.
b) Protein-rich foods + colour-rich foods + grain/starchy veg method is encouraged at breakfast, lunch and dinner to ensure meals are balanced.
c) Refer to the Australian Guide to Healthy Eating for portion sizes.
Disclaimer. This should be used as a guide only. This is not appropriate for all individuals living with (or without) acne. An accredited practising dietitian is required to assess cultural and dietary needs to formulate an individualised plan.

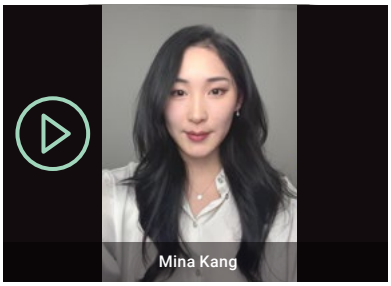
Figure 2. *Sample Meal Plan to Reduce Acne Severity [reference to come]*

and increases antioxidant intake, both helping to improve acne. The role of a multidisciplinary team in the acne setting is required to support medical interventions by advocating for nutritional adequacy to improve patient care holistically.

References

1. Fiedler F, Stangl GI, Fiedler E, Taube KM. Acne and Nutrition: A Systematic Review. Acta Derm Venereol. 2017;97(1):7-9.
2. Penso L, Touvier M, Deschasaux M, Szabo de Edelenyi F, Hercberg S, Ezzedine K, et al. Association Between Adult Acne and Dietary Behaviors: Findings From the NutriNet-Santé Prospective Cohort Study. JAMA Dermatol. 2020;156(8):854-62.
3. Di Landro A, Cazzaniga S, Parazzini F, Ingordo V, Cusano F, Atzori L, et al. Family history, body mass index, selected dietary factors, menstrual history, and risk of moderate to severe acne in adolescents and young adults. J Am Acad Dermatol. 2012;67(6):1129-35.
4. Burris J, Rietkerk W, Woolf K. Relationships of self-reported dietary factors and perceived acne severity in a cohort of New York young adults. J Acad Nutr Diet. 2014;114(3):384-92.
5. Augustin LSA, Kendall CWC, Jenkins DJA, Willett WC, Astrup A, Barclay AW, et al. Glycemic index, glycemic load and glycemic response: An International Scientific Consensus Summit from the International Carbohydrate Quality Consortium Nutr Metab Cardiovasc Dis. 2015;25(9):795-815.
6. Kwon HH, Yoon JY, Hong JS, Jung JY, Park MS, Suh DH. Clinical and histological effect of a low glycaemic load diet in treatment of acne vulgaris in Korean patients: a randomized, controlled trial. Acta Derm Venereol. 2012;92(3):241-6.
7. Burris J, Shikany JM, Rietkerk W, Woolf K. A Low Glycemic Index and Glycemic Load Diet Decreases Insulin-like Growth Factor-1 among Adults with Moderate and Severe Acne: A Short-Duration, 2-Week Randomized Controlled Trial. J Acad Nutr Diet. 2018;118(10):1874-85.
8. National Health and Medical Research Council. Australian Guide to Healthy Eating. https://www.eatforhealth.gov.au/guidelines/australian-guide-healthy-eating
9. Adebamowo CA, Spiegelman D, Berkey CS, Danby FW, Rockett HH, Colditz GA, et al. Milk consumption and acne in adolescent girls. Dermatol Online J. 2006;12(4):1.
10. Adebamowo CA, Spiegelman D, Berkey CS, Danby FW, Rockett HH, Colditz GA, et al. Milk consumption and acne in teenaged boys. J Am Acad Dermatol. 2008;58(5):787-93.
11. Adebamowo CA, Spiegelman D, Danby FW, Frazier AL, Willett WC, Holmes MD. High school dietary dairy intake and teenage acne. J Am Acad Dermatol. 2005;52(2):207-14.
12. LaRosa CL, Quach KA, Koons K, Kunselman AR, Zhu J, Thiboutot DM, et al. Consumption of dairy in teenagers with and without acne. J Am Acad Dermatol. 2016;75(2):318-22.
13. Ulvestad M, Bjertness E, Dalgard F, Halvorsen JA. Acne and dairy products in adolescence: results from a Norwegian longitudinal study. J Eur Acad Dermatol Venereol. 2017;31(3):530-5.
14. Aalemi AK, Anwar I, Chen H. Dairy consumption and acne: a case control study in Kabul, Afghanistan. Clin Cosmet Investig Dermatol. 2019;12:481-7.
15. Baldwin H, Tan J. Effects of Diet on Acne and Its Response to Treatment. Am J Clin Dermatol. 2021;22(1):55-65.
16. Romo Ventura E, Konigorski S, Rohrmann S, Schneider H, Stalla GK, Pischon T, et al. Association of dietary intake of milk and dairy products with blood concentrations of insulin-like growth factor 1 (IGF-1) in Bavarian adults. Eur J Nutr. 2020;59(4):1413-20.
17. Akpinar Kara Y. Evaluation of serum insulin-like growth factor-1, insulin, glucose levels in patients with adolescent and post-adolescent acne. J Cosmet Dermatol. 2022;21(3):1292-6.
18. Sports Dietitians Australia. Protein and Amino Acid Supplementation. https://www.sportsdietitians.com.au/wp-content/uploads/2015/04/110701-Protein-Supplementation_General.pdf
19. Melnik B. Dietary intervention in acne: Attenuation of increased mTORC1 signaling promoted by Western diet. Dermatoendocrinol. 2012;4(1):20-32.
20. National Health and Medical Research Council. Nutrient Reference Values for Australia and New Zealand. Fats: Total fat & fatty acids. https://www.nrv.gov.au/nutrients/fats-total-fat-fatty-acids
21. Jung JY, Kwon HH, Hong JS, Yoon JY, Park MS, Jang MY, et al. Effect of dietary supplementation with omega-3 fatty acid and gamma-linolenic acid on acne vulgaris: a randomised, double-blind, controlled trial. Acta Derm Venereol. 2014;94(5):521-5.
22. Huang X, Zhang J, Li J, Zhao S, Xiao Y, Huang Y, et al. Daily Intake of Soft Drinks and Moderate-to-Severe Acne Vulgaris in Chinese Adolescents. J Pediatr. 2019;204:256-262.e3.
23. Claudel JP, Auffret N, Leccia MT, Poli F, Dréno B. Acne and nutrition: hypotheses, myths and facts. J Eur Acad Dermatol Venereol. 2018;32(10):1631-7.
24. Vongraviopap S, Asawanonda P. Dark chocolate exacerbates acne. Int J Dermatol. 2016;55(5):587-91.
25. Di Landro A, Cazzaniga S, Cusano F, Bonci A, Carla C, Musumeci ML, et al. Adult female acne and associated risk factors: Results of a multicenter case-control study in Italy. J Am Acad Dermatol. 2016;75(6):1134-1141.e1.

Skin and gut microbiome: Good skin takes guts



CLICK IMAGE TO LINK TO VIDEO DURATION_00:54

Mina Kang[1,2], Philip L Tong[1,3,4], Nicholas P West[3]

1. Department of Dermatology, St Vincent's Hospital, Darlinghurst, NSW, Australia
2. Faculty of Medicine, University of New South Wales, Randwick, NSW, Australia
3. School of Pharmacy and Medical Science and Menzies Health Institute QLD, Griffith University, Parklands, QLD, Australia
4. The Skin Hospital, Darlinghurst, NSW, Australia

Correspondence: Mina Kang mina.kang@health.nsw.gov.au

Disclosures: PLT is a speaker for Bioderma, Galderma and Avene and served on the advisory board for Johnson and Johnson Asia Pacific.

OUTLINE: The human body is home to a dynamic ecosystem of the microbiome, in which there exists a symbiotic relationship between the host and the millions of commensal microorganisms. The microbiome relies on the host environment and its nutrients, and in return, the microbiome modulates the immune system, protects against pathogens, provides necessary metabolites and regulates cellular metabolism for healthy functioning of the host. The gut is home to the largest number of microorganisms of any organ, and maintaining homeostasis with the diversity of its commensal organisms is critical to optimal health and function. Considering the systemic immunomodulatory role of the gastrointestinal microbiome on organs like the skin, there has been heightened interest in the area of the 'gut-skin-axis'. The gut microbiome carries out important functions within the gastrointestinal tract, such as the metabolisation of non-fermentable fibres, vitamin synthesis and protection against pathogens. The microbiome can also alter gut epithelial integrity. Metabolite end-products, like short chain fatty acids, and translocation of bacteria have systemic immunomodulatory, metabolic and endocrine effects. Such systemic effects, in particular the effects on the immune system, have been shown to play pathogenic roles in various inflammatory skin conditions including acne vulgaris, atopic dermatitis and psoriasis. Treatment with probiotics and prebiotics to restore gut microbiome homeostasis and improve gut epithelial integrity has been trialled in numerous skin conditions, with promising early results in psoriasis. Continued clinical investigations are required to determine the dose and administration of specific probiotics and prebiotics for the treatment of inflammatory skin conditions. "Omics" approaches, a term used informally as branches of science in various disciplines of biology that end in the suffix -omics, that facilitate molecular and proteomic pathways in inflammatory skin conditions provide new pathways and molecules for personalised interventions.

KEYWORDS: Gut-skin-axis (GSA), microbiome, gut, acne, psoriasis, atopic dermatitis

Kang M, Tong PL, West NP. Skin and gut microbiome: Good skin takes guts. Opin Prog Cosmet Dermatol 2022;2(2):45-50.

Introduction

The human body is a dynamic ecosystem harbouring millions of microorganisms such as bacteria, viruses and fungi, collectively termed the microbiome. The expansive surface areas of the skin and gastrointestinal tract offer a large host area of population for the microbiome, where up to 1000 species colonise the gut of a healthy human adult.[1] The skin has an average surface area of 30 m^2, when including the various skin openings and appendages such as hair follicles, eccrine and apocrine ducts, and sebaceous glands and the gastrointestinal tract is lined by over 400 m^2 of intestinal epithelium.[2,3] Most of the microbiota of the skin and the gut are non-pathogenic, but consist of commensal microorganisms, in particular bacteria. They exist in a symbiotic relationship where the microbiota rely on the host environment and its nutrients,[4] and in return, the microbiome modulates the immune system, protects against pathogens, provides necessary metabolites and regulates cellular metabolism.[5,6] Thus, the skin and gut must maintain homeostasis with its diverse commensal organisms present on epithelial surfaces and dysbiosis may result in dysregulation of the immune system.

Considering the systemic immunomodulatory role of the gut microbiome on distant organs, such as the skin, there has recently been heightened interest in the 'gut-skin-axis'.[7] The concept of the 'brain-gut-skin-axis' was first conceptualised by Stokes and Pillsbury[8] in 1930 where it was hypothesised that negative

emotional states like depression and anxiety alter the gut function and result in changes of the normal gut flora, increased intestinal permeability and systemic inflammation. Since then, there has been increasing evidence that there is a complex interplay between the local gut microbiome and the innate and adaptive immune systems of the skin, or vice-versa. However, the exact mechanism, or the direction of causality remain poorly understood. There are several studies to suggest a bidirectional relationship between gut dysbiosis and skin homeostasis dysregulation, especially in the context of inflammatory skin conditions.[9-11] The aim of this review is to provide an overview of the gut microbiome and its relationship with skin immunity, in particular the hypothesised mechanisms of the gut-skin-axis, and review the literature on links between intestinal microbiome and skin diseases.

Gastrointestinal microbiome

The dynamic ecosystem of the gastrointestinal microbiome is home to myriad of distinct species of microorganisms that colonise the entire mucosal lining including bacteria, viruses protozoa and fungi.[12, 13] With the emergence of novel genomic sequencing techniques, over 10 million genes in the gut microbiome have been identified.[14] While the microbial composition of the skin is predominantly determined by the environment such as wet, dry and sebaceous areas,[14, 15] the gut microbiome is heavily reliant on several exogenous factors, such as diet, antibiotic use and obesity.[16-18] Bacteria are by far the most abundant kingdom of organisms colonising the gut and anaerobic bacteria such as phyla *Bacteroidetes* and *Firmicutes* are the most common types. Both the skin and gut rely on their commensal microbiota to maintain epithelial homeostasis and overall health of the tissue. The gut microbiome carries out a wide array of important functions within the gastrointestinal tract, a lot of which have systemic effects on the body.

Metabolic function and effects on metabolism and immunity

The gut microbiome is responsible for metabolising indigestible complex polysaccharides into essential nutrients such as vitamin K and B12, butyrate and propionate.[19, 20] Propionate in turn improves epithelial barrier integrity and protection from pathogens. Beyond this, the resultant metabolic by-products are anti-oncogenic as they have been shown to induce apoptosis in colorectal tumour cells.[21] Furthermore, the short-chain fatty acids (SFCAs) have the potential to alter the host's metabolism. SCFAs are released from the intestinal microbiome's metabolism of complex carbohydrates and fermentation of prebiotics as catabolic end-products. SFCAs enhance the epithelial barrier function and decrease the permeability of the intestinal barrier. Not only that, they alter the lipid metabolism of free fatty acids (FFAs).[22] FFAs have been shown to be inflammatory mediators by affecting gene expression of macrophages, adipocytes and endothelial cells, as well as modulating the release of chemokines and cytokines.[23-25] Further, SFCAs alter the activation and apoptosis of immune cells by inhibiting histone deacetylase and deactivating NF-kB signalling pathways. Histone deacetylase inhibition stimulates the proliferation of regulatory cells involved in numerous skin physiologic functions like regulation of hair follicle stem cell differentiation and wound healing.

Immune effects

The gut microbiome has immunomodulatory effects through additional pathways. Metabolites such as retinoic acid and polysaccharide A from *Bacteroides fragilis* and *Faecalibacterium prausnitzii*, and enhance accumulation of regulatory T cells and lymphocytes which promote anti-inflammatory responses.[26] In addition, epithelial-associated bacteria such as segmented filamentous bacteria adhere tightly to intestinal endothelial cells and stimulate T-helper 17 (Th17) and T-helper 1 (Th1) response to protect against pathogenic organisms.[27]

Endocrine effects

In addition to effects on the host's metabolism and immunity, the gut microbiome can also have systemic endocrine effects, releasing over 30 hormone-like compounds and neurotransmitters such as secondary bile acids, cortisol, serotonin, dopamine, tryptophan and ghrelin.[28] Not only that, there seems to be a bidirectional relationship where certain species of the microbiome respond to the hormonal output of the host. For example, increased levels of noradrenaline concentrations in acute stress stimulates the growth of non-pathogenic commensal *Escherichia coli* and other gram-negative bacteria.[29]

Links between intestinal microbiome and skin diseases

There has been heightened interest in research investigating the associations between the gut microbiome and dermatologic conditions such as acne vulgaris, atopic dermatitis, and psoriasis through direct changes in epithelial integrity and via immune regulation, and the production of secondary metabolites (Figure 1).

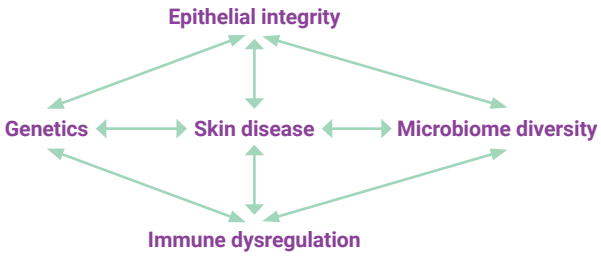


Figure 1. *The bi-directional relationship of the purported role of the microbiome with epithelial integrity and immune regulation in skin disease*

Acne vulgaris

Acne vulgaris is a common chronic inflammatory skin condition that involves the pilosebaceous unit. The pathogenesis includes increased sebum production, abnormal follicular keratinisation, dysregulation of the cutaneous microbiome related to *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*) resulting in a pro-inflammatory state. Acne vulgaris has much higher prevalence in Western countries, which is thought to be related to the Western diet that is high in glycaemic index. High glycaemic states promote the signalling of insulin and insulin-like growth factor-1 (IGF-1), which results in sebaceous gland hyperproliferation, lipogenesis and hyperplasia of acroinfundibular keratinocytes via the mTORC1 and FoxO1 pathway.

Gut microbiome dysbiosis has been shown to be associated with acne vulgaris, where such patients have a distinct gut microbiome composition, with decreased gut microbiome diversity, consisting of lower population of *Firmicutes*, compared to *Bacteroidetes*.[30] There is also overall decreased levels of probiotic species such as *Lactobacillus* and *Bifidobacterium* compared to the healthy population.[31] These species have anti-inflammatory functions via inducing regulatory dendritic cells and T cells resulting in hyporesponsive B cells and T helper cells as well as supressing cytokine production. The beneficial role of probiotics is also supported by several studies, albeit at varying levels of evidence, that demonstrated improvements in inflammatory acne lesions by 30% to 67% and reduction in serum levels of IGF-1 through daily consumption of probiotics for 4 months, in particular those containing *Lactobacillus*.[32-34] Although acne vulgaris is a complex pathology with multiple pathogenic mechanisms at play, the gastrointestinal microbiome appears to be an important factor that should not be overlooked.

Atopic dermatitis

Atopic dermatitis (AD) is the most prevalent chronic inflammatory skin disease, affecting one fifth of children worldwide.[35] Epithelial dysfunction and altered innate and adaptive immune responses in a genetically predisposed individual are the primary pathogenic drivers of AD.[36, 37] There has been a disproportionate rise of atopy disorders in developed nations compared to developing nations,[38] giving rise to the "hygiene hypothesis"[39] that postulates that environmental and nutritional factors may cause ecological dysbiosis of the skin, gut or lung microbiome, resulting in inappropriate Th2 responses to harmless antigens. This theory highlights the importance of early exposure to microbial antigens for appropriate Th1 mediated immunity, rather than the Th2 mediated response. This theory, however, does not explain the concurrent rise in prevalence of Th1-mediated autoimmune diseases in developed nations. More recently, the diet-microbiome[40-42] theory attributes the rise of allergic diseases to reduced robustness of immune homeostasis, rather than from overreaction to innocuous environmental cues. This is postulated to be due to the low fibre and high fat diet in Western countries, which alters the gut microbiome, and reduction in helpful immunomodulatory metabolites such as the SFCAs. Foods such as margarine, fish, ω-6 polyunsaturated fatty acid (PUFA), and ω-3 PUFA have been associated with AD.[43]

The association between gut dysbiosis and AD is supported in several other studies. In one study, the microbiome of patients with AD was higher in *Faecalibacterium prausnitzii*, with increased genes encoding for production of molecules that destroy intestinal epithelial integrity and decreased levels of helpful anti-inflammatory metabolites like butyrate and propionate.[42] Multiple studies demonstrated relative increase in pro-inflammatory bacteria such as *Clostridium* and *Escherichia*, and depletion in butyrate-producing (anti-inflammatory) bacteria such as *Coprococcus* in children with AD compared to the healthy counterparts. *Clostridium* and *Escherichia* lead to a pro-inflammatory state by contributing to overgrowth of pathogen bacteria in the gut, resulting in cytokine stimulation.[44-47] Inconsistent results were obtained from studies assessing the efficacy of probiotics in the treatment of AD. Meta-analysis results support the use of probiotics for treatment of AD in infants, but the World Allergy Organization likely attributes this benefit to primary prevention of AD.[48, 49] Future studies are required for more conclusive evidence on the impact of dietary modifications in managing AD.

Psoriasis

Psoriasis is an immune-mediated chronic relapsing-remitting inflammatory dermatosis, caused by complex interplay between exogenous and endogenous triggers in a genetically predisposed individual. It is primarily considered a Th17 disease with a major role for interleukin (IL)-23/IL-17-mediated inflammation, where tumour necrosis factor (TNF) enhances the inflammatory feedback loop. Improved understanding of the pathophysiology of psoriasis has revolutionised treatment methods with targeted biologic therapy. Gut microbiome dysbiosis has been reported in patients with psoriasis. Psoriasis patients have an overall decreased diversity of gut microbiota. Studies reported increased prevalence of *Firmicutes* and decreased prevalence of *Bacteroidetes* compared to controls, and the degree of this imbalance was proportional to the severity of symptoms.[50, 51] Reduced levels of *Faecalibacterium prausnitzii*, a major source of SCFAs, has also been reported in patients with psoriasis.[52] SCFAs play a critical role in regulating Th17-mediated response and therefore are closely related to the pathophysiology of psoriasis, highlighting a link between gut dysbiosis, SCFAs and immune dysregulation in this disease. Interestingly, the pattern

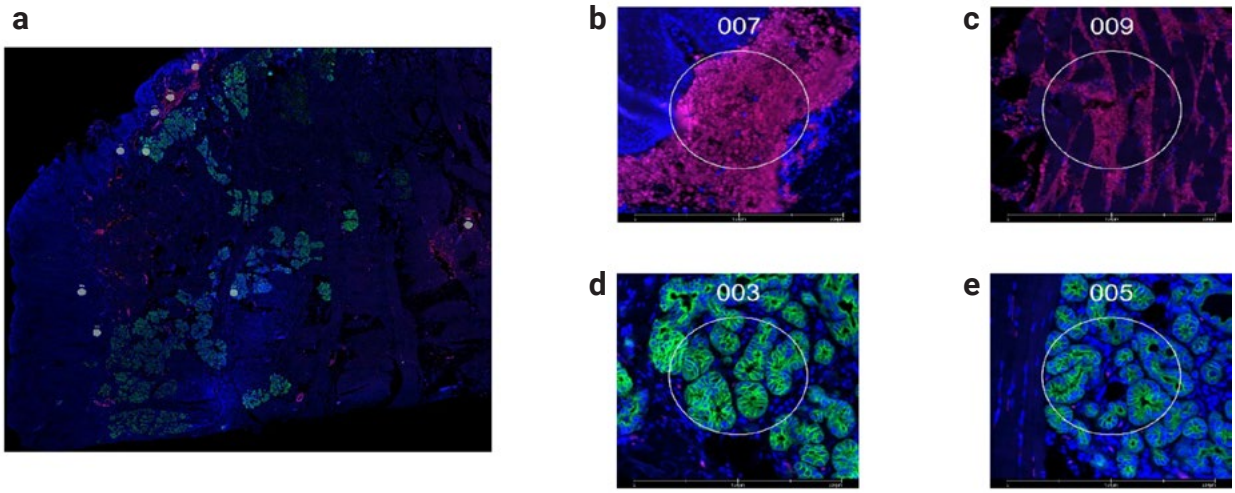


Figure 2. *An image of a gut tissue section from the NanoString GeoMx platform*

(a) *Whole slide mounted tissue stained with CK8/18, CD45 and FAP.*

(b-e) Regions of interest selected from the stained tissue for high-plex analysis.

The white highlighted sections in (a) are the regions of interest selected across the whole tissue.

of dysbiosis in psoriasis resembles that of inflammatory bowel disease, and the two pathologies often co-exist. Gut dysbiosis in psoriasis has also been evaluated for treatment with probiotics. A double blind placebo-controlled trial demonstrated improved reduction in Psoriatic Area and Severity Index (PASI) in patients treated with an oral probiotic mixture combined with topical betamethasone and calcipotriol versus without the probiotic mixture, and this effect was maintained at 6 months after intervention.[53] Recently, an oral derivative of a single strain of *Prevotella histicola* was tested for psoriasis, and shown to be effective in the imiquimod-induced murine psoriasis model, and was tested in a phase 2 trial in humans. The PASI reduction was 20% in the probiotic group, compared to 9% in the placebo group at 16 weeks. The effects were maintained 24 weeks after intervention.[54]

Future directions

Inflammatory skin conditions are heterogeneous with complex pathophysiology that encompasses immune and microbial elements.[55, 56] The innate epithelial/mucosal immune system of the gut and skin include a vast array of cells, chemical secreted factors and mechanical barriers with overlapping functions. This complexity requires the integration of immune and microbial data to identify networks driving dysregulation of homeostasis and inflammatory activity. Approaches that identify combinations of microbial and inflammatory biomarkers will allow for earlier diagnosis of immune/microbial dysregulation in the skin or increased susceptibility for inflammatory skin conditions. These biomarkers can also be monitored for responses to treatments and interventions.

The ability to utilise high-throughput genomic and proteomic methods to reveal interactions between complex biological processes has increased in recent years. These new technologies and data approaches allow for better characterisation, monitoring and prediction of disease processes and trajectories. New spatial profiling technologies, such as the NanoString GeoMx™ platform or the Fluidigm Helios™ Mass Cytometry platform, that allow for the identification and characterisation of molecules and cells in their morphological architecture hold promise for the development of new strategies and treatments for inflammatory skin conditions.[57, 58] The NanoString GeoMx platform allows for the quantification of protein and RNA at significantly higher multiplex levels than other technologies, (80-100 proteins and 18,000 RNA targets) from defined regions of interest within formalin-fixed paraffin embedded tissue (Figure 2). The multiplex nature of these platforms allows for assessment of immune and epithelial activity simultaneously. These *in vivo* technologies provide a unique opportunity to examine topical approaches that exert a local effect on the immune and microbial ecosystems of the skin. They also allow for the investigation of niches within the skin that may have specific impacts on disease severity and prevent signals from non-diseased skin from confusing understanding of the pathophysiological mechanisms underlying disease. Further to this, identification of local inflammatory targets or microbial species associated with inflammatory skin diseases will open up the potential to understand the pathophysiological mechanisms associated with other diseases of the skin.

Further to contemporary Omics approaches, research in the gut microbiota continues to expand with the use of metagenomics to understand the functional activities of local and intestinal microbes. While not yet conclusive, probiotics and prebiotics appear to have positive impacts on inflammatory skin conditions.[59] A better understanding of the structure and function of the microbiome, both locally and in the gut, will allow for targeted manipulation of the microbiome for specific benefits and the realisation of personalised approaches for inflammatory skin conditions.

Conclusion

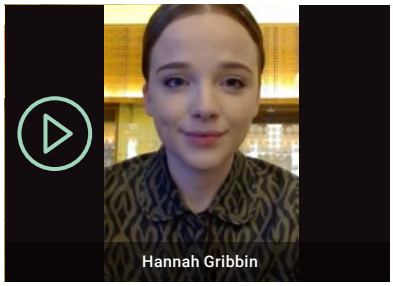
The gut microbiome plays a significant and yet complex immunomodulatory, metabolic and endocrine role in distant organs, in particular the skin. Heightened interest in the concept of the gut-skin-axis has revealed the pathogenic impact of gut microbiome dysbiosis in numerous inflammatory skin conditions including acne vulgaris, AD and psoriasis. Early research in the utility of probiotics and prebiotics in restoring the gut microbiome has shown potential in the field, in particular, for the treatment of psoriasis. The field of Omics approaches provide novel methods to explore the molecular and proteomic pathways in inflammatory skin conditions.

References

1. Zhao Q, Elson CO. Adaptive immune education by gut microbiota antigens. Immunology. 2018;154:28-37.
2. Eyerich S, Eyerich K, Traidl-Hoffmann C, Biedermann T. Cutaneous Barriers and Skin Immunity: Differentiating A Connected Network. Trends Immunol 2018; 39: 315-327.
3. Gallo RL. Human Skin Is the Largest Epithelial Surface for Interaction with Microbes. J Invest Dermatol. 2017;137:1213-4.
4. Harnett MM, Harnett W. Can Parasitic Worms Cure the Modern World's Ills? Trends Parasitol. 2017;33:694-705.
5. Thursby E, Juge N. Introduction to the human gut microbiota. Biochem J. 2017;474: 1823-36.
6. Tralau T, Sowada J, Luch A. Insights on the human microbiome and its xenobiotic metabolism: what is known about its effects on human physiology? Expert Opin Drug Metab Toxicol. 2015;11:411-25.
7. Arck P, Handjiski B, Hagen E, Pincus M, Bruenahl C, Bienenstock J, et al. Is there a 'gut-brain-skin axis'? Exp Dermatol. 2010;19:401-5.
8. Stokes JH, Pillsbury DM. The Effect on The Skin of Emotional and Nervous States: III. Theoretical and Practical Consideration of a Gastro-Intestinal Mechanism. Arch Derm Syphilol. 1930;22:962-93.
9. Shah KR, Boland CR, Patel M, Thrash B, Menter A. Cutaneous manifestations of gastrointestinal disease: part I. J Am Acad Dermatol. 2013;68:189.e1-21.
10. Thrash B, Patel M, Shah KR, Boland CR, Menter A. Cutaneous manifestations of gastrointestinal disease: part II. J Am Acad Dermatol. 2013;68:211.e211-33.
11. Rahvar M, Kerstetter J. Cutaneous manifestation of gastrointestinal disease. J Gastrointest Oncol. 2016;7:S44-54.
12. Diehm C, Trampisch HJ, Lange S, Schmidt C. Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency. Lancet. 1996;347:292-4.
13. Pelaseyed T, Bergström JH, Gustafsson JK, Ermund A, Birchenough GM, Schütte A, et al. The mucus and mucins of the goblet cells and enterocytes provide the first defense line of the gastrointestinal tract and interact with the immune system. Immunol Rev. 2014;260:8-20.
14. Grice EA, Kong HH, Conlan S, Deming CB, Davis J, Young AC, et al. Topographical and temporal diversity of the human skin microbiome. Science. 2009;324:1190-2.
15. Oh J, Byrd AL, Park M, NISC Comparative Sequencing Program, Kong HH, Segre JA. Temporal Stability of the Human Skin Microbiome. Cell. 2016;165:854-66.
16. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014;505:559-63.
17. Maurice CF, Haiser HJ, Turnbaugh PJ. Xenobiotics shape the physiology and gene expression of the active human gut microbiome. Cell. 2013;152:39-50.
18. Yallapragada SG, Nash CB, Robinson DT. Early-Life Exposure to Antibiotics, Alterations in the Intestinal Microbiome, and Risk of Metabolic Disease in Children and Adults. Pediatr Ann. 2015;44:e265-9.
19. Scott KP, Gratz SW, Sheridan PO, Flint HJ, Duncan SH. The influence of diet on the gut microbiota. Pharmacol Res. 2013;69:52-60.
20. LeBlanc JG, Milani C, de Giori GS, Sesma F, van Sinderen D, Ventura M. Bacteria as vitamin suppliers to their host: a gut microbiota perspective. Curr Opin Biotechnol. 2013;24:160-8.
21. Gläser R, Harder J, Lange H, Bartels J, Christophers E, Schröder JM. Antimicrobial psoriasin (S100A7) protects human skin from Escherichia coli infection. Nature Immunology. 2005;6:57-64.
22. Rodríguez-Carrio J, Salazar N, Margolles A, González S, Gueimonde M, de Los Reyes-Gavilán CG, et al. Free Fatty Acids Profiles Are Related to Gut Microbiota Signatures and Short-Chain Fatty Acids. Front Immunol. 2017;8:823.
23. Frommer KW, Schäffler A, Rehart S, Lehr A, Müller-Ladner U, Neumann E. Free fatty acids: potential proinflammatory mediators in rheumatic diseases. Ann Rheum Dis. 2015; 74: 303-310.
24. Schaeffler A, Gross P, Buettner R, et al. Fatty acid-induced induction of Toll-like receptor-4/nuclear factor-kappaB pathway in adipocytes links nutritional signalling with innate immunity. Immunology 2009; 126: 233-245.
25. Håversen L, Danielsson KN, Fogelstrand L, Wiklund O. Induction of proinflammatory cytokines by long-chain saturated fatty acids in human macrophages. Atherosclerosis 2009;202:382-93.
26. Forbes JD, Van Domselaar G, Bernstein CN. The Gut Microbiota in Immune-Mediated Inflammatory Diseases. Front Microbiol. 2016;7:1081.
27. Salem I, Ramser A, Isham N, Ghannoum MA. The Gut Microbiome as a Major Regulator of the Gut-Skin Axis. Front Microbiol. 2018;9:1459.
28. Clarke G, Stilling RM, Kennedy PJ, Stanton C, Cryan JF, Dinan TG. Minireview: Gut microbiota: the neglected endocrine organ. Mol Endocrinol. 2014;28:1221-38.
29. Lyte M, Ernst S. Catecholamine induced growth of gram negative bacteria. Life Sci. 1992;50:203-12.

30. Deng Y, Wang H, Zhou J, Mou Y, Wang G, Xiong X. Patients with Acne Vulgaris Have a Distinct Gut Microbiota in Comparison with Healthy Controls. Acta Derm Venereol. 2018;98:783-90.
31. Yan HM, Zhao HJ, Guo DY, Zhu PQ, Zhang CL, Jiang W. Gut microbiota alterations in moderate to severe acne vulgaris patients. J Dermatol. 2018;45:1166-71.
32. Fabbrocini G, Bertona M, Picazo Ó, Pareja-Galeano H, Monfrecola G, Emanuele E. Supplementation with Lactobacillus rhamnosus SP1 normalises skin expression of genes implicated in insulin signalling and improves adult acne. Benef Microbes. 2016; 7:625-30.
33. Jung GW, Tse JE, Guiha I, Rao J. Prospective, randomized, open-label trial comparing the safety, efficacy, and tolerability of an acne treatment regimen with and without a probiotic supplement and minocycline in subjects with mild to moderate acne. J Cutan Med Surg. 2013;17:114-22.
34. Kim J, Ko Y, Park YK, Kim NI, Ha WK, Cho Y. Dietary effect of lactoferrin-enriched fermented milk on skin surface lipid and clinical improvement of acne vulgaris. Nutrition. 2010;26:902-9.
35. Laughter D, Istvan JA, Tofte SJ, Hanifin JM. The prevalence of atopic dermatitis in Oregon schoolchildren. J Am Acad Dermatol. 2000;43:649-55.
36. Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. Allergy. 2014;69:17-27.
37. Kim JE, Kim HS. Microbiome of the Skin and Gut in Atopic Dermatitis (AD): Understanding the Pathophysiology and Finding Novel Management Strategies. J Clin Med. 2019;8(4):444.
38. Tan TH-T, Ellis JA, Saffery R, Allen KJ. The role of genetics and environment in the rise of childhood food allergy. Clin Exp Allergy. 2012;42:20-9.
39. Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989;299:1259-60.
40. Purchiaroni F, Tortora A, Gabrielli M, Bertucci F, Gigante G, Ianiro G, et al. The role of intestinal microbiota and the immune system. Eur Rev Med Pharmacol Sci. 2013; 17:323-33.
41. Kim HJ, Kim HY, Lee SY, Seo JH, Lee E, Hong SJ. Clinical efficacy and mechanism of probiotics in allergic diseases. Korean J Pediatr. 2013;56:369-76.
42. Song H, Yoo Y, Hwang J, Na YC, Kim HS. Faecalibacterium prausnitzii subspecies-level dysbiosis in the human gut microbiome underlying atopic dermatitis. J Allergy Clin Immunol. 2016;137:852-60.
43. Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. J Allergy Clin Immunol. 2005;115:1109-17.
44. Kalliomäki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. J Allergy Clin Immunol. 2001;107:129-34.
45. Penders J, Thijs C, van den Brandt PA, Kummeling I, Snijders B, Stelma F, et al. Gut microbiota composition and development of atopic manifestations in infancy: the KOALA Birth Cohort Study. Gut. 2007;56:661-7.
46. Lee E, Lee SY, Kang MJ, Kim K, Won S, Kim BJ, et al. Clostridia in the gut and onset of atopic dermatitis via eosinophilic inflammation. Ann Allergy Asthma Immunol. 2016; 117:91-92.e91.
47. Kirjavainen PV, Arvola T, Salminen SJ, Isolauri E. Aberrant composition of gut microbiota of allergic infants: a target of bifidobacterial therapy at weaning? Gut. 2002; 51:51-5.
48. Chang Y-S, Trivedi MK, Jha A, Lin YF, Dimaano L, García-Romero MT. Synbiotics for Prevention and Treatment of Atopic Dermatitis: A Meta-analysis of Randomized Clinical Trials. JAMA Pediatrics. 2016;170:236-42.
49. Zuccotti G, Meneghin F, Aceti A, Barone G, Callegari ML, Di Mauro A, et al. Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis. Allergy. 2015;70:1356-71.
50. Scher JU, Ubeda C, Artacho A, Attur M, Isaac S, Reddy SM, et al. Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. Arthritis Rheumatol. 2015;67:128-39.
51. Gao Z, Tseng C-h, Strober BE, Pei Z, Blaser MJ. Substantial Alterations of the Cutaneous Bacterial Biota in Psoriatic Lesions. PLoS One. 2008;3:e2719.
52. Eppinga H, Sperna Weiland CJ, Thio HB, van der Woude CJ, Nijsten TE, Peppelenbosch MP, et al. Similar Depletion of Protective Faecalibacterium prausnitzii in Psoriasis and Inflammatory Bowel Disease, but not in Hidradenitis Suppurativa. J Crohns Colitis. 2016;10:1067-75.
53. Navarro-López V, Martínez-Andrés A, Ramírez-Boscá A, Ruzafa-Costas B, Núñez-Delegido E, Carrión-Gutiérrez MA, et al. Efficacy and Safety of Oral Administration of a Mixture of Probiotic Strains in Patients with Psoriasis: A Randomized Controlled Clinical Trial. Acta Derm Venereol. 2019;99:1078-84.
54. Maslin D, Mihaylov Y, Macaro D, Carpenter N, Mehraei G, Bodmer M, et al. A phase 2 study investigating the effect of EDP1815, an orally-delivered, anti-inflammatory, gut-restricted commensal microbe in the treatment of mild and moderate plaque psoriasis. 2022 American Academy of Dermatology Annual Meeting. Boston, United States 2022.
55. Bay L, Ring HC. Human skin microbiota in health and disease: The cutaneous communities' interplay in equilibrium and dysbiosis: The cutaneous communities' interplay in equilibrium and dysbiosis. Apmis. 2021; Dec 17.
56. Sinha S, Lin G, Ferenczi K. The skin microbiome and the gut-skin axis. Clin Dermatol. 2021;39:829-39.
57. Wu J, Fang Z, Liu T, Hu W, Wu Y, Li S. Maximizing the Utility of Transcriptomics Data in Inflammatory Skin Diseases. Front Immunol. 2021;12:761890.
58. Piñeiro AJ, Houser AE, Ji AL. Research Techniques Made Simple: Spatial Transcriptomics. J Invest Dermatol. 2022;142:993-1001.e1.
59. Habeebuddin M, Karnati RK, Shiroorkar PN, Nagaraja S, Asdaq SMB, Khalid Anwer M, et al. Topical Probiotics: More Than a Skin Deep. Pharmaceutics. 2022;14(3):557.

Topical preparations for acne treatment



CLICK IMAGE TO LINK TO VIDEO DURATION_00:44

Hannah Gribbin[1, 2, 3, 4], Lisa Byrom[1, 4, 5, 6, 7]

1. South East Dermatology, Annerley, QLD, Australia
2. Sunshine Coast University Hospital, Dermatology Department, QLD, Australia
3. Princess Alexandra Hospital, Dermatology Department, QLD, Australia
4. University of Queensland, Brisbane, QLD, Australia
5. Dermatology Solutions, Rockhampton, QLD, Australia
6. Mater Hospital, Brisbane, QLD, Australia
7. Townsville University Hospital, QLD, Australia

Correspondence: Hannah Gribbin gribbinhannah@gmail.com

Disclosures: *none*

OUTLINE: Topical acne treatments are typically first line management for people with acne. These include washes, lotions, creams and gels and include active ingredients both as monotherapy and combination products. These products can be over-the-counter and prescription. We will review the most used ingredients within these products.

KEYWORDS: Acne, topical treatment, retinoids, antimicrobials, anti-androgens

Gribbin H, Byrom L. Topical preparations for acne treatment. Opin Prog Cosmet Dermatol 2022;2(2):51-58.

Introduction

Topical treatments for acne remain the cornerstone of acne management. We will review the current literature for over-the-counter and prescription formulations. Topical treatments for acne are chosen based on their specific properties, for example, anti-comedolytic, antibacterial and anti-inflammatory effects.

Over the counter preparations

In patients who are unable to tolerate or cannot use topical retinoids (e.g., those who are pregnant or breastfeeding) benzoyl peroxide (BPO), azelaic acid (AzA) and salicylic acid may offer effective alternatives.

A recent Cochrane review analysed trials that compared these common topical acne treatments.[1] While only low or moderate quality evidence was available, the review concluded that BPO was the most efficacious, and they were equivocal regarding tolerability.[1]

Benzoyl peroxide

BPO is an effective and comparatively affordable topical acne treatment. BPO's lipophilic nature enables it to penetrate the stratum corneum and concentrate in the sebaceous follicles, where it has bactericidal activity against *Cutibacterium acnes*, and exhibits mildly comedolytic, sebum-regulating and anti-inflammatory properties.[2] Studies have shown BPO to have comparable efficacy and tolerability to adapalene for comedonal acne.[3]

BPO prevents development of bacterial resistance when combined with both topical and oral antibiotics.[4] Furthermore, when combined with topical antibiotics, BPO improves efficacy, in comparison to topical antibiotics alone. Ninety percent of patients using topical BPO/clindamycin combination reported improvement at 12 weeks, compared with 45% of patients using topical clindamycin monotherapy.[5]

BPO is available in a several formulations (gels, washes, lotions and creams) and concentrations (2.5-10%).[5] Studies have not shown any preparation to have superior efficacy. Novel delivery systems for BPO, such as gel microsphere formulations, have not been thoroughly compared with existing preparations to demonstrate significant benefit.[6]

BPO concentration correlates with occurrence of adverse effects, such as application site irritation, dryness and erythema. High concentrations do not increase efficacy, thus, lower concentrations of BPO (2.5%, 5%) are generally preferable. In addition to

local adverse effects, patients should be warned about potential of BPO to bleach or discolour clothing. There are rare reports of hair bleaching by BPO.[4]

Azelaic acid

AzA primarily treats acne through its anti-comedonal properties, but also exhibits anti-inflammatory, antibacterial, anti-keratinising, antioxidant and tyrosinase-inhibiting effects.[6] AzA is also used in the treatment of post-inflammatory hyperpigmentation.

AzA is available in several concentrations (15% and 20%) and formulations, including lotions, creams and gels.[4] One study showed AzA 20% cream was effective in reducing both inflammatory and non-inflammatory acne lesions, with similar efficacy to topical 0.05% tretinoin.[7] Improvement in acne lesions generally occur within 4 weeks of commencing twice daily treatment with AzA.[6]

AzA has a favourable safety profile and there are no reports of bacterial resistance to AzA.[2] The most frequently reported adverse effects include burning/stinging/tingling, erythema and pruritus, and are generally most prominent in the first 4-8 weeks of treatment.[6] AzA may safely be used in pregnancy and breastfeeding.[8] However, AzA should be used with caution in patients with Fitzpatrick skin types IV-VI due to the risk of skin lightening.[9]

Niacinamide

The anti-inflammatory and sebostatic effects of niacinamide makes it an effective topical acne treatment. When applied twice daily, nicotinamide 5% gel can significantly improve acne.[10] Some studies have suggested that topical niacinamide 4% gel is as effective as topical clindamycin 1% gel and erythromycin 4% gel in clearing inflammatory acne lesions.[11] Niacinamide is often combined with other topical acne treatments, such as BPO. Evidence suggests that the combination of 2.5% BPO and 5% niacinamide is more effective than 2.5% BPO alone for treatment of mild to moderate facial acne vulgaris.[12]

Alpha hydroxy acids

Alpha hydroxy acids include lactic acid (from dairy and fermented vegetables), glycolic acid (from sugarcane) and malic acid (from apples). Alpha hydroxy acids promote skin peeling and limit follicular occlusion and, thus, have activity against acne lesions.[13] Evidence shows that a cleansing solution containing glycolic acid 1% results in a significant reduction in lesions when used daily for at least 6 weeks in patients with mild acne.[14] Furthermore, there is some evidence that alpha hydroxy acids may be helpful in improving acne scars. A small retrospective study demonstrated that >90% of patients treated with retinoic acid 0.025% and glycolic acid 12% showed significant reduction in acne scars over a 12-week period.[15]

Beta hydroxy acids

Beta hydroxy acids are closely related to alpha hydroxy acids but their two functional groups (carboxylic acid and hydroxy) are separated by two carbon atoms compared to one. These acids are derived from willow tree bark, wintergreen leaves or sweet birch bark.

Salicylic acid promotes corneocyte desquamation and subsequently exhibits comedolytic properties.[2] Salicylic acid is available over the counter in various concentrations (0.5-2%) in both leave-on and wash-off products.[4] Furthermore, dermatologists commonly offer salicylic acid treatment in higher concentrations as chemical peels.[16] Studies have shown salicylic acid to be only moderately effective in the treatment of comedonal acne, particularly when used as monotherapy, and is generally considered less potent than topical retinoids.[17] It has been suggested that salicylic acid be considered a third-line agent in topical acne treatment, predominantly offering an alternative treatment option in patients who are unable to tolerate topical retinoid therapy.[17] However, salicylic acid in combination with other acne treatments can be highly effective. A small single centre study comparing oral isotretinoin treatment with oral isotretinoin (20 mg daily) combined with 20% salicylic acid peels showed the combination treatment was significantly more effective in the first 12 weeks of treatment (93% reduction in acne lesion count, compared with 73%).[18]

Lipohydroxy acid is a beta hydroxy acid derived from salicylic acid and thus has skin comedolytic properties.[19] In one study, lipohydroxy acid demonstrated comparable efficacy to topical BPO in treating mild acne, while also showing greater tolerability.[19] Thus, lipohydroxy acid may have an important role in patients who are unable to tolerate topical BPO. Furthermore, lipohydroxy acid/BPO combination therapy has been shown to cause less erythema than combined topical BPO/clindamycin, while achieving similar rates of acne clearance.[20] Thus, lipohydroxy acid may provide an effective alternative to topical antibiotic combination therapy.

Sodium hypochlorite

In a double-blind randomised controlled trial, 0.005% sodium hypochlorite applied three times per day to facial acne resulted in a statistically significant decrease in acne lesions after one month of therapy, compared to placebo.[21] Sodium hypochlorite was demonstrated to be well-tolerated and safe.[21] Given its comparable affordability and few side effects, sodium hypochlorite may represent a suitable option for acne treatment in some patients.

Zinc

Zinc is a metallic element with bacteriostatic activity against *C. acnes* and when combined with antibiotics can reduce antibiotic resistance.[22] In a study comparing erythromycin 2% gel with combined zinc acetate

1.2%/erythromycin 2% gel, both topical treatments resulted in a significant decrease in acne lesions after only 3 weeks of treatment.[22] However, there was no statistical difference between erythromycin monotherapy and erythromycin-zinc combination therapy.[22] Thus, zinc may play a role in acne treatment with respect to reducing the risk of bacterial resistance to topical antibiotics.

Tea tree oil

Tea tree oil is commonly incorporated in over-the-counter topical acne treatments.[23] A review of the use of tea tree oil in acne found that patients with mild to moderate acne experienced a reduction in acne lesions (ranging from 23.7% to 62.1%) after 4-8 weeks of use.[23] Comparative studies demonstrated similar efficacy to topical BPO and erythromycin, though the quality of these studies is low[23].

Green tea extract

Green tea extract has anti-inflammatory and antioxidant properties. In a systematic review and meta-analysis topical application showed a significant reduction in inflammatory, but not non-inflammatory, lesions.[24] However, the quality of these studies was low.

Myrtle

Myrtle (*Myrtus communis*) has been used for the treatment of skin disease in Persian medicine. When used twice daily for 12 weeks its clinical efficacy was similar to 1% clindamycin lotion.[25]

Cedar

Cedar (*Ziziphus spina-christi*) has anti-bacterial activity and has also been used in the treatment of skin diseases in Persian medicine. In the treatment of mild to moderate acne, cedar solution combined with 1% clindamycin had led to statistically significant improvement in acne, compared to 1% clindamycin monotherapy at 6 weeks and 8 weeks.[26]

Topical antimicrobials

Antimicrobials are used for their action against *C. acnes* and anti-inflammatory properties.

Erythromycin, clindamycin

Historically, erythromycin and clindamycin have been the most commonly used antimicrobials in the treatment of acne.[27] Topical erythromycin is available in several different formulations, including gel, solution, ointment, pledget or thin film.[6] Efficacy of topical erythromycin in the treatment of acne has been demonstrated in numerous randomised studies.[28]

Topical clindamycin is available in gel, solution or lotion formulations.[27] Several studies have shown that topical clindamycin is more effective than placebo in the treatment of inflammatory acne lesions.[28] The use of topical clindamycin in acne treatment is generally considered safe, with the most common adverse effects being limited to cutaneous complications (erythema, dry skin, scaling, burning).[27] However, two cases of pseudomembranous colitis secondary to topical clindamycin have been reported in the literature.[29]

Due to concern around increasing *C. acnes* resistance with prolonged use, topical antimicrobials as monotherapy in the treatment of acne has essentially become extinct in routine clinically practice. Combinations with topical retinoids and BPO are clinically used and will be discussed later. By contrast, topical minocycline has lower rates of bacterial resistance.[30, 31]

Minocycline

Topical minocycline 4% foam is the first topical minocycline product. Unlike water-based topical agents, its high lipid content facilitates efficient drug delivery through sebum to the pilosebaceous units, with minimal penetration beyond the stratum corneum.[32]

Phase III clinical trials demonstrated that short-term treatment (12 weeks) with once-daily topical minocycline foam 4% significantly improved acne lesion counts in both paediatric (≥9 years) and adult patients, compared to foam vehicle placebo.[33, 34] Extension data demonstrated continued benefit for up to 52 weeks of therapy.[33, 34]

Topical minocycline foam was well tolerated by patients, over both short-term (12 weeks) and long-term (up to 52 weeks) treatment.[33, 35] The most common adverse effects reported by patients included application site discoloration, dry skin, pruritus and yellowing of nails.[33, 34] Studies have found no evidence of clinically relevant phototoxicity, photoallergy or sensitisation with topical minocycline foam treatment in healthy volunteers.[36]

Topical retinoids

Topical retinoids, as monotherapy or in combination with BPO or topical antibiotics, have been a mainstay of acne treatment since the development of the first retinoid approximately 50 years ago.[37] Retinoids have been shown to benefit both comedonal and inflammatory acne through binding to retinoic acid receptor (RARs) and subsequent downstream effects on comedolysis and reduction of microcomedonal formation.[38] Different retinoids have varying affinity for RAR subtypes (RAR-α, RAR-β, RAR-γ). There is no convincing evidence that retinoid receptor subtypes impact efficacy or tolerability.[37]

Several topical retinoids, in varying formulations, are available and regularly prescribed in Australia, and are summarised in the following table.

Table 1. Topical retinoids available in Australia

Retinoid	Trade names	Generation	Receptors	Formulation strength	Vehicle
Tretinoin	Retin A* Re Trieve Steiva-A	First	RAR–α RAR–β RAR–y	0.025% 0.05% 0.1%	Gel, cream, liquid, lotion, ointment, gel microsphere and polymer cream
Adapalene	Differin	Third	RAR–β RAR–y	0.1% 0.3%	Cream Gel
Tazarotene**	Zorac	Third	RAR–β RAR–y	0.05% 0.1%	Gel, cream and foam
Trifarotene	Aklief	Fourth	RAR–y	0.005%	Cream

**Retin A has been discontinued in Australia.*

***Tazarotene (as Zorac™) was discontinued in Australia in 2019, though may still be accessed through compounding pharmacies.*

Side effects of topical retinoids

The most common adverse effects reported by patients include dry skin, peeling and erythema, with most of these effects being mild in severity.[37, 38] All topical retinoids appear to cause comparable levels of skin irritation. However, studies have suggested that, compared to tretinoin and adapalene, tazarotene is associated with significantly greater levels of skin irritation at weeks 4 and 8 of treatment.[39, 40] This difference subsided by the end of the treatment course (week 12).[40] Generally, the tolerability of all topical retinoids improves after approximately 2–4 weeks of continuous treatment.[37]

Formulations

Topical retinoids are available in a wide variety of formulations, including gels, creams and lotions, as well as modern gel microsphere formulations. While there is no convincing evidence demonstrating superiority of effect or tolerability for any traditional formulation, there is some evidence to suggest that the development of gel microsphere formulations may help minimise irritation and improve patient adherence to treatment.[38, 41]

Tretinoin

Tretinoin was the first retinoid approved for use in acne treatment. A hydroalcoholic vehicle was used in its original formulation, and is now believed to be responsible for the significant application site irritation reported by patients.[42]

The efficacy of topical tretinoin in acne patients is well-established. There is evidence for improved efficacy with increasing concentration of tretinoin. In two separate studies, 12 weeks of tretinoin therapy (0.1% and 0.025%) reduced microcomedones by 80% and 35%, respectively.[43] However, when tretinoin is formulated in a gel microsphere, lower concentrations (0.04%) can be used without a reduction in efficacy.[44] Studies have suggested lower concentrations correlate with less initial skin dryness.[45]

Adapalene

Adapalene was specifically engineered to a particle size of 3-10 microns to enhance delivery to hair follicles, and is stable in the presence of UV light and BPO.[37, 46] Several studies have demonstrated the superior efficacy of adapalene over its vehicle in both cream and gel formulations.[47, 48] As with tretinoin, there is evidence that increased concentration of adapalene (0.1% vs 0.3% adapalene gel) provides a greater reduction of total acne lesions.[48]

Tazarotene

As with adapalene, tazarotene is stable to UV light.[38] Tazarotene has demonstrated clinical efficacy in acne treatment in several large, multicentre double-blind studies.[49, 50] Tazarotene in gel, cream and foam formulations, at concentrations of 0.05% and 0.1%, resulted in significantly improved non-inflammatory and inflammatory lesion counts, compared to vehicle placebo, over 12 weeks of treatment.[49, 51]

Trifarotene

The phase III PERFECT$_1$ and PERFECT$_2$ trials assessed the effect of trifarotene cream, versus cream vehicle, on moderate facial and truncal acne in 2420 participants over a 12-week period.[52] In both studies, trifarotene demonstrated significantly higher treatment success (clear or almost clear skin at week 12), and reduced

inflammatory and non-inflammatory lesion counts, compared to the vehicle cream.[52] Further research has established the long-term safety and efficacy of trifarotene in a 52-week phase III trial. However, cost may be a prohibitive factor for some patients.[53]

Currently, all published studies have assessed trifarotene as monotherapy and in the single strength (0.005%) cream formulation.[54] There are no studies comparing trifarotene efficacy and tolerability with that of older, clinically established retinoids.[53] As multi-agent treatment regimens form the majority of acne treatment plans, an upcoming study investigating the effect of trifarotene in combination with oral doxycycline will provide helpful information on how best to incorporate this novel agent into clinical practice.[54]

Dapsone

The clinical effects of dapsone on acne are due to both anti-inflammatory and anti-bacterial actions. A phase IV open-label 12-week study showed once daily dapsone 7.5% gel applied to the face, upper chest, upper back and shoulders was safe, effective and well-tolerated in patients 9 years and older.[55] After 4 weeks, facial acne was clear or almost clear in 47% of patients. Systemic absorption was assessed separately with dapsone applied under occlusion for one week and was reported as low.[55] Overall rates of adverse events were low with either no or mild stinging, dryness and erythema reported.[55]

Topical anti-androgen therapy

Topical anti-androgens are a new addition to the topical treatments for acne which may provide an alternative to patients unable to tolerate oral anti-androgenic agents.

Spironolactone

Topical spironolactone inhibits the binding of dihydrotestosterone to its receptor within sebocytes, resulting in inhibition of the sebocyte proliferation and a subsequent decrease in sebum production.[56] There is limited literature on the effect of topical spironolactone in the treatment of acne, with published studies on small patient cohorts.

Small studies have reported that patients with mild to moderate acne have a significant decrease in the number of papules and open and closed comedones after 4 and 8 weeks of treatment with spironolactone 5% cream or gel, compared to vehicle placebo.[56] However, effect on acne severity index is varied.[57] A comparative study of spironolactone 2% solution and clindamycin 1.5% solution demonstrated superiority of spironolactone in reducing the number of comedones and pustules, as well as acne severity index.[58]

Studies on topical spironolactone to date have confirmed its safety and tolerability in both female and male patients, with application site itch and irritation being the most commonly reported adverse effects.[56, 58]

Clascoterone

Clascoterone is a first-in-class topical androgen receptor inhibitor that competes with dihydrotestosterone for binding and, thus, reduces androgen-regulated lipid and inflammatory cytokines.[59] Efficacy of topical clascoterone 1% cream was confirmed in two large (n=1440), phase III randomised controlled trials in patients with moderate to severe acne (based on Investigator's Global Assessment). At 12 weeks, 16.1–18.7% of those in the treatment group versus 4.7–7.0% in the vehicle group had at least a 2-point reduction in IGA and were either 'clear' or 'almost clear' ($p < 0.01$).[60]

In these trials, clascoterone was well tolerated, with adverse effects reported at similar frequencies to the vehicle placebo. The most frequently reported adverse effects included dryness, erythema, pain, hypertrichosis, hypersensitivity and contact dermatitis.[60] A phase IIa study showed that 7% (3/42) patients demonstrated hypothalamic-pituitary-adrenal axis suppression after 2 weeks of clascoterone. This corrected within one month of ceasing clascoterone.[61] No clinically meaningful drug-drug interactions have been reported involving clascoterone; though this must be further elucidated. Animal studies provided mixed results regarding safety in pregnant and/or breastfeeding women. Thus, it is reasonable to advise this patient population to avoid clascoterone.[62]

To date, clascoterone has been studied as monotherapy only, and there are no head-to-head studies comparing clascoterone with traditional treatments in acne, such as topical retinoids. Consequently, its most appropriate use, potentially alongside existing acne treatments, is unknown.[62]

Clascoterone has been approved by the United States Food and Drug Administration for the topical treatment of acne in patients 12 years and older, though it is currently unavailable in Australia.[63]

Combination therapy

Combination therapy for the treatment of acne is widely prescribed and extensively cited throughout the literature as a highly effective treatment. Increasing rates of *C. acnes* resistance to topical antibiotics, especially when used as monotherapy, have resulted in current recommendations advising that they should only be prescribed in combination with BPO or topical retinoids.[64, 65]

There are many different combination treatments for acne. We will concentrate on the formulations available in Australia:

- BPO/clindamycin: "Duac"
- BPO/adapalene "EpiDuo", "EpiDuo Forte"
- Clindamycin/tretinoin "Acnatac"

BPO/topical antibiotics ("Duac")

Products containing BPO and topical antibiotics are most commonly used in fixed-dose combinations. In Australia, "Duac" gel, containing clindamycin 1%/BPO 5%, is the most widely available BPO/topical antibiotic combination therapy. Using BPO in combination with a topical antibiotic reduces antimicrobial resistance. Evidence shows that topical BPO/clindamycin combination gel significantly reduces both inflammatory and non-inflammatory acne lesion counts, outperforming both BPO and clindamycin monotherapy.[20, 66]

Furthermore, there is some evidence that topical BPO/antibiotic combination treatments result in less skin irritation than either compound used alone.[67] Given the convincing superiority of BPO/antibiotic combination therapy, particularly in the context of increasing rates of *C. acnes* resistance to topical antibiotics, it has been suggested that antibiotic monotherapy should be avoided entirely.

Topical retinoid/BPO

Fixed dose combinations of topical retinoid and BPO are available on the market as adapalene 0.1%/BPO 2.5% ("Epiduo") and adapalene 0.3%/BPO 2.5% ("EpiDuo Forte").

Topical retinoid/BPO combination therapy treats both inflammatory and non-inflammatory lesions, and results in faster, more complete clearance of acne, compared with its component monotherapies.[2] Evidence suggests a significant reduction (19%) in acne lesions after just 1 week of adapalene/BPO combination therapy compared with adapalene (11.3%) and BPO (13%) monotherapy.[68] Furthermore, at 12 weeks, the topical adapalene/BPO combination results in greater clearance rates of acne, relative to adapalene and BPO alone (70.5%, 50.4% and 53.7%, respectively).[68]

The tolerability profile of combined topical adapalene /BPO is comparable to adapalene monotherapy.[69]

Topical retinoid/topical antibiotic

In Australia, topical clindamycin and tretinoin are available in a fixed-dose combination as "Acnatac" (clindamycin 1%/tretinoin 0.025%). As with other combination therapies, topical clindamycin/tretinoin gel produces more rapid and complete clearance of acne lesions, compared to its individual components alone.[2]

In one study, the median time to 50% reduction in total acne lesions was 8 weeks with clindamycin/tretinoin combination therapy, which was significantly faster than each individual component alone (12% for both clindamycin and tretinoin).[70] Adverse effects of dryness and irritation reported by patients using clindamycin/tretinoin are similar to those using tretinoin alone.[2]

Future directions

Epidermal growth factor

A possible role for epidermal growth factor (EGF) in acne treatment was revealed after it was observed that patients on EGF inhibitors experienced acneiform reactions that responded to topical EGF.[71] A single-blinded, prospective study showed that patients with mild to moderate acne had a significant reduction in both acne lesion and acne scar counts after 12 weeks of twice daily EGF ointment use.[71] Histological evaluation of the treated areas showed decreased expression of keratin 16, NF-κB, p65, interleukin (IL)-1α, and IL-8, and increased expression of transforming growth factor (TGF)-β1, elastin, and collagen type 1, 3 after treatment.[71]

Topical bakuchiol

Backuchiol is a plant-derived compound with anti-inflammatory and anti-oxidant properties.[72] In an open-label pilot study (ISRCTN13992386) patients with Fitzpatrick skin types III and IV with mild or moderate acne had twice daily application for 12 weeks. There was significant reduction in inflammatory lesion counts and reduction in existing post-inflammatory hyperpigmentation. This formulation was well tolerated by all subjects.[72]

Conclusion

Topical therapies for acne are often readily available as over the counter products. Many patients may have previously used these products or are currently on them. Topical acne formulations can be complementary to each other and oral treatments. It is important to match your patients' skin type and acne subtype with the best combination of skin care and active topical formulations for optimal response.

References

1. Liu H, Yu H, Xia J, Liu L, Liu GJ, Sang H, et al. Topical azelaic acid, salicylic acid, nicotinamide, sulphur, zinc and fruit acid (alpha-hydroxy acid) for acne. Cochrane Database Syst Rev. 2020;5:CD011368.
2. Valente Duarte de Sousa IC. Guidance for the pharmacological management of acne vulgaris. Expert Opin Pharmacother. 2022;23(1):49-62.

3. Thiboutot DM, Weiss J, Bucko A, Eichenfield L, Jones T, Clark S, et al. Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: results of a multicenter, randomized double-blind, controlled study. J Am Acad Dermatol. 2007;57(5):791-9.
4. Eichenfield DZ, Sprague J, Eichenfield LF. Management of Acne Vulgaris: A Review. JAMA. 2021;326(20):2055-67.
5. Mohd Nor NH, Aziz Z. A systematic review of benzoyl peroxide for acne vulgaris. J Dermatolog Treat. 2013;24(5):377-86.
6. Otlewska A, Baran W, Batycka-Baran A. Adverse events related to topical drug treatments for acne vulgaris. Expert Opin Drug Saf. 2020;19(4):513-21.
7. Katsambas A, Graupe K, Stratigos J. Clinical studies of 20% azelaic acid cream in the treatment of acne vulgaris. Comparison with vehicle and topical tretinoin. Acta Derm Venereol Suppl (Stockh). 1989;143:35-9.
8. Kong YL, Tey HL. Treatment of acne vulgaris during pregnancy and lactation. Drugs. 2013;73(8):779-87.
9. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. Lancet. 2012;379(9813):361-72.
10. Shahmoradi Z, Iraji F, Siadat AH, Ghorbaini A. Comparison of topical 5% nicotinamid gel versus 2% clindamycin gel in the treatment of the mild-moderate acne vulgaris: A double-blinded randomized clinical trial. J Res Med Sci. 2013;18(2):115-7.
11. Khodaeiani E, Fouladi RF, Amirnia M, Saeidi M, Karimi ER. Topical 4% nicotinamide vs. 1% clindamycin in moderate inflammatory acne vulgaris. Int J Dermatol. 2013;52(8):999-1004.
12. Kaewsanit T, Chakkavittumrong P, Waranuch N. Clinical Comparison of Topical 2.5% Benzoyl Peroxide plus 5% Niacinamide to 2.5% Benzoyl Peroxide Alone in the Treatment of Mild to Moderate Facial Acne Vulgaris. J Clin Aesthet Dermatol. 2021;14(6):35-41.
13. Conforti C, Giuffrida R, Fadda S, Fai A, Romita P, Zalaudek I, et al. Topical dermocosmetics and acne vulgaris. Dermatol Ther. 2021;34(1):e14436.
14. Abels C, Reich H, Knie U, Werdier D, Lemmnitz G. Significant improvement in mild acne following a twice daily application for 6 weeks of an acidic cleansing product (pH 4). J Cosmet Dermatol. 2014;13(2):103-8.
15. Chandrashekar BS, Ashwini KR, Vasanth V, Navale S. Retinoic acid and glycolic acid combination in the treatment of acne scars. Indian Dermatol Online J. 2015;6(2):84-8.
16. Arif T. Salicylic acid as a peeling agent: a comprehensive review. Clin Cosmet Investig Dermatol. 2015;8:455-61.
17. Araviiskaia E, Dreno B. The role of topical dermocosmetics in acne vulgaris. J Eur Acad Dermatol Venereol. 2016;30(6):926-35.
18. Kar BR, Tripathy S, Panda M. Comparative study of oral isotretinoin versus oral isotretinoin + 20% salicylic Acid peel in the treatment of active acne. J Cutan Aesthet Surg. 2013;6(4):204-8.
19. Zeichner JA. The Use of Lipohydroxy Acid in Skin Care and Acne Treatment. J Clin Aesthet Dermatol. 2016;9(11):40-43.
20. Draelos ZD, Shalita AR, Thiboutot D, Oresajo C, Yatskayer M, Raab S. A multicenter, double-blind study to evaluate the efficacy and safety of 2 treatments in participants with mild to moderate acne vulgaris. Cutis. 2012;89(6):287-93.
21. Dorostkar A, Ghahartars M, Namazi M, Todarbary N, Hadibarhaghtalab M, Rezaee M. Sodium Hypochlorite 0.005% Versus Placebo in the Treatment of Mild to Moderate Acne: A Double-Blind Randomized Controlled Trial. Dermatol Pract Concept. 2021;11(3):e2021046.
22. Sayyafan MS, Ramzi M, Salmanpour R. Clinical assessment of topical erythromycin gel with and without zinc acetate for treating mild-to-moderate acne vulgaris. J Dermatolog Treat. 2020;31(7):730-33.
23. Hammer KA. Treatment of acne with tea tree oil (melaleuca) products: a review of efficacy, tolerability and potential modes of action. Int J Antimicrob Agents. 2015;45(2):106-10.
24. Kim S, Park TH, Kim WI, Park S, Kim JH, Cho MK. The effects of green tea on acne vulgaris: A systematic review and meta-analysis of randomized clinical trials. Phytother Res. 2021;35(1):374-83.
25. Salmanian M, Shirbeigi L, Hashem-Dabaghian F, Mansouri P, Azizkhani M, Alavi S, et al. The Effects of Myrtle (Myrtus communis) and Clindamycin Topical Solution in the Treatment of Mild to Moderate Acne Vulgaris: A Comparative Split-Face Study. J Pharmacopuncture. 2020;23(4):220-9.
26. Shakiba R, Nilforoushzadeh MA, Hashem-Dabaghian F, Minaii Zangii B, Ghobadi A, Shirbeigi L, et al. Effect of Cedar (Ziziphus spina-christi) topical solution in mild to moderate acne vulgaris: a randomized clinical study. J Dermatolog Treat. 2021;32(2):197-202.
27. Tripathi SV, Gustafson CJ, Huang KE, Feldman SR. Side effects of common acne treatments. Expert Opin Drug Saf 2013;12(1):39-51.
28. Bonati LM, Dover JS. Treating Acne With Topical Antibiotics: Current Obstacles and the Introduction of Topical Minocycline as a New Treatment Option. J Drugs Dermatol. 2019;18(3):240-44.
29. Parry MF, Rha CK. Pseudomembranous colitis caused by topical clindamycin phosphate. Arch Dermatol. 1986;122(5):583-4.
30. Xu H, Li H. Acne, the Skin Microbiome, and Antibiotic Treatment. Am J Clin Dermatol. 2019;20(3):335-44.
31. Biswal I, Gaind R, Kumar N, Mohanty S, Manchanda V, Khunger N, et al. In vitro antimicrobial susceptibility patterns of Propionibacterium acnes isolated from patients with acne vulgaris. J Infect Dev Ctries. 2016;10(10):1140-5.
32. Onge ES, Mobley WC. Minocycline Topical Foam: A New Drug for the Treatment of Acne. Ann Pharmacother. 2021;55(1):105-10.
33. Raoof TJ, Hooper D, Moore A, Zaiac M, Sullivan T, Kircik L, et al. Efficacy and safety of a novel topical minocycline foam for the treatment of moderate to severe acne vulgaris: A phase 3 study. J Am Acad Dermatol 2020;82(4):832-7.
34. Gold LS, Dhawan S, Weiss J, Draelos ZD, Ellman H, Stuart IA. A novel topical minocycline foam for the treatment of moderate-to-severe acne vulgaris: Results of 2 randomized, double-blind, phase 3 studies. J Am Acad Dermatol. 2019;80(1):168-77.
35. Stein Gold L, Dhawan S, Weiss J, Draelos ZD, Ellman H, Stuart I. Open-label Extension Study Evaluating Long-term Safety and Efficacy of FMX101 4% Minocycline Foam for Moderate-to-Severe Acne Vulgaris. J Clin Aesthet Dermatol. 2019;12(10):16-23.
36. Dosik J, Ellman H, Stuart I. Topical minocycline foam 4%: Results of four phase 1 studies evaluating the potential for phototoxicity, photoallergy, sensitization, and cumulative irritation. J Immunotoxicol. 2019;16(1):133-9.
37. Baldwin H, Webster G, Stein Gold L, Callender V, Cook-Bolden FE, Guenin E. 50 Years of Topical Retinoids for Acne: Evolution of Treatment. Am J Clin Dermatol 2021;22(3):315-27.
38. Kolli SS, Pecone D, Pona A, Cline A, Feldman SR. Topical Retinoids in Acne Vulgaris: A Systematic Review. Am J Clin Dermatol 2019;20(3):345-65.
39. Webster GF, Berson D, Stein LF, Fivenson DP, Tanghetti EA, Ling M. Efficacy and tolerability of once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.025% gel in the treatment of facial acne vulgaris: a randomized trial. Cutis. 2001;67(6 Suppl):4-9.

40. Shalita A, Miller B, Menter A, Abramovits W, Loven K, Kakita L. Tazarotene cream versus adapalene cream in the treatment of facial acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. J Drugs Dermatol. 2005;4(2):153-8.
41. Kircik LH. Microsphere technology: hype or help? J Clin Aesthet Dermatol. 2011;4(5):27-31.
42. Rigopoulos D, Ioannides D, Kalogeromitros D, Katsambas AD. Comparison of topical retinoids in the treatment of acne. Clin Dermatol. 2004;22(5):408-11.
43. Lavker RM, Leyden JJ, Thorne EG. An ultrastructural study of the effects of topical tretinoin on microcomedones. Clin Ther. 1992;14(6):773-80.
44. Eichenfield LF, Nighland M, Rossi AB, Cook-Bolden F, Grimes P, Fried R, et al. Phase 4 study to assess tretinoin pump for the treatment of facial acne. J Drugs Dermatol. 2008;7(12):1129-36.
45. Berger R, Rizer R, Barba A, Wilson D, Stewart D, Grossman R, et al. Tretinoin gel microspheres 0.04% versus 0.1% in adolescents and adults with mild to moderate acne vulgaris: a 12-week, multicenter, randomized, double-blind, parallel-group, phase IV trial. Clin Ther. 2007;29(6):1086-97.
46. Shroot B. Pharmacodynamics and pharmacokinetics of topical adapalene. J Am Acad Dermatol. 1998;39(2 Pt 3):S17-24.
47. Lucky A, Jorizzo JL, Rodriguez D, Jones TM, Stewart DM, Tschen EH, et al. Efficacy and tolerance of adapalene cream 0.1% compared with its cream vehicle for the treatment of acne vulgaris. Cutis. 2001;68(4 Suppl):34-40.
48. Thiboutot D, Pariser DM, Egan N, Flores J, Herndon JH Jr, Kanof NB, et al. Adapalene gel 0.3% for the treatment of acne vulgaris: a multicenter, randomized, double-blind, controlled, phase III trial. J Am Acad Dermatol. 2006;54(2):242-50.
49. Shalita AR, Chalker DK, Griffith RF, Herbert AA, Hickman JG, Maloney JM, et al. Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicenter, double-blind, vehicle-controlled study. Cutis. 1999;63(6):349-54.
50. Shalita AR, Berson DS, Thiboutot DM, Leyden JJ, Parizadeh D, Sefton J, et al. Effects of tazarotene 0.1 % cream in the treatment of facial acne vulgaris: pooled results from two multicenter, double-blind, randomized, vehicle-controlled, parallel-group trials. Clin Ther. 2004;26(11):1865-73.
51. Feldman SR, Werner CP, Alio Saenz AB. The efficacy and tolerability of tazarotene foam, 0.1%, in the treatment of acne vulgaris in 2 multicenter, randomized, vehicle-controlled, double-blind studies. J Drugs Dermatol. 2013;12(4):438-46.
52. Tan J, Thiboutot D, Popp G, Gooderham M, Lynde C, Del Rosso J, et al. Randomized phase 3 evaluation of trifarotene 50 mug/g cream treatment of moderate facial and truncal acne. J Am Acad Dermatol. 2019;80(6):1691-9.
53. Bell KA, Brumfiel CM, Haidari W, Boger L. Trifarotene for the Treatment of Facial and Truncal Acne. Ann Pharmacother. 2021;55(1):111-6.
54. Brumfiel CM, Patel MH, Bell KA, Cardis MA. Assessing the Safety and Efficacy of Trifarotene in the Treatment of Acne Vulgaris. Ther Clin Risk Manag. 2021;17:755-63.
55. Moore AY, Lain EL, McMichael A, Kircik L, Zaenglein AL, Hebert AA, et al. Once-daily Dapsone 7.5% Gel for the Treatment of Acne Vulgaris in Preadolescent Patients: A Phase IV, Open-label, 12-week Study. J Clin Aesthet Dermatol. 2021;14(4):43-8.
56. Ayatollahi A, Samadi A, Bahmanjahromi A, Robati RM. Efficacy and safety of topical spironolactone 5% cream in the treatment of acne: A pilot study. Health Sci Rep. 2021;4(3):e317.
57. Afzali BM, Yaghoobi E, Yaghoobi R, Bagherani N, Dabbagh MA. Comparison of the efficacy of 5% topical spironolactone gel and placebo in the treatment of mild and moderate acne vulgaris: a randomized controlled trial. J Dermatolog Treat. 2012;23(1):21-5.
58. Noaimi A, Al-Saadi SR. Treatment of Acne Vulgaris by Topical Spironolactone Solution Compared With Clindamycin Solution. Cureus. 2021;13(8):e17606.
59. Rosette C, Agan FJ, Mazzetti A, Moro L, Gerloni M. Cortexolone 17alpha-propionate (Clascoterone) Is a Novel Androgen Receptor Antagonist that Inhibits Production of Lipids and Inflammatory Cytokines from Sebocytes In Vitro. J Drugs Dermatol. 2019;18(5):412-8.
60. Hebert A, Thiboutot D, Stein Gold L, Cartwright M, Gerloni M, Fragasso E, et al. Efficacy and Safety of Topical Clascoterone Cream, 1%, for Treatment in Patients With Facial Acne: Two Phase 3 Randomized Clinical Trials. JAMA Dermatol. 2020;156(6):621-30.
61. Mazzetti A, Moro L, Gerloni M, Cartwright M. Pharmacokinetic Profile, Safety, and Tolerability of Clascoterone (Cortexolone 17-alpha propionate, CB-03-01) Topical Cream, 1% in Subjects With Acne Vulgaris: An Open-Label Phase 2a Study. J Drugs Dermatol. 2019;18(6):563.
62. Piszczatoski CR, Powell J. Topical Clascoterone: The First Novel Agent for Acne Vulgaris in 40 Years. Clin Ther. 2021;43(10):1638-44.
63. Dhillon S. Clascoterone: First Approval. Drugs. 2020;80(16):1745-50.
64. Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74(5):945-73.e33.
65. Nast A, Dreno B, Bettoli V, Degitz K, Erdmann R, Finlay AY, et al. European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol Venereol. 2012;26 Suppl 1:1-29.
66. Thiboutot D, Zaenglein A, Weiss J, Webster G, Calvarese B, Chen D. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for the once-daily treatment of moderate to severe acne vulgaris: assessment of efficacy and safety in 2813 patients. J Am Acad Dermatol. 2008;59(5):792-800.
67. Ozolins M, Eady EA, Avery AJ, Cunliffe WJ, Po AL, O'Neill C, et al. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. Lancet. 2004;364(9452):2188-95.
68. Tan J, Gollnick HP, Loesche C, Ma YM, Gold LS. Synergistic efficacy of adapalene 0.1%-benzoyl peroxide 2.5% in the treatment of 3855 acne vulgaris patients. J Dermatolog Treat. 2011;22(4):197-205.
69. Tan JK. Adapalene 0.1% and benzoyl peroxide 2.5%: a novel combination for treatment of acne vulgaris. Skin Therapy Lett. 2009;14(6):4-5.
70. Dreno B, Thiboutot D, Gollnick H, Bettoli V, Kang S, Leyden JJ, et al. Antibiotic stewardship in dermatology: limiting antibiotic use in acne. Eur J Dermatol. 2014;24(3):330-4.
71. Kim DH, Yang JH, Cho SI, Yoon JY, Kim JW, Choi S, et al. Clinical and Histological Effects of Topical Epidermal Growth Factor on Acne and Acne Scars. Dermatology. 2022:1-9.
72. Brownell L, Geen S, Yapping E, Lee WL. A Clinical Study Evaluating the Efficacy of Topical Bakuchiol (UP256) Cream on Facial Acne. J Drugs Dermatol. 2021;20(3):307-10.

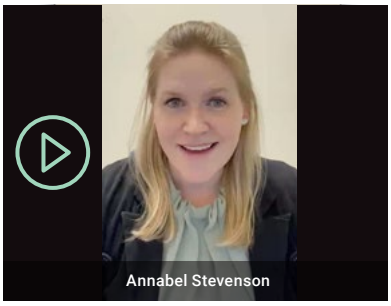
Systemic therapies for acne

Annabel I Stevenson[1]

1. The Queen Elizabeth Hospital and Dermatology SA, Adelaide, SA, Australia

Correspondence: Annabel I Stevenson stevenson.bel@gmail.com

Disclosures: *tbc*



CLICK IMAGE TO LINK TO VIDEO DURATION_00:39

OUTLINE: Systemic therapies for acne are used when there is a risk of scarring in severe acne, or if moderate acne fails to respond. In addition to oral antibiotics, other therapies can help, including hormonal agents and oral retinoids. Prior to prescribing, the fertility plans of the patient must be discussed and appropriate contraception planned if needed. This review will examine the main clinical considerations for each medication and delve into controversies surrounding some of the systemic therapies.

KEYWORDS: Antibiotics, isotretinoin, scarring, oral contraceptive pill

Stevenson AI. Systemic therapies for acne. Opin Prog Cosmet Dermatol 2022;2(2):59-64.

Acne vulgaris affects more than 90% of Australians in late adolescence and the spectrum of disease is wide. The general principles of managing acne would aim to prevent permanent scarring at all costs using the least invasive modalities (i.e., generally topicals would first be trialled unless scarring was evident at presentation). Systemic therapies can be used – often added to the regimen – when topical therapies fail as monotherapy (Table 1).[1] Systemic therapies may include oral antibiotics, oral retinoids, hormonal therapies as well as some emerging therapies and are summarised below.

Table 1. Proposed treatment algorithm for acne vulgaris[1]

	MILD	MODERATE	SEVERE
1st line treatment	benzoyl peroxide (BP) or topical retinoid -or- topical combination therapy** BP + antibiotic or retinoid + BP or retinoid + BP + antibiotic	topical combination therapy** BP + antibiotic or retinoid + BP or retinoid + BP + antibiotic -or- oral antibiotic + topical retinoid + BP -or- oral antibiotic + topical retinoid + BP + topical antibiotic	oral antibiotic + topical combination therapy** BP + antibiotic or retinoid + BP or retinoid + BP + antibiotic -or- oral isotretinoin
Alternative treatment	add topical retinoid or BP (if not on already) -or- consider alternate retinoid -or- consider topical dapsone	consider alternate combination therapy -or- consider change in oral antibiotic -or- add combined oral contraceptive or oral spironolactone (females) -or- consider oral isotretinoin	consider change in oral antibiotic -or- add combined oral contraceptive or oral spironolactone (females) -or- consider oral isotretinoin

Oral antibiotics

Oral antibiotics utilise their dual mechanisms of lowering inflammation and inhibiting the proliferation of *Cutibacterium acnes* within the pilosebaceous unit to reduce acne lesion counts. Different classes of antibiotics may be used, however the tetracyclines reign in importance. It is recommended that oral antibiotics be used in conjunction with either benzoyl peroxide and/or a topical retinoid to reduce antibiotic resistance (Table 1).[1] Use should be restricted to 3–4 months before re-evaluation to minimise bacterial resistance (the risk of which increases with longer-term use). If the clinical picture has improved, discontinue the oral antibiotics and maintain with topical treatment alone. The oral contraceptive pill may be safely combined with antibiotics (with the exception of rifampicin or trimethoprim-sulfamethoxazole [TMP/SMX] that is not usually prescribed for acne vulgaris) without affecting the efficacy of the pill.

Tetracyclines

The tetracyclines (Table 2)[2] are the most frequently prescribed oral antibiotic for acne and should be considered first-line therapy in moderate to severe acne, except when contraindicated (e.g., pregnancy, <8 years of age, or allergy). Tetracyclines reversibly bind to the 30S subunit of the bacterial ribosome which halts the growth and replication of the bacterial organism, producing a bacteriostatic effect. They also have a raft of anti-inflammatory effects through proinflammatory chemokine inhibition, reactive oxygen species inhibition and downregulation of matrix metalloproteinases (MMP).[2]

The role of first-generation tetracycline, initially used in the 1950s, has diminished due to minimal production. It must be taken distant from food (>1 hour) to allow adequate absorption. An early randomised controlled trial did however show a significant improvement in acne severity in patients taking it over placebo.[3]

The second generation tetracyclines, doxycycline and minocycline, are the antibiotic workhorses for acne treatment, both available on the Pharmaceutical Benefits Scheme (PBS) for severe acne. Gastrointestinal upset from doxycycline presents the commonest adverse effect and may manifest with oesophagitis and has been associated with the development of Crohn's disease. Dose-related phototoxicity can also occur, which is of significant relevance in Australia. A placebo-controlled, randomised, crossover study with patients taking 100 mg of doxycycline per day led to a significant decrease in inflammatory lesion count.[4]

Minocycline, similarly, showed significant reductions in inflammatory lesion counts in randomised placebo-controlled trials.[5] As the most lipophilic tetracycline, it most easily crosses the blood-brain barrier leading to headache, dizziness and vertigo in some patients.

Emerging resistance has heralded the need for better antibiotic stewardship. Tetracycline-resistant bacteria was first identified 40 years ago and a recent US study suggested over 50% of *C. acnes* isolated from acne patients were resistant to doxycycline.[2]

Table 2. Tetracycline antibiotics used in acne vulgaris[2]

	FDA approval year	Recommended dose for acne	Available on PBS for acne	Adverse effects: Photosensitivity	Adverse effects: GI upset	Adverse effects: Vestibular AE	Adverse effects: Other	Notes
1st generation							Teeth staining in those with developing teeth, benign intracranial hypertension, not safe in pregnancy or breastfeeding	
Tetracycline	1953	250-500 mg po bd	No	++	++	0		Broad spectrum, take on an empty stomach distant from food
2nd generation								
Doxycycline	1967	50-100mg bd	Yes	+++	+++	0		Both immediate and modified release formulations available. Subantimicrobial dosing (20-40mg) not available in Australia
Minocycline	1971	50-100mg bd	Yes	++	++	++		Rare side effects include skin hyper-pigmentation, serum sickness reaction and drug-induced lupus or hepatitis, DRESS
3rd generation								
Sarecycline	2018	Daily dosage (weight based chart)	No	0	+	0		Narrow spectrum – cutaneous bacteria (*C. acnes*), effective for truncal acne

The new third generation tetracycline, sarecycline, demonstrates a lower propensity for development of bacterial resistance and can be effective even against bacteria that have already developed resistance mechanisms to other tetracyclines. Two randomised, double-blinded, placebo-controlled trials showed a significant reduction of inflammatory lesions compared to placebo.[6,7] Sarecycline's narrow spectrum means it can effectively target *C. acnes* without affecting Gram-negative bacteria (resident flora of the gastrointestinal tract). Sarecycline is not yet available in Australia.

Earlier guidelines[8] suggested that minocycline be used as a first-line tetracycline, however its collection of adverse effects often mean that doxycycline may be trialled first.

Macrolides

Erythromycin and azithromycin are occasionally used for acne where tetracyclines are not suitable. They work in acne by binding the 50S subunit of the bacterial ribosome as well as possessing some anti-inflammatory effects. Erythromycin and azithromycin can be used in pregnancy and breastfeeding and in children younger than eight (Table 3).[9–12] However, its use has been associated with increased bacterial resistance, approaching 50% for erythromycin. Although macrolides have been shown to be effective for acne, superiority over tetracyclines has not been demonstrated.[13] To decrease resistance, they should always be paired with an appropriate topical (Table 1) and should be considered a second-line oral antibiotic.

Trimethoprim-sulfamethoxazole

This combination agent is considered a third-line agent for refractory acne. Trimethoprim (TMP) is a competitive inhibitor of dihydrofolate reductase and blocks the conversion of dihydrofolic acid into tetrahydrofolic acid. Sulfonamides, such as sulfamethoxazole (SMX), inhibits the conversion of para-aminobenzoic acid to dihydrofolic acid. A double-blind, randomised, placebo-controlled study showed TMP/SMX to be better at clearing acne than placebo, and a separate study found TMP/SMX to be as effective as oxytetracycline.[12] Given the pivotal role of TMP/SMX in treating methicillin-resistant *Staphylococcus aureus* (MRSA) as well as a significant collection of rare but important adverse effects (Table 3), its use should be reserved for treatment-refractory acne.[14]

Oral retinoids

Isotretinoin alone targets all areas of acne pathophysiology. It arrests the proliferation of basal sebocytes, reducing sebum secretion by 80% after a few weeks.[15] It alters the follicular microenvironment, diminishing *C. acnes* populations. There are multiple anti-inflammatory effects, notably reduced neutrophil mobility and MMP levels.

Although isotretinoin is listed on the PBS for "severe cystic acne", in practice it is often used in less severe acne where other options have failed. The traditional dosage regime suggests medium to high dosages (0.5 mg–1 mg/kg/day) over a period of 15–20 weeks. In the author's experience, these dosages are commonly employed in the United States, perhaps due to the increased regulatory hurdle of IPLEDGE (monthly pregnancy tests with only one month's supply dispensed at a time). In Australia, low doses (0.1–0.3 mg/kg/day), for a longer time period, are more commonly prescribed. This is often favourable as it leads to a lower burden of dose-related adverse effects and in particular, lower dose-related phototoxicity (important due to Australia's high ambient UV levels). Therapeutic endpoints are controversial: some dermatologists aim for a cumulative dose of 120–150 mg/kg, whereas some aim for no active acne lesions for a number of months prior to stopping.[15] Only a fifth of patients need to have a further course of isotretinoin after completing a first,

Table 3. Non-tetracycline antibiotics used in acne vulgaris[9-12]

	Recommended dose	Indications	Adverse effects
Macrolides			
Erythromycin	500 mg po bd	Refractory acne in pregnancy, breastfeeding, child < 8	Gastrointestinal upset (esp erythromycin), candida, headache
Azithromycin	Many studied regimes (i.e., 3 days/week; 4 days/month)		
Roxithromycin	150 mg bd		
Combination agents			
Trimethoprim-sulfamethoxazole	80/400 mg bd	Treatment-refractory acne, gram negative acne/folliculitis	Multiple drug eruptions (Fixed drug eruptions, Stevens-Johnson syndrome etc.), blood dyscrasia, oral contraception failure

with this risk increased by: lower dose regimens (0.1-0.5 mg/kg); the presence of severe acne; being a female over the age of 25 at the onset of therapy; and having a prolonged history of acne.[16]

Patients can exhibit hesitancy to take isotretinoin due to well-publicised potential adverse effects. Some of these happen in most patients to a certain degree and are dose-related (i.e., pruritus, mucocutaneous dryness) while others are idiosyncratic and somewhat controversial (i.e., mood disturbances, lipid abnormalities, development of inflammatory bowel disease, altered bone mineralisation, diffuse idiopathic skeletal hyperostosis). Most recent studies have not found a causal link between taking isotretinoin and the development of mood disorders[17] or inflammatory bowel disease,[18] however as conflicting studies exist, it is prudent to counsel patients and monitor for any changes in mood or bowel function. It is important that oral tetracyclines are discontinued prior to starting isotretinoin as their combination leads to an increased risk of benign intracranial hypertension.

It is, however, recognised that isotretinoin is teratogenic. Exposure in utero to isotretinoin was associated with a 25-times higher risk of certain malformations (craniofacial, cardiac, thymic, and central nervous system structures).[19] It is imperative that patients be counselled about this risk. Dermatologists must ensure patients have a negative pregnancy test prior to commencing therapy, that effective contraception is in place during treatment and for 1 month after stopping isotretinoin.

Hormonal therapies

Oral contraceptive pills

Oral contraceptive pills (OCPs) reduce both comedonal and inflammatory acne lesions by decreasing androgen production at the level of the ovary and increasing sex hormone–binding globulin (SHBG). This binds free circulating testosterone and renders it unavailable to bind and activate the androgen receptor. All OCPs consist of ethinyloestradiol paired with a progestin (or progestin-like agent i.e., cyproterone acetate). Since their introduction in the 1960s, the dosage of ethinyl oestradiol has decreased, alongside adverse effects such as venous thromboembolism (VTE). Each new progestin generation is less androgenic than the last, and fourth-generation progestin "drospirenone" is considered antiandrogenic. A Cochrane Review did not find any important distinction between OCP types in treating acne, but found all OCP agents useful in treating acne. The only head-to-head trial undertaken against minocycline did not show a significant difference.[20]

OCPs are safe in conjunction with other medications used in acne, in which pregnancy must be avoided (i.e. tetracyclines, isotretinoin and spironolactone).

Patients must be counselled about the rare yet present risks of OCPs. Although the relative risk of OCP-related VTE (3-9/10,000 patient years) is higher than non OCP-related VTE (1-5/10,000 patient years), it is still very low in absolute terms. An increased relative risk of breast cancer, cervical cancer, and myocardial infarction (especially for smokers/diabetics/hypertensives) also exists for those taking OCPs but still represent low relative risks.[21]

OCPs are recommended for use in moderate acne (Table 1), and a six-month trial should be sufficient to determine whether it will be effective for an individual's acne.[22]

Spironolactone

This aldosterone antagonist works through androgen receptor blockage, inhibition of 5α-reductase, and SHBG upregulation.[23] It is viewed as being equivalent in efficacy to systemic antibiotics or the OCP[1] and is especially useful for female patients with other signs of hyperandrogenism (i.e., hirsutism, androgenetic alopecia).

Adverse effects are generally mild and well tolerated, including menstrual irregularities, breast tenderness, breast enlargement, and central nervous system symptoms (fatigue, dizziness, and headaches). Although hyperkalaemia is often cited as a potential side effect, in practice, young healthy women using spironolactone have the same incidence of hypokalaemia as the baseline population.[24] It may however be prudent to monitor potassium levels in older women, those taking chronic non-steroidal anti-inflammatory agents and angiotensin-converting enzyme inhibitors, and those with renal insufficiency or severe cardiac disease. Although some animal studies have found an association between spironolactone and breast cancer, large studies have not found this to be the case for humans.[25] Pregnancy must be avoided in patients taking spironolactone, as there is a risk of feminisation of the male foetus.

Dosages can range from 25 mg daily to 200 mg daily. A recent retrospective review of all patients at the Mayo clinic over a 10-year period taking spironolactone for acne, found approximately two-thirds of patients (66.1%) had a complete response; 85.1% had a complete response or a partial response greater than 50%.[26]

Cyproterone acetate

Cyproterone acetate (CPA) works as an antiandrogen and an inhibitor of gonadotropin secretion. It upregulates metabolic testosterone clearance, reduces androgen production and binds to androgen receptors. Although not available in the United States, in Australia it is either used as Dianne-35 OCP (2 mg CPA/35 mg ethinyloestradiol) or using the Hammerstein's reverse sequential regimen (with supplementary

100 mg CPA for the first 10 days; postmenopausal and hysterectomised women received 50 mg CPA/day continuously as monotherapy).[27] CPA was found to be effective for treating women with moderate to severe hyperandrogenic acne in a randomised controlled trial, where it was comparable to low-dose flutamide.[28] It is not clear whether efficacy is related to dosage. Adverse effects include weight gain, fatigue, loss of libido, nausea, mastodynia, headaches and depression. It is not recommended for use in pregnancy due to the risk of feminisation of the male foetus. Aminotransferase derangement has been recorded, so monitoring is advocated at higher doses.

Flutamide

Flutamide is a non-steroidal antiandrogen that competitively binds androgen receptors throughout the body. It has been shown to be effective for acne, however it is reserved for very treatment-resistant cases due to reported fatal cholestatic hepatitis.[29] Other adverse effects include hot flushes, loss of libido, impotence and gastrointestinal upset. Dosage is 250 mg three times daily.

Oral corticosteroids

Oral corticosteroids have been shown to be effective for the treatment of acne and seborrhoea. Their use, however, must be reserved for specific circumstances due to the well-documented side effects. Prednisolone may be used at a low dose (5-15 mg daily) in patients with documented adrenal hyperandrogenism, as this will suppress adrenal production of androgens.[30] They may also be used for a short course in pregnant women with nodulocystic acne, after the first trimester.[31] Oral prednisolone may also be used at higher doses (0.5-1 mg/kg) for acne fulminans. They are often employed as an adjunct to slowly increasing doses of isotretinoin in very inflammatory nodulocystic acne to prevent an acne fulminans-like flare.[32]

Agents on the horizon

Acne remains an important area for research and new therapies are on the horizon.[33-39] A summary is found in Table 4. Sarecycline is discussed above.

Summary

Acne vulgaris remains an important area for future research given the significant numbers of patients affected. Clinicians must remain committed to preventing antibiotic resistance and exploration of existing and new modalities to best treat their patients. It is important that patients have appropriate contraception in place prior to commencing isotretinoin to reduce the risk of teratogenicity.

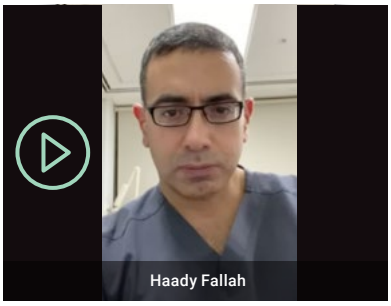
Table 4. New treatments for acne

Treatment	Mechanism	Dose	Reference(s)
Finasteride	Competitive inhibitor of 5α-reductase (anti-androgen)	5 mg daily for women; 23.5-33.5 mg daily for men	36, NCT02502669
Levamisole	Anthelminthic agent (immunomodulatory effect)	150 mg once-twice/week (with either doxycycline or azithromycin)	33, 34
Metformin	Enhances peripheral tissue sensitivity to insulin, reducing IGF-1 levels and androgenic hormones	500 mg bd – 200 mg daily	35
Serratiopeptidase	Anti-inflammatory, anti-oedema and fibrinolytic activity	5 mg tds	37
Preventative vaccination	Vaccination using surface sialidase or heat-killed *C. acnes* as antigen suppresses *C. acnes*-induced inflammation	N/A	38
Monoclonal antibodies	Neutralisation of CAMP factor secreted by *C. acnes* (Christie, Atkins, and Munch–Petersen (CAMP) factor, a secretory protein with hemolytic activity)	N/A	39
Gevokizumab	IL-1β monoclonal antibody	30 or 60 mg given subcutaneously day 0, 28 and 56	NCT01498874
Bermekimab	Anti-IL-1α monoclonal antibody	100 mg or 200 mg given subcutaneously day 0, 21 and 42	NCT01474798
Zileuton	Selective oral 5-lipoxygenase inhibitor, inhibiting sebum secretion	600 mg qid	NCT00098358
Acebilustat	Leukotriene A4 hydrolase inhibitor leading to decreased leukotriene production —> reduced sebum production and comedogenesis	100 mg daily	NCT02385760
Talarozole	Retinoic acid metabolism blocking agent	1 mg daily	NCT00725439

References

1. Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74(5):945-73 e33.
2. Graber EM. Treating acne with the tetracycline class of antibiotics: A review. Dermatological Reviews. 2021;2:321-30.
3. Lane P, Williamson DM. Treatment of acne vulgaris with tetracycline hydrochloride: a double-blind trial with 51 patients. Br Med J. 1969;2(5649):76-9.
4. Plewig G, Petrozzi JW, Berendes U. Double-blind study of doxycycline in acne vulgaris. Arch Dermatol. 1970;101(4):435-8.
5. Fleischer AB, Jr., Dinehart S, Stough D, Plott RT, Solodyn Phase 2 Study Group, Solodyn Phase 3 Study Group. Safety and efficacy of a new extended-release formulation of minocycline. Cutis. 2006;78(4 Suppl):21-31.
6. USFDA. Seysara labeling-package. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209521s007lbl.pdf.
7. Moore A, Green LJ, Bruce S, Sadick N, Tschen E, Werschler P, et al. Once-Daily Oral Sarecycline 1.5 mg/kg/day Is Effective for Moderate to Severe Acne Vulgaris: Results from Two Identically Designed, Phase 3, Randomized, Double-Blind Clinical Trials. J Drugs Dermatol. 2018;17(9):987-96.
8. Strauss JS, Krowchuk DP, Leyden JJ, Lucky AW, Shalita AR, Siegfried EC, et al. Guidelines of care for acne vulgaris management. J Am Acad Dermatol. 2007;56(4):651-63.
9. Australian Medicines Handbook, January 2022, available online https://shop.amh.net.au/products/digital.
10. Kim JE, Park AY, Lee SY, Park YL, Whang KU, Kim HJ. Comparison of the Efficacy of Azithromycin Versus Doxycycline in Acne Vulgaris: A Meta-Analysis of Randomized Controlled Trials. Ann Dermatol. 2018;30(4):417-26.
11. Ferahbas A, Utas S, Aykol D, Borlu M, Uksal U. Clinical evaluation of roxithromycin: a double-blind, placebo-controlled and crossover trial in patients with acne vulgaris. J Dermatol. 2004;31(1):6-9.
12. Bhambri S, Del Rosso JQ, Desai A. Oral trimethoprim/sulfamethoxazole in the treatment of acne vulgaris. Cutis. 2007;79(6):430-4.
13. Ochsendorf F. Systemic antibiotic therapy of acne vulgaris. J Dtsch Dermatol Ges. 2006;4(10):828-41.
14. McCarty M, Rosso JQ. Chronic administration of oral trimethoprim-sulfamethoxazole for acne vulgaris. J Clin Aesthet Dermatol. 2011;4(8):58-66.
15. Rigopoulos D, Larios G, Katsambas AD. The role of isotretinoin in acne therapy: why not as first-line therapy? facts and controversies. Clin Dermatol. 2010;28(1):24-30.
16. Stainforth JM, Layton AM, Taylor JP, Cunliffe WJ. Isotretinoin for the treatment of acne vulgaris: which factors may predict the need for more than one course? Br J Dermatol. 1993;129(3):297-301.
17. Jacobs DG, Deutsch NL, Brewer M. Suicide, depression, and isotretinoin: is there a causal link? J Am Acad Dermatol. 2001;45(5):S168-75.
18. Etminan M, Bird ST, Delaney JA, Bressler B, Brophy JM. Isotretinoin and risk for inflammatory bowel disease: a nested case-control study and meta-analysis of published and unpublished data. JAMA Dermatol. 2013;149(2):216-20.
19. Lammer EJ, Chen DT, Hoar RM, Agnish ND, Benke PJ, Braun JT, et al. Retinoic acid embryopathy. N Engl J Med. 1985;313(14):837-41.
20. Arowojolu AO, Gallo MF, Lopez LM, Grimes DA. Combined oral contraceptive pills for treatment of acne. Cochrane Database of Systematic Reviews. 2012(7).
21. ACOG. Risk of Venous Thromboembolism Among Users of Drospirenone-Containing Oral Contraceptive Pills https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2012/11/risk-of-venous-thromboembolism-among-users-of-drospirenone-containing-oral-contraceptive-pills2012.
22. Berenson AB, Odom SD, Breitkopf CR, Rahman M. Physiologic and psychologic symptoms associated with use of injectable contraception and 20 microg oral contraceptive pills. Am J Obstet Gynecol. 2008;199(4):351 e1-12.
23. Husein-ElAhmed H. Management of acne vulgaris with hormonal therapies in adult female patients. Dermatol Ther. 2015;28(3):166-72.
24. Plovanich M, Weng QY, Mostaghimi A. Low Usefulness of Potassium Monitoring Among Healthy Young Women Taking Spironolactone for Acne. JAMA Dermatol. 2015;151(9):941-4.
25. Rozner RN, Freites-Martinez A, Shapiro J, Geer EB, Goldfarb S, Lacouture ME. Safety of 5alpha-reductase inhibitors and spironolactone in breast cancer patients receiving endocrine therapies. Breast Cancer Res Treat. 2019;174(1):15-26.
26. Roberts EE, Nowsheen S, Davis MDP, McEvoy MT, Newman CC, Sartori Valinotti JC, et al. Treatment of acne with spironolactone: a retrospective review of 395 adult patients at Mayo Clinic, 2007-2017. J Eur Acad Dermatol Venereol. 2020;34(9):2106-10.
27. De Leo V, Morgante G. Different effectiveness of cyproterone acetate doses in treatment of acne. Clin Endocrinol (Oxf). 2003;58(2):246.
28. Carmina E, Lobo RA. A comparison of the relative efficacy of antiandrogens for the treatment of acne in hyperandrogenic women. Clin Endocrinol (Oxf). 2002;57(2):231-4.
29. Gao J, Mahto A. Anti-Androgen Therapy in Female Adult Acne. J Dermatol Res Ther. 2016;2(2).
30. Nader S, Rodriguez-Rigau LJ, Smith KD, Steinberger E. Acne and hyperandrogenism: impact of lowering androgen levels with glucocorticoid treatment. J Am Acad Dermatol. 1984;11(2 Pt 1):256-9.
31. Dreno B, Layton A, Zouboulis CC, Lopez-Estebaranz JL, Zalewska-Janowska A, Bagatin E, et al. Adult female acne: a new paradigm. J Eur Acad Dermatol Venereol. 2013;27(9):1063-70.
32. Jansen T, Plewig G. Acne fulminans. Int J Dermatol. 1998;37(4):254-7.
33. Ansarin H, Savabynasab S, Behzadi AH, Sadigh N, Hasanloo J. Doxycycline plus levamisole: combination treatment for severe nodulocystic acne. J Drugs Dermatol. 2008;7(8):737-40.
34. Nakatsuji T, Liu YT, Huang CP, Zouboulis CC, Gallo RL, Huang CM. Vaccination targeting a surface sialidase of P. acnes: implication for new treatment of acne vulgaris. PLoS One. 2008;3(2):e1551.
35. Holland C, Mak TN, Zimny-Arndt U, Schmid M, Meyer TF, Jungblut PR, et al. Proteomic identification of secreted proteins of Propionibacterium acnes. BMC Microbiol. 2010;10:230.
36. Mikhael E, Mohammed M. Serratiopeptidase a Hope in a Rapid and Better Improvement of Inflammatory Acne Vulgaris. Iraqi J Pharm Sci. 2012;21:78-81.
37. Rassai S, Mehri M, Yaghoobi R, Sina N, Mohebbipour A, Feily A. Superior efficacy of azithromycin and levamisole vs. azithromycin in the treatment of inflammatory acne vulgaris: an investigator blind randomized clinical trial on 169 patients. Int J Clin Pharmacol Ther. 2013;51(6):490-4.
38. Bernhardt MJ, Myntti MF. Topical Treatment With an Agent Disruptive to P. acnes Biofilm Provides Positive Therapeutic Response: Results of a Randomized Clinical Trial. J Drugs Dermatol. 2016;15(6):677-83.
39. Yen H, Chang YT, Yee FJ, Huang YC. Metformin Therapy for Acne in Patients with Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis. Am J Clin Dermatol. 2021;22(1):11-23.

Treatment of acne vulgaris with isotretinoin: An update



CLICK IMAGE TO LINK TO VIDEO DURATION_00:36

Haady Fallah[1, 2], Marius Rademaker[3]

1. The University of Sydney, Sydney, NSW, Australia
2. Department of Dermatology, Concord Repatriation General Hospital, Concord, NSW Australia
3. Waikato Clinical School, Hamilton, Auckland Medical School, New Zealand

Correspondence: Marius Rademaker marius.rademaker@gmail.com

Disclosures: Dr Rademaker has performed several clinical trials on isotretinoin, some of which have been funded by Douglas Pharmaceuticals, Auckland, New Zealand, a manufacturer of isotretinoin, but he has no financial or other conflict of interest to declare.
Dr Fallah has no conflict of interest to declare.

OUTLINE: Isotretinoin revolutionised the treatment of acne vulgaris when first introduced and has been shown to be very helpful in a number of other dermatological conditions, including rosacea. However, despite almost four decades of widespread use, isotretinoin is still used suboptimally.[1, 2] Isotretinoin is the most effective treatment for acne.[3, 4] A recent study has shown that, of the recent published clinical trials of acne treatments, only isotretinoin achieved success according to United States Food and Drug Administration guidance of reaching Investigator Global Assessment of clear or almost clear skin (87% isotretinoin vs <40% all other treatments).[5] We review the current evidence of the ongoing controversies associated with isotretinoin and make practical recommendations.

KEWYORDS: Acne vulgaris, low dose isotretinoin, adverse effects, isotretinoin

Fallah H, Rademaker M. Treatment of acne vulgaris with isotretinoin: An update. Opin Prog Cosmet Dermatol 2022;2(2):65-76.

Pharmacokinetics

13-*cis*-retinoic acid, or isotretinoin, is a naturally occurring retinoid in human serum.[6, 7] Following oral administration of isotretinoin, the bioavailability is approximately 25%. The metabolism of isotretinoin is linked with that of its isomer, all-*trans*-retinoic acid, as the two isomers are interconverted *in vivo*.[8] The principal metabolite of isotretinoin is 13-*cis*-4-oxo-retinoic acid.[7] After stopping treatment, isotretinoin and 13-*cis*-4-oxo-retinoic acid levels decline rapidly, with mean terminal elimination half-lives of approximately 19 and 29 hours respectively, with endogenous concentrations being reached within two weeks of stopping 0.5-1.0 mg/kg/day.[9]

Mechanism of action

The traditional understanding of how isotretinoin improves acne is fourfold:

- the reduction in the size of sebaceous glands with consequent decrease in sebum production;
- normalisation of follicular keratinisation;
- inhibition of *Cutibacterium acnes* and;
- reduction in inflammation.[10]

Isotretinoin may exert its sebo-supressive activity through conversion to all-*trans*-retinoic acid and subsequent binding to retinoic acid receptors.[11] However, suppression of sebaceous glands may also occur through a retinoic acid receptor independent mechanism, by causing cell cycle arrest and inducing apoptosis in SEB-1 sebocytes.[12, 13] The mechanism for sebocyte apoptosis may be increased induction of key genes including Tumour necrosis factor

Related Apoptosis Inducing Ligand (TRIAL) as well as the Lipocalin 2 (LCN2) gene which encodes for Neutrophil Gelatinase-Associated Lipocalin (NGAL).[14, 15] The mechanism for cell cycle arrest may be induction of FOX01.[16] FOX01 supresses proliferation of human primary keratinocytes, enhancing both their differentiation and apoptosis.[17] There is likely a dosage effect on apoptosis of sebocytes, and their progenitor cells, which explains the longer clinical effects of larger dosages of isotretinoin (i.e., 40 weeks after a course of 0.1 mg/kg/day versus 80 weeks after 1.0 mg/kg/day).[18]

Recent work suggests that isotretinoin may have a significant positive effect on the microbiome, with both an increase in microbial diversity and a reduction in the more pathogenic *C. acnes* strains.[19, 20, 21] This may further explain the prolonged remission seen following a course of isotretinoin. Isotretinoin also exerts an anti-inflammatory effect through a reduction in monocyte Toll-like receptor-2 expression and an attenuation of the subsequent inflammatory cytokine response to *C. acnes*. The anti-inflammatory effect may also occur through inhibition of neutrophil and monocyte chemotaxis,[22] and through a reduction in matrix metalloproteinase (MMP)-9 and MMP-13 in sebum.[23]

Ongoing controversies

Despite millions of courses of isotretinoin over 40 years, there remain a number of controversial areas, including best daily dose, the ideal duration of treatment, the relevance of cumulative dose, the causality of several specific adverse effects and the severity of the acne that should be treated. Most of these controversies are under-pinned by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) mandated use of high doses (0.5-1 mg/kg/day) of isotretinoin for fixed periods of time (usually 4 to 6 months); the rationale for high dose isotretinoin has been to reduce the length of drug exposure in an attempt to minimise potential teratogenicity in women of child bearing potential.

This has led to a reluctance to use lower dose (10-20 mg/day) isotretinoin for less severe acne, despite it being equally as effective as high dose isotretinoin, but with a substantial reduction in adverse effects.

Indications, precautions and contraindications

The listed indications for isotretinoin vary from country to country: in some countries it is limited to the treatment of severe nodulocystic acne, whilst in others, it can be used for any grade of acne and many other disorders of keratinisation. Increasingly isotretinoin is being used to treat persistent low-grade acne in adult women as an alternative to repeated courses of antibiotics, or hormonal therapy.[1] This is partly due to the growing concern over antibiotic usage, but increasingly due to the recognition that isotretinoin is the most effective treatment for all grades of acne.[1, 5]

The contraindications to isotretinoin vary internationally. Absolute contraindications include pregnant patients or patients likely to become pregnant, hypersensitivity to isotretinoin or its ingredients, and hypervitaminosis A.[1] Relative contraindications are largely dose dependant but include significant leucopenia, hyperlipidaemia, or hepatic dysfunction, and breast feeding mothers.

Several drug-drug interactions have been described with isotretinoin. Concurrent tetracyclines and higher dose isotretinoin may increase the risk of benign intracranial hypertension; it is unclear whether low dose isotretinoin also increases the risk of benign intracranial hypertension. Other possible interactions include with alcohol, anti-epileptics (carbamazepine, sodium valproate, and phenytoin may decrease serum concentrations of isotretinoin; isotretinoin may alter the bioavailability or clearance of carbamazepine) and smoking. Smoking may affect CYP26 mediated metabolism of all-*trans*-retinoic acid leading to a reduced response to isotretinoin. Isotretinoin may diminish the efficacy of micro dosed progesterone preparations (minipill).

Dosing considerations

Dosing of isotretinoin can be divided into high dose (≥1 mg/kg/day), medium dose (0.5 mg/kg/day), low dose (0.1 mg/kg/day), intermittent dose (0.5 mg/kg/day for 7 days each 28 days) or fixed daily dose (e.g., 5-20 mg/day irrespective of body weight). Duration of treatment can vary from 4 months to several years, with the option to alter the dose during the course of treatment. As a general rule, use the lowest effective dose for the appropriate length of time.

Several countries' regulators still mandate higher dose isotretinoin (0.5-1.0 mg/kg/day) for 4 months, to minimise the exposure time with respect to potential pregnancy. The original study of isotretinoin for acne used an average dose of 2 mg/kg/day (range 1.0 to 3.3 mg/kg/day) for 4 months.[24] Within a year, dose-ranging studies of 0.1 to 1.0 mg/kg/day were published demonstrating no difference in either the speed of response, nor the clearance of acne,[25, 26] but with substantially less adverse effects.

There are now numerous comparative and non-comparative studies that have examined the efficacy of isotretinoin at different daily dosages (Table 1 and 2). Two randomised controlled trials compared the dosages of 0.1 mg/kg daily, 0.5 mg/kg daily or 1 mg/kg daily

for a fixed period in patients with moderate to severe acne[27, 28, 29] there were no statistically significant differences in clinical response at the end of treatments. In a placebo double blinded randomised controlled trial of adult patients with low grade acne, isotretinoin 5 mg daily for 16-32 weeks was found to be very effective in reducing the number of acne lesions and improving dermatological quality of life.[30] In 40% of patients, the acne remained in remission three years after completing the study; the remainder had mild recurrence a mean of six months after stopping, for which 48% elected to restart isotretinoin, often as low as 5 mg twice/week.[31]

There is no strong evidence to support the conventional recommendation to aim for a cumulative dose of between 120-150 mg/kg of isotretinoin in patients with acne. The recommendation is often supported by data from studies that were not designed to evaluate the effect of cumulative dose on relapse rates.[32, 33] In many of these studies, the isotretinoin treatment regimens were of fixed duration; this limitation does not generally exist in everyday clinical practice. Furthermore, they often only assessed relapse rates 6-12 months after isotretinoin was ceased, rather than 3-5 years, which would be more in keeping with the natural history of acne vulgaris. Studies in which isotretinoin did not need to be prescribed to a fixed duration have not generally demonstrated a relationship between risk of relapse and cumulative dose of more than 120 mg/kg versus less than 120 mg/kg.[34, 35] However, if relapse is to occur, it tends to happen earlier after low-dose isotretinoin (0.1 mg/kg/day), at 40 weeks after stopping treatment, compared to 80 weeks after stopping high dose isotretinoin (1 mg/kg/day).[18] Whilst, some patients can manage mild relapse with topical therapy, many prefer to restart very low dose isotretinoin. A small number of patients (1-2%) require multiple or continuous courses of isotretinoin over many years to manage their persisting acne.

We recommend that treatment with isotretinoin be continued until the acne has cleared completely, and then for a further 3 months. The dose of isotretinoin can be reduced during the later stages to as low as 5 mg/day or 10 mg two to three times per week. The minimum effective daily dose is approximately 2 mg/day. When assessing for clearance, it is important to ensure that both the inflammatory lesions and comedonal lesions have cleared. Persistent small closed comedones are more easily visualised with adequate lighting and stretching of the skin.

Factors predictive of increased risk of relapse

The factors associated with increased risk of relapse post isotretinoin include failure to clear acne (usually due to stopping isotretinoin after a fixed time period), a strong family history of acne, age (both under 14 years and over 25 years of age), untreated polycystic ovarian syndrome (PCOS), and smoking.

Factors predictive of slow response to isotretinoin

Slow responders are those who still have significant active acne despite six months of isotretinoin. The presence of closed comedonal acne, and in particular, multiple macrocomedones predisposes to slower response to isotretinoin.[35, 36, 37] These can be treated by a number of physical techniques such as diathermy, without the need to stop low-dose isotretinoin. Although an underlying hormonal disorder such as PCOS may theoretically predispose to a slower response, this was a less common reason for slow response compared with the presence of multiple macrocomedones or the presence of nodular acne in a series of 476 patients.[37] It is unclear if variation in the activity of cytochrome P450 (CYP26) metabolism of all-*trans*-retinoic acid may play a role, which can be affected by smoking.

Managing slow response to isotretinoin

In patients with persistent inflammatory lesions, it is important to exclude a staphylococcal infection, which if present should be treated with appropriate non-tetracycline-based antibiotics, such as cephalexin.

Cigarette smokers should be encouraged to stop smoking, PCOS should be treated appropriately, and macrocomedones can be treated with diathermy or surgically. Adding trimethoprim for 2-3 months can also be helpful.

Most slow responders do eventually respond satisfactorily to isotretinoin, although this may occasionally take 18-24 months.

Acne flare

Patients with very severe acne, or numerous macrocomedones, have a higher risk of developing a flare of their acne (and in some cases acne fulminans) during the first few weeks of isotretinoin therapy.

In these patients isotretinoin should be started at a low dose (5-10 mg daily) to minimise the risk of flare and, if necessary, only increase the dosage after approximately 4-8 weeks. Depending on the likelihood of a flare, co-prescription of a non-tetracycline based antibiotic (e.g. erythromycin or trimethoprim) for 6-12 weeks may be indicated. Additionally, for patients at high risk of flare or scarring, prednisone/

prednisolone 0.25-0.5 mg/kg/day, tapered over 4-6 weeks may be considered. There is also some evidence that concurrent treatment with an antihistamine agent may reduce the risk of a flare of acne during treatment with isotretinoin.[38]

Concurrent procedures

Several recent commentaries/guidelines have questioned the traditional recommendation that isotretinoin be stopped six months before any laser, dermabrasion or surgical procedure to avoid excessive scarring[39, 40, 41] There is insufficient evidence to recommend any delay in focal or superficial manual dermabrasion to treat localised acne scars on the face. However, full face non-fractionated laser resurfacing and/or mechanical dermabrasion with rotary devices should still be avoided until 6 months after completion of isotretinoin treatment.[40, 41] Superficial chemical peels can be administered safely in patients on isotretinoin,[39] although the evidence for the safety (or harm) of medium and deep peels is still lacking. There is insufficient evidence to support delaying treatment with laser or light (e.g. intense pulse light [IPL]) hair removal devices, vascular lasers, and non-ablative or ablative fractional laser devices. Increasingly, low doses of isotretinoin (e.g. 5-10 mg/day) are being actively prescribed, or continued, during the above acne scar treatments with excellent outcomes.[42]

Adverse effects

One of the strongest barriers to the use of isotretinoin for acne is concerns about its side effect profile. The most common adverse effects are mucocutanous; these are easily managed, particularly if a lower dose (5-20 mg/day) is used. Of these, cheilitis is the most common adverse effect and is dose dependent, often with a degree of photosensitivty.[43]

Depression

A possible association between isotretinoin and depression has been a source of much controversy. Acne itself is associated with an increased risk of depression and suicidal ideation.[44, 45, 46] Retinoids are lipid soluble and it has been hypothesised that isotretinoin may lead to depressive symptoms by decreasing hippocampal neurogenesis, and/or by altering the expression of components of the serotonergic neurotransmitter system, thereby leading to impaired serotonin signalling.[47]

Prospective studies examining the relationship between isotretinoin and depression have been overwhelmingly reassuring.[48-52] Meta-analyses have indicated that depression scores improve with isotretinoin treatment.[53, 54] Nevertheless, case reports of patients who developed depression while on isotretinoin, which settled on dechallenge and recurred after rechallenge suggest that a small subset of acne patients may be susceptible to mood change which should be monitored.[55, 56] This possibility should be conveyed to all patients and their familes prior to commencing isotretinoin and the patients advised to report any symptoms of mood disturbance occurring during therapy.

Given the potential for isotretinoin to improve psychological health and quality of life, isotretinoin should actively be considered in patients with a history of a mood disorder who have acne. In such cases, it would be prudent to monitor the patient in liaison with their family physician and/or mental health care professional, especially in the first few months of therapy.

Inflammatory bowel disease

A possible link between isotretinoin and inflammatory bowel disease has also been a source of concern for prescribers and patients. Concerns initially arose from several case reports and a single case control study indicating that exposure to isotretinoin was associated, in a dose dependent fashion, with an increased risk of ulcerative colitis but not Crohn's disease.[57] However a subsequent study using the same database found no association with either ulcerative colitis or Crohn's disease; the main difference being that the latter study was a nested study which reduced possible confounding from the oral contraceptive pill.[58] Data from several case control studies and retrospective cohort studies have been reassuring, as has a large meta-analysis published in the gastroenterology literature.[59-62] There is no obvious biological mechanism for an association between inflammatory bowel disease and isotretinoin, although several possible mechanisms have been speculated. On the other hand the anti-inflammatory properties of all-*trans*-retinoic acid and its ability to enhance gut barrier function suggests that isotretinoin would have a beneficial effect on inflammatory bowel disease.[63]

Patients with established inflammatory bowel disease have been treated safely with isotretinoin.[64, 65] In a retrospective chart review of patients with acne and known inflammatory bowel disease prior to treatment with isotretinoin, 100% of the patients on isotretinoin had clinical remission of inflammatory bowel disease compared to 37% of patients who were not on isotretinoin (p=0.078).[66] Patients with established inflammatory bowel disease who have significant acne not responsive to topical therapy should actively be considered for treatment with isotretinoin.

Benign intracranial hypertension

Benign intracranial hypertension is an important adverse effect for clinicians and patients to be aware of as it can lead to permanent visual impairment. It is characterised by a new headache or headache that is different to the patient's usual headache, especially when associated with other symptoms such as visual disturbances and tinnitus. The mean time from commencement of isotretinoin to the diagnosis of benign intracranial hypertension was 2.3 months in a review of 179 cases.[67] Unfortunately the dose of isotretinoin was only recorded in one patient, who was on 120 mg/day. Since benign intracranial hypertension has also been associated with the tetracycline group of antibiotics, concurrent use of isotretinoin and tetracycline-based antibiotics is best avoided. A seven-day washout period between stopping minocycline/doxycycline and the commencement of isotretinoin has been suggested (level 4 evidence). Safe co-prescribing of isotretinoin and tetracyclines has been described, but concomitant use of these medications should only occur when the potential benefits outweigh the risks, the dose of both drugs kept as low as possible, and the patient is monitored carefully.[68]

Isotretinoin has been used safely in patients with a previous history of drug-induced benign intracranial hypertension.[69] In such scenarios it would be prudent to use low dosages of isotretinoin (e.g. 10 mg/day) and to monitor the patient closely for symptoms and signs of raised intracranial pressure, and to co-manage the patient with a neurologist/ophthalmologist.

Ocular effects

In a retrospective cohort study of 14,682 patients, the most common reported ocular effects of isotretinoin were conjunctivitis, hordeolum, chalazion, blepharitis, eye pain and dry eyes, with the peak risk at 4 months after first prescription of isotretinoin.[70] The dose and duration of isotretinoin were not recorded, but the adverse effects were likely dose-related.

Dermatologists are aware of the possible effects of isotretinoin on night vision.

There are several reports of patients with persistent changes in dark adaptation testing/electro-retinogram, although in most reports, pre-treatment testing was not performed, and the dosage and duration of isotretinoin was not reported.[71, 72] In many cases, changes in objective testing were not accompanied by any clinical symptoms of night vision impairment.[73]

Decline in night vision appears to be in most cases reversible upon cessation of isotretinoin, although subclinical abnormalities in electrophysiological tests may last longer than initially thought.[74] The underlying mechanism may be inhibition of ocular retinol dehydrogenases by isotretinoin, leading to a reduction in the formation of the visual chromophore 11-*cis*-retinal.[75]

Prospective pilots (and long-distance truck drivers) should be counselled appropriately and liaison with their aviation medical specialist may be necessary. If isotretinoin is to be used, the dosage should be kept low (10 mg/day) as this may reduce the likelihood of clinical or subclinical abnormalities in night vision. However, data to confirm this is lacking.

Bone changes

The data regarding an association between isotretinoin and Diffuse Idiopathic Skeletal Hyperostosis (DISH) has been conflicting.[76, 77, 78] The most methodologically robust study, a randomised controlled trial in skin cancer prevention, shows a possible association, although the participants were not acne patients and were significantly older.[78] Premature epiphyseal closure has been linked to treatment with isotretinoin. Between 1985 and 2021, the United States FDA received 41 reports worldwide of premature epiphyseal closure related to isotretinoin in patients aged under 18, with 22 of these related to acne treatment.[79] However, the cases lack pertinent details such as medical history and how a diagnosis of premature epiphyseal closure was made. In the literature, most reported cases of premature epiphyseal closure have been associated with very high dose isotretinoin for indications other than acne. There are rare case reports of premature epiphyseal closure occurring in patients treated with isotretinoin for acne.[80, 81, 82] The underlying mechanism may involve specific retinoid receptors. Animal studies have shown that guinea pigs treated with all-*trans*-retinoic acid and a retinoic acid receptor (RAR) selective agonist developed dose-dependent closure of the proximal tibial epiphyseal plate.[83] When isotretinoin is required in pre-pubertal children, it would be sensible to use lower dosages (e.g. 0.1 mg/kg/day), even though the risk is undetermined.

Muscular effects

Myalgia is a common dose-dependent adverse effect of isotretinoin. Myalgia related to isotretinoin is usually mild, and quickly reversible on discontinuation or reduction in dose.[84] Elevations of creatine kinase levels may occur in patients on isotretinoin but are usually asymptomatic.[85] There have, however been rare reports of rhabdomyolysis occurring in patients treated with isotretinoin, including a case with a fatal outcome.[86] Patients who develop myalgia or creatine kinase elevations while on isotretinoin may require dose reduction or temporary discontinuation of isotretinoin.

These patients should be encouraged to avoid strenuous activity and contact sports, while on isotretinoin. There is no evidence to support regular monitoring of creatine kinase, or limiting exercise, in physically active patients who are asymptomatic.

Pregnancy

Isotretinoin is a well-known teratogen, which leads to malformations particularly affecting craniofacial, cardiac, thymic, and central nervous system structures.[87] The underlying mechanism for isotretinoin embryopathy may be related to an exaggeration of neural crest cell apoptosis via upregulation of the pro-apoptotic transcription factor p53.[88] In one study of 94 prospectively ascertained pregnancies exposed to isotretinoin which ended in birth, 28% resulted in congenital malformation (number needed to harm of 3.5).[89]

If a patient on isotretinoin becomes pregnant, isotretinoin should immediately be stopped, and advice sought from a perinatal specialist. There is currently no evidence that very low doses of isotretinoin (e.g., 5 mg/day) are safe in pregnancy, although a daily dose of 10,000 IU vitamin A (approximately equivalent to 3 mg isotretinoin), appears to be safe.[90]

Male and female fertility

Despite some initial concerns, male fertility is not adversely affected by isotretinoin.[91] On the contrary, several studies have demonstrated positive benefits of low dose isotretinoin on sperminogram parameters and infertility.[92] Male sexual dysfunction in association with isotretinoin was first reported in 1994, at which time Roche had received 150 reports of male sexual dysfunction over a 10-year period, including 32 potency disorders and two reports of ejaculatory failure.[93] To put this in context, this was 0.008% of the 18,000 reports of adverse reactions; of note, the underlying prevalence of sexual dysfunction in men age 18-59 in the United States is 31%.[94]

In one study the levels of anti-Mullerian hormone, ovarian volume and antral follicle counts were decreased in females at the end of six months treatment with isotretinoin, but these levels increased with time and at 18 months post treatment, were statistically similar to baseline.[95]

Laboratory monitoring

A meta-analysis has shown that while isotretinoin was associated with statistically significant changes in the mean value of white blood cell counts, hepatic enzyme and lipid levels, the mean changes did not meet *a priori* criteria for high risk, and the proportion of patients with laboratory abnormalities was low.[96]

Leucopenia and thrombocytopenia related to isotretinoin tend to be mild and tend to remain stable or resolve without interrupting treatment. Monitoring of full blood count in the absence of any risk factors is therefore not warrented.[97] Mild elevations of transaminases (<3 times the upper limit of normal) are often transient and do not usually necessitate interruption of isotretinoin treatment. In our experience, they are often related to other factors such as an intercurrent viral illness or the introduction of another medication or supplement.

Lipid abnormalities are the most common laboratory abnormalities seen in patients taking isotretinoin.[98] In a cohort study of 1863 patients treated with isotretinoin, grade 3 abnormalities in triglycerides occurred in fewer than 1% of patients.[99] A systematic review found only four cases of hypertriglyceridemia-induced pancreatitis in patients on isotretinoin, with most cases of isotretinoin-associated pancreatitis thought to be idiosyncratic.[100] In our experience, the occurrence of very high hypertriglyceridemia in patients on low dose isotretinoin (0.1-0.25 mg/kg/day) with normal baseline lipids is rare. Mild elevations do not usually necessitate treatment interruption and can be managed through lifestyle/dietary modification.

Current guidelines and recommendations regarding practical prescribing

European guidelines published in 2016 recommend a dose of 0.3-0.5 mg/kg for severe papulopustular acne/moderate nodular acne, and a dose of >0.5 mg/kg for conglobate acne.[101] The recommended duration of therapy is for at least 6 months, but no recommendation is made in relation to targeting a specific cumulative dose.[101] The American Academy of Dermatology guidelines, published in 2016, recommend that in patients with severe acne, isotretinoin is commenced at a dose of 0.5 mg/kg/day, increasing to 1 mg/kg/day and continuing treatment until a dose of 120-150 mg/kg is achieved.[102] For patients with moderate acne, a dose of 0.3-0.5 mg/kg/day is recommended. NICE guidelines published in 2021 recommend dosages of 0.5-1 mg/kg, but to consider lower doses in those at increased risk of adverse effects.[103] They recommend continuing until a cumulative dose of 120-150 mg/kg is achieved but suggest considering stopping sooner if an adequate response has been achieved and no new acne lesions have developed for 4-8 weeks.

An international consensus published by the Global Alliance to Improve Outcomes in Acne in 2018, makes

no specific recommendations regarding isotretinoin dosages.[33] Rather it simply recommends continuing isotretinoin until full clearance, plus an additional month, independent of cumulative dose.

We no longer target a specific weight-based dosage. Our starting dosages are between 5-20 mg daily for the majority of patients with acne. Dosages may be increased with time but in our experience dosages of >20 mg/day are seldom required to clear acne. Once the acne has improved, many patients are able to reduce their dosage to 5 mg/day, or 10 mg on alternate days, or even less often. Rather than targeting a specific cumulative dose, we typically continue the isotretinoin for 3 months after clearance of acne; typically, this means patients are treated for 8 to 12 months, and sometimes longer.

The advantage of this approach is a significant reduction in the dose-dependent adverse effects of isotretinoin[43] and the cost of treatment. The need for repeated blood tests is much reduced. However, in females of childbearing potential, this advantage needs to be balanced against the increased exposure time to the potential risk of pregnancy. In scenarios where it is important to complete the treatment in a relatively short period of time, for instance to mitigate the risk of pregnancy, higher dosages over a shorter period may be advantageous. Furthermore, in our experience there is a very small group of patients who require dosages higher than 0.5 mg/kg in order to achieve control of their acne.

Key points

When to use:	All grades of acne that have not responded to 3 months of topical therapies; lower threshold to commencing isotretinoin where there is a high risk of scarring or associated psychological distress
Starting dose:	Fixed dose of 5-20 mg/day
Maintenance dose (once cleared):	Maintain same dose or consider reducing to 5-10 mg/day or 10 mg x3/week
Duration of treatment:	No fixed length; continue until clear and then for another 3 months
Relapse:	Consider starting 10 mg/day for 6 months, then 10 mg x2-3/week for 1 year

Laboratory testing:

- Baseline: blood count, liver enzymes and lipids
- Ongoing: recheck lipids and liver enzymes two months after maximal dose; no further checks necessary if results are normal and no risk factors are present
- Pregnancy testing: monthly

Slow responders:

- Treat any macrocomedones
- Treat any PCOS
- Stop smoking
- Consider adding trimethoprim 300 mg/day for 3 months
- At six months, consider increasing dose of isotretinoin to 0.5-1 mg/kg/day for 1 month

Table 1. Comparative studies of isotretinoin dosage

Study	Design	Subjects	Isotretinoin regimen used	Findings
Strauss 1984[27]	Prospective, double blinded	N=150 Treatment resistant, severe nodulocystic acne	Group A: 0.1 mg/kg/day Group B: 0.5 mg/kg/day Group C: 1 mg/kg/day 20 weeks fixed duration	No significant differences in response in different dosage groups at end of treatment and 12-week follow-up. Proportion of patients needing re-treatment with isotretinoin highest in Group A and lowest in Group C
Jones 1983[29] Jones 1984[28]	Prospective, randomised, double blinded	N=76 Moderate to severe acne	Group A: 0.1 mg/kg/day Group B: 0.5 mg/kg/day Group C: 1 mg/kg/day 16 weeks fixed duration	No significant differences in response in different dosage groups at end of treatment. Higher proportion of patients in Group A required retreatment based on data from questionnaire at 88 weeks
Lee 2011[104]	Prospective, randomised, open, with blinded assessment trial	N=60 Moderate acne	Group A: 0.5-0.7 mg/kg/day Group B: 0.25-0.4 mg/kg/day Group C: 0.5-0.7 mg/kg/day for 1 week out of every 4 weeks 24 weeks fixed duration	No statistically significant difference in Global Acne Grade score at the end of treatment or at one year follow up between Groups A and B. Group C inferior to both Group A and B
Agarwal 2011[105]	Prospective, randomised	N=120 Mild, moderate and severe acne	Group A: 1 mg/kg/day Group B: 1 mg/kg/day alternate days Group C: 1 mg/kg/day for one week out of four weeks Group D: 20 mg alternate days 16 weeks fixed duration	By end of treatment course, results in Groups A, B and D were comparable while Group C performed the worst. In the severe acne subgroup, Group A did better than the other subgroups. In the moderate acne subgroup, all groups were similar except for Group C which did not do as well. In the mild acne subgroup, all groups did equally well
Mandekou-Lefaki 2013[106]	Unclear if prospective	N=64 Moderate to severe acne	Group A: 0.15-0.4 mg/kg Group B: 0.5-1 mg/kg No fixed duration	"Therapeutic results" not significantly different between two groups
Dhaked 2016[107]	Prospective, randomised	N=240 Moderate to severe acne	Group A: 20 mg/day Group B: 20 mg alternate daily 24 weeks fixed duration	Proportion of patients acne free at 24 weeks was 69% in Group A and 56% in Group B, (p=0.30) and at 36 weeks, 51% in Group A and 40% in Group B (p=0.51). In patients with severe acne, Group A had significantly better response rates than Group B throughout study, but in cases of moderate acne, a statistically significant difference was observed only up to 12 weeks
Almas 2020[108]	Prospective, randomised	N=180 Moderate to severe acne	Group A: 0.5 mg/kg/day Group B: 0.25 mg/kg/day 3 months fixed duration	No difference in proportion of patients demonstrating effective response in two groups

Table 2. Prospective, non-comparative studies of lower dose isotretinoin therapy

Study	Subjects	Isotretinoin regimen used	Findings
Amichai 2006[109]	N=638, moderate acne	20 mg/day 6 months fixed duration	At end of treatment, complete or almost complete remission of acne lesions occurred in 95% of patients aged 12-20 and 93% of patients aged 21-35. During 4-year follow-up period, "relapse" (emergence of pre-treatment severity of acne) occurred in 4% of patients aged 12-20 and 6% of patients aged 21-35
Sardana 2009[110]	N=320, moderate acne	Fixed dose 20 mg alternate days (0.15-0.28 mg/kg/day) + topical 1% clindamycin 6 months Mean cumulative dose 38 mg/kg	68% showed "very good" response (complete or >80% resolution of acne lesions). 19% showed "good" response (50-80% resolution of acne lesions). 12% experienced treatment failure (no improvement, requiring subsequent increase in isotretinoin dosage or even additional treatment at the end of 6 months). In further 6 months follow-up 16% of patients relapsed (relapse = emergence of pretreatment severity of acne in the treated patient)
De 2011[111]	N=70, Grade 3-4 acne (US FDA global scores)	0.3 mg/kg/day + pulsed oral azithromycin (500 mg/day over three consecutive days every 2 weeks) Treatment continued until complete clearance of lesions or to 16 weeks, whichever came later. Mean cumulative dose 50 mg/kg	94% of patients had complete clearance of disease activity after a mean treatment duration of 21 weeks. 11% had "relapse" (any grade of acne) in 12-month follow-up post treatment
Rao 2014[112]	N=50, moderate to severe acne	20 mg/day (0.3-0.4 mg/kg/day) 3 months	12 weeks post treatment, 6% of patients had complete clearance of acne, and a further 90% had >75% clearance. Relapse (not defined) occurred in 2 patients during 6-month follow-up
Yap 2017[113]	N=150, moderate to severe acne	10 mg/day until cumulative dose of 90-110 mg/kg	At end of treatment, all patients achieved total clearance. Twelve months post treatment "mild" relapse (recurrence of acne) occurred in 4% of patients
Rademaker 2014[30]	N=58, low grade adult acne	Group 1: 5 mg/day for 32 weeks Group 2: placebo for 16 weeks then open label isotretinoin for 16 weeks	After 16 weeks, highly significant difference in acne lesion count. Significant reduction in acne lesion count in Group 2 but only from week 20

References

1. Fallah H, Rademaker M. Isotretinoin in the management of acne vulgaris: practical prescribing. Int J Dermatol. 2021; 60: 451-60.
2. Fallah H, Rademaker M. Isotretinoin for acne vulgaris – an update on adverse effects and laboratory monitoring. J Dermatolog Treat. 2022 Mar 23:1-11.
3. Vallerand IA, Lewinson RT, Farris MS, Sibley CD, Ramien ML, Bulloch AGM, et al. Efficacy and adverse events of oral isotretinoin for acne: a systematic review. Br J Dermatol. 2018;178(1):76-85.
4. Chernyshov PV, Tomas-Aragones L, Manolache L, Svensson A, Marron SE, Evers AWM, et al. Which acne treatment has the best influence on health-related quality of life? Literature review by the European Academy of Dermatology and Venereology Task Force on Quality of Life and Patient Oriented Outcomes. J Eur Acad Dermatology Venereol. 2018;32(9):1410-9.
5. Patel K, Nole BK, Fleischer A. Acne Vulgaris: The Majority of Patients Do Not Achieve Success According to FDA Guidance. J Drugs Dermatol. 2021;20(6):648-51.
6. Tang GW, Russell RM. 13-Cis-Retinoic Acid Is an Endogenous Compound in Human Serum. J Lipid Res. 1990;31(2):175-82.
7. Blaner WS. Cellular metabolism and actions of 13-cis-retinoic acid. J Am Acad Dermatol. 2001;45(5):129-35.
8. Allen JG, Bloxham DP. The pharmacology and pharmacokinetics of the retinoids. Pharmacol Ther. 1989;40(1):1-27.
9. Wiegand UW, Chou RC. Pharmacokinetics of oral isotretinoin. J Am Acad Dermatol. 1998;39(2):8-12.
10. Thielitz A, Krautheim A, Gollnick H. Update in retinoid therapy of acne. Dermatol Ther. 2006;19(5):272-9.

11. Tsukada M, Schroder M, Roos TC, Chandraratna RA, Reichert U, Merk HF, et al. 13-cis retinoic acid exerts its specific activity on human sebocytes through selective intracellular isomerization to all-trans retinoic acid and binding to retinoid acid receptors. J Invest Dermatol. 2000;115(2):321-7.
12. Tsukada M, Schroder M, Roos TC, Chandraratna RA, Reichert U, Merk HF, et al. 13-cis retinoic acid exerts its specific activity on human sebocytes through selective intracellular isomerization to all-trans retinoic acid and binding to retinoid acid receptors. J Invest Dermatol. 2000;115(2):321-7.
13. Nelson AM, Gilliland KL, Cong Z, Thiboutot DM. 13-cis retinoic acid induces apoptosis and cell cycle arrest in human SEB-1 sebocytes. J Invest Dermatol. 2006;126(10):2178-89.
14. Nelson AM, Cong Z, Gilliland KL, Thiboutot DM. TRAIL contributes to the apoptotic effect of 13-cis retinoic acid in human sebaceous gland cells. Br J Dermatol. 2011;165(3):526-33.
15. Nelson AM, Zhao W, Gilliland KL, Zaenglein AL. Neutrophil gelatinase-associated lipocalin mediates 13-cis retinoic acid-induced apoptosis of human sebaceous gland cells. J Clin Invest. 2008;118(4):1468-78.
16. Melnik BC. Apoptosis may explain the pharmacological mode of action and adverse effects of isotretinoin, including teratogenicity. Acta Derm Venereol. 2017;97(2):173-81.
17. Shi G, Liao P-Y, Cai X-L, Pi XX, Zhang MF, Li SJ, et al. FoxO1 enhances differentiation and apoptosis in human primary keratinocytes. Exp Dermatol. 2018;27(11):1254-60.
18. Rademaker M. Making sense of the effects of the cumulative dose of isotretinoin in acne vulgaris. Int J Dermatol. 2016;55(5):518-23.
19. King K, Jones DH, Daltrey DC, Cunliffe WJ. A double-blind study of the effects of 13-cis-retinoic acid on acne, sebum excretion rate and microbial population. Br J Dermatol. 1982;107(5):583-90.
20. McCoy WH, Otchere E, Rosa BA, Martin J, Mann CM, Mitreva M. Skin Ecology during Sebaceous Drought-How Skin Microbes Respond to Isotretinoin. J Invest Dermatol. 2019;139(3):732-5.
21. Dréno B, Pécastaings S, Corvec S, Veraldi S, Khammari A, Roques C. Cutibacterium acnes (Propionibacterium acnes) and acne vulgaris: a brief look at the latest updates. J Eur Acad Dermatol Venereol. 2018;32 Suppl 2:5-14.
22. Norris DA, Osborn R, Robinson W, Tonnesen MG. Isotretinoin produces significant inhibition of monocyte and neutrophil chemotaxis in vivo in patients with cystic acne. J Invest Dermatol. 1987;89(1):38-43.
23. Papakonstantinou E, Aletras AJ, Glass E, Tsogas P, Dionyssopoulos A, Adjaye J, et al. Matrix metalloproteinases of epithelial origin in facial sebum of patients with acne and their regulation by isotretinoin. J Invest Dermatol. 2005;125(4):673-84.
24. Peck GL, Olsen TG, Yoder FW, Strauss JS. Prolonged remissions of cystic and conglobate acne with 13-cis-retinoic acid. N Engl J Med. 1979;300:329-33.
25. Jones H, Blanc D, Cunliffe WJ. 13-cis retinoic acid and acne. Lancet. 1980;2(8203):1048-9.
26. Farrell LN, Strauss JS, Stranieri AM. The treatment of severe cystic acne with 13-cis-retinoic acid: Evaluation of sebum production and the clinical response in a multiple-dose trial. J Am Acad Dermatol. 1980;3(6):602-11.
27. Strauss JS, Rapini RP, Shalita AR, Konecky E, Pochi PE, Comite H, et al. Isotretinoin therapy for acne: Results of a multicenter dose-response study. J Am Acad Dermatol. 1984;10(3):490-6.
28. Jones DH, Cunliffe WJ. Remission rates in acne patients treated with various doses of i3-cis-retinoic acid (isotretinoin). Br J Dermatol. 1984;111(1):123-5.
29. Jones DH, King K, Miller AJ, Cunliffe WJ. A dose-response study of I3-cis-retinoic acid in acne vulgaris. Br J Dermatol. 1983;108(3):333-43.
30. Rademaker M, Wishart JM, Birchall NM. Isotretinoin 5 mg daily for low-grade adult acne vulgaris - A placebo-controlled, randomized double-blind study. J Eur Acad Dermatology Venereol. 2014;28(6):747-54.
31. Rademaker M, Wishart J, Birchall N. Long term remission of persistent adult acne following very low-dose (5 mg/day) isotretinoin. Australas J Dermatol. 2017;58(1):69.
32. Peck GL, Olsen TG, Yoder FW, Strauss JS. Prolonged remissions of cystic and conglobate acne with 13-cis-retinoic acid. N Engl J Med. 1979;300:329-33.
33. Thiboutot DM, Dréno B, Abanmi A, Alexis AF, Araviiskaia E, Barona Cabal MI, et al. Practical Management of Acne for Clinicians: An International Consensus from the Global Alliance to Improve Outcomes in Acne. J Am Acad Dermatol. 2018;78:S1-23.
34. Borghi A, Mantovani L, Minghetti S, Giari S, Virgili A, Bettoli V. Low-cumulative dose isotretinoin treatment in mild-to-moderate acne: Efficacy in achieving stable remission. J Eur Acad Dermatol Venereol. 2011;25(9):1094-8.
35. Lehucher-Ceyrac D, De La Salmonière P, Chastang C, Morel P. Predictive factors for failure of isotretinoin treatment in acne patients: Results from a cohort of 237 patients. Dermatology. 1999;198(3):278-83.
36. Layton A. The use of isotretinoin in acne. Dermatoendocrinol. 2009;1(3):162-9.
37. Clark SM, Goulden V, Cunliffe WJ. The management of acne patients who respond slowly to oral isotretinoin. Br J Dermatol. 1996;135(Supplement 47):20.
38. Lee HE, Chang IK, Lee Y, Kim CD, Seo YJ, Lee JH, et al. Effect of antihistamine as an adjuvant treatment of isotretinoin in acne: a randomized, controlled, comparative study. J Eur Acad Dermatol Venereol. 2014; 28(12):1654-60.
39. Spring LK, Krakowski AC, Alam M, Bhatia A, Brauer J, Cohen J, et al. Isotretinoin and timing of procedural interventions: A systematic review with consensus recommendations. JAMA Dermatology. 2017;153(8):802-9.
40. Waldman A, Bolotin D, Arndt KA, Dover JS, Geronemus RG, Chapas A, et al. ASDS Guidelines Task Force: Consensus Recommendations Regarding the Safety of Lasers, Dermabrasion, Chemical Peels, Energy Devices, and Skin Surgery during and after Isotretinoin Use. Dermatologic Surg. 2017;43(10):1249-62.
41. Mysore V, Mahadevappa OH, Barua S, Majid I. Standard guidelines of care: performing procedures in patients on or recently administered with isotretinoin. J Cutan Aesthet Surg. 2017;10:186-94.
42. Xia J, Hu G, Hu D, Geng S, Zeng W. Concomitant Use of 1,550-nm Nonablative Fractional Laser With Low-Dose Isotretinoin for the Treatment of Acne Vulgaris in Asian Patients: A Randomized Split-Face Controlled Study. Dermatol Surg. 2018;44(9):1201-8.
43. Rademaker M. Adverse effects of isotretinoin: A retrospective review of 1743 patients started on isotretinoin. Australas J Dermatol. 2010;51(4):248-53.
44. Halvorsen JA, Stern RS, Dalgard F, Thoresen M, Bjertness E, Lien L. Suicidal ideation, mental health problems, and social impairment are increased in adolescents with acne: A population-based study. J Invest Dermatol. 2011;131(2):363-70.

45. Yazici K, Baz K, Yazici A, Köktürk A, Tot S, Demirseren D, et al. Disease-specific quality of life is associated with anxiety and depression in patients with acne. J Eur Acad Dermatology Venereol. 2004;18(4):435-9.
46. Vallerand IA, Lewinson RT, Parsons LM, Lowerison MW, Frolkis AD, Kaplan GG, et al. Risk of depression among patients with acne in the U.K.: a population-based cohort study. Br J Dermatol. 2018:194-195.
47. O'Reilly K, Bailey SJ, Lane MA. Retinoid-Mediated Regulation of Mood: Possible Cellular Mechanisms. Exp Biol Med. 2008;233(3):251-8.
48. Luvizotto PP, Schmitt JV. Depressive symtpoms before and during treatment of acne with isotretinoin and its correlations: a prospective study. An Bras Dermatogia. 2020;95(6):760–70.
49. Bray AP, Kravvas G, Skevington SM, Lovell CR. Is there an association between isotretinoin therapy and adverse mood changes? A prospective study in a cohort of acne patients. J Dermatolog Treat [Internet]. 2019;30(8):796–801. Available from: https://doi.org/10.1080/09546634.2019.1577545
50. Gnanaraj P, Karthikeyan S, Narasimhan M, Rajagopalan V. Decrease in "Hamilton rating scale for depression" following isotretinoin therapy in acne: An open-label prospective study. Indian J Dermatol. 2015;60(5):461–4.
51. Yesilova Y, Bez Y, Ari M, Kaya MC, Alpak G. Effects of isotretinoin on obsessive compulsive symptoms, depression, and anxiety in patients with acne vulgaris. J Dermatolog Treat. 2012;23(4):268–71.
52. Ergun T, Seckin D, Ozaydin N, Bakar Ö, Comert A, Atsu N, et al. Isotretinoin has no negative effect on attention, executive function and mood. J Eur Acad Dermatology Venereol. 2012;26(4):431–9.
53. Huang YC, Cheng YC. Isotretinoin treatment for acne and risk of depression: A systematic review and meta-analysis. J Am Acad Dermatol. 2017;76(6):1068-1076.e9.
54. Li C, Chen J, Wang W, Ai M, Zhang Q, Kuang L. Use of isotretinoin and risk of depression in patients with acne: A systematic review and meta-analysis. BMJ Open. 2019;9(1).
55. Wysowski DK, Pitts M, Beitz J. Depression and suicide in patients treated with isotretinoin. N Engl J Med. 2001;344(6):460.
56. Bachmann C, Grabarkiewicz J, Theisen FM, Remschmidt H. Isotretinoin, depression and suicide ideation in an adolescent boy. Pharmacopsychiatry. 2007;40(3):128.
57. Crockett SD, Porter CQ, Martin CF, Sandler RS, Kappelman MD. Isotretinoin use and the risk of inflammatory bowel disease: A case-control study. Am J Gastroenterol. 2010;105(9):1986-93.
58. Etminan M, Bird ST, Delaney JA, Bressler B, Brophy JM. Isotretinoin and Risk for Inflammatory Bowel Disease. JAMA Dermatology 2013;149(2):216.
59. Racine A, Cuerq A, Bijon A, Ricordeau P, Weill A, Allemand H, et al. Isotretinoin and risk of inflammatory bowel disease: A french nationwide study. Am J Gastroenterol. 2014;109(4):563-9.
60. Rashtak S, Khaleghi S, Pittelkow MR, Larson JJ, Lahr BD, Murray JA. Isotretinoin exposure and risk of inflammatory bowel disease. JAMA Dermatology. 2014;150(12):1322-6.
61. Alhusayen RO, Juurlink DN, Mamdani MM, Morrow RL, Shear NH, Dormuth CR. Isotretinoin use and the risk of inflammatory bowel disease: A population-based cohort study. J Invest Dermatol. 2013;133(4):907-12.
62. Lee SY, Jamal MM, Nguyen ET, Bechtold ML, Nguyen DL. Does exposure to isotretinoin increase the risk for the development of inflammatory bowel disease? A meta-analysis. Eur J Gastroenterol Hepatol. 2015:1.
63. Crockett SD, Gulati A, Sandler RS, Kappelman MD. A causal association between isotretinoin and inflammatory bowel disease has yet to be established. Am J Gastroenterol. 2009;104(10):2387-93.
64. Godfrey KM, James MP. Treatment of severe acne with isotretinoin in patients with inflammatory bowel disease. Br J Dermatol. 1990;123(5):653-5.
65. Schleicher SM. Oral isotretinoin and inflammatory bowel disease. J Am Acad Dermatol. 1985;13(5):834-5.
66. Mejer J, Dierckls G, Pas H. Is isotretinoin safe in patients with acne and inflammatory bowel disease? J Invest Dermatol. 2018;138(5):S71.
67. Fraunfelder FW, Fraunfelder FT, Corbett JJ. Isotretinoin-associated intracranial hypertension. Ophthalmology. 2004;111(6):1248-50.
68. Kadam P, Whitfeld M. Isotretinoin and doxycyline use in treating acneiform eruption following chemotherapy. Australas J Dermatol. 2018;59(S1):76.
69. Tintle SJ, Harper JC, Webster GF, Kim GK, Thiboutot DM. Safe use of therapeutic-dose oral isotretinoin in patients with a history of pseudotumor cerebri. JAMA Dermatology. 2016;152(5):582-4.
70. Neudorfer M, Goldshtein I, Shamai-Lubovitz O, Chodick G, Dadon Y, Shalev V. Ocular adverse effects of systemic treatment with isotretinoin. Arch Dermatol. 2012;148(7):803-8.
71. Maclean H, Wright M, Choi D, Tidman MJ. Abnormal night vision with isotretinoin therapy for acne. Clin Exp Dermatol. 1995;20(1):86.
72. Mollan SP, Woodcock M, Siddiqi R, Huntbach J, Good P, Scott RAH. Does use of isotretinoin rule out a career in flying? Br J Ophthalmol. 2006;90(8):957-9.
73. Grattan CEH, Brown RD, Cowan MA, Ryatt KS. Retinoids and the eye - reduced rod function with isotretinoin. Br J Dermatol. 1987;117(s32):23.
74. Weleber RG, Denman ST, Hanifin JM, Cunningham WJ. Abnormal retinal function associated with isotretinoin therapy for acne. Arch Ophthalmol. 1986;104(6):831-7.
75. Law WC, Rando RR. The molecular basis of retinoic acid induced night blindness. Biochem Biophys Res Commun. 1989;161(2):825-9.
76. Kilcoyne RF, Cope R, Cunningham W, Nardella FA. Minimal spinal hyperostosis with low-dose isotretinoin therapy. Invest Radiol. 1986;21:41-4.
77. Gerber LH, Helfgott RK, Gross EG, Hicks JE, Ellenberg SS, Peck GL. Vertebral abnormalities associated with synthetic retinoid use. J Am Acad Dermatol. 1984;10(5):817-23.
78. Tangrea JA, Kilcoyne RF, Taylor PR, Helsel WE, Adrianza ME, Hartman AM, et al. Skeletal Hyperostosis in Patients Receiving Chronic, Very-Low-Dose Isotretinoin. Arch Dermatol. 1992;128:921-5.
79. Alazawi S, Hendriksz T. Analysis of the effects of isotretinoin on the premature epiphyseal closure in pediatric populations: a literature review. Journal of Osteopathic Medicine 2021;122(1):45-53.
80. Steele RG, Lugg P, Richardson M. Premature epiphyseal closure secondary to single-course vitamin A therapy. Aust N Z J Surg. 1999;69(11):825-7.
81. Tran A, Walker J, Shulakewych M. Premature epiphyseal closure in pediatric patients on isotretinoin therapy. J Am Acad Dermatol. 2008;58(Supplement 2):AB7.
82. Luthi F, Eggel Y, Theumann N. Premature epiphyseal closure in an adolescent treated by retinoids for acne: An unusual cause of anterior knee pain. Jt Bone Spine. 2012;79(3):314-6.

83. Standeven AM, Davies PJA, Chandraratna RAS, Mader DR, Johnson AT, Thomazy VA. Retinoid-induced epiphyseal plate closure in guinea pigs. Fundam Appl Toxicol. 1996;34(1):91-8.
84. Chroni E, Monastirli A, Tsambaos D. Neuromuscular Adverse Effects Associated with Systemic Retinoid Dermatotherapy. Drug Saf. 2010;33(1):25-34.
85. Landau M, Mesterman R, Ophir J, Mevorah B, Alcalay J, Harel A, et al. Clinical significance of markedly elevated serum creatine kinase levels in patients with acne on isotretinoin. Acta Derm Venereol. 2001;81(5):350-352.
86. Hartung B, Merk HF, Huckenbeck W, Daldrup T, Neuen-Jacob E, Ritz-Timme S. Severe generalised rhabdomyolysis with fatal outcome associated with isotretinoin. Int J Legal Med. 2012;126(6):953-6.
87. Lammer EJ, Chen DT, Hoar RM, Agnish ND. Retinoic acid embryopathy. N Engl J Med. 1985;313(14):837-41
88. Melnik BC. Overexpression of p53 explains isotretinoin's teratogenicity. Exp Dermatol. 2018;27(1):91-3.
89. Dai WS, LaBraico JM, Stern RS. Epidemiology of isotretinoin exposure during pregnancy. J Am Acad Dermatol. 1992;26(4):599-606.
90. World Helath Organization. Vitamin A supplementation during pregnancy. https://www.who.int/elena/titles/guidance_summaries/vitamina_pregnancy/en/. Accessed January 7, 2020.
91. Cinar SL, Kartal D, Ergin C. The effect of systemic isotretinoin on male fertility. Cutan Ocul Toxicol. 2016;35(4):296-9.
92. Amory JK, Ostrowski KA, Gannon JR, Berkseth K, Stevison F, Isoherranen N, et al. Isotretinoin administration improves sperm production in men with infertility from oligoasthenozoospermia: a pilot study. Andrology. 2017;5(6):1115-1123.
93. Coleman R, MacDonald D. Effects of isotretinoin on male reproductive system. Lancet. 1994;344(8916):198.
94. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999;281(6):537-44.
95. Cinar SL, Kartal D, Aksoy H, Cinar E, Aydin T, Öz L, et al. Long-term effect of systemic isotretinoin on female fertility. Cutan Ocul Toxicol. 2017;36(2):132-4.
96. Lee YH, Scharnitz TP, Muscat J, Chen A, Gupta-Elera G, Kirby JS. Laboratory monitoring during isotretinoin therapy for acne a systematic review and meta-analysis. JAMA Dermatology. 2016;152(1):35-44.
97. Hansen TJ, Lucking SM, Miller JJ, Kirby JS, Thiboutot DM, Zaenglein AL. Standardized laboratory monitoring with use of isotretinoin in acne. J Am Acad Dermatol. 2016;75(2):323-8.
98. Zane LT, Leyden WA, Marqueling AL, Manos MM. A population-based analysis of laboratory abnormalities during isotretinoin therapy for acne vulgaris. Arch Dermatol. 2006;142(8):1016-22.
99. Barbieri JS, Shin DB, Wang S, Margolis DJ, Takeshita J. The clinical utility of laboratory monitoring during isotretinoin therapy for acne and changes to monitoring practices over time. J Am Acad Dermatol. 2019;82(1):72-9.
100. Opel D, Kramer ON, Chevalier M, Bigby M, Albrecht J. Not every patient needs a triglyceride check, but all can get pancreatitis: a systematic review and clinical characterization of isotretinoin-associated pancreatitis. Br J Dermatol. 2017;177(4):960-6.
101. Nast A, Dréno B, Bettoli V, Bukvic Mokos Z, Degitz K, Dressler C, et al. European evidence-based (S3) guideline for the treatment of acne – update 2016 – short version. J Eur Acad Dermatol Venereol. 2016;30(8):1261-8.
102. Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74(5):945-973e33.
103. National Institute for Health and Care Excellece. Acne Vulgaris: management. 2021 https://www.nice.org.uk/guidance/ng198/resources/acne-vulgaris-management-pdf-66142088866501. Accessed 10th April, 2022.
104. Lee JW, Yoo KH, Park KY, Han TY, Li K, Seo SJ, et al. Effectiveness of conventional, low-dose and intermittent oral isotretinoin in the treatment of acne: A randomized, controlled comparative study. Br J Dermatol. 2011;164(6):1369-75.
105. Agarwal U, Bhola K, Besarwal R. Oral isotretinoin in different dose regimens for acne vulgaris: A randomized comparative trial. Indian J Dermatol Venereol Leprol. 2011;77(6):688.
106. Mandekou-Lefaki I, Delli F, Teknetzis A, Euthimiadou R, Karakatsanis G. Low-dose schema of isotretinoin in acne vulgaris. Int J Clin Pharmacol Res. 2003;23(2-3):41-6.
107. Dhaked D, Meena R, Maheshwari A, Agarwal U, Purohit S. A randomized comparative trial of two low-dose oral isotretinoin regimens in moderate to severe acne vulgaris. Indian Dermatol Online J. 2016;7(5):378.
108. Almas U, Kharaba ZJ, Khalid M, Buabeid MA, Sattar F, Tahir R, et al. Effectiveness of conventional versus low-dose oral isotretinoin in the treatment of moderate to severe acne. Lat Am J Pharm. 2020;39(5):986-90.
109. Amichai B, Shemer A, Grunwald MH. Low-dose isotretinoin in the treatment of acne vulgaris. J Am Acad Dermatol. 2006;54(4):644-6.
110. Sardana K, Garg VK, Sehgal VN, Mahajan S, Bhushan P. Efficacy of fixed low-dose isotretinoin (20 mg, alternate days) with topical clindamycin gel in moderately severe acne vulgaris. J Eur Acad Dermatol Venereol. 2009;23(5):556-60.
111. De D, Kanwar AJ. Combination of low-dose isotretinoin and pulsed oral azithromycin in the management of moderate to severe acne: A preliminary open-label, prospective, non-comparative, single-centre study. Clin Drug Investig. 2011;31(8):599-604.
112. Rao PK, Bhat RM, Nandakishore B, Dandakeri S, Martis J, Kamath GH. Safety and efficacy of low-dose isotretinoin in the treatment of moderate to severe acne vulgaris. Indian J Dermatol. 2014;59(3):316.
113. Yap FB. Safety and efficacy of fixed-dose 10 mg daily isotretinoin treatment for acne vulgaris in Malaysia. J Cosmet Dermatol. 2017;16(3):348-52.

Forever Clear BBL®

Get Clear...Clear from acne and discoloration

Forever Clear™ BBL® takes a multi-step approach to combating acne.

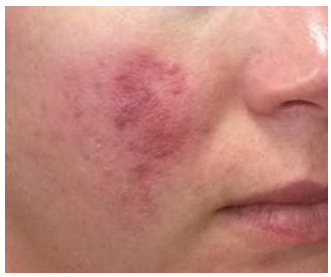
1. Starting at the the root cause, it eliminates acne-causing bacteria
2. Treats and reduces redness and hyper-pigmentation left from breakouts
3. Boosts the healing process for more radiant and healthy-looking skin

Great for teens and adults

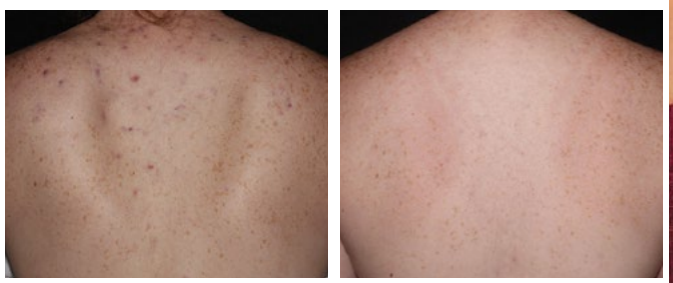
Treatment in as little as 15 min.

Start wearing makeup the next day!

Learn more at BBLbySciton.com



Forever Clear™ BBL® | 5 months post 7 treatments
courtesy of Carrie Labert, PA-C



Forever Clear™ BBL® | 4 months post 6 treatments
courtesy of Patrick Bitter, Jr., MD

SCITON®
BECAUSE RESULTS MATTER

LEARN MORE: WWW.SCITON.COM.AU

Phone: +61 409 470 692 | Email: anz@sciton.com

Australasian Society of Cosmetic Dermatologists
www.ascd.org.au/medical_journal

Thank you to the ASCD Industry Partners

Advanced Cosmeceuticals Medical

Allergan Aesthetics an AbbVie company

Cryomed Aesthetics

SCITON BECAUSE RESULTS MATTER

CUTERA FACE + BODY AESTHETIC SOLUTIONS

Lumenis Energy to Healthcare

SOLTAMEDICAL A DIVISION OF VALEANT PHARMACEUTICALS

BTL AESTHETICS

Pierre Fabre

DMS DIGITAL MEDICAL SYSTEMS CONFIDENT IT

CYNOSURE BEAUTIFUL ENERGY