IADVL

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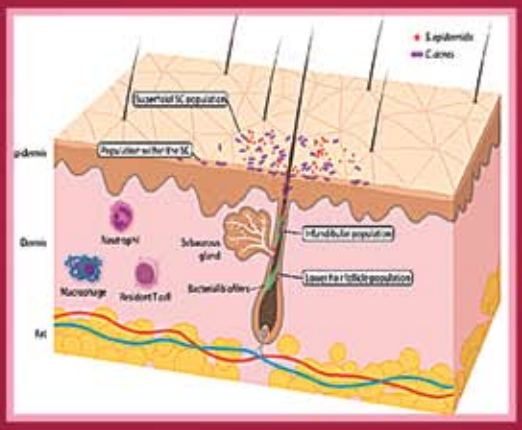
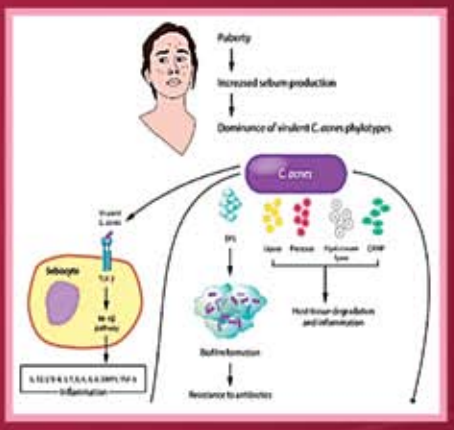
Coordinator





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FOREWORD

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Acne and appendageal disorders like hidradenitis suppurativa (HS), hyperhidrosis, and rosacea form a large section of patients we see in clinical practice. “Acne” as a topic, never fails to amaze.

Newer concepts in etiopathogenesis, clinical diversity across ages, innovative therapeutic molecules, and the struggle to quell the antibiotic -resistant Cutibacterium acnes, are some of the challenges we face today. The Covid epidemic described a new acne phenotype, aptly named “maskne”.

We are now also aware of the role of the microbiome and the brain-gut-skin connect for all the above diseases. Diseases like HS, rosacea, and hyperhidrosis impair an individual's QoL, and require a lot of “hand-holding” during the course of treatment. This newsletter discusses the above and much more. We have also included a quiz to titillate your grey cells.

We are grateful to our editorial team Dr. Dipali Rathod, Dr. Abhineeta Hosthota and Dr. Shashank Bhargava, for planning and executing this for us. Also, a special thanks to all our SIG members who have contributed to this issue.

On behalf of our SIG members of “Acne and Appendageal Disorders” we are delighted to release our first newsletter of 2022-2023.

Wish you all happy reading!

From,

COORDINATOR - Dr. Nina Madnani

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MICROBIOME IN ACNE

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KEY POINTS:

- Inflammatory acne is related to a loss of the diversity of phylotypes of C. acnes.
- C. acnes and Staphylococcus epidermidis play a role in the process of inflammation in the skin.
- Treatments other than antibiotics are needed to restore the diversity and balance of the microbiome.

INTRODUCTION:

Acne is a highly prevalent inflammatory skin condition involving sebaceous sites. It develops due to the interplay of multiple factors and the interaction between skin microbes and host immunity.

The term 'microbiome' covers a whole range of microorganisms, including bacteria, viruses, fungi, and the environment surrounding them. The word 'microbiota' is more confined, describing the group of commensals, symbiotic, and pathogenic micro-organisms found in a fixed environment.

Human skin is the body's largest organ and provides the first line of defence against external agents. It functions as both a physical and immunological barrier by providing innate and adaptive immunity. Resident skin microbes stabilize the host's barrier by fighting pathogens by interacting and modifying host immunity. Therefore, the skin microbiome is as an essential part of human health, and dysbiosis causes or aggravates acne.

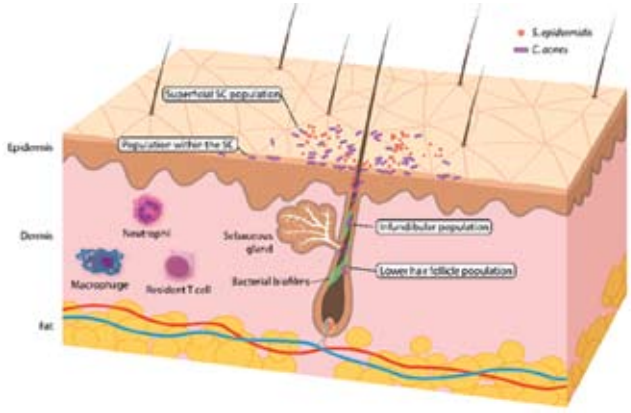

Figure 1: Overview of the skin (pilosebaceous unit) and the C. acnes population within it.

The bacterial composition varies among individuals & the body sites. Environmental factors such as the use of soaps, cosmetics, antibiotics, occupation, temperature, humidity, and UV exposure also influence microbial colonization. Sebaceous sites such as the forehead, retro-auricular area, back, and alar crease, show the lowest bacterial diversity. Cutibacterium species are the main isolates, as they can survive in anaerobic, lipid-rich conditions. Microbiome takes shape in these sites during puberty, as hormonal changes activate the sebaceous glands.

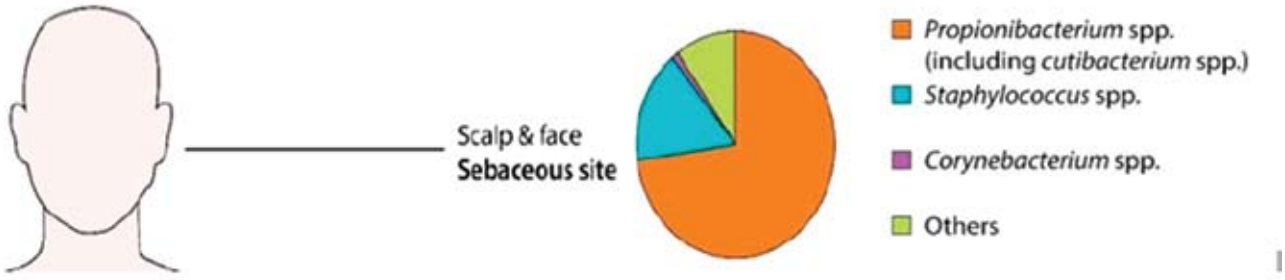

Figure 2: Propionibacterium spp. (including Cutibacterium spp.) are most prevalent in sebum-rich areas.

SKIN MICROBIOME AND ACNE

C. acnes accounts for up to 90% of the microbiota in sebum-rich sites. C. acnes is an aerotolerant, anaerobic, Gram-positive, pleomorphic rod that belongs to the Actinobacteria phylum. It is scarce on the skin in childhood, gradually increases from puberty to adulthood, and then decreases later with age. C. acnes is primarily a beneficial commensal. It helps maintain a low skin pH by releasing free fatty acids, and it blocks pathogens (i.e., Staphylococcus aureus and Streptococcus) from colonizing the skin.

C. acnes was grouped into phylotype I as C. acnes subsp. acnes, phylotype II as C. acnes subsp. defendens, and phylotype III as C. acnes subsp. elongatum. It is identified that acne-related strains generate more porphyrin, a substance that generates reactive oxygen species (ROS) and can stir up inflammation in keratinocytes.

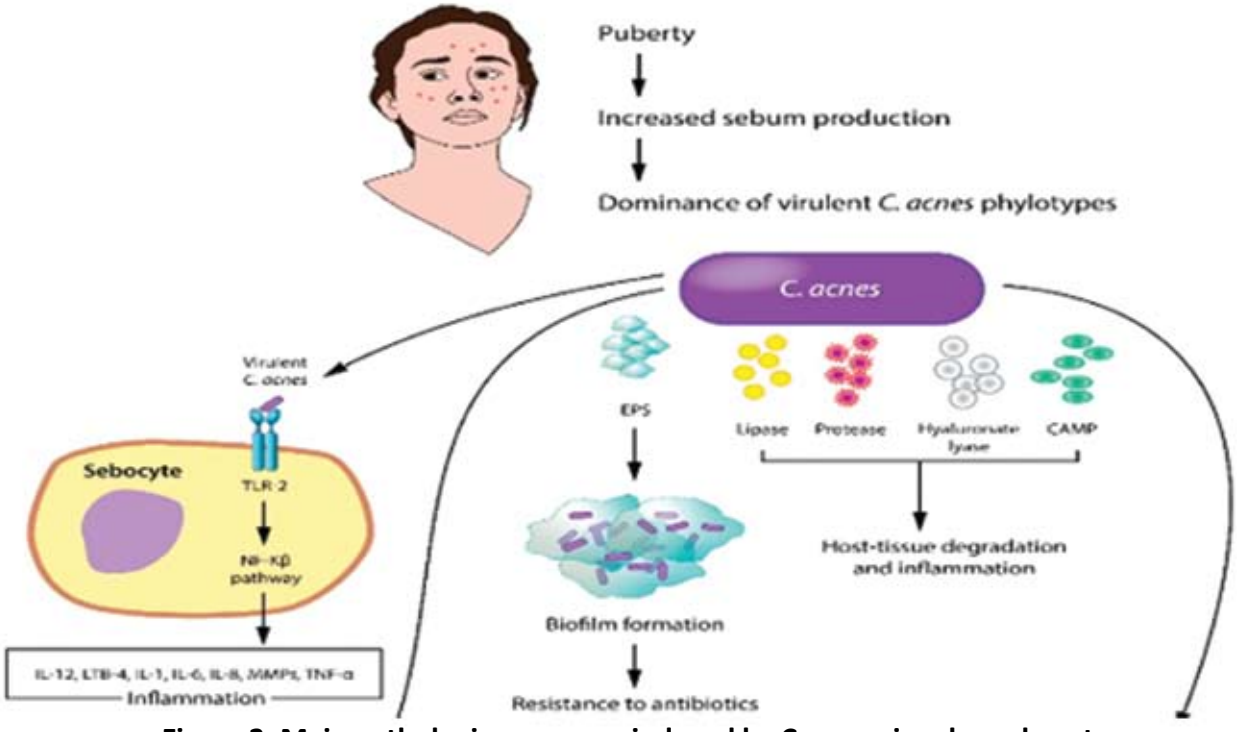

Figure 3: Main pathologic processes induced by C. acnes involve sebocytes

C. acnes and S. epidermidis were more prevalent in acne patients. S. epidermidis was found to prevent acne and exert antimicrobial activity by producing antimicrobial peptides such as epidermin, phenol-soluble modulins, Pep5, and epilancin. S. epidermidis was shown to generate staphylococcal lipoteichoic acid, which dampens C. acnes-related inflammation by blocking TLR-2 expression in keratinocytes. Thus, S. epidermidis might play a role in acne prevention.

C. granulosum is highly abundant in the comedones and pustules of acne patients. Furthermore, C. granulosum displays stronger virulence (i.e., lipase activity) than C. acnes. Malassezia, a cutaneous fungal organism, hydrolyses sebum triglycerides into free fatty acids, which causes hyper-keratinization of hair follicular ducts and comedone formation. It also chemo-attracts neutrophils and promotes the release of pro-inflammatory cytokines from monocytes.

The understanding of the microbiome in pathophysiology of acne has to continue to develop new therapeutic armamentarium. Novel systemic and topical interventions that influence the microbiome needs intense research.

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THE ROLE OF THE SKIN IMMUNE SYSTEM IN ACNE

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KEY POINTS

- Acne is hypothesized now to be a primary inflammatory dermatitis.
- Presence of a few inflammation markers like IL-1 in microcomedones.
- Targeted therapies for acne are under clinical trials.
- The role of Gevokizumab (anti IL-11β humanized monoclonal immunoglobulin IgG2 antibody) in acne has been studied and has a potential role in the future.

INTRODUCTION

Acne vulgaris is a dermatological condition affecting usually adolescents and young adults. The salient pathogenic events are well studied and understood but little is known about the role of skin immune cells in the development of acne. Earlier, it was believed that acne developed upon the abnormal sloughing of keratinocytes that line the sebaceous gland, which resulted in excessive keratosis of the pilosebaceous duct and the formation of microcomedones. But recently, there has been a shift in the understanding of acne pathogenesis, and it is currently believed that it is a primary inflammatory dermatitis.

IMMUNOLOGY

Over time it is found that a subclinical infection in normal skin develops before the occurrence of microcomedones. The studies showed the presence of inflammatory markers in the contents of microcomedones. It was also shown that IL-1 was present in comedonal contents. It is worth noting that the so-called “inflammatory components”, i.e., CD4+ T cells and macrophages, are also present in the skin and are unaffected by acne lesions. Myeloid cells of the skin also serve as a connection between innate and adaptive immune responses (Figure 1). In recent years, it was proven that immunogenic proteins of C. acnes released to the sebaceous gland duct may be processed by Langerhans cells, which in turn may present antigens to CD4+ T cells in local lymph nodes and play a significant role in the activation of Th17. Hence, acne was called T helper type 17 (Th17) mediated disease. Furthermore, inflammation may occur in acne lesions independently of these bacteria. The process is mediated by androgens or by neurogenic activation, followed by the secretion in the skin of pro-inflammatory neuropeptides.

APPLIED ASPECT

Cutibacterium acnes interacts with the innate

system via 4 pathways namely through Toll-like receptors (TLRs), activating inflammosomes, inducing the production of matrix metalloproteinases (MMPs) and stimulating antimicrobial peptide (AMP) activity. It is very important to further understand the role of the skin's immune cells in the pathogenesis of acne which would contribute to the application of modern therapeutic strategies that would avoid addiction to antibiotics. Targeted therapy for acne vulgaris is still under research and clinical trials. One of these therapeutics includes the inhibitors of interleukin-1β signaling, for example, Gevokizumab (XOMA 052). It is an anti-Il-1β humanized monoclonal immunoglobulin IgG2 antibody and is studied in clinical trials (ClinicalTrial.gov Identifier: NCT01498874). The trial suggests that the inhibitors of interleukin-1β could be potentially used in acne treatment in the future. Another study has emphasized role of vitamin A (all-trans-retinoic acid) and vitamin D (1,25-dihydroxyvitamin D3) in suppressing this inflammatory stimulation. This discovery might be used to develop another acne therapy option in the future.

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ANTIBIOTICS IN ACNE – AN UPDATE, CONTROVERSIES, BEST PRACTICES AND OPTIMIZATION

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KEY POINTS:

- Oral antibiotics still feature in the major guidelines for acne management
- Antibiotic stewardship should be adhered to strictly, to optimize treatment outcomes and to limit resistance.
- Tetracyclines are preferred over Macrolides (exceptions in special situations for pregnancy, nursing, and age under 8 years where Macrolides will be preferred)

INTRODUCTION:

Antibiotics in acne have been used since evermore. There is, in fact, more evidence on the usage patterns of antibiotics in acne as compared with any other therapeutic option. Cumulative usage to be limited to 3 months continuous / 6 months interrupted. Lower doses, extended-release formulations must be encouraged. Combination with topical benzoyl peroxide and / or adapalene must be used.

RATIONALE OF USE:

The purported rationale for using select classes of systemic antibiotics, namely macrolides and tetracyclines is that they confer an anti-inflammatory and/or immunomodulatory effect on acnegenic skin rather than simply limiting the colonization of C. acnes. This writeup will focus on topicals and systemic agents, distinctly, and attempt to establish best practices and optimizing use patterns of the same. Furthermore, microbiologic testing is non-standard, and a reduction in bacterial numbers does not vary the outcome, in any way, which is a testament to the fact that the remarkability of antibiotics working on the immune system trumps their antibacterial effect. The anti-inflammatory effect occurs due to the inhibition of neutrophil chemotaxis, cytokine production, and macrophage function. Very recently, USFDA approved the usage of Oral Sarecycline for moderate to severe acne.

Topical and Systemic antibiotics feature in nearly all global guidelines. (AAD, BAD, IADVL, NICE) A concise summary sheet of each of the guidelines is appended herewith, with regard to antibacterial usage – both topical and systemic.

For brevity and the sake of easy recall, the following abbreviations have been used – BPO for benzoyl peroxide, TRET for tretinoin, ADP for Adapalene, and CDM for Clindamycin will feature throughout the article.

IAA Consensus, as per IADVL

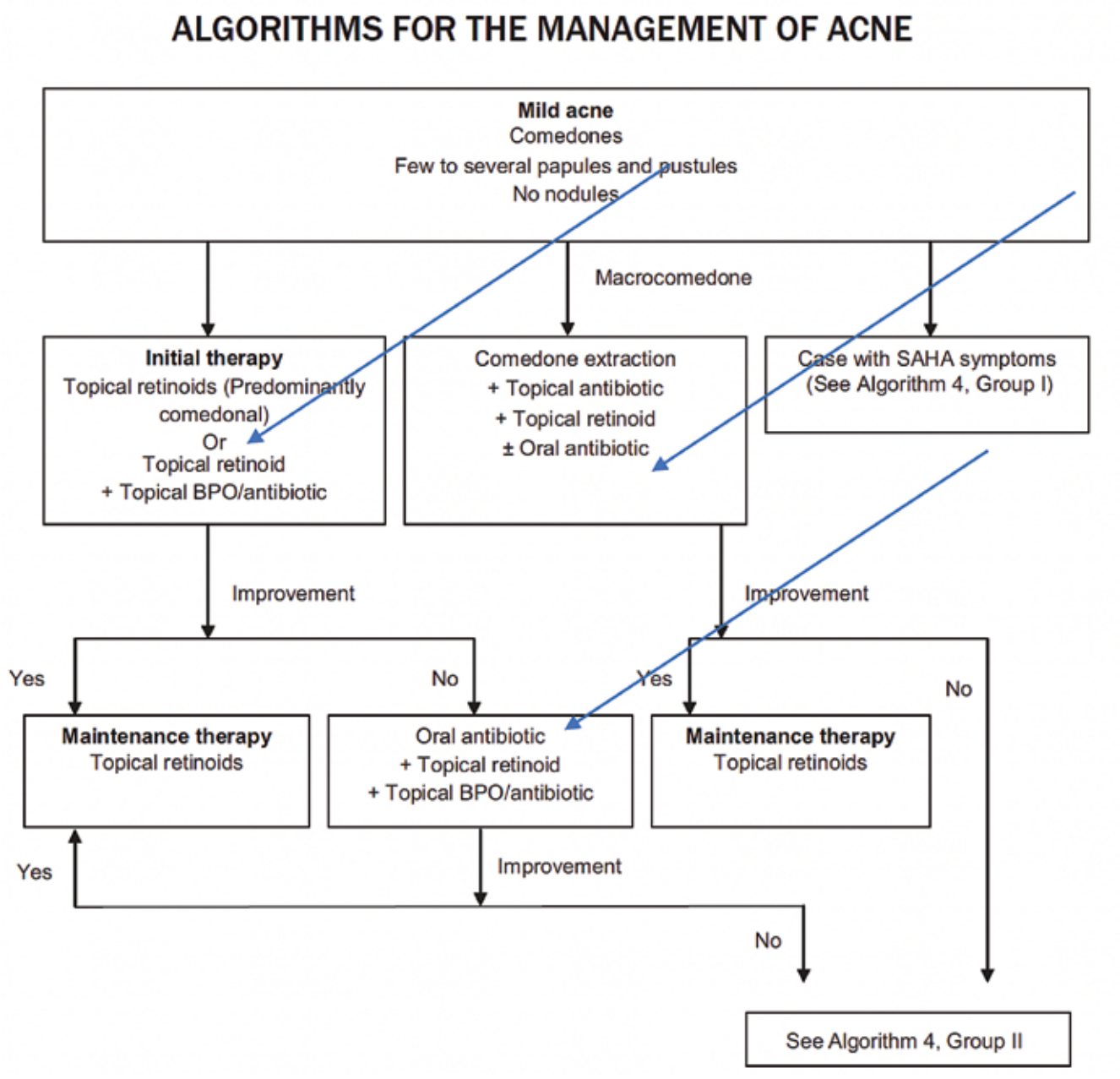

Figure 1 – Adapted from Kubba et al.

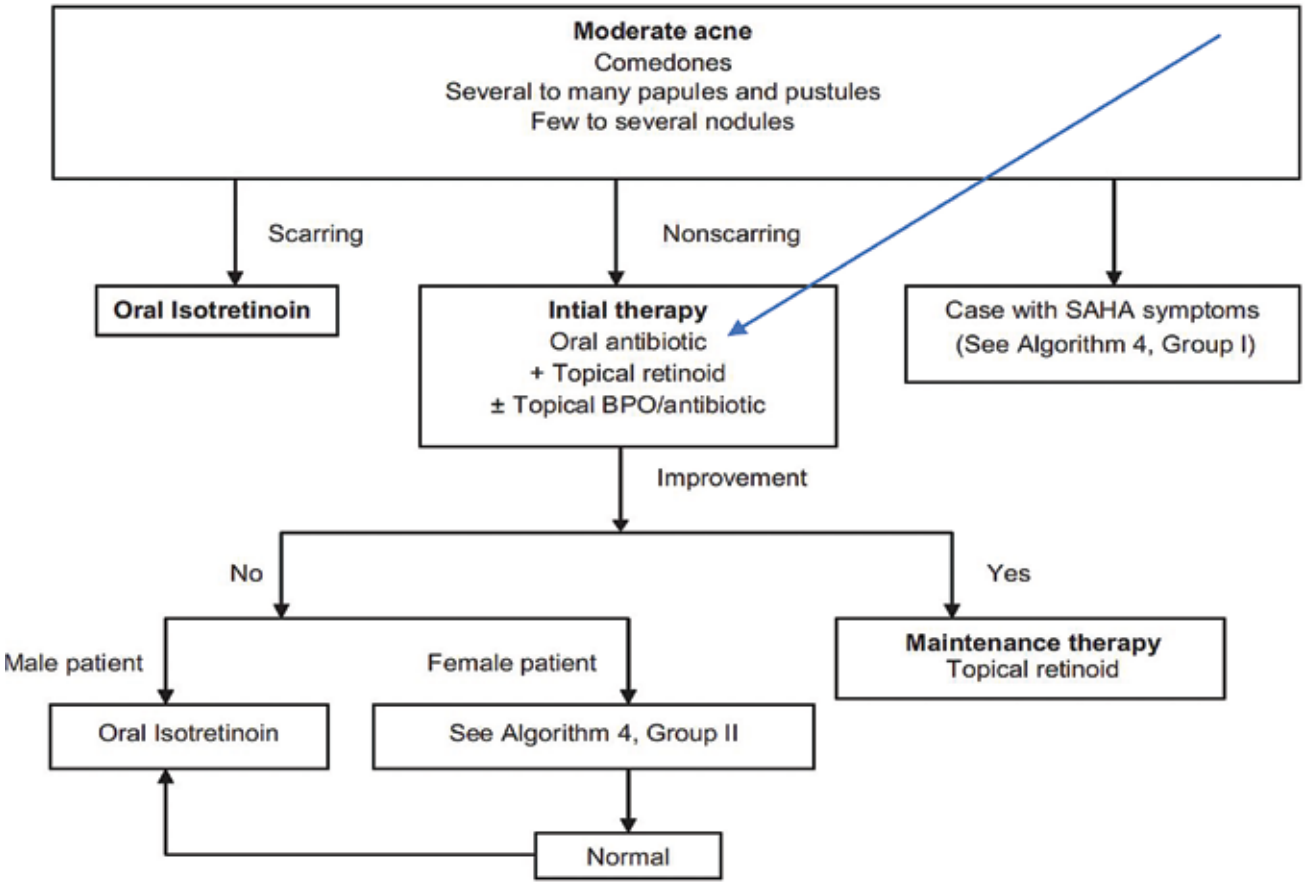

Figure 2 – Adapted from Kubba et al.

AAD guidelines with regards to antibacterials

- "Moderate to severe inflammatory acne" resistant to topicals
- Combine with topical ADP / TRET / BPO
- Systemic Therapeutic Options
    - Doxycycline
    - Tetracycline
    - Minocycline
    - Lymecycline
    - Erythromycin
    - Azithromycin
    - Trimethoprim – Sulphamethoxazole
    - Cephalexin
- Topical Options – Clindamycin

'NICE guidelines' and 'American Acne and Rosacea Society' mention the following with regard to antibiotics

Mild – Moderate Acne

1st Line – Topical TRET / topical BPO with topical CDM

Moderate – Severe Acne

1st Line – Oral Lymecycline / Doxycycline with topical ADP or BPO

Never Monotherapy / Never > 3 months continuous (maximum 6 months)

For special situations, the following benchmark may be adhered to. These are situations where other anti-acne agents are not fit to be administered.

- Pediatric Age Group (upto 8 years) – Macrolides
- > 8 years – Tetracyclines
- Pregnancy – Macrolides only, if deemed necessary

POOLED GUIDELINES ON THE USE PATTERN OF ANTIBIOTIC THERAPY

- Usage - 3 months continuous or till subsistence of inflammatory lesions (maximum 6 months)
- Low dose (Subantimicrobial dose)
- Tetracyclines > Macrolides (exceptions in special situations for pregnancy, nursing, and age under 8 years where Macrolides will be preferred)
- Extended-Release formulations are preferred (limit adverse effects, limit resistance)
- Combination therapy (topical BPO/retinoids) (resistance)
- Adherence to antibiotic stewardship guidelines

These stewardship guidelines will help prevent antibacterial resistance in the long run, and make antibiotic usage more scientific.

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SARECYCLINE IN ACNE

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KEY POINTS

- Sarecycline is a novel, narrow-spectrum tetracycline-derived oral antibiotic showing one of the promising treatment options for acne, given once daily with or without food; and improvement can be seen in inflammatory lesions as early as 3 weeks.
- Found to be effective in perioral dermatitis, and papulopustular rosacea.
- Due to its consistent safety profile with a low incidence of GI, vestibular, and phototoxic side effects, sarecycline remains a safe option while treating patients for longer periods of time.
- Head-to-head studies comparing sarecycline to other commonly used tetracyclines for acne shall be helpful to determine its superiority in efficacy and safety.
- Antibiotic monotherapy should be avoided.

INTRODUCTION

Tetracyclines are often prescribed by dermatologists in the management of moderate to severe inflammatory acne and rosacea. Tetracycline-class antibiotics have three generations: first (tetracycline); second (doxycycline & minocycline) and third generation (sarecycline). Antibiotic resistance is a limiting factor for prescribing it alone or for longer periods. Compared to older tetracyclines which are broad spectrum; sarecycline; is an immediate release tetracycline derivative having a narrow antibacterial spectrum due to its modified structure. Compared to doxycycline and minocycline, sarecycline has a narrower antibacterial spectrum, with limited activity against enteric gram-negative bacteria.

MECHANISM OF ACTION

The antimicrobial effect of all tetracyclines; is due to binding to the bacterial 30s-ribosomal subunit and blocking the union of aminoacyl-tRNA with the acceptor. Sarecycline inhibits microbial protein and DNA synthesis; explains its anti-inflammatory effects with neglectable effects on lipid biosynthesis, RNA synthesis and cell wall synthesis.

EVIDENCE AND INDICATIONS

Sarecycline demonstrated a favourable safety and tolerability profile in the treatment of acne vulgaris compared with broad-spectrum tetracyclines in two large phase III clinical trials. Narrow-spectrum sarecycline is less active compared with minocycline against 79% of human gut microorganisms tested. Therefore, it “spares the gut microbiome” and due to reduced activity against Gram-negative gastrointestinal organisms observed the low gastrointestinal toxicity in the phase III clinical trials. Sarecycline has demonstrated to have low potential in crossing BBB compared to minocycline so probably related side effects would be less compared to minocycline.

It has been studied in both inflammatory and non-inflammatory acne lesions and found to be safe for up to one year and having few adverse effects. But further studies are needed to monitor the adverse effects.

Sarecycline got FDA approval in the year 2018 for once daily treatment of inflammatory (non-nodular) moderate to severe acne vulgaris for the age 9 years above, can be taken once daily with or without food, and has demonstrated in clinical trials efficacy against facial and truncal acne, often with improvement as early as 3 weeks. Apart from acne vulgaris, sarecycline has been tried and found to be effective in treating periorificial dermatitis and papulopustular rosacea. In a small sample size trial, it has been shown to be clinically effective for patients in the treatment of cutaneous staphylococcal infections, inflammatory dermatoses, and autoimmune blistering disorders.

DOSAGE

In a study (phase 2 trial) three dosage regimens were evaluated; they were 0.75 mg/kg, 1.5mg/kg and 3 mg/kg sarecycline or placebo (1:1:1:1). At 12 weeks doses 1.5 mg/kg and 3 mg/kg demonstrate significant reduction of inflammatory acne lesions compared to baseline (52.7% and 51.8%) vs placebo. Since it was observed that the response with 1.5 mg/kg and 3 mg/kg is almost similar; 1.5 mg/kg was identified as a therapeutic dose.

ADVERSE EFFECTS

Sarecycline is generally well-tolerated. Since it has a narrow spectrum of activity which results in less disruption of commensal organisms leading to a low incidence of vulvovaginal candidiasis and gastrointestinal side effects. Unlike doxycycline and minocycline, it does not cross the blood-brain-barrier, hence fewer chances of neurological side effects. In clinical trials, the most common adverse effect is nausea, which occurred more than the placebo group. Though there is a low risk of photosensitivity and phototoxicity in clinical trials, it showed phototoxic potential in mice, hence sarecycline may cause an increased risk of sunburn, and during treatment patients should minimize or avoid exposure to sunlight and take appropriate sun protection measures.

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UPDATE ON DRUG RESISTANCE IN ACNE

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KEY POINTS

- The phenomenon of antimicrobial resistance (AMR) in acne is a real threat.
- Resistance to most of the commonly used antibiotics limits our therapeutic armamentarium at present.
- The need of the hour is to explore newer therapies in acne viz. phage therapy, antimicrobial cationic peptides, ectopeptidase inhibitors, and plant extracts.
- Most of the therapeutic guidelines for acne strictly prohibit antibiotic monotherapy.

THE SCOPE OF THE PROBLEM

The world health organization (WHO) has recognized antimicrobial resistance (AMR) as a real threat. Indiscriminate usage of antibiotics over the years has led to prominent levels of resistance to most of the commonly used antibiotics. Antibiotics were first used in acne in 1951, by Andrews and his team. Tetracycline, doxycycline, minocycline, and sulfonamides were gradually added to antibiotic therapy for acne. Among topical therapies, clindamycin and erythromycin have been extensively used in acne. Currently, most countries report resistance to these agents.

Worldwide, resistance to erythromycin and clindamycin remains high. Resistance to doxycycline and tetracycline is high in India. Azithromycin and clarithromycin show higher resistance rates than erythromycin in our country. Cross-resistance among antibiotics is common. Topical antibiotic usage generates more AMR than oral usage.

WHAT IS THE RATIONALE FOR USING ANTIBIOTICS FOR ACNE?

Acne is classified as an inflammatory disorder, hence the rationale of using long-term antibiotics for acne is not justifiable. Although Cutibacterium acnes is implicated in the causation of acne, it is a normal commensal of the pilosebaceous unit and thus the mere presence of this organism does not indicate infection. Antibiotics in acne are used for their anti-inflammatory properties, thus prolonged usage is not acceptable.

NEWER ALTERNATIVES TO ANTIBIOTICS

1. Non-antibiotic antibacterial agents: benzoyl peroxide, azelaic acid, retinoids, and zinc gluconate are effective agents with anti-bacterial action that have been tried in acne.
2. Sub-antimicrobial dosing has been recommended for acne. Well-performed clinical trials recommended the usage of 20 mg of doxycycline twice daily. This dose was well tolerated and prevented the emergence

of resistance. Further studies are warranted to confirm the efficacy of this regimen.

3. Sarecycline HCL is a narrow-spectrum tetracycline that preserves the gut microbiome through reduced activity against enteric gram-negative bacteria. C acnes strains have shown a low propensity to develop resistance against this agent.

FUTURE AGENTS SHOWING PROMISING ACTION AGAINST C. ACNES

1. Taurine bromamine: it has antioxidant, anti-inflammatory, and microbicidal action, Topical usage in trials has shown promising activity against C acnes. The limiting factor was its instability in topical preparations.
2. Antimicrobial cationic peptides: these are ribosomal synthesized and possess antimicrobial, antifungal, and anti-inflammatory properties.
3. Ectopeptidase inhibitors: they act by causing suppression of sebocyte proliferation, suppression of enhanced terminal sebocyte differentiation, cause the upregulation of the anti-inflammatory cytokine IL-1 receptor antagonist. However, in-vivo studies and clinical evidence are lacking.
4. Zileuton: it is a 5-lipoxygenase inhibitor showing Inhibition of sebum synthesis along with Anti-inflammatory activity. The limitations are a lack of direct anti-bacterial action and the requirement of further clinical evidence.
5. Lipids with antimicrobial action: certain lipids with antimicrobial activity cause modulation of TLR2
6. Plant extracts: extracts from the magnolia species namely Honokiol and magnolol have shown anti-bacterial action against C acnes and C granulosum. Flavonoids, like kaempferol and quercetin, too showed efficacy against c acnes.
7. Phage therapy: using bacteriophages against C acnes is a novel potential area in resistant acne cases.

GENERAL GUIDELINES FOR ANTIBIOTIC USAGE IN ACNE

DO's	DON'Ts
1. Use antibiotics only in severe cases of acne when indicated	1. Antibiotics are not recommended in grade 1, & 2 acne
2. Antibiotics should be used for the shortest required period. Switch over to alternate therapies at the earliest	2. Avoid topical antibiotic monotherapy
3. Oral antibiotics should be ideally combined with a topical retinoid or benzoyl peroxide	3. In case of topical antibiotic usage, choose a combination of antibiotic with benzoyl peroxide or adapalene
4. In case of failure of response to respond to an antibiotic after 12 weeks, suspect resistance and switch over to an alternate antibiotic	4. Do not use antibiotics beyond 12 weeks for therapy

5. Retinoids have microbiome modulating effects in addition to their efficacy in acne and should be used more frequently although with precautions.	5. Avoid simultaneous usage of antibiotics with different chemical structures
	6. Avoid multiple courses of antibiotics
	7. Never use antibiotics for maintenance therapy

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FACE-TO-FACE WITH MASKNE

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KEY POINTS

- Maskne, or mask acne, refers to the skin irritation and breakouts that can occur as a result of wearing a face mask.
- The combination of heat, moisture, and friction from a mask can lead to clogged pores and acne, particularly around the nose, mouth, and chin.
- To prevent this, it's important to wear a clean mask made of breathable material and cleanse your face before and after wearing a mask.
- The treatment is the same as acne vulgaris and is important to visit a dermatologist for the same.

INTRODUCTION

Facemasks are omnipresent signs of the times and part of our future for a bit longer. They play a vital role in reducing the spread of the coronavirus. Maskne", a portmanteau of the words "mask" and "acne", is a type of acne mechanica, a form of acne in either O-zone or U-zone of the face or any areas that are covered by facial mask secondary to the prolonged use of facial masks.

It can affect acne-prone individuals, but may start de novo after the use of a mask for around 6 weeks or may cause exacerbation of the previous acne. The exact cause remains unanswered in literature, but it is probably multifactorial

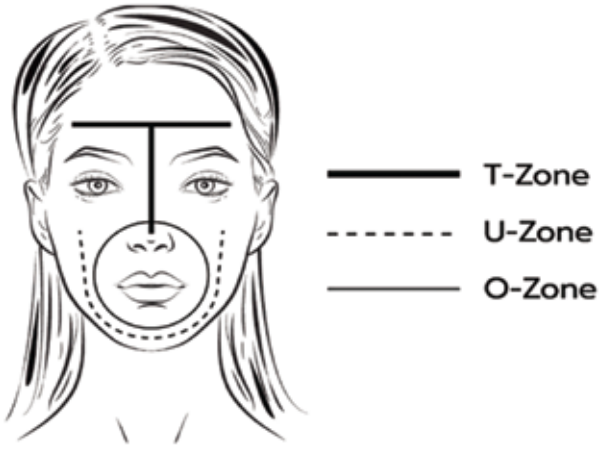

Figure 1 showing O,U and T zones of the face

including heat, sweat, mechanical stress (pressure, friction, and rubbing) and occlusion by mask, and microbiome dysbiosis.

During the ongoing COVID-19 pandemic, an increase in facial dermatoses, such as irritant contact dermatitis, seborrheic dermatitis, and rosacea, has been reported due to mask use. It is important to rule out and address the differential diagnoses of dermatological conditions triggered by mask-use. Since approved guidelines for the treatment of maskne do not exist, instructions are taken from acne vulgaris therapies, as we do in our experience.

As far as therapeutic strategies, maskne requires the correct use of skin care ingredients for acne-

prone skin and the use of topical treatments, i.e., sebum-regulators and emollients. Here are some preventive measures:

MASK RELATED

1. **Wear the right mask. To reduce skin problems, look for masks that offer the following:**

- A snug, but comfortable fit with at least two layers of fabric
- Soft, natural, and non-synthetic breathable fabric, such as cotton, on the inside layer that rests against your skin or silk (no friction)
- To take care of the excessive sweat build-up inside the mask, two layers of gauze can be placed inside the mask
- People with oily skin can regularly wipe their faces with a wet towel / wipe containing moisturizers

2. **Take a 15-minute mask break every 2 hours. Of course, only remove your mask when it's safe to do so and after washing your hands.**

   Wear masks with different types of ties and ear loops and wear a different type each day to stop the ear soreness.

3. **Wash your cloth masks.**

a. Wash the masks in hot water unless the instructions say otherwise.

b. Use a fragrance-free, hypoallergenic laundry detergent. Avoid fabric softeners.

4. It is advisable to change the masks regularly and advise to replace the surgical mask every 4 h to 6 h and N95 mask every 3 days.

5. Do not use the mask with an abrasive metallic nose clip which can cause nickel sensitization.

6. Physical sunscreen should be preferred over chemical sunscreens which could cause irritation and promote comedogenicity under the mask.

7. Wash hands before putting on the mask and after removing it and avoid touching the mask frequently.

8. Ideally Ultraviolet protection factor (UPF) 50 + fabric masks should be used which will also offer photoprotection. Development of biofunctional textiles for use in masks is underway and holds promising results. They have a high evaporation/cooling coefficient and are water resistant, preventing biofluid spread. High thread count and tightly woven fabrics have higher UPF and minimize textile-skin friction, relevant to individuals with atopic conditions.

9. Apply non-comedogenic moisturizers before and after mask use and if required use light make-up only or ditch it. Use of cosmetic products under the mask is likely to cause irritation and flare of acne, avoid it.

SKINCARE

1. Thoroughly cleanse your skin before and after wearing your face mask. Use mild gentle cleansers close to the skin's natural pH (pH: 5), and avoid irritants and toners that can disrupt the skin's protective barrier.

2. Use of dermocosmetics: Application of dermo-cosmetic cream has the aim of sealing, moistening, and moisturizing the epidermis by reducing water loss, attracting water to the dermis. and makes the skin smooth and soft, respectively. Apply this 30min before putting on the mask.

3. Use an oil-free moisturizer (for sensitive skin and oily skin) prior to applying a mask. Look out for contents like green tea, aloe vera, allantoin and licochalcone to reduce inflammation. Natural

moisturizing factors such as sodium hyaluronate, ceramides and polyglutamic acid are humectants that reduce transepidermal water loss without any irritation when worn under occlusion. Avoid occlusive agents under the mask.

4. Moisturize frequently and use an exfoliating cleanser with salicylic acid or glycolic acid or benzoyl peroxide only at night. Avoid any exfoliating products or products with retinol during the day when the mask is to be worn.
5. Look for creams containing niacinamide or zinc acetate that have sebostatic and anti-inflammatory effects. Patients affected by hyperhidrosis could benefit from powder formulations that prevent occlusion and absorb excess moisture. Products based on zinc oxide formulations reduce humidity and are stable in powder compounds.
6. Avoid scrubbing of affected areas and popping of pimples to prevent irritation.
7. Use cleansing wipes or towelettes or silicon barrier wipes during mask break time.

MANAGEMENT OF ACNE

For treatment, conventional topical and oral medication as used in acne vulgaris can be followed depending on acne severity and as advised by a dermatologist.

Topicals antibiotics, benzoyl peroxide and retinoid for mild acne especially at night; while for moderate and severe grade of acne we may need an additional oral antibiotic or oral retinoid. Hydrogel carrier formulations of retinoid/antibiotic combination topicals can minimise local irritation by ensuring better drug tolerance and efficacy. Try not to overapply the retinoid and avoid leave-on products.

For recalcitrant or severe form of maskne, consider a course of oral isotretinoin but use it with caution due to its inherent irritant potential. Sometimes, it's hard to care for your skin as planned. Visit your nearest dermatologist before using anti-acne products.

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ACNE, ROSACEA, HIDRADENITIS SUPPURATIVA (HS)- A BRAIN - GUT – SKIN LINKAGE?

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KEY POINTS

- Newer aetiopathogenic concepts are evolving, of which the gut-brain-skin connection has been an eye-opener.
- A relationship between gut, skin and mental health has been established in skin diseases like acne, rosacea, hidradenitis suppurativa, atopic dermatitis and psoriasis.
- The gut microbes influence the skin renewal via signalling processes. “Cross-talk” between the gut and skin takes place via the immune system.
- When the gut pH changes, colonic bacteria enter the intestines, and augment the bacterial dysbiosis resulting in an inflammatory response indirectly causing the skin pathogens to become dysbiotic resulting in inflammatory skin disease.

INTRODUCTION

The relationship between gut, skin and mental health was first hypothesised almost 80 years ago by John H. Stokes and Donald M. Pillsbury. Since then, there is growing evidence that this holds true in various skin diseases like acne, rosacea, hidradenitis suppurativa, atopic dermatitis and psoriasis. The normal gut microbiota includes Lactobacillus, Clostridium, Enterococcus, Bacillus, and Ruminococcus. These attach themselves to the gut lining, and together with IgA, dendritic cells, and T cells form a “mucosal firewall” thus preventing entry of noxious pathogens like Clostridium difficile and H. pylori.

The gut microbes influence skin renewal via signalling processes. “Cross-talk” between the gut and skin takes place via the immune system. Gut dysbiosis leads to the gut - lining damage, allowing the dysbiotic gut-bacteria to cross the mucosal wall, secrete toxins and neurotransmitters. The outcome is hyper-responsiveness of B cells, impact on T-cell differentiation, and reduction of gut IgA secretion.

An impaired barrier allows leakage of the inflammatory mediators and toxins into the circulation. These ultimately reach the skin and cause skin pathogens to become dysbiotic resulting in inflammatory skin disease. Also, when the gut pH changes, colonic bacteria enter the intestines, and augment the bacterial dysbiosis resulting in an inflammatory response.

Acne

Newer aetiopathogenic concepts are evolving, of which the gut-brain-skin connection has been an eye-opener. The normal flora in the acne-affected sebo-follicles restrain the multiplication of C. acnes. Gut dysbiosis occurs under the following conditions:

- Stress and acne connection has been hypothesized via the secretion of Factor P and the stress hormone cortisol via the HPA–axis
- Anxiety, depression, and stress cause the gut bacteria to secrete neuro-transmitters like acetylcholine, serotonin and norepinephrine which aggravate skin inflammation
- Patients with acne have lower levels of Lactobacillus and Bifidobacterium species (essential for maintaining intestinal mucosal integrity and decreased production of cytokines) leading to high levels of P. acnes
- High fat diet influences the gut mucosa to produce higher levels of Firmicutes over Bacteroides
- Probiotics and a low carbohydrate diet reduce acne inflammation by reducing the inflammatory cytokines

Rosacea

Several reports have substantiated the relationship between H. pylori and rosacea.

- H pylori, small intestine bacterial overgrowth (SIBO), and IBD have been associated with this disease
- H pylori disrupts the gut flora, and increases nitric oxide levels resulting in inflammation, and the clinical picture of rosacea
- IL-8 and TNF-α levels are also increased, leading to more inflammation
- Certain antibiotics and probiotics have been shown to eradicate H pylori to control the inflammation and alleviate rosacea

Hidradenitis Suppurativa

Although HS is included under "follicular occlusion disorder", the exact cause is still an enigma.

- Studies have shown that a high fat diet, causes dysbiosis of the colonic microbial population, leading to the secretion of inflammatory mediators like IL – 17, TNF-α, IL-1β, which upregulate the production of matrix metalloproteinases, and inflammation
- Patients were seen to have lower levels of Faecalibacterium prausnitzii and increased populations of E coli
- Many of the patients have IBD, metabolic disease and PCOS

MANAGEMENT STRATEGIES

More work needs to be done to determine the accurate aetiopathogenesis of the appendageal diseases in order to translate into therapeutic success.

Restore the normal microbial gut flora by:

a. Modifying diet to include high fibre, low fat and low sugar/carbohydrates (western diet related to low levels of Bifidobacterium and Lactobacillus)

b. Probiotics (living bacterial populations of Lactobacillus rhamnosus, and Bifidobacterium) inclusion in the diet, inhibits C. acnes by virtue of antimicrobial peptides

c. Stress management

d. Application of creams containing probiotics to restore the skin pH and increase skin ceramide levels and microbial skin population

e. Antibiotics for rosacea and acne to reduce the pathogenic bacterial populations

f. Newer biologics which target the inflammatory pathways as is seen with the TNF- α inhibitors and the IL-17A inhibitors

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UPDATES IN MANAGEMENT OF HIDRADENITIS SUPPURATIVA (HS)

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KEY POINTS

- HS is refractory to conventional treatments, and its management remains a great challenge.
- In mild HS, monotherapy is usually considered, but in the advanced stage, combination of various therapies remains crucial.
- Although Tetracyclines (tetracycline, doxycycline, minocycline, lymecycline) are considered the first-line oral treatment for HS, the latest additions to the armamentarium include lasers, biologics, and photobiomodulation.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease affecting the apocrine gland-bearing areas of the body and ranges from mild to dreadful severity. The exact pathogenesis of HS is not yet well understood. The mild disease is usually controlled with lifestyle modifications, weight reduction, abstinence from smoking, oral antibiotics, and topical treatment; whereas moderate-to-severe HS is frequently refractory to the conventional treatments, and its management remains a great challenge for the clinicians, and hence new therapeutic avenues are under study.

TREATMENT

Topical treatment:

For the treatment of HS, antibiotics are commonly used as the first-line therapy and for several years the role of the microbiome has been studied, but monotherapy with antimicrobial agents alone is unlikely to completely cure HS. However, for mild disease, monotherapy is usually considered, but in the advanced stage, combination therapy remains the cornerstone of management.

i. Recently, a topical formulation of nanostructured lipid carriers containing clindamycin and rifampicin was evaluated in vitro study. Accumulation of both antibiotics was observed in the follicle, suggesting that this combination could be a promising formulation in HS..

ii. Another open-label study of 65 patients with Hurley I and II HS showed good clinical response to once daily application of 15% resorcinol. Overall, 85.2% (52/65) of patients achieved Hidradenitis Suppurativa Clinical Response (HiSCR) at week 12, and >80% of reduction in AN count was noticed. At week 12, with ultrasonography a significant reduction in the average thickness and length of the sinus tracts was observed, however, their number remained unchanged.

iii. Topical gentian violet as an antiseptic and wound healing agent is being evaluated in a phase II open-label study for HS.

iv. Similarly, a phase II open-label study is going on to evaluate the antimicrobial and anti-inflammatory effects of topical LTX-109 in the HS treatment.

v. Topical ruxolitinib 1.5% cream, a JAK1/JAK2 inhibitor is being tried in a phase II open-label trial.

vi. As the biofilm contributes to an inflammatory response in HS, its composition and changes after using a topical antibiofilm surfactant gel is understudy.

Systemic treatment

i. Systemic antibiotics

Tetracyclines (tetracycline, doxycycline, minocycline, lymecycline) are considered the first-line oral treatment for HS.

A retrospective study that compared the efficacy of the combination therapy consisting of clindamycin and rifampicin (600 mg plus 600 mg daily) versus lymecycline (300 mg daily) in 52 patients (26 in each group) for a duration of 10 weeks observed a 53.8% and 57.7% HiSCR achievement, respectively.

ii. Oral retinoids

A single prospective uncontrolled study evaluated alitretinoin in 14 females at the dose of 10mg/kg/d for a total of 24 weeks. Approximately, 78.5% of patients reported significant clinical improvement as assessed by the Modified Sartorius Score (mSS).

Other treatment modalities:

i. Intralesional corticosteroids

The efficacy of intralesional ultrasound-guided injections of triamcinolone plus lincomycin were evaluated at baseline and after 2 weeks in an interventional prospective study, which at week 4 showed clinical and symptomatic improvement in 36 patients out of a total of 37.

ii. Lasers

The efficacy of Alexandrite hair removal laser is being evaluated in an open-label study of 20 patients with HS in the axilla or groin bilaterally, where one side shall serve as control and the other side shall be treated. In a few case reports and case series, the Alexandrite laser has shown promising results. However, between various studies, the response rates are not comparable, but better response rates and outcomes are observed with intralesional PDT in the axillary area.

iii. Photobiomodulation

It has been proposed as a third-line adjuvant treatment for the management of HS. A non-invasive treatment for HS has been reported to have beneficial effects in an in-vitro model on promoting angiogenesis, vasodilation, wound healing, and relief from pain and inflammation.

iv. Biologics

Table 1 shows the list of Biologics proven effective/ that have shown efficacy in HS with evidence. These include Bermekimab, Guselkumab, Brodalumab, Binekizumab, IFX-1, Risankizumab, CSL324 and Adalimumab.

CONCLUSION:

HS is a complex multifactorial disease that requires lifestyle modifications along with combination of various therapeutic options like antimicrobial agents, hormonal therapy, surgery, and biologic therapy, if necessary. Due to the lack of effective treatments for moderate-to-severe HS, new therapeutic options are being studied, targeting specific cytokines involved in HS pathogenesis. The treatment of a multifactorial disease with complex pathogenesis such as HS is necessarily multipronged, with treatment algorithms based on the disease severity.

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Table no. 1 shows clinical trials of various biologicals in the management of HS

Biologicals	Target	Status of study/ efficacy
Bermekimab Dosed at 7.5mg/kg every 14 days up to 7 infusions	IL-1α	Low (one double-blind RCT of 20 patients) 2 clinical trials updated on clinicaltrials.gov as active but not yet recruiting NCT03512275 NCT04019041
Guselkumab	IL-23	One open-label trial of 3 patients, one retrospective chart review of 8 patients, and one case study A phase II clinical trial registered on clinicaltrials.gov (NCT03628924) A pilot open-label study is active but not recruiting (NCT04084665)
Brodalumab	IL-17	A phase 0 clinical trial to assess for safety on clinicaltrials.gov is recruiting (NCT03960268) A phase II clinical trial is currently listed but not yet recruiting (NCT03910803)
Bimekizumab	IL-17A and IL-17F	Completed phase II study on clinicaltrials.gov, no results available yet (NCT03248531)
IFX-1	C5a	A phase II clinical trial has been completed but results have not been published (NCT03001622); another phase II clinical trial is active but not recruiting (NCT03487276)
Risankizumab	IL-23/17, JAK2	Phase II recruiting (NCT03926169)
CSL324	G-CSF stimulating mab	A phase I clinical trial on clinicaltrials.gov is listed but not recruiting (NCT03972280)
MSB11022 (Adalimumab biosimilar)	TNFa	A phase I clinical trial listed on clinicaltrials.gov is currently recruiting (NCT04018599)

QUALITY OF LIFE IN HYPERHIDROSIS

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KEY POINTS

- Hyperhidrosis can cause frequent inconvenience and profound social and psychological embarrassment to the patients.
- Hyperhidrosis can lead to reduced social relationships, impairments in their study or work life, and reduced emotional well-being.
- The hyperhidrosis quality of life index assesses the impact of hyperhidrosis on daily life activities and psychosocial well-being of the patient.
- An integrated approach involving various healthcare professionals like psychiatrists and counsellors along with a dermatologist is necessary to deal with the psychosocial impairment associated with the disease.

INTRODUCTION

Hyperhidrosis is a disorder of the autonomic nervous system that is characterized by excessive sweating more than what is required for thermoregulation and has a worldwide prevalence ranging from 0.72-9%. It can be either primary, due to a sympathetic dysregulation leading to disproportionate sweating, or secondary, due to an underlying medical condition (infections, neurological disorders, metabolic disorders, neoplasms, anxiety, and stress) or the use of prescription medications.

HYPERHIDROSIS AND IMPACT ON QUALITY OF LIFE:

Hyperhidrosis can cause frequent inconvenience and profound social and psychological embarrassment to the patients leading to limited daily activities, fewer social relationships, impairments in their study or work life, and reduced emotional well-being. People with palmar hyperhidrosis are often embarrassed to shake or hold hands and have difficulty holding objects or tools. They may be disqualified from certain jobs like defense forces and have difficulty in doing jobs requiring the wearing of gloves like OT nurses, food handling. Generalized hyperhidrosis and axillary hyperhidrosis can alter a patient's choice of clothing, particularly, the material, colour and design of clothes. The individuals face difficulty in maintaining personal relationships as there is fear of other person's reaction towards excessive sweating. These individuals over a period of time develop social anxiety disorders and phobias. Negative emotions are the most prevalent psychologic effect of hyperhidrosis. Hyperhidrosis also puts the patient on a financial burden on personal hygiene and treatment of the disease. Unsurprisingly, hyperhidrosis patients

are characterized by a tremendous impairment of quality of life equal to that reported with severe psoriasis, kidney failure, and advanced-stage rheumatoid arthritis.

ASSESSING THE IMPACT OF HYPERHIDROSIS ON QUALITY OF LIFE:

In order to improve the understanding of hyperhidrosis from the patient's point of view, assessing the quality of life has become a standard outcome measure in most studies. Several patient reported outcome measures (PROMs) have been developed to assess the impact of hyperhidrosis on patients. These are: Hyperhidrosis Quality of Life Index (HidroQoL),

Hyperhidrosis Quality of Life Questionnaire (HQLQ), Hyperhidrosis Impact Questionnaire (HHIQ), Hyperhidrosis Disease Severity Scale (HDSS) and Axillary Sweating Daily Diary (ASDD). In addition, generic PROMs such as the Dermatology Life Quality Index (DLQI) or the short-form health survey (SF-36) can also be used to study the impact of hyperhidrosis on patient's life. Gabes et al., in a systemic review concluded that the HidroQoL, Hyperhidrosis Questionnaire (HQ) and the Sweating Cognitions Inventory (SCI), can be recommended for use in hyperhidrosis. Results obtained with these three instruments were valid and trustworthy.

HYPERHIDROSIS QUALITY OF LIFE INDEX

Hyperhidrosis Quality of Life Index was developed and validated by Kamudoni et al in 2014 as there were no reliable tools to assess the impact of hyperhidrosis. HidroQoL which can be used in a clinical setting and for research purposes as well. It can be used to enhance the diagnosis and management of the condition. It contains 18 items distributed under two domains. The daily life activities domain contains 6 items and the psychosocial impact domain contains 12 items (Table 1). All the items were scored on a 3-point scale: no, not at all = 0; a little = 1; and very much = 2.

CONCLUSION

Hyperhidrosis affects various aspects of a patient's life, with psycho-social effects being the utmost importance. Pharmacological therapy alone may not address all the needs of the patient. An integrated approach incorporating various healthcare professionals like the psychiatrists and counsellors along with a dermatologist is necessary to deal with the psychosocial impairment associated with hyperhidrosis. This could be delivered as part of a well-orchestrated patient-centered dermatologic care. HidroQOL stimulation should be incorporated in the practice to improve the care of hyperhidrosis as well as monitoring response to the treatment.

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Table 1: Hyperhidrosis Quality of Life Index (HidroQoL)				
Domain 1: Daily life activities		**Very much**	**A little**	**Not at all**
1.	My choice of clothing is affected			
2.	My physical activities are affected			
3.	My hobbies are affected			
4.	My work is affected			
5.	I worry about the additional activities in dealing with my condition			
6.	My holidays are affected (e.g. planning, activities)			
Domain 2: Psychosocial Life				
1.	I feel nervous			
2.	I feel embarrassed			
3.	I feel frustrated			
4.	I feel uncomfortable physically expressing affection (e.g. hugging)			
5.	I think about sweating			
6.	I worry about my future health			
7.	I worry about people's reactions			
8.	I worry about leaving sweat marks on things			
9.	I avoid meeting new people			
10.	I avoid public speaking (e.g. presentations)			
11.	My appearance is affected			
12.	My sex life is affected			

QUIZ-PART : 1

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QUESTIONS

1. **Drug of choice in a female with acne having irregular menses**

   A. Isotretinoin B. Combined oral contraceptive pill C. Antibiotics D. Spironolactone

2. **Topical agent having good efficacywith less side effects on all three -acne, rosacea and hyper pigmentation is**

   A. Tretinoin B. Niacinamide C. Benzoyl peroxide D. Azelaic acid

3. **Which of these statements is not correct for primary hyperhidrosis**

   A. Most common site affected is the palm B. It is unilateral and asymmetric C. Affects younger patients D. Occurs more often in daytime

4. **Rosacea is associated with**

   A. Hypertension B. Inflammatory bowel disease C. Anxiety and depression D. All of the above

5. **Systemic antibiotic of choice in patients with inflammatory acne lesions**

   A. Tetracyclines B. Cephalosporins C. Fluoroquinolones D. Rifampicin

ANSWERS

1. B. Antiandrogenic progesterones help suppress hyperandrogenism leading to improvement of acne. Combined oral contraceptives, especially those with cyproterone acetate or drospirenone, have added benefits of regularising menses in patients with irregular cycles.
2. D. Azelaic acid is a very versatile molecule having benefits in acne, rosacea (FDA approved) and hyperpigmentation. It has lower irritation potential good efficacy in all three conditions.
3. B. Sweating in primary hyperhidrosis is bilaterally symmetrical, affecting palms, soles, axillae and face. Due to hyperactivity of the sympathetic nervous system and an impaired feedback mechanism, the body sweats more than what is needed for temperature regulation.
4. D. Rosacea is associated with multiple systemic comorbidities and awareness of these is needed in order to screen patients. Strongest evidence exists for hypertension, dyslipidemia, inflammatory bowel disease, anxiety, and depression.
5. A. Doxycycline and minocycline are used in acne both for their anti-microbial as well as anti-inflammatory properties. Anti-inflammatory effects are achieved at lower (subantimicrobial) doses.

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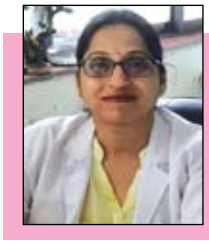
QUIZ-PART : 2



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QUESTIONS

1. A Synonym for Hidradenitis Suppurativa is

a. McDonald Acne
b. Verneuil Disease
c. Dercum disease
d. Morbihan's Syndrome

2. Amongst the following, which marker level is increased in Hidradenitis Suppurativa?

a. IL-1b
b. IL-2
c. IL-4
d. INF-gamma

3. Exacerbation of Hidradenitis Suppurativa occurs on the use of which of the following medication?

a. Cyclosporine
b. Isotretinoin
c. Sirolimus
d. None of the above

4. Which of the following genodermatosis is not associated with Hidradenitis Suppurativa?

a. Keratosis Icthyosis Deafness Syndrome
b. Pachyonychia Congenita
c. Dowling Degos disease
d. Netherton Syndrome

5. All of the following therapies are used in Hidradenitis Suppurativa except?

a. Adalimumab
b. Apremilast
c. Acitretin
d. Mycophenolate Mofetil

ANSWERS

1. B (Verneuil's disease is more commonly known as Hidradenitis Suppurativa and is also called acne inversa. It is a chronic disease of the hair follicles causing the formation of nodules, abscesses, and scarring. It affects 0.05 to 4.10% of the population, occurring mostly in young African American or biracial women).
2. A (Matching cellular IL-1 receptor levels, dermal fibroblasts showed both the strongest and broadest IL-1β response, which was not clearly shared or strengthened by other cytokines. The IL-1β signature was specifically present in HS lesions and could be reversed by application of IL-1 receptor antagonist).
3. C (An exacerbation or onset of Hidradenitis suppurativa has been reported following lithium and sirolimus therapy).
4. D (Genodermatoses associated with Hidradenitis Suppurativa or HS like lesions include keratosis ichthyosis deafness syndrome, pachyonychia congenita, steatocystoma multiplex and Dowling–Degos disease).
5. D (Three randomized controlled trials (RCTs) have been conducted with adalimumab. They indicated that approximately twice as many patients treated actively achieved a significant effect (as defined by HiSCR) using a dosing regimen similar to that used for inflammatory bowel disease (a loading dose of 160 mg at week 0 and 80 mg at week 2, followed at week 4 by 40 mg every week, for a total of 12 weeks) as compared with patients not treated actively (58.9% versus 27.6% respectively. case series suggest that acitretin (50 mg or more daily) may be effective in a significant proportion of patients and in some cases offers long-term remissions. Apremilast is a potential long-term treatment option in patients with HS, and this study shows prolonged clinical efficacy in initial responders after 1 and 2 years of treatment. Similar results were seen in a previously published case report describing stable disease course during 72 weeks of treatment).

RECOMMENDED READING

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